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Plasma exchange, Methylprednisone, IVIG, and now Anakinra support continued PICU equipoise in management of Hyperferritinemia associated Sepsis/MODS/MAS/Secondary HLH syndrome

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Of the 75,000 children treated in the U.S. each year for severe septic shock (1), there is small subset that, in fact, have a pathologic activation of the immune system that can require a different set of diagnostic and therapeutic modalities. This hyperimmune state, characterized by a cytokine storm and systemic inflammatory response syndrome, can be divided into two broad categories: 1) 1°- or familial hemophagocytic lymphohistiocytosis (FHLH) caused by an autosomal recessive mutation(s) in genes required for NK and CD8+ T-cells to exocytose cytotoxic granules and kill viruses and cancer cells, as well as induce programmed cell death in activated immune cells, thereby limiting the host immune response and ability to turn off macrophage and lymphocyte activation and proliferation, and 2) hyperferritinemia associated sepsis/multiorgan dysfunction syndrome (MODS)/macrophage activation syndrome (MAS)/2°-HLH caused by pathologic immune activation in patients without a perforin related genetic defect in Natural Killer (NK) or cytotoxic T lymphocyte (CTL) function.

In 1994, to address the dismal 4% survival rate attributed to FHLH if left untreated (2), the Histiocyte Society launched a prospective multicenter study (HLH-94) using combined treatment with etoposide, cyclosporine A, and dexamethasone ± IT methotrexate ± bone

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marrow transplantation that resulted in 55% 3-year survival (3). Unfortunately, as reported by Castillo and Carcillo (4), the clinical and laboratory criteria used for HLH-94, subsequently HLH-2004, have low specificity for FHLH. Genetic studies, although clinically available, require upwards of three weeks for results and are therefore used primarily to judge risk of recurrence and identify at-risk family members. Natural Killer (NK)-cell degranulation assays have shown promising results in a study by Bryceson et al. (5), however they are not widely available for clinical use. In pediatric sepsis, decreased NK activity is the norm but it is related to acutely reduced numbers of NK cells leading to decreased NK activity per PBMC (6) rather than decreased NK cell granulation per cell which leads to decreased NK activity in FHLH.

As a result of these limitations, and to ensure adequate treatment of children with FHLH, patients with hyperferritinemia associated sepsis/MAS/MODS/2°-HLH may be unnecessarily treated with highly immunosuppressive regimens. The current standard of care for sepsis/MODS/MAS is intensive care support for failing organ systems, appropriate antibiotics use, and limited immunosuppression (7–9). In septic patients, who often have normal individual NK cell function but a reduced number of NK-cells (6), the use of chemotherapeutic agents may prevent recovery of NK cell and cytotoxic T lymphocyte (CTL) numbers leading to immunoparalysis and opportunistic secondary infections. Demirkol et al. (7) published a cohort study comparing the HLH-94 protocol to a less immunosuppressive regimen for children with hyperferritinemia, hemophagocytosis, and sepsis/MODS/MAS/2°-HLH. Their univariate and multivariate analysis demonstrated improved survival in children treated with plasma exchange and methylprednisolone (not dexamethasone) and/or IVIG compared to children who received highly immunosuppressive regimens based on HLH-94 (survival 100% vs. 50%; $p=0.002$). The results suggest that patients with hyperferritinemia associated sepsis/MAS/MODS/2°-HLH can have improved outcomes with control of inflammation that does not cause significant immune suppression or prevention of NK-cell/CTL recovery.

Anakinra (Kineret; Amgen), a recombinant interleukin-1 (IL-1) receptor antagonist has been shown to control inflammation in multiple disease processes, including hemophagocytic syndromes (8–11), and would not be expected to cause significant cytopenias or risk of secondary infection.

In this issue of *Pediatric Critical Care Medicine*, Rajasekaran et al. (12) present a single-center case series of eight critically-ill patients with hyperferritinemia associated sepsis/MAS/MODS/2°-HLH treated with anakinra. The diagnosis was based on HLH-2004 criteria which requires at least 5/8 clinical features: fever, splenomegaly, cytopenia 2 cell lines, hypertriglyceridemia or hypofibrinogenemia, hemophagocytosis, hyperferritinemia 500ng/mL, low NK-cell activity, and elevated soluble CD25 (sCD25). Ultimately, the diagnosis and decision to use anakinra was made in consultation with subspecialty services and after infectious etiologies had been excluded. Anakinra was started at median hospital day 5 (range 3–13 days) and continued until there was improvement in patient symptoms and inflammatory markers (range 5–31 days). Several children additionally received intravenous immunoglobulin and/or corticosteroids. The primary findings from this series are a mortality rate of 12% (1/8), a 67.1% decline in CRP ($p=0.03$), and a 63.8% decline in

ferritin ($p=0.3$) after starting anakinra. Importantly, neutrophil and lymphocyte counts were not observed to change significantly and no infections were attributed to anakinra treatment.

