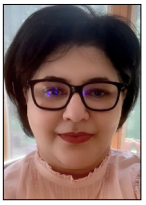
ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

Diagnosis and Treatment of Secondary Hemophagocytic Lymphohistiocytosis in Adults



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H&O What is hemophagocytic lymphohistiocytosis (HLH), and what forms of it occur?

JR HLH is a hyperinflammatory response—an overactivation of the immune system that is driven primarily by the interferon gamma (IFN-γ) cytokine. Primary HLH is a genetic disease that most often appears in childhood but in rare cases appears in adulthood. Secondary HLH (sHLH) may be driven by malignancy, infection, drug reactions, or autoimmune disease. Most HLH cases that first appear in adulthood are the secondary form, although we are learning that underlying genetic factors also seem to play a role in sHLH.

H&O How common is sHLH, and is it becoming more common?

BS We do not have formal epidemiologic studies, but an approximate number of sHLH/macrophage activation syndrome (MAS)/hyperferritinemic sepsis cases can be estimated on the basis of sepsis cases. Sepsis is reported to affect 1.7 million adults in the United States[1] and 50 million adults in the world.[2] We also have 2 studies suggesting that 4% to 5% of patients in the intensive care unit who are presumed to have sepsis may actually have sHLH.[3,4] Although clinicians are increasingly recognizing this condition, we do not have the data to determine if this is due to an increase in frequency or just a recognition bias.

H&O How often does malignancy trigger sHLH?

JR Malignancy appears to be the most common trigger of sHLH, with epidemiologic studies suggesting that it accounts for 30% to 35% of HLH cases in adults.[5-7] B-cell lymphoma is especially likely to lead to HLH, although HLH can also occur with Hodgkin lymphoma and T-cell lymphoma. Any time we suspect HLH in a patient with lymphoma, the malignancy is very likely a contributing factor. That does not, however, rule out infection as the trigger, so we always need to do a detailed workup that includes evaluation for infection. Infections account for approximately 25% to 30% of cases of sHLH.[7]

H&O What is the prognosis for people with sHLH?

JR The prognosis is driven by 2 very important factors: the timing of recognition and the underlying trigger of HLH. Regarding the timing of recognition, late recognition of HLH universally entails an extremely poor prognosis. If the condition is recognized very late, when the patient is in the intensive care unit, therapy will need to be aggressive, and then the complications of treatment can be every bit

as deadly as the HLH itself. Early recognition in the acute setting is therefore extremely important. Regarding the underlying trigger, the 1-year mortality rate is in the 80% range if the driver is lymphoma or another malignancy because we do not yet know how to treat this type of HLH optimally.[8] The prognosis is much better if the HLH is triggered by a rheumatologic condition or an infection, with mortality rates often in the 10% to 20% range.[9]

H&O When should oncologists suspect HLH?

JR The Histio UK group has developed a useful mnemonic, the "3 *F*s," which stand for *fever*, *ferritin*, and *falling blood counts*.[10] Remembering these 3 findings can help us detect HLH earlier. The fevers are not simply isolated episodes; these are unrelenting fevers that continue for many days. The ferritin level rises significantly, and blood counts fall. The platelet count usually falls first, but drops in the white blood cell count are the most specific for IFN-γ–driven inflammation. The hemoglobin level is variable.

BS The recently published guidance on the diagnosis and treatment of early sHLH/MAS[11] emphasizes persistent abnormalities that do not respond appropriately to treatment as part of the clinical presentation of HLH. Examples include severely abnormal or increasing liver enzymes, severely abnormal or worsening coagulopathies, and any sepsis-like scenarios that do not respond to appropriate sepsis treatment. These signs should alert the physician that something else may be occurring.

It is crucial to understand that suspecting HLH and diagnosing HLH are 2 separate processes. I strongly encourage colleagues to maintain a high index of suspicion for HLH and start treatment as soon as they suspect a case, rather than wait for confirmation of the diagnosis, because the patient's life is at stake.

