Recognizing and Managing Secondary Hemophagocytic Lymphohistiocytosis in Adults

A Practical Clinical Guide

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KEYWORDS

• Secondary hemophagocytic lymphohistiocytosis • Hyperinflammation
• Hematologic malignancies • Cytokine storm • Hemophagocytosis

KEY POINTS

- Diagnosing and managing secondary hemophagocytic lymphohistiocytosis (HLH) should prioritize identifying and addressing the underlying trigger.
- Therapeutic strategies must balance controlling hyperinflammation while avoiding interference with detecting underlying conditions, such as hidden lymphomas or infections.
- Emerging evidence suggests genetic predispositions to HLH are more common than previously recognized, highlighting the need for further research.

INTRODUCTION

History

Hemophagocytic lymphohistiocytosis (HLH) was first identified in 1939 by Scott and Robb-Smith, who described a syndrome characterized by persistent fever, wasting, lymphadenopathy, and spleen and liver enlargement. Pathologic findings revealed widespread proliferation of histiocytes and their precursors in lymphoreticular

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Abbreviations	
AOSD	adult-onset Still's disease
CHIP	clonal hematopoiesis of indeterminant potential
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CRS	cytokine release syndrome
EBV	Epstein-Barr virus
GC	glucocorticoid
HL	Hodgkin lymphoma
HLH	hemophagocytic lymphohistiocytosis
HSCT	hematopoietic stem cell transplantation
IEC-HS	immune effector cell-associated HLH-like syndrome
IFN-γ	interferon-gamma
IVIG	intravenous immunoglobulin
MAS	macrophage activation syndrome
MDS	myelodysplastic syndrome
MPN	myeloproliferative neoplasms
NTM	nontuberculous mycobacteria
OHI	Optimized Hyper Inflammatory
RA	rheumatoid arthritis
sHLH	secondary hemophagocytic lymphohistiocytosis
sJIA	systemic juvenile idiopathic arthritis
SLE	systemic lupus erythematosus
TB	tuberculosis
TCL	T-cell lymphoma
VEXAS	Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic

tissue.[1] Soon after, the syndrome was described in familial and cancer-associated contexts under different terminologies.[2,3] The term "hemophagocytic lymphohistiocytosis" became widely used in the 1980s to describe this pathologic hyperinflammatory process.[4–6] In the 1990s, "macrophage activation syndrome" (MAS) was introduced to describe a similar condition in patients with rheumatologic disorders.[7,8] A breakthrough occurred with the discovery of the perforin gene defect,[9] leading to the first mouse model of the genetic disease in 2004.[10] While HLH interest was focused on the familial form (FHL) in most of the early years, interest in secondary HLH (sHLH) has grown significantly in the last decade.[11] Awareness of sHLH was further amplified by the introduction of immune-activating therapies and their the U.S. Food and Drug Administration (FDA) approval in 2017.[12]

FHL treatment has expanded from etoposide-based regimens (HLH-94[13] and HLH-2004[14] Protocols) to the development of targeted therapies, including emapalumab, an anti-interferon-gamma (IFN-γ) antibody approved by the FDA in 2018.[15] All therapies for FHL are essentially preparations for definitive curative treatment with allogeneic bone marrow transplantation. In contrast, treatments for secondary HLH are still under investigation and are mostly based on small studies and expert opinions. Fortunately, interest in sHLH is increasing, and efforts are being made to identify better treatment strategies for these patients. The current consensus in the field is that sHLH is best termed hyperinflammatory syndrome, and the key to successful therapy is identifying and treating the trigger when possible.

Pathogenesis

Familial hemophagocytic lymphohistiocytosis

FHL is a severe autosomal recessive immune disorder characterized by defective cytotoxic function of CD8 + T-cells and natural killer (NK) cells.[16] The pathophysiology

of FHL centers on mutations in genes crucial for the cytotoxic granule exocytosis pathway, including PRF1, UNC13D, STX11, STXBP2, LYST, and RAB27A, which encode perforin, Munc13-4, syntaxin 11, Munc18-2, lysosomal trafficking regulator, and Rab27a, respectively. These genetic defects impair lytic granule assembly, docking, and fusion, resulting in ineffective target cell elimination.[17] Consequently, antigen-presenting cells persist, leading to sustained T-cell activation and excessive production of proinflammatory cytokines, particularly IFN-γ. The elevated IFN-γ levels trigger a cascade of immune pathologies, including macrophage activation, hemophagocytosis, and inflammatory organ injury. Clinical manifestations include fever, hepatosplenomegaly, cytopenias, coagulopathy, and multiorgan dysfunction. Understanding this complex pathophysiology has guided the development of targeted therapeutic approaches, such as cytokine blockade and hematopoietic stem cell transplantation, which have significantly improved outcomes for FHL patients.

Knowns and unknowns secondary hemophagocytic lymphohistiocytosis etiology

sHLH is a complex hyperinflammatory disease process characterized by severe immune dysregulation, classically associated with triggers such as acute infections, malignancies, or immune activation in underlying rheumatologic conditions.[16] When sHLH develops in the context of autoimmune or autoinflammatory diseases, it is often referred to as MAS, with some groups classifying MAS as a distinct syndrome and others placing it on the sHLH spectrum.[18,19] The pathogenesis of MAS appears to overlap with FHL driven by excessive cytokine production (interleukin [IL]-1β, IL-6, IL-10, IL-18, IFN-γ, tumor necrosis factor-alpha [TNF-α]), upregulation of type I and type II interferon signaling pathways, and potentially acquired cytotoxicity impairments.[20,21] In contrast, immune profiles are largely uncharacterized in other secondary forms of HLH.[22] In clinical practice, multiple secondary etiologies can often contribute, and sHLH can develop due to a multifactorial accumulation of risk factors prompting an acute HLH presentation.[23] Underlying immune dysregulation driven by hematologic malignancies, autoimmunity, and/or iatrogenic immunosuppression (chemotherapy, immunomodulators, and transplant) may predispose individuals to develop hyperinflammation. Infections, more commonly, serve as the trigger prompting acute progression of symptoms or clinical decompensation.

