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Hemophagocytic Lymphohistiocytosis

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Abstract

Hemophagocytic lymphohistiocytosis is a life-threatening disorder characterized by unbridled activation of cytotoxic T lymphocytes, natural killer (NK) cells, and macrophages resulting in hypercytokinemia and immune-mediated injury of multiple organ systems. It is seen in both children and adults and is recognized as primary (driven by underlying genetic mutations that abolish critical proteins required for normal function of cytotoxic T cells and NK cells) or secondary (resulting from a malignant, infectious, or autoimmune stimulus without an identifiable underlying genetic trigger). Clinical and laboratory manifestations include fever, splenomegaly, neurologic dysfunction, coagulopathy, liver dysfunction, cytopenias, hypertriglyceridemia, hyperferritinemia, hemophagocytosis, and diminished NK cell activity. It is treated with immune suppressants, etoposide, and allogeneic hematopoietic stem cell transplantation; more than 50% of children who undergo transplant survive, but adults have quite poor outcomes even with aggressive management. Newer agents directed at subduing the uncontrolled immune response in a targeted fashion offer promise in this highly morbid disease.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a potentially life-threatening syndrome characterized by an unchecked and persistent activation of cytotoxic T lymphocytes and natural killer (NK) cells. Failure to control the immune response leads to increased secretion of inflammatory cytokines and macrophage activation, causing systemic inflammatory symptoms and signs. The magnitude of pathologic inflammation, which produces potentially life-threatening immune-mediated injury of multiple organs, distinguishes it from other inflammatory disorders. Clinically, HLH presents a diagnostic challenge because there is no one pathognomonic clinical manifestation or laboratory finding and signs are often nonspecific. Manifestations, findings, or signs may variably include fever, organomegaly (including lymphadenopathy, hepatomegaly, and splenomegaly), liver injury, consumptive coagulopathy, hypertriglyceridemia, cytopenias, neurologic dysfunction, dermatologic abnormalities, and elevations of acute phase reactants (notably serum ferritin) that may be striking in magnitude. HLH is often classified as primary or familial (occurring in the presence of an underlying predisposing genetic defect in immune function) or as secondary or reactive (occurring in the absence of an underlying predisposing defect, typically in the setting of an infectious, malignant, or autoimmune trigger). The disorder may occur secondary to specific (and maladaptive) interactions within the underlying immune system of the host when faced with an immune challenge, such that an impaired host immune system provides an overactive but ineffective response to the inciting challenge. Because the inciting challenge is not adequately eliminated by the host immune response, satisfactory removal of the immunologic stimulus is not achieved and the immune system does not undergo physiologic downregulation, which instead initiates a deleterious cycle of amplified cytokine release and intensified immune activation. Treatment is directed at breaking this vicious cycle and downmodulating the immune response with myelosuppressive and immunosuppressive therapies, which may be challenging in patients who often have multi-organ system failure at the time of diagnosis. Furthermore, a search for any underlying trigger, and proper management of that stimulus, is critical (1).

HLH, initially named histiocytic medullary reticulosis, was first reported in the literature in 1939 by Scott & Robb-Smith (2), who described a child as having a neoplastic histiocytic disorder. The disorder was first recognized as familial by Farquhar & Claireaux (3) in 1952. For most of the nearly 80 years that HLH has been recognized as a distinct clinical entity, it has been considered to be a hereditary disorder of children. We now understand that patients of any age may develop HLH and that the disease is most often triggered by a combination of underlying genetics and acquired exposures. Indeed, adults now comprise approximately 40% of HLH cases (4).

PATHOPHYSIOLOGY AND PATHOGENESIS

Dysregulation of Cytotoxic T Lymphocytes, Natural Killer Cells, and Macrophages

Under normal physiologic circumstances, upon encountering a virally infected cell or tumor cell, CD8+ cytotoxic T cells and NK cells release cytolytic granules containing perforin (a protein that forms pores in the target cell, facilitating the entrance of granzymes and destabilizing the membrane of the target cell) and granzymes (proteins involved in triggering apoptosis in the target cell) that promote cytolytic destruction of the target cell. In order for this process to proceed normally, perforin and granzymes must be structurally normal and properly trafficked within the cell and packaged into granules. These granules must then undergo exocytosis into the immunologic synapse between the cytotoxic cell and its target, after which the contents of the granules must enter the target cell. Disruption of this process via genetic mutations predisposes to the development

of primary, or familial, HLH. Under normal circumstances, perforin and granzymes contribute to the destruction of target cells and elimination of the immune-activating stimulus; this results in reduced antigen stimulation of the cytotoxic immune cells and their eventual apoptosis. This physiologic downregulation, termed activation-induced cell death, is critical for control of the immune response. The inability to clear the antigenic stimulus results in persistence and amplification of the immune response. Proinflammatory cytokines released by the activated immune cells result in high levels of macrophage activation with resultant hemophagocytosis, tissue damage, organ failure, and the other inflammatory manifestations of the syndrome (5).

Secondary or acquired HLH may result from a malignant, infectious, or autoimmune stimulus in the absence of an identifiable underlying genetic trigger. Different patterns of T lymphocyte activation and differentiation have been observed in secondary HLH patients as opposed to those with primary HLH, which suggests possible underlying differences in the pathogenesis of these two entities (6). Lymphomas that result in HLH have been shown to produce proinflammatory cytokines that provide the initial and enduring stimulus for activation of cytotoxic T lymphocytes and NK cells as the trigger for the syndrome (7). Epstein-Barr virus (EBV) is the most common infectious trigger for both primary and secondary HLH. EBV, which normally infects B lymphocytes, can result in EBV-associated HLH via infection of CD8+ cytotoxic T lymphocytes. This infection drives their uncontrolled activation and aberrant activity (8). Macrophage activation syndrome (MAS) is a subtype of HLH in which the syndrome develops in the background of autoimmune disease. A spectrum of underlying immune dysfunction is thought to predispose patients with certain systemic autoimmune disorders to the development of HLH, although it is recognized that some patients may have acquired functional abnormalities in perforin-mediated cytolysis by NK cells (9). Secondary HLH has been seen following allogeneic hematopoietic stem cell transplantation (HSCT) in patients who have immune activation secondary to tissue-damaging cytotoxic conditioning agents and high-level cytokine production from proliferating engrafting hematopoietic cells. These patients are also subject to reactivation of latent viruses in the setting of significant immunologic dysfunction (10). These triggers of secondary HLH are the most common and most important; additional triggers for secondary HLH have been proposed in the literature.

Dramatic Elevations in Cytokine Levels

Hypercytokinemia was identified relatively early in the understanding of HLH pathophysiology. A 1989 study found significant elevations in levels of the soluble interleukin-2 receptor (sIL2R) in patients with HLH; these elevations were in line with levels seen in lymphoid neoplasms and resolved with clinical improvement (11), which led to the designation of sIL2R as a marker for disease activity (12). A 1991 study examining interferon (IFN)-γ, tumor necrosis factor (TNF), and IL-6 levels in nine children with familial HLH found elevated levels of IFN-γ (seven out of seven children), TNF (six out of six), and IL-6 (two out of six) (13).

