

Hemophagocytic Lymphohistiocytosis for the Internist and Other Primary Care Providers

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) syndrome is a hyperinflammatory state that leads to life-threatening, disproportionate activation of the immune system and may be confused for and concomitantly exist with sepsis. However, its treatment differs from sepsis, requiring early initiation of immunosuppressive treatment. While HLH syndrome is more commonly diagnosed in children, internists and other primary care providers must be familiar with the diagnosis and treatment of adult patients with HLH in the hospital and outpatient setting. In this article, we review the essentials that an internist and other primary care providers managing adult HLH patients should know.

Keywords

hemophagocytic lymphohistiocytosis, HLH, primary care

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Essentials of Hemophagocytic Lymphohistiocytosis for the Primary Care Provider

Hemophagocytic lymphohistiocytosis (HLH) syndrome is characterized by uncontrolled activation of the immune system that leads to a hyperinflammatory state, distinguished from autoimmunity by the lack of specific activation against the self.^{1,2} Typically, diagnostic evaluation and initial treatment of HLH are completed in an inpatient or acute care setting due to the syndrome's imminent threat to life. Primary care providers may find themselves intimidated by the prospect of caring for patients with HLH after discharge from the hospital. Here, we endeavor to provide a primer regarding HLH, from diagnosis to treatment and outpatient follow up, for primary care providers.

Overview

Animal models have shown that HLH is caused by overactive CD8+ T cells, leading to the overactivation of macrophages through interferon-gamma; thus, it is the immune system, not an infection or malignancy, that drives HLH.^{2,3} The most substantive HLH literature has centered on pediatric populations, although epidemiologic studies of HLH

are sparse overall.² Pediatric patients usually develop the primary, or familial/heritable, form of HLH, which is defined by immune deficiencies.^{4,5} When observed in adolescent and adult patients, HLH generally is acquired, secondary to such causes as autoimmune disease, malignancy with special emphasis on lymphomas, infections, especially EBV, and/or the so-called cytokine release syndrome, associated with novel cancer treatments such as chimeric antigen receptor T cell (CAR-T) immunotherapy.^{1,5} Of all of the conditions commonly associated with HLH, malignancy carries the poorest prognosis and accounts for up to 70% of adult cases.⁵

It is challenging to characterize the incidence and prevalence of HLH in the adult population due to suspected underdiagnosis and high mortality prior to the relatively recent introduction of chemotherapy as a cornerstone of treatment. A retrospective analysis of the 2016 United States National Inpatient Sample showed that 330 adult cases, with a mean age of 50.1, were diagnosed during

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Table 1. Diagnostic Criteria for HLH Syndrome.

HLH-2004 diagnostic criteria	HScore criteria
1. An HLH-associated molecular diagnosis	1. Known underlying immunosuppression
2. Fulfillment of 5 out of 8 diagnostic criteria:	2. Degree of temperature elevation
A. Fever	3. Hepatomegaly and/or splenomegaly
B. Splenomegaly	4. Number of cytopenias
C. Cytopenias affecting at least 2 of 3 peripheral cell lines: Hemoglobin <90 g/L Platelets <100 × 10 ⁹ /L Neutrophils <1.0 × 10 ⁹ /L	5. Degree of hyperferritinemia
D. Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides ≥265 mg/dL Fibrinogen ≤1.5 g/L	6. Degree of hypertriglyceridemia
E. Hemophagocytosis in bone marrow, spleen, or lymph nodes without evidence of malignancy	7. Hypofibrinogenemia
F. Low/no natural killer cell activity	8. Elevated aspartate aminotransferase
G. Ferritin ≥500 µg/L (9083 µg/L in ICU patients per Knaak et al)	9. Presence of hemophagocytosis on bone marrow aspirate
H. Soluble CD25 (IL-2 receptor) ≥2400 U/mL	

