REVIEW ARTICLE

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Hemophagocytic Lymphohistiocytosis

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CME

Hemophagocytic lymphohistiocytosis (HLH) is a severe and life-threatening syndrome characterized by overwhelming inflammation that often leads to multiorgan failure and death if not treated promptly and appropriately. Biologically, HLH has taught us about the immune system and the detrimental consequences of insufficient immune down-regulation. Clinically, HLH is often treatable but is still largely underdiagnosed, resulting in many unnecessary deaths.

The HLH syndrome is often classified into a primary (genetic, mendelian) form and a secondary (acquired, nonmendelian) form (Table 1).[1] Primary HLH, including its most common form, familial HLH, typically affects children, mostly infants, whereas the secondary form is much more common in adults. The most common triggers for secondary HLH are infections, cancers, and autoimmune diseases[2]; HLH with an autoimmune trigger is also referred to as macrophage activation syndrome (MAS-HLH).

Familial HLH is a success story in modern medicine. Initially a disease that was largely unknown and fatal, it is now understood on a molecular level and is curable. Moreover, HLH is an archetype of hyperinflammation, a state of life-threatening massive inflammation that physicians in many medical specialties, including hematology, oncology, infectious diseases, pediatrics, rheumatology, intensive care, neurology, gastroenterology, genetics, and immunology, should recognize.

History

In 1939, Scott and Robb-Smith described a fatal disorder in adults, characterized by fever, wasting, cytopenia, hepatosplenomegaly, and active phagocytosis, which they called histiocytic medullary reticulosis, possibly referring to HLH associated with cancers.[3] Familial HLH is often reported as having first been described in 1952 by Farquhar and Claireaux, but it is likely that two siblings described in 1951 by Reese and Levy as having familial Letterer–Siwe disease also had familial HLH.[4,5] In 1979, a virus-associated hemophagocytic syndrome (i.e., secondary HLH) was reported.[6]

In 1999, the first disease-causative gene associated with familial HLH was reported (*PRF1*), representing a major breakthrough. Now we know that familial HLH is caused by biallelic variants in four specific genes, *PRF1*, *UNC13D*, *STX11*, and *STXBP2*, which encode the proteins perforin, Munc13-4, syntaxin-11, and syntaxin-binding protein 2 (Munc18-2) and cause familial HLH types 2 through 5, respectively. The closely related Griscelli's syndrome type 2 (GS2) is caused by variants in *RAB27A*, encoding the small guanosine triphosphatase (GTPase) Rab27a, a member of the Ras family that has a role in lysosome trafficking. These proteins are all essential for normal functioning of natural killer (NK) cells and cytotoxic T cells, findings that confirmed that the underlying cause of familial HLH is defective lymphocyte cytotoxicity.[7-10]

KEY CLINICAL POINTS

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

- Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome of overwhelming inflammation (hyperinflammation) that causes multiorgan failure and death, making prompt and appropriate treatment imperative.
- Primary (mendelian) HLH, an inherited deficiency of immune down-regulation mainly seen in children, is typically caused by defective cytotoxic lymphocytes (natural killer cells and cytotoxic T cells) with various defects in the perforin–granzyme cell-death pathway.
- Secondary (nonmendelian) HLH is an acquired condition, mainly seen in adults, that is most often triggered by infections, cancers, or autoimmune diseases.
- In all patients with the HLH syndrome, a search for and treatment of the underlying trigger (or triggers) is crucial; if the trigger is difficult to find in an adult, it is often a cancer.
- Although life-threatening and treatable, HLH is still underdiagnosed, and numerous lives could be saved through increased awareness of the disorder.
- HLH should be considered, and ferritin levels checked, in patients with sepsislike critical illness that does not respond to adequate empirical treatment.

EPIDEMIOLOGY

The prevalence of HLH varies greatly from country to country. The incidence of primary HLH among children in Sweden has been estimated to be approximately 1 case per 50,000 live births; in comparison, the incidence of severe combined immunodeficiency is 1 case per 38,500 live births. These two disorders are probably the most common inherited, rapidly fatal immunodeficiencies in humans.[10,11] The frequencies of all main primary immunodeficiencies in a large national registry have been published in a French report.[12] Since familial HLH is an autosomal recessive syndrome, it occurs most often in areas where consanguinity is common. The median age at onset is 3 to 6 months.[13,14]

The prevalence of secondary HLH is less well established. The overall incidence of all forms of HLH was estimated to be 4.2 cases per 1 million population in 2018 in England.[15] The annual incidence of HLH associated with cancer (i.e., malignancy-associated HLH) for the period from 2012 through 2018 in Sweden was reported to be at least 6.2 cases per 1 million adults, with regional variations probably attributable to variations in awareness of the disorder.[16] Secondary HLH is still largely underdiagnosed worldwide.

