Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a non-malignant, life-threatening hyperinflammatory condition resulting from dysregulation of normal innate and adaptive immune responses. In the years since its first description, HLH has been recognized as a clinical syndrome with an unusual constellation of presenting features. It is caused by many disparate, but related etiologies, rather than as a single, discrete, unified disease process. In this regard and others, HLH bears resemblance to sepsis, which also has a multitude of pathologic processes at its root. Indeed, HLH may often be mistaken for culture negative sepsis.

Based on current knowledge, HLH is separated into two general classes: primary and secondary. Primary HLH is caused by defined genetic mutations in genes whose protein products participate in immunologic regulatory pathways. These diseases often present with classic familial inheritance patterns. Secondary HLH is believed to occur sporadically, induced by specific infectious or inflammatory insults. However, as more is discovered about the immune mechanisms involved, the distinction between these subsets is blurring. It may be that many individuals with presumed secondary HLH have subtle defects of immune regulation that predispose to disease activation by specific immunologic challenges.
Table 26.1 Diagnostic guidelines for Hemophagocytic Lymphohistiocytosis (HLH)

The diagnosis of HLH can be established by fulfilling either or both of the two criteria below

1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria (five out of the eight criteria must be met)
   (a) Fever
   (b) Splenomegaly
   (c) Cytopenias (affecting at least two of three lineages in the peripheral blood)
      (i) Hemoglobin <90 g/L (in infants < 4 weeks: hemoglobin <100 g/L)
      (ii) Platelets <100 × 10^9/L
      (iii) Neutrophils <1.0 × 10^9/L
   (d) Hypertriglyceridemia and/or hypofibrinogenemia
      (i) Fasting triglycerides ≥3.0 mmol/L (i.e., ≥265 mg/dl)
      (ii) Fibrinogen ≤1.5 g/L
   (e) Hemophagocytosis in bone marrow, spleen, lymph nodes, or cerebrospinal fluid
   (f) Low or absent NK-cell activity
   (g) Ferritin ≥500 μg/L
   (h) Soluble CD25 (soluble IL-2 receptor) above normal limits for age

HLH was first described by Farquhar and Claireux in 1952. They named the condition “familial haemophagocytic reticulosis,” [1] but through the years it has also been called familial erythrophagocytic lymphohistiocytosis, [2] viral-associated hemophagocytic syndrome, [3] and malignancy associated hemophagocytic syndrome [4]. It is believed by many that the macrophage activation syndrome (MAS), observed in association with rheumatologic disorders, is likely a variant of HLH as both have similar clinical phenotypes and share some underlying mechanisms [5–11]. The International Histiocyte Society formally adopted the name of hemophagocytic lymphohistiocytosis in 1998 and defined criteria for its diagnosis which were updated in 2007 (Table 26.1) [4,12,13].

The true incidence and prevalence of HLH are unknown and would appear difficult to ascertain accurately; however, they do seem to vary by ethnicity. The diagnosis of HLH is problematic due to its variable presentation and the many nonspecific clinical features it shares with other disease processes. HLH is considered to be rare, but increasing awareness and recognition of the syndrome is leading to more frequent diagnoses. Currently, it is estimated that the autosomal recessive forms of familial HLH have a prevalence of 1/50,000 live births. A recent report estimated the incidence of HLH in tertiary care pediatric hospitals at one case of HLH per 3,000 inpatient admissions [14].

Pathogenesis

The principle characteristic of HLH is one of intense, prolonged, systemic inflammation. It is this underlying inflammation that drives the clinical features and contributes to the multisystem organ failure observed in this disorder. Histiocytes are phagocytic antigen presenting cells derived from the bone marrow mononuclear myeloid/granulocyte progenitor lineage. Monocytes, macrophages, and dendritic cells are considered histiocytes. In the normal immune response to infection or tissue injury, these cells function to activate and direct the innate and subsequent adaptive responses through cytokine/chemokine signaling and antigen presentation to their lymphoid counterparts. B cells, as well as helper and effector T cells, contribute to the inflammatory milieu through their own cytokine elaboration. They also assist with pathogen elimination via antibody production, activation of phagocytic killing, and by direct assassination of infected cells. Beyond coordinating the specific activities of various immune cells, cytokines exert systemic effects on various organs to initiate a stress response designed to protect tissue integrity and function, mobilize metabolic substrate necessary for the increased immunologic demand, and to establish an environment conducive to pathogen eradication. Natural killer (NK) cells are crucial to all aspects of this process. They help coordinate the initiation, effector, and resolution phases of the immune response by modulating initial histiocyte signaling, eradicating infected/damaged cells, and by ultimately culling the expanded effector lymphocyte and histiocyte population. They accomplish these effects through their own cytokine signaling and by utilizing granule-mediated activation-induced apoptosis.

