Hemophagocytic Lymphohistiocytosis

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• ***Context.***—**Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening disorder of immune regulation that can eventually result in end-organ damage and death. HLH is characterized by uncontrolled activation of cytotoxic T lymphocytes, natural killer cells, and macrophages that can lead to a cytokine storm. The diagnosis of HLH is often challenging due to the diverse clinical manifestations and the presence of several diagnostic mimics. The prognosis is generally poor, warranting rapid diagnosis and aggressive management.**

Objective.—**To provide a comprehensive review of the pathogenesis, clinical features, diagnosis, and management of HLH.**

Data Sources.—**Peer-reviewed literature.**

Conclusions.—**HLH is a condition where a complete understanding of the pathogenesis, early diagnosis, and proper management has an important role in determining patient outcome. Genetic mutations causing impairment in the function of cytotoxic T lymphocytes and natural killer cells have been identified as the root cause of familial HLH; however, the specific pathogenesis of acquired HLH is unclear. The HLH-2004 protocol used in the diagnosis of HLH was originally developed for the pediatric population. The HLH-2004 protocol still forms the basis of the diagnosis of HLH in adults, although its use in adults has not been formally validated yet. Treatment of HLH is primarily based on the HLH-94 protocol, which involves suppressing the inflammatory response, but the treatment needs to be modified in adults depending on the underlying cause and comorbidities.**

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Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal disorder characterized by a dysregulated activation of cytotoxic T lymphocytes, natural killer (NK) cells, and macrophages resulting in hypercytokinemia and immune-mediated injury of multiple organ systems. Definitive diagnosis is often delayed because the symptoms are often atypical and polymorphous.[1] Pathologic evaluation and recognition of hemophagocytic histiocytes is a key component of the diagnosis; however, published literature suggests that marrow evaluation for hemophagocytic histiocytes has poor correlation with disease probability overall.[2]

The first case of HLH was reported in a child in 1939 by Scott and Robb-Smith,[3] who described the child as having a neoplastic histiocytic disorder. The disease was initially termed histiocytic medullary reticulosis. The disease was identified to be familial by Farquhar and Claireaux[4] in 1952. For a long time, HLH had been considered a purely familial disorder occurring in the pediatric population. The identification of acquired HLH and the effect of immune triggers in the disease pathogenesis has only been recent. The significance of this finding lies in the fact that adults comprise 40% of HLH cases.[5]

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The existing literature on HLH shows how far we have come in understanding this disorder; however, it also brings to light how much is still unknown. This article provides a broad review that covers the important aspects of HLH with a focus on the recent advances in the pathogenesis, diagnosis, and treatment.

EPIDEMIOLOGY

According to epidemiologic studies conducted in the pediatric population, the incidence of HLH ranges from 1 to 225 per 300 000 live births and appears to vary depending on the geographic region.[6–8] The mean age of occurrence of HLH in children is 1.8 years, as reported by a retrospective study conducted in Texas by Niece et al.[9] Pediatric HLH is equally distributed among both the sexes.[6] There are fewer studies that document the epidemiology of HLH in adults. A review of multiple patient cohorts suggests a mean age at presentation of approximately 50 years, with a predominance in males[10] except for macrophage activation syndrome (MAS), a subset of HLH that is more frequently observed in women.[11] The incidence of HLH in adults is estimated to be 1 out of every 2000 adult admissions at tertiary medical centers.[12] There has not been a clear racial or ethnic predilection observed in HLH. The racial distribution of HLH observed in the various studies tends to coincide with the racial demographics of the geographic location of the study.[1]

TYPES OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

HLH has been traditionally classified as primary and secondary. Primary HLH is also known as familial HLH (F-HLH). F-HLH is caused by genetic mutations inherited in a

Table 1. Genetic Mutations Associated With Hemophagocytic Lymphohistiocytosis (HLH)[a]

Disease	Inheritance	Cytogenetic Localization	Involved Gene	Protein	Function
Familial HLH type 1	AR	9q21.3-22	Unknown	Unknown	Unknown
Familial HLH type 2	AR	10q21-22	*PRF1*	Perforin	Pore formation
Familial HLH type 3	AR	17q25	*UNC13D*	Munc13-4	Granule priming
Familial HLH type 4	AR	6q24	*STX11*	Syntaxin-11	Granule fusion
Familial HLH type 5	AR	19p13.2	*STXBP2*	Munc18-2	Granule fusion
Chediak-Higashi syndrome	AR	1q42-43	*LYST*	LYST	Granule trafficking
Griscelli syndrome type 2	AR	15q21	*Rab27A*	Rab27A	Granule docking
Hermansky-Pudlak syndrome type 2	AR	5q14.1	*AP3B1*	AP3B1	Granule trafficking
X-linked lymphoproliferative disease type 1	XLR	Xq25	*SH2D1A*	SAP	Signaling in T and NK cells
X-linked lymphoproliferative disease type 2	XLR	Xq25	*BIRC4*	XIAP	Signaling pathways involving NF-κB
IL-2-inducible T-cell kinase deficiency	AR	5q34	*ITK*	ITK	Signaling in T cells
CD27 deficiency	AR	12p13	*CD27*	CD27	Lymphocyte costimulatory molecule
NLRC4-MAS[b]	AD	2p22.3	Gain of function mutation of *NLRC4*	NLRC4	Inflammasome activation
Adenosine deaminase deficiency	AR	20q13.11	*ADA*	ADA	Metabolism of nucleic acids
Purine nucleoside phosphorylase deficiency	AR	14q13.1	*PNP*	PNP	Metabolism of nucleic acids
IL-2Rα chain (CD25) deficiency	AR	10p15–14	*IL-2RA*	IL2Rα	T-cell activation and regulation
Common γ chain deficiency	XLR	Xq13	*IL-2RG*	IL2Rγ	IL-2R: T-cell activation and regulation
Wiskott-Aldrich syndrome	XLR	Xp11.23–22	*WASP*	WASP	Cytoskeleton
DiGeorge syndrome	AD	22q11.2	*DCGR*	Unknown/various	Unknown/various
X-linked agammaglobulinemia	XLR	Xq21.3-q22	*BTK*	BTK	B-cell maturation and proliferation
Hyper-IgD syndrome	AR	12q24	*MVK*	Mevalonate kinase	Cholesterol and lipid synthesis
Lysinuric protein intolerance	AR	14q11.2	*SLC7A7*	y+LAT-1	Transport of amino acid
Multiple sulfatase deficiency	AR	3p26	*SUMF1*	FGE	Transcriptional activation of sulfatase
Cobalamin C disease	AR	1p	*MMACHC*	MMACHC	Metabolism of vitamin B12
Holt-Oram syndrome	AD	12q24.1	*TBX5*	TBX5	Promotes cardiomyocyte differentiation
Heme oxygenase-1 deficiency	AR	22q13.	*HMOX1*	HMOX1	Oxidation of heme to biliverdin

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; IL-2, interleukin-2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK cell, natural killer cells; XLR, X-linked recessive.