Patients with HLH have dramatically elevated levels of numerous serum proinflammatory cytokines, including IL-1β, IL-2, IL-6, IL-12, IL-16, IL-18, TNF-α, and IFN-γ (14, 15), and higher measured cytokine levels have been correlated with poorer outcomes (14). Elevated levels of anti-inflammatory cytokines have also been observed in HLH, particularly of IL-10, suggesting that patients do retain a mechanism (although clearly an inadequate one) to suppress activation of T lymphocytes, monocytes, and macrophages (16, 17). Of the cytokines dramatically elevated in HLH, IFN-γ may be especially noteworthy. High levels of IFN-γ result in macrophage activation and subsequent increased production of other proinflammatory cytokines. In a perforin-deficient mouse model, in which HLH was induced via infection with lymphocytic choriomeningitis virus,

the combination of CD8+ T cells and IFN-γ was shown to be uniquely required for the HLH phenotype (18), supporting IFN-γ inhibition as a potential target for therapy of HLH (described in the section titled "Treatment and Prognosis of Hemophagocytic Lymphohistiocytosis").

CLASSIFICATION AND EPIDEMIOLOGY OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Classification

HLH is designated as a subset of the broader family of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. This family includes the L (Langerhans-related) group, the C (cutaneous and mucocutaneous histiocytoses) group, the M (malignant histiocytoses) group, the R (Rosai-Dorfman disease) group, and the H (hemophagocytic lymphohistiocytosis and macrophage activation syndrome) group. A simplified schema of the most updated (2016) classification of the H group is presented in **Table 1** (19).

Most children with primary HLH have identifiable genetic defects inherited in Mendelian fashion as either homozygous or compound heterozygous lesions. These genes are nearly all null mutations that abolish critical proteins required for normal function of cytotoxic T cells and NK cells. Adult HLH is generally termed secondary HLH that arises because of external triggers. More recent analysis has demonstrated that about 15% of patients with adult HLH harbor mutations in familial HLH genes that may serve as predisposing alleles for the development of HLH, though still in response to typical triggers (20). These hypomorphic alleles are considered to be host factors that may impart a baseline risk for the development of HLH but that do not usually cause disease; some of these alleles occur in 5–10% of the population, so their contribution to the development of HLH may be small. This is in contrast to those mutations that lead to near universal occurrence of HLH in infancy or early childhood and tend to result in complete loss of protein function; complete loss of perforin is one example (21). An intermediate between these two extremes involves missense mutations that result in residual protein function. Missense mutations are found in primary HLH patients and correlate with later onset of disease, though the vast majority still present by adolescence (22).

Epidemiology

Epidemiologic data on HLH are derived primarily from large cohorts on whom retrospective analyses have been published in the literature. A retrospective series from a large academic hospital in Texas suggested a prevalence of HLH in Texas of 1 in 100,000 children, with a median age at diagnosis of 1.8 years (23). The incidence of HLH in children is estimated at 1 to 225 per 300,000 live births and appears to vary by geographic region (24). A retrospective series from Sweden analyzing data collected from 1971 to 1986 suggested an incidence of 1.2 per 1,000,000 children yearly, though in retrospect this number may reflect substantial underdiagnosis that occurred prior to more widespread understanding about the syndrome (25).

Epidemiologic data are sparser in adults. A review of multiple patient cohorts suggests an average age at presentation of approximately 50 years when the disorder occurs in adulthood (4, 26). Although the incidence of HLH in adults is not precisely known, it has been estimated to account for as many as 1 out of every 2,000 adult admissions at tertiary medical centers (27). The existence of significantly fewer published cohorts of adult patients over a shorter time span has important consequences for the diagnosis and treatment of the condition. Whereas the clinical

Table 1 Histiocytoses of the H group: classification of HLH by the Histiocyte Society

Primary HLH (with associated gene)	Secondary HLH
HLH associated with lymphocyte cytotoxic defects Familial HLH type 2 (*PRF1*) Familial HLH type 3 (*UNC13D*) Familial HLH type 4 (*STX11*) Familial HLH type 5 (*STXBP2*) X-linked lymphoproliferative disorder type 1 (*SH2D1A*) Griscelli syndrome type 2 (*RAB27A*) Chediak-Higashi syndrome (*LYST*)	Infection-associated HLH Virus-associated HLH Epstein-Barr virus–associated HLH Cytomegalovirus-associated HLH HLH associated with other herpes virus infections Human immunodeficiency virus–associated HLH Influenza-associated HLH HLH associated with other viral infections Bacteria-associated HLH Parasite-associated HLH Fungal-associated HLH
HLH associated with abnormalities of inflammasome activation X-linked lymphoproliferative disorder type 2 (*BIRC4*) Mutation of Nod-like receptor family, caspase recruitment domain-containing 4 (*NLRC4*)	Malignancy-associated HLH Malignancy-triggered HLH (HLH at onset of malignancy) Hematological malignancies T cell lymphoblastic lymphoma/leukemia T cell nonlymphoblastic lymphomas B cell leukemias B cell lymphomas (non-Hodgkin) Hodgkin lymphomas NK cell lymphomas/leukemias Myeloid neoplasia Other hematological malignancies Solid tumors Unclassified malignancies HLH occurring during chemotherapy HLH associated with a malignancy, but not further defined
HLH associated with defined Mendelian disorders affecting inflammation Lysinuric protein intolerance (*SLC7A7*) Mutation of heme oxygenase 1 (*HMOX1*)	HLH associated with defined rheumatologic conditions (macrophage activation syndrome) HLH associated with systemic onset juvenile idiopathic arthritis HLH associated with adult-onset Still disease HLH associated with systemic lupus erythematosus HLH associated with vasculitis HLH associated with other defined autoimmune conditions HLH associated with an undefined autoimmune condition
Familial (apparently Mendelian) HLH of unknown origin	Transplant-related HLH
	HLH associated with iatrogenic immune activation
	HLH associated with iatrogenic immune suppression
	HLH associated with other apparently non-Mendelian conditions

Modified from Emile et al. (19).
Abbreviations: HLH, hemophagocytic lymphohistiocytosis; NK, natural killer.

presentation has important recognized differences between children and adults, the most widely used diagnostic criteria in adults, the HLH-2004 criteria (described in detail in the section titled "Diagnosis of Hemophagocytic Lymphohistiocytosis"), were derived from studies in children (28). Moreover, no prospective studies on first-line therapy for HLH in adults exist, and consequently, pediatric data are usually extrapolated to guide therapeutic decision making in adult patients.

