

# Hemophagocytic Syndrome—An Approach to the Management

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## INTRODUCTION

Hemophagocytic syndrome also known as hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition first described in 1939 by pediatricians Ronal Scott and Robb-Smith. They called it as histiocytic medullary reticulosis. It was later renamed as familial hemophagocytic reticulosis in 1952 by Farquhar and Claireaux.<sup>1</sup> The Histiocyte Society proposed the name of this condition as hemophagocytic lymphohistiocytosis with first set of diagnostic guidelines, in 1991.<sup>2</sup> The term hemophagocytosis means the ingestion of cellular blood components and their precursors by macrophages resulting in cytopenias. This disease is characterized by an uncontrolled and ineffective immune response, triggered due to various causes like malignancy, infections and some autoimmune disorders which leads to severe hyperinflammation and fatal multiple organ damage. In 2016, Histiocyte Society classified HLH in 3 subtypes — primary hemophagocytic lymphohistiocytosis (Mendelian inherited conditions), secondary hemophagocytic lymphohistiocytosis (apparently non-Mendelian) and hemophagocytic lymphohistiocytosis of unknown/uncertain origin.<sup>3</sup>

## PRIMARY OR FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Familial forms result from defects in genes controlling function of natural killer (NK) cells and cytotoxic T-cells. It is an autosomal recessive condition, which explains why the family history is often negative despite its familial nature. Recent Swedish national registry found incidence of Familial Hemophagocytic Lymphohistiocytosis (FHLH) to be 1.8 per 100,000 live births with median age of onset 5.1 months. Most children are asymptomatic at birth but 70% children have onset of disease in first year of life.<sup>4</sup> There are at least 12 genetic mutations currently associated with FHLH. Primary HLH has five subtypes: types 1–5. Each subtype is caused by a mutation in a different gene. Genetic defect in type 1 is not known at present and has been described only in 4 consanguineous Pakistani families. Type 2 is the most common form in African American families where it accounts for >50% of FHLH and is caused by mutation in PRF1 gene.<sup>5</sup> FHLH 3 is caused by genetic mutation in UNC13D gene and 20–30%, and it is seen worldwide. FHLH 4 and 5 are due to genetic mutation in STX11 gene and STXBP2 gene, respectively. It should be kept in mind that in approximately 30% of FHLH patients, there are no identified gene defects, so normal genetic test results do not necessarily rule out the diagnosis of FHLH. Even though there are various genetic defects known and unknown, all mutations responsible for FHLH reside in genes that code for proteins in the cytolytic pathway employed by CD8+ T and NK cells to destroy host cells.

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## SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Secondary HLH or acquired HLH is seen mainly in adults and occurs after strong immunologic activation that occurs with systemic infection, immunodeficiency or underlying malignancy. There is no data available on true incidence of adult HLH due to diagnostic dilemma. A retrospective review of 775 reported cases identified male to female ratio of 1:7 and mean age at diagnosis of 49 years. The same study found 41.1% of adult HLH to be triggered by infections, and 38.8% by malignancies.<sup>6</sup>

### Triggers

- Infections
  - Viral (most common)- EBV (Epstein Barr virus), HIV, human herpes virus, Cytomegalovirus
  - Bacterial
  - Fungal
  - Parasitic.
- *Malignancy associated HLH (MAHL)*: It is commonly observed that MAHL is manifested either during remission phase of cancer, where it is attributed to iatrogenic immune dysregulation (HLH during chemotherapy) or in aggressive uncontrolled cancer where it is likely due to hypercytokinemia potentiated by malignant clone. Lymphomas or leukemias of the T or NK cell lineages are most common causes of MAHL; however, it is also seen in association with anaplastic large cell lymphoma, early B lineage lymphoblastic leukemia, myeloid leukemias, mediastinal germ cell tumors, and rarely other solid tumors.
- *Autoimmune diseases*: More than 30 autoimmune diseases are associated with HLH. The two most closely associated diseases are systemic lupus erythematosus (SLE) and adult-onset Still's disease, followed by rheumatoid arthritis and vasculitis.
- *Macrophage activation syndrome (MAS)*: MAS is a severe inflammatory condition seen in association with rheumatologic disorders such as systemic-onset juvenile idiopathic arthritis

and SLE. Since this syndrome has many similarities with HLH; some investigators consider it as a form of HLH. Clinical and laboratory findings are similar to HLH except for cytopenias which is a late finding in MAS as these patients typically have elevated blood counts during active disease.