hospitalization in 1 year.⁶ Similarly, a 2014 meta-analysis of 775 international cases by Ramos-Casals et al⁷ calculated a mean age at diagnosis of 49.03. In both studies, the sample population was predominantly male, with women making up 37% of Ramos-Casals' cohort and 44% of the NIS cohort, although women did comprise 70% of the latter's subset with autoimmune disease-associated HLH. Although reliable data pertaining to HLH's prevalence in American adult outpatient practice were not readily available at the time of this writing, a retrospective study of 86 patients with HLH in the Polish Adult Leukemia Group demonstrated a median survival of 144 days; 29 patients (33.7%) survived at least 1 year, with only 2 of these 29 ultimately dying, both of HLH relapse.⁸ Thus, it can be concluded that a significant percentage of HLH patients does survive to the point of requiring outpatient surveillance, and that ongoing surveillance is necessary to detect deadly HLH relapse.

HLH is a distinct entity from sepsis, but the 2 conditions may coexist.⁹ Since the treatment of HLH differs from that of sepsis, it is essential for providers to maintain an elevated index of suspicion for HLH in septic patients who do not improve despite control of the infectious source, initiation of appropriate antibiotic therapy, and fluid administration.

Diagnosis

A patient must fulfill of 1 or both of the following HLH-specific criteria in order to be diagnosed with HLH syndrome: a molecular diagnosis consistent with HLH; and/or 5 out of 8 HLH-2004 criteria (Table 1).¹⁰ Importantly, the presence of hemophagocytosis on bone marrow aspirate is not required to make the diagnosis, with a sensitivity of 83% and specificity of only 60%.^{11,12} The HLH-2004 protocol, formulated by Henter et al,¹³ is a widely accepted revision of

1990s-era criteria and includes treatment guidelines. Henter et al¹³ defined hyperferritinemia somewhat arbitrarily as ≥500 µg/L, but later evidence by Knaak et al¹⁴ demonstrated that a ferritin cutoff of 9083 µg/L has optimal sensitivity and specificity (92.5% and 91.9%, respectively) in ICU patients. However, the HLH-2004 protocol focuses on the pediatric population. In the adult, "secondary" HLH population, the HLH-2004 protocol must be utilized with recognition of possible limitations. In the last decade, the HScore, developed by Fardet et al,¹⁵ has emerged as a useful risk assessment tool. It incorporates 3 clinical, 5 biologic, and 1 cytologic variables to estimate a patient's risk of having HLH, with each variable being assigned a certain number of points (Table 1). An HScore cutoff of 169 is associated with 93.0% sensitivity and 86.0% specificity in non-ICU patients, while an HScore of 168 has been found to confer 100% sensitivity and 94.1% specificity in a cohort of ICU patients.^{14,15} Figure 1 outlines an algorithm for HLH management from diagnosis, which relies on HLH-2004 criteria with supplementary risk assessment using the HScore, through treatment, and follow up.

Often, patients meet 4 of the 8 HLH-2004 criteria even without obtaining specialized molecular testing such as natural killer cell function and soluble CD25. Typically, these are send-out studies that are performed in specialized laboratories,¹⁶ so results may not be available for more than 24h. Suspicion for HLH syndrome in these cases should remain high. According to Knaak et al,¹⁴ fulfillment of 4 HLH-2004 criteria even without confirmatory genetic or molecular testing has 95% sensitivity and 93.6% specificity for diagnosis. Therefore, it is reasonable for providers to consult a hematologist in such cases to proceed with HLH-directed treatment, particularly if a patient's clinical status is deteriorating rapidly.

