

## Chloroquine-Resistant Malaria in Malawi

**TO THE EDITOR:** In their article on the efficacy of chloroquine against *Plasmodium falciparum* in Blantyre, Malawi, Laufer and colleagues (Nov. 9 issue)<sup>1</sup> report adequate clinical and parasitologic responses to chloroquine and the microevolutionary replacement of the T76 marker for the *P. falciparum* chloroquine-resistance transporter gene (*PfCRT*)<sup>2</sup> by the sensitive wild-type marker for chloroquine susceptibility (K76) — the prevalence of which increased in local parasite populations after use of the drug had been suspended for several years<sup>3</sup> — as a result of restored fitness of the wild-type strains. If the authors' recommendation to largely withdraw chloroquine from use as a treatment for malaria and reserve it for future chemotherapy and prophylaxis (including its use in intermittent preventive treatment strategies) were to become a public health initiative, potential cross-resistance would have to be considered. Amodiaquine is a partner drug for artemisinin-based combination therapies in many African countries. There is strong evidence that the mechanisms of resistance to chloroquine and amodiaquine are similar, since *in vivo* amodiaquine resistance is also associated with the critical T76 *PfCRT* mutation.<sup>4,5</sup> Persistent drug pressure exerted by amodiaquine might be a biologic barrier against the successful return of chloroquine-sensitive phenotypes.

Robin Kobbe, M.D.

Christian G. Meyer, M.D.

Jürgen May, M.D.

Bernhard Nocht Institute for Tropical Medicine  
D-20359 Hamburg, Germany

1. Laufer MK, Thesing PC, Eddington ND, et al. Return of chloroquine antimalarial efficacy in Malawi. *N Engl J Med* 2006;355:1959-66.
2. Sidhu AB, Verdier-Pinard D, Fidock DA. Chloroquine resistance in *Plasmodium falciparum* malaria parasites conferred by *pfcr* mutations. *Science* 2002;298:210-3.
3. Kublin JG, Cortese JF, Njunju EM, et al. Reemergence of chloroquine-sensitive *Plasmodium falciparum* malaria after cessation of chloroquine use in Malawi. *J Infect Dis* 2003;187:1870-5.
4. Happi CT, Gbotosho GO, Folarin OA, et al. Association between mutations in *Plasmodium falciparum* chloroquine resistance transporter and *P. falciparum* multidrug resistance 1 genes and *in vivo* amodiaquine resistance in *P. falciparum* malaria-infected children in Nigeria. *Am J Trop Med Hyg* 2006;75:155-61.
5. Holmgren G, Gil JP, Ferreira PM, Veiga MI, Obonyo CO, Bjorkman A. Amodiaquine resistant *Plasmodium falciparum* malaria *in vivo* is associated with selection of *pfcr* 76T and *pfmdr1* 86Y. *Infect Genet Evol* 2006;6:309-14.

**TO THE EDITOR:** Laufer et al. report that chloroquine is once again effective in Malawi and suggest that a chloroquine-containing drug combination might be a treatment option. However, a combination including the standard dose of 25 mg of chloroquine per kilogram of body weight might rapidly select for the chloroquine-resistant genotype *PfCRT* T76, leaving a partner drug unprotected. In Guinea-Bissau, the officially recommended dose of 25 mg of chloroquine per kilogram has 80% efficacy at day 28. Doubling the dose to 50 mg per kilogram increases the efficacy to 92%.<sup>1</sup> Chloroquine is routinely prescribed at an average dose of 76 mg per kilogram in health centers in Bissau.<sup>2</sup> We found *PfCRT* T76 in only 23 of 109 blood samples obtained from children who were recruited during the first year of a recently completed study. The low prevalence of *PfCRT* T76, the improved efficacy of chloroquine at a dose of 50 mg per kilogram, and the decreased fitness of resistant parasites suggest that treatment with higher doses of chloroquine may limit the spread of chloroquine-resistant parasites.

Johan Ursing, M.D.

Karolinska Hospital  
171 76 Stockholm, Sweden  
johan.ursing@ki.se

Amabelia Rodrigues, M.D., Ph.D.

Projecto de Saúde de Bandim  
Bissau 1004, Guinea-Bissau

Poul-Erik Kofoed, M.D., Ph.D.

Kolding Hospital  
6000 Kolding, Denmark

1. Kofoed PE, Ursing J, Poulsen A, et al. Different doses of amodiaquine and chloroquine for treatment of uncomplicated malaria in children in Guinea-Bissau: implications for future treatment recommendations. *Trans R Soc Trop Med Hyg* 2007;101:231-8.
2. Kofoed PE, Lopez F, Johansson P, et al. Treatment of children with *Plasmodium falciparum* malaria with chloroquine in Guinea-Bissau. *Am J Trop Med Hyg* 2002;67:28-31.