CLINICAL AND LABORATORY FEATURES

FAMILIAL HLH

A typical presentation of familial HLH is a sepsis-like condition associated with cytopenias and hepatosplenomegaly in a child, often an infant, with a febrile illness.[13,17] Thrombocytopenia, anemia, and, to a lesser extent, neutropenia are common. Hemophagocytosis is not always present, particularly not in the early phase of the disease, nor is hemophagocytosis specific for HLH.[17]

Hepatosplenomegaly and elevated levels of aminotransferases and ferritin are almost always present in patients with familial HLH. Hyperbilirubinemia, predominantly conjugated, and elevated γ-glutamyl transferase and lactate dehydrogenase levels are common.[13,17] In a British study involving 78 children with acute liver failure who were younger than 24 months of age, 30 of the children had HLH, of whom 19 had genetic variants associated with HLH.[18] On histopathological assessment, infiltration in the portal tract, resembling chronic, persistent hepatitis, may be found.[13] Disseminated intravascular coagulation, severe acute bleeding, and hypofibrinogenemia are common.[13,17]

At diagnosis, approximately one third of patients have neurologic alterations that may be severe, including seizures, decreased consciousness, and signs of meningism.[19] Ataxia and psychomotor retardation may develop. Neurologic symptoms, most commonly ataxia or gait disturbance and seizures, may be the first manifestation of familial HLH, particularly in older children and adolescents.[20] Approximately half of affected children have a moderately increased lymphocyte count or protein content in the cerebrospinal fluid (or both).[19] Diffuse, multifocal white-matter lesions and cerebellar involvement are common findings on magnetic resonance imaging (MRI).[20] In rare

Table 1. Classification of Hemophagocytic Lymphohistiocytosis (HLH).*

Category of HLH	Associated Conditions or Triggers
Primary (mendelian) HLH	
HLH associated with lymphocyte cytotoxic defects	Familial HLH type 2 (*PRF1*) Familial HLH type 3 (*UNC13D*) Familial HLH type 4 (*STX11*) Familial HLH type 5 (*STXBP2*) X-linked lymphoproliferative disease type 1 (*SH2D1A*) Griscelli's syndrome type 2 (*RAB27A*) Chédiak–Higashi syndrome (*LYST*)
HLH associated with abnormalities of inflammasome activation	X-linked lymphoproliferative disease type 2 (*BIRC4*) Defective NLRC4 (*NLRC4*)
HLH associated with other defined mendelian disorders	Lysinuric protein intolerance (*SLC7A7*) Wolman's disease (*LIPA*) Various inborn errors of immunity
Familial (apparently mendelian) HLH of unknown origin	
Secondary (apparently nonmendelian) HLH	
Infection-associated HLH	
Virus-associated HLH	Epstein–Barr virus Cytomegalovirus Other defined herpesviruses Human immunodeficiency virus Influenza virus Other defined viruses
Bacteria-associated HLH	
Parasite-associated HLH	
Fungus-associated HLH	
Malignancy-associated HLH	
Triggered by cancer (HLH at diagnosis or relapse of a cancer)	Hematologic cancers (T-cell lymphoblastic lymphomas or leukemias, T-cell nonlymphoblastic lymphomas, B-cell leukemias, B-cell lymphomas (non-Hodgkin's), Hodgkin's lymphomas, natural killer cell lymphomas or leukemias, myeloid neoplasias, or other hematologic cancers) Solid tumors Unclassified cancer
Occurring during chemotherapy (not associated with diagnosis or relapse of a cancer)	
Associated with a cancer but not further defined	
HLH associated with an autoimmune condition (macrophage activation syndrome–HLH)	Systemic-onset juvenile idiopathic arthritis Adult-onset Still's disease Systemic lupus erythematosus Vasculitis Other defined autoimmune conditions Undefined autoimmune condition
HLH associated with transplantation	
HLH associated with iatrogenic immune activation	
HLH associated with iatrogenic immune suppression	
HLH associated with other apparently nonmendelian conditions	
HLH of unknown or uncertain origin	

* Primary (mendelian) HLH may have a triggering factor, which is usually an infection. Secondary (nonmendelian) HLH is almost always associated with a trigger, most often an infection, cancer, or an autoimmune condition. The classification is adapted from Emile et al.[1]

cases, the posterior reversible encephalopathy syndrome is associated with HLH.[14]

Other findings include petechiae, purpura, transient maculopapular rash, and lymph-node enlargement. Albumin and sodium levels may be reduced, and triglyceride levels elevated.[13,17] Soluble interleukin-2 receptor α (sCD25) levels are often markedly elevated and together with ferritin levels are used as biomarkers for monitoring HLH disease activity. In GS2, silvery gray hair and eyelashes are common, with large pigment clumps in hair shafts on light microscopy. *STXBP2* variants may cause severe diarrhea, which may persist despite successful hematopoietic stem-cell transplantation (HSCT).[9,21]

SECONDARY HLH

The signs and symptoms of all forms of HLH are generally quite similar, and it is often difficult to distinguish between the primary and secondary forms, except that primary HLH is more common in infants and secondary HLH is more common in older children and adults. Secondary HLH often manifests as a critical illness with sepsis-like manifestations that are unresponsive to sepsis-directed therapy, and this form of the disorder may be difficult to recognize because of overlapping characteristics with other inflammatory conditions in critically ill patients.