NK cells share with cytotoxic T cells the ability to induce apoptosis in target cells by releasing granules whose constituents permeate the target cell plasma membrane and activate an intrinsic apoptotic cascade within that cell. This process begins as the effector T cell or the NK cell ‘surveys’ the target cells by sampling their surface proteins and receptor repertoire. Inappropriate epitopes displayed within major histocompatibility complex (MHC) molecules or abnormal surface protein patterns activate the effector cell and induce the formation of a circular immunologic synapse. This circular immunologic synapse is created with tight junctions fashioned at the periphery by interactions between effector cell lymphocyte function-associated antigen 1 (LFA1) and target cell intercellular adhesion molecule 1 (ICAM1) proteins. The effector intracellular cytoskeletal scaffold microtubule organizing center (MTOC) is oriented toward the synapse, reorganizing and directing the intracellular secretory apparatus, to direct specialized membrane bound vesicles at the target cell. These vesicles, which contain cytotoxic granules, are transported down the microtubule fibers, fuse with the plasma membrane, and exocytose their contents into the immunologic synapse. The granules contain several cytotoxic constituents most notably perforin and granzyme proteins. The tight junctions bounding the synapse prevent diffusion of these toxic substances away from the target cell. Perforin inserts itself into the target cell plasma membrane and facilitates the internalization of the various granzyme proteins. The granzyme proteins then trigger target cell
apoptotic mechanisms, in part via activation of caspase enzymes, thereby killing the target cell (Fig. 26.1). The effector cell subsequently releases the synapse and moves on to survey other cells [15–17].

This process is essential to both the NK and T cell effector functions including the ability of NK cells to quell excessive or unnecessary immunologic activation. Defects in these mechanisms underlie the various forms of familial HLH and
relative dysfunction in these pathways may contribute to secondary forms of HLH. Indeed, some degree of abnormality of NK cell function (although rarely in NK cell number) has been observed in all forms of HLH [18].

In HLH, a fundamental deficit in the regulation of proinflammatory signaling, due in part to NK cell dysfunction, leads to intense activation and proliferation of histiocytes and CD8 cytotoxic T cells. It is possible that excessive signaling through macrophage toll like receptors (TLRs) may contribute to this pathogenesis. Recent research has demonstrated that repeated stimulation of TLR9 induces a cytokine storm and that disruption of MyD88, a protein involved in the intracellular propagation of TLR signaling, can suppress HLH in a mouse model [19,20]. The ensuing hypercytokinemia and tissue infiltration of activated cytotoxic T cells induces the clinical features observed in HLH and contributes to the severe multisystem organ failure through mechanisms yet to be elucidated. Hemophagocytosis, the ingestion of red blood cells, is a prominent feature of macrophages driven by excessively elevated cytokine levels (Fig. 26.2) [21].

There are many genetic causes of HLH; the majority of which are inherited in an autosomal recessive manner. Mutations in the perforin gene were the first to be directly associated with HLH [22]. Without perforin, the granzyme enzymes cannot enter target cells to initiate apoptotic cascades. Perforin mutations account for 15–20% of HLH in certain geographic areas. HLH secondary to mutations in the perforin gene is known as familial hemophagocytic lymphohistiocytosis 2 (FHL2). FHL2 has both mild and severe phenotypes; the severity inversely correlating with the amount of mature perforin protein that is produced [23,24]. MUNC 13-4, a protein essential to the exocytotic process whereby cytotoxic granules are released by effector cells, is mutated in FHL3 [25]. FHL3 has a worldwide distribution and accounts for 15–20% of all inherited forms of HLH. FHL4 is caused by mutations in the protein syntaxin 11, a member of the SNARE family of proteins, which is necessary for the fusion of cytotoxic vesicles with the plasma membrane and release of their granules [26–28]. A mutation in the syntaxin binding protein 2, also related to NK cell degranulation, has been initially
designated FHL5 [29]. The genetic defect responsible for FHL1 has not been identified and no mutations in granzyme proteins have been associated with HLH. An X-linked variant of familial HLH has recently been described that is associated with XIAP (X-linked inhibitor of apoptosis protein) deficiency [30]. The exact pathologic mechanism has not been elucidated, but it may be related to accentuated T cell receptor-mediated T cell survival during an immune response.

Immunodeficiencies caused by defects in lysosomal trafficking have also been linked to life-threatening episodes of HLH. These include Chediak Higashi syndrome, Griscelli syndrome, and Hermansky-Pudlak syndrome type II [17,31–33]. The HLH syndrome has occasionally been observed as well in DiGeorge syndrome, chronic granulomatous disease, X-linked agammaglobulinemia, and X-linked nuclear factor-κB essential modulator (NEMO) defects [34–36]. In the X-linked lymphoproliferative syndrome (XLP), an immunodeficiency characterized by malignant lymphomas, dysgammaglobulinemia, and Epstein-Barr virus- (EBV) triggered HLH, a deletion in the SH2D1A gene disrupts the signal transduction protein which is necessary for normal T and NK cell activation and proliferation [37]. Lymphocytes from individuals with XLP demonstrate decreased activation-induced apoptosis. This pathophysiology is similar to that of familial HLH which may, at least in part, explain the underlying predisposition of patients with XLP to develop HLH [38].

