Artesunate Versus Quinine: Keeping Our Options Open

Anne E. P. Frosch^{1,2}

¹Hennepin Healthcare Research Institute, and ²University of Minnesota, Minneapolis

(See the Major Article by El Ket et al on pages 280–7.)

Keywords. severe malaria; artesunate; quinine; *Plasmodium falciparum*.

The work presented by Dr El Ket and her colleagues [1] comparing artesunate and quinine for the treatment of severe malaria in this edition of *Clinical Infectious Diseases* is a bit stinging for us US-based infectious disease providers. It paints a picture of robust drug availability in France, where practitioners have the ability to choose between multiple therapies for tropical diseases. In contrast, in the United States, the hallmark of treating these infections—severe malaria in particular—is searching for an appropriate drug and biding time with inferior therapy [2]. Recently, the Centers for Disease Control and Prevention announced that on 1 April 2019, quinidine, the only intravenous quinoline approved for use in the United States, will no longer be available for purchase, which leaves us with limited stocks of artesunate that are located at a small number of quarantine centers throughout the country [3]. I teach students that severe malaria should be approached with an urgency similar to bacterial meningitis, but in reality, in the United States, receiving an appropriate therapy within hours is respectable considering the logistics. Although not part of the study design or conclusions, one of the

most salient take-home messages for me, in light of these recent events, is the stark contrast between American and European drug availability. This paper provides American physicians with some hope that pharmaceutical markets can not only work to serve some of our most vulnerable patients, but even optimize their care.

Many consider artesunate versus quinine for severe malaria a settled matter after numerous studies, including 2 large, multicenter, randomized, controlled trials, have demonstrated the superiority of artemisinins [4–11]. However, the premise of the study presented here is sound. International recommendations endorsing artesunate are largely dictated by research done in countries endemic for malaria, which is appropriate. Accordingly, many study sites in these trials did not have robust intensive care services, including hemodynamic monitoring and low nurse-patient ratios that can be critical to outcomes for severe malaria patients. The large differences in severe malaria mortality between the Artesunate Versus Quinine in the Treatment of Severe Falciparum Malaria in African Children (AQUAMAT) trial [11] and South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) [10] (8.5–22% mortality) and the data presented by Dr El Ket and her colleagues (3% mortality) [1] highlight that the health system has much more of an impact on survival than drug choice. In this context, it is plausible that the benefits of artesunate will not be the same in high-resource settings and low-resource

settings: indeed, this is what these authors found. In their analysis, there were similar outcomes between the 2 therapies when compared in over 1544 patients and across of span of 7 years of clinical practice in France, including both for 30-day mortality rates and hospital lengths of stay.

The authors propose that the most likely scenario is that artesunate outperforms quinine but, that with low baseline mortality, this effect is not detectable. This certainly could be, particularly with the strong evidence of artesunate's biologic superiority, measured in faster parasite clearance times. Nonetheless, the author's findings warrant closer examination. Are there other reasons that artesunate might not have done as well as expected? While they did an exceptional job trying to account for sources of bias, there are considerable limitations in this study inherent to the design. The most significant of these, of course, is selection bias in the choice of therapy. The study team used propensity scoring to correct for this, but the complexity and variability that guides treatment decisions and implementation makes it make it difficult to trust that this scoring can fully control all sources of bias. Further, there is considerable missing data on important factors that could affect mortality rates and lengths of stay: most notably, data on medical comorbidities that could have shown whether more complicated patients were overrepresented in 1 treatment group. Overall though, in spite of the study design limitations, this paper presents us with a compelling result from a rigorous and thoughtful examination of real clinical practice.

Received 15 April 2019; editorial decision 16 April 2019; accepted 27 April 2019; published online May 2, 2019.

Correspondence: A. E. P. Frosch, Division of Infectious Diseases, Department of Medicine, Hennepin Healthcare, HCMC Building 01.340, 701 Park Avenue, Minneapolis, MN 55415 (park0587@umn.edu).

Clinical Infectious Diseases® 2020;70(2):288–9

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So where do we go from here? With the sample size that would be needed and the ethical barriers, I agree with Dr El Ket et al [1] that further randomized, controlled trials do not seem feasible. At this point, clinicians in countries with a high level of supportive care and multiple treatment options will need to judge what approach is best for the patient in front of them. While the authors conclude that the results of their study demonstrate that there is a role for artesunate in high-resource settings, the lack of meaningful superiority of artesunate also begs the more controversial conclusion: perhaps there may still be a role for quinine. This seems particularly relevant as artemisinin resistance spreads, drug shortages are becoming increasingly common, and previously lost antimicrobials gain renewed efficacy [12–15]. Further, in 10–20 years, health care in malaria-endemic countries may be closer to the current French practice than to what was present in the AQUAMAT and SEAQUAMAT trials. Infectious disease practice is dynamic because of evolution in the organisms we treat, the changing vulnerability of the populations we serve, and the transformed global economy in which we

now work. Quinine and artesunate may be a story of the value in keeping our therapeutic options open in hopes of keeping us resilient as we face these changes.

Note

Potential conflicts of interest. The author: No reported conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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