

# Hemophagocytic lymphohistiocytosis: review of etiologies and management

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**Abstract:** Hemophagocytic lymphohistiocytosis (HLH) covers a wide array of related life-threatening conditions featuring ineffective immunity characterized by an uncontrolled hyperinflammatory response. HLH is often triggered by infection. Familial forms result from genetic defects in natural killer cells and cytotoxic T-cells, typically affecting perforin and intracellular vesicles. HLH is likely under-recognized, which contributes to its high morbidity and mortality. Early recognition is crucial for any reasonable attempt at curative therapy to be made. Current treatment regimens include immunosuppression, immune modulation, chemotherapy, and biological response modification, followed by hematopoietic stem-cell transplant (bone marrow transplant). A number of recent studies have contributed to the understanding of HLH pathophysiology, leading to alternate treatment options; however, much work remains to raise awareness and improve the high morbidity and mortality of these complex conditions.

**Keywords:** macrophage activation syndrome, hyperinflammatory response

## Introduction

Hemophagocytosis is the engulfment of hematopoietic cells by activated macrophages acting outside of usual immune system regulations. Hemophagocytic lymphohistiocytosis (HLH) covers a wide array of related diseases including HLH, autosomal recessive familial HLH (FHL), familial erythrophagocytic lymphohistiocytosis, viral-associated hemophagocytic syndrome, and autoimmune-associated macrophage activation syndrome (MAS). These disorders feature severe cytopenias due to this uncontrolled hemophagocytosis. Other laboratory signs and clinical symptoms result from disordered immune regulation and cytokine storm. The term primary HLH refers to an underlying genetic abnormality causing the disorder, whereas secondary HLH indicates that the disorder is secondary to underlying conditions such as infection, autoimmune/rheumatologic, malignant, or metabolic conditions. For the purposes of this review, FHL will indicate cases with a primary genetic cause, secondary HLH will refer to cases secondary to infection, malignancy, or metabolic disorders, and MAS will refer to cases associated with autoimmune diseases.

Much has been learned about HLH in the 75 years since it was first discovered. One of the earliest descriptions of the disease was in 1939 when Scott and Robb-Smith<sup>1</sup> described a disorder featuring erythrophagocytosis by proliferating histiocytes in the lymphoreticular system and called it “histiocytic medullary reticulosis” or HMR. It was later classified among malignant histiocytosis. Later in 1952, the familial form of HLH, FHL, was more fully described by Farquhar and Claireaux<sup>2</sup> with the cases of two siblings who succumbed to HLH, and later in 1958, another sibling from this

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same family presented in the same manner.<sup>3</sup> Risdall was among the first to describe a viral association with HLH and proposed that the condition be called virus-associated HLH, distinct from malignant histiocytosis.<sup>4</sup> In the years since, researchers have recognized the wide scope of this disease and the fact that infection often triggers both primary and secondary HLH. Regardless of cause, physiologically, HLH is characterized by defective cytotoxic cell function coupled with unbridled macrophage activity, leading to excessive cytokine production, subsequent immune dysregulation, and tissue damage. Left untreated, the dysregulated inflammatory response causes severe neutropenia, and patients often die from bacterial or fungal infections. The condition carries high morbidity and mortality.<sup>5</sup> Long-term survival in 1983 was estimated to be as low as 4%.<sup>6</sup> The median survival without treatment is estimated at <2 months.<sup>6</sup>

## Diagnosis

The diagnosis of FHL or secondary HLH is based on a number of clinical signs and laboratory findings. Due to the relatively nonspecific nature of the clinical signs and symptoms, and significant overlap with other illnesses, diagnosis is often delayed. The official diagnosis of HLH, established by the Histiocyte Society, is based on fulfilling one or both of the following criteria:

1. A molecular diagnosis consistent with HLH
2. Five out of the following nine diagnostic criteria for HLH: fever, splenomegaly, cytopenias (affecting two or more of three lineages in the peripheral blood), hypertriglyceridemia, hypofibrinogenemia, elevated ferritin, hemophagocytosis in bone marrow/spleen/lymph nodes, low or absent natural killer (NK)-cell activity, or elevated soluble CD25 (interleukin [IL]-2 receptor).<sup>7,8</sup>

All of the clinical and laboratory findings are readily linked to the pathophysiology of HLH. Fever is the result of high IL levels. Splenomegaly is the direct result of infiltration by lymphocytes and macrophages. Cytopenias can be explained by high concentrations of tumor necrosis factor (TNF)- $\alpha$  and interferon (IFN)- $\gamma$ , as well as direct hemophagocytosis. High triglycerides are secondary to decreased lipoprotein lipase activity initiated by increased TNF- $\alpha$  levels. Elevated ferritin >10,000  $\mu\text{g/L}$  has been demonstrated to be 90% sensitive and 96% specific for HLH.<sup>9-12</sup> Ferritin is believed to accumulate during the anti-inflammatory process of macrophage scavenging of heme via the CD163 receptor. High concentrations of soluble IL-2 receptor are produced by activated lymphocytes.<sup>13</sup>

A summary of clinical and laboratory findings is provided in Table 1.