- HLH is also seen in patients on total parenteral nutrition and it may be attributed to the activation of macrophages due to fat overload, but the exact pathogenesis is unknown.
- *Other:* HLH can occur following transplantation, vaccination, surgery, severe burns and drugs.

### PATHOPHYSIOLOGY

Main function of macrophages is to serve as antigen-presenting cells and present foreign antigens to lymphocytes for either direct destruction or antibody development. A defect in granule-mediated cytotoxicity, which is important in killing cells, is responsible for HLH in both genetic and secondary forms. Resultant deficient cytotoxic activity prevents elimination of antigenic targets, and thus results in continuous immune activation. It also prevents curtailing of the immune response. These patients generally do not have chronic or unusual infections, but instead have dangerous hyperinflammation. Enhanced antigen presentation and repeated stimulation of Toll-like receptors lead to uncontrolled activation of macrophages, histiocytes and T cells. These activated cells further proliferate, migrate and infiltrate various organs giving rise to organ dysfunction. This activation also produces an exaggerated inflammatory response, a cytokine storm. The cytokine storm of HLH involves elevations in gamma interferon (IFN- $\gamma$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and various interleukins (IL) such as IL-1, IL-2, IL-6, and IL-18. The final result of this cytokine storm is overwhelming systemic inflammation, hemodynamic instability, multiple organ dysfunction and potentially death. The specific cytokine pattern of markedly elevated levels of IFN- $\gamma$  and IL-10 with only modestly elevated IL-6 levels has been shown to have high diagnostic accuracy for diagnosing HLH in children.<sup>7</sup>

### PATIENT PRESENTATION

Presentation is generally nonspecific with fever and lymphadenopathy. Nearly half of these patients may present to ICU with sepsis like features and organ dysfunction. Patients may present with respiratory symptoms like cough, dyspnea or respiratory failure, especially where trigger is respiratory infection.

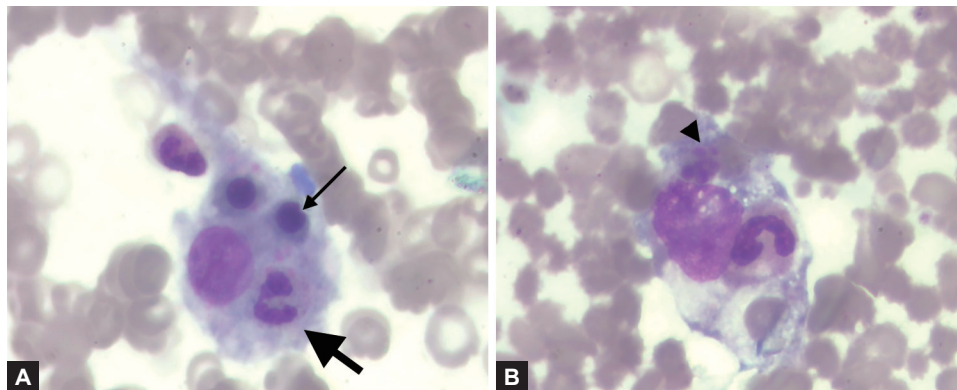
Around 25% cases may present with neurological symptoms like seizures, meningitis or cerebral hemorrhage. The median time from onset to diagnosis of HLH is 3.5 months, and the activated inflammatory cytokines often persist for 100 days.<sup>8,9</sup>

### DIAGNOSIS

Delay in diagnosis and multiorgan involvement is associated with worsened outcomes and hence quick diagnosis and prompt therapy is the key to better outcome.