Secondary HLH has also been associated with a variety of microbial agents. As mentioned above, EBV triggers a secondary HLH syndrome in XLP, but EBV and many other viruses can also induce HLH in individuals without prior known familial mutations [39]. The incidence of EBV-associated HLH appears to be higher in Asia for unknown reasons [4,39]. Additional members of the herpes virus family have also been observed to trigger HLH including cytomegalovirus, varicella zoster virus, human herpes virus 6 (HHV6), and HHV8 [40–43]. Other viruses reported sporadically in the literature to be associated with HLH include human immunodeficiency virus (HIV), influenza, parvovirus, adenovirus, and hepatitis B [43–47]. Non-viral infectious agents have been described with HLH as well including mycobacteria, leishmaniasis, malaria, candida and aspergillus [45]. It is important to note that in considering infection associated HLH, a recent study of Chinese children with EBV-associated HLH revealed seven novel mutations in the perforin, MUNC 13-4, and XIAP genes. These findings suggest that many forms of secondary HLH triggered by a specific infectious insult may be due to a genetic predisposition [48].

Malignancies associated with HLH are predominantly lymphoid in nature with a tendency toward T and NK cell lymphomas. These, however, are described primarily in adults rather than in children [49]. HLH type syndromes can also be observed in autoimmune conditions such as juvenile idiopathic arthritis, systemic lupus erythematosus, and Crohn’s disease, but in the context of autoimmune disease, it is often referred to as the MAS [6,7,9,50].

### Clinical Features

The classic presentation of HLH consists of prolonged, high fevers (usually present for 1–2 weeks prior to diagnosis), hepatosplenomegaly, and cytopenias [51,52]. Neurologic symptoms are often prominent features with symptoms of irritability, ataxia, hypo- or hypertonia, evidence of increased intracranial pressure, meningismus, depressed mental status, cranial nerve palsies, and seizures [53]. The most common neurologic features in one large pediatric study were irritability and seizures [54]. Other, less frequently observed symptoms include lymphadenopathy, rash, jaundice, diarrhea, and edema. The rashes are polymorphous and vary from diffuse erythematous maculopapular to scattered petechial rashes.

Biochemical and cellular abnormalities noted on clinical laboratory assessment include anemia, thrombocytopenia, neutropenia, elevated liver transaminases, hyperbilirubinemia, hypofibrinogenemia, coagulation abnormalities, hypoalbuminemia, hyponatremia, hypertriglyceridemia, and hyperferritinemia. Cerebrospinal fluid (CSF) pleocytosis is often seen on lumbar puncture in patients with significant neurologic involvement. Occasional inflammatory hemophagocytic cells may even be present in the CSF.

The onset of disease in the primary (familial) form is typically during infancy or early childhood, but can present at any age [55]. There are even reports of intrauterine cases of familial HLH manifesting as hydrops fetalis [56,57]. Infectious triggers can often be identified in primary HLH. Secondary HLH is clinically indistinguishable from primary disease and can occur at any age.

In the early days to months of illness, symptoms may exhibit a relapsing-remitting course with spontaneous improvement, but subsequent recrudescence [58]. In time, the clinical trajectory becomes more severe as significant tissue injury accumulates and organ failure sets in. Patients can also present acutely with an abrupt cardiopulmonary decomposition and a clinical picture that appears very similar to septic shock and ARDS [59,60]. In this scenario, respiratory distress is usually the first symptom noted by care providers with the rapid development of tachycardia and hypotension. Children often display agitation progressing to depressed mental status. Multigorgan system failure ensues with oliguria and liver failure characterized by jaundice and coagulopathy.

Radiologic abnormalities frequently observed in HLH are consistent with the involved organ systems. On chest x-ray, alveolar-interstitial opacities are often visualized in patients with respiratory distress, and are occasionally associated with pleural effusions. Abdominal imaging (ultrasound and computerized tomography) frequently reveals hepatosplenomegaly with gallbladder wall thickening and diffuse adenopathy. Cranial imaging often demonstrates periventricular white matter signal abnormalities with cerebral volume loss and enlargement of ventricles and extra-axial fluid spaces.
Subcortical, enhancing white matter lesions and cerebral edema may occasionally be observed [61].

Children with primary HLH who survive an episode invariably have repeat events until they succumb to the disease, if not treated. Those with secondary forms of HLH may expect disease free survival if the underlying trigger of their illness is completely eradicated.