In a review involving 661 critically ill adults with HLH, infections were the most common trigger (in 50% of the patients), followed by cancers (in 28%), and autoimmune diseases (in 12%).[22] The most common infectious triggers were Epstein–Barr virus (EBV) (in 25% of the patients), bacteria (in 20%), and cytomegalovirus (in 7%). Lymphomas accounted for 76% of malignant triggers, followed by leukemias (8%). Among autoimmune triggers, systemic lupus erythematosus and adult-onset Still's disease were most common (accounting for 39% and 21% of cases, respectively); other autoimmune triggers included systemic vasculitis and inflammatory bowel disease.[2,22]

In children, infection-associated HLH is the most common form, followed by autoimmune-associated HLH, which is seen most often in children with systemic juvenile idiopathic arthritis (affecting approximately 10% of such children) and in those with systemic lupus erythematosus. Malignancy-associated HLH is much less common in children.[16]

Neurologic symptoms are heterogeneous and occur less often in patients with secondary HLH than in those with familial HLH, affecting 10 to 25% of patients with secondary HLH in larger studies.[2,23] Half these patients have abnormal findings on MRI.[23]

PATHOPHYSIOLOGY

GENETIC DEFECTS IN PRIMARY HLH

The frequency of gene variants that cause primary (mendelian) HLH varies among ethnic groups, but variants in *PRF1*, *UNC13D*, and *STXBP2* are most common.[24,25] Although most variants are associated with severe disease and an early onset, some may cause a milder phenotype with a later onset.[26]

Several other genetic defects that are not detailed in this review also confer a predisposition to HLH, including the Chédiak–Higashi syndrome (*LYST*) and X-linked lymphoproliferative syndrome (XLP) type 1 (*SH2D1A*),[27,28] both of which are also associated with reduced lymphocyte cytotoxicity; several inborn errors of metabolism, such as Wolman's disease (*LIPA*) and lysinuric protein intolerance (*SLC7A7*); and numerous inborn errors of immunity.[10,29] Defective NLR (nucleotide-binding oligomerization domain [NOD] leucine-rich repeat) receptors, CARD (caspase recruitment domain)–containing protein 4 (*NLRC4*), and XLP type 2 (*BIRC4*) are associated with dysregulated inflammasome activation.[30,31]

DEFECTS IN LYMPHOCYTE CYTOTOXICITY CAUSING FAMILIAL HLH

In familial HLH and GS2, initiation of the immune response is appropriate; the problem is an inability to terminate the response (Fig. 1A and 1B),[7-10] which leads to massive overactivation of inflammatory cells (i.e., hyperinflammation), with markedly elevated levels of inflammatory cytokines, including interferon-γ, interleukin-1β, interleukin-6, interleukin-10, interleukin-18, and tumor necrosis factor.[7-10] Interferon-γ plays a pivotal role in both primary and secondary HLH.[32,33] Serum levels of CXCL-9 (C-X-C motif chemokine ligand 9), an interferon-γ–induced chemokine that serves as a surrogate marker for interferon-γ, are also elevated; an assay measuring CXCL-9 is the preferred means of testing for circulating interferon-γ.[32,33] Signs and symptoms of familial HLH reflect this hypercytokinemia (Table 2).[14,21,35] Ultimately, the inability to terminate the exces-