The diagnosis of HLH can be established if either 1 or 2 below is fulfilled

1. Biallelic pathogenic variants in any one of PRF1, UNC13D, STX11, or STXBP2
2. At least 5 of the 8 following criteria based on the diagnostic guidelines of the Histiocyte Society
  - i. Prolonged fever (>7 days) — may occur due to infections, which precipitate secondary HLH. High interleukin levels further contribute to fever. Fever is found in 100% cases of HLH both primary and secondary types.
  - ii. Cytopenias affecting two or three of the three lineages in the peripheral blood which occurs due to engulfment of hematopoietic cells by activated macrophages: Hemoglobin <90 g/L (for infants age <4 weeks: Hb <100 g/L), Platelets <100 $\times 10^9$ /L, Neutrophils <1.0  $\times 10^9$ /L.
  - iii. Splenomegaly — due to infiltration by lymphocytes and macrophages.
  - iv. Hypertriglyceridemia and/or hypofibrinogenemia.
    - Fasting triglycerides  $\geq 2.0$  mmol/L or >3 standard deviation of the normal value for age. This is secondary to decreased lipoprotein lipase activity initiated by increased TNF- $\alpha$  levels.
    - Fibrinogen  $\leq 1.5$  g/L
  - v. Hemophagocytosis in bone marrow, spleen or lymph nodes (Fig. 1) — This is not a common feature in secondary HLH at presentation and may not be seen until late in disease progression. Repeat bone marrow studies may be necessary to show these findings in secondary cases. However, in primary HLH prominent hemophagocytosis is seen from the presentation itself. Also, it is not specific and can be present in patients with advanced malignancies, sepsis and multiorgan failure in critically ill patients.<sup>10</sup>



**Figs 1A and B:** Oil immersion view (100X) from bone marrow aspirate depicts hemophagocytosis. (A) Macrophages engulfing nucleated erythroid cells (thin arrow), neutrophils (thick arrow); (B) Platelets (arrowhead)

- vi. Low or absent NK cell activity with normal circulating NK cells number — In FHL, NK cell activity is always low or absent, however in secondary HLH it has been found to be fluctuating over time.
- vii. Hyperferritinemia: Serum ferritin concentration  $\geq 500 \mu\text{g/L}$  (normal 10–290  $\mu\text{g/L}$ ). Serum ferritin concentration is a marker of generalized inflammation. It is, however, markedly elevated in the majority of patients with HLH and is a very sensitive indicator of HLH when serum concentrations are markedly increased. Ferritin  $>10,000 \mu\text{g/L}$  has been demonstrated to be 90% sensitive and 96% specific for HLH.<sup>11</sup>
- viii. High plasma concentrations of soluble CD25  $\geq 2400 \text{ U/mL}$ . CD 25 is soluble IL2 receptor which is present on surface of activated T cell, increased levels of which indicate excessive activation of T cells. This is very useful in the diagnosis as very high levels are not seen in any other condition except HLH.

Positive family history of affected siblings and/or parental consanguinity in a symptomatic individual can be used to support the diagnosis of FHL.

### Clinical Workup

Physical examination — look for skin rashes, lymphadenopathy, hepatosplenomegaly, features suggestive of neurological involvement such as irritability, neck stiffness, hypo- or hypertonia, cranial nerve palsies, blindness, convulsions, etc.

- CBC and bone marrow evaluation
- LFTs
- Search for infections especially viral infections
- CSF
- MRI brain
- Coagulation studies including fibrinogen levels
- Ferritin levels
- Soluble CD-25
- NK cell activity
- Molecular genetic testing for PRF1, UNC13D, STX11, and STXBP2 variant.

### H Score

Since from most of the diagnostic criteria, HLH may be difficult to distinguish from severe sepsis or flare of an underlying disease, many standardized criteria have been proposed to improve the diagnosis. In 2014 Fardet et al.<sup>12</sup> created and validated the H Score, which includes 9 weighted variables and probability of HLH as shown in Tables 1 and 2.

### CNS Involvement

Though occurrence of neurological symptoms is not included as a diagnostic criterion of HLH, a large number of patients with primary and secondary HLH have CNS involvement due to infiltration of activated lymphocytes and macrophages into the meninges and brain. The reported incidence of CNS involvement ranges from 30 to 73% of all HLH cases.<sup>13</sup> Seizures are the most common sign. Mental status changes, such as irritability, disturbance of consciousness, and encephalopathy also occur commonly. Focal neurological signs, such as hemiparesis, cranial neuropathies, and ataxia, are seen in 10–20% cases. Diffuse peripheral neuropathy with pain and weakness can be seen due to myelin destruction by macrophages. Cerebrospinal fluid (CSF) findings include either pleocytosis, increased CSF protein or both and may sometimes

