Cotrimoxazole for childhood febrile illness in Malaria-endemic regions

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The efficacy of co-trimoxozole for the treatment of *Plasmodium falciparum* parasitaemia in children younger than 5 years of age was evaluated in Malawi. 46 children with *P falciparum* parasitaemia, 37% of whom also met clinical criteria for a diagnosis of acute lower respiratory tract infection, were treated with 20 mg/kg co-trimoxazole twice daily for five days. Parasitaemia (mean clearance time 2.7 days) and symptoms were rapidly abolished and improvement was maintained during follow-up for 14 days. Co-trimoxazole may be an effective single treatment for febrile illness in young children in areas where malaria is endemic, resources are few, and diagnosis must rely on clinical findings alone.

Two of the commonest causes of childhood mortality in sub-Saharan Africa are malaria and acute lower respiratory tract infection (ALRI). Because of limitations in diagnostic technology and personnel, disease-specific clinical case definitions have been devised to standardise treatment for these and other major causes of childhood illness. The case definition for malaria, when microscopy is unavailable, is based on the presence or history of fever without other obvious cause. In practice, the World Health Organisation (WHO) recommends that in highly endemic areas all young children with fever should be treated for malaria, because of the likelihood of malaria infection as a complicating factor. The case definition for ALRI is cough or a history of cough and an increase in respiratory rate (rate of or above 60 breaths/min for children under 2 months of age, 50 breaths/min for children 2-12 months old, and 40 breaths/min for children over 12 months of age). But the poor specificity of these definitions may lead to multiple diagnoses and multiple therapies.

The World Health Organisation at present recommends that children who meet case definitions for both malaria and ALRI should receive both antibacterial and antimalarial drugs. Co-trimoxazole, the combination of trimethoprim and sulphamethoxazole, is recommended for the treatment of childhood ALRI, it affects the same enzymes as the combination of pyrimethamine and sulfadoxine, used for treatment of chloroquine-resistant *Plasmodium falciparum* infections. Co-trimoxazole is known to be an effective treatment of *P falciparum* in children older than 5 years and in adults, with cure rates above 98%. We set out to assess the efficacy of co-trimoxazole for the treatment of *P falciparum* in children under 5 years of age, who might have less immunity to *P falciparum*, in an area of intense chloroquine resistance.

Children under 5 years of age with complaints of fever, cough or dyspnoea were selected from patients brought to the outpatient clinic of the largest hospital in Lilongwe, Malawi, during the two months of highest malaria transmission. After a standard clinical examination thick blood-smears were examined for *P falciparum* infection; parasite density was estimated by standard methods. Children were screened for previous antimalaria drug use with the Saker-Solomon urine test for 4-aminoquinolines. Chest radiographs were assessed by a paediatric radiologist unaware of the clinical details.

Children entered into the study were non-randomly selected from the screened children if they met the following criteria age between 3 months and 5 years, confirmed pure *P falciparum* infection of at least 2000 asexual parasites/ml, and informed parental consent. Children who required hospital admission were excluded. Initially, only children with negative urine tests for previous chloroquine use were enrolled, later, positive children were also included.

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Children were treated with co-trimoxazole at a dosage of 20 mg/kg (based on sulphamethoxazole) twice daily for 5 days, the recommended treatment regimen for childhood ALRI; each dose was administered by a member of the study team. Follow-up consisted of a clinical examination on each day of treatment and on days 7 and 14, with blood smears, respiratory rates, and haemoglobin concentrations obtained on each assessment day. Axillary temperatures and history of fever, vomiting, diarrhoea, cough, rash, or other adverse reactions to treatment were obtained twice daily during treatment and on days 7 and 14.

Response to therapy was assessed by three criteria: parasite clearance, fever clearance, and resolution of clinical symptoms. Parasite clearance was defined as the time between the start of treatment and the first of two consecutive negative blood smears. Fever clearance was defined as the time between the start of treatment and the first of two consecutive normal axillary temperatures (below 37.5°C) in children who were initially febrile. Children were considered to have clinically responded if they no longer met the case definitions for either malaria or ALRI and were judged to be active and well by the mother or guardian.

Of 1605 children examined during the initial screening process, 979 (61%) met the malaria case definition alone, 449 (28%) met both malaria and ALRI definitions, and 32 (2%) met the ALRI definition alone, 46 children were entered into the co-trimoxazole study. 2 moved out of the study area after day 7, so 44 (95%) children were followed to day 14. The median age was 18 months (range 3.5-52.6) and 26 (56.5%) were girls. The geometric mean parasite density on enrolment was 21807 asexual parasites/ml (range 2747-113212). 40 (86.9%) had negative Saker-Solomon urine tests; the response to co-trimoxazole of those with positive urine tests did not differ from those with negative tests, so the results have been merged.

20 children initially complained of fever without cough, 7 of cough without fever, and 19 of both fever and cough. 33 (71.7%) were febrile when brought to the clinic, with a mean temperature of 38.3°C (range 36.0-40.7); mean fever clearance time was 1.5 days. 17 (37.0%) children met the ALRI case definition (15 of whom were also febrile), and 5 (10.9%) had radiographic evidence of pneumonia. Of the 17 children who met the ALRI case definition, 14 (82.4%) no longer met the definition by day 14. Children who did and who did not meet the ALRI case definition had similar mean parasite clearance times (2.6 and 2.8 days, respectively; p=0.5), but children who met the ALRI case definition had a longer mean fever clearance time than those who did not (1.9 days and 1.1. days, respectively; p=0.01). Children with radiographic evidence of pneumonia had a mean parasite clearance of 2.2 days and a mean fever clearance of 1.0 day. Parasitaemia was abolished in all 44 children followed up for 14 days, with a mean parasite clearance time of 2.7 days (range 1-5). All but one child remained parasite-free to day 14; the exception had a blood smear with 300 asexual parasites/ml on day 14, but blood smears were negative on days 15, 16, 19 and 21 without additional treatment.

The study population illustrates the difficulties that may arise from strict application of case definitions for malaria and ALRI. 28% of patients entered into the initial screening process met the definition for both malaria and ALRI and would thus have been considered for multiple therapy. Similarly, of the 46 children with parasitaemia entered into the co-trimoxazole study, 17 (37%)also met the ALRI case definition, 5(10.9%) of whom had radiographic evidence of pneumonia. Co-trimoxazole effectively and rapidly cleared *P falciparum* parasitaemia and clinical symptoms in these young Malawian children. Because of its lengthy dosage regimen, co-trimoxazole is a poor drug for the treatment of malaria alone and its use is limited to areas where *P falciparum* remains sensitive to folate antagonists. Nevertheless, use of co-trimoxazole alone represents an effective treatment for young children in areas where the children with ALRI alone cannot reliably be distinguished from those with both ALRI and malaria.

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