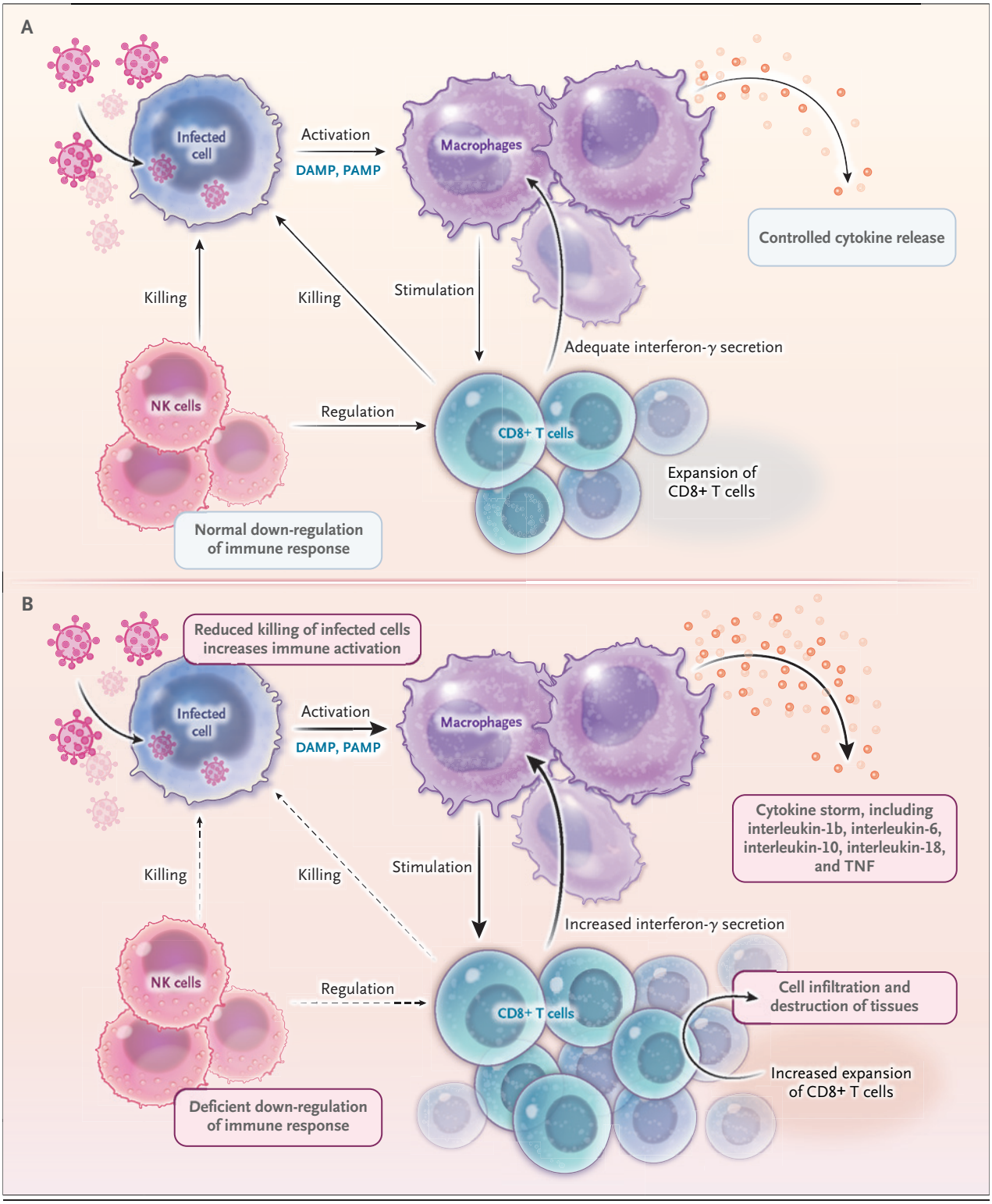

Figure 1 (facing page). Normal Immune Response and Immune Response in a Patient with Familial Hemophagocytic Lymphohistiocytosis (HLH).

In a normal immune response, after infection by an intracellular pathogen, macrophages are activated by pattern-recognition receptors, at which point they secrete proinflammatory cytokines and present antigens (Panel A). Antigen-specific CD8+ T cells are recruited and then respond to foreign antigens, expand, eliminate infected cells, and produce interferon-γ, which stimulates innate immune cells and increases antigen presentation. Natural killer (NK) cells can reduce the number of activated CD8+ T cells by induction of apoptosis, thereby down-regulating the immune response. After the pathogen has been eradicated, most involved immune cells die a programmed cell death, and the immune response is down-regulated in an orderly fashion, leaving only a small number of memory CD8+ T cells. In a person with familial HLH, the immune response is initiated appropriately, but the ability to kill infected cells and efficiently terminate the immune response is impaired (Panel B). With an infectious trigger, the antigen-specific CD8+ T cells expand, but impaired target-cell killing and pathogen elimination exacerbate interferon-γ production. Macrophages are activated, but cytotoxic CD8+ T cells fail to kill excessive antigen-presenting cells and down-regulate immune responses, and NK cells fail to eliminate the activated, but defective, CD8+ T cells. The resulting excessive immune response leads to proinflammatory lytic cell death (pyroptosis), which mediates cytokine release. Altogether, this results in the release of damage-associated molecular pattern (DAMP) molecules and pathogen-associated molecular pattern (PAMP) molecules, both of which activate interferon-γ–primed macrophages. A vicious circle of immune activation ensues, leading to a cytokine storm that causes escalating tissue destruction in several organs, with a high risk of multiorgan failure and death.

sive immune response leads to a vicious circle of hyperinflammation and subsequent tissue destruction in several organs, which leads to multiorgan failure and death.

The underlying cellular defect in familial HLH and GS2 is impaired lymphocyte cytotoxicity in NK cells and cytotoxic T cells. In persons without these conditions, these cells kill target cells, such as virus-infected and cancer-transformed cells, by inducing programmed cell death (apoptosis) in the immunologic synapse through activation of the perforin–granzyme cell-death pathway, as depicted in Figure 1A, in a process resembling the secretion of neurotransmitters at the neurologic synapse.[7-10] In familial HLH and GS2, however, this process is deficient as a result of either insufficient production of perforin or reduced secretion of perforin-containing granules from cytotoxic cells (Fig. 2).[7-10]

Defective lymphocyte cytotoxicity elicits an uncontrolled expansion of antigen-specific effector T cells, sustained by the inability of CD8+ T cells to deplete antigen-presenting cells and defective down-regulation of the immune response by cytotoxic cells. Activated lymphocytes secrete high levels of interferon-γ, further activating macrophages, which in turn activate more T cells (Fig. 1B).[7-10] This circle of immune activation can develop in the absence of apparent infectious stimuli, such as in utero.[36] Altogether, familial HLH has taught us that granule-mediated cytotoxicity is essential in human immunoregulation.

Persons with biallelic *PRF1* mutations who live to at least 10 years of age without familial HLH developing are at almost a 50% risk for the development of at least one hematologic cancer in childhood or adolescence, which suggests a link between defective cytotoxicity and susceptibility to cancer.[37] Among monoallelic carriers of *UNC13D* mutations, the reported risk of lymphoma is 3 times as high as among noncarriers, possibly because of unidentified defects in lymphocyte cytotoxicity.[38]

MECHANISMS CAUSING SECONDARY HLH

The cause of secondary (nonmendelian) HLH is multifactorial, with one underlying cause often predominant, although the pathophysiological mechanisms are still incompletely understood. According to the threshold model described by Brisse et al., various factors (genetic defects, background inflammation, underlying immunosuppression, and infectious triggers) combine to eventually reach a threshold at which inflammation becomes uncontrolled and fulminant HLH develops (Fig. 3).[9] Persons with secondary HLH may carry genetic variants, such as digenic mutations, that impair but do not completely eliminate the ability to terminate the immune response. Moreover, severe HLH in adults may correlate with HLH-related gene variants.[39] Thus, diverse pathways and causes can result in the same end stage of hyperinflammation, at which point it may be difficult to identify the underlying cause.[9]