It is not clear whether there is a racial or ethnic predilection for HLH. Most series in the literature are retrospective, reflecting the experience of a single center or a collection of regional centers; therefore, the racial and ethnic makeup of the patients within them tends to approximate what would be expected from the geographic location of the study. For example, in one US study of 68 adult patients with HLH from three large academic medical centers in Boston, Massachusetts, 65% of patients were white, 13% black, 10% Asian, and 7% Hispanic (29). In contrast, 43% of HLH patients were Latino in a large series of pediatric patients from a large hospital in Texas (23). It has been demonstrated, however, that certain subtypes of familial HLH are more common in certain ethnic or national groups (30). The sex ratio in children appears to be close to 1:1 (25). In adults, there may be a slight male predominance (4); in the previously mentioned Boston series, 63% of patients were male (29). In contrast, MAS may be slightly more common in females (31), probably reflecting the increased prevalence in women of associated autoimmune disease.

ETIOLOGY OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Primary Hemophagocytic Lymphohistiocytosis and Associated Genetic Abnormalities

Table 2 lists the genetic abnormalities associated with primary HLH, including the five subtypes

Table 2 Primary HLH genetic defects

HLH type	Defective gene	Function	Notable clinical findings
Familial HLH type 2	*PRF1*	Pore formation	No notable clinical findings
Familial HLH type 3	*UNC13D*	Vesicle priming	Increased incidence of CNS involvement
Familial HLH type 4	*STX11*	Vesicle fusion	Mild, recurrent HLH; colitis
Familial HLH type 5	*STXBP2*	Vesicle fusion	Colitis; hypogammaglobulinemia
Syndromes			
Griscelli syndrome type 2	*RAB27A*	Vesicle docking	Partial albinism; silvery-gray hair
Chediak-Higashi syndrome	*LYST*	Vesicle trafficking	Partial albinism; bleeding tendency; recurrent pyogenic infection
Hermansky-Pudlak syndrome type 2	*AP3B1*	Vesicle trafficking	Partial albinism; bleeding tendency; immunodeficiency
EBV-driven			
X-linked lymphoproliferative disorder type 1 (XLP-1)	*SH2D1A*	T cells, NK cells, and NK T cell signaling	Hypogammaglobulinemia; lymphoma
X-linked lymphoproliferative disorder type 2 (XLP-2)	*BIRC4*	Signaling pathways involving nuclear factor kappa-light-chain enhancer of activated B cells	Mild, recurrent HLH; colitis
IL2-inducible T cell kinase deficiency	*ITK*	Signaling in T cells	Hodgkin lymphoma
CD27 deficiency	*CD27*	Lymphocyte costimulatory molecule	Combined immunodeficiency
X-linked immunodeficiency with magnesium defect (XMEN)	*MAGT1*	T cell activation via T cell receptor	Combined immunodeficiency; chronic viral infections; lymphoma

Modified from Chandrakasan et al. (1).
Abbreviations: CNS, central nervous system; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; NK, natural killer.

of familial HLH, the associated immunodeficiency syndromes, and the mutations predisposing to EBV-driven disease (1). Cases have been published of patients with heterozygous mutations in two different HLH-associated genes, resulting in a possible synergistic risk of development of HLH (32).

Five types of familial HLH have been identified and described. Familial HLH type 1 is due to a genetic abnormality in the 9q21 locus on chromosome 9, although the specific causative gene has yet to be identified (33). Familial HLH type 2 results from mutations in *PRF1*, which codes for the perforin protein. This protein is normally contained within cytolytic granules and results in pore formation in the target cell membrane, facilitating entrance of other cytolytic proteins and promoting osmotic lysis of the cell (34). Familial HLH type 3 results from mutations in *UNC13D*, which codes for the protein Munc-13-4. This protein is normally involved in the regulation of cytolytic granule maturation and exocytosis (35). Familial HLH type 4 results from mutations in *STX11*, which codes for syntaxin 11, a protein responsible for normal transport and exocytosis of cytolytic granules (36). Familial HLH type 5 results from mutations in *STXBP2*, which codes for syntaxin-binding protein 2; this protein normally binds to syntaxin 11 and promotes membrane fusion of and release of cytolytic granules (37). Patients with mutations in these genes that result in complete loss of protein function develop primary HLH in childhood.

Numerous genotype-phenotype studies of patients with familial HLH have been performed to arrive at these conclusions. In one such study, the phenotype of 37 patients with biallelic *STXBP2* mutations was analyzed. The 13 patients with exon 15 splice site mutations in *STXBP2* developed clinical manifestations of HLH much later than those with other mutations (median age of 4.1 years for exon 15 splice site mutations and 2 months for other mutations) (38). In another study of 124 patients with biallelic *PRF1* mutations, later disease onset and residual cytotoxic function were found in patients with at least one missense mutation (39). In 84 patients with biallelic *UNC13D* mutations, patients with two disruptive mutations (defined as indels, deletions, nonsense mutations, and splice errors) were more likely to have disease onset at a younger age than those with two missense mutations (40).

Secondary Hemophagocytic Lymphohistiocytosis and Associated Acquired Disorders

Most cases of HLH in adults for which a clear trigger may be identified are associated with infection (typically herpesviruses), malignancy, or autoimmune disease. Other less common etiologies include medication exposures, pregnancy, post–allogeneic HSCT, and post-solid organ transplantation (41).

Infectious agents. Infection is usually associated with HLH and is the most common precipitant for HLH in children with primary HLH. Viral infection, either primary infection or viral reactivation, is a known trigger for HLH, especially in an immunosuppressed host. DNA viruses from the family *Herpesviridae* are the most frequent viral agents, with EBV as the most commonly implicated infectious agent overall, resulting in disease via proliferation and hyperactivation of EBV-infected T lymphocytes (8). Other human herpesviruses reported to trigger HLH include cytomegalovirus (42), herpes simplex viruses 1 and 2 (43, 44), varicella-zoster virus (45), roseolovirus (46), and Kaposi's sarcoma-associated herpesvirus (47). Beyond the herpesviruses, numerous other DNA and RNA viruses across a broad spectrum of viral families have been reported to trigger HLH. In particular, numerous etiologic agents of the viral hemorrhagic fever syndromes have been associated, including dengue virus (48), Ebola virus (49), and Crimean-Congo hemorrhagic fever virus (50). Indeed, because of the considerable overlap in clinical manifestations between the viral hemorrhagic fever syndromes and HLH, some authors have postulated that the clinical

manifestations of viral hemorrhagic fever syndromes due to these viruses may actually represent a reactive HLH (51).

Several nonviral pathogens have been associated with the disease. Among the bacteria, cases describing HLH in association with *Rickettsia* (52) and *Mycobacterium* (53) are particularly numerous; some case studies implicate a host of other bacteria as well (54–56). The most common fungal pathogen associated with HLH is the endemic dimorphic fungus *Histoplasma* (57). The most common parasites implicated include *Plasmodium*, *Leishmania*, and *Babesia* (58–60).