Coagulopathy is a prominent feature of HLH, as low fibrinogen is found in the majority of patients. Further coagulation studies have demonstrated normal factor V and VIII levels and an absence of fibrin split products. These findings provide evidence against disseminated intravascular coagulation, a diagnosis that may overlap with HLH due to the shared findings of thrombocytopenia and hypofibrinogenemia.<sup>21</sup> It is believed that macrophages may secrete plasminogen activators which accelerate the conversion of plasminogen to plasmin, subsequently degrading fibrinogen. Fibrin split products may be phagocytized by macrophages in the reticuloendothelial system. Given the normal coagulation factors measured in HLH, liver failure, while often present, is not related to the coagulopathy. The hepatomegaly, elevated transaminases, and bilirubin are believed to be the direct result of organ infiltration by lymphocytes and histiocytes.<sup>18</sup>

Ironically, despite the fact that hemophagocytosis is prominently featured in the name of this disease, it is rarely found at presentation in secondary cases and may not be visible until late in disease progression. Bone marrow biopsies performed early in the course of secondary disease may be normal or demonstrate very nonspecific findings such as increased or decreased unilineage or multilineage hematopoiesis. Repeat studies may be necessary to show these findings. FHL, on the other hand, may demonstrate prominent hemophagocytosis from the start. An immunohistochemical stain for CD163 may be useful, as upregulation of this receptor facilitates hemophagocytosis.<sup>22</sup> In cases in which cerebrospinal fluid is obtained, pleocytosis is sometimes noted with lymphocytes, histiocytes, and an increased protein level. Microscopic review of spun cerebrospinal fluid may demonstrate hemophagocytosis.<sup>6</sup> While many of the laboratory tests are readily available, evaluation of IL-2 receptor and NK-cell activity may require sending specimens out to specialized reference laboratories and may not be a timely option for clinical diagnosis. When available, comparison of IFN- $\gamma$ , IL-10, and IL-6 may be useful for distinguishing between bacterial sepsis, viral infections, and HLH. Using the criteria IFN- $\gamma$  >75  $\text{pg/mL}$ , and IL-10 60  $\text{pg/mL}$ , sensitivity and specificity of diagnosing HLH is 98.9% and 93.0%, respectively.<sup>23</sup> Additionally, measuring plasma levels of CD163, a receptor for hemoglobin-haptoglobin complexes, may also be helpful in distinguishing HLH from other purely infectious diseases.<sup>24</sup>

Flow cytometry may be used to identify and quantify levels of several useful markers involved in the

**Table 1** Incidences of clinical and laboratory findings in FHL and secondary HLH

Finding	Percentage of FHL cases with finding at diagnosis <sup>6,13-15</sup>	Percentage of secondary HLH cases with finding at diagnosis <sup>16,17</sup>	Diagnostic criteria <sup>7,14,18</sup>
Fever	~100%	~100%	>37°C
Hepatosplenomegaly	~100%	~80%–90%	Radiographic or physical exam evidence
Cytopenias	~100%	~80%	Hemoglobin <9 g/dL Platelets <100 × 10 <sup>9</sup> /L Neutrophils <1.0 × 10 <sup>9</sup> /L
Hypertriglyceridemia (fasting)	70%	40%	>3 mmol/L
Hypofibrinogenemia	60%–65%	40%	<1.5 g/L
Elevated ferritin	70%	95%	>500 µg/L
Hemophagocytosis	85%	Variable and not necessary to make initial diagnosis if other features present <sup>19,20</sup>	Bone marrow or other tissue biopsy
Decreased NK-cell activity	100%	30%	<10% activity by flow cytometric assays
Elevated sCD25	90%	Percentage not found in secondary HLH literature	>2,400 U/mL
LDH	40%–45%	100%	≥500 U/L
ALT	30%–35%	Percentage not found in secondary HLH literature	≥100 U/L
AST	30%–35%	Percentage not found in secondary HLH literature	≥100 U/L
Bilirubin	~30%	Percentage not found in secondary HLH literature	≥34 µmol/L
CSF cells	35%–40%	Percentage not found in secondary HLH literature	≥5/µL
CSF protein	45%	Percentage not found in secondary HLH literature	≥0.5 g/L

**Abbreviations:** ALT, alanine transaminase; AST, aspartate aminotransferase; CSF, cerebrospinal fluid; FHL, familial HLH; HLH, hemophagocytic lymphohistiocytosis; LDH, lactate dehydrogenase; NK, natural killer; sCD25, soluble CD25.

pathophysiology of HLH. A rapid flow cytometric analysis of intracellular X-linked inhibitor of apoptosis protein (XIAP) has been developed for detection for X-linked lymphoproliferative disease and carrier state, which has also proven useful following bone marrow transplant to monitor reconstitution.<sup>25,26</sup> A prospective evaluation of degranulation assays was found to be useful in the differential diagnosis of FHL. CD107 may serve as a useful surrogate marker for reduced or absent NK-cell and cytotoxic T-cell activity. Using an assay for surface upregulation of CD107a on NK-cells and cytotoxic T-lymphocytes in a large cohort of patients under evaluation for HLH, the vast majority of patients with FHL subtypes 3–5 and Griscelli syndrome (GS) type 2 or Chediak–Higashi syndrome (CHS) had abnormal resting NK-cell degranulation. NK-cell degranulation was found to be normal in the majority of patients with FHL type 2 and X-linked lymphoproliferative disease. Instead these patients were found to have diminished intracellular SAP (SLAM [signaling lymphocytic activation molecule]-associated protein), XIAP, and perforin expression. Most patients with secondary HLH did not have abnormalities of

NK-cell degranulation. Thus, degranulation assays may help speed the diagnosis of HLH and allow treatment to begin more rapidly.<sup>27</sup> Degranulation of CD107 may be associated with a specific type of FHL (FHL-5) in which missense mutations lead to decreased lymphocyte stability of syntaxin binding protein 2 (Munc18-2) and syntaxin 11. These proteins would normally be involved in regulating vesicle transport to the plasma membrane, which is key to the pathophysiology of HLH.<sup>28</sup>

Flow cytometry for perforin staining in cytotoxic lymphocytes, including NK-cells, CD8+ T-cells, and CD56+ T-cells, seems to be useful as a quick and reliable marker for perforin gene mutations seen in HLH. In a study of eleven unrelated HLH patients and 19 family members, four of seven patients with FHL showed lack of intracellular perforin in all cytotoxic cell types, which corresponded to mutations in the perforin gene. The parents of these patients also had abnormal perforin staining, indicative of their carrier state for perforin mutations. Evaluation of cytotoxic T-cells from the other three patients with FHL demonstrated normal percentages of perforin staining cytotoxic T-cells. The four patients with