In secondary HLH, unlike the familial form, the number of circulating NK cells and cytotoxic T cells is often reduced.[40] Qualitative defects in lymphocyte cytotoxicity have also been reported, including high expression of exhaustion

Table 2. Clinical and Laboratory Features of HLH and Suggested Biologic Mechanisms.*

Feature	Cutoff Value	Included in HScore†	Suggested Mechanism
Revised HLH-2004 diagnostic criteria (HLH-2024 diagnostic criteria)			
Fever	≥38.5°C	Yes	Elevated pyrogens
Splenomegaly	≥2 cm below costal margin	Yes	Infiltration by lymphocytes and histiocytes
Cytopenia	≥2 of the cell lines below	Yes	Multicausal: suppression by cytokines, ferritin, hemophagocytosis
Hemoglobin	<90 g/liter (in neonates <100 g/liter)		
Platelets	$<100 \times 10^9$/liter		
Neutrophils	$<10^9$/liter		
Hypofibrinogenemia or hypertriglyceridemia	Fibrinogen level of ≤1.5 g/liter or triglyceride level of ≥3.0 mmol/liter	Yes	Plasminogen activator production by macrophages; lipoprotein lipase suppression by cytokines
Hyperferritinemia	≥500 μg/liter	Yes	Macrophage activation
Hemophagocytosis	Bone marrow, other tissues	Yes	Macrophage activation
Elevated soluble CD25‡	≥2400 U/ml	No	T-cell activation
Other features			
Natural killer cell activity§	Reduced or absent	No	Genetic defect, transient dysfunction
Hepatomegaly		Yes	Infiltration by lymphocytes and histiocytes
Elevated aminotransferases		Yes	Infiltration by lymphocytes and histiocytes
Elevated bilirubin		No	Infiltration by lymphocytes and histiocytes
Elevated lactate dehydrogenase		No	Cell death
Elevated D-dimers		No	Hyperfibrinolysis
Elevated CSF cells or CSF protein		No	Cell infiltration in CNS disease
Known underlying immunosuppression		Yes	

* The HLH-2004 diagnostic criteria were revised in 2024 by the Histiocyte Society. With the HLH-2004 criteria, at least five of a total of eight criteria must be fulfilled to make the diagnosis.[14] With the revised criteria, natural killer cell activity is removed as a criterion, and five of the remaining seven criteria must be met to make the diagnosis.[34] For the complete revision of the diagnostic guidelines, see Henter et al.[34] and Table S1 in the Supplementary Appendix. The information in the table is adapted from Janka and Lehmberg.[21] CNS denotes central nervous system, and CSF cerebrospinal fluid.

† The HScore is a weighted scoring system based on nine variables. The score for each criterion and the probability of HLH according to the HScore are shown in Tables S2 and S3, respectively; see also Fardet et al.[35]

‡ Soluble CD25 is also known as soluble interleukin-2 receptor α.

§ This criterion was included in the HLH-2004 diagnostic criteria but not in the revised 2024 criteria, since cytotoxicity assays there represent a separate diagnostic pathway.

markers.[41] Infectious agents, such as EBV and H5N1 influenza virus, can suppress cytotoxicity. Most cytotoxicity defects in secondary HLH are transient and reversible.[9]

The pathophysiological mechanisms underlying MAS-HLH partially differ from those of other forms of HLH. It has been hypothesized that interleukin-18 overproduction is a hallmark pathogenic mechanism in MAS-HLH,[42,43] as well as in its antecedent condition, Still's disease.

DIAGNOSIS

Prompt initiation of treatment for HLH is essential to reduce mortality and morbidity, in particular neurologic complications. For screening purposes, monitoring of ferritin levels is suggested, since they are almost always elevated, often markedly so.[44] However, hyperferritinemia is a less specific finding for HLH in adults than in children, since several other disorders are also associated with hyperferritinemia.