H&O How is HLH diagnosed?

BS Three major criteria sets are used to diagnose HLH. The HLH-2004 criteria[12] have been validated for use in the genetic form of HLH, which occurs mostly in children. Although these criteria are widely used for sHLH in adults as well, the disease process in adults is often advanced by the time the criteria sets are met, leading to high mortality rates. Those of us who conduct research on HLH in adults do not rely on these criteria alone. Instead, we also recommend using the HScore to define and diagnose HLH in adults with different underlying causes.[13] All the tests that are used to derive the HScore are readily available, even in settings where more specialized testing—such as measurement of the CD25 protein—is limited. Therefore, HScore testing is accessible for any clinician with access to routine laboratory tests. Importantly, the HScore provides a probability in addition to a hard cutoff, which makes it easier to use in the clinical setting. In addition, diagnostic criteria for MAS are available for patients who have underlying systemic juvenile idiopathic arthritis, but these are not a good way to diagnose HLH in adults.

JR We do not have diagnostic criteria for each HLH subset, so the future of diagnosis will likely involve the use of novel biomarkers, such as chemokine C-X-C motif ligand 9 (CXCL9). Although we do not fully understand the function of CXCL9, it serves as an excellent surrogate marker for activation of IFN-γ, which is the major driver of HLH pathogenesis. CXCL9 not only provides real-time information about the degree of HLH-like inflammation but also is a targetable chemokine with IFN-γ–directed therapies.

H&O What are the challenges of treating adults with HLH?

JR The biggest challenge is convincing treating physicians to initiate therapy. These patients are critically ill, and many times they have active infections that become the focus of treatment. Lowering the threshold for suspecting HLH is important because these patients need a degree of immune suppression in addition to covering potential active infections. The patient's immune system is so activated that it can drive multiorgan failure independently. Infection-triggered HLH can cause such severe hyperinflammation that standard antibiotic therapies may not be sufficient and immunosuppressive therapy may be required.

H&O What treatment approaches are used?

BS We need to take a multifaceted approach to these critically ill patients. The first step is aggressive supportive care, which may include mechanical ventilation for respiratory failure, vasopressor support for hemodynamic instability, and renal replacement therapy for kidney failure. The second step is empiric antibiotic therapy for any suspected infection, along with prophylactic antibiotics to prevent infections that could arise from immunosuppression. The third step is safe immunomodulation that will effectively control hyperinflammation without causing additional complications. We start immunomodulation as soon as we suspect HLH.

The 3 primary options for initial immunomodulation are corticosteroids, intravenous immunoglobulin (IVIG), and anakinra (Kineret, Sobi). Patients generally require at least 2 of these treatments and sometimes all 3 of them.

Corticosteroids are safe in the short term, although we should not rely on them for long-term management. We often start with pulse-dose methylprednisolone at up to 1000 mg/d for 3 days in adults with severe HLH, followed by prednisone or its equivalent at 1 to 2 mg/kg daily, tapering weekly or as quickly as the clinical situation allows on the basis of improvements in clinical status and inflammatory markers. IVIG is very safe and can be administered at 2 g/kg divided over 2 to 5 days. Anakinra is particularly appealing because it is the recombinant form of a naturally occurring molecule (interleukin 1 [IL-1] receptor antagonist) that the body generates to counteract the inflammatory effects of IL-1. Anakinra can help the patient's immune system overcome the overwhelming inflammatory response that occurs in HLH, and it should be given early in the inflammatory process.

> "We also need to distinguish between a true recurrence and a relapse."
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> —Bita Shakoory, MD

The trigger of the sHLH should be addressed as soon as it is identified. For instance, a patient with underlying lupus may need rituximab, a patient with a malignancy will need appropriate chemotherapy, and a patient with an infection will need IVIG and a change in antibiotics. Epstein-Barr virus infection has proved particularly challenging to manage, causing multiple layers of immune dysregulation, and it often requires combination antiviral and immunomodulatory therapy that may include rituximab and/or chemotherapy.

