Treatment and prevention of falciparum malaria in Africa

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Malaria remains as much a scourge as ever, primarily to the estimated 2 billion people (almost half the world's population) who live in endemic areas, but also to travellers. Of the four species of Plasmodia capable of infecting man it is *Plasmodium falciparum* with which we have most problems: this species not only causes life-threatening illness (probably because of its ability to sequester in the microvasculature) but has also developed resistance to most classes of antimalarial drugs. It is also true that, although falciparum malaria is a problem in much of the tropics, most associated deaths are seen in sub-Saharan Africa, predominantly in young children; this brief review consequently has an African perspective.

Treatment

It is not feasible to provide chemoprophylaxis for the bulk of exposed populations (see below), nor is it usually possible satisfactorily to control mosquito numbers. Consequently, the adequate provision of effective drugs for curative treatment, and not chemoprophylaxis, is the mainstay of most 'control' programmes.

Non-severe falciparum malaria

In the past decade much effort has been spent on the treatment of cerebral malaria (CM), as a result of which treatment regimens have been considerably improved. However, in Africa severe malaria represents only a small fraction of all *P. falciparum* infections (though, of course, it remains a leading cause of mortality). Uncomplicated falciparum malaria, on the other hand, is the commonest cause of outpatient attendance in much of Africa, and often affects the only wage-earner in a family on the borderline of absolute poverty. Furthermore, although most non-severe malaria cases are treated as outpatients, the disease is always potentially life-threatening, particularly in young children, and prompt effective treatment is essential. In the past, uncomplicated malaria was adequately managed with a very cheap drug—chloroquine (CQ). However, nowadays, though the clinical response to CQ is usually good, recrudescence with associated clinical diseases is increasingly common [1], and it seems likely that CQ will prove unreliable for uncomplicated malaria in the near future. This may well prove medically and economically disastrous unless alternatives are identified.

Fansidar (pyrimethamine + sulphadoxine; PSD) has a clear advantage in cost over the potential alternatives mefloquine and halofantrine, and is preferable to quinine (QN) for non-severe disease, because it is more practical. However, both components of PSD are eliminated very slowly [2], which is associated with two major disadvantages: the selection of resistant parasites, and toxicity to the host. In preliminary studies in Kenya, patients treated with PSD uniformly cleared parasites from the initial infection, but on reinfection during the long period of drug elimination, antifolate-resistant parasites predominated. These data are preliminary evidence for a powerful selective pressure exerted by these slowly eliminated drugs upon the emergence of resistant organisms. Furthermore, sulphonamides have a high incidence of idiosyncratic adverse reactions, particularly skin rashes, some of which are life-threatening. The sulphonamide component of PSD, sulphadoxine, seems to be responsible for frequent life-threatening skin reactions when used for malaria prevention [3], and there is evidence that such reactions to sulphonamides are more commonly associated with slowly eliminated drugs [4].

It seems possible, therefore, that the widespread adoption of PSD for non-severe malaria in Africa will lead to its early redundancy through parasite resistance and toxicity. However, many effective antifolate antimalarial drugs were developed during the era of CQ supremacy [5,6], only to be discarded because they offered no advantage over CQ. The situation has now changed and re-evaluation of the efficacy and toxicity of these rapidly eliminated drugs is underway.

Childhood cerebral malaria

Of the various life-threatening complications of falciparum malaria in children [7] CM and anaemia are the commonest. The management of malarial anaemia hinges on resuscitation from heart failure and timely blood transfusion: effective drugs (antimalarial and others) are essential, but can usually be given orally. It is in the treatment of CM that the optimal design of

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parenteral drug regimens becomes critical to the patient's survival.

In research centres CM has a mortality rate of 10–40%, and carries about a 10% risk of neurological sequelae [8,9]. However, awful though these figures are, they probably underestimate the 'real' situation, because in more typical African health-care facilities drugs and equipment and, most crucial of all, staff are often in much shorter supply. It is clear that major inroads into mortality from CM will require the commitment of considerable funds to raise basic standards of care. Accepting that this is unlikely (and, in fact, that the situation will probably get worse), what can be done?

It should be possible to define cheap and simple clinical interventions in CM by focusing research effort on the pathological processes which contribute to mortality and morbidity, and on those drugs available to ameliorate such processes. A brief synopsis of some of the areas receiving attention at the moment is set out below.

Optimising the use of conventional antimalarial drugs

(a) *Quinine (QN).* Parenteral QN remains the first-line drug for severe malaria, but although it has been extensively studied [10–13] most of the work was conducted in adults. More work is needed to optimise the use of QN in young children with CM. Our group in Kenya has recently studied QN therapy in such patients, and three main conclusions emerged: 1. young children with CM achieve higher QN concentrations (both in plasma and free in plasma water) than adults with CM given the same regimen; 2. with the standard QN regimen (see below), free QN concentrations in children may cross the threshold of toxicity; and 3. the plasma protein binding of QN diminishes as pH falls within the range 7.4 to 6.95.