[a] Modified from Al-Samkari and Berliner,[1] Ishii,[14] and Morimoto et al.[121]

[b] NLRC4-MAS—though associated with a genetic mutation produces a macrophage activation syndrome–like clinical picture.

homozygous or compound heterozygous pattern, resulting in disruptive mutations that fully eliminate the function of cytotoxic T cells and NK cells.[1] The frequency of these mutations varies with different ethnicities. In North America, *PRF1* mutations are the most common followed by *UNC13D* and *STX11*.[13] Primary HLH is also associated with various immunodeficiency disorders. Some of the genetic mutations causing HLH have been identified, which are outlined in Table 1. F-HLH is diagnosed during the first year of life in 70% to 80% of cases. However, the diagnosis of F-HLH cannot be excluded in a patient with age greater than 1 year.[14]

Secondary or acquired HLH arises because of external triggers like infection, malignancy, rheumatologic disease, postallogeneic hematopoietic stem cell transplantation (HSCT), drug hypersensitivity, or other underlying causes. The most common infectious agent associated with HLH is the Epstein-Barr virus (EBV). HLH triggered by EBV infection is more frequently seen in children and adolescents harboring gene mutations associated with F-HLH and primary immune disorders like X-linked lymphoproliferative syndromes type 1 and 2.[15] In adults, EBV-associated HLH is most often caused by EBV reactivation due to immunosuppression.[5] Of note, the lymphocytes infected in EBV that cause HLH are predominantly T cells in the Asian population and B cells and T cells equally in the Caucasian population.[16] HLH is also associated with infections by other viral, bacterial, parasitic, and fungal infections. A cytokine storm similar to that seen in HLH has been reported in patients with severe COVID-19 infection. The cytokine storm seen in COVID-19 patients is characterized by increased interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, interferon (IFN)-γ inducible protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 α, and tumor necrosis factor (TNF)-α.[17] IL-6 has been shown to play an important role in the progression of COVID-19 to acute respiratory distress syndrome.[18] A study by Clark et al[19] that assessed the HScore, a diagnostic scoring system for HLH, in 152 patients with COVID-19 infection observed that patients with severe disease admitted in the intensive care unit had a higher HScore than patients with mild disease. However, the HScore of the vast majority of patients, including patients admitted in the intensive care unit, did not

Table 2. Important Causes of Acquired Hemophagocytic Lymphohistiocytosis (HLH)[a]	
Secondary HLH	**Inducer**
Infection-associated	Virus: Epstein-Barr virus, cytomegalovirus, and other viruses from the Herpesviridae family, adenovirus, human immunodeficiency virus, parvovirus, measles virus
	Bacteria: *Brucella*, *Rickettsia*, *Leptospira*, *Mycobacterium*, *Borrelia*, *Bartonella*, *Listeria*, *Mycoplasma*, *Ehrlichia*
	Parasites: *Leishmania*, *Malaria*, *Toxoplasma*, *Babesia*
	Fungi: *Candida*, *Cryptococcus*, *Penicillium*, *Pneumocystis*, *Histoplasma*
Malignancy-associated	Hematologic malignancies
	T-cell lymphomas: peripheral T-cell lymphoma, primary cutaneous γδ-T-cell lymphoma, anaplastic large cell lymphoma, lymphoblastic lymphoma, angioimmunoblastic T-cell lymphoma
	B-cell lymphomas: commonly diffuse large B-cell lymphoma
	B- and T-cell leukemias
	NK-cell lymphoma/leukemias
	Hodgkin lymphoma
	Myeloid neoplasia
	Others: Langerhans cell histiocytosis, histiocytic sarcoma, multicentric Castleman disease
	Solid tumors
Autoimmune disease-associated	Systemic-onset juvenile idiopathic arthritis, adult-onset Still disease, systemic lupus erythematosus, vasculitis
Transplant-associated	Immunological reaction at engraftment, graft-versus-host disease
Drug-associated	Carbamazepine, phenobarbital, sulfamethoxazole, cancer immunotherapy drugs

[a] Modified from Al-Samkari and Berliner,[1] Morimoto et al,[121] Gosh et al,[122] and Wang et al.[123]

approach the diagnostic threshold for HLH. Nevertheless, screening for hyperinflammation is recommended in patients with severe COVID-19 infection by measuring serum ferritin levels, erythrocyte sedimentation rate, HScore, and by monitoring for a decreasing trend in the platelet count. Studies have shown that in patients with signs of hyperinflammation, corticosteroids, anakinra, tocilizumab, JAK inhibition, and intravenous immunoglobulin may be beneficial.[20] Malignancies, seen in 45% of cases, are the most common cause of HLH in adults.[21] In children, malignancies are a less common cause for HLH and are only seen in 8% of cases.[21] Malignancies cause HLH through increased production of proinflammatory mediators by the tumor cells or by the loss of inhibitory immune regulation or as the result of bone marrow dysfunction due to therapy.[22] Hematologic malignancies are more common triggers of HLH than nonhematologic malignancies. Hematologic malignancies associated with HLH include both lymphoid and myeloid neoplasms.[1] According to data from a systematic review in adult patients with HLH, 93.7% of cases of malignancy-associated HLH are because of an underlying hematologic neoplasm. Solid tumors and nonspecified neoplasms account for 3.1% and 3.2% of malignancy-associated HLH. Among the hematologic neoplasms, T-cell or NK-cell lymphoma or leukemia are the most common (35.2%), followed by B-cell lymphoma (31.8%), other nonspecified hematologic neoplasms (14.4%), leukemia (6.4%), and Hodgkin lymphoma (5.8%).[5] While diagnosing malignancy-associated HLH, it is important to know that EBV viremia can sometimes coexist with a malignancy and that sCD25 can sometimes be disproportionately elevated compared with other markers of HLH in patients with occult lymphomas. Malignancy-associated HLH is associated with a rapidly deteriorating clinical course and high mortality rates, thus, necessitating immediate HLH-directed and malignancy-directed therapy. HLH, when associated with rheumatologic conditions, is commonly known as MAS. Immune dysfunction owing to autoimmune conditions is considered to be the primary mechanism precipitating HLH in these patients. Acquired dysfunction in perforin-mediated cytolysis has also been identified in some patients with MAS.[23] Important causes of secondary HLH are outlined in Table 2.