Epstein–Barr virus (EBV)-associated secondary HLH had depressed numbers of NK-cells but increased CD8+ T-cells with perforin expression.<sup>29</sup> Flow cytometry studies have proven to be a rapid and useful modality to reliably diagnose HLH and shorten the time to treatment.<sup>29</sup>

## Epidemiology

It is difficult to assess the true epidemiology of HLH. The disease has been studied extensively in Sweden, where the incidence of FHL is estimated at 1 in 50,000 live births.<sup>14,30</sup> Overall, an estimate of HLH in children <18 years old across ethnicities and races is approximately 1 in 100,000.<sup>31</sup> Other large series have been described in Hong Kong and Taiwan; however, worldwide, the incidence of FHL is unknown, and even less epidemiologic data are available regarding acquired HLH cases.<sup>15,32–34</sup> It is largely believed that the condition is underrecognized, as hemophagocytosis is often not pathologically evident until autopsy. The familial types are usually diagnosed in childhood, while secondary HLH can occur at any age.

## Associated illnesses

A number of conditions are associated with secondary HLH. By prevalence, these include viral infections (29%), other infections (20%), malignancies (27%), rheumatologic disorders (7%), and immune deficiency syndromes (6%).<sup>35</sup> These inciting conditions are addressed below.

## Infections

Both sporadic and familial cases of HLH can be initiated by infectious causes; however, it is important to distinguish between primary, genetic cases versus secondary, as treatment of the underlying condition may be attempted in the latter. All patients who meet the criteria should be tested for a precipitating infection, including culture of blood and urine, chest radiography, and screening for EBV, cytomegalovirus, parvovirus B19, human immunodeficiency virus (HIV), and human herpes virus-6. Throat and rectal swabs for viral culture may also prove useful. HLH has also been linked to HIV-associated infections such as pneumocystosis and histoplasmosis, so appropriate screening of infected patients should be considered. It is also recommended that patients with a travel history be screened for relevant infections.<sup>36</sup>

The possible role of infectious diseases in causing HLH was first elucidated in 1979 in a case series describing renal transplant patients with a viral-associated HLH (viral-associated hemophagocytic syndrome).<sup>4</sup> EBV,

a DNA (deoxyribonucleic acid) virus and member of the Herpesviridae family has been the most consistently reported virus associated with HLH.<sup>36–52</sup> The majority of EBV-associated HLH cases have been reported in Asia, with limited information on the incidence elsewhere in the world. A Japanese study estimated the annual incidence of HLH at 1 in 800,000 persons per year, with 90% of these cases being secondary and one-third of these secondary cases being related to EBV. This leads to an estimated annual incidence of 0.4 cases of EBV-associated HLH per million persons. Some have theorized that the higher rates of EBV-associated HLH in Asian countries may be due to a more pathogenic strain of EBV.<sup>53</sup> Several studies have performed sequence analysis of the EBV nuclear antigen 2 (*EBNA-2*) gene and latent membrane protein-1 (*Imp-1*). These studies have demonstrated that no single sub-strain of EBV has been linked to HLH as of yet.<sup>54–56</sup> It appears that new infection as well as reactivation of latent EBV infection may predispose individuals to HLH. Quantitative determination of EBV genome copy numbers in peripheral blood may be useful in predicting prognosis and effectiveness of therapy.<sup>57,58</sup> Interestingly, male patients with EBV-associated HLH may have mutations in the *SH2D1A* gene, which is traditionally associated with X-linked lymphoproliferative syndrome (XLPS). XLPS is characterized by immunodeficiency to EBV. A Japanese study performed genetic analysis of the *SH2D1A* gene in 40 male patients presenting with severe EBV-associated illnesses, including fulminant infectious mononucleosis, EBV-positive lymphoma, and chronic EBV infection, finding mutations in a quarter of these patients. Given this strong association, it is recommended that male patients with EBV-associated HLH be screened for XLPS.<sup>59</sup> While fulminant infectious mononucleosis may overlap with EBV-associated HLH, higher viral loads are seen in EBV-associated HLH.<sup>54</sup>

While not as commonly reported nor as well defined as EBV, many other viruses may be associated with HLH. These can be best organized by DNA or RNA (ribonucleic acid) and, subsequently, by virus family, as listed in Table 2.

A few years after Risdall et al<sup>103</sup> described a possible viral etiology for HLH, this group discovered links to bacteria as well. The most common bacterial infections associated with HLH are given in Table 3.

After the first bacteria-associated HLH cases were identified, a connection to protozoan, parasitic, and fungal infections was not far behind. Numerous reports of parasite-associated HLH have also been reported, with leishmaniasis<sup>83,128–140</sup> and malaria<sup>141,142</sup> being the most common. A more comprehensive

**Table 2** Viruses associated with secondary HLH

Nucleic acid	Virus family	Virus	Notes
DNA	Adenoviridae	Adenovirus	Primary adenovirus pneumonia and a case of adenovirus infection after bone marrow transplant <sup>60,61</sup>
	Parvoviridae	Parvovirus B19	Complication of treatment for hematologic malignancy and post-solid organ transplant <sup>48,57,62-65</sup>
	Herpesviridae	Herpes simplex virus	Infected neonates and a pregnant woman <sup>66,67</sup>
		HHV-8	Immunosuppressed children and also adults co-infected with HIV <sup>68-70</sup>
		Varicella zoster	Reactivation of virus in immunosuppressed patients, not readily recognized <sup>71</sup>
	Poxviridae	Cytomegalovirus	Patients with autoimmune disease on immunosuppressive drugs <sup>72,73</sup>
	Hepadnaviridae	Hepatitis B	Hepatitis B and C infected patient who developed hemophagocytosis <sup>74</sup>
RNA	Reoviridae	Rotavirus	Described in a rare case report of encephalopathy and HLH following rotavirus infection <sup>75</sup>
	Picornaviridae	Enterovirus	Neonatal enterovirus sepsis with encephal meningitis <sup>76</sup>
		Coxsackie	Vertical transmission to a neonate
	Coronaviridae	SARS	Lung pathology of this virus and in patient data of an early SARS epidemic in Taiwan <sup>77,78</sup>
	Togaviridae	Rubella virus	Concurrent infection with <i>Mycoplasma pneumonia</i> in an infant with HLH, unclear as to causation <sup>79</sup>
	Flaviviridae	Dengue virus	Rare cases in adults <sup>80,81</sup>
		Hepatitis C	Described in adults with co-infection with other hepatitis strains <sup>82</sup>
	Orthomyxoviridae	Influenza viruses A, B, and C	Various influenza viruses implicated, several fatal H5N1 cases <sup>83-91</sup>
Paramyxoviridae	Measles virus	Children with measles <sup>92,93</sup>	
Bunyaviridae	Hantavirus	Adult living in rural area of South Korea <sup>94</sup>	
		Crimean-Congo hemorrhagic fever	Turkish patients <sup>95-98</sup>
RNA reverse transcribed into DNA	Retroviridae	HIV	Patients usually have infections secondary to defective immunity due to HIV <sup>57,99-102</sup>