DISCUSSION

The Approach to Secondary Hemophagocytic Lymphohistiocytosis

Identifying hyperinflammation

Suspicion of HLH should be raised when a patient presents with the "3 Fs"—fever, elevated ferritin, and falling blood counts (https://gettingitrightfirsttime.co.uk/wp-content/uploads/2024/07/HLH-Guide-final-version-v1.1-July-2024.pdf). While these signs are not specific to HLH, they should prompt a thorough investigation to confirm or rule out hyperinflammation (**Fig. 1**). Elevated ferritin was recently validated as a screening tool for hyperinflammatory disorders.[18]

When identifying HLH, it is important to recognize that the feed-forward loop between T/natural killer (NK)-cells and macrophages represents a syndrome characterized by the elevation of a relatively small set of key inflammatory mediators—which can include a wide spectrum of disease severity. Moreover, patients diagnosed relatively early, with less severe inflammation, have improved outcomes.[24,25] Hence, utilizing characteristic biomarkers to identify HLH-spectrum immune activation can dramatically improve patient outcomes. Nonetheless, no single clinical criteria can universally and reliably distinguish patients with this syndrome.

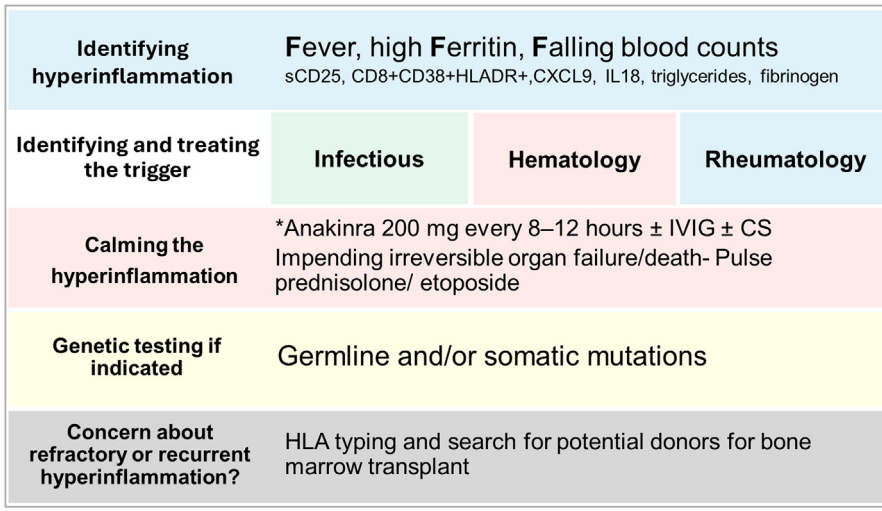

Fig. 1. A framework for the management of hyperinflammation. * May be increased or doubled every 24–48 hours, up to a maximum of 200 mg/hour continuous infusion. Consider adding emapalumab or ruxolitinib.

Ferritin and soluble CD25 (soluble interleukin 2 receptor, or sCD25) are the 2 single markers most recognized with HLH. Low levels of these markers should prompt reconsideration of an HLH-spectrum hyperinflammatory diagnosis.[26] Ferritin primarily reflects macrophage activation,[27] while sCD25 serves as an indicator of T-cell activation.[28] Although ferritin is readily accessible and useful as a screening tool, sCD25—available only through specialized laboratories—is more specific for sHLH,[29] and may predict poor outcomes.[30]

More recently, IL-18 and C-X-C motif chemokine ligand 9 (CXCL9) have emerged as 2 specific markers for sHLH. IL-18 is elevated in many forms of HLH,[31] with extremely high levels thought to be specific for sHLH/MAS associated with systemic juvenile idiopathic arthritis (sJIA) or adult-onset Still's disease (AOSD).[18,19] CXCL9, a biomarker of IFN-γ production, is elevated in most patients with sHLH and correlates with disease activity.[32] Recently, C-reactive protein has been proposed as a useful marker in distinguishing HLH from Still's disease, particularly when analyzed in combination with ferritin 3,[33] or sCD25.[34]

Numerous criteria have been developed to identify sHLH in the context of specific underlying conditions: these include the H-Score[35] and HLH-2004 criteria,[14] the Optimized HLH/Hyper Inflammatory (OHI) index[36] which was developed for malignancy-associated HLH, and European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) criteria for systemic lupus erythematosus (SLE) and sJIA-associated HLH/MAS.[37] These universally employ hyperferritinemia, cytopenias, organ-specific manifestations, and hypofibrinogenemia. Many also incorporate characteristic laboratory abnormalities like hypertriglyceridemia, aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) elevation, and bone marrow biopsy results. These criteria should be considered a valuable aid rather than a rigid checklist. An overreliance on predefined clinical parameters may lead to missed opportunities in identifying early or milder cases of HLH-spectrum hyperinflammation.