The accepted QN regimen for CM in adults, which is also widely used for children, comprises the administration of 20 mg/kg as an infusion over 4 hours, followed by 8-hourly maintenance doses of 10 mg/kg, given over 2 hours. Based on our data, a loading dose of 15 mg/kg followed by maintenance doses of 10 mg/kg every 12 hours (all infusions given over 2 hours) would achieve more acceptable plasma profiles in children (and reduce dose number by one-third—a major advantage in poorly staffed hospitals [14]. This amended regimen is now undergoing evaluation. The clinical relevance of the effect of pH on QN protein binding is less clear: certainly accurate measurement of unbound QN fraction in stored plasma requires careful control of pH [15]. However, whether metabolic acidosis changes QN binding *in vivo* and whether this matters (considering that the drug is likely to be rendered less lipophilic as pH falls) remain to be established.

(b) *Pyrimethamine.* Pyrimethamine/sulphadoxine (PSD) has been available as a parenteral formulation for many years. It would be practical therapy for severe malaria in poorly staffed centres, since it is given as a single intramuscular dose at comparable cost to a course of parenteral QN. However, outside francophone West Africa, PSD has seen little use in severe malaria. This has been partly because of the risk of encountering resistant parasites, and partly because the onset of action of the drug was thought to be too slow to be reliable in severe disease. Certainly, sporadic resistance to PSD has been reported [16–19] but the drug remains highly effective in much of Africa [20,21]. As to the suggestion of a 'slow onset of action', clinical and parasitological results with PSD are comparable to those with QN and chloroquine [22,23]. Although pyrimethamine is absorbed more slowly after intramuscular PSD than after oral PSD in non-severe malaria [2], in severe disease the pyrimethamine component of intramuscular PSD is absorbed more rapidly. It seems likely that intramuscular PSD will be studied in the near future for the treatment of childhood CM in peripheral health centres.

Agents which may interfere with parasite sequestration

Although QN is the only consistently effective drug for CM in Africa it is not ideal. *Plasmodium falciparum* exhibits stage-specific changes in drug sensitivity [24] and QN seems to have little effect on those stages preceding sequestration. This may seem acceptable, since the sequestered forms are probably the most pathogenic. However, patients with established CM can still have up to 2×10^6 ring forms in their peripheral blood, which are relatively unaffected by QN and available to sequester, possibly exacerbating organ damage. Artemisinine, the active compound in the Chinese herbal medicine qinghaosu, and its semi-synthetic derivatives artemether (ARTm) and arteether, lower circulating parasite numbers faster than QN [25], possibly because of activity against ring forms of the parasite, and may as a result offer protection against parasite sequestration. The theoretical advantages of ARTm over QN in childhood CM are the subject of a multi-centre study, the results of which are awaited with interest. On a practical note, ARTm is given intramuscularly once daily, a significant advantage over QN, but its cost to African hospitals, when it finally becomes generally available, is not clear.

Prevention of seizures

While reductions in the mortality and morbidity of CM will certainly require the optimal use of antimalarial drugs, this approach alone would be inadequate. Over 50% of deaths from CM occur 12 hours or more after the start of treatment, by which time antimalarial drug levels should be within their 'therapeutic range'. The need for careful attention to supportive care in CM is already recognised by clinicians, but in the past it may not have been emphasised enough. Of the various

facets of supportive care, this review will touch on seizure prevention, the management of raised intracranial pressure, and lactic acidosis.

Seizures occur in about 60% of children with CM, and they adversely affect outcome [9]. A single intramuscular injection of phenobarbitone (PB), at low dosage (3.5 mg/kg), was found to reduce the incidence of seizures in Thai patients (mainly young adults) with CM [26]. Prophylactic PB would be very practicable in Africa, since it is cheap and widely available, but unfortunately children with CM given a single dose of 10 mg/kg failed to achieve effective blood concentrations, and did not seem to be protected against seizures [27]. This last study was not either placebo-controlled or blinded, and its results should therefore be interpreted with caution. However, until the results of a placebo-controlled trial of prophylactic PB in children with CM are published, its general recommendation would be premature.

Management of raised intracranial pressure

In the past it was thought that cerebral oedema caused coma in most patients with CM. Raised intracranial pressure (ICP) has been documented during lumbar puncture in adults [28] and children [29,30] with CM, but the demonstration that the blood-brain barrier is intact in CM [28], that cerebral oedema is usually agonal and that dexamethasone is deleterious in CM [31] largely dismissed this theory. The cause(s) and significance of the observed elevation in ICP were not investigated further.