**Table 1:** Variables of H score

Parameter	No. of points (criteria for scoring)
Known underlying immunosuppression	0 (no) or 18 (yes)
Temperature (°C)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
No. of cytopenias	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin (ng/ml)	0 (<2,000), 35 (2,000–6,000), or 50 (>6,000)
Triglyceride (mmoles/liter)	0 (<1.5), 44 (1.5–4), or 64 (>4)
Fibrinogen (g/L)	0 (>2.5) or 30 ( $\leq 2.5$ )
Serum glutamic oxaloacetic transaminase (IU/L)	0 (<30) or 19 ( $\geq 30$ )
Hemophagocytosis features on bone marrow aspirate	0 (no) or 35 (yes)

**Table 2:** Probability of hemophagocytic syndrome according to the H score

H score	Probability of hemophagocytic syndrome (%)
90	<1
100	1
110	3
120	5
130	9
140	16
150	25
160	40
170	54
180	70
190	80
200	88
210	93
220	96
230	98
240	99
250	>99

show haemophagocytosis. CNS involvement is divided into three neuropathological stages:

- Stage I with leptomeningeal inflammation,
- Stage II with perivascular infiltration,
- Stage III with massive tissue infiltration, blood vessel destruction, and tissue necrosis.

CSF analysis and magnetic resonance imaging (MRI) should always be done in all cases of HLH regardless of the presence or absence of neurological signs or symptom. MRI findings reveal nonspecific periventricular white-matter abnormalities, brain-volume loss, enlargement of extra-axial fluid spaces, discrete lesion, leptomeningeal enhancement or global cerebral edema. Orbital myopathy has also been described. Neurological involvement in HLH is associated with poor outcome reducing 5-year survival from 67 to 40%.<sup>14</sup>

## Treatment

HLH has a life-threatening course. If left untreated, patients with familial HLH survive only a few months. Treatment has been developed primarily at pediatric centers where main cause of HLH is FLH. However, it is often difficult to distinguish between familial and secondary HLH at presentation, unless there is another child in the family affected with HLH. Hence HLH specific therapy can be started in presence of severe HLH irrespective of whether it is familial or secondary.

Since HLH is often caused by triggers like infection or malignancy, and it is characterized by cytokine overproduction that can lead to multiorgan damage and hemodynamic instability, the treatment should be three pronged and directed towards 3 main presenting features

1. Stabilization of the patient and organ support
2. Actively search for trigger like infection or malignancy and try to manage it.
3. Suppression of overactive inflammatory response — as pathophysiologic data suggested a predominant T cell-dependent immune-dysregulation, recently treatment is mainly focused on T cell dependent immune-regulation.

Earlier, the long-term survival in HLH patients was very low. In 1989, the Histiocyte Society maintained a HLH registry in which 122 patients were reported with a 5-year survival of 21%.<sup>15</sup> In 1994, the first international treatment protocol for HLH was developed by the Histiocyte Society that resulted in a dramatic increase in the survival rate to 55% with a median follow-up of 3.1 years.<sup>16</sup> Although HLH 94 protocol resulted in a significantly improved outcome; early mortality was still a problem. Hence in 2004, HLH -2004 protocol was developed which was based on HLH 94 protocol with a few modifications to overcome the problems with HLH 94-protocol.

- Due to high early mortality in the prehematopoietic cell transplantation (HCT) phase in HLH 94, initial treatment was intensified by administering cyclosporine A (CSA) in the induction treatment itself.
- Corticosteroids (prednisolone) were added to the intrathecal (IT) methotrexate (MTX) treatment which was recommended for a subset of patients.

Compared with HLH 94, HLH 2004 reduced the pre-HCT mortality from 27 to 19% and time from start of treatment to HCT was significantly shorter.<sup>17</sup> Another single centre study replaced etoposide with antithymocyte globulin and showed comparable survival rates with less toxicity but a higher relapse rate.<sup>18</sup>

## HLH-94 Regimen

### Initial Therapy (Induction Therapy)

With the exception of MAS and malignancy associated HLH, prompt treatment with etoposide and corticosteroids is required to halt the inflammatory process associated with HLH in severely ill patients.