Some physicians believe that treating just the underlying trigger will be sufficient to manage HLH, but we do not yet know when this approach will reverse the sHLH. Until we have that information, we must treat both the underlying cause and the overlay of sHLH.

We advise against use of etoposide in most cases of sHLH. Exceptions include certain cases of HLH that are associated with malignancy or EBV or that are difficult to treat. Although this drug can be effective, less-toxic immunomodulators are available that achieve the same results without exposing the patient to the potential side effects.

JR One of the benefits of newer agents like ruxolitinib (Jakafi, Incyte), emapalumab (Gamifant, Sobi), and anakinra in patients with suspected HLH is that these drugs have relatively short half-lives, so they clear quickly from the body if any problems develop. Etoposide, by contrast, has long-lasting effects and should be reserved for situations in which the patient has a malignancy. A very good study by Zoref-Lorenz and colleagues showed that adding etoposide to the backbone of chemotherapy in lymphoma-associated HLH may decrease mortality.[14] I would not use etoposide in a patient who does not have a malignancy.

H&O What roles do different specialists play in the care of patients with HLH?

BS This is a challenging question, but the work done in the United Kingdom by the Histio UK group demonstrates that a multidisciplinary approach is optimal.[10] Boston Children's Hospital also employs a multidisciplinary team approach for these patients.[15,16] The multidisciplinary approach is valuable because physicians from different specialties may interpret symptoms in the same patient differently. For example, an intensivist may focus on respiratory support for sepsis, a rheumatologist may focus on treating with corticosteroids, and a hematologist may want to give etoposide in the same patient. When these 3 specialists collaborate, they can achieve a much better perspective and offer a comprehensive and detailed treatment that includes input from all of them.

H&O How often does HLH recur after successful treatment, and what treatment approaches should be used in recurrent cases?

JR We still have many unknowns regarding recurrence. We know that patients who clearly have a rheumatologic disease such as adult-onset Still disease are very likely to experience recurrences of HLH throughout their lifetime that are related to flares of their rheumatic disease. These recurrences are often treatable, especially if recognized early. In cases of malignancy-related HLH, recurrences are very unlikely if the malignancy is successfully treated. In many cases, it is recurrence of the underlying malignancy that drives long-term mortality. For patients who have an unclear driver of HLH, the recurrence rate is completely unknown because we have so few longitudinal studies in adults with HLH. I am currently conducting a natural history study of HLH at the National Institutes of Health (NIH), and this is one of the endpoints we are examining (NCT06339177). When we treat recurrences, we generally take an approach similar to that used for initial therapy, but the second round of treatment often does not work as well. We need more data to determine how likely the same approach is to succeed in patients with recurrence and what alternative approaches might be more effective.

BS We also need to distinguish between a true recurrence and a relapse. Sometimes, the treatment is inadequate or not optimized after the initial (partial) improvement, which results in an incomplete response. Failing to resolve the inflammatory process completely can allow symptoms to return with greater severity (relapse). We must ensure complete treatment of the initial episode.

Regarding true recurrences, an important consideration is that recurrences are more likely in people who have heterozygous genetic abnormalities, although not everyone who experiences a recurrence has a recognized genetic mutation.

H&O What promising new treatments or approaches are on the horizon for HLH?

JR This is an exciting time in the field because multiple studies are ongoing, and we anticipate significant new data. In addition to the natural history study of HLH that we are conducting at the NIH, the NIH is hoping to open multiple trials soon that will examine new drugs for adults with HLH. Our group has several manuscripts under review, and we have some exciting data on emapalumab that we hope to present later this year.

A phase 2/3 clinical trial is studying the use of ELA026 in sHLH (NCT05416307). This agent is a monoclonal antibody that depletes activated macrophages and activated T cells without the toxicity associated with drugs like etoposide.

