Malaria: treatment
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Editor – In his recent article on the treatment of malaria, Peter Winstanley suggests that the first-line treatment of uncomplicated falciparum malaria in the UK is not oral quinine (May/June 1998, pp203–7). Instead, he advocates mefloquine, halofantrine, pyrimethamine-sulfadoxine or atovaquone-proguanil. Most falciparum malaria is imported to the UK from sub-Saharan Africa. Atovaquone-proguanil has proved to be an effective antimalarial in Africa, but experience in the UK is limited. In Nigeria, almost 30% of Plasmodium falciparum infections are resistant to pyrimethamine-sulfadoxine, and those who respond initially have an 8% recrudescence rate: this makes the use of pyrimethamine-sulfadoxine alone unacceptable in the UK. Halofantrine is an effective treatment for falciparum malaria, but prolongs the QT interval, and has been associated with ventricular tachyarrhythmias and sudden death in a young woman; the British National Formulary (BNF) warns about its use. Mefloquine is also effective but the treatment dose is much higher than the weekly prophylactic dose, with its frequent and disturbing side effects.

The BNF still recommends quinine as the drug of first choice and we concur with this. To limit its side effects of tinnitus and nausea, the duration of quinine treatment may be reduced from seven to three days. These side effects are reversible and most patients can tolerate them. However, in order to prevent recrudescence of resistant strains, we never use quinine alone, and supplement it with both pyrimethamine-sulfadoxine (three tablets at the outset of treatment), followed by doxycycline (200mg daily for one week). Prompt diagnosis and prompt treatment with a combination of drugs are important to prevent fatalities from falciparum malaria in non-immune Caucasians. We would commend UK physicians to follow initial treatment as advised in the BNF.

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In response

Drs. Venkatesan, Dedicoat and Ellis take issue with one aspect of my recent review article on the treatment of malaria: specifically the choice of oral medication in the management of uncomplicated falciparum malaria in a non-immune patient. Quinine is, as they point out, one of the drugs recommended by the British National Formulary (BNF). I have not questioned the role of parenteral quinine in severe malaria, but in uncomplicated disease oral quinine has disadvantages which, in my opinion, can make its use difficult, particularly in the outpatient setting. First, quinine is rapidly-eliminated and needs to be given for several days (usually 8-hourly) to avoid recrudescence, making the possibility of poor compliance with monotherapy a major concern. Second, although it is true that quinine toxicity is rarely life-threatening and usually reversible, symptomatic adverse effects from standard doses (including malaise, vomiting, deafness and vertigo) are common and persist throughout the course. Third, quinine has a relatively narrow therapeutic range, and accidental or deliberate overdose is dangerous.

My recent article, while describing the standard dose regimen of quinine for uncomplicated falciparum malaria, suggested mefloquine, halofantrine, atovaquone-proguanil and pyrimethamine-sulfadoxine as possible alternatives in certain patients. Venkatesan et al accept that mefloquine is usually effective (indeed it is listed by the BNF as a drug of choice in this setting) but point out that 'the treatment dose is much higher than the weekly prophylactic dose, with its frequent and disturbing side effects.' This seems a rather weak argument for avoiding mefloquine: a) mefloquine can be administered in two doses six hours apart, making supervision of compliance straightforward; b) while it is true that the adverse effects of mefloquine can be disturbing they are rarely life-threatening and are usually self-limiting; and c) oral quinine also causes disturbing toxicity which often persists for longer than seven days if BNF guidelines are followed. Mefloquine remains a convenient drug so long as attention is paid to the possibility of resistance, and BNF guidelines on dosage and contraindications are followed. Venkatesan et al are also concerned about the toxicity of halofantrine; this I had pointed out as a concern, and I accept that cardiotoxicity limits this drug's usefulness. However, in patients without contraindications, halofantrine remains a practicable option. BNF dosing guidelines should be followed, and the possibility of halofantrine-resistance should be kept in mind (especially when the infection originated in Southeast Asia). Venkatesan et al accept that atovaquone-proguanil...
that atovaquone-proguanil tolerated malaria (another drug listed by the current BNF as possible treatment for uncomplicated malaria) has proved to be an effective antimalarial in Africa but are concerned that experience in the UK is limited: this is certainly true, since the combination has only just been released. However, current data suggest that it is a well-tolerated drug. The main utility of atovaquone-proguanil is likely to be in cases where resistance to other antimalarials is suspected or proven.