**Abbreviations:** DNA, deoxyribonucleic acid; H5N1, avian flu; HHV, human herpes virus; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; RNA, ribonucleic acid; SARS, severe acute respiratory syndrome virus.

discussion of zoonoses associated with HLH is presented in Cascio et al.<sup>83</sup> The most common protozoans associated with HLH are presented in Table 4.

Fungal organisms may cause HLH, either as a primary cause or in association with immunosuppression, as in HIV infection. Common fungal organisms associated with HLH are listed in Table 5.

## Malignancy-related

Malignancies are associated with a significant percentage of secondary HLH cases (up to 27%).<sup>35</sup> Among these cases, hematologic malignancies are most prevalent. These hematologic disorders can be best classified according to cell type. In children, HLH is most commonly associated with acute B-lymphoblastic leukemia.<sup>154</sup> The cytokines released in malignancy, mainly IL-2, IL-6, IL-10, IL-12, IFN- $\gamma$ , and TNF- $\alpha$  are believed to be the

inciting factor for malignancy-associated HLH. An overview of malignancies associated with HLH is given in Table 6.

An added complication to the understanding of HLH is the observation that HLH has been seen in the first 4 weeks following hematopoietic stem-cell transplant (HSCT) for malignant disease.<sup>61,63,166-168</sup> Post-transplant HLH can be particularly difficult to diagnose, as clinical and laboratory signs overlap with recovering bone marrow.

## Autoimmune disease

HLH is well known to occur in the setting of various autoimmune disorders. Lupus erythematosus is one of the more common conditions reported.<sup>35,169-178</sup> MAS is a serious and often fatal complication in children with systemic juvenile idiopathic arthritis (sJIA)<sup>175,179-186</sup> and in adults with Still's disease.<sup>35,181,187-189</sup> While MAS is generally considered a type of secondary HLH,

**Table 3** Bacteria associated with secondary HLH

Bacterium	Notes
<i>Babesia</i> sp.	Asplenic, immunosuppressed patients <sup>104,105</sup>
<i>Bartonella</i> sp.	Described in renal transplant patients <sup>106</sup>
<i>Borrelia</i> sp.	Rare case found in Lyme disease <sup>107</sup>
<i>Brucella</i> sp.	Infections primarily seen in Turkish children <sup>108–110</sup>
<i>Coxiella burnetii</i>	Variety of patients with Q fever <sup>111–113</sup>
<i>Ehrlichia chaffeensis</i>	Children <sup>114–117</sup>
<i>Leptospira</i> sp.	Rare case noted in a Hungarian journal with English abstract available <sup>118</sup>
<i>Listeria</i> sp.	Hematopoietic stem cell transplant patient <sup>119</sup>
<i>Mycoplasma pneumoniae</i>	Rare cases in children with no other risk factors for HLH <sup>79,120</sup>
<i>Mycobacterium avium</i>	Complication in a patient with systemic lupus erythematosus <sup>121</sup>
<i>Mycobacterium bovis</i> – weakened form (Bacillus Calmette–Guérin)	Vaccination in endemic tuberculosis regions has been linked to rare cases of HLH <sup>122,123</sup>
<i>Mycobacterium tuberculosis</i>	Variety of cases including patients with FHL, immunosuppression, and HLH, with tuberculosis as the inciting agent <sup>101,124–127</sup>

**Abbreviations:** FHL, familial HLH; HLH, hemophagocytic lymphohistiocytosis.

some children with sJIA may have heterozygous expression of some genes associated with HLH.<sup>182</sup> MAS often presents in sJIA children shortly after initiation of non-steroidal anti-inflammatory drugs. Other rheumatologic conditions have been associated with HLH, including polyarteritis nodosa, mixed connective disease, pulmonary sarcoidosis, systemic sclerosis, and Sjögren's syndrome.<sup>35</sup> MAS is considered a unique type of HLH and is detailed in the literature elsewhere.