Identifying and treating the trigger

Once a diagnosis of hyperinflammatory syndrome has been established, a comprehensive evaluation for underlying immune dysregulation driven by malignancy or autoimmune disease is essential for all patients with sHLH. Equally important is a detailed work-up for infectious agents that could serve as the acute trigger for presentation (Fig. 2). New onset of hematologic malignancies or acute flares of autoimmunity can also serve as sHLH triggers; however, when a hyperinflammatory syndrome is suspected, blood cultures and respiratory viral testing should be checked in everyone to search for common infections, especially in the setting of impending initiation of immunosuppression. CT of the chest, abdomen, and pelvis should be performed to evaluate for lymphadenopathy and/or hepatosplenomegaly with a low threshold to biopsy suspicious lymph nodes for malignancy and stains for mycobacteria/fungi. Serologies for EBV, CMV, hepatitis viruses, and human immunodeficiency virus (HIV) should be performed in combination with polymerase chain reaction (PCR) testing for EBV and CMV in all comers. Bone marrow biopsy can be considered to evaluate for leukemia, lymphoma, and disseminated infections. Those living in or with recent travel to endemic areas should always be evaluated for ehrlichiosis/anaplasmosis (PCR testing, consider empiric doxycycline) and leishmaniasis (PCR testing and biopsy staining). A tiered testing approach can be pursued based on underlying risk factors, predisposing conditions, and clinical severity, as highlighted in Fig. 3.

DIAGNOSIS AND TREATMENT OF SPECIFIC TRIGGERS FOR HYPERINFLAMMATION

Infection-Associated Hyperinflammation

Although HLH is relatively uncommon, infectious triggers most closely associated with the syndrome are very common, which suggests that the development of sHLH should prompt suspicion of underlying host immune dysregulation. Consideration of many infectious triggers (see Fig. 3; Fig. 4) and empiric antimicrobial therapy (Fig. 5) is often essential.[38] Even mild infections, such as respiratory viruses (influenza, respiratory syncytial virus, severe acute respiratory syndrome coronavirus 2, and rhinovirus), can trigger life-threatening hyperinflammation in immunologically predisposed individuals. Bacteremia, candidemia, and pyogenic infections (pneumonia, meningitis, and

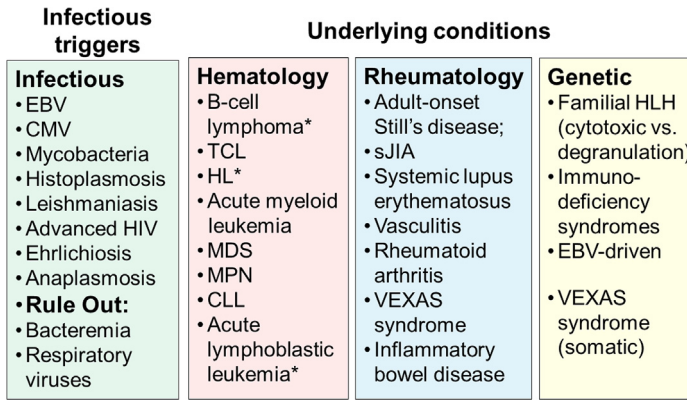

Fig. 2. Triggers and underlying conditions. CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; sJIA, systemic juvenile idiopathic arthritis; TCL, T-cell lymphoma. * May be triggered by immune-activating therapies.

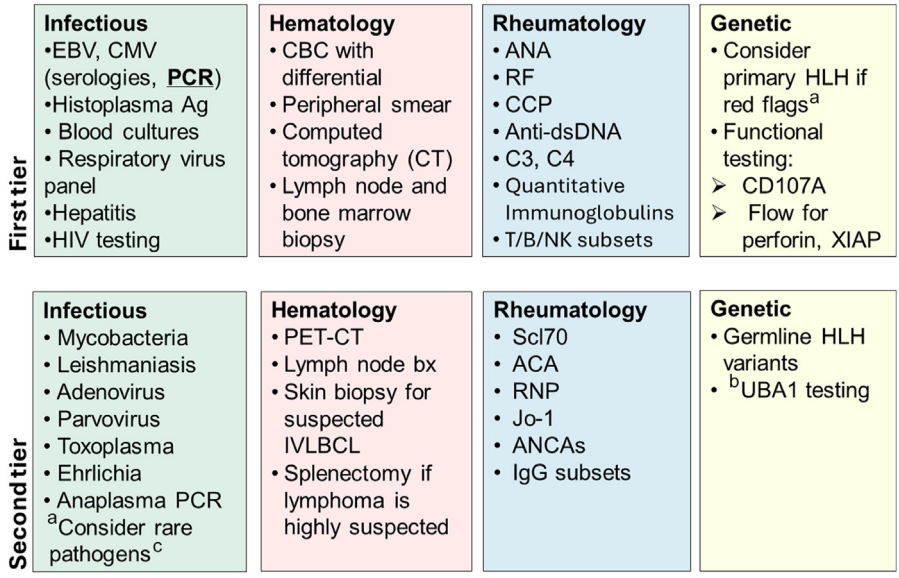

Fig. 3. Trigger-oriented diagnostic approach. [a]Red flags—A young patient (especially male), family history, or refractory disease. [b]UBA1 testing-male, Indicated for males over 50 with an MDS-like disease, relapsing polychondritis features, or neutrophilic dermatosis. [c]Please refer to Fig. 4 for a comprehensive infectious workup.

abdominal abscess) always require clinical evaluation as hyperinflammatory syndromes often lead to friable mucosal barriers, especially in critically ill patients where sepsis and HLH can have overlapping features.