The overall contribution of infection in the pathogenesis of HLH may be best illustrated via examination of several large case series in the literature. In a large retrospective multicenter US case series of 68 adults with HLH as defined by the HLH-2004 criteria, 22 (33%) of the patients were found to have an infectious trigger for their disease, most commonly EBV (6 patients) and cytomegalovirus (6 patients); other less common triggers in the series included varicella-zoster virus, human immunodeficiency virus, adenovirus, influenza A, hepatitis C virus, hepatitis B virus, roseolovirus, *Helicobacter pylori*, *Morganella* spp., *Staphylococcus epidemidis*, *Klebsiella* spp., *Clostridium difficile*, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, *Aspergillus* spp., and *Babesia microti* (29). In a published study of 96 adult patients with HLH, 30 (31%) were associated with infection. Of these 30 patients, 46% had bacterial infections, 41% had viral infections, and 13% had fungal infections (61). In a series of 30 patients receiving biologic agents for autoimmune disease or hematologic malignancy, 20 patients had suspected infectious triggers of HLH (62).

Malignancy. Malignancies are the most common trigger for the development of HLH in adults (approximately 45% of cases), although they are a minor cause in children (approximately 8% of cases) (20). These patients may develop HLH as a result of immune activation by neoplastic cells or by loss of inhibitory immune function from disease or treatment-induced bone marrow dysfunction (41). Patients with malignancy, particularly hematologic malignancy, present with a baseline level of immune dysfunction secondary to the cancer, and this dysfunction is often worsened via institution of antineoplastic therapy.

Hematologic malignancies are much more common triggers than solid tumors, and both lymphoid and myeloid neoplasms have been associated with the development of HLH. Lymphoma is the most common neoplastic trigger for HLH, with T and NK cell lymphomas most common. In a large retrospective multicenter US case series of 68 adults with HLH, 33 patients (49%) had an underlying neoplasm. Nine patients had a myeloid neoplasm (acute myeloid leukemia, chronic myeloid leukemia, polycythemia vera, or myelodysplastic syndrome); 22 had a lymphoid neoplasm (most commonly Hodgkin lymphoma, diffuse large B cell lymphoma, peripheral T cell lymphoma, NK/T cell lymphoma, or chronic lymphocytic leukemia); and two patients had a solid tumor (prostate cancer or insulinoma) (29). In a retrospective multicenter European series of 29 children with malignancy-associated HLH, 21 patients developed HLH in the context of their neoplasm prior to treatment with chemotherapy; six of these patients also had a clear infectious trigger (EBV in five of the six cases). Eight patients developed HLH during chemotherapy, of whom seven had clear infectious triggers. Every patient had a hematologic malignancy, with T cell neoplasms accounting for most cases (63).

Autoimmune disorders (macrophage activation syndrome). Initially described in 1985 in a patient with systemic juvenile idiopathic arthritis (sJIA), secondary HLH that occurs in the setting of rheumatologic disease is termed MAS (64). It is most commonly seen in patients with sJIA, adult-onset Still disease, systemic lupus erythematosus, and Kawasaki disease, but has been described as occurring secondary to numerous rheumatologic conditions in published case reports (31).

Approximately 30–40% of sJIA patients develop some degree of MAS, of which approximately one-third is clinically overt (31, 65). A detailed discussion of MAS is beyond the scope of this review; the reader is directed to a recent comprehensive review by Ravelli and colleagues (31) for more regarding this entity.

CLINICAL PRESENTATION OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Clinical Characteristics

Patients with HLH frequently present with a constellation of signs and symptoms that include some combination of fever, organomegaly (lymphadenopathy, hepatomegaly, or splenomegaly), neurologic dysfunction (such as encephalitis, seizures, or coma), edema, dermatologic manifestations, and stigmata of liver dysfunction or coagulopathy (such as jaundice or bruising). Patients are often critically ill and rapidly progress toward a septic shock–like clinical picture. The HLH-2004 criteria include several of these findings as diagnostic criteria. Because HLH was originally characterized as a pediatric illness, the HLH-2004 diagnostic criteria and much of the literature concerning the clinical presentation of the syndrome are based on pediatric HLH. We now understand that some differences exist in the presentation of HLH between pediatric and adult populations. For example, hepatomegaly occurs in 95% of children but only 18–67% of adults (66). **Table 3** summarizes the clinical characteristics of HLH in adults and children, collected from several large HLH patient cohorts.

Neurologic manifestations attributable to HLH are common in pediatric patients. A pediatric neuropathologic study in 1984 revealed infiltration of the meninges by lymphocytes and histiocytes as well as diffuse proliferation of histiocytes within the brain parenchyma (67). Neurologic manifestations are more common in children and vary from peripheral neuropathies or focal neurologic deficits to encephalopathic changes, seizure, or even coma (68). Analyses may find

Table 3 Clinical manifestations of hemophagocytic lymphohistiocytosis (HLH) in children and adults

Clinical presentation	Pediatric HLH (1)	Adult-onset HLH (1, 4, 28, 38, 80, 101, 102)	Prognostic impact
Age (median, range)	8 months (0–15 years) 76% <2 years	49 years (41–67 years) Case reports >70 years	Age <6 months and >50 years, poor prognosis
Fever[a] (38.5°C for >7 days)	+++++ (~100%)	+++++ (~100%)	Not defervesce in 3–7 days, poor prognosis
Splenomegaly[a] (tip >3 cm below costal margin)	+++	+++ (50–83%)	Potentially poor prognosis in adults
Hepatomegaly[a]	++++ (95%)	+++ (18–67%)	
Neurological symptoms	++ (33%)	+ (9–25%)	Poor prognosis children, not as common in adults
Others	++ (<40%) edema, rash, lymphadenopathy, jaundice	++ (<33%) lymphadenopathy, skin rash ++ (42%) pulmonary involvement	

[a]Diagnostic criteria on HLH-2004 grading schema.
Modified from Nikiforow & Berliner (66).

that patients have a pleocytosis in cerebrospinal fluid (CSF), and variable, nonspecific findings on magnetic resource imaging may be noted, including leptomeningeal enhancement, white matter lesions, and evidence of stroke (69). Retrospective studies have suggested a worse prognosis in patients with neurologic involvement (68).

Dermatologic manifestations may also be seen and are varied. Thrombocytopenia may result in petechiae, purpura, or ecchymoses. Widespread systemic inflammation may result in erythematous maculopapular rashes or widespread erythroderma (70, 71).

Laboratory Characteristics

Numerous laboratory and pathologic abnormalities are associated with HLH, but unfortunately none are pathognomonic. Cytopenias (usually of two or three cell lines), hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, elevated levels of the sIL2rα chain (CD25), reduced NK cell function, abnormal liver function testing, and hemophagocytosis may be seen in any combination, along with several other less common abnormalities. **Table 4** summarizes the laboratory characteristics of HLH in adults and children, collected from several large HLH patient cohorts.

