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The treatment of malaria in children

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Malaria is responsible for a huge amount of morbidity and mortality, the majority of which is in African children. Drug resistance is widespread and, though effective treatments like the artemisinins are available, their price remains a barrier to their use in many places. This review summarises the lifecycle of the *plasmodium* species and the features of severe and uncomplicated disease. The antimalarial drugs are discussed as well as ancillary treatments for the complications of severe disease.

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Introduction

Malaria is the most important parasitic infection in the world and is responsible for 0.7–2.7 million deaths each year and up to 500 million symptomatic infections[1]. The vast majority of these deaths are caused by *Plasmodium falciparum*, in young children in Africa. For people living in high transmission areas, the development of a degree of immunity against local strains of the parasite means that older children and adults rarely suffer the more severe forms of the disease and often carry parasites in their blood without symptoms (the main exceptions to this are pregnant women, especially primigravidae). For the increasing numbers of travellers to malarious areas and those living in areas of low-level malaria transmission, there is no protective immunity and severe disease manifests itself at all ages.

Antimalarial drug resistance is now widespread and exists to some extent to most drugs. 'Combination therapy' of two or more independently acting drugs taken together is now being promoted to try to slow the development of resistance and bring about a sustained improvement in cure rates[2]. The cost of using more effective drugs is the major barrier to the provision of effective treatment in many parts of the world. The Global Fund to fight AIDS, tuberculosis and malaria (GFATM) has been established to enable poorer countries, where these diseases are most prevalent, to buy effective drugs[3].

This review will focus on chemotherapeutic options for the treatment of malaria in children as well as treatments for the complications of severe malaria. Some of these treatments are expensive and/or not practical for use in resource poor countries but have been included for the sake of completeness.

The malaria parasites and the pathogenic basis of the disease

Four species of the *Plasmodium* genus cause human malaria, *falciparum, vivax, ovale*, and *malariae*, but our main problems are with *falciparum*. Malaria sporozoites are inoculated into humans in the saliva of a biting female *Anopheles* mosquito. These invade hepatocytes and undergo a variable period of replication. The duration of this stage depends on the species involved, the presence of

antimalarial prophylactics in the blood and other host and parasite factors. At the end of this period, millions of merozoites are released to invade circulating red blood cells (RBCs) and replicate again. Approximately 48 or 72 hours later, the red cells rupture, releasing more merozoites (to infect more RBCs) and other parasite antigens. This triggers the release of pro-inflammatory cytokines like tumour necrosis factor (TNF) from host mononuclear cells and with it the onset of fever[4]. At some point, usually two or three weeks later, some of these merozoites differentiate into male or female gametocytes, which are the stage of the parasites that is infectious to another biting mosquito; gametocytes are not pathogenic. *Ovale* and *vivax* have an additional life stage with the development of a dormant liver infection, called a "hypnozoite", which can cause a relapse of malaria symptoms and parasitaemia many years after successful treatment of the primary infection.

Uncomplicated malaria is characterised by fever, arthralgia, and headache. Severe disease in children commonly presents with impaired consciousness, prostration, repeated fits, and respiratory distress due to metabolic acidosis[5]. Cerebral malaria is a descriptive term for impaired consciousness in the presence of parasitaemia where there is no other obvious cause. Laboratory features of severe malaria include hypoglycaemia, severe anaemia (haemoglobin ≤5g/dl) and hyperparasitaemia (≥5% in a non-immune child)[6]; the cerebrospinal fluid is normal even in the most severe cases of cerebral malaria. *Falciparum* is responsible for nearly all cases of severe disease. The other malarias, called the "benign" malarias, may make the child feel very unwell but are unlikely to cause death.