Viruses are potentially the most common HLH-inducing infectious agents, and EBV should always be sought with antibody and PCR testing. The role of EBV in

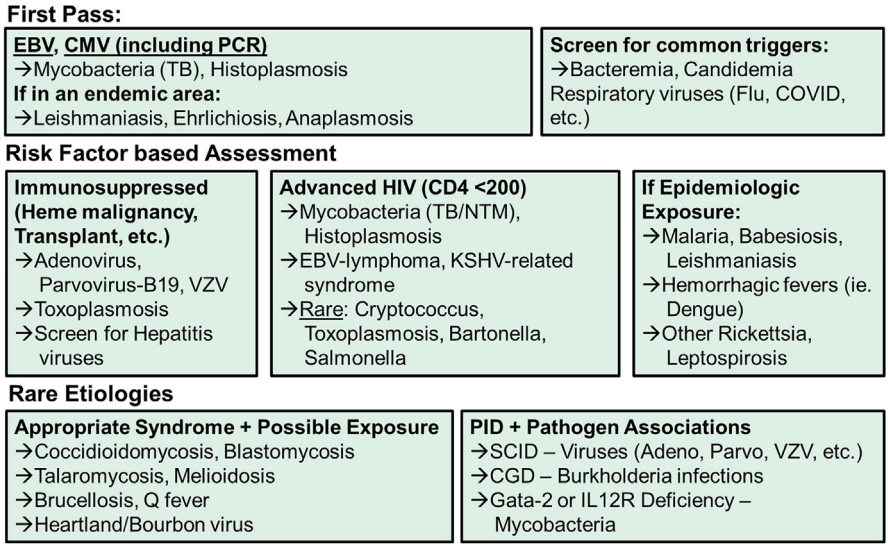

Fig. 4. Infection-specific diagnostic workup.

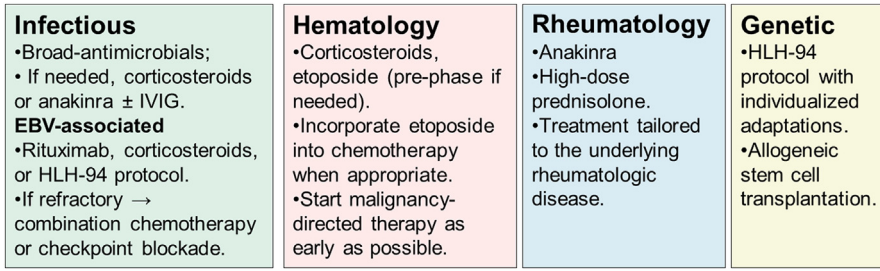

Fig. 5. Trigger appropriate therapy. Appropriate treatment strategies by specific triggers and underlying conditions.

contributing to HLH pathogenesis is complex, as it can drive a diversity of malignancies and lymphoproliferative syndromes.[39] Acute EBV infection is notorious for triggering HLH, especially in children or young adults with germline predisposition syndromes. In adults, EBV reactivations, even at only 3 to 4 $\log_{10}$ IU/mL, should prompt suspicion for EBV-driven lymphomas, which require aggressive evaluation; however, low-grade EBV reactivation can also occur in any immunosuppressed or hyperinflammatory state. Progressively increasing or high-level EBV viremias may indicate germline predisposition or other EBV lymphoproliferative syndromes in which EBV may actively infect B-cells or T-/NK-cells. Identifying the EBV cellular tropism by flow cytometry, biopsy stains, or cell sorting can be beneficial as it helps drive treatment decisions (targeting B-cells or T-/NK-cells); rituximab should always be a part of the therapy of EBV-associated HLH to clear the reservoir of HLH in B-cells, but it cannot be the sole therapy as EBV-HLH is associated with and driven by EBV infection of T-cells. Thus, rituximab and corticosteroids are reasonable first-line treatment options while monitoring EBV levels.[39,40] If HLH recurs or EBV viremia persists/progresses, then more aggressive therapy, often using HLH 94/2004 regimens or multimodal chemotherapy targeting T-/NK-cells, will likely be required.[41] However, other novel approaches, including regimens utilizing checkpoint inhibitors, are currently under study.[42] Throughout treatment, EBV viral levels must be closely monitored until complete virus elimination is achieved to ensure long-term control and prevent relapse.

CMV, a close relative to EBV, is another common HLH trigger, especially in immunocompromised hosts.[43] Although distinguishing CMV reactivation from true infection remains a constant clinical challenge, monitoring and potentially treating CMV reactivation should be pursued, especially when initiating and/or escalating immunosuppression. Low-level CMV reactivations in the plasma of 2 to 3 $\log_{10}$ IU/mL without biopsy-proven end-organ involvement can likely be monitored weekly, but if the viremia is continually increasing greater than 3 $\log_{10}$ IU/mL, then treatment should be considered as any persistent antigenic stimulation can propagate the hyperinflammatory syndrome. Ganciclovir is the first line but can contribute to cytopenias with prolonged therapy. The optimal treatment duration is unknown but should be minimized whenever possible with discontinuation as the hyperinflammation is resolving and weaning of immunosuppression has begun. Other herpesviruses (HSV1/2, varicella-zoster virus [VZV], HHV6) are unlikely triggers for HLH except potentially in very immunosuppressed hosts. In advanced HIV, Kaposi sarcoma herpesvirus can drive hyperinflammatory syndromes such as multicentric Castleman's disease, which clinically resembles HLH and may share some pathogenic overlap.[44] However, these syndromes require different treatment regimens and should not be confused with sHLH.