### Diagnosis

Because of the severe nature of this disorder and the existence of disease altering therapies, it is crucial to identify patients early in their course and provide them treatment in order to decrease morbidity and mortality. To facilitate the recognition of HLH and to assist with its timely diagnosis, the International Histiocyte Society has established diagnostic criteria employing both clinical features and laboratory findings (Table 26.1) [10,13]. Laboratory verification of a known genetic defect confirms the diagnosis independent of the presence or absence of any clinical signs or symptoms. Otherwise, five of the eight clinical criteria must be met. It is important to note that NK cell dysfunction is only identified in about 50 % of patients with HLH. Additionally, hemophagocytosis may not be detected early in the HLH disease process. Therefore, serial assessments may be required if that diagnostic criterion is to be met [62]. Finally, the interpretation of soluble IL-2 receptor levels must be undertaken with care as normal levels change with age and method of analysis.

Many of the criteria used for these diagnostic guidelines are found in other infectious or inflammatory disorders including hemophagocytosis. In the arena of pediatric critical care, there is a high degree of overlap between the more severe presentations of HLH and the characteristic features and biochemical abnormalities of sepsis and septic shock with multisystem organ failure [63]. The manner in which clinicians distinguish the two diagnostically is important. The clinical history and specific constellation of symptoms must be taken into account and, in and of themselves, can provide guidance. Although children with septic shock can manifest each one of the HLH criteria in isolation and occasionally in combination, the specific constellation seen with HLH is quite characteristic. Despite a few small reports of increased soluble IL-2 receptor levels in sepsis, [64–66] significant elevations of this marker are rarely observed outside the context of HLH. The rapid availability of such results, however, is often compromised by the fact that most institutions must send patient samples to referral laboratories.

In contrast, because of its ready availability in most hospitals, the serum ferritin level can serve as an important adjunct to the decision-making process. The HLH diagnostic guidelines define a cutoff at greater than 500 μg/L, which may be observed in sepsis or other hyperinflammatory conditions. Ferritin levels in HLH are usually dramatically higher with some series finding mean levels near 45,000 μg/L [67,68]. A recent review of elevated ferritin values at a large pediatric academic tertiary care hospital demonstrated that a ferritin level greater than 10,000 was 90 % sensitive and 96 % specific for HLH [69]. Due to the fact that studies of NK cell function and soluble IL-2 receptor levels may take some time to result, a diagnostic algorithm to facilitate the differentiation of HLH from sepsis has been proposed that is based on early evaluation of serum ferritin levels (Fig. 26.3) [70].

---

**Fig. 26.3** Suggested algorithm for using serum ferritin in the evaluation of suspected HLH (Adapted from [70] With permission from BMJ Publishing Group LTD)
Treatment

Without treatment, HLH can be rapidly fatal. An early review of familial HLH described a mean survival from onset of symptoms of less than 1 month and an overall 1 year survival from diagnosis of 5 % [71]. Reported mortality for untreated secondary HLH is 50 % [4]. However, with current therapies, survival rates ranging from 50 to 70 % are now being reported [72]. Therefore, it is recommended that specific therapy be initiated as soon as there is a high clinical suspicion for HLH even if confirmatory diagnostic or genetic studies are still pending. Specific protocols to standardize the rational treatment of HLH were established first in 1994 and then revised in 2004 [13,73].

In the critically ill child, excellent provision of supportive care must undergird any HLH specific intervention. Children manifesting with ARDS or severe neurologic decompen-sation often require intubation and mechanical ventilation. Shock should be treated with appropriate fluid resuscitation and inotropic support. Individuals with significant kidney injury may need renal replacement therapy. Antimicrobial therapy must be provided to eradicate comorbid infections or infections that may have triggered a secondary form of HLH. In this regard, broad spectrum antibiotics are essential early in the course of disease that should be appropriately narrowed once an organism has been identified. Prophylactic trimethoprim-sulfamethoxazole and fluconazole are commonly given. Rituximab can be helpful in the setting of EBV driven HLH by depleting EBV-laden B cells.

The objectives of HLH specific therapy are to counteract the pathophysiologic processes driving the symptomatology and organ failure [10,14,70,74]. Corticosteroids are used for their nonspecific anti-inflammatory properties to suppress hypercytokinemia and promote lymphocyte apoptosis. Dexamethasone is the preferred agent because of its ability to cross the blood brain barrier and quench inflammation in the central nervous system. Etoposide induces cell cycle arrest, and therefore, interferes with lymphocyte proliferation. Cyclosporin disrupts intracellular signal transduction pathways preventing T cell activation and cytokine elaboration. Children with persistent or progressive central nervous system involvement are given intrathecal methotrexate which is toxic to the rapidly dividing immune cells. In addition, efficacy has been reported anecdotally with non-protocol therapies. For example, antithymocyte globulin (ATG) selectively depletes T cells, [75] while alemtuzumab (Campath®, humanized anti-CD52) targets both antigen presenting cells and T cells for elimination [76,77]. Abatacept (Orencia®), a fusion protein capable of blocking the B7 co-stimulatory signals necessary for T cell activation, has also been reported to improve symptoms [74]. Consultation with subspecialists experienced in the treatment of HLH is essential to appropriately navigate the application of these nuanced interventions.