P. falciparum is much more pathogenic than the other malarias because infected RBCs are able to adhere to vessel walls and to each other and sequester within the capillary beds and post-capillary venules of the brain, spleen and other organs. The precise mechanism by which sequestration leads to pathology is not clear, although there are several hypotheses[4]:

- mechanical obstruction of the microvasculature causing local ischaemia
- alterations in capillary permeability and the blood-brain-barrier leading to oedema
- the release of pro-inflammatory cytokines like TNF and interleukin-1 and the induction of nitric oxide synthesis

Treatment of falciparum malaria

The vast majority of cases of malaria are uncomplicated and the child makes a full recovery. The diagnosis of malaria should be confirmed by blood film examination, although in many parts of Africa, treatment is undertaken on the basis of symptoms/signs rather than microscopy. This is necessary because of the lack of diagnostic facilities, and the high prevalence of infection: 80% of apparently healthy children can be infected in many parts of Africa, making parasitaemia a poor diagnostic tool in many places[7]. Furthermore, a single negative blood film result cannot be relied upon to rule out malaria especially in those with some degree of immunity. In cases where clinical suspicion is high, a therapeutic trial of antimalarials should be given without delay even in the absence of a positive test. Malaria can rapidly progress to severe disease and death, especially in the non-immune.

In an outpatient setting, the practicality of the treatment is important; the shorter the treatment regime and the fewer side effects the better the compliance. The choice of treatment will also be influenced by:

- the severity of the illness
- the likely parasite drug sensitivity
- prior treatment
- the degree of immunity in the child
- the cost and availability of the drug

For uncomplicated malaria, the aims of treatment are to prevent the progression to severe disease and to provide rapid symptomatic relief. In the developed world children with malaria are routinely admitted for inpatient care while in high transmission areas, treatment is usually given on an outpatient basis. In addition to antimalarial therapy, attention should be paid to maintaining hydration and managing anaemia and fever.

Drugs for falciparum malaria

Artemisinin derivatives

The artemisinins cause the fastest decline in parasite numbers of all the antimalarials, there is no known *in vivo* resistance and they are well tolerated[8]. There are four artemisinin derivatives in common use – dihydroartemisinin, artesunate, artemether, and arteether. These are available as oral preparations for uncomplicated malaria, and suppositories and parenteral preparations for more severe disease. Few adverse effects have been reported although neurotoxicity has been observed in animal studies[9]. In humans these effects have not been demonstrated in any studies to date involving many thousands of patients, although one recent study reported ototoxicity[10]. The artemisinins are all teratogenic in both rats and rabbits at doses similar to those used in man[11]. No birth defects have been reported in humans and this is reassuring, although it must be

noted that there are relatively few rigorously documented cases of use in the first trimester (around 100 to 200 cases). The World Health Organization (WHO) advises that the artemisinins ought not to be taken in the first trimester of pregnancy unless the mother's life is at risk[12]. In fact, since pregnancy testing is generally unavailable, increasing numbers of children will be born to mothers who were exposed to these drugs in early pregnancy.

The artemisinins may be used as sole treatment for malaria, in which case they should be taken for 7 days (which is often operationally impractical). As *Artemisinin combination therapy* (ACT) for uncomplicated malaria, they are taken for 3 days with another antimalarial. The only fixed-ratio (both drugs co-formulated as a single tablet) ACT commercially available at the present time is Artemether-lumefantrine (Coartem). As a six dose regimen, it is effective against multi-drug resistant parasites and has been adopted as first line treatment for uncomplicated malaria in several African countries[13]. Other fixed-ratio ACTs are at various stages of development.

Arylaminoalcohols

Mefloquine is effective against African *falciparum* but in parts of Thailand the parasites have developed resistance[14]. It is taken orally so is suitable only for uncomplicated malaria. The dose is best split and taken 6 hours apart to reduce the not infrequent side effect of vomiting. This has obvious implications for efficacy, especially where children are treated as outpatients.

Quinine remains effective against multi-drug resistant *P. falciparum* though in parts of SE Asia there is a decline in sensitivity. In malaria endemic areas it is reserved for the treatment of severe disease or where first line therapy for uncomplicated disease has failed. In non-immune children, it is often used for uncomplicated malaria. Orally it is taken 3 times a day, and a full treatment course is 7 days. It can be combined with clindamycin or doxycycline in children older than 12 years for 7 days, or a dose of sulfadoxine-pyrimethamine where decreased susceptibility to quinine is suspected to improve cure rates if no alternative is available. In semi-immune children in Africa, the treatment course is often shortened to 3–5 days and followed by treatment with sulfadoxine-pyrimethamine. Quinine has marked symptomatic adverse effects (tinnitus, dizziness, nausea) occurring in most individuals even at normal doses. In the USA, quinidine is preferred to quinine for severe malaria – a matter of availability rather than pharmacological properties.