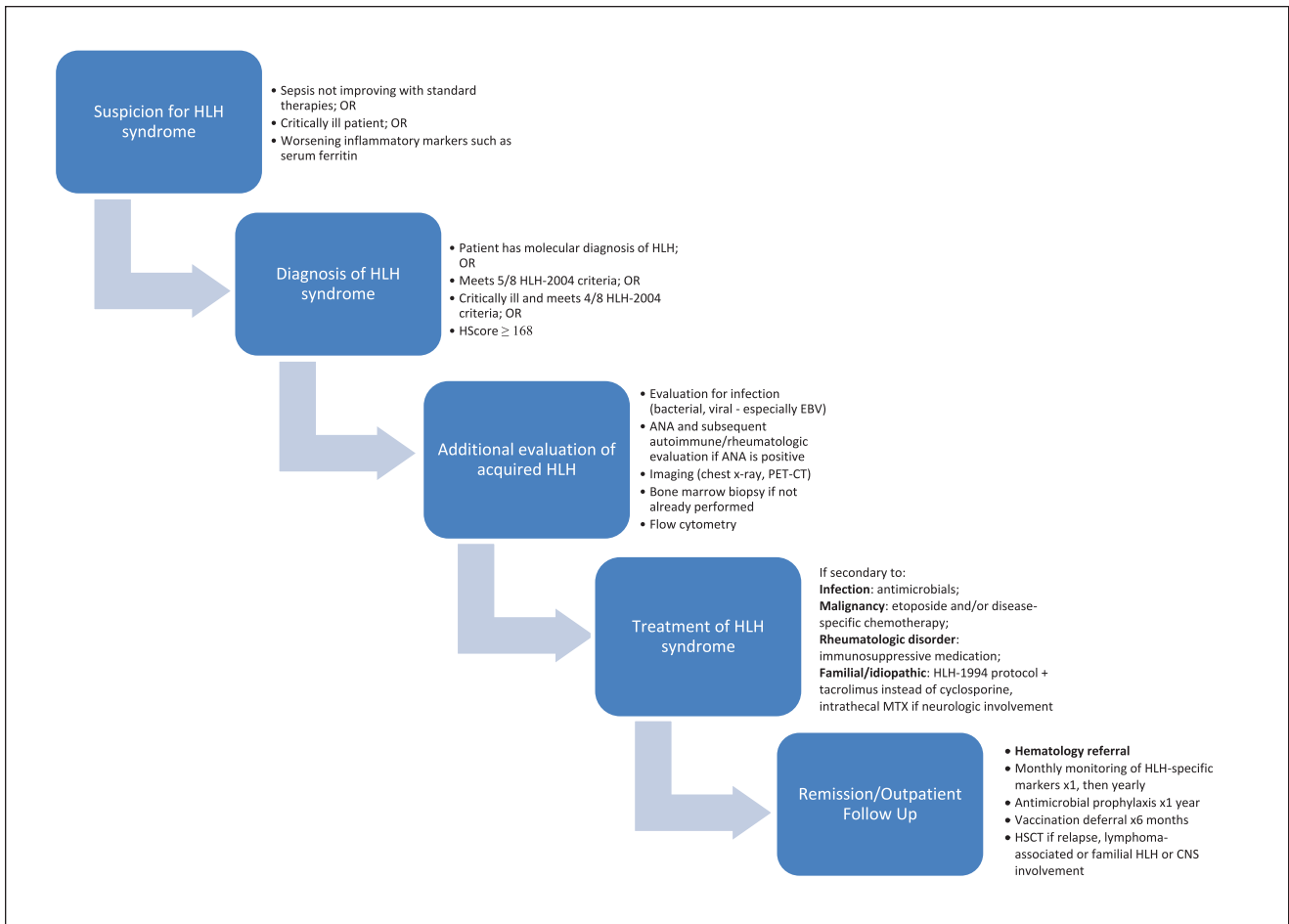


Figure 1. Algorithm for the management of HLH syndrome in adults.

The differential diagnosis of HLH syndrome is broad and includes sepsis and macrophage activation syndrome (MAS). While sepsis may lead to cytopenias, fever, and hepatic dysfunction, serum ferritin levels typically do not increase to the same degree as in HLH syndrome, and leukocytosis, rather than leukopenia, is more commonly seen in sepsis.⁹ Given the overlap between sepsis and HLH syndrome, serum ferritin should be checked in septic patients, particularly those with cytopenias and/or splenomegaly who do not improve despite treatment.¹⁷ MAS is a hemophagocytic syndrome that occurs in the setting of a rheumatologic disorder and should be considered in a severely ill patient with known rheumatologic disease or suggestive features such as a rash or arthralgias.¹⁸