Hemophagocytosis is the pathologic finding of engulfment of erythrocytes, platelets, or white blood cells by macrophages, identified by the presence of whole blood cells or blood cell fragments within macrophage cytoplasm (**Figure 1**). It may be seen on examination of bone marrow, spleen, liver, or lymph node. Unfortunately, due to nomenclature, it may be incorrectly presumed that the presence of hemophagocytosis on a biopsy specimen is required for diagnosis, or that its absence rules out the disorder. Indeed, hemophagocytosis is found in a majority of cases of HLH and is not considered sensitive or specific to the disorder (66). It is included in essentially all diagnostic criteria for HLH.

Because HLH is a hyperinflammatory syndrome characterized by extreme elevations in proinflammatory cytokine levels, acute phase reactants are often elevated, sometimes to dramatic levels (the exception to this is the erythrocyte sedimentation rate, which may be low due to hypofibrinogenemia). The acute phase reactant most associated with HLH is the serum ferritin. It is thought that extensive macrophage activation may be responsible for the significantly elevated levels that are often seen, as the primary storage site for ferritin is within tissue macrophages (72). Therefore, elevation in serum ferritin levels is a component in essentially all widely accepted clinical diagnostic criteria for HLH. Its utility as a diagnostic marker, however, varies between children and adults. A 2008 retrospective study of children with HLH from Texas Children's Hospital revealed that elevation in serum ferritin levels above 10,000 μg/L is 90% sensitive and 98% specific for pediatric HLH (73). A 2015 retrospective study of adults with HLH from multiple large academic medical centers in Boston, however, revealed that dramatically elevated ferritin levels were neither sensitive nor specific for HLH in adults (74). Ferritin levels of greater than 50,000 μg/L were seen most frequently in patients with renal failure, liver injury, infection, and hematologic malignancies, with only 19% of this group diagnosed with HLH. Not surprisingly, the majority of these HLH patients also had concomitant renal failure or liver injury, and many had both. The authors concluded that there was no ferritin value above which serum ferritin was specific for HLH in adults. The negative predictive value of a normal serum ferritin level for HLH is felt to be high in adult patients, however (41).

Elevated aminotransferase levels, although not part of the HLH-2004 diagnostic criteria, have been shown to be present in >75% of both adults and children with HLH (51). Elevated levels of aspartate aminotransferase (serum glutamic oxaloacetic transaminase) are part of the HScore diagnostic score for HLH (discussed below). All patterns of liver injury may be seen in HLH (hepatocellular injury, cholestatic injury, or mixed injury patterns). Pathologic examination of

Table 4 Laboratory and pathologic findings of HLH in children and adults

Laboratory or pathologic finding	Pediatric HLH (1)	Adult-onset HLH (1, 4, 28, 38, 80, 101, 102)	Prognostic/diagnostic impact
Cytopenias of >2 lines[a] Hemoglobin <9 g/dL Platelet count $<100 \times 10^9$/L Absolute neutrophil count $<1 \times 10^9$/L	+++++ (~100%) ++++ (88%) ++++ (97%) +++ (69%)	++++ (>85%) +++ (67–94%) +++ (78–94%) +++ (60–69%)	Platelet count $<40 \times 10^9$/L, poor prognostic sign in adults
Hypertriglyceridemia[a] (fasting >265 mg/dL)	+++	+++ (45–85%)	
Hypofibrinogenemia[a] (<150 mg/dL)	+++	++ (36–70%)	
Ferritin >500 ng/mL[a] >10,000 ng/mL	+++++ (~100%) ++++ (90%) Specificity 86%–96% (103)	++++ (85–100%) ++ (43%) Specificity 60% (104)	Higher initial or persistent ferritin elevation, poor prognosis in children and adults
sIL2R >2,400 U/mL[a] >5,000 U/mL	+++++ (~100%) ++++ (93%)	+++++ (~100%) ++++ (90%) Specificity 77%	Absolute level >10,000 U/mL or slow rate of decline, poor prognosis in children
sIL2R/ferritin ratio >2.0	NR	+++ (81%) Specificity 85% (105)	Elevated particularly in lymphoma-associated HLH
Hypoalbuminemia	+++ (69%)	++++ (90–95%)	Poor prognosis in adults
Abnormal renal function	+/– (9%)	++ (16–52%)	
Abnormal liver function tests	+++ (76%)	+++ (71–100%)	
CSF pleocytosis	++ (40%)	Infrequently reported	Poor prognostic sign in children
Hemophagocytosis Bone marrow or spleen Lymph nodes CSF	++++ (92%) +++ (73%) ++ (43%) ++ (31%)	++++ (62–95%)	Amount of bone marrow phagocytosis does not correlate with probability of HLH
Low/absent NK cell activity[a]	NR NK degranulation <5%; sensitivity 96%, specificity 88% (76)	++ (36–67%)	8–15% of adults had NK studies sent

[a]Diagnostic criteria on HLH-2004 grading schema.
Modified from Nikiforow & Berliner (66).
Abbreviations: CSF, cerebrospinal fluid; HLH, hemophagocytic lymphohistiocytosis; NK, natural killer; NR, not reported; sIL2R, soluble interleukin-2 receptor.

the liver in patients with HLH may show lymphocytic infiltration of portal triads as in other causes of chronic active hepatitis (41). Coagulopathy is frequently seen in HLH, and its cause is multifactorial, owing to thrombocytopenia, liver injury and impairment in synthetic function of coagulation factors, and disseminated intravascular coagulation. The presence of hypofibrinogenemia is one of the eight HLH-2004 diagnostic criteria.

Reduced NK cell activity may be seen in HLH as a reflection of an underlying immune defect (75) and is one of the eight HLH-2004 diagnostic criteria. It is typically measured via a radiolabeled chromium release assay; release of cytotoxic granules (containing the radionuclide ^{51}Cr) from NK