Induction therapy of HLH-94 regimen consists of etoposide (150 mg/m<sup>2</sup> twice weekly for two weeks and then weekly) and dexamethasone (initially 10 mg/m<sup>2</sup> for two weeks followed by 5 mg/m<sup>2</sup> for two weeks, 2.5 mg/m<sup>2</sup> for two weeks, 1.25 mg/m<sup>2</sup> for 1 week and one week of tapering).<sup>19</sup>

During induction therapy, patients should be monitored meticulously to look for signs of improvement as well as potential complications. Patients who respond well to the initial treatment show resolution of symptoms and normalization of laboratory parameters. However, salvage therapy needs to be started in patients who do not respond to the treatment within 2–3 weeks of

starting therapy or in patients who show recurrence of symptoms and rise in laboratory markers after initial improvement.

Patients with nonfamilial disease who undergo resolution of symptoms after initial therapy are recommended to stop the therapy. Treatment needs to be restarted in these patients only on reactivation.

HLH-94 recommends antifungal treatment during the initial dexamethasone therapy and continuous cotrimoxazole treatment, equivalent to 5 mg/kg of trimethoprim 3 times weekly, as *Pneumocystis carinii* prophylaxis.<sup>19</sup>

### Continuation Therapy

Continuation therapy and HCT is indicated in patients with proven familial disease or persistent or relapsing nonfamilial disease.

Continuation therapy consists of dexamethasone pulse therapy (10 mg/m<sup>2</sup> per day for 3 days every second week) and etoposide (150 mg/m<sup>2</sup> every alternating second week) in combination with daily oral CSA (aiming at trough levels of 200 µg/L). The aim of continuation therapy is to keep patients in a stable condition till HCT can be performed.<sup>19</sup>

### CNS Involvement

From the available data of HLH 94 protocol, it is not completely clear whether intrathecal methotrexate along with systemic therapy is beneficial in patients with CNS involvement. Systemic induction therapy reduces CNS involvement in majority of patients.<sup>16</sup>

Hence, according to HLH-94 protocol, intrathecal (IT) methotrexate therapy is given in patients if CNS symptoms persist after 2 weeks or if CSF abnormality does not improve after two weeks of systemic therapy. Intrathecal treatment is recommended for a maximum of 4 doses (weeks 3–6). The dosage of methotrexate is as follows: <1 year 6 mg; 1–2 years 8 mg; 2–3 years 10 mg; >3 years 12 mg each dose.<sup>17</sup>

### Salvage Therapy

HLH 94 or HLH 2004 protocols do not include a regimen for salvage therapy.

Approximately 25–50% of patients do not achieve complete response to initial therapy. Also, patients who respond to therapy earlier, may experience a relapse of symptoms. Patients who relapse after initial response, may be treated with reintensification of standard therapy.<sup>20</sup>

Recently, a salvage treatment comprising of liposomal doxorubicin, etoposide and methylprednisolone (the DEP regimen) showed promising results in a prospective clinical trial for adult HLH.<sup>21</sup> However, its use in pediatric patients is not studied.

A few case reports have studied the use of alemtuzumab, infliximab, daclizumab, anakinra, vincristine as salvage therapies for refractory HLH.

Further research and prospective trials are needed to establish efficacy and safety of various treatment modalities for refractory HLH in order to improve outcome of these patients.

### Secondary HLH

It is crucial to search for triggers of HLH and their treatment for resolution of secondary HLH. In adults, majority of patients have secondary HLH and it is commonly diagnosed in ICU where initially they are misdiagnosed as sepsis or MODS (multiorgan dysfunction syndrome) as many features of HLH and SIRS (systemic inflammatory response syndrome) or sepsis are common.



Viral infections especially EBV infections are commonly associated with secondary as well as primary HLH. EBV infection responds to HLH-94 based therapy consisting of etoposide. In less severe disease, a conservative treatment with steroids and/or IVIG (intravenous immunoglobulin) can be started. Rituximab can be added to HLH directed therapy in EBV triggered HLH because it can eliminate B cells where EBV proliferates.

In MAHL, a balance of tumor-specific therapy and HLH specific therapy is important. Initial treatment with corticosteroids and/or IVIG is used to reduce inflammation. Etoposide-based therapy is sometimes required in severe disease before starting tumor-specific treatment. Etoposide can be added to CHOP or CHOP like regimens in treatment of lymphomas. High-dose consolidation chemotherapy followed by autologous stem cell transplantation can be considered in selected patients who are in remission. Decision for allogeneic transplantation in these patients needs individualized approach.