## Other conditions

The genetic causes of HLH can be divided into two groups: 1) FHL and 2) immune deficiencies such as CHS, GS, and XLPS. FHL was first described in 1952 by Farquhar and Claireaux,<sup>2</sup> with HLH as the only manifestation.<sup>3</sup> They described the tragic case of two siblings who developed a rapidly fatal illness, with fever, diarrhea, and vomiting, at 9 weeks of age and termed the illness familial hemophagocytic reticulosis. The children had hepatosplenomegaly without lymphadenopathy. They also had pancytopenia. Both infants died, and at autopsy, histiocyte proliferation with active hemophagocytosis was readily apparent

**Table 4** Protozoa associated with secondary HLH

Protozoa	Notes
<i>Leishmania</i> sp.	Described in children and adults in endemic countries <sup>130,138–140</sup>
<i>Plasmodium</i> sp.	Primarily <i>Plasmodium vivax</i> infections <sup>141,142,147</sup>
<i>Toxoplasma gondii</i>	Post-renal and hematopoietic stem-cell transplant patients <sup>148,149</sup>

**Table 5** Fungi associated with secondary HLH

Fungus	Notes
<i>Candida</i> sp.	Found in an HIV-infected patient <sup>150</sup>
<i>Cryptococcus neoformans</i>	Child with cryptococcal meningitis <sup>151</sup>
<i>Histoplasma capsulatum</i>	Primarily in HIV-infection, other immunodeficiencies/suppression, or malignancy <sup>143–146,152</sup>
<i>Penicillium marneffeii</i>	Woman with Sjögren's syndrome <sup>153</sup>

**Abbreviation:** HIV, human immunodeficiency virus.

in the lymph nodes, spleen, liver, and kidney. A third child from the same family was unaffected, but the fourth was affected, as reported by Farquhar in 1958.<sup>3</sup> Numerous other cases under various other names have been reported in the medical literature, including familial erythrophagocytic lymphohistiocytosis, familial lymphohistiocytosis, and generalized lymphohistiocytic infiltration to name a few.<sup>190–196</sup> A high percentage (up to 24%) of FHL cases are associated with parental consanguinity.<sup>8</sup>

As for immune deficiency syndromes associated with HLH, CHS, and GS, both have abnormalities of cellular granules. CHS typically features albinism and recurrent pyogenic infections due to deficient white blood cells with decreased chemotaxis and containing giant lysosomal inclusion bodies. GS also features albinism/hypopigmentation and neutrophil dysfunction. XLPS is associated with a marked vulnerability to EBV infection and subsequent viral-associated HLH and an immune system predisposed to lymphomas and dysgammaglobulinemia.<sup>18</sup> Up to 60% of patients may develop EBV-HLH in this rare condition. Other conditions associated with a predisposition to HLH and reported in the literature include common variable immunodeficiency,<sup>197,198</sup> renal transplant patients,<sup>144,199</sup> Hermansky–Pudlak syndrome,<sup>200,201</sup> to name a few.

## Pathophysiology

An understanding of the defective function of several types of immune cells in HLH has greatly enhanced our knowledge of normal physiology of cytotoxic cells. Several cell types are involved in the pathophysiology of HLH, including macrophages, NK-cells, and cytotoxic T-lymphocytes. Macrophages typically serve as antigen presenting cells to present foreign antigens to lymphocytes for either direct destruction or antibody development. In various forms of HLH, macrophages become activated and secrete cytokines. Cytokines, in turn, can cause organ damage when excreted in excessive amounts. NK-cells directly destroy damaged or infected cells, independent of the major histocompatibility complex (MHC). Cytotoxic T-lymphocytes, while similar to NK-cells, kill autologous cells carrying foreign antigens associated with MHC Class I. An alternate theory

**Table 6** Hematologic malignancies associated with secondary HLH

Hematologic malignancy	Notes
T-cell lymphoma	
Angioimmunoblastic T-cell lymphoma	Adult with B-symptoms <sup>155</sup>
Enteropathy-associated T-cell lymphoma	Adult with 3-week history of diarrhea, family history of celiac disease, and rapid deterioration <sup>156</sup>
Peripheral T-cell lymphoma not otherwise specified	Adult patient with composite B-cell small lymphocytic lymphoma <sup>157</sup>
Hepatosplenic T-cell lymphoma	Described in patients with $\gamma\delta$ T-cell lymphoma <sup>158</sup>
Mycosis fungoides/Sézary syndrome	Elderly woman treated aggressively for Sézary syndrome, with rapid deterioration
Anaplastic large cell lymphoma	Adolescent female <sup>159</sup>
NK-cell lymphoma	
Aggressive NK-cell lymphoma/leukemia	Twenty patients with NK-cell lymphoma-associated HLH <sup>160</sup>
B-cell lymphoma	
B-cell lymphoma associated with hemophagocytic syndrome	An entity described in Asian countries, with alterations in chromosome 19q13 and loss of 8p21, believed to be involved in the pathogenesis <sup>161</sup>
Diffuse large B-cell lymphoma	Described in diffuse large B-cell lymphoma, not otherwise specified, and T-cell rich variants, all with bone marrow involvement <sup>158</sup> and intravascular large B-cell lymphoma, Asian variant <sup>162</sup>
Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma	Case from retrospective study in Sweden <sup>163</sup>
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Case from retrospective study in Sweden <sup>163</sup>
Hodgkin lymphoma	
Classical Hodgkin lymphoma	Woman with protracted prodromal phase of HLH as initial presentation in Hodgkin lymphoma <sup>164</sup>
Lymphocyte depleted Hodgkin lymphoma	Case report and literature review <sup>165</sup>
Non-hematologic malignancy	
Neuroblastoma	Two pediatric cases in Turkey <sup>154</sup>
Rhabdomyosarcoma	Two pediatric cases in Turkey <sup>154</sup>

**Abbreviations:** HLH, hemophagocytic lymphohistiocytosis; NK, natural killer.

proposes ineffective antigen removal, which results in ongoing immune stimulation and inappropriate hemophagocytosis.<sup>202</sup> Defects in NK-cell function may vary within the various types of HLH, indicating that several aspects of cell signaling are likely involved in NK-cell dysfunction seen in the disease.<sup>203–205</sup> In particular, patients with type 3 NK-cell deficiency with completely absent NK-cell function are likely to need hematopoietic cell transplant.<sup>203,204</sup> Patients with CHS, which is associated with a high frequency of HLH, often have defects in CTLA-4

(cytotoxic T-lymphocyte-associated antigen 4), such that secretory lysosomes cannot move to the cell membrane.<sup>206</sup> Deficient apoptosis appears to be the underlying mechanism behind at least some forms of FHL, a theory further supported by the success of etoposide, a drug used to trigger apoptosis.<sup>207</sup>