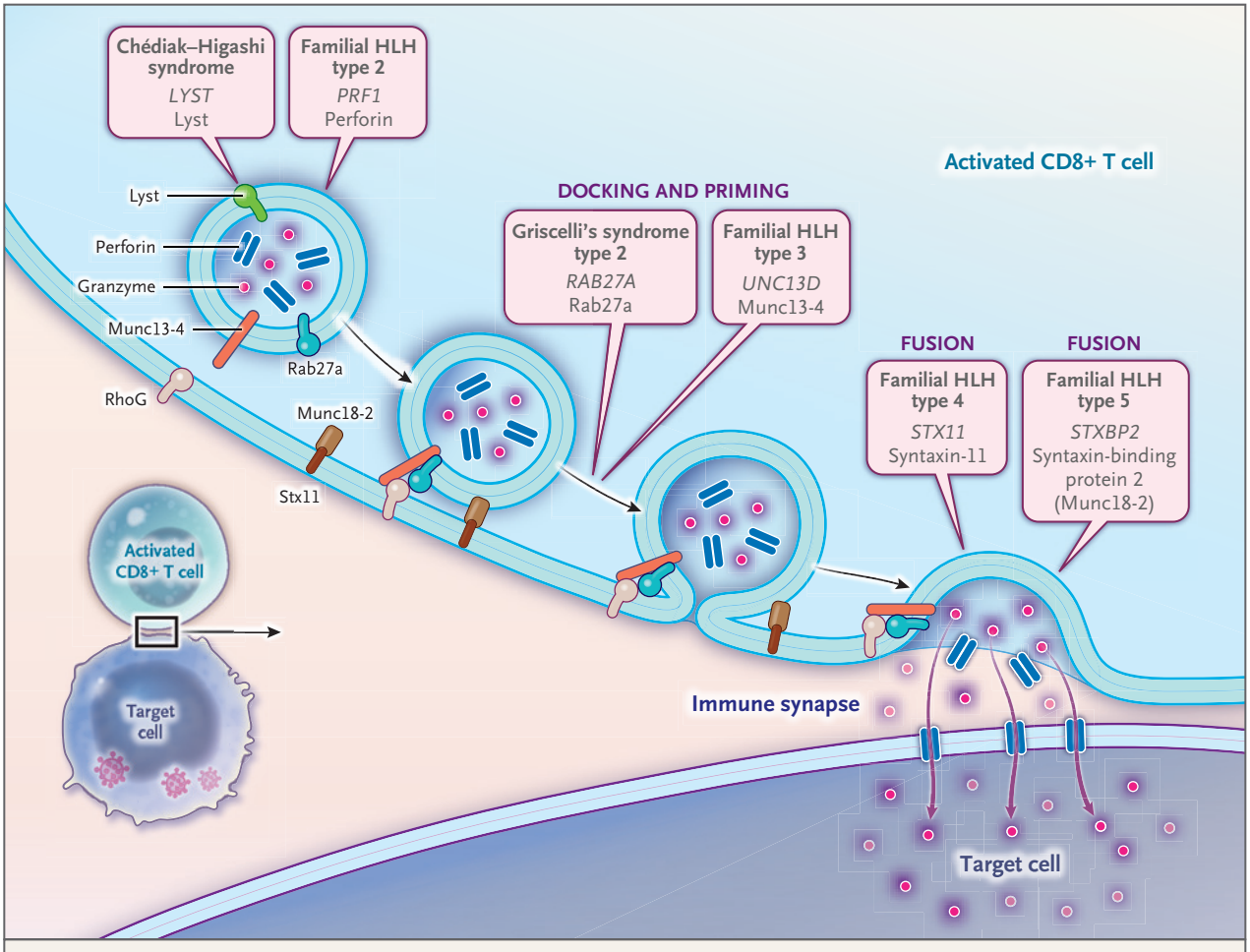

Figure 2. Genes Associated with Familial HLH Encoding Proteins Required for Lymphocyte Exocytosis and Target-Cell Killing.

Perforin (deficient in familial HLH type 2) is expressed by cytotoxic lymphocytes (i.e., NK cells and CD8+ T cells) and stored in specialized secretory lysosomes. These perforin-containing cytotoxic vesicles can be transported to activating immune synapses formed with susceptible target cells. Lyst (deficient in patients with the Chédiak–Higashi syndrome) facilitates biogenesis of secretory lysosomes. Rab27a (deficient in patients with Griscelli's syndrome type 2) facilitates trafficking of secretory lysosomes along microtubules to immune synapses. Munc13-4 (deficient in familial HLH type 3) is separately recruited to secretory lysosomes, binds Rab27a, and promotes docking of the cytotoxic vesicles at the immune synapse through RhoG, a protein that can bind Munc13-4. Syntaxin-11 (deficient in familial HLH type 4) and Munc18-2 (deficient in familial HLH type 5) are trafficked to immune synapses by recycling endosomes. Syntaxin-11 is incorporated into the plasma membrane and can facilitate fusion of secretory lysosomes releasing perforin and granzymes toward the target cell. Perforin monomers bind to the target cell and form multimeric pores in the cell membrane, allowing for the entry and passive diffusion of granzymes (proapoptotic proteases) into the target cell to promote programmed cell death. Perforin itself can also mediate cell lysis. If this perforin-mediated cytotoxic machinery is defective, the capacity to kill infected, neoplastic, and malignant cells is reduced and the ability to down-regulate immune responses is impaired. The figure is adapted from de Saint Basile et al.,[7] Pachlopnik Schmid et al.,[8] Brisse et al.,[9] and Meeths and Bryceson.[10]

Clinical diagnostic criteria have been developed to facilitate early diagnosis of familial HLH. The majority of these criteria are easily measured. In the HLH-2004 trial, five of the following eight criteria had to be met for diagnosis: fever, splenomegaly, bicytopenia (hemoglobin, platelets, and neutrophils), hypertriglyceridemia or hypofibrinogenemia, hemophagocytosis, hyperferritinemia, low or absent NK-cell activity, and elevated sCD25 levels (Table 2).[14] In a recent revision of the HLH-2004 diagnostic guidelines (also referred to as the HLH-2024 diagnostic criteria), the Histiocyte Society suggests genetic and lymphocyte cytotoxicity assays as two separate diagnostic strategies, with five of the remaining seven criteria (i.e., excluding NK-cell activity) as the

third diagnostic strategy (Table 2, and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[34]

Familial HLH may already be present at birth or even in utero,[36] whereas less severe forms, which may have a less typical clinical presentation and therefore be diagnostically challenging, may develop during adolescence or adulthood.[26] Not all patients with familial HLH fulfill the clinical diagnostic criteria, and HLH-directed therapy sometimes has to be initiated on the basis of a strong clinical suspicion of HLH, before overwhelming disease activity causes irreversible damage of one or more organs, such as the brain.