HLH occurring during chemotherapy for malignancy is often not recognized early due to the nature of primary malignancy, ongoing chemotherapy and neutropenia. At present, there is limited literature regarding treatment of HLH during chemotherapy. Since an infectious trigger for HLH is common in this subgroup of patients, active search and appropriate antimicrobial treatment should be started. Corticosteroids and IVIG can be given in these patients. Etoposide should be used cautiously as it may delay bone marrow recovery.

In MAS, traditionally, corticosteroids are the mainstay of treatment. High-dose pulse methylprednisolone (1 g/d for 3–5 consecutive days) can be tried initially. CSA can be added in patients with an inadequate response. In patients not responding to steroids and CSA, etoposide may be considered.<sup>22</sup>

The established treatment protocols (HLH-94 and HLH 2004) are made primarily for children and extrapolated for adult HLH patients. Therefore, the treatment plan needs to be individualized according to the disease severity, patient's comorbidities, age and type of HLH trigger.

### Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is the definitive treatment for HLH. It is indicated in documented familial HLH, recurrent or progressive disease despite intensive therapy and CNS involvement.

Search for a suitable donor should ideally be started at the time of diagnosis irrespective of the etiology of HLH as the time taken for transplant is an important prognostic factor. Disease remission before starting HCT has better prognosis.

If HLA identical donor is not available, a matched unrelated donor can be sought for HCT. Because of the familial nature of the disease, the risk of sibling having the disease must be taken into consideration.

There are a few different regimens for pretransplant conditioning of HLH patients. Early transplant-related mortality has been shown to be lower with reduced intensity conditioning (RIC) as compared to myeloablative conditioning (MAC); but it was associated with post-transplant mixed chimerism.<sup>23</sup>

### Supportive Care

Increased expertise and advances in supportive care have contributed to improved survival in HLH patients. In general, supportive care should be similar to patients undergoing HCT including prophylaxis for *Pneumocystis jirovecii*, fungal prophylaxis,

IVIG supplementation whenever needed and precautions similar to those for neutropenic patients.

Any new fever should be evaluated for HLH reactivation, as well as opportunistic infection, and empiric broad-spectrum antibiotic therapy initiated.

Because of consumption coagulopathy and platelet defects, these patients are at risk of bleeding. Platelet count should be maintained above  $50 \times 10^9$  /L. Prophylactic heparin is not recommended in acutely ill patients. Acute bleeding episodes should be treated with fresh frozen plasma, cryoprecipitate, platelets and factor VII in selected cases.

### Role of Therapeutic Plasma Exchange

Therapeutic plasma exchange (TPE) is an extracorporeal blood purification technique used for the removal of various toxins and inflammatory mediators. TPE can improve clinical and laboratory findings in HLH by reducing circulating inflammatory mediators. It has also been shown to increase the response to steroids by reducing IL-6, soluble IL-2, and TNF $\alpha$  levels. It is used as a bridging therapy till other therapies have chance to work or till stem cell transplantation can be done.<sup>24</sup>

### PROGNOSIS

Before initiation of modern treatment regimens, the prognosis of familial HLH was dismal. After introduction of HLH-94 protocol by Histiocytic Society, overall mortality in FHL fell to 45%, with a probability of survival of 62% after hematopoietic cell transplantation (HCT).<sup>19</sup> With the introduction of better drugs and increased experience, survival after HCT has improved to 92%.<sup>23</sup> Reported mortality in secondary HLH varies from 8 to 24%.