**TO THE EDITOR:** Laufer et al. build on previous observational studies of malaria treatment in Malawi. One question that is still outstanding is the implication that this study was conducted at Ndirande Health Center, on the outskirts of Blantyre. The question is whether the findings of Laufer et al. are representative of the general malaria-related drug-parasite interaction in Malawi. In addition, the possible importation of chloro-

quine resistance from neighboring countries where significant chloroquine resistance can still be found, such as Mozambique, Zambia, and Tanzania, remains a concern.

Adamson S. Muula, M.D.

University of North Carolina at Chapel Hill  
Chapel Hill, NC 27514  
muula@email.unc.edu

**THE AUTHORS REPLY:** Kobbe and colleagues raise the possibility of continued selection of chloroquine-resistant malaria by amodiaquine, which is being used in combination with artesunate in some African countries. Indeed, it will be of interest to track and compare the prevalence of the molecular marker for chloroquine resistance in areas where chloroquine is being withdrawn and replaced by combinations that include amodiaquine and in areas where it is being replaced by drugs that are unrelated to chloroquine. Such molecular ecologic studies may inform strategies for rotating drugs in specific sequences to prevent the emergence and reemergence of resistant phenotypes.

Ursing and colleagues suggest that doubling the dose of chloroquine may deter the emergence of resistant phenotypes if chloroquine is used in combination therapies. Their hypothesis that increasing the dose of medication may improve activity against drug-resistant parasites is sound. However, the effect of the higher dose on the emergence and spread of resistance requires extensive investigation. In the small studies they cite, the higher dose of chloroquine appeared to be safe, but doubling or tripling the standard dose of a medication requires a much more thorough safety assessment. Chloroquine has a narrow therapeutic index, and reported ingestions

of two to five times the therapeutic dose of chloroquine have been associated with fatal poisonings.<sup>1</sup> In areas where malaria is endemic, children may receive repeated doses of antimalarial medication, increasing the risk of toxicity.

Muula wonders whether our findings from the single-center study in Blantyre can be generalized to other parts of Malawi. Similar reductions in chloroquine resistance have been found in Salima, a town located on Lake Malawi, approximately 200 miles from Blantyre.<sup>2</sup> We are currently analyzing specimens obtained from other regions of Malawi to determine the geographic extent of this phenomenon. As we noted in our discussion, chloroquine resistance remains prevalent in the region, and the reintroduction of chloroquine for intermittent preventive therapy or as a component of combination therapy should be considered only after chloroquine-resistant malaria has been eliminated from widespread areas — possibly from the entire African continent. Population genetics studies on a regional level are needed to gain a better understanding of the ebb and flow of drug-resistant malaria in Africa.

Miriam K. Laufer, M.D.

Christopher V. Plowe, M.D., M.P.H.

University of Maryland School of Medicine  
Baltimore, MD 21201  
cplowe@medicine.umaryland.edu

Terrie E. Taylor, D.O.

Michigan State University College of Osteopathic Medicine  
East Lansing, MI 48828

1. Cann HM, Verhulst HL. Fatal acute chloroquine poisoning in children. *Pediatrics* 1961;27:95-102.

2. Mita T, Kaneko A, Lum JK, et al. Recovery of chloroquine sensitivity and low prevalence of the *Plasmodium falciparum* chloroquine resistance transporter gene mutation K76T following the discontinuance of chloroquine use in Malawi. *Am J Trop Med Hyg* 2003;68:413-5.

## Left Ventricular Assist Devices and Drug Therapy in Heart Failure

**TO THE EDITOR:** The article by Birks et al. (Nov. 2 issue)<sup>1</sup> is an important contribution to further development of a therapeutic approach to idiopathic dilated cardiomyopathy that remains controversial despite being repeatedly proved.<sup>2-4</sup> The high recovery rate reported by the authors is encouraging, although it might have been facilitated by patient selection. Thus, Patient 11, with a small left ventricle and normal cardiac index value, un-

derwent implantation of a left ventricular assist device with the diagnosis of idiopathic dilated cardiomyopathy. The survival rate after explantation in the study cohort (81.8% at 4 years) is similar to that among our 35 patients with idiopathic dilated cardiomyopathy who were weaned from left ventricular assist devices since 1995 (78.1% at 6 years). Freedom from recurrence of heart failure was higher among the patients in the study