The other major subset of infectious triggers for sHLH is intracellular pathogens, primarily including rickettsia (such as ehrlichiosis and anaplasmosis), endemic fungi (histoplasmosis), mycobacteria (tuberculosis [TB], nontuberculous mycobacteria [NTM]), and parasites (leishmaniasis).[45–47] Every patient that lives in or recently traveled to an endemic area for ehrlichiosis, anaplasmosis, histoplasmosis, or leishmaniasis requires targeted testing (PCR ± antigen testing) and potentially empiric coverage with doxycycline and/or amphotericin-B if rapid initiation of immunosuppressive therapy is warranted. Immunosuppressive therapy may still be required if any of these pathogens are identified, but virtually all respond to shorter courses of corticosteroids or anakinra. A thorough history of TB risk factors should be elicited, although diagnosis can be difficult. Mycobacterial blood cultures can be checked in at-risk hosts, and acid-fast staining should be performed on all biopsies.

Although the pathogens above represent the most common infections associated with HLH, other organisms should be considered in the right immunologic and epidemiologic settings. Patients with transplants and/or active hematologic malignancies are at risk for adenovirus, parvovirus-B19, and toxoplasmosis, which can trigger HLH. PCR can evaluate these, and they represent treatable infections in high-risk hosts. HIV testing should be performed on all patients. While untreated HIV alone can mimic an HLH syndrome due to inflammasome activation and persistent CD8 T-cell stimulation,[48,49] it always improves with the initiation of antiretroviral therapy. However, people with advanced HIV (CD4 <200 cells/mL) are at risk for several HLH-inducing infections, most commonly mycobacteria (TB/NTM), histoplasmosis, and/or EBV-driven and Kaposi's sarcoma-associated herpesvirus (KSHV)-driven malignancies. During immune reconstitution, after starting antiretroviral therapy, people with HIV can develop immune reconstitution inflammatory syndrome that has HLH-like features due to residual antigenic stimulation (TB/NTM and histoplasmosis), despite appropriate antimicrobial treatment and can require prolonged immunosuppression therapy usually with corticosteroids.[50,51] Severe opportunistic infections with disseminated cryptococcus, salmonellosis, and toxoplasmosis can also drive an HLH phenotype in advanced HIV patients but are often easily treated with antiretroviral and antimicrobial therapies.

Additional pathogens are rare and uncommonly associated with HLH but require consideration and specialized testing in specific circumstances. Individuals with notable hemolysis and recent travel to endemic areas should have an evaluation for malaria. Babesia, caused by a protozoan related to *Plasmodium*, can also mimic malaria and trigger HLH in North American and European countries.[45] Hemorrhagic fevers can also lead to HLH-like presentations, and history should be evaluated before traveling to endemic locations. Severe dengue is the most common and can be evaluated with PCR and antigen testing, although optimal management strategies remain unknown.[52] Obscure triggers for infection-associated HLH also deserve consideration if an appropriate pathogen syndrome is present and/or if patients have traveled to endemic areas. This includes pathogens such as endemic mycoses (*Coccidioides* and *Blastomyces*), *Talaromyces*, *Burkholderia pseudomallei*, *Brucella*, *Coxiella*, and the Heartland or Bourbon viruses.

Finally, pathogen-specific risks associated with primary immune diseases merit consideration, especially in children and infants. Initial presentations of severe combined immune deficiencies and DOCK8 deficiency can resemble HLH triggered by adenovirus, parvovirus-B19, VZV, or similar viruses.[53] *Burkholderia* infections have a predisposition for leading to HLH in those with chronic granulomatous disease.[54] Disseminated mycobacterial infections, even in adults, may resemble HLH and occur due to later-onset immunodeficiencies, including GATA binding protein 2 (GATA-2)

deficiency and IL-12 receptor deficiency.[43] These unique situations are extraordinarily difficult to manage due to the balance of chronic antimicrobial therapy, treatment of hyperinflammation, and definitive management of the underlying immunodeficiency syndrome.

Malignancy-Associated Hyperinflammation

The first reports of HLH were identified in patients with cancer, and malignancy remains the most common trigger of HLH in adults.[55] It occurs predominantly in the context of hematologic malignancies, either at the onset of the cancer, during chemotherapy, or following immune-activating therapies. It is most frequent in lymphomas but can complicate any hematologic malignancy.[38] Additionally, HLH can manifest in the context of solid tumors, particularly after checkpoint blockade therapies.[56] Early identification of these patients is critical, as they face a dire prognosis with a median survival of approximately 2 months from diagnosis.[57]

sHLH can be an early sign of an underlying hematologic malignancy, particularly in hepatosplenic T-cell lymphoma, intravascular large-cell lymphoma, and other challenging-to-diagnose hematologic cancers.[58] A sCD25/ferritin ratio greater than 2 is associated with an underlying lymphoma as the HLH trigger.[59] Therefore, all patients presenting with HLH should undergo an active investigation for an underlying malignancy. This evaluation should include a PET-computed tomography, lymph node biopsy if accessible, bone marrow biopsy, and blind skin biopsies searching for intravascular large B-cell lymphoma. In cases where no alternative diagnosis is identified and a high suspicion of malignancy is present, a diagnostic splenectomy should also be considered (see **Fig. 3**).