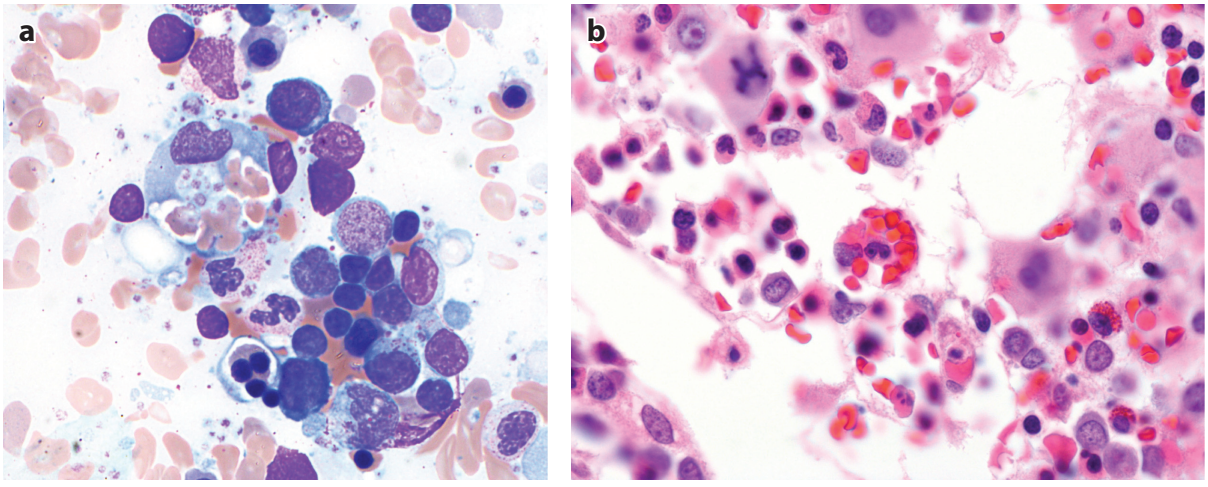

Figure 1

Pathologic images of hemophagocytosis. (*a*) Hemophagocytosis of multiple erythrocytes and platelets by an activated macrophage on a bone marrow aspirate. (*b*) Hemophagocytosis of multiple erythrocytes and a neutrophil by an activated macrophage on a bone marrow core biopsy. Photos courtesy of Dr. Robert Hasserjian.

cells may be reduced in patients with HLH. The sensitivity and specificity of reduced NK cell activity for the diagnosis of HLH appear to be much better in children with HLH than adults (76). Due to the limited availability of the assay and its poor predictive value in adults, it is seldom performed even in large academic centers; in an analysis of multiple large series from academic medical centers, it was sent in only 8–15% of adult patients with HLH (66).

Elevated levels of sIL2Rα, also known as soluble CD25, are among the HLH-2004 diagnostic criteria for the disorder. Dramatically elevated levels of CD25 appear to be relatively specific for HLH (41), and a relatively high soluble CD25/ferritin ratio is useful in the differentiation of lymphoma-associated HLH from so-called benign HLH (nonmalignant etiologies of HLH) (77).

Soluble CD163, the macrophage-specific scavenger receptor for native and chemically modified hemoglobins, is elevated in disorders that result in a significant degree of macrophage activation, such as HLH, but also malignancy, autoimmunity, and infection (78, 79). Levels tend to be much higher in HLH than these other disorders, however. So although it is not specific for HLH, this marker may be assayed to aid in diagnosis (41). This test is not routinely sent at the current time, however, and the sensitivity, specificity, and predictive values of the test have not been well defined.

DIAGNOSIS OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

HLH-2004 Diagnostic Criteria

Timely diagnosis of HLH is of special importance, as patients may be critically ill and delays in diagnosis may result in poor outcomes. Moreover, high-dose immunosuppressive therapy and cytotoxic chemotherapy are typically not administered for other conditions on the differential diagnosis for the disorder, such as bacterial sepsis or life-threatening viral infection. Diagnosis is based on clinical criteria, and no single diagnostic laboratory assay or pathognomonic clinical finding exists that can establish a diagnosis. The most commonly used and widely accepted diagnostic criteria for HLH are the HLH-2004 criteria from the Histiocyte Society:

- Fever
- Splenomegaly
- Cytopenias affecting ≥2 lineages
  - Hemoglobin <9 g/dL
  - Platelet count $<100 \times 10^9$/L
  - Absolute neutrophil count $<1 \times 10^9$/L
- Hypertriglyceridemia and/or hypofibrinogenemia
  - Triglycerides ≥265 mg/dL
  - Fibrinogen ≤150 mg/dL
- Hemophagocytosis in bone marrow, spleen, or lymph nodes
- Low or absent NK cell activity
- Ferritin ≥500 μg/L
- sCD25 (sIL2Rα) ≥2,400 U/ml

These are the criteria (five of eight must be present) utilized for the diagnosis of HLH from the currently ongoing prospective pediatric trial, HLH-2004, modified from the older HLH-94 diagnostic criteria (which required five out of five criteria for HLH diagnosis) (80). Additionally, confirmation of a pathogenic genetic mutation of familial HLH may also be used to establish a diagnosis of familial HLH. There is no consensus on the guidelines for the diagnosis of MAS. Some investigators advocate for use of the HLH-2004 criteria (31), whereas others advocate for specific diagnostic criteria for the MAS complicating sJIA (81).

HScore

A multicenter retrospective cohort of 312 patients judged by an expert panel to have ($n = 162$) or to not have ($n = 104$) HLH, or in whom the diagnosis was not clear ($n = 46$), was used to construct and validate a diagnostic score, dubbed the HScore (also referred to as the H-score by some publications). This score was originally published in 2014. Nine criteria (the presence of immunosuppression, fever, organomegaly; elevations in triglyceride levels, ferritin levels, aspartate aminotransferase/serum glutamic oxaloacetic transaminase levels, and fibrinogen levels; and the presence of cytopenias and hemophagocytosis on bone marrow aspirate) were evaluated for their association with HLH, and logistic regression was used to calculate the weight of each criterion to create a score between 0 and 337, with a higher score corresponding to a higher probability of HLH. The creators of the score found an optimal threshold of 169, which corresponded to a sensitivity of 93% and a specificity of 86%, and accurately classified 90% of the patients in the cohort (82).

The HScore has been compared with the HLH-2004 diagnostic criteria. A Belgian retrospective study analyzed the performance of the HScore in accurately diagnosing 147 patients (73 children and 74 adults) who had a bone marrow biopsy and aspirate performed because of suspected HLH, or whose bone marrow examination revealed hemophagocytosis (regardless of the indication for the biopsy). This cohort of patients included 20 adults and 16 children ultimately diagnosed with HLH. Each patient in the cohort was then evaluated by the HLH-2004 criteria and the HScore. At presentation, the HScore was more efficient than the HLH-2004 criteria at correctly identifying HLH for both children and adults, with a diagnostic sensitivity and specificity of 100% and 80% for children and 90% and 79% for adults, respectively. The performance of the HScore dropped to similar levels as the HLH-2004 criteria once the patient's clinical status worsened, with a sensitivity of 73% for the same specificity. The authors concluded that for children, the HScore was generally more useful than the HLH-2004 criteria, and that for

adults, the HScore was most useful only during initial presentation of the patient. The authors also concluded that the originally published optimal cutoff of 169 should be adapted depending on the target population (83). This has been done in a group of patients with HLH secondary to autoimmune diseases. In a cohort of 94 patients with rheumatologic disease (of whom 30 had HLH and 64 were controls), the optimal cutoff value was found to be 190.5 (sensitivity of 96.7% and specificity of 98.4%) (84).

Other Diagnostic Scoring Systems and Criteria

Other diagnostic scoring systems and criteria have been examined for certain HLH populations (e.g., MAS), but none has gained widespread acceptance (82).

TREATMENT AND PROGNOSIS OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Treatment Rationale

Because HLH is a syndrome of unbridled immune activation, the goal of therapy is to reverse the deleterious uncontrolled immune response. The mainstay of acute therapy includes immunosuppressive and myelosuppressive agents, most frequently high-dose corticosteroids, typically dexamethasone, and the epipodophyllotoxin topoisomerase-II inhibitor etoposide. Without treatment, primary HLH is nearly uniformly fatal (85). Mortality rates in patients with secondary HLH without treatment are not as well defined, but the current literature suggests a mortality rate of 50–75% (24).