The terms "primary" and "secondary," though used widely, is not preferred by many as it is said to oversimplify the pathogenesis of HLH and lacks clarity from a clinical standpoint. The members of the HLH committee from the North American Consortium for Histiocytosis have recommended a new classification system for HLH, which categorizes those syndromes that respond to immunosuppressive treatment as "HLH disease." Conditions that do not respond or are unlikely to respond to immunosuppressive therapy are designated as "HLH mimics." "HLH disease" includes further subgroups, such as F-HLH or familial HLH with clear genetic etiology, M-HLH or HLH associated with malignancy, Rh-HLH or HLH associated with rheumatologic conditions (also called MAS), Rx-HLH or HLH observed after immune-activating therapies (iatrogenic HLH, also called cytokine release syndrome), IC-HLH or HLH associated with immune compromise (either primary immune deficiency or treatment-related immune suppression), and HLH not associated with other specific conditions (HLH-NOS). Mild HLH/MAS and forme fruste HLH refer to syndromes that resemble HLH but do not fulfil the diagnostic criteria. The North American Consortium for Histiocytosis recognizes that there is potential for overlap among the various subgroups of HLH with each other and with the HLH mimics.[24]

PATHOPHYSIOLOGY

Familial Hemophagocytic Lymphohistiocytosis

Impairment in the function of cytotoxic T lymphocytes and NK cells have been identified as the primary cause of F-HLH. Genetic mutations affecting the cytotoxic pathway lead to an inability to clear the antigenic stimulus. This causes an interminable inflammatory response, which leads to uncontrolled hypercytokinemia with sustained macrophage activation and tissue infiltration. In a healthy

individual, cytotoxic T lymphocyte and NK cells release granules that contain granzymes and perforins, into the immunologic synapse between the cytotoxic cells and the target cells, in response to a viral infection or tumor cells. Perforins create pores on infected cells that cause osmotic lysis of the target cell. Perforins are also necessary for the uptake of granzymes, which mediate protein degradation of the target cells, eventually leading to apoptosis. The apoptosis of the target cells with clearing of the antigenic stimulus causes termination of the immune response. This is known as activation-induced cell death.[25] All of the genetic mutations linked to F-HLH involve either perforin itself (*FHL2*) or are owing to defective granule exocytosis (*FHL3-5* and some of the immunodeficiency syndromes). These steps are dependent on an intact cytoskeleton and microtubules, which are involved in docking and fusion of the granules into the cell membrane.[26] Numerous proinflammatory cytokines are seen in HLH that include IFN-γ, TNF-α, IL-1 β, IL-2, IL-6, IL-12, IL-16, and IL-18.[27,28] The chronic stimulation of macrophages by these cytokines, especially IFN-γ and TNF-α, result in chronic activation and abnormal behavior of macrophages.[29] Primary mechanisms by which these cytokines cause hemophagocytosis are by the upregulation of the prophagocytic molecules like calreticulin on the mature blood cells and by the downregulation of CD47 on the hematopoietic stem cells. Downregulation of CD47 results in inhibition of the CD47–signal regulatory protein α interaction, which leads to the phagocytosis of hematopoietic stem cells. The upregulation of calreticulin results in engulfment of mature blood cells.[30]

Acquired Hemophagocytic Lymphohistiocytosis

The pathophysiology of acquired HLH has not yet been completely elucidated and is likely multifactorial. Studies conducted by Zhang et al,[31] Chen et al,[32] and Miao et al[33] on adult patients with HLH have shown the presence of a single mutated allele of some genes affected in F-HLH, which do not fully impair the function of affected proteins. It has been suggested that acquired HLH could be the result of the combination of inherited genetic mutations and extrinsic triggers like infection, neoplasm, or autoimmunity.[34] Then again, Carvelli et al[35] were unable to detect any cytotoxicity dysfunction in patients with acquired HLH who had monoallelic mutations affecting *LYST*, *UNC13D*, *PRF1*, and *STX11*, thereby creating uncertainty whether these monoallelic mutations have any role in the pathogenesis of acquired HLH. Some of these studies mentioned limitations like small sample size due to the rarity of HLH, and most of these studies used targeted genomic sequencing. Gene analysis by whole genomic sequencing will help get a better idea of the genetics of acquired HLH.

Overproduction of proinflammatory cytokines is seen in acquired HLH.[36] The mechanisms underlying this hypercytokinemia are not clear. It has been suggested that the overproduction of proinflammatory mediators may be because of the sustained toll-like receptor activation by infectious or autoimmune triggers. Animal studies have demonstrated the development of an HLH-like syndrome by the sustained stimulation of the toll-like receptors using ligands like cytosine guanine dinucleotides[37] and lipopolysaccharides.[38] MAS seen in the recently described NLRC4 inflammasome syndrome is owing to gain of function mutations affecting the inflammasome NLRC4 component. These mutations result in IL-18 overproduction leading to a MAS phenotype.[39,40] The pathogenesis of HLH along with the key inflammatory mediators and important etiologic factors are outlined in Figure 1.

CLINICAL FEATURES

The clinical manifestations of HLH are serious, frequently leading to complications like sepsis, bleeding, and multiorgan failure. Common signs and symptoms of HLH include fever, organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy), neurologic involvement, stigmata of liver dysfunction, anemia, and coagulopathy (hemorrhage, petechiae, ecchymosis, purpura, and disseminated intravascular coagulation).[41] Other nonspecific clinical manifestations like edema, rashes, and gastrointestinal symptoms like diarrhea, nausea, vomiting, and abdominal pain may also be seen. High, persistent fever is consistently seen and is often present at onset.[42] In patients with severe disease, pulmonary, renal, or cardiac involvement may be seen.[5,43] Neurologic manifestations are more often seen in pediatric HLH and includes seizures, meningismus, peripheral neuropathy, cranial nerve involvement, ataxia, dysarthria, lethargy, encephalopathy, and coma.[1,5,44] There are some differences in the clinical manifestation of HLH in the pediatric and adult population, which are summarized in Table 3.

DIAGNOSIS

Two diagnostic scoring systems are well accepted in HLH. The most commonly used is the Revised HLH-2004 criteria derived from the HLH-94 diagnostic criteria from the Histiocyte Society (Table 4). The HLH-probability calculator (HScore) is another widely accepted diagnostic scoring system.

The HScore is a Web-based online calculator that takes into consideration the following 9 criteria: the presence of immunosuppression, fever, organomegaly, elevation in triglyceride level, ferritin levels, aspartate aminotransferase/serum glutamic oxaloacetic transaminase levels, fibrinogen levels, presence of cytopenias, and hemophagocytosis in bone marrow samples. Each criterion is assigned a value based on logistic regression and a total score ranging from 0 to 337 is calculated from it. A higher score corresponds to a higher probability of HLH. The creators of the score found an optimal cutoff of 169, which corresponded to a sensitivity of 93% and a specificity of 86% in their study.[45] Debaugnies et al[46] compared the performance of the HScore with the HLH-2004 criteria in adult and pediatric patients with suspected HLH. The study concluded that the HScore is more predictive in diagnosing HLH than the HLH-2004 criteria. The sensitivity and specificity of the HScore were found to be greater in the pediatric group (100% and 80%, respectively) than in adults (90% and 79%, respectively). The study also showed that in adults, as their clinical condition worsened, there was not much difference in the performance of HScore and the HLH-2004 criterion.