## Genetics

FHL syndromes are sub-classified into FHL-1 through FHL-5, based upon functional protein anomalies and the prerequisite

**Table 7** Genetic defects associated with FHL

FHL subclass	Chromosome	Gene	Gene function	Protein
FHL-1	9q21.3-q22	Unknown	Unknown	Unknown
FHL-2	10q21-22	<i>PFR1</i>	Induction of apoptosis	Perforin
FHL-3	17q25	<i>UNC13D</i>	Vesicle priming	Munc13-4
FHL-4	6q24	<i>STX11</i>	Vesicle transport	Syntaxin 11
FHL-5	19p13.2-3	<i>STXBP2 (UNC18B)</i>	Vesicle transport	Munc18-2
<b>Other HLH-associated diseases</b>				
CHS-1	1q42.1-q42.2	<i>LYST</i>	Vesicle transport	Lyst
GS-2	15q21	<i>RAB27A</i>	Vesicle transport	Rab27a
XLP-1	Xq25	<i>SH2D1A</i>	Signal transduction and activation of lymphocytes	SAP
XLP-2	Xq25	<i>BIRC4</i>	Various signaling pathways	XIAP

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**Abbreviation:** FHL, familial hemophagocytic lymphohistiocytosis.

gene mutations responsible. The genetic abnormalities identified in these syndromes are outlined in Table 7.

Generally, the forms of HLH associated with infants and young children are caused by defects in immune regulation, such as mutations in genes controlling the function of cytotoxic T-lymphocytes and NK-cells. With older children and adults, HLH is more likely to be secondary to infection, malignancy, or autoimmune disease. While rare, some familial cases have been undetected until adulthood. Even children with a defined genetic cause of HLH often have a secondary assault such as infection that triggers HLH, in keeping with the two-hit hypothesis required for the development of many diseases.

The first genetic defect described in FHL was a mutation in the perforin gene (*PRF1*) in 1999 by Stepp et al.<sup>208</sup> Perforin is found in secretory granules of cytotoxic cells and plays an important role in apoptosis and immune modulation. Perforin mutations are causative in the majority of FHL cases, accounting for up to 58%, and are considered a defining feature of FHL-2.<sup>31,125,183,186,209–221</sup> Patients presenting later in life may have residual perforin expression, but patients presenting in early childhood usually have no perforin in their NK- or CD8+ cells. The HLH Study Group of the Histiocyte Society identified 63 specific mutations within the perforin gene that demonstrate varying prevalence among ethnic groups. Three of the more common mutations were specifically associated with Turkish, African/African American, and Japanese origins, respectively. A common perforin polymorphism C272T (A91V) seen in late-onset FHL has been demonstrated to lead to a dysfunctional perforin.<sup>212,222</sup> More detailed discoveries about the role of perforin in HLH, lymphoma, and other immune-mediated diseases have been recently described.<sup>31,210,212,213,216,218,222–229</sup>

Genes involved in cytotoxic granule exocytosis have been demonstrated to bear mutations in FHL-3, FHL-4, and FHL-5. FHL-3 cases, which account for 10%–32% of genetic HLH feature *UNC13D* mutations.<sup>30</sup> The essential role of the *UNC13D* gene in the fusion of cytolytic granules and involvement in FHL was first described in 2003 by Feldmann et al.<sup>230</sup> Patients with disruptive mutations presented at a younger age than FHL-3 patients with missense mutations, but older than FHL-2 patients. FHL-3 is marked by more central nervous system involvement than the other subclasses.<sup>30,180,182,211,218,231–237</sup> FHL-4 is characterized by *SYNTAXIN11* (*STX11*) mutations and is found almost exclusively in patients of Turkish/Kurdish descent.<sup>31,211,238–240</sup> The gene mutation causing FHL-5 was described as recently as 2009 by Zur Stadt et al and also by Côte et al.<sup>28,240–243</sup> The FHL-1 locus on chromosome 9p21.3-q22 codes for a yet unknown gene and

protein involved in the development of FHL-1 and accounts for fewer cases of FHL at approximately 10%.<sup>212</sup>

Aside from FHL, the immune deficiency syndromes associated with HLH, including CHS-1, GS, and XLPS can be grouped based on molecular features. Similar to FHL, from a molecular standpoint, CHS-1 and GS can be characterized by intracellular vesicle content, docking, and fusion defects. Both are characterized by albinism, neutrophil granule dysfunction, and recurrent infections. XLPS on the other hand is molecularly distinct in that XLPS lacks normal immune function of T-lymphocytes rather than having neutrophil granule defects. Genetic defects associated with these conditions are presented in Table 7.

Gene expression analysis of mononuclear cells from patients with various genotypes of HLH demonstrates increased expression of IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and IL-8. Along with the clinical diagnosis of HLH, gene expression profiling may be useful in predicting the risk of relapse and response to treatment.

## Treatment

Prior to the use of modern treatment regimens, survival with HLH was close to 0%.<sup>202</sup> Broadly, treatment of HLH involves immune-suppressive and modulatory agents, biological response modifiers, treatment of the inciting illness if secondary, and subsequent stem-cell transplantation. Therapy is aimed at suppressing the hyperinflammatory state and immune dysregulation that leads to life-threatening organ damage and susceptibility to deadly infections. It is also important to kill infected antigen-presenting cells to remove the stimulus for ongoing immune activation. Treatment of HLH may vary according to cause. Discussion of treatment is subdivided into FHL, infection-related, malignancy-associated, and autoimmune diseases.