The presence of verified pathogenic genetic variants is essential to confirm the diagnosis of familial HLH. This process is facilitated by the increasingly rapid turnaround time for genomic testing. However, lymphocyte cytotoxicity assays, which are often faster, may suggest genetic HLH and support treatment decisions. The absence of perforin expression on a flow-cytometric assay quantifying intracellular perforin expression in cytotoxic cells suggests *PRF1* variants.[45] Mutations in *UNC13D*, *STXBP2*, *STX11*, and *RAB27A* may be detected on the basis of reduced or absent CD107a fluorescence at the cell membrane, a finding that indicates decreased or defective perforin exocytosis.[46] Flow-cytometric screening, including screening for CD107a, perforin, and if the patient is male, XLP1 and XLP2, is suggested in children and young adults and worth considering

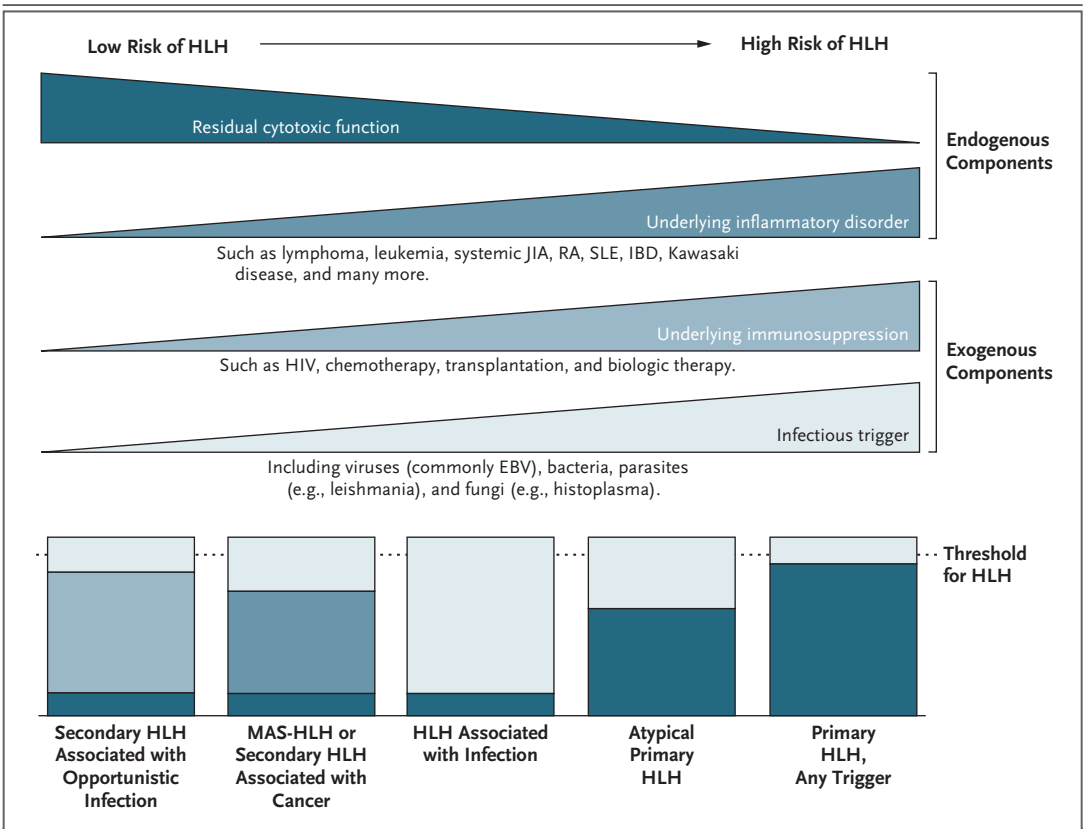

Figure 3. Endogenous and Exogenous Components Causing HLH.

Primary HLH is typically caused by deficient cytotoxic function; an infection sometimes triggers its onset, but primary HLH may also develop without any apparent triggers. The cause of secondary HLH can be multifactorial, often with a predominant underlying cause, but the pathophysiological mechanisms are still incompletely understood. According to the threshold model, described by Brisse et al.,[9] various endogenous components (genetic factors affecting cytotoxic function and background inflammation) and exogenous components (underlying immunosuppression and infectious triggers) combine to eventually reach a threshold at which inflammation becomes uncontrolled and fulminant HLH develops. EBV denotes Epstein–Barr virus, HIV human immunodeficiency virus, IBD inflammatory bowel disease, JIA juvenile idiopathic arthritis, RA rheumatoid arthritis, and SLE systemic lupus erythematosus.

in other adults. In unaffected siblings of patients with familial HLH, genetic and lymphocyte cytotoxicity studies are recommended. If the pathogenic gene variant is known, prenatal testing is possible.