MAS, due to its categorization as a subset of HLH, is diagnosed in many centers by the HLH-2004 criteria.[47] Because patients with an underlying autoimmune disease, especially systemic-onset juvenile idiopathic arthritis (SJIA), have leukocytosis and thrombocytosis, the HLH-2004 criteria can often lead to delayed diagnosis of MAS. The increased inflammation in SJIA patients can directly cause increased fibrinogen levels. The cut off level of fibrinogen in the HLH-2004 criteria cannot be considered adequate for the diagnosis of MAS due to SJIA. There are alternate

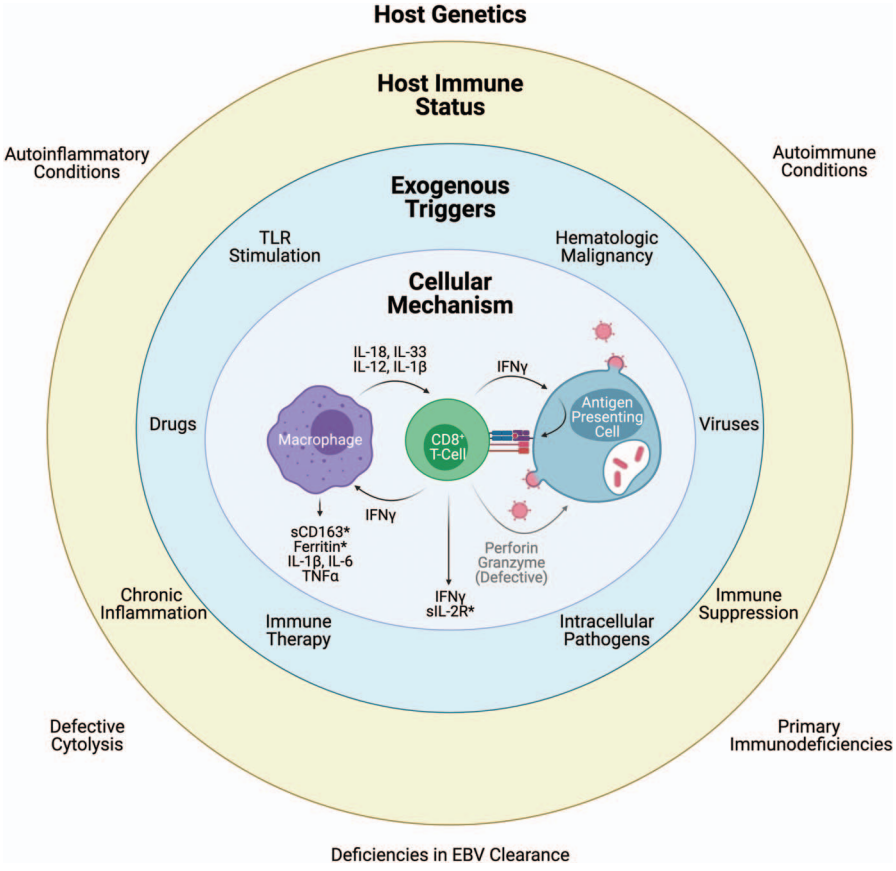

Figure 1. *Hemophagocytic lymphohistiocytosis (HLH) is a disease process that is not the result of a single condition or stimulus but is instead caused by a constellation of genetic predispositions, changes in immune status, and triggers all of which result in sustained CD8⁺ T-cell activation. The cells most classically involved in this activation are macrophages and antigen-presenting cells each contributing to an inflammatory milieu. Some of the values most classically used to detect these changes are (1) ferritin, (2) sCD163, and (3) sIL-2R (all demarked by * in the figure). The cellular activation can be caused by direct alterations to the immune system through genetic deficiencies, primary immune deficiency, or impaired host response to Epstein-Barr virus (EBV) infection all of which contribute to the uncontrolled activation of CD8⁺ T-cell and the runaway amplification of cytokine signaling seen in HLH. As a whole, HLH could be worsened by either an overactive immune system or underactive immune system; however, triggering events are often emphasized in the literature. Such triggers include intracellular pathogens, innate immune activation caused by toll-like receptor stimulation, drugs, immunotherapy, or hematologic malignancy. Figure created with Biorender.com.*

diagnostic guidelines with higher sensitivity and specificity for the diagnosis of MAS. They include the preliminary diagnostic guidelines for a MAS-complicating SJIA condition proposed by Ravelli et al[48] in 2005, the recent 2016 classification criteria for MAS-complicating SJIA condition as stated by Ravelli et al,[49] and the diagnostic criteria for MAS in an active SJIA proposed by Kostik et al[50] and Parodi et al.[51] Despite the presence of these diagnostic guidelines with high predictive value, the best method for early diagnosis in a real-world scenario is observing the relative changes in the overall parameters from the baseline.[52]

MORPHOLOGIC FINDINGS

The characteristic microscopic finding of HLH is the prominent and diffuse accumulation of lymphocytes and macrophages, which occasionally exhibit hemophagocytosis (Figure 2, A through F). These infiltrates are classically seen in the bone marrow. However, they have also been described in the spleen, lymph nodes, liver, skin, lungs, meninges, cerebrospinal fluid (CSF), and rarely in the subcutaneous tissue.[53–56]

The bone marrow may be initially hypocellular or hypercellular but eventually becomes hypoplastic.[30] There is usually hyperplasia of histiocytes with florid hemopha-

Table 3. Clinical Characteristics of Pediatric Hemophagocytic Lymphohistiocytosis (HLH) Versus HLH in Adults Based on Findings From Several Large HLH Patient Cohorts

Clinical Finding	Pediatric HLH[a]	HLH in Adults[b]	Comments
Fever	~100%	~100%	May be absent in neonates
Splenomegaly	70%–95%	40%–87%	Most commonly enlarged organ in HLH overall
Hepatomegaly	95%	14%–71.87%	More seen in pediatric HLH and is part of the diagnostic criterion in the HScore but not the HLH-2004 criterion
Neurologic symptoms	33%	9%–25%	Uncommon in adults and associated with poor prognosis in children
Miscellaneous	Rashes (65%), edema (<40%), lymphadenopathy, jaundice	Lymphadenopathy (<33%), rash, pulmonary involvement (42%)	

[a] Data for pediatric HLH derived from Nikiforow and Berliner,[41] Chandrakasan and Filipovich,[124] Rosado and Kim,[26] and Machowicz et al.[79]
[b] Data for HLH in adults derived from Nikiforow and Berliner,[41] Chandrakasan and Filipovich,[124] Ramos-Casals et al,[5] Filipovich,[125] Li at al,[126] Tseng et al,[127] Park et al,[128] Parikh et al,[12] Rivière et al,[129] Otrock and Eby,[130] Dholaria et al,[131] Birndt et al,[132] Lim et al,[133] Schram et al,[119] Apodaca et al,[134] Qiaolei et al,[135] and Zhou et al.[136]

Table 4. Diagnostic Guidelines According to the Hemophagocytic Lymphohistiocytosis (HLH)—2004 Criteria