Recently, opening pressure at lumbar puncture was measured [32] in 26 young children with CM and found to be elevated in all cases (mean value 16.7 mmHg). Physical signs of tentorial herniation were seen in 35% of survivors and in all the children who died. These data suggest that raised ICP plays an important pathophysiological role in determining outcome in young children with CM. Studies are now in progress to examine the underlying mechanisms, of which raised intracranial blood volume seems the most likely. Supportive therapy in childhood CM using mannitol or hyperventilation to lower ICP, and/or positively inotropic drugs to raise cerebral perfusion pressure, now have a rational basis. It will be necessary to determine the best ways to use these drugs in CM and whether their use reduces mortality.

Management of lactic acidosis

Lactic acidosis (LA) is common in patients with CM, and results from an interaction between disturbances of the host's microcirculatory flow and the parasite's anaerobic glycolysis. Profound LA is currently treated with intravenous sodium bicarbonate but this is associated with disadvantages, including the large sodium load and the risk of inducing alkalosis. Dichloroacetate (DCA) stimulates mammalian pyruvate dehydrogenase, increases the rate of oxidative utilisation of lactate, and has been used in man for treating LA in other diseases. Holloway *et al.* [33] studied LA in a rodent model of severe malaria and found that DCA attenuated concentrations of lactate compared with control values. Studies are now needed to examine the benefits and risks of DCA in severe human malaria.

Chemoprophylaxis

Endemically infected populations

Although the populations of areas with stable transmission usually develop partial immunity to local strains of *P. falciparum,* this is 'bought' at a horrendous cost in childhood mortality. Furthermore, though adults in such areas seldom develop life-threatening malaria, illness bad enough to prevent work is common, and is an enormous burden to poor families. However, it is very difficult to prevent one's children or oneself from contracting malaria when one lives in a shack on an income of £20 per month or less. On the same note, it is difficult for governments to support effective malaria control programmes while hampered by overseas debt, the AIDS pandemic, or war.

Consequently chemoprophylaxis is impractical for most people in much of sub-Saharan Africa. However, it is often possible to use chemoprophylaxis in 'target groups', including pregnant women, sickle-cell homozygotes, and beta thalassaemia homozygotes. There can be no general recommendation for the choice of drug(s) because of geographical variation in parasite sensitivity and drug availability/costs: on the Kenyan coast proguanil appears at the moment to be a safe, effective, and affordable drug. For the rest of the population alternative means of prevention continue to be the subject of much research effort: the use of insecticide-impregnated bednets is probably the most cost-effective intervention and reduces mortality [34].

Travellers

The current status of travellers' malaria has been thoroughly reviewed by Steffen and Behrens [35], and the present paper will be confined to summarising the most essential points.

Increasing numbers of travellers from Europe visit sub-Saharan African countries each year for holidays, on business, or to visit relatives. Other than in South Africa and parts of Namibia and Botswana, *P. falciparum* is transmitted throughout sub-Saharan Africa, with the greatest risk of transmission probably being on the west coast. The estimated mortality of imported malaria in Europe is 43 per 100,000 travellers per month in cases from West Africa and 27 per 100,000 per month from East Africa (this compares with 1.4 per 100,000 from India and 0.16 per 100,000 from South America). Risk of transmission increases with duration of stay (ranging from passengers in transit

through malarious areas to long-term residents). One particular group of travellers warranting special attention are recent immigrants to Europe visiting their country of origin: such people may well have lost their previously acquired partial immunity to the disease, and may be unaware of their risk.

The combined use of insect repellents, long clothing, and insecticide, essentially risk-free measures, is employed by only 4% of American and European travellers: medical advisors should stress their importance. Likewise the proper use of insecticide impregnated mosquito nets, and insect-screened tents (used during holiday safaris) needs to be emphasised. Nets should be tucked in under the mattress (mosquitoes may rest under the bed) or, if the net extends to the floor, insecticide should be sprayed under the bed; tents should be thoroughly sprayed with insecticide and then sealed before retiring.

No chemoprophylactic regimen gives 100% protection, and all carry the risk of adverse reactions. For travellers staying in a malarious area longer than a few nights, chemoprophylaxis should be started a week before departure (to allow daily drugs like proguanil to reach steady state), and should continue for four weeks after return (to allow the 'suppressant' effect of the drugs time to deal with sub-clinical infection). The combination of chloroquine (300 mg of the free base once weekly) plus proguanil (200 mg daily) is effective in much of Africa and is safe, even during pregnancy [36]. The relatively new drug mefloquine probably gives better protection than chloroquine plus proguanil in Africa. However, the risks of adverse effects and teratogenicity from mefloquine are not yet fully known, and its use abroad is not recommended by UK authorities for longer than three weeks because of the risk of drug accumulation.

The final safeguard for the traveller against death from malaria is for him and his doctor to maintain a high index of suspicion in case of illness. It cannot be stressed enough that doctors should always ask patients whether they have recently travelled to malarious areas, and that blood slides should be examined by an expert if they have. Furthermore, doctors should be aware that an apparently negative blood slide does not exclude malaria and that, if malaria is suspected, further slides should be examined (preferably every six hours) while the clinical possibility persists.

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