Children who have no identified genetic defect and whose symptoms resolve may discontinue therapy after 8 weeks [13]. However, some require longer courses before remission is achieved. In all cases, ferritin and soluble IL-2 receptor levels are followed to monitor response to therapy. Indeed, the rate of decline in ferritin has recently been reported as an important prognostic indicator [78]. All patients with primary HLH require hematopoietic stem cell transplant (HSCT) and those with secondary forms who experience persistent disease or relapse should seriously be considered for HSCT as well [14,70,72,74,79]. Active disease at the time of HSCT is a poor prognostic indicator, and thus, considerable effort to induce remission should be undertaken [72,79].

Prognosis

As noted above, significant strides have been made in the treatment of HLH with survival now generally ranging from 50 to 70 % [72]. In children with non-familial HLH overall survival was 72 %, but only 20 % of them did not require HSCT [80]. Survival is increased in children, irrespective of genetic status, who receive HSCT from matched rather than unmatched donors [72]. Reduced-intensity pre-transplant conditioning regimens which are less inflammatory than myeloablative protocols appear to further decrease mortality [81]. The best outcomes in HSCT are seen in children who have a rapid and complete response to pre-transplant therapies and who do not exhibit significant neurologic involvement [54]. Patients with significant neurologic involvement can suffer severe and permanent sequelae even if they survive [53,82].

Conclusion

HLH is a severe, life-threatening, hyper-inflammatory disorder caused by dysregulation of the immune response that leads to critical multisystem organ dysfunction and death if untreated. Primary (familial) and secondary (acquired) forms exist, but all identified defects have in common the feature of immune effector cell cytotoxic impotence. Many isolated clinical characteristics are shared with other disease processes, including septic shock, but specific criteria have been established to facilitate the appropriate diagnosis. Disease specific treatment should be started as soon as possible to prevent progression of morbidity and mortality. HLH cannot be reversed by critical care interventions alone. Dexamethasone, etoposide, and cyclosporin form the mainstay of pre-transplant therapy. All children with primary HLH and many children with secondary HLH require HSCT to eradicate their disease. Current overall survival rates have improved to approximately 60–70 %. In the future, as the molecular mechanisms of HLH are more clearly elucidated, targeted interventions may provide even better outcomes for this life-threatening disease.
References