In patients with a known hematologic malignancy, diagnosing hyperinflammation is particularly challenging,[60–62] and the OHI index—defined as sCD25 greater than 3900 U/mL and ferritin greater than 1000 ng/mL—can be a valuable tool for the early detection of hyperinflammation, enabling timely intervention.[36] The OHI index identifies a larger portion of patients with hyperinflammation than those identified with traditional diagnostic indices. Emerging evidence suggests that HLH represents only the visible "tip of the iceberg" of toxic hyperinflammation associated with cancer, highlighting the broader spectrum of immune dysregulation in these patients that may be identified with newer tools such as the OHI index.[63]

Although awareness of hyperinflammation in cancer is growing and cases are being identified more frequently,[64] there is still insufficient evidence to guide the development of standardized treatment protocols.[55] As a result, treatment strategies are largely based on expert opinions, single-arm studies, and experiences from individual centers.[65] As data from clinical trials and observational studies accumulate, evidence-based guidelines for managing hyperinflammation in cancer are anticipated to be developed. A key principle in managing malignancy-associated HLH is that treatment should be tailored to the specific clinical context in which the condition arises.[66]

HLH/hyperinflammation at the onset of malignancy is most commonly observed in lymphomas.[38] The standard approach focuses on managing hyperinflammation with agents such as anakinra, corticosteroids, etoposide, or newer therapies, allowing for the prompt initiation of malignancy-directed treatment.[57,63] Despite these interventions, patient outcomes remain suboptimal, with B-cell lymphomas generally associated with better prognoses than T-/NK-cell lymphomas. Although not universally agreed upon, evidence suggests that incorporating etoposide into malignancy-directed protocols, when appropriate, may improve outcomes.[67] Furthermore, testing these patients for EBV by PCR is crucial to identify and address EBV as a potential modifiable trigger.

Hyperinflammation during chemotherapy can occur in multiple hematologic malignancies but is most commonly observed in patients with acute myeloid leukemia undergoing induction therapy, with a reported incidence of 9.2%.[68] Management requires a comprehensive evaluation to identify underlying infectious agents and cautious administration of immunosuppressive therapies. Anakinra and corticosteroids are the preferred treatments in these cases, while etoposide is generally avoided to mitigate potential risks. Intravenous immunoglobulin (IVIG) may also be considered to provide additional immunomodulatory support, particularly in viral infections.

Hyperinflammation associated with immune-activating therapies is becoming increasingly prevalent, particularly with the widespread use of immune-effector cell therapies such as chimeric antigen receptor (CAR) T-cell therapy. This condition is categorized into cytokine release syndrome (CRS) and immune effector cell-associated HLH-like syndrome (IEC-HS). CRS affects up to 90% of CAR T-cell recipients, with severe cases (grades 3–4) occurring in 10% to 30%, typically manifesting within 2 to 3 days of infusion. It is characterized by fever, multiorgan dysfunction, and elevated cytokines, including IL-6, IL-10, and IFN-γ.[69–71] CRS-related mortality is relatively low (1%–3%), and treatment involves tocilizumab, corticosteroids, and supportive care, with anakinra used in refractory cases.[72,73] In contrast, IEC-HS, a rarer but more severe complication with ~3.5% incidence,[74] often develops after CRS and exhibits overlapping symptoms such as persistent fever, cytopenias, and elevated ferritin levels. Differentiating severe CRS from IEC-HS remains challenging due to their shared clinical features and the lack of definitive diagnostic criteria. IEC-HS treatment typically begins with anakinra and corticosteroids, escalating to agents such as ruxolitinib, emapalumab, or etoposide in refractory cases.[75]

Early recognition and prompt, aggressive management are critical for improving outcomes in these life-threatening conditions. Additionally, further translational research and clinical trials are necessary to develop evidence-based guidelines that can enhance the prognoses of these patients.

Rheumatologic Disease-Associated Hyperinflammation

While HLH-associated hyperinflammation is best characterized in the context of sJIA, it has also been described in numerous other rheumatic diseases.[76] In children, juvenile SLE is the second most common rheumatic disease associated with MAS/HLH, and EULAR has developed specific criteria to identify MAS/sHLH in the context of pediatric SLE.[77] In the US adults, 8% to 20% of MAS/sHLH is associated with a preexisting autoimmune disease.[37,78] The 3 most common diagnoses associated with MAS/sHLH are SLE, vasculitis, and rheumatoid arthritis (RA); of these, vasculitis is associated with the highest in-hospital mortality.[78]

Rheumatic diseases are reported as the primary contributor to sHLH in 2% to 26% of patients.[37] This range may be so wide because rheumatologic diseases may represent an underlying immune dysregulation condition in a patient whose acute sHLH episode is triggered by a second factor. Rheumatic diseases associated with sHLH include AOSD, SLE, vasculitis, and RA; inflammatory bowel disease is also reported in association with sHLH.[78] Because some diagnostic tests (ie, autoantibodies) may not return for several days, it is reasonable to initiate a workup relatively early (see **Fig. 3**)—particularly if treatment with IVIG is considered, as this can cause false-positive autoantibody results. If a rheumatologic disease with potential end-organ damage is suspected, early diagnostic testing can also improve long-term outcomes; for example, early diagnosis of SLE can prevent kidney damage from lupus nephritis. Similarly, early identification of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis is critical to prevent rapidly progressive pauci-immune glomerulonephritis and diffuse alveolar

hemorrhage. However, even in patients with underlying autoimmune or autoinflammatory diseases, efforts should be made to identify other acute triggers: patients with underlying rheumatic diseases are susceptible to conventional and opportunistic infections.[79,80]

Anti-inflammatory treatment should be initiated promptly (see **Fig. 5**). Anakinra is a rapid-acting IL-1 receptor antagonist commonly used to treat many autoinflammatory disorders, including sJIA and AOSD.[37] In a retrospective study, anakinra improved survival in sHLH when used as a first-line agent compared with etoposide-based regimens.[81] Because anakinra is a competitive inhibitor that high levels of IL-1b can displace, it is critical to administer anakinra at high enough doses to suppress IL-1 signaling adequately. In children with HLH, dosing starts at 5 to 10 mg per kg per day and is titrated upward to doses as high as 48 mg per kg per day.[37,82] IL-18 is also implicated in HLH/MAS, particularly in sJIA/AOSD, SLE, and other rheumatologic diseases.[18] The bispecific IL-1/IL-18 blocker MAS825 has been reported effective in refractory sHLH/MAS, although clinical trials are still ongoing.[83,84]