## FHL

Early attempts at treating HLH included vinblastine (a vinca alkaloid) and corticosteroids. The epipodophyllotoxins, etoposide (VP-16), and teniposide (VM-26), in combination with steroids showed some promise in achieving prolonged remissions. In 1994, the Histiocyte Society proposed the first protocol for the treatment of HLH (HLH-94). The protocol began in 1994, 5 years before genetic markers for FHL were found. At the time, FHL was defined by having an affected sibling. HLH-94 offered an established chemotherapy regimen (epidodophyllotoxin and corticosteroids) in conjunction with immunotherapy with cyclosporine A (CSA). The original eligibility requirements for the trial included only patients



under the age of 16 years. HLH-94 included 8 weeks of initial chemotherapy and immunotherapy, attempting to achieve complete remission, followed by continuation therapy until an acceptable bone marrow donor could be found. The first 8 weeks consisted of dexamethasone at a starting dosage of 10 mg/m<sup>2</sup> body surface area, then tapering down by half in 2-week increments for 6 weeks, then 1 week of 1.25 mg/m<sup>2</sup>, and a subsequent week of taper. Concurrently with the dexamethasone taper, VP-16 therapy was initiated twice weekly during the first 2 weeks, then weekly. After week 8, CSA therapy began and extended for the duration of therapy. Intrathecal methotrexate was included in selected patients with evidence of central nervous system (CNS) involvement. After 8 weeks, pulses of dexamethasone were given at regular intervals. HSCT was recommended for all children with a suitable allogeneic donor. Supportive care may have included an intensive care unit stay, broad-spectrum antibiotics until appropriate culture results were available, microbiological surveillance, HLA testing of patient and family in anticipation of HSCT, and prophylactic antifungals.<sup>7</sup> Conditioning regimens prior to HSCT included busulfan, cyclophosphamide, etoposide, and if the donor was unrelated, antithymocyte globulin (ATG).<sup>244</sup>

Retrospective reviews of the HLH-94 treatment protocol morbidity and mortality for 249 patients with long-term follow-up revealed that overall survival and response to therapy did not differ in patients with versus without family history. Overall survival rates were 54%. In this study, 114 (46%) died, and 72 did not receive transplant. Of patient deaths, 64 (89%) occurred in the first year. Of the eight deaths occurring after 1 year of therapy, two had progressive disease without an available HSCT donor, one could not be transplanted due to severe neurological disease, and five relapsed. Overall, HLH-94 achieved complete remission or allowed survival to HSCT in 71% of patients.<sup>244</sup>

Given the success of the HLH-94 protocol, in 2004, a revised protocol called HLH-2004 was proposed, which aimed to 1) evaluate a revised initial and continuation therapy with an end goal of HSCT, 2) evaluate and improve results of HSCT with various types of donors, 3) evaluate the prognostic importance of state of remission at the time of HSCT, 4) evaluate long-term neurologic sequelae, and 5) improve understanding of the pathophysiology of HLH by including genotype–phenotype studies and evaluate the prognostic value of NK-cell activity subtyping. HLH-2004 essentially took HLH-94 and moved cyclosporine from

later in the regimen to an initial therapy, concurrent with dexamethasone and VP-16. Dexamethasone and VP-16 dosing was the same as in HLH-94. Intrathecal methotrexate was still included for select patients with CNS involvement. In general, HLH-2004 approaches all patients with an initial 8 weeks of chemotherapy, and supports the patient until HSCT can be performed in the case of patients with genetically determined disease or persistent non-genetic disease. Cases which resolve or are non-genetic can cease therapy unless relapse occurs, in which case HSCT would be undertaken. Eligibility requirements include children <18 years old. Separate concurrent studies have been undertaken on patients >18 years old, and those with CHS, GS, or XLPS.<sup>7</sup> The HLH-2004 protocol officially ceased enrolment at the end of 2011. Long-term outcomes are still under evaluation.

An alternative regimen for FHL was first described by Stephan et al<sup>245</sup> in 1993 and in an expanded trial described by Mahlaoui et al<sup>246</sup> in 2007. The development of these regimens was based on the recognition that T-lymphocytes play a role in the pathology of HLH as well as macrophages. This discovery was based on the detection of major histocompatibility complex class II positive T-cells, high levels of soluble serum IL-2, CD8, and IFN- $\gamma$  in the serum of FHL patients. This regimen featured a combination of ATG with corticosteroids, CSA, and intrathecal methotrexate. The Stephan study evaluated six patients and was successful in achieving remission quickly, although two patients died from CNS disease. In the expanded study, the regimen was used to treat 38 consecutive patients with FHL over the course of 14 years. The patients received 45 courses of ATG, with a total dosage of 50 mg/kg or 25 mg/kg varying by severity of disease over the course of 5 days. Methylprednisolone at 4 mg/kg/day was administered with the ATG for 5 days then tapered. Intrathecal methotrexate and corticosteroids were given at various dosages determined by patient age and at intervals varying according to the severity of CNS involvement. Patients also received supportive care with fibrinogen infusions, irradiated packed red blood cells, and platelets. Broad spectrum antibiotics and intravenous immunoglobulins were also given. CSA was added to reach a plasma concentration of 150 ng/mL prior to HSCT. Immediate adverse effects of ATG were relatively minor and presented as fever and chills during infusion that rapidly resolved and did not preclude further treatment. After approximately 2 weeks of ATG treatment, bacterial, viral, or fungal infections were encountered. Infections were

more common in patients receiving ATG as a secondary treatment for relapse than in first-line therapy. Once a complete response was achieved as evidenced by normalization of clinical and biological parameters, HSCT was performed for patients with an available HLA identical donor. Patients without a complete response or without a viable donor were given maintenance therapy. Overall, the efficacy of ATG therapy in achieving complete remission was 73%. Using ATG as a first-line treatment had a higher success rate of 82% of patients achieving complete remission versus only about 50% achieving complete remission with second-line ATG treatment. The best outcomes were seen with patients who received HSCT shortly after starting ATG therapy.<sup>246</sup>

### Infection-associated HLH

While treating the inciting infectious agent is important in the treatment of infection-related HLH, treating the identified organism alone is not enough. Most cases of infection-related HLH should be treated aggressively with standard HLH protocols. The exception to this rule is in Leishmania-related HLH, which has been treated successfully with liposomal amphotericin alone.<sup>129–135,140,247</sup> In particular, the prognosis for EBV-associated cases has improved dramatically with chemotherapy and immune modifying agents. In a multivariate analysis of patients on regimens consisting of corticosteroids alone, intravenous immunoglobulins alone, CSA alone, or a combination of treatments without etoposide versus another group of patients receiving etoposide, early introduction of etoposide was the only significant variable for improved survival.<sup>248</sup> Etoposide appears to interfere with EBV-induced lymphocyte transformation and suppresses formation of EBV nuclear antigen. Despite its potential risks, the benefits of etoposide justify its early use in light of the fact that even seemingly mild cases may deteriorate quickly.

