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CORRESPONDENCE

Severe Anemia in Malawian Children

TO THE EDITOR: Calis et al. (Feb. 28 issue)[1] report a significant association of bacteremia with severe anemia in Malawi. Bacteremia in case patients and control patients was mainly due to nontyphoid salmonella. The study showed that nontyphoid salmonella bacteremia was present in 10.0% of case patients with severe anemia and in 1.5% of controls. This association has been consistently noted in other studies of childhood bacteremia in tropical Africa.[2]

As discussed in the report, the association does not necessarily mean that nontyphoid salmonella bacteremia is a common cause of severe anemia. There are data suggesting that nontyphoid salmonella bacteremia is more likely to be a consequence of severe anemia, especially when anemia is due to hemolysis rather than to other causes, such as blood loss.[2-4] The question of whether nontyphoid salmonella bacteremia is a cause or a consequence of severe anemia has implications for clinical management and potential preventive strategies.

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1. Calis JCJ, Phiri KS, Faragher EB, et al. Severe anemia in Malawian children. N Engl J Med 2008;358:888-99.
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TO THE EDITOR: The conclusion by Calis et al. that iron deficiency was not a prominent cause of severe anemia in Malawian children would have been more convincing if the results of bone marrow iron staining in the case patients had been reported. Analysis of the amount of stainable iron in bone marrow aspirates is considered to be the most valuable tool for assessing whether sufficient iron is available for erythropoiesis. Furthermore, the accuracy of the ratio of soluble transferrin receptor (TfR) to log ferritin for diagnosing iron deficiency may have been hampered by the high prevalence of viral, bacterial, and parasitic infections in the case patients. TfR levels are predominantly determined by erythropoietic activity,[1] and suppressed erythropoiesis is a common observation in infections,[2] such as malaria and human immunodeficiency virus infection. Moreover, inflammation increases ferritin levels independently of body iron stores.[3]

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THIS WEEK'S LETTERS

The New England Journal of Medicine
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1. Beguin Y. Soluble transferrin receptor for the evaluation of erythropoiesis and iron status. Clin Chim Acta 2003;329:9-22.
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TO THE EDITOR: On the basis of plasma folate measurements, Calis et al. assert that folate deficiency was absent among Malawian children with severe anemia. However, the authors did not conclusively rule out folate deficiency by measurement of plasma homocysteine (and methylmalonic acid).[1,2]

Low plasma folate values support the diagnosis of folate deficiency in uncomplicated anemia, but because erythrocyte folate values are 30 times as high as plasma folate values, even a small degree of (intravascular) hemolysis can raise plasma folate values and mask cellular folate deficiency. The burden rests on these investigators to unambiguously establish the absence of folate deficiency in sick and undernourished children.[3]

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1. Antony AC. Megaloblastic anemias. In: Hoffman R, Benz EJ Jr, Shattil SJ, et al., eds. Hematology: basic principles and practice. 4th ed. Philadelphia: Churchill Livingstone, 2005:519-56.
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THE AUTHORS REPLY: In response to Graham: bacteremia — and especially nontyphoid salmonella — is a common finding in severely anemic children in Malawi. Excessive hemolysis may benefit the growth of nontyphoid salmonella,[1] and thus, nontyphoid salmonella may not necessarily cause severe anemia. We found that gross hemolysis was not a major feature in our population (unpublished data). Alternatively, nontyphoid salmonella may cause or worsen the anemia and can jeopardize bone marrow function. We concluded that, since 15% of the severely anemic children had bacteremia, routine treatment with antibiotics may be justified.

In response to de Mast and colleagues: we assessed the diagnostic accuracy of peripheral-blood markers for iron status using iron-stained bone marrow slides as the standard and found that the ratio of soluble TfR to log ferritin best predicted bone marrow iron status.[2] Using this ratio, we assessed the iron status in the case–control study and found a reversed odds ratio. We validated this finding using four other, well-known markers of iron deficiency (see Table 3 of our article). All analyses showed the same reversed odds ratio, which makes it unlikely that our findings can be explained by an effect of inflammation on erythropoiesis.

In response to Antony: it is theoretically possible that hemolysis and vitamin B_{12} deficiency have masked folate deficiency. We performed an additional analysis to study the possible confounding effect of hemolysis. Laboratory values compatible with hemolysis were found in only a minority of severely anemic children. We found folate deficiency in the absence of abnormal hemolysis. We did not evaluate the source of dietary folate intake in these children in detail, but green vegetables and fruits account for a large proportion of the dietary intake of children in Malawi and are well-known sources of folate. Considering the diet in Malawi and the findings of previous studies from Africa on folate deficiency and supplementation, our findings are not surprising.[3,4]

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1. Chlosta S, Fishman DS, Harrington L, et al. The iron efflux protein ferroportin regulates the intracellular growth of Salmonella enterica. Infect Immun 2006;74:3065-7.
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