4 Aminoquinolines

Chloroquine (CQ) remains the first-choice drug for infections by *P. vivax, P. ovale* and *P. malariae* (see below). It is still the most widely used treatment for *P. falciparum* worldwide despite widespread resistance. In parts of Central America, *P. falciparum* remains relatively CQ sensitive, but elsewhere it cannot be recommended as a treatment for *falciparum* malaria. Amodiaquine (AQ) – a compound similar in structure and activity to CQ – retains some utility against CQ resistant parasites and is increasingly being considered and used as a treatment for uncomplicated malaria in Africa[15]. When used for prophylaxis, AQ caused severe adverse effects, agranulocytosis and hepatitis, but as a treatment it appears safe (although continued pharmacovigilance is required)[16, 17].

Anti-folates

Sulfadoxine-pyrimethamine (SP) and chlor-proguanil-dapsone (CD) inhibit parasite folate synthesis, the component drugs acting synergistically. SP has replaced CQ as first line treatment for uncomplicated malaria in many countries in Africa but resistance has quickly developed. CD has some utility in Africa against SP resistant parasites and is available now as a fixed-ratio treatment for uncomplicated malaria[18]. CD is a new drug and, as with any new drug, its use needs to be monitored with care: WHO-TDR (funded by the Gates Foundation) has established a programme of Phase IV studies to examine the safety and utility of CD under operational conditions. In most parts of SE Asia, parasites carry an additional anti-folate resistance mutation, and are resistant to both SP and CD[19].

Atovaquone-proguanil

This is an effective treatment for uncomplicated multi-drug resistant malaria but too expensive for widespread use in Africa. Resistance has been documented in a few case reports from Africa.

Severe falciparum malaria

Approximately 1–2% of children infected with *falciparum* develop severe disease which has a mortality rate of between 15 and 50% depending on the settings[20]. Of those who survive cerebral malaria, about 10% will have neurological sequelae; commonly ataxia, hemiplegia, and blindness[21]. Many of these will improve with time so that within 6 months only around 4% of the children will have a persistent deficit. Treatment must be given parenterally, at least until there is sufficient improvement to allow oral dosing. In addition, the recognition and proper management

of complications is paramount. Repeated parasite counts should be done to confirm parasite clearance (though in the early hours of treatment this may rise as sequestered parasites re-enter the peripheral blood), and regular clinical examination and blood glucose monitoring are essential. IV quinine remains the standard therapy though parenteral artemisinins have been shown to be equally safe and effective[22]. Rectal artesunate has been shown to be an effective initial treatment for unconscious patients who are unable to quickly access hospital services[23]. Table 1 details the WHO recommended therapy for severe malaria[6].

Table 1 Treatment for children with severe malaria

IV quinine therapy
- Give a loading dose of 20 mg salt/kg body weight by slow IV infusion to achieve parasitocidal concentrations as soon as possible. Quinine must be given diluted in 10 ml/kg of dextrose or dextrose / saline
- Do not give a loading dose if the child has taken quinine / quinidine / halofantrine / mefloquine in the previous 12 hours
- Maintenance doses of 10 mg salt/kg body weight are given every 12 hours, the first 12 hours after the start of the loading dose
- If the child still requires parenteral therapy after 48 hours, the dose should be halved to prevent drug accumulation
- Switch to oral quinine as soon as able to swallow tablets. The dose is 10 mg salt/kg body weight every 8 hours
- If decreased quinine sensitivity is suspected, add clindamycin or doxycycline (in children over 12) for 7 days once the child is able to swallow. Alternatively, sulfadoxine-pyrimethamine may be used, though parasites from SE Asia are likely to be resistant to this

IM quinine if IV access fails and no alternatives available
- The dose is the same as IV and may be given IM into the anterior thigh, the total dose divided between the two sites. The buttocks should not be used for IM quinine injections