With regard to pyrimethamine-sulfadoxine, Venkatesan et al are particularly concerned about the dangers of drug resistance, which were referred to in my article. Venkatesan et al cite an 8.3% recrudescence figure from Nigeria: however, not all new parasitaemic episodes are due to recrudescence in a transmission area, since reinfection is a continuing hazard. In our own data from Kenya, although 19.7% (95% CI 13.5, 27.2%) of patients treated with pyrimethamine sulfadoxine had developed a new parasitaemia by day 28, the relative risk of new parasitaemia (in comparison with an initially aparasitaemic control group) was 0.63 (0.43, 0.93) suggesting reinfection rather than recrudescence. However, our more recent (unpublished) data from the same study area suggest that clinical cases of pyrimethamine-sulfadoxine failure are becoming more common, and Venkatesan et al are right to urge caution: I tried to convey the same sentiment. I agree with them that resistance in sub-Saharan Africa may soon render pyrimethamine-sulfadoxine redundant for use in the UK, but I am not sure that this is yet the case (especially in semi-immune patients).

I note that the Birmingham group currently uses quinine in a 3-day course, accompanied by pyrimethamine (three tablets at the outset of treatment), followed by doxycycline (200mg daily for one week); they imply that this regimen is recommended in the BNF. This is probably a sound regimen and would certainly reduce the duration of quinine toxicity and minimise the risk of treatment failure. However, their regimen is itself a departure from BNF recommendations (where the quinine course is for seven days [not three] followed by either pyrimethamine-sulfadoxine or doxycycline [not both]); furthermore, in view of the probability that pyrimethamine-sulfadoxine resistance will become more common in Africa, this drug may soon contribute little to the regimen and will need to be kept under review.

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Drug resistant tuberculosis in adults and its treatment
CME Infectious diseases II

Editor – Dr Drobniewski provided a resume of the epidemiology, the principles of management, details of the second-line or reserve drugs sometimes required particularly in multi-drug resistant tuberculosis (MDRTB), and of possible immunotherapy (July/August 1998, pp314–8). Detailed evidence-based guidelines on the chemotherapy and management of tuberculosis, including single, multiple and MDRTB, have recently been published by the Joint Tuberculosis Committee of the British Thoracic Society.

In addition, an Expert Working Group on TB in HIV infection and on MDRTB at the Department of Health has drawn up evidence-based advice on the principles of treatment and the different infection control measures required for such groups of patients, which will be released in the very near future by the Department of Health. Your readers should be made aware of these evidence-based documents, one published and one ‘in press’, which set the recommended standards for the treatment and infection control of tuberculosis in the UK.

Community acquired pneumonia
CME Infectious diseases II

Editor – Since the incidence of pneumonia is four to five times more common in the elderly and the very young than in other ages, it is surprising that this recent review of the management of pneumonia (July/August 1998, pp328–32) did not specifically mention the problems unique to elderly patients, including the need to confirm bacteraemia, choice of antimicrobial therapy, and age-related susceptibility to Clostridium difficile colitis following the use of broad spectrum antibiotics.

In the elderly, it is particularly important to make every effort to establish a bacteriological diagnosis, so that antibiotics least likely to predispose to Clostridium difficile colitis infection can be chosen. In the absence of bacteriological validation, penicillin, clarithromycin and ciprofloxacin should be prescribed. An alternative is the combination of benzylpenicillin and trimethoprim. Collection of blood