HLH—2004 Diagnostic Criteria
Molecular diagnosis consistent with HLH
Or
5 of the 8 criteria listed below
1. Fever ≥38.3°C
2. Splenomegaly
3. Cytopenia (affecting at least two of the three lineages in the peripheral blood)
Hemoglobin <9 g/dL (infants <4 weeks: hemoglobin <10 g/dL)
Platelets $<100 \times 10^3/\mu L$
Neutrophils <1000/μL
4. Hypertriglyceridemia (≥265 mg/dL) and/or hypofibrinogenemia (≤150 mg/dL)
5. Hemophagocytosis in bone marrow or spleen or lymph nodes or liver
6. Low or absent NK cell activity
7. Ferritin ≥500 ng/mL
8. sCD 25 (sIL2Rα) ≥2400 U/mL

gocytosis. Additional findings include granulocytic and erythroid hypoplasia with variable megakaryocytic hyperplasia. The adjacent marrow can show features pointing to the underlying triggering process. For instance, in infectious causes of HLH, increased plasma cells, immunoblasts, or granulomas may be seen in the bone marrow.[54]

In the liver, hyperplasia of the Kupffer cells as well as portal and sinusoidal cytotoxic T-cell infiltrates are seen, similar to the biopsy specimen findings in chronic persistent hepatitis.[55] Hemophagocytosis may be seen. Other patterns, such as leukemia-like, giant cell hepatitis-like, and storage disease-like, depending on the predominant cell type, have also been described in the liver.[57]

According to the HLH-2004 criteria, the presence of hemophagocytosis, while suggestive, is neither specific nor required for a diagnosis of HLH. Because hemophagocytosis is often cyclical, a given biopsy specimen may yield a negative result at the first examination.[57] Furthermore, hemophagocytosis is not specific to the diagnosis of HLH when other clinical features of the disease are absent. Rare erythrophagocytosis is commonly seen in bone marrow aspirates, and increased hemophagocytosis may be encountered in the setting of sepsis, blood transfusions, major surgeries, hematopoietic transplantation, chemotherapy, and myelodysplastic syndrome.[2,58–60]

Hemophagocytosis is the only HLH-2004 diagnostic criterion without a defined threshold value. Gars et al[61] were able to create a quantitative diagnostic threshold for hemophagocytosis from a retrospective study on a cohort of patients with clinical characteristics that were concerning for HLH. The study concluded that hemophagocytosis of at least 1 granulocyte per 1000 nucleated cells, 4 nucleated erythrocytes per 1000 nucleated cells, 6 cells from any 4 lineages of cells including red blood cells, nucleated red blood cells, neutrophils and lymphocyte per 1000 nucleated cells, or the presence of at least 1 hemophagocyte containing multiple nucleated cells can accurately predict the diagnosis of HLH. This diagnostic threshold needs further prospective study and external validation to be implemented in the routine diagnosis of HLH.

LABORATORY FINDINGS

A wide variety of laboratory findings may be seen in HLH. Unfortunately, none are pathognomic.[1] Cytopenia (usually of 2 or 3 cell lines), hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, elevated levels of the sIL2rα chain (sCD25), reduced NK-cell function measured by chromium release assay, soluble CD 163, and abnormal liver function test results are some of the common findings in HLH.[1]

Rather than solely due to hemophagocytosis, cytopenias in HLH also occur as a result of high levels of IFN-γ and TNF-α produced by Th1 type T cells. TNF-α and IFN-γ act on the precursor cells in the bone marrow to suppress hematopoiesis and induce apoptosis of these cells.[29]

Acute phase reactants are often elevated, sometimes to very high levels, because of the hyperinflammatory state. An exception to this is the erythrocyte sedimentation rate, which may be low due to hypofibrinogenemia. The acute phase reactant that is most notable in HLH is serum ferritin. The increase in serum ferritin is caused by the upregulation of heme oxygenase, a heat shock protein expressed in response to inflammatory cytokines.[62] The predictive value of serum ferritin in HLH varies between children and adults. A study by Allen et al[63] reported ferritin levels above 10 000 ng/mL to have a sensitivity of 90% and specificity of 96% in identifying pediatric cases of HLH. A study conducted by Schram et al[64] in adults showed that serum ferritin levels can be elevated to more than 50 000 ng/mL due to renal failure, liver injury, infection, and hematologic malignancies. In their study, patients with HLH who had elevated ferritin levels more than 50 000 ng/mL had a concomitant liver injury, renal failure, or both. Another study in adults by Wormsbecker et al[65] showed that even ferritin levels greater than 3000 ng/mL were not predictive of HLH. Both these studies in adults concluded that high serum ferritin levels are neither sensitive nor specific for HLH. However, the negative predictive value of serum ferritin using a cut off of 500 ng/mL—the current diagnostic cut-off according to HLH-2004 criteria—is quite high in both adults and children.[64]

IL-2 receptor alpha chain (CD25) is a marker of activated lymphocytes. These activated lymphocytes release the soluble form of CD25 (sCD25), which can be measured by an enzyme-linked immunosorbent assay and is relatively specific for diagnosing HLH.[23] A high sCD25/ferritin ratio is useful to differentiate lymphoma-associated HLH from HLH due to nonmalignant etiologies.[66] NK-cell activity or NK-cell cytotoxicity test is the measure of the ability of NK cells to degranulate and kill the target cells and can be quantified by a ^{51}Cr release assay. Reduced or absent release of the radionuclide may be seen in HLH and is a part of the HLH-2004 criteria. Owing to the poor predictive value in adults and limited availability, the NK-cell cytotoxicity test is not commonly performed in most centers.[1,10] Soluble CD163 is a macrophage-specific scavenger receptor for native and chemically modified hemoglobin. It is a marker of macrophage activation, elevated not only in HLH but also in malignancy, autoimmunity, and infection. This marker, though not very specific, can aid in the diagnosis of HLH.[1] Table 5 summarizes the laboratory characteristics of HLH in adults and children with data collected from several large HLH patient cohorts.