Parenteral artemisinin therapy
- IV artesunate: 2.4 mg/kg loading dose then 1.2 mg/kg 12 and 24 hours later, then 1.2 mg/kg daily for 6 days
- IM artemether 3.2 mg/kg loading dose, then 24 hours later, 1.6 mg/kg daily for 6 days
- PR artesunate 200 mg at 0, 4, 8, 12, 24, 36, 48 and 60 hours followed by an oral antimalarial if possible

Complications of severe falciparum malaria and their management

The more common complications of severe malaria seen in young children and their management are listed below. In older non-immune children, severe malaria may be complicated by pulmonary oedema, renal failure, coagulopathies and jaundice. The presence of any of these complications is associated with increased mortality[5].

Impaired consciousness

This may be due to "cerebral malaria" – an encephalopathy that seems to result from extensive sequestration of parasitised RBCs in the brain – or occur as a consequence of hypoglycaemia, convulsions, acidosis or severe anaemia. These should be treated if present as well as standard management of a comatosed patient. Bacterial meningitis should be considered in the differential diagnosis of a child with impaired consciousness and fever. In a resource rich setting, the clinician may wish to perform a lumbar puncture to exclude this diagnosis. In tropical Africa, where cerebral malaria is more common, the need for a routine lumbar puncture on all parasitaemic children with impaired consciousness is debatable and will depend on local experience and available resources. Certainly when the clinician is suspicious of bacterial meningitis a lumbar puncture must be performed.

Hypoglycaemia

This should be suspected in any child with impaired consciousness, fits or where there is a clinical deterioration. Blood sugars should be checked regularly and hypoglycaemia treated with 1 ml/kg body weight of 50% dextrose given IV. This should be diluted in an isotonic solution to approximately 10–20% and given over several minutes. This should be followed up with a slow infusion of 10% dextrose[6].

Convulsions

Around 50% of children with cerebral malaria have convulsions[24]. These may be generalised seizures or more subtle and harder to recognise with intermittent nystagmus, salivation or twitching of the mouth or a digit. Diazepam or alternatively paraldehyde is the first line treatment of choice but if the seizures persist, phenytoin or phenobarbitone can be used. There is no evidence to support the use of prophylactic anticonvulsants in cerebral malaria; a single dose of IM phenobarbitone at 20 mg/kg in a study in Kenya did reduce the frequency of subsequent fits but was associated with a higher mortality[25]. Whether a similar effect would be seen using a lower dose or a different drug is not known.

Respiratory distress/metabolic acidosis

Deep 'sighing' respiration with intercostal indrawing, in the absence of any localising signs in the chest, is suggestive of metabolic acidosis[26]. In children, systemic lactic acidosis is the major cause, the result of poor tissue perfusion, anaerobic metabolism and reduced clearance of lactate[26]. Adequate resuscitation (with crystalloids or blood) and termination of fits is required and response monitored by observing the rate and depth of respiration and the degree of peripheral circulation shutdown. Cardiac failure is rare in these children and transfusion and resuscitation should not be delayed or slowed for fear of precipitating pulmonary oedema. Dichloroacetate, which stimulates the metabolism of lactate, has been

shown to reduce blood lactate levels in both rat and human malaria infections. A survival benefit was shown in rats but no benefit has so far been demonstrated in humans with severe malaria[27,28]. Sodium bicarbonate is not recommended as an intervention to correct acidaemia.

Anaemia

Anaemia is a common complication of malaria infection and may develop rapidly especially where there is a high parasitaemia. Severe anaemia (haemoglobin concentration ≤ 5 g/dl) was present in 17.6% of Kenyan children hospitalised with malaria and is associated with a mortality rate of between 5 and 15%[29]. This mortality is further increased if there is concomitant respiratory distress. The decision to transfuse depends on the clinical condition of the child and also on the availability of a safe blood. In Africa, where there are concerns about the safety and availability of blood, transfusion should be reserved for the sickest children. In practise this means all those with a haemoglobin of ≤4 g/dl and those in the range 4–5 g/dl with signs of respiratory distress or impaired consciousness[5]. This policy should not be rigidly adhered to and decisions should be made on an individual basis. Hyperparasitaemia is another indication for transfusion in children who already have low haemoglobins in the expectation of a further fall in the next 24–48 hours.