The report of Rajasekaran et al. (12) is a retrospective case series and therefore primarily descriptive. Similar to other reports on HLH, there is difficulty and controversy in making a definitive diagnosis for these eight patients given the overlapping phenotypic presentations. However, their use of anakinra is supported by additional case reports and small case series of successful treatment for patients with hyperferritinemia associated sepsis/MAS/MODS/2°-HLH with and without the HLH-2004 protocol. Reports of anti-inflammatory management include: 1) Demirkol et al.⁷ treatment with plasma exchange, IVIG, and corticosteroids 2) Teachey et al. (13) report successful treatment of 2°-HLH associated with blinatumomab with IL-6 receptor directed therapy 3) IFN- α was successful in two patients with reactive HLH (14) (possibly by inducing hepatic production of IL-1ra) and 4) several additional reports on the use of anakinra (8–11). In addition, a post-hoc analysis by Shakoory et al. (15) of the randomized placebo controlled trial of anakinra in adults with severe sepsis, finds anakinra infusion at 1–2mg/kg/h for 72h reduced mortality two-fold in adults with severe sepsis and MAS/HPS defined by hepatobiliary dysfunction and DIC.

Concurrently, our understanding of the pathophysiologic mechanisms and treatment of primary and secondary HLH/MAS are being advanced through basic and translational research. Animal models have been developed for familial HLH using genetic knockouts and, more recently, a model of secondary HLH/MAS was reported using repeated immune stimulation in genetically normal animals (16). In this murine model, reported by Behrens et al., Toll-like receptor 9 (TLR9) of the innate immune system is stimulated with CpG oligodeoxynucleotides leading to cytopenias, splenomegaly, hyperferritinemia, and hepatitis. Similarly, in a murine model of peritonitis and liver injury, CpG injection is shown to induce cytokine production by macrophages and hepatic mononuclear cells with increased mortality (17). This hyperferritinemia associated sepsis/MAS/MODS/2°-HLH phenotype associated with TLR9 stimulation is exacerbated in knockout mice deficient in native hepatic IL-1ra production and ameliorated by IFN- α induced production of IL-1ra or with direct administration of recombinant IL-1ra (anakinra) *in vivo* (18). In addition, a role for ferritin as a pro-inflammatory cytokine was demonstrated in hepatic stellate cells *in vitro* via NF- κ B activation and increased expression of IL-1 β , iNOS, and other pro-inflammatory mediators (19). Rosário et al. (20) have proposed including four clinical syndromes commonly associated with hyperferritinemia – MAS, Still's disease, septic shock, and catastrophic antiphospholipid syndrome – under a common syndrome termed “Hyperferritinemia Syndrome”. Developing phenotypes of pathologic immune activation, in addition to the phenotypes of patient symptoms, will continue to be important for the study and treatment of these patients moving forward.

At present, without randomized studies in children it is still reasonable to consider any approach from supportive management to anti-inflammatory management to use of HLH-94 protocol to manage children with hyperferritinemia associated sepsis/MAS/MODS/2°-HLH. For what it is worth, in our clinical practice we use a ‘risk factors’ approach as described by Demirkol et al. (7). For patients meeting at least 5/8 HLH-2004 criteria we consider the following factors as high-risk for FHLH: 2 years of age, consanguinity, death of a family

member due to unspecified febrile illness, or primary CNS disease classified as high-risk for primary HLH. For those who do not have these risk factors we consider plasma exchange, solumedrol, IVIG, and anakinra which have all performed well in case series in this population, or tocilizumab, daclizumab, and interferon alpha which have also been successful in case reports for this group. Equipose in the treatment of hyperferritinemia associated sepsis/MAS/MODS/2°-HLH is prudent until randomized clinical trials to guide therapy are evident.

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