Reply to Eisenhut

To the Editor—We appreciate the comments of Eisenhut [1] regarding the possibility that the correlation of elevated erythropoietin (EPO) levels with mortality in our recent study may in fact reflect a role for increased hemolysis in cerebral malaria [2]. Dr Eisenhut’s comments led us to conduct additional analysis of markers of hemolysis in our study participants.
First, we assessed the correlation of EPO levels to levels of multiple markers of hemolysis, including hemoglobin levels and plasma lactate dehydrogenase (LDH), haptoglobin, and bilirubin levels. EPO levels were indeed strongly correlated with each of these markers (P < .001 for all). Next, we compared levels of each of these markers of hemolysis in children with cerebral malaria who survived vs those who died (Table 1). Plasma LDH, haptoglobin, and bilirubin levels did not differ in children who survived vs died, whereas hemoglobin levels were lower in the children who survived, not those who died. A lower hemoglobin level would be expected in children who had a greater degree of hemolysis, although multiple other factors could also affect hemoglobin level. Together, the findings did not demonstrate any association of increased hemolysis with increased mortality. To address the issue of nitric oxide scavenging, we compared nitric oxide levels in children who survived vs those who died. Nitric oxide levels also did not differ between the 2 groups (Table 1).

Finally, we assessed the correlation of plasma EPO levels with mortality and coma duration after adjustment for hemoglobin level, and levels of LDH, haptoglobin, and bilirubin. The increased risk of mortality was unchanged after adjustment for these factors (odds ratio [OR], 1.93; 95% confidence interval [CI], 1.10–3.39), as was the association with coma duration (OR, 0.23; 95% CI, 0.07–0.39).

Together, these analyses suggest that hemolysis alone does not appear to be related to mortality in these children with cerebral malaria, and that EPO levels in these children are related to mortality and coma duration independent of the degree of hemolysis. However, our measurements at a single point in time may be an incomplete reflection of the hemolytic process occurring in the study children. Furthermore, hemoglobin, LDH, and haptoglobin may be tertiary or quaternary markers of hemolysis, as pointed out by Hebbel [3]. Red cell half-life and reticulocyte count, the primary and secondary biomarkers of hemolysis, were not assessed in this study. (However, the bone marrow suppression seen in malaria could blunt reticulocyte counts and alter their utility as a marker of hemolysis.) The role of free hemoglobin and heme, also not measured in our study, in the vascular injury and inflammation of severe malaria has been highlighted by Soares and colleagues [4,5] and Belcher et al [6]. Thus we cannot completely rule out that hemolysis affects outcomes in children with cerebral malaria.

In future studies, we will assess additional factors such as reticulocyte count, methemoglobin, and free hemoglobin level to gain further insight into the contributions of hemolysis to severity of disease in children with cerebral malaria.