This review discusses treatment of HLH in both children and adults, although there are no prospective clinical trials of the first-line treatment of HLH in adults; much of the treatment recommendations in adults are extrapolated from the data in children. Similarly, patients with primary HLH and those with secondary HLH are generally initially treated the same (indeed, the presence or absence of underlying genetic defects is almost never known at the time of initial presentation). An important distinction, however, is that of postremission management. Primary HLH patients are universally receive stem cell transplant following achieving remission of their initial disease if it is not contraindicated, whereas this is more variable in secondary HLH.

History

In 1980, Ambruso and colleagues (86) published the first successful cases of remission induction in two children with HLH treated with etoposide; although the use of this cytotoxic therapy proved successful at induction of a first remission, patients would invariably relapse and often succumb to fatal central nervous system (CNS) disease. In 1985, Fischer and colleagues (87) published a series of four children with HLH in which remission was successfully induced using a combination of etoposide, corticosteroids, intrathecal methotrexate, and cranial irradiation, allowing for a more durable remission. Similarly, the efficacy of the related epipodophyllotoxin topoisomerase-II inhibitor teniposide in remission induction was demonstrated in 1986 (88).

Unfortunately, even with an approach that incorporated CNS-directed therapy as part of induction, children with familial HLH who achieved remission would eventually relapse and die of HLH. Fischer and colleagues (89) published the first case of successful allogeneic HSCT in a child with primary, familial HLH in 1986. Furthermore, in 1993, an alternative treatment approach utilizing immunotherapeutic agents in lieu of an epipodophyllotoxin was published (90).

The authors treated six patients with a combination of methylprednisolone, rabbit antithymocyte globulin, and cyclosporin A, which was successful in five of the six cases.

HLH-94 Trial

The HLH-94 trial was the first international HLH clinical trial, and combined myelosuppressive/cytotoxic treatment with epipodophyllotoxins with immunosuppressive therapy. A total of 249 children (<16 years old) with HLH as defined by the HLH-94 diagnostic criteria (requiring the presence of all five of the following: fever, splenomegaly, bicytopenia or pancytopenia, hypertriglyceridemia or hypofibrinogenemia, and evidence of hemophagocytosis without evidence of underlying malignancy) were enrolled from July 1994 through December 2003. These patients were treated with an initial 8-week-long therapeutic course of etoposide (150 mg/m^2 twice weekly for two weeks and then weekly) plus dexamethasone (initial dose of 10 mg/m^2, slowly tapered over the 8-week initial course of treatment). After the initial 8-week therapy, children with either known familial disease or persistent nonfamilial disease received continuation therapy as a bridge to allogeneic HSCT. Continuation therapy consisted of cyclosporine A, dexamethasone, and etoposide, with intrathecal methotrexate administered in the case of progressive neurological symptoms or a persistently abnormal CSF. Conditioning for allogeneic HSCT included cyclophosphamide, busulfan, and etoposide, with horse antithymocyte globulin added in transplants from matched unrelated donors; graft-versus-host-disease prophylaxis was carried out with a combination methotrexate and cyclosporine A (91). The most recent publication of long-term outcomes from the trial, published in 2011, demonstrated an estimated 5-year probability of survival of 54% +/− 6% (median follow-up of 6.2 years) (28). 29% of patients died before receiving allogeneic HSCT stem cell transplantation, and 5-year survival for those who did receive HSCT was 66 +/− 8%. No patient with familial HLH survived without receiving a stem cell transplant.

HLH-2004 Trial

The HLH-2004 trial, the second international HLH study and successor to HLH-94, is currently ongoing. HLH-2004 protocol modified the HLH-94 criteria, adding low or absent NK cell activity, hyperferritinemia, and high sIL2Rα levels to the five diagnostic criteria from HLH-94, and requiring five of eight criteria to be satisfied for diagnosis and study inclusion. The HLH-2004 chemoimmunotherapy protocol was modified from its predecessor, adding cyclosporine A during the initial therapy phase and adding intrathecal prednisolone to intrathecal methotrexate in the treatment of CNS disease (80). The results of this trial are not yet available, although preliminary reports suggest that adding upfront cyclosporine offered no clinical advantage; therefore, most centers still utilize the HLH-94 protocol for the treatment of HLH.

Treatment of Adult Patients

As previously noted, no prospective trials for the first-line treatment of HLH in adults exist. Adult patients are therefore treated with regimens that approximate the HLH-94 protocol. Although traditionally used only in patients who relapse, transplantation is used increasingly in patients with disease that is difficult to control, that responds slowly to therapy, or that recurs following remission. Reduced intensity conditioning, such as with fludarabine and busulfan, has been shown to be superior to fully myeloablative conditioning in patients with HLH, and this approach has been widely adopted (92). Moreover, conditioning regimens have been modernized, incorporating

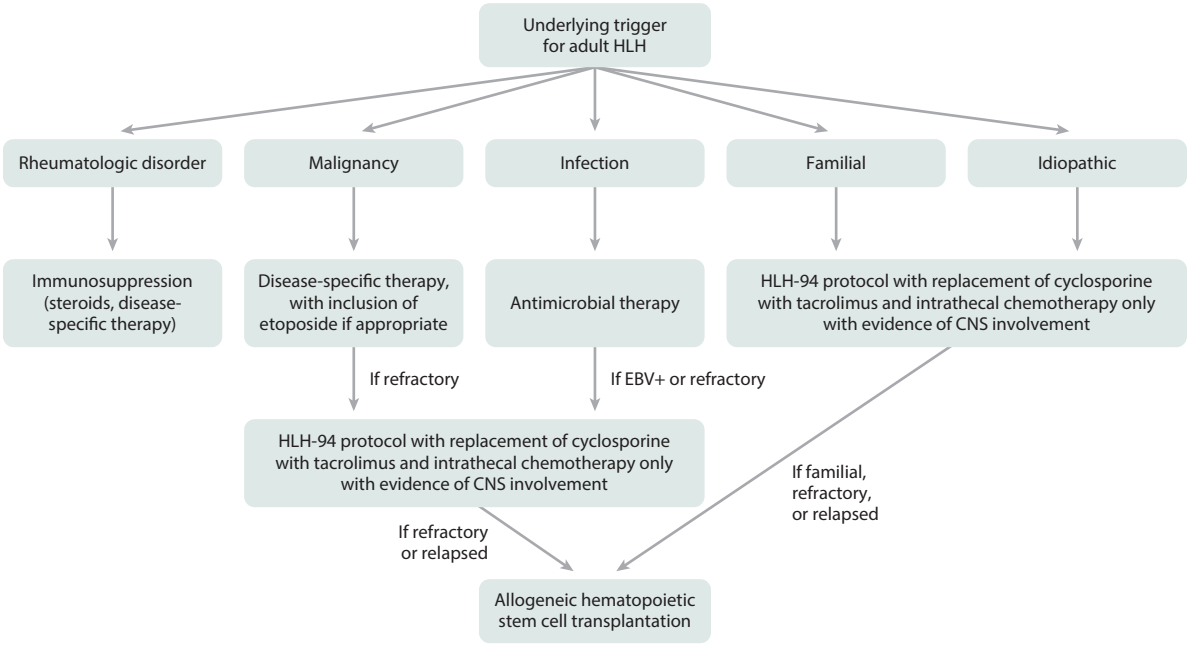

Figure 2

Graphical representation of the authors' algorithm for the treatment of adult HLH. Abbreviations: CNS, central nervous system; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis.

the anti-CD52 monoclonal antibody alemtuzumab as a preparatory agent (93). A representative algorithm for the treatment of adult patients with HLH is shown in **Figure 2**.