At high doses, anakinra may cause rare side effects like suppressed blood cell counts or hepatotoxicity,[85] which could be mistaken for sHLH symptoms. Anakinra and other IL-1 blockers can also rarely be associated with lung disease in sJIA/AOSD patients, raising concern for sHLH.[37] Like HLH, this lung disease is mediated by IFN-γ and IL-18, but unlike HLH, IL-1 and IL-6 blockers may increase its risk.[86] The pathogenesis is unclear, with hypotheses suggesting hypersensitivity or "cytokine plasticity." While guidelines do not recommend stopping anakinra in these cases, some experts adjust therapies.[86] This remains an area of ongoing research.

Underlying genetic conditions predisposing to hyperinflammation

As noted earlier, FHL is primarily associated with genetic impairment of granule-dependent cytotoxicity. However, increasing genetic complexity has been recognized in pediatric patients with HLH, where some genetic defects affect the inflammasome (XIAP, NLRC4, and CDC42), while others affect T-cell signaling/activation (SH2D1A, ITK, MAGT1, etc), and others alter macrophage phenotypes (HMOX1 and SLC7A7). Additionally, HLH is increasingly recognized in patients with a variety of primary immune deficiencies (especially chronic granulomatous disease) and deep-seated or intractable infections. With both classic FHL and these other genetically defined etiologies of HLH, most patients present during childhood. However, with both classic and most nonclassic genetic causes of HLH, initial presentations in adulthood have been described.[87–93] Thus, consideration of germline genetic etiologies in adult patients may be warranted, especially in young adults or in the absence of clear nongenetic etiologies.

Most cases of HLH in adults are not known to be associated with germline genetic abnormalities.[94] However, in many reported cases, ambiguous or single-allele germline abnormalities in HLH-associated genes are reported in adults with sHLH.[95] Whether these abnormalities are relevant, perhaps as predisposing factors in combination with other factors/triggers, remains uncertain. Acquired genetic abnormalities in either malignant or nonmalignant cell types may be of even greater relevance to sHLH in adults than germline abnormalities. Acquired genetic abnormalities in hematopoietic cells in the absence of malignancy, so-called clonal hematopoiesis of indeterminant potential (CHIP), have been observed at elevated frequencies in patients with adult-onset sHLH.[96] More recently, somatic variants in *UBA1* were found to cause an adult-onset autoinflammatory and hematologic disease called VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome. HLH has been reported in the context of this disease.[97,98] In some cases, somatic variants

can coexist with other underlying causes. For example, clonal hematopoiesis has been reported in an adult patient with sHLH in the context of CVID related to LRBA.[99] The role of germline and somatic variants as acute triggers of sHLH and underlying immune dysregulation predisposing patients to HLH is under continued investigation and may become clearer over time.

The role of genetic testing in adult-onset HLH remains unclear. On the one hand, genetic conditions are thought to be underrecognized in adults, and identification can have important treatment implications. Conversely, the chance of identifying an actionable genetic cause of HLH in an adult patient is relatively low. Red flags for genetic etiologies include relatively young age, atypical/opportunistic or recurrent infection, central nervous system (CNS) involvement, family history, and consanguinity. VEXAS syndrome should be suspected in older male patients with *characteristic autoinflammatory features* (ie, relapsing polychondritis, neutrophilic dermatosis, and relapsing polychondritis) or myelodysplastic syndrome (persistent thrombocytopenia and macrocytic anemia), especially if these preceded the development of HLH. Testing for other somatic variants (eg, CHIP) does not currently exist outside research studies. Functional testing may be valuable when considering the presentation of classic FHL in adult patients. Function of the degranulation pathway or specific proteins (eg, perforin, XIAP, and SAP) can be measured directly.

Calming the hyperinflammation

Once sHLH is diagnosed, efforts to identify both the acute trigger and any underlying condition should be initiated in parallel with treatment aimed at rapidly interrupting the hyperinflammatory cycle to prevent end-organ damage. While glucocorticoids (GCs) are considered the mainstay of anti-inflammatory therapy, many physicians choose to start therapy with anakinra to avoid compromising diagnostic procedures of the underlying triggers. Anakinra has a minimal side effect profile and can be initiated in doses of 200 mg q8-12. In a recent large, population-based, multicenter, retrospective study, anakinra treatment resulted in a significantly higher 1-year overall survival than etoposide-based therapies in adults with sHLH.[81] However, as the authors note, this study was hampered by the fact that there was insufficient clinical detail to determine the triggers in patients without malignancy (all patients with malignancy received accompanying chemotherapy), and other small studies have shown that anakinra is especially effective in patients with MAS.[100] The role of single-agent anakinra in other forms of sHLH in adults remains to be determined.