1. Farquhar JW, Claireaux AE. Familial haemophagocytic reticulosis. Arch Dis Child. 1952;27:519–25.
2. Weiss CZ, Norris DG. Familial erythrophagocytic lymphohistiocytosis. J Med Soc N J. 1977;74:539–41.
3. Close P, Friedman D, Uri A. Viral-associated hemophagocytic syndrome. Med Pediatr Oncol. 1990;18:119–22.
4. Janka G, Imashuku S, Elinder G, Schneider M, Henter JI. Infection- and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am. 1998;12:435–44.
5. Sawahey S, Woo P, Murray KJ. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. Arch Dis Child. 2001;85:421–6.
6. Grom AA. Natural killer cell dysfunction: a common pathway in systemic-onset juvenile rheumatoid arthritis, macrophage activation syndrome, and hemophagocytic lymphohistiocytosis? Arthritis Rheum. 2004;50:689–98.
7. Ravelli A, Magni-Manzonzi S, Pistorio A, et al. Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Pediatr. 2005;146:598–604.
8. Hazen MM, Woodward AL, Hofmann I, et al. Mutations of the hemophagocytic lymphohistiocytosis-associated gene UNC13D in a patient with systemic juvenile idiopathic arthritis. Arthritis Rheum. 2008;58:567–70.
9. Zhang K, Biroschak J, Glass DN, et al. Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis is associated with MUNC13-4 polymorphisms. Arthritis Rheum. 2008;58:2892–6.
10. Filipovich A, McClain K, Grom A. Histiocytic disorders: recent insights into pathophysiology and practical guidelines. Biol Blood Marrow Transplant. 2010;16(1 Suppl):S82–9.
11. Grom AA, Mellins ED. Macrophage activation syndrome: advances towards understanding pathogenesis. Curr Opin Rheumatol. 2010;22:561–6.
12. Henter JI, Aricò M, Elinder G, Imashuku S, Janka G. Familial hemophagocytic lymphohistiocytosis. Primary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am. 1998;12:417–33.
13. Henter J-I, Horne A, Aricò M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124–31.
14. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How we treat hemophagocytic lymphohistiocytosis. Blood. 2011;116:2635–43.
15. Marsh RA, Madden L, Kitchen BJ, et al. XIAP deficiency: a unique primary immunodeficiency best classified as X-linked familial hemophagocytic lymphohistiocytosis and not as X-linked lymphoproliferative disease. Blood. 2010;116:1079–82.
16. Kaya Z, Ehl S, Albayrak M, et al. A novel single point mutation of the LYST gene in two siblings with different phenotypic features of Chediak Higashi syndrome. Pediatr Blood Cancer. 2011;56:1136–9.
17. Arneson LN, Brickshawana A, Segovis CM, et al. Cutting edge: synergy in Toll-like receptor-4 and CD40 stimulation of macrophage and T-cell responses. J Immunol. 2004;173:4341–8.
18. Egelrud RM, Shapiro R, Loechelt B, Filipovich A. Characteristic immune abnormalities in hemophagocytic lymphohistiocytosis. J Pediatr Hematol Oncol. 1996;18:340–7.
19. Behrens EM, Canna SW, Slade K, et al. Repeated TLR9 stimulation results in macrophage activation syndrome-like disease in mice. J Clin Invest. 2011;121:2264–77.
20. Krebs P, Crozat K, Popkin D, Oldstone MB, Beutler B. Disruption of MyD88 signaling suppresses hemophagocytic lymphohistiocytosis in mice. Blood. 2011;117:6582–8.
21. Zoller EE, Lykens JE, Terrell CE, et al. Hemophagocytosis causes a consumptive anemia of inflammation. J Exp Med. 2011;208:1203–14.
22. Stepp SE, Dufourcq-Lagelouse R, Le Deist F, et al. Perforin gene defects in familial hemophagocytic lymphohistiocytosis. Science. 1999;286:1957–9.
23. Risma KA, Frayer RW, Filipovich AH, Sumegi J. Aberrant maturation of mutant perforin underlies the clinical diversity of hemophagocytic lymphohistiocytosis. J Clin Invest. 2006;116:182–92.
24. Trizzino A, zur Stadt U, Ueda I, et al. Genotype-phenotype study of familial haemophagocytic lymphohistiocytosis due to perforin mutations. J Med Genet. 2008;45:15–21.
25. Feldmann J, Callebaut I, Raposo G, et al. Munc13-4 is essential for cytolytic granules fusion and is mutated in a form of familial hemophagocytic lymphohistiocytosis (FHL3). Cell. 2003;115:461–73.
26. zur Stadt U, Schmidt S, Kasper B, et al. Linkage of familial hemophagocytic lymphohistiocytosis (FHL)-type 4 to chromosome 6q24 and identification of mutations in syntaxin 11. Hum Mol Genet. 2005;14:827–34.
27. Bryceson YT, Rudd E, Zheng C, et al. Defective cytotoxic lymphocyte degranulation in syntaxin-11 deficient familial hemophagocytic lymphohistiocytosis type 4 (FHL4) patients. Blood. 2007;110:1906–15.
28. Arneson LN, Brickshawana A, Segovis CM, et al. Cutting edge: syntaxin 11 regulates lymphocyte-mediated secretion and cytotoxicity. J Immunol. 2007;179:3397–401.
29. Meeths M, Entesarian M, Al-Herz W, et al. Spectrum of clinical presentations in familial hemophagocytic lymphohistiocytosis type 5 patients with mutations in STXBP2. Blood. 2010;116:2635–43.
30. Marsh RA, Madden L, Kitchen BJ, et al. XIAP deficiency: a unique primary immunodeficiency best classified as X-linked familial hemophagocytic lymphohistiocytosis and not as X-linked lymphoproliferative disease. Blood. 2010;116:1079–82.
31. Kaya Z, Ehl S, Albayrak M, et al. A novel single point mutation of the LYST gene in two siblings with different phenotypic features of Chediak Higashi syndrome. Pediatr Blood Cancer. 2011;56:1136–9.
32. Meeths M, Bryceson YT, Rudd E, et al. Clinical presentation of Griscelli syndrome type 2 and spectrum of RAB27A mutations. Pediatr Blood Cancer. 2010;54:563–72.
33. Enders A, Ziegler B, Schwarz K, et al. Lethal hemophagocytic lymphohistiocytosis in Hermansky-Pudlak syndrome type II. Blood. 2006;108:81–7.
34. Aricò M, Bettinacci A, Maccario R, et al. Hemophagocytic lymphohistiocytosis in a patient with deletion of 22q11.2. Am J Med Genet. 1999;87:329–30.
35. Parekh C, Hofstra T, Church JA, Coates TD. Hemophagocytic lymphohistiocytosis in children with chronic granulomatous disease. Pediatr Blood Cancer. 2011;56:460–2.
36. Pacholpik Schmid JM, Junge SA, Hossle JP, et al. Transient hemophagocytosis with deficient cellular cytotoxicity, monoclonal immunoglobulin M gammopathy, increased T-cell numbers, and hypomorph NEMO mutation. Pediatrics. 2006;117:e1049–56.
37. Coffey AJ, Brookbank RA, Brandau O, et al. Host response to EBV infection in X-linked lymphoproliferative disease results from mutations in an SH2-domain encoding gene. Nat Genet. 1998;20:129–35.
38. Filipovich AH, Zhang K, Snow AL, Marsh RA. X-linked lymphoproliferative syndromes: brothers or distant cousins? Blood. 2010;116:3398–408.
39. Maakaronen NR, Moanna A, Jacob JT, Albrecht H. Viral infections associated with haemophagocytic syndrome. Rev Med Virol. 2010;20:93–105.
40. Knorr B, Kessler U, Pöschl J, Fickenscher H, Linderkamp O. A haemophagocytic lymphohistiocytosis (HLH)-like picture following breastmilk transmitted cytomegalovirus infection in a preterm infant. Scand J Infect Dis. 2007;39:173–6.
41. Astigarraga I, Prats JM, Navajas A, Fernández-Teijeiro A, Urberuaga A. Near fatal cerebellar swelling in familial hemophagocytic lymphohistiocytosis. Pediatr Neurol. 2004;30:361–4.
42. Re A, Facchetti F, Borlenghi E, et al. Fatal hemophagocytic syndrome related to active human herpesvirus-8/Kaposi sarcoma-associated herpesvirus infection in human immunodeficiency virus-negative, non-transplant patients without related malignancies. Eur J Haematol. 2007;78:361–4.

