Etiology of Metabolic Changes in Severe Plasmodium falciparum Malaria

To the Editor—A recent investigation assessed endothelial nitric oxide bioavailability, skeletal muscle microvascular function, and oxygen consumption in Indonesian children with severe and moderately severe malaria and compared these data to those from healthy controls [1]. The investigators found decreased endothelial and microvascular function and increased oxygen consumption but also increased lactate levels in children with severe malaria. The authors stated that the mechanism of increased oxygen consumption in falciparum malaria was unclear and thought that the increased oxygen consumption was at odds with the increased lactate level found.

The key to understanding how these findings are causally interconnected is the basic pathophysiology of a severe acute systemic inflammatory response in general and of severe Plasmodium falciparum malaria specifically. The authors found that there was significantly increased body temperature in individuals with severe P. falciparum malaria. This increased body temperature is generated by increased muscle contractions stimulated by cytokine influence on the temperature-regulating centers of the brain. The increased skeletal muscle contractions lead to increased oxygen consumption, and because energy demand outstrips supply by oxidative phosphorylation in skeletal muscle mitochondria, they also lead to increased lactate levels generated by anaerobic glycolysis. The associated increased mitochondrial activity may also explain the reduced bioavailability of nitric oxide. The cause of a reduction of nitric oxide levels may be accelerated nitric oxide consumption through increased metabolism to peroxynitrite by increased superoxide anion production as a result of mitochondrial activity. This increased consumption of nitric oxide then may secondarily induce vasospasm [2], reflected in the correlates of endothelial and microvascular dysfunction found by the investigators in children with severe malaria and also contributing to increased lactate levels because of ischemia-induced hypoxia. Increasing nitric oxide bioavailability by removing iron, which inhibits inducible nitric oxide synthase [3], through iron chelator therapy reduced coma duration during cerebral malaria [4]. This effect may have been
attributable to resolution of cerebral vaso-
spasm [5] and could resolve the microvas-
cular dysfunction the authors reported.

Note

Potential conflict of interest. Author certifies
no potential conflicts of interest.

The author has submitted the ICMJE Form for
Disclosure of Potential Conflicts of Interest. Con-
flicts that the editors consider relevant to the con-
tent of the manuscript have been disclosed.

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509707.

Received 21 December 2014; accepted 10 February 2015;
electronically published 23 February 2015.
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The Journal of Infectious Diseases® 2015;212:167-8
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DOI: 10.1093/infdis/jiv084