Treatment

Treatment delays in a patient with worsening clinical status and a high likelihood of HLH may result in increased morbidity and/or mortality. According to the HLH-2004 protocol, immunosuppression in the form of intravenous

corticosteroids, specifically dexamethasone for increased central nervous system penetration, and etoposide, a chemotherapeutic drug that acts against T cell proliferation, is the mainstay of initial treatment.^{5,13,19} Treatment guidelines for adult patients are based on the HLH-1994 protocol and include the addition of intrathecal methotrexate for HLH-induced neurologic dysfunction.¹⁰ Tacrolimus, a calcineurin inhibitor preferred to cyclosporine in adults due to reduced risk of nephrotoxicity, is generally added after 2 to 3 months of treatment.

Consensus guidelines suggest that the treatment regimen should consider adult patients' comorbidities and risk of organ failure, which may mean reductions in dose and duration of therapy.⁵ Increasingly, alternative therapies are being considered, including anakinra, an IL-1 receptor antagonist.²⁰ Some pediatric studies suggest that anakinra possesses an improved safety profile and mortality benefit compared to etoposide and other emerging therapies for HLH, at least with regard to myelosuppression and hepatotoxicity, and should be considered as an option for first-line treatment.²¹⁻²⁴

Outpatient Follow-up Care

Upon recovery and discharge from the hospital, patients will see their primary care provider for close follow-up. The risk of HLH relapse is highest within 1 year of disease remission, so HLH-specific markers such as serum ferritin should be monitored at least monthly during the first year, followed by at least annual monitoring.¹⁰ Other factors that should prompt concern for possible HLH relapse include fevers of unknown source and new cytopenias, while poor prognostic markers that necessitate closer outpatient surveillance include low serum albumin, which may suggest poor synthetic function secondary to HLH-associated liver dysfunction or malnutrition, and a history of malignancy-associated HLH.²⁵ Evaluation for the etiology of secondary HLH should continue if it has not yet been elucidated, even if the patient has completed treatment.⁵ In patients with central nervous system (CNS) involvement, cerebrospinal fluid analysis to assess for post-treatment disease activity should be completed.¹⁰ *Pneumocystis jirovecii* Prophylaxis against opportunistic infections such as viruses, fungi, and is advised, as initial treatment for HLH leads to immunocompromise.⁵ Immunizations should be deferred for at least 6 months after remission, as some case reports highlight reactivation of HLH syndrome after common adult vaccinations such as the influenza and COVID-19 vaccines.²⁶⁻²⁸

All patients should be referred to a hematologist as soon as possible following hospitalization to continue HLH-specific treatment if indicated, assist primary care providers with close monitoring for relapse, and assess for hematological malignancy in patients with acquired HLH of unknown etiology. Even if general practitioners may be limited as far as therapies that they can offer to patients who relapse, they can provide comfort and support to patients' families. Hematopoietic stem cell transplantation (HSCT) generally is indicated in the event of relapse, lymphoma-associated HLH, or CNS involvement.^{5,10} All patients should undergo testing for genetic causes of HLH if history, physical examination, and initial testing are consistent with HLH syndrome, but genetic counseling for the patient's relatives also may be considered if there is a suspicion for familial HLH syndrome.²⁹ Diagnosis of familial HLH is an indication for HSCT.¹⁰

Conclusions

Based on a study of 151 patients with mean follow-up time of 17 months, acquired HLH syndrome in adults carried an all-cause mortality rate greater than 50%, with the specific mortality rate varying by the etiology of HLH and subsequent complications.³⁰ Given this statistic, outpatient care of adult HLH patients may seem daunting to primary care providers. Improving providers' understanding of the basic mechanisms and management of HLH syndrome may

increase confidence as it pertains to these patients' follow-up care and prevent misdiagnosis and undertreatment of this condition that is likely to be significantly underdiagnosed. As patients transition from inpatient to outpatient management, collaborative care between the primary care provider and a board-certified hematologist and/or medical oncologist is necessary to ensure that relapse is not missed and that a full course of treatment, which may require HSCT, is completed.

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