Intensive care requirement, rather than degree of serum ferritin elevation, predicts mortality in macrophage activation syndrome

To the Editor:

We read with interest the recent publication on elevated serum ferritin levels associated with increased mortality and critical care in pediatric patients. Bennett et al (1) reported an increased risk of death and intensive care admission for patients with maximum serum ferritin >3000 ng/mL and suggested this may be evidence of systemic inflammatory response. Serum hyperferritinemia is seen in hemophagocytic lymphohistiocytosis as well as the "secondary" or "acquired" form of hemophagocytic lymphohistiocytosis, macrophage activation syndrome (2).

To determine whether elevated ferritin was predictive of mortality or critical care admission at our institution, we reviewed patients who had ferritin levels >3000 ng/mL from 2007 (when the current pediatric rheumatology department was created) to December 2011. The need for informed consent was waived by the University of Alabama—Birmingham Institutional Review Board. All records in the electronic medical record were searched; patients with transfusion-related iron overload (International Classification of Diseases-9—275.0) or medications for iron chelation (e.g., deferasirox) were excluded to clarify the patients with ferritin as a marker of inflammation. Forty-six patients were identified and 18 of 46 (39%) were admitted to an intensive care unit (ICU) during or within 1 wk of maximum ferritin (13 in pediatric ICU, five in neonatal ICU). Eleven of the total 46 patients (24%) died, all of whom were in an ICU (11 of 18, 61%); these numbers were very similar to those recently reported by Bennett et al (1).

In addition, we evaluated the treatments received by the patients with elevated serum ferritin levels, especially with regard to immunomodulation or immunosuppressive medication. Of the ICU patients who died, four of 11 received immunomodulation with anakinra (interleukin-1 receptor antagonist), corticosteroids, etoposide, and cyclosporine (hemophagocytic lymphohistiocytosis-2004 protocol) (3); two of 11 received chemotherapy (one, induction for pre-B cell leukemia; one, etoposide and dexamethasone); and five of 11 received antibiotics or other supportive therapy. Of the seven ICU patients who survived, two received anakinra and steroids (one also received cyclosporine A); one received corticosteroid alone; two received antibiotics; one received ursodiol; and one received mechanical ventilation only.

Intriguingly, of the 28 patients who did not require critical care management, 22 patients (79%) received immunomodulating therapy, most often corticosteroid. In addition, anakinra was used in nine patients including four in whom it was used as monotherapy. Initially, anakinra was studied in the setting of sepsis. It did not significantly alter primary outcomes but did statistically benefit several secondary measures (4). Since then, anakinra has been used successfully in patients with corticosteroid and cyclosporine refractory macrophage activation syndrome (5).

Although the mortality (61%) of the ICU patients vs. the mortality (0%) of the non-ICU patients was markedly different, their ferritin values were not (range 3134–206,115, mean 40,428 ng/mL in ICU patients vs. range 3013–155,886, mean 18,475 ng/mL in non-ICU patients). This intimates similar levels of inflammation in the two groups. This further suggests the contribution of a different variable to the mortality rate; perhaps, the early recognition and treatment of macrophage activation syndrome lowers the need for intensive care and the associated mortality. Instead of using an elevated serum ferritin level as a marker for mortality, it should be considered a marker of uncontrolled systemic inflammation, which indicates the need for early addition of immunomodulatory therapy.

The authors have not disclosed any potential conflicts of interest.

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The authors reply:

We appreciate the comments by Drs. Mannion and Cron (1) regarding our article (2) and also the opportunity to reply provided to us by the editors. In their letter, Drs. Mannion and Cron report data regarding 46 patients at their own institution with ferritin levels >3000 ng/mL, including descriptive information about immunosuppressive therapies received by the patients, and briefly review the literature on anakinra use for macrophage activation syndrome (MAS).

Drs. Mannion and Cron note that among their 46 patients, no mortality was seen in those not admitted to the intensive care unit (ICU), and that the ranges of ferritin levels observed in their patients admitted to the ICU and not admitted to the ICU were similar. On the basis of this observation, they suggest that "[i]nstead of using an elevated serum ferritin level as a marker for mortality, it should be considered a marker of uncontrolled systemic inflammation, which indicates the need for early addition of immunomodulatory therapy" (1). We agree, and stated in our article that "ferritin levels >3000 ng/mL may be useful in identifying patients who may benefit from work up

for MAS or hemophagocytic lymphohistiocytosis and consideration of immunosuppressive therapy. It seems likely that early recognition of these conditions may limit disease progression and improve outcomes" (2).

The data in the letter regarding anakinra use in patients with MAS are very intriguing, but unfortunately, neither our study nor the accompanying letter contains sufficient data for a rigorous evaluation of the effect of immunosuppression on outcomes in patients with serum hyperferritinemia of various etiologies. We agree that such studies are urgently needed.

Our analysis and the data reported in the accompanying letter are limited by their observational nature. In contrast to our study, the authors of the accompanying letter do not report data on children with peak ferritin levels within the 1000–3000 ng/mL range we used as a comparison group and do not report whether ferritin levels were associated with mortality. The local indications for and timing of ICU admission may have affected both studies, as eight of 103 (8%) of the patients not admitted to the ICU in our study died during the observation period (not shown in our original article). Drs. Mannion and Cron did not report in their letter the length of the observation period for mortality events after each patient's peak ferritin level. The title of the letter refers to patients with MAS, but our study and the data in their letter included patients based on a ferritin level and not a physician's diagnosis of MAS. As we noted in our article, the hospital-specific practices regarding the drawing of ferritin levels could affect the patient cohort, as patients whose levels were never checked could not be included.

We are pleased that our study has drawn interest. We hope that increased attention to the disease processes that can produce high serum ferritin levels in children will result in further studies of strategies to improve the care and outcomes of those patients.

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