Shock

A secondary bacterial infection should be considered and treated in any severely ill malaria patient with signs of sepsis[30]. Non-typhoidal *Salmonella* bacteraemia or septicaemia is associated with severe malarial anaemia in children[31]. Third generation cephalosporins, ciprofloxacin, or the combination of chloramphenicol and gentamicin are possible choices depending on local availability and resistance patterns. In addition, hypotension may be a manifestation of inadequate fluid resuscitation.

Hyperparasitaemia

The relationship between peripheral parasitaemia and disease severity varies in different patient populations. Semi-immune children can tolerate very high parasitaemias (>10%) with mild or no symptoms whereas, in non-immune children, disease severity is more strongly associated with the level of parasitaemia. Exchange blood transfusion is proposed as a measure to rapidly remove these parasites and harmful cytokines from the circulation[32]. One meta-analysis found no significant difference in mortality with the addition of exchange transfusion to anti-malarial therapy though these studies were not randomised and significant differences existed between the patient groups[33]. It is uncertain as to whether this is a useful therapeutic measure and for which patients it is indicated. Without a safe and available blood supply, this intervention cannot be considered.

Pulmonary oedema, renal failure, coagulopathies and "blackwater fever"

Pulmonary oedema may occur due to increased pulmonary capillary permeability the cause of which is unknown. It may also be associated with renal failure. Treatment is with frusemide and where fluid overload is present, haemodialysis or peritoneal dialysis. Acute renal failure is usually reversible though the child may require a period of dialysis support. Massive intravascular haemolysis with haemoglobinuria is the cause of blackwater fever. Most cases are transient though severe anaemia and renal failure may be associated. Thrombocytopenia is common and not usually associated with any bleeding tendency. Rarely disseminated intravascular coagulation with significant bleeding is seen and managed with transfusion of fresh blood and clotting factors.

Other interventions

A number of the pathological processes sometimes observed in severe malaria (such as raised intra-cranial pressure, acidosis and increased blood cytokines) have been targeted as potential treatment interventions but results have been disappointing. Dexamethasone gave no survival advantage in one large trial and increased morbidity[34]; monoclonal antibodies against TNF were shown to reduce fever duration but had no effect on mortality[35]. Other interventions of no proven benefit include mannitol, adrenaline, heparin, desferrioxamine (iron chelator), and immunoglobulin[5].

Treatment of non-falciparum malaria

Chloroquine remains the treatment of choice for the "benign" malarias though CQ resistant *vivax* malaria is found in parts of the Western Pacific and SE Asia[36]. Alternative treatments include atovaquone-proguanil, quinine and mefloquine. All these drugs are effective only against the blood stages of the parasite life-cycle. Thus, to prevent relapse in *P. ovale* and *P. vivax* infections – which have liver stages lacking in *falciparum* or *malariae* – liver 'hypnozoites' must also be eradicated. A 2 week course of primaquine at 250 mcg/kg will usually result in so-called 'radical cure' (although there are variations in the sensitivity of *P. vivax*

from different regions and a higher dose or longer duration of therapy may be required). However, the risks of primaquine treatment often outweigh the benefits: (a) *vivax* and *ovale* rarely cause serious illness, (b) reinfection is likely in endemic populations and (c) primaquine may cause haemolysis, especially in glucose-6-phosphate dehydrogenase 'deficient' individuals.

Conclusions

Malaria continues to causes a huge burden of morbidity and mortality. The treatment of severe disease relies mostly on quinine though in time the artemisinins, because of their rapid action, may become standard therapy. Artemisinin combinations therapies are being promoted for uncomplicated malaria and the existence of international funding bodies like the GFATM should allow poorer countries to access these drugs. Ensuring rapid access to effective drugs is probably the most important intervention that will improve overall mortality in severe disease rather than new therapeutic strategies.

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