43. Hoang MP, Dawson DB, Rogers ZR, Scheuermann RH, Rogers BB. Polymerase chain reaction amplification of archival material for Epstein-Barr virus, cytomegalovirus, human herpesvirus 6, and parvovirus B19 in children with bone marrow hemophagocytosis. Hum Pathol. 1998;29:1074–7.

44. Rouphael NG, Talati NJ, Vaughan C, et al. Infections associated with haemophagocytic syndrome. Lancet Infect Dis. 2007;7:814–22.

45. Zhang X-Y, Ye X-W, Feng D-X, et al. Hemophagocytic lymphohistiocytosis induced by severe pandemic influenza A (H1N1) 2009 virus infection: a case report. Case Rep Med. 2011;2011:951910.

46. Takenaka H, Kishimoto S, Ichikawa R, et al. Virus-associated haemophagocytic syndrome caused by rubella in an adult. Br J Dermatol. 1998;139:877–80.

47. Aleem A, Al Amoudi S, Al-Mashhadani S, Siddiqui N. Haemophagocytic syndrome associated with hepatitis-B virus infection responding to etoposide. Clin Lab Haematol. 2005;27:395–8.

48. Zhizhuo H, Junmei X, Yuelin S, et al. Screening the PRF1, UNC13D, STX11, SH2D1A, XIAP, and ITK gene mutations in Chinese children with Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2011. doi: 10.1002/pbc.23216. Epub ahead of print.

49. Janka GE. Hemophagocytic syndromes. Blood Rev. 2007;21:245–53.

50. Bizzan VF, Sheth MK, Talano J, et al. Association of Crotbn’s disease, thiorurines, and primary Epstein-Barr virus infection with hemophagocytic lymphohistiocytosis. J Pediatr. 2011;159(5):808–12.

51. Henter JI, Elinder G, Söder O, Ast A, Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. Acta Paediatr Scand. 1991;80:428–35.

52. Palazzi DL, McClain KL, Kaplan SL. Hemophagocytic syndrome in children: an important diagnostic consideration in fever of unknown origin. Clin Infect Dis. 2003;36:306–12.

53. Haddad E, Sulis ML, Jabado N, et al. Frequency and severity of central nervous system lesions in hemophagocytic lymphohistiocytosis. Blood. 1997;89:794–800.

54. Horne A, Trottetnam H, Arićo M, et al. Frequency and spectrum of central nervous system involvement in 193 children with haemophagocytic lymphohistiocytosis. Br J Haematol. 2008;140:327–35.

55. Clementi R, Emmi L, Maccario R, et al. Adult onset and atypical presentation of hemophagocytic lymphohistiocytosis in siblings carrying PRF1 mutations. Blood. 2002;100:2266–7.

56. Malloy CA, Polinski C, de Saint Basile G, Bertrand Y, Pondarré C. Hemophagocytic lymphohistiocytosis. Dermatol. 1998;139:877–80.

57. Bechara E, Dijoud F, de Saint Basile G, Bertrand Y, Pondarré C. Hemophagocytic lymphohistiocytosis with Munc13-4 mutation: a case report. Bone Marrow Transplant. 2008;42:175–80.