### REFERENCES

1. Farquhar JW, Claireaux AE. Familial haemophagocytic reticulosis. *Arch Dis Child*. 1952;27:519–525.
2. Henter JI, Elinder G, Ost A, and the The FHL Study Group of the Histiocyte Society. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. *Semin Oncol* 1991;18:29–33.
3. Emile JF, Ablu O, Fraitag S, Horne A, Haroche J, Donadieu J, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood*. 2016;127:2672–2681.
4. Meeths M, Horne A, Sabel M, Bryceson YT, Henter JI. Incidence and clinical presentation of primary hemophagocytic lymphohistiocytosis in Sweden. *Pediatr Blood Cancer* 2015;62:346–352.
5. Rosado FG, Kim AS. Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. *Am J Clin Pathol*. 2013;139:713–727.
6. Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet*. 2014;383(9927):1503–1516.
7. Xu XJ, Tang YM, Song H, Yang SL, Xu WQ, Shi SW. Diagnostic accuracy of a specific cytokine pattern in hemophagocytic lymphohistiocytosis in children. *J Pediatr*. 2012;160:984–990.
8. Tang Y, Xu X, Song H, Yang S, Shi S, Wei J, et al. Early diagnostic and prognostic significance of a specific Th1/Th2 cytokine pattern in children with haemophagocytic syndrome. *Br J Haematol*. 2008;143:84–91.
9. Osugi Y, Hara J, Tagawa S, Takai K, Hosoi G, Matsuda Y, et al. Cytokine production regulating Th1 and Th2 cytokines in hemophagocytic lymphohistiocytosis. *Blood*. 1997;89:4100–4103.
10. Strauss R, Neureiter D, Westenburger B, Wehler M, Kirchner T, Hahn EG. Multifactorial risk analysis of bone marrow histiocytic hyperplasia with hemophagocytosis in critically ill medical patients—a postmortem clinicopathologic analysis. *Crit Care Med* 2004;32:1316–1321.

11. Allen CE, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2008;50:1227–1235.
12. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheum (Munch)*. 2014;66:2613–2620.
13. Jovanovic A, Kuzmanovic M, Kravljanc R, Micic D, Jovic M, Gazikalovic S, et al. Central nervous system involvement in hemophagocytic lymphohistiocytosis: a single-center experience. *Pediatr Neurol*. 2014;50:233–237.
14. Horne A, Trottestam H, Aricò M, Egeler RM, Filipovich AH, Gadner H, et al. Frequency and spectrum of central nervous system involvement in 193 children with haemophagocytic lymphohistiocytosis. *Br J Haematol*. 2008;140:327–335.
15. Aricò M, Janka G, Fischer A, Henter JI, Blanche S, Elinder G, et al. FHL Study Group of the Histiocyte Society. Hemophagocytic lymphohistiocytosis. Report of 122 children from the International Registry. *Leukemia*. 1996;10:197–203.
16. Henter JI, Horne A, Aricò M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48:124–131.
17. Bergsten E, Horne A, Aricò M, Astigarraga I, Egeler RM, Filipovich AH, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. *Blood*. 2017;130:2728–2738.
18. Mahlaoui N, Ouachée-Chardin M, de Saint Basile G, Neven B, Picard C, Blanche S, et al. Immunotherapy of familial hemophagocytic lymphohistiocytosis with antithymocyte globulins: a single-center retrospective report of 38 patients. *Pediatrics*. 2007;120:e622–e628.
19. Henter JI, Samuelsson-Horne A, Aricò M, Egeler RM, Elinder G, Filipovich AH, Gadner H, Imashuku S, Komp D, Ladisch S, Webb D, Janka G. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood*. 2002;100:2367–2373.
20. Marsh RA, Jordan MB, Talano JA, Nichols KE, Kumar A, Naqvi A, et al. Histiocyte Society Salvage Therapy Working Group. Salvage therapy for refractory hemophagocytic lymphohistiocytosis: A review of the published experience. *Pediatr Blood Cancer*. 2017;64:e26308.
21. Wang Y, Huang W, Hu L, Cen X, Li L, Wang J, et al. Multicenter study of combination DEP regimen as a salvage therapy for adult refractory hemophagocytic lymphohistiocytosis. *Blood*. 2015;126:2186–2193.
22. La Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood*. 2019;133:2465–2477.
23. Marsh RA, Vaughn G, Kim MO, Li D, Jodele S, Joshi S, et al. Reduced intensity conditioning significantly improves survival of patients with hemophagocytic lymphohistiocytosis undergoing allogeneic hematopoietic cell transplantation. *Blood*. 2010;116:5824–5831.
24. Bosnak M, Erdogan S, Aktekin EH, Bay A. Therapeutic plasma exchange in primary hemophagocytic lymphohistiocytosis: Reports of two cases and a review of the literature. *Transfus Apher Sci*. 2016;55:353–356.