Because a significant minority of adults do not respond to treatment according to the HLH-94 protocol or its variations, investigations into salvage therapeutic options have been undertaken in recent years. In 2015, the results of a prospective, multicenter Chinese trial examining the utility of combination doxorubicin, etoposide, and methylprednisolone (DEP) in refractory adult HLH patients were published (94). Unlike the HLH-94 trial in children (which excluded patients with underlying malignancy or immunosuppression), nearly half of the 63 patients enrolled had lymphoma-associated HLH. Of this refractory adult population, 27.0% achieved a complete response, 49.2% achieved a partial response, and the remaining patients died within 4 weeks of receiving therapy. Of the 48 responding patients, 29 survived to receive further chemotherapy, allogeneic HSCT, or splenectomy. This was the first prospective clinical trial in adult HLH. The following year, the same group published results of a modified DEP regimen plus PEG-asparaginase (L-DEP) for the treatment of refractory EBV-associated HLH, which resulted in an overall response rate of 85.7% (95).

Experimental Agents

Over the past several years, novel targeted agents have been identified as possible treatments for HLH. Two of these agents are discussed briefly in this section.

Ruxolitinib. The Janus kinase 1/2 inhibitor ruxolitinib, currently FDA approved in the United States for the treatment of primary myelofibrosis and polycythemia vera, has been examined

in a murine model of HLH. Cytotoxicity-impaired *PRF1*(−/−) and *Rab27a*(−/−) mice with the manifestations of HLH were treated with ruxolitinib, with improvement in manifestations in both murine models (specifically improvement in cytopenias, rapid decrease in serum IL-6 and TNF-α levels, improvement in liver injury, and reduction in CNS involvement). Such positive results of an off-the-shelf, currently available agent are encouraging because clinical trials could readily be undertaken in humans (96).

Emapalumab. Emapalumab (NI-0501, Novimmune) is a fully human, high-affinity anti-IFN-γ monoclonal antibody that binds to and neutralizes human IFN-γ. In 2015, the first results from an open-label phase II study of emapalumab in 13 children with primary HLH were reported (97). Twelve of the children were refractory to standard first-line therapy or intolerant of it; one child was treated with emapalumab in the first-line setting. The majority of the patients were felt to have severe disease, and nine had a known HLH-associated genetic defect. Nine of the 13 patients achieved a satisfactory response, with seven proceeding to allogeneic HSCT; in total, 11 of the 13 patients were alive at 8 weeks.

Treatment of Macrophage Activation Syndrome

No controlled studies on the management of MAS exist, and so treatment is primarily based on case series and expert recommendations. It is clear that these patients, unlike those with primary HLH, do not require first-line therapy with cytotoxic agents according to the HLH-94 protocol and instead are best treated with high-dose corticosteroids plus any relevant therapy directed at the underlying autoimmune disease (31). Cases refractory to corticosteroids have been successfully treated with cyclosporine A (98), and the efficacy of this agent has led to its use in first-line therapy by some investigators (31).

The efficacy of cytotoxic agents such as etoposide in the refractory setting is not well defined. Targeted anticytokine therapies, such as etanercept, anakinra, and tocilizumab, have also shown promise in the treatment of MAS (31).

Prognosis

Early studies of children with familial HLH demonstrated that the disease is almost uniformly fatal without therapy (85). Long-term follow-up from the HLH-94 trial demonstrated an estimated 5-year probability of survival of 54% with a median follow-up of 6.2 years. Factors in this trial that predicted poor prognosis included very young age at the start of therapy (41% survival at <6 months of age versus 65% survival at >6 months of age) and neurologic involvement (40% versus 67%); the presence or absence of a causative mutation was not predictive of a worse outcome, although the vast majority of patients with causative mutations underwent allogeneic HSCT, versus approximately half of those without causative mutations (28). The rate of decline of serum ferritin in children with HLH was found to be prognostic in a retrospective study, which demonstrated a substantial increase in the likelihood of death for patients who had a ferritin decline of <50% versus those with a 96% or greater decline with treatment [odds ratio (OR) = 17.42]; a higher-peak ferritin measured within the first 3 weeks after presentation was also a poor prognostic indicator (OR = 5.6) (99).

The most common late effects in HLH-94 trial survivors were neurologic (such as severe mental retardation, cranial nerve palsies, and epilepsy), occurring in 19% of all surviving patients and 31% of surviving familial HLH patients. Non-neurologic late effects, which occurred in

16% of patients, included nutritional problems, growth retardation, hypertension, impaired renal function, obstructive bronchiolitis, and hearing impairment (28).

Conclusions regarding the prognosis of adults with HLH have been drawn from large published case series; outcomes have generally been poor. In a recent large retrospective US cohort of 68 adults with HLH, 31% of patients were alive after 32.2 months of median follow-up; the median overall survival was 4 months. Patients with malignancy-associated HLH had the worst prognosis, with a median survival of 2.8 months (versus 10.7 months for those with nonmalignancy-associated disease). The median survival for patients receiving an allogeneic HSCT was 21.5 months (29). In a large European cohort of 162 adult patients with HLH, features associated with a poor prognosis in multivariate analysis were advanced age, lower platelet count, underlying lymphoma, and lack of inclusion of etoposide in the initial therapeutic regimen (100).

CONCLUSION

HLH is a multisystem disorder of immune dysregulation, typically in the setting of an immunologic challenge, that results in serious morbidity and mortality. Although HLH was originally described in 1939, it is within the past three decades that the majority of the literature has been published, and therefore, the current understanding of the disorder has developed. Understanding of the pathophysiology of the disease is incomplete and epidemiologic data in adults are sparse. Very few prospective trials have been performed in the treatment of this rare disease, and fewer still in adult patients, with the first prospective trial of treatment of adult HLH published in 2015. Improved understanding of the disorder, refined diagnostic criteria, and advancements in measurable markers of disease will allow for earlier diagnosis and prompt initiation of novel disease-modifying therapies, which will improve outcomes for this challenging, life-threatening syndrome.

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