58. Horne A, Janka G, Maarten Egeler R, et al. Haematopoietic stem cell transplantation in haemophagocytic lymphohistiocytosis. Br J Haematol. 2005;129:622–30.

59. Henter JI, Aričo M, Egeler RM, et al. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. HLH study Group of the Histiocyte Society. Med Pediatr Oncol. 1997;28:342–7.

60. Filipovich AH. Hemophagocytic lymphohistiocytosis and other hemophagocytic disorders. Immunol Allergy Clin North Am. 2008;28:293–313. vii.

61. Mahlaoui N, Ouachée-Chardin M, de Saint Basile G, et al. Immunotherapy of familial hemophagocytic lymphohistiocytosis with antithymocyte globulins: a single-center retrospective report of 38 patients. Pediatrics. 2007;120:e622–8.

62. Strout MP, Seropian S, Berliner N. Alemtuzumab as a bridge to allogeneic SCT in atypical hemophagocytic lymphohistiocytosis. Haematol. 2005;129:622–30.

63. Castillo L, Carcillo J. Secondary hemophagocytic lymphohistiocytosis and severe sepsis/systemic inflammatory response syndrome/multiorgan dysfunction syndrome/macrophage activation syndrome share common intermediate phenotypes on a spectrum of inflammation. Pediatr Crit Care Med. 2009;10:387–92.

64. Takala A, Jousela I, Jansson SE, et al. Markers of systemic inflammation predicting organ failure in community-acquired septic shock. Clin Sci. 1999;97:529–38.

65. Takala A, Jousela I, Takkunen O, et al. A prospective study of inflammation markers in patients at risk of indirect acute lung injury. Shock. 2002;17:252–7.

66. Santana Reyes C, García-Muñoz F, Reyes D, et al. Role of cytokines (interleukin-1beta, 6, 8, tumour necrosis factor-alpha, and soluble receptor of interleukin-2) and C-reactive protein in the diagnosis of neonatal sepsis. Acta Paediatr. 2003;92:221–7.

67. Wang W, Knovich MA, Coffman LG, Torti FM, Torti SV. Serum ferritin: past, present and future. Biochim Biophys Acta. 1800;2010:760–9.

68. Bennett TD, Hayward KN, Farris RWD, et al. Very high serum ferritin levels are associated with increased mortality and critical care in pediatric patients. Pediatr Crit Care Med. 2011;12(6):e233–6.

69. Allen CE, Yu X, Kozinets CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2008;50:1227–35.

70. Freeman HR, Ramanan AV. Review of haemophagocytic lymphohistiocytosis. Arch Dis Child. 2011;96:688–93.

71. Janka GE. Familial hemophagocytic lymphohistiocytosis. Eur J Pediatr. 1993;140:221–30.

72. Horne A, Janka G, Maarten Egeler R, et al. Haematopoietic stem cell transplantation in haemophagocytic lymphohistiocytosis. Br J Haematol. 2005;129:622–30.

73. Henter JI, Aričo M, Egeler RM, et al. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. HLH study Group of the Histiocyte Society. Med Pediatr Oncol. 1997;28:342–7.

74. Filipovich AH. Hemophagocytic lymphohistiocytosis and other hemophagocytic disorders. Immunol Allergy Clin North Am. 2008;28:293–313. vii.

75. Hamalainen P, Aho J, Kokki H, et al. A case series of 38 patients with haemophagocytic lymphohistiocytosis in Finnish patients with X-linked lymphoproliferative disease. J Pediatr. 2011;158(5):825–31.

76. Lin TF, Fertic-Stark LL, Allen CE, Kozinets CA, McClain KL. Rate of decline of ferritin in patients with hemophagocytic lymphohistiocytosis as a prognostic variable for mortality. Pediatr Blood Cancer. 2011;56:154–5.

77. Baker KS, Filipovich AH, Gross TG, et al. Unrelated donor hematopoietic cell transplantation for hemophagocytic lymphohistiocytosis. Bone Marrow Transplant. 2008;42:175–80.

78. Horne J-I, Samuelsson-Horne A, Aričo M, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunomodulation and bone marrow transplantation. Blood. 2002;100:2367–73.

79. Marsh RA, Jordan MB, Filipovich AH. Reduced-intensity conditioning significantly improves survival of patients with hemophagocytic lymphohistiocytosis undergoing allogeneic hematopoietic cell transplantation. Blood. 2010;116:5824–31.

80. Lin TF, Fertic-Stark LL, Allen CE, Kozinets CA, McClain KL. Neuropathologic findings and neurologic dysfunction predicting multiorgan dysfunction syndrome/macrophage activation syndrome share common intermediate phenotypes on a spectrum of inflammation. Pediatr Crit Care Med. 2009;10:387–92.