### MAS

MAS is rather unique in that these HLH cases may respond quite well to high dose corticosteroids alone. One of the first reports of treating MAS associated HLH with corticosteroids, was a case series of sJIA in France which described seven children with hemorrhagic, hepatic, and neurologic features, later realized to be MAS. The children were treated with high-dose steroids, and five out of seven survived.<sup>249</sup> Several other case series had similar outcomes.<sup>184</sup> CSA therapy has also become a prominent therapy in addition to corticosteroids in MAS associated with sJIA, as CSA may preferentially inhibit lymphocytes by targeting transcription factors that activate

various cytokine genes.<sup>250</sup> CSA likely inhibits the cytokine storm of MAS. Cyclophosphamide has also been used to target lymphocytes in MAS.<sup>251</sup> Etoposide-based regimens such as HLH-94 and HLH-2004 can be used in MAS, but the risks must be weighed carefully.

### HSCT

Virtually all genetic cases of HLH and many secondary cases should be treated with HSCT. The first report of successful HSCT was reported in 1986.<sup>252</sup> Several studies have demonstrated that HSCT is the only true hope for permanent control of the disease or essentially a cure.<sup>253–257</sup> A study of 86 children treated with HLH-94 followed by HSCT demonstrated similar long-term disease-free survival (70% at 3 years) with matched unrelated donor transplants as with matched sibling transplants. Survival with family haploidentical donor transplants or mismatched unrelated transplants showed much less favorable results with long-term disease-free survival of only 50%.<sup>258</sup> Cord blood transplant has been successful in some patients. However, overall transplant morbidity and mortality remains high. The same pediatric study showed a mortality rate of 26 out of 86 patients, with deaths resulting from pulmonary and liver complications.<sup>258</sup> Patients responding well to pre-transplant induction therapy appear to respond best to HSCT. Pre-transplant conditioning regimens generally include busulfan, etoposide, and cyclophosphamide. Busulfan levels must be carefully monitored, and clonazepam or phenytoin may be useful as anticonvulsive prophylaxis. Dexamethasone may be used to prevent VP-16-induced anaphylactic-like symptoms. Mesna can be used for protection against cyclophosphamide-induced bladder injury. Trimethoprim/sulfamethoxazole may be used for pneumocystis prophylaxis, and acyclovir prophylaxis is recommended.<sup>7</sup>

Acute graft versus host disease (GVHD) appears to be the most common complication post-transplant, with rates as high as 32% and chronic GVHD rates at about 9%.<sup>259</sup> Additionally, some patients may develop mixed chimerism necessitating regular donor lymphocyte infusions.<sup>30</sup> With reduced intensity conditioning at an experienced transplant center, patients surviving to HSCT have an approximate survival rate of 92%.<sup>202</sup> The unifying thread of all treatments is that the best success rates occur when complete remission is achieved rapidly and HSCT closely follows.

### CNS manifestations

CNS manifestations are of particular concern, as long-term deficits are possible. Both primary and reactivation HLH

protocols include systemic treatment with dexamethasone, which can cross the blood–brain barrier. For patients with persistent cerebrospinal fluid abnormalities, intrathecal therapy such as methotrexate is recommended, despite the fact that a study of 35 patients demonstrated that the probability of achieving normalization of CNS symptoms is roughly equal with or without intrathecal therapy.<sup>260</sup> Given the devastating cognitive, neurological, and developmental defects that can result from HLH, many would argue that the benefits of intrathecal therapies justify potential risk.

## Salvage therapy

Despite advances in treatment regimens, up to 25% of children with HLH cannot undergo HSCT due to advancing disease. Due to the rarity of HLH and short survival, salvage therapies have been described in various case reports but few large studies, leaving clinicians with few evidence-based options for refractory HLH. Removal of cytokines via plasmapheresis has been described to support patients until other therapies have reached therapeutic effect.<sup>90,261,262</sup> Recombinant human thrombopoietin has been used as supportive therapy for thrombocytopenia in HLH.<sup>263</sup> The use of monoclonal antibodies such as alemtuzumab, infliximab, and daclizumab has been described in various case reports. Alemtuzumab targets the CD-52 antigen, which is expressed on most lymphocytes, monocytes, macrophages, and dendritic cells.<sup>264–266</sup> Infliximab targets TNF, and daclizumab targets CD-25. Both have been used with reported success.<sup>267–269</sup> Additionally, etanercept, a TNF inhibitor, was used with success in a patient with acute lupus hemophagocytic syndrome.<sup>178</sup> Various case reports have elaborated on treatment of refractory cases with splenectomy<sup>270</sup> and even liver transplant for the damage caused by the unbridled macrophage activity.<sup>271</sup> However, given the scarcity of literature on the subject, it is unclear what role these measures will play in the treatment of HLH.

## Conclusion

HLH is a diverse condition with many causes and is likely under-recognized, which contributes to its high morbidity and mortality. Early recognition is crucial for any reasonable attempt at curative therapy to be made. HLH-94, HLH-2004, and ATG treatment regimens followed by HSCT have greatly increased survival in this devastating disease. A number of recent studies have contributed to the understanding of HLH pathophysiology, leading to alternate treatment options; however, much work remains to raise awareness and improve the effectiveness of treatment regimens.

## Disclosure

The author has no disclosures to make in relation to this article.

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