GC is given in doses ranging from high dose (1–2 mg/kg per day) to “pulse” dose (up to 1 g of methylprednisolone daily), while dexamethasone is initiated at 10 mg/m^2. Specific regimens and routes of administration are chosen and adjusted based on individual patient factors. For example, if CNS involvement is suspected, dexamethasone may be chosen based on its superior CNS penetration relative to methylprednisolone. GCs have dose-dependent side effects and can obscure diagnostic testing—particularly for underlying malignancy. Therefore, diagnostic testing should be attempted, whenever possible, before the initiation of GCs, and patients should be treated with the lowest effective dose. Nonetheless, in very severe cases, pulse-dose dexamethasone or methylprednisolone are often required.[37] Etoposide, one of the first therapies tested for HLH, also remains an option and continues to be used as primary therapy at many centers. It also shows efficacy in refractory cases, particularly malignancy-associated HLH or EBV-HLH, in single doses for rapidly deteriorating patients or within the HLH-94/2004 protocols.[101]

A second immunomodulator can be considered in patients not responding to high doses of anakinra and/or GCs and/or etoposide or in whom these therapies cannot

be tapered. Given the central role of IFN-γ in HLH pathogenesis, it is no surprise that 2 key treatments for refractory HLH target this cytokine and downstream signaling: pathways. Emapalumab is a monoclonal anti-IFN-γ antibody that is FDA-approved for primary HLH and has shown efficacy in clinical trials for AOSD/sJIA-associated sHLH/MAS.[86] Emapalumab has also been used to treat EBV-related and malignancy-related HLH[102,103]; however, no studies confirm its efficacy in adult patients. IFN-γ activates STAT1 via JAK1 and JAK2; the JAK inhibitor ruxolitinib has shown efficacy for autoimmunity and autoinflammation-associated HLH, virus-associated HLH, and malignancy-associated HLH.[104,105] While ruxolitinib was not tested in large studies in adult HLH, there are increasing reports of small cohorts demonstrating significant efficacy.[106] Other therapies used for refractory HLH include alemtuzumab, calcineurin inhibitors, IVIG, and rituximab—particularly for EBV-associated HLH.[37]

Monitoring and de-escalation of therapy for HLH also has no standardized approach.[37] Where possible, conventional disease activity parameters (ie, complete blood count, ferritin, triglycerides, fibrinogen, and C-reactive protein [CRP]) are monitored at least daily. HLH-specific biomarkers like CXCL9 and IL-18 are monitored less frequently, although CXCL9 levels can help guide the dosing of IFN-targeted therapies. Once patients have achieved clinical remission, HLH-directed therapies can be slowly weaned with the ultimate therapeutic plan dependent on the underlying immune dysregulation condition. In patients in whom underlying infectious triggers have been identified, treatment of the infectious trigger can often allow immunomodulatory therapy to be titrated back to basal, pre-HLH regimens. Patients with malignancy-associated HLH require antineoplastic therapy, while patients with genetic conditions may benefit from other targeted therapies or hematopoietic stem cell transplantation. Patients with sJIA/AOSD are typically transitioned to outpatient IL-1 or IL-6 blocking therapies, while patients with SLE are typically treated with conventional disease-modifying antirheumatic drugs like mycophenolate mofetil.

A role for allogeneic hematopoietic stem cell transplantation?

FHL present during childhood requires allogeneic hematopoietic stem cell transplantation (HSCT) for long-term cure. Due to the severity of the underlying immune abnormalities, these patients will inevitably and fatally recur if not corrected. The role of HSCT in treating adults with sHLH is less clear. A comprehensive review in this series discusses the role of HSCT in both adults and children in detail.[107] One would certainly consider allogeneic HSCT in adults with HLH as a salvage therapy in those with refractory disease or as a consolidative therapy in those with reactivating disease. This is perhaps the most important role of HSCT in this patient population. Several larger case series/reviews have suggested that HSCT may improve survival in adult patients with sHLH.[108–110] In adult patients, specifically with EBV-associated HLH, there appears to be important utility for this therapy.[111] Overall, this area has limited data, and clinical judgment remains central to considering HSCT. Due to the possible need for HSCT, referral for transplant consideration, HLA typing, and assessment of donor options early during the course of HLH should be considered optimal management.

SUMMARY

sHLH, predominantly affecting adults, requires a trigger-based diagnostic and therapeutic approach. While suppressing the hyperinflammatory process is often critical to preventing organ damage, identifying and treating the underlying trigger is paramount for long-term success. Emerging trigger-based protocols are refining the management of sHLH by integrating targeted diagnostics and therapies.

CLINICS CARE POINTS

- *Think hemophagocytic lymphohistiocytosis (HLH) early*: HLH diagnosis requires clinical suspicion; failure to consider it will delay identification and treatment.
- *Discriminate inflammation*: Not every inflammatory state equates to HLH.
- *Secondary hemophagocytic lymphohistiocytosis is mostly a complication of the underlying condition, not a standalone diagnosis.*
- *Assess immunosuppression need*: Evaluate whether the patient will benefit from immunosuppressive therapy at diagnosis and during disease progression.
- *Use biomarkers for monitoring*: Early assessment of sCD25 and repeated ferritin measurements are crucial for diagnosing and monitoring HLH activity.
- *Leverage the Optimized Hyper Inflammatory (OHI) index*: The OHI index aids in early diagnosis of malignancy-associated hyperinflammation.
- *Focus on triggers*: Always identify and address the underlying triggers, particularly EBV and lymphoma, as these are common culprits.
- *Prioritize trigger-directed therapy*: Targeted treatments addressing the root cause improve outcomes and prevent relapse.
- *Consider hematopoietic stem cell transplantation*: Evaluate eligibility for transplantation early in the disease course.

DISCLOSURE

A. Zoref-Lorenz received consulting fees from Sobi Inc and is on their Adult HLH Advisory Board. J. Rocco is on Sobi's Adult HLH Advisory Board. M. Jordan received consulting fees and research support from Sobi, Sweden and is on their Adult HLH Advisory Board.

DISCLOSURE

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