Regarding CXCL9, we are learning that patients with elevated levels of this biomarker demonstrate a response to IFN-γ blockade, whether with a JAK inhibitor such as ruxolitinib, which blocks downstream IFN-γ signaling, or with a monoclonal antibody against IFN-γ such as emapalumab. There are barriers to obtaining immediate CXCL9 test results, and furthermore, CXCL9 testing is not commercially available in most countries. We hope these limitations will be eliminated because CXCL9 testing is needed for guiding treatment with IFN-γ–blocking agents, which have shown greater success when used earlier rather than later in patients who have a high HScore.

The future is very promising for improvements in the evaluation of HLH and long-term outcomes. We have many dedicated researchers working on HLH across the country and internationally, and we will know significantly more in the coming years about optimal care for these patients.

Disclaimer

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Disclosures

Drs Shakoory and Rocco have attended advisory board meetings (no honoraria or funding) for Sobi.

References

1. Rhee C, Dantes R, Epstein L, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. *JAMA*. 2017;318(13):1241-1249.
2. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet*. 2020;395(10219):200-211.
3. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. *Crit Care Med*. 2016;44(2):275-81.
4. Kyriazopoulou E, Leventogiannis K, Norrby-Teglund A, et al. Macrophage activation-like syndrome: an immunological entity associated with rapid progression to death in sepsis. *BMC Med*. 2017;15(1):172.
5. Löfstedt A, Jädersten M, Meeths M, Henter JI. Malignancy-associated hemophagocytic lymphohistiocytosis in Sweden: incidence, clinical characteristics, and survival. *Blood*. 2024;143(3):233-242.
6. Miao Y, Zhang J, Chen Q, et al. Spectrum and trigger identification of hemophagocytic lymphohistiocytosis in adults: a single-center analysis of 555 cases. *Front Immunol*. 2022;13:970183.
7. George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. *J Blood Med*. 2014;5:69-86.
8. Setiadi A, Zoref-Lorenz A, Lee CY, Jordan MB, Chen LYC. Malignancy-associated haemophagocytic lymphohistiocytosis. *Lancet Haematol*. 2022;9(3):e217-e227.
9. Zoref-Lorenz A, Rocco J, Schwartz DM, Jordan M. Recognizing and managing secondary hemophagocytic lymphohistiocytosis in adults: a practical clinical guide. *Hematol Oncol Clin North Am*. 2025;39(3):577-596.
10. Cox MF, Mackenzie S, Low R, et al. Diagnosis and investigation of suspected haemophagocytic lymphohistiocytosis in adults: 2023 hyperinflammation and HLH across speciality collaboration (HiHASC) consensus guideline. *Lancet Rheumatol*. 2024;6(1):e51-e62.
11. Shakoory B, Geerlinks A, Wilejto M, et al. The 2022 EULAR/ACR points to consider at the early stages of diagnosis and management of suspected haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). *Ann Rheum Dis*. 2023;82(10):1271-1285.
12. Henter JI, Sieni E, Eriksson J, et al. Diagnostic guidelines for familial hemophagocytic lymphohistiocytosis revisited. *Blood*. 2024;144(22):2308-2318.
13. Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol*. 2014;66(9):2613-20.
14. Zoref-Lorenz A, Murakami J, Gurion R, et al. The OHI index predicts early mortality from organ dysfunction and survival benefit from etoposide in lymphoma patients [online April 18, 2025]. *Blood Adv*. doi:10.1182/bloodadvances.2024014005.
15. Halyabar O, Chang MH, Schoettler ML, et al. Calm in the midst of cytokine storm: a collaborative approach to the diagnosis and treatment of hemophagocytic lymphohistiocytosis and macrophage activation syndrome. *Pediatr Rheumatol Online J*. 2019;17(1):7.
16. Henderson LA, Abraham RS, Ahmed A, et al. Multidisciplinary approach to treating complex immune dysregulation disorders: an adaptive model for institutional implementation. *Front Immunol*. 2025;16:1519955.