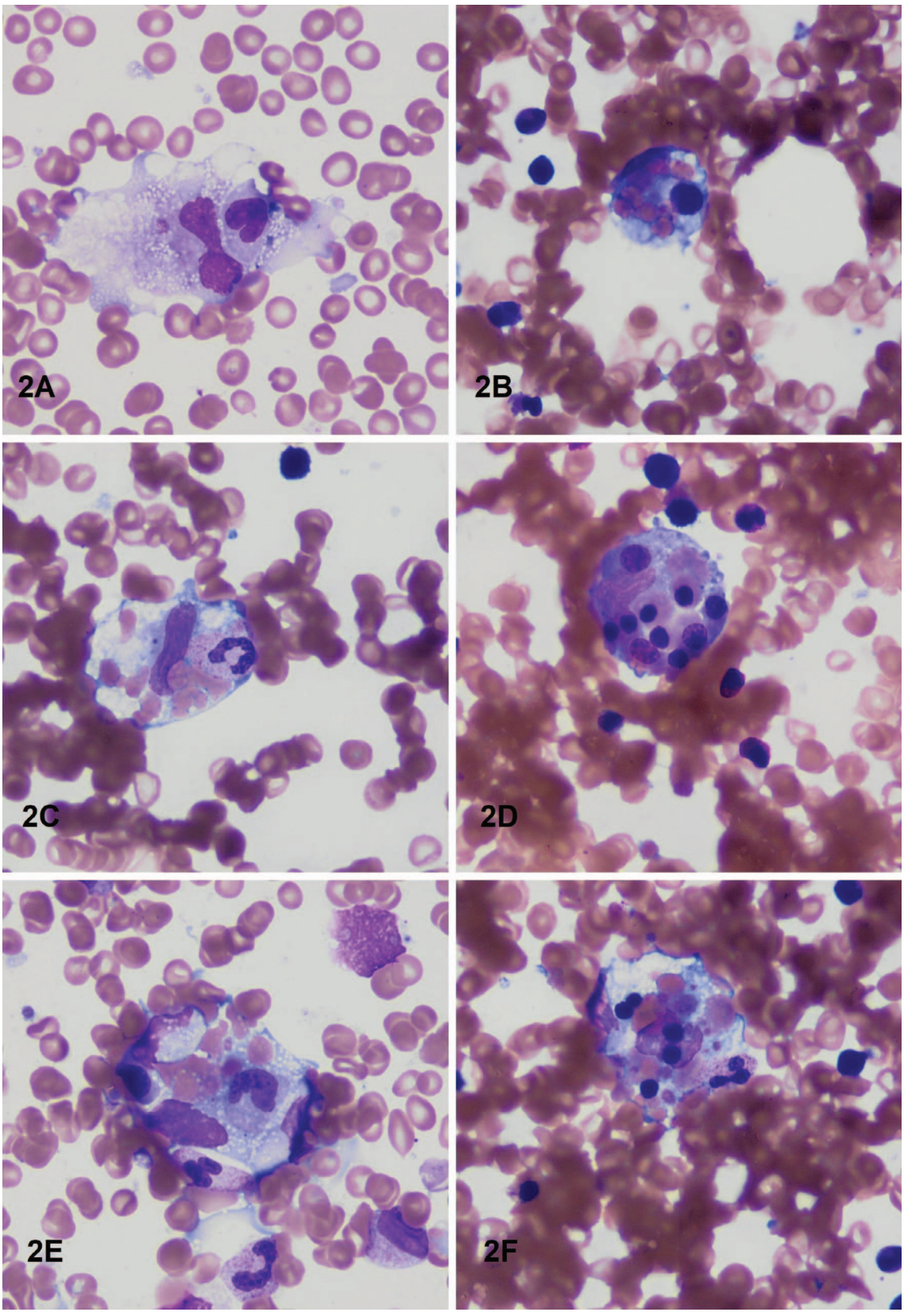

Figure 2. *Bone marrow aspirate smears demonstrating hemophagocytic activity within histiocytes. A, An activated histiocyte with cytoplasmic projections in a patient with hemophagocytic lymphohistiocytosis (HLH). Ingested cells may be mature erythrocytes (B), neutrophils (C), or erythroid precursors (D). E, A histiocyte with intracytoplasmic erythroid and granulocytic cells. F, A histiocyte with intracytoplasmic mature erythrocytes, platelets, and nuclear debris (Wright-Giemsa stain, original magnification ×100 [A through F]). Images courtesy of Sanam Loghavi, MD, The University of Texas MD Anderson Cancer Center.*

Table 5. Laboratory Findings in Pediatric Hemophagocytic Lymphohistiocytosis (HLH) Versus HLH in Adults			
Laboratory Finding	**Pediatric HLH[a]**	**Adult HLH[b]**	**Comments**
Cytopenias of >2 lines	~100%	>85%	Anemia and thrombocytopenia are more common. Leukopenia is less common
Hypertriglyceridemia (fasting >265 mg/dL)	40%–85%	22.1%–88.6%	Caused by elevated TNF-α which inhibits lipoprotein lipase
Hypofibrinogenemia (<150 mg/dL)	53%–79%	24%–93.3%	Associated with poor prognosis
Ferritin >500 ng/mL	~100%	77.2%–100%	High negative predictive value in both children and adults
Elevated soluble CD-25 (>2400 U/mL)	~100%	100%–76.2%	Level >10,000 U/mL or slow rate of decline is associated with poor prognosis in children
Hypoalbuminemia	69%	86.3%–97%	Associated with poor prognosis in adults
Abnormal renal function	9%	16%–61%	Associated with poor prognosis. Acute kidney injury is the most common renal manifestation of HLH
Elevated transaminases	76%	63%–98.1%	Elevated AST is one of the diagnostic criteria of the HScore but not the HLH-2004 criterion
Hemophagocytosis	92%	53.3%–100%	Not sensitive nor specific to the diagnosis of HLH in children and adults
Low or absent NK cell activity	22%–100%	28.6%–86%	Predictive value is better for HLH in children than in adults

Abbreviations: NK cell, natural killer cells; TNF-α, tumor necrosis factor-α.

[a] Data for pediatric HLH derived from Nikoforow and Berliner,[41] Chandrakasan and Filipovich,[124] and Machowicz et al.[79]
[b] Data for HLH in adults derived from Tseng et al,[127] Park et al,[128] Parikh et al,[12] Rivière et al,[129] Li et al,[126] Otrock and Eby,[130] Dholaria et al,[131] Birndt et al,[132] Lim et al,[133] Schram et al,[119] Apodaca et al,[134] Qiaolei et al,[135] and Zhou et al.[136]

ANCILLARY STUDIES

Mutation testing is a criterion in the HLH-2004 diagnostic guidelines. It is not routinely done in cases where an urgent diagnosis is required. It is also not recommended for adult HLH cases because it is seldom that abnormalities are detected. The clinical and laboratory criteria can be obtained faster. Mutation testing may be done prophylactically in children with a strong family history of HLH. It should, at a minimum, include the analysis of the known FHL mutations like *PRF1*, *UNC13D*, *STX11*, and *UNC18B*. Specific testing for the genetic defects related to X-linked lymphoproliferative disorder, Chediak-Higashi syndrome (CHS), Griscelli syndrome type 2 (GS2), or Hermansky-Pudlak syndrome type 2 (HPS2) may be warranted in the appropriate clinical setting. A negative mutation study does not rule out HLH.[1]

