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Factors contributing to delay in parasite clearance in uncomplicated falciparum malaria in children

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Abstract

Background: Drug resistance in *Plasmodium falciparum* is common in many endemic and other settings but there is no clear recommendation on when to change therapy when there is delay in parasite clearance after initiation of therapy in African children.

Methods: The factors contributing to delay in parasite clearance, defined as a clearance time > 2 d, in falciparum malaria were characterized in 2,752 prospectively studied children treated with anti-malarial drugs between 1996 and 2008.

Results: 1,237 of 2,752 children (45%) had delay in parasite clearance. Overall 211 children (17%) with delay in clearance subsequently failed therapy and they constituted 72% of those who had drug failure, i.e., 211 of 291 children. The following were independent risk factors for delay in parasite clearance at enrolment: age less than or equal to 2 years (Adjusted odds ratio [AOR] = 2.13, 95% confidence interval [CI]1.44-3.15, P < 0.0001), presence of fever (AOR = 1.33, 95% CI = 1.04-1.69, P = 0.019), parasitaemia >50,000/ul (AOR = 2.21, 95% CI = 1.77-2.75, P < 0.0001), and enrolment before year 2000 (AOR= 1.55, 95% CI = 1.22-1.96, P < 0.0001). Following treatment, a body temperature ≥ 38°C and parasitaemia > 20000/μl a day after treatment began, were independent risk factors for delay in clearance. Non-artemisinin monotherapies were associated with delay in clearance and treatment failures, and in those treated with chloroquine or amodiaquine, with *pfmdr 1/pfcrt* mutants. Delay in clearance significantly increased gametocyte carriage (P < 0.0001).

Conclusion: Delay in parasite clearance is multifactorial, is related to drug resistance and treatment failure in uncomplicated malaria and has implications for malaria control efforts in sub-Saharan Africa.

Background

The emergence and spread of multidrug resistance in *Plasmodium falciparum* is a major obstacle to successful chemotherapeutic control of the disease. Resistance to chloroquine (CQ) and sulphadoxine-pyrimethamine (SP) is now widespread in sub-Saharan Africa, South Asia and South America [1,2] and there is an increased chance that resistance to mefloquine (MQ), already widespread in Southeast Asia [3-6], may spread to Africa. With increasing failure of amodiaquine (AQ) in areas of intense transmission [7-9] and increasing selection of *P. falciparum* multidrug resistance gene 1 (*Pfmdr 1*) in asexual and sexual parasites following treatment of infections with artemether-lumefantrine (AL) [10], there is a rising spectre of reduced responses to artemisinin-based combination therapy (ACT) in Africa.

Despite increasing drug treatment failure, there is no clear guidelines, at least in Nigeria, about the time to change anti-malarial drug treatment if parasites do not clear quickly from peripheral blood following treatment of uncomplicated acute infections in African children. It is postulated in the present study that, parasite clearance exceeding two days is associated with risk of treatment failure and resistance and could be used as a criterion to change therapy in very young children. The present

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