Flow cytometry can be used to identify mutations causing genetic HLH. It is not a very sensitive diagnostic tool as it can only look at the protein expression and not directly gene mutations. Despite these limitations, the fast turnaround time of flow cytometry makes it a very useful diagnostic tool when compared with mutation analysis. Intracellular stains are available that measure perforin, SAP (X-linked lymphoproliferative syndrome type 1), and XIAP (X-linked lymphoproliferative syndrome type 2).[67,68] Munc13-4 protein expression in platelets has been reported as a potential new rapid screen for FHL-3 and is awaiting testing in a larger cohort.[69] Perforin, syntaxin11, Munc18-2, and Rab27a can be directly tested using antibodies by Western blot.[70–72] Mutations in genes related to granule trafficking and exocytosis can be determined by the NK-cell degranulation test, which quantifies the surface expression of CD107a (LAMP-1) in the peripheral blood mononuclear cells following stimulation with phytohemagglutinin or anti-CD3. The cytotoxic cells in our body normally release CD107a containing intracytoplasmic granules to the surface upon contact with the target cell. The absence of CD107a expression on the cytotoxic cell surface is indicative of a defective pathway of granule exocytosis.[73] However, intact CD107a expression on NK-cell degranulation test only means that granule exocytosis is intact. It does not necessarily mean that the cytotoxic cells are able to cause the death of the target cells. If NK-cell degranulation test is unremarkable, additional testing to evaluate NK-cell cytotoxicity by ^{51}Cr release assay may be needed.[73] Assessment of NK-cell degranulation is useful in identifying FHL3-5, GS2, CHS, and HPS2[74–76] but not FHL2, X-linked lymphoproliferative syndrome type 1, and X-linked lymphoproliferative syndrome type 2, where granule exocytosis is normal.[77] While flow cytometry immunophenotyping for HLH-associated antigens is not readily available across all centers in the US, select specialized clinical laboratories do include testing for perforin and CD107a and have found these tests to be superior to the NK-cell cytotoxicity test in screening for genetic HLH.[77] Flow cytometry for SAP and XIAP, and Western blot techniques are not readily accessible to all pathologists.

DIFFERENTIAL DIAGNOSIS

There is significant overlap in the clinical features of sepsis and HLH, as hyperinflammation is present in both conditions. Hence, it is imperative to differentiate these 2 conditions as the treatment of HLH is targeted toward suppression of the immune response that could be detrimental in a patient with sepsis.[21] It is important to note that HLH may be triggered or complicated by sepsis and that HLH and sepsis may coexist. HLH must be considered in patients with sepsis who do not respond to conventional therapy with antimicrobials and supportive measures.[78] The presence of profound hyperferritinemia, splenomegaly, marked cytopenia, hypofibrinogenemia, or thrombocytopenia in the absence of disseminated intravascular coagulation, low C-reactive protein, or elevated triglyceride levels in adults are uncommon features of sepsis and should prompt the evaluation for HLH using the HLH-2004 diagnostic criteria. However, it is important to bear in mind that NK-cell activity test, sCD25, fever, and hemo-

phagocytosis are features common to both HLH and sepsis.[79]

Many atypical infections due to visceral leishmaniasis, atypical/tuberculous mycobacteria, histoplasmosis, *Ehrlichia*, *Bartonella* and *Brucella* species, disseminated adenovirus, and disseminated herpes simplex may lead to cytopenia and elevations of inflammatory markers with an HLH-like picture. In most of these cases, the etiology is not immune-related. Direct treatment of the infection is superior to immunosuppression in these patients as immunosuppression can potentially worsen the underlying infection.[24]

Drug reaction with eosinophilia and systemic symptoms (DRESS) may present as HLH but should be managed by discontinuing the offending drug, with or without additional corticosteroids.[24]

An important differential diagnosis in a newborn with fulminant liver failure, in addition to HLH, includes gestational alloimmune liver disease, also known as neonatal hemochromatosis. While patients with neonatal hemochromatosis can present with hyperferritinemia and coagulopathy, hemophagocytosis and other signs of inflammation are absent. Hepatic hemosiderosis is also typically present in gestational alloimmune liver disease.[26]

Storage diseases in infants, such as Wolman disease and Gaucher disease, may present with extreme organomegaly or pancytopenia. These conditions may simulate HLH and, can on occasion, fulfil the HLH-2004 criteria. It is important to have a high index of suspicion while diagnosing HLH in such patients. This is because the treatment of HLH, which is immunosuppression, is not beneficial in managing both Wolman and Gaucher disease.[80–83]

Differential diagnosis in HLH producing isolated central nervous system disease includes viral encephalitis,[84] autoimmune disseminated encephalomyelitis, central nervous system vasculitis, multiple sclerosis, Rasmussen encephalitis, febrile infection-related epilepsy syndrome and acute necrotizing encephalopathy, or interferonopathies.[85] In Rasmussen encephalitis, a single hemisphere is only usually affected. Acute necrotizing encephalopathy typically exhibits symmetric thalamic necrosis and absence of extensive white matter changes. Interferonopathies may demonstrate cerebral calcifications.[86] Febrile infection–related epilepsy remains poorly characterized and, in some patients, may represent undiagnosed HLH.[87]

Hematologic disorders like Langerhans cell histiocytosis involving the marrow and/or visceral organs and the multicentric Castleman disease, especially the thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly variant, may also closely resemble HLH. Treatment of the underlying condition with or without additional corticosteroids are effective in managing both of these conditions.[24]

TREATMENT

Early and aggressive treatment is needed for most patients with HLH. With the development of standardized treatment protocols with HSCT, the survival rate of HLH improved from a 1-year survival rate of less than 5%[88] to a 5-year survival rate of 21%.[89]

HLH-94 Treatment Protocol

The HLH-94 protocol, developed by the Histiocyte Society in 1994, resulted in a remarkable improvement in the 5-year survival rate to 54 ± 6%.[90] There was also an improved response to treatment in XLP, GS2, and CHS. This treatment protocol includes an initial 8-week long therapeutic course of etoposide (150 mg/m^2 twice weekly for 2 weeks and then weekly) plus dexamethasone (initial dose of 10 mg/m^2 slowly tapered over 8 weeks). Patients with known F-HLH or persistent nonfamilial disease can receive continuation therapy as a bridge to allogeneic hematopoietic stem cell transplant. Continuation therapy consists of pulses of dexamethasone (10 mg/m^2 for 3 days every second week) and etoposide (150 mg/m^2 every alternating second week) in combination with daily oral cyclosporine therapy. Intrathecal methotrexate can be administered in case of progressive neurologic symptoms or a persistently abnormal CSF.[91] The HLH-94 treatment protocol is most accepted in the pediatric population where F-HLH is predominant. Much of the treatment recommendations in adults are extrapolated from the data in children. Adults, especially elderly patients, may have chronic comorbidities. This makes them more vulnerable to end-organ damage caused by the cytokine storm in HLH and the HLH-94 chemotherapy. Moreover, adults usually have different HLH initiating triggers, such as infection, malignancy, autoimmune/autoinflammatory, drug-induced, and so on. In adults, individual adaptation regarding the length and dosing of the HLH-94 treatment plan may be done by taking into consideration the associated comorbidities and HLH initiating triggers.[78]

HLH-2004 Treatment Protocol

HLH-2004 protocol is derived from the HLH-94 treatment protocol and similarly has an 8-week-long initial phase followed by a continuation phase. The dosage and frequency of administering etoposide and dexamethasone are also the same as in the HLH-94 treatment protocol. The major difference is the initiation of cyclosporine A at the beginning of the initial phase of treatment to oppose the action of IFN-γ and achieve increased immunosuppression. Furthermore, the HLH-2004 protocol proposes performing HSCT on patients as soon as a donor is available and administering intrathecal prednisone, in addition to intrathecal methotrexate, for HLH causing progressive neurologic symptoms. There was a decrease in the pre-HSCT mortality from 27% (with the HLH-94 treatment protocol) to 19% (with the HLH-2004 treatment protocol). The strength of this association is, however, not statistically significant ($P = .06$). The 5-year survival post-HSCT, in patients who received the HLH-2004 treatment protocol, was 66%, which was not considerably better than in patients who received the HLH-94 treatment protocol.[92] Thus, most centers still use the HLH-94 treatment protocol, as the current evidence shows no significant clinical advantage over the HLH-94 treatment protocol.[1]

Salvage Treatment of Relapsed and Refractory HLH

In relapsed/refractory HLH, salvage treatment with chemotherapeutic agents, such as the cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)–like regimens with etoposide, use of the anti-CD52 antibody alemtuzumab, cytokine adsorption using filter columns or plasma exchange, off-label treatment with the JAK2 inhibitor ruxolitinib, or the anti–IFN-γ antibody emapalumab have shown reasonable efficacy. Allogeneic hematopoietic stem cell transplantation can be performed in these patients after successful salvage treatment. The general rule is that the

treatment needs to be personalized according to the most likely underlying cause.[78]

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation can cure F-HLH and may be performed in patients with high-risk hematologic malignancy as consolidation treatment or in relapsed HLH after successful salvage treatment. The degree of remission before starting HSCT is an important survival factor, especially in patients who lack human leukocyte antigen-identical donors.[93,94] Because HLH is invariably fatal without HSCT, if matched donors are unavailable, haploidentical or mismatched unrelated donors may be used depending on the availability. Unrelated umbilical cord blood is an easily available alternate donor source.[90] Furtado-Silva et al[95] has reported a 6-year survival rate of 55% with the umbilical cord blood in a study performed on 118 patients receiving predominantly busulfan-based conditioning. The bone marrow should first undergo myeloablative conditioning using busulfan, cyclophosphamide, etoposide with or without antithymocyte globulin, or reduced-intensity conditioning using melphalan/treosulfan, fludarabine, and alemtuzumab with or without antithymocyte globulin.[96] Reduced-intensity conditioning has been reported to be associated with less mortality than myeloablative conditioning in children.[97] A study by Li Fu et al[98] does not show much superiority of reduced-intensity conditioning over myeloablative conditioning in adults.

Treatment of Macrophage Activation Syndrome

Patients with MAS do not require first-line therapy with any of the cytotoxic agents in the HLH-94 protocol. They are instead treated with high-dose corticosteroids.[99] In patients not responding to corticosteroids, additional usage of cyclosporine A is recommended.[100–102] The HLH-2004 treatment protocol is only considered in patients who do not respond to high-dose corticosteroids and cyclosporine A.[99] Antithymocyte globulin may be considered in patients with refractory MAS or with contraindications to the first-line drugs.[103] However, antithymocyte globulin is associated with severe infection and increased mortality.[104] Intravenous immunoglobulin, cyclophosphamide, and plasma exchange have also been considered in the treatment of MAS but have resulted in variable outcomes.[99] A recent advance in the management of MAS is the use of biological agents like Anakinra, an IL-1 receptor antagonist, that has shown to be quite promising in the treatment of MAS and can be used as first-line therapy for MAS.[105–108] Monoclonal antibodies targeting IL-6 receptor (tocilizumab), IL-1β (canakinumab), and TNF receptor (etanercept) have been studied as a potential therapy for MAS, but studies have shown inconsistent results.[109]

Future Therapeutic Options for HLH

Clinical trials evaluating the efficacy of treatments targeting IL-18 in pediatric patients with NLRC4-MAS and XIAP deficiency are currently ongoing and appear to show some potential in attenuating the inflammatory processes in these diseases.[110] Monoclonal antibodies against IL-1, IL-6, and TNF-α are being extensively studied in the treatment of acquired HLH with some studies showing encouraging results.[111,112] Because these cytokines are also elevated in F-HLH, monoclonal antibodies against IL-1, IL-6, and TNF-α can be potentially used in the management of F-HLH as well. However, the efficacy of these monoclonal antibodies as a first-line therapy or rescue therapy in the management of F-HLH has not been clearly documented yet.[113] Gene therapy targeting the genes affected in XLP1,[114] FHL2,[115] and FHL3[116,117] deficiency have shown encouraging results in preclinical murine studies. This brings about the possibility of clinical trials in the future evaluating gene therapy as a potential treatment for F-HLH.

PROGNOSIS

Pediatric HLH has a poor prognosis without treatment and has a median survival of 1 to 2 months.[91] Long-term follow-up from the HLH-94 trial conducted in the pediatric population has revealed a 5-year survival rate of 54 ± 6%. Factors in this trial that predicted poor prognosis included very young age at the start of therapy and neurologic involvement.[90] A laboratory parameter associated with prognostic significance in pediatric HLH is serum ferritin. Lin et al[118] stated that a rate of decline of serum ferritin levels less than 50% in pediatric HLH is associated with 17 times greater risk of dying than a rate of decline of serum ferritin levels greater than or equal to 50%. The HLH-94 trial has reported some long-term sequelae in survivors of HLH. Neurologic complications, such as severe mental retardation, cranial nerve palsies, and epilepsy, were seen occurring in 19% of all surviving patients. Nonneurologic sequelae were observed in 16% of patients and included nutritional problems, growth retardation, hypertension, impaired renal function, obstructive bronchiolitis, and hearing impairment.[90]

The outcome of HLH in adults is variable with the worst prognosis for malignancy-associated HLH.[119] In a retrospective study by Yoon et al[120] on adults with acquired HLH other than malignancy-associated HLH, HLH caused by EBV had a worse 5-year overall survival compared with HLH caused by autoimmune disease, other infections, or unknown causes (25.1% versus 82.4%, 78.7%, and 55.5%, respectively). According to the study, not achieving a minimum of a stable and partial response to treatment at 8 weeks was the most powerful predictive factor for poor overall survival. Other factors associated with poor prognosis included EBV, age greater than 45 years, hyperferritinemia, and thrombocytopenia.

CONCLUSIONS

HLH is a challenging disorder to manage owing to its overlap with many other clinical conditions and because of the necessity of an early diagnosis. The development of standardized treatment protocols has drastically improved the survival rates in patients with HLH. However, the present mortality rate is still very high. There is a lot of ongoing research seeking improvement in the diagnosis and treatment of HLH. A better understanding of the disease pathogenesis, development of more predictive diagnostic tests, and newer treatment modalities will improve the outcome associated with this rare, life-threatening disease.

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