Diagnosis of secondary HLH is challenging, since there is no exact diagnostic test for the disorder, but the HLH-2004 criteria have often been used. An alternative or complementary approach is the HScore, a weighted scoring system for adults based on nine variables: fever, organomegaly, known underlying immunosuppression, hemophagocytosis, number of cytopenias, and levels of ferritin, triglycerides, fibrinogen, and aspartate aminotransferase (Table 2).[35] Calculation of the HScore and an interpretation of the probability of HLH according to the score are shown in Tables S2 and S3, respectively. Both the HLH-2004 criteria and the HScore have been reported to have good diagnostic accuracy in critically ill adults. The best predictive accuracy for an HLH diagnosis is provided by four fulfilled HLH-2004 criteria (95.0% sensitivity and 93.6% specificity) and an HScore of 168, on a scale from 0 to 337 (100% sensitivity and 94.1% specificity).[47]

If the underlying triggering factor is not identified initially, a meticulous search for it should be continued in all patients, including patients who are receiving ongoing HLH treatment. The most common triggers not identified early on are cancers. An elevated ratio of sCD25 to ferritin (≥2.0) has been reported to have a positive predictive value of 85% for identifying lymphoma-associated HLH (96% for the combined findings of an elevated sCD25:ferritin ratio and an sCD25 level of ≥5000 U per milliliter).[48] Common lymphoma subtypes that trigger HLH include NK cell–T-cell lymphoma, angioimmunoblastic T-cell lymphoma, subcutaneous panniculitis-like T-cell non-Hodgkin's lymphoma, and intravascular large B-cell lymphoma.[49]

Different forms of inflammation have characteristic inflammatory cytokine profiles. In patients with EBV-associated HLH, interferon-γ levels are markedly elevated but interleukin-6 levels are only moderately elevated, whereas patients with bacterial sepsis in the absence of HLH have high levels of interleukin-6 but only slightly elevated levels of interferon-γ.[50] T-cell activation profiles can also help to differentiate sepsis from HLH.[51] Extremely high interleukin-18 levels (typically >25,000 ng per liter) strongly suggest Still's disease and certain autoinflammatory diseases that confer a high risk of MAS-HLH.[43]

TREATMENT

GENERAL APPROACH

The general approach to the treatment of HLH has three main components. First, the hyperinflammation must be promptly calmed in order to prevent organ damage. How aggressively this is done can vary, as detailed below. In parallel with treatment for the hyperinflammation, major efforts should be made to find and treat a possible triggering factor, since such a trigger may be present in patients with primary HLH and is almost always present in patients with secondary HLH. In addition, whether the patient would benefit from HSCT, as is the case for most patients with primary HLH, should be determined.

PRIMARY HLH

In 1983, Janka reported that the median survival among patients with familial HLH was 1 to 2 months.[13] The person who is today probably the longest-surviving patient with familial HLH received the diagnosis in 1982.[52] The first international treatment protocol for familial HLH (the HLH-94 protocol), launched in 1994, had two main parts[53]: prompt control of the hyperinflammation to reduce the risk of early death and damage to the central nervous system (CNS), and a definitive cure through replacement of the defective immune system by means of HSCT, as originally reported in 1986 by Fischer et al.[54]

Pretransplantation Therapy

The most established treatment protocols for primary HLH, the HLH-94 and subsequent HLH-2004 protocols, are based on the use of etoposide, dexamethasone, and cyclosporine. Among the children with verified familial or genetic disease, these therapies resulted in pre-HSCT survival of 73% (44 of 60 children) in the HLH-94 study and 81% (135 of 167) in the HLH-2004 study. Altogether, 92% of the children (55 of 60) and 89% (148 of 167), respectively, were alive or had undergone HSCT at 2 months, and the overall 5-year survival was 50% and 59%, respectively.[14,53] An international HLH registry recently reported an astonishing pre-HSCT survival rate of 91% among 57 symptomatic patients with veri-

fied primary HLH who received first-line treatment with etoposide.[55] With a survival rate of 85% after HSCT, the 3-year probability of survival was 77%.

Etoposide causes potent selective depletion of activated T cells.[56] It also promotes apoptosis in activated lymphocytes from patients with HLH.[57] Altogether, this results in efficient suppression of inflammatory cytokine production.[56] In patients with MAS-HLH, markedly elevated levels of HMGB1 are greatly reduced by etoposide.[42] Side effects of etoposide include dose-limiting bone marrow suppression — in particular, neutropenia — and a low (<0.5%) risk of treatment-related acute myeloid leukemia, as reported in the HLH-94 and HLH-2004 studies.[14,53]

With alemtuzumab, a monoclonal antibody directed against the CD52 antigen expressed on lymphocytes, and emapalumab, an interferon-γ blocking antibody, pretransplantation survival rates of 92% and 57%, respectively, among previously untreated patients with primary HLH has been reported.[32,58] Ruxolitinib, a Janus kinase inhibitor that suppresses several inflammatory cytokines, is a promising drug under investigation in several clinical trials.[59] Currently, the HLH-94 and HLH-2004 protocols remain standard care.

Hematopoietic Stem-Cell Transplantation

A complete remission before HSCT is beneficial but not mandatory for survival after HSCT. Post-HSCT survival has now reached as high as 85 to 100% at experienced centers.[55,58,60] Of note, in a registry study, HSCT in 10 asymptomatic patients resulted in 100% survival, a finding that underscores the benefit of newborn screening.[55] Sibling donors should be evaluated for potential mutations.

A current trend is toward "reduced-toxicity" conditioning in patients with HLH who undergo HSCT. Such regimens are aimed at reducing the toxic effects and mortality associated with traditional myeloablation and the higher risk of graft failure associated with reduced-intensity conditioning.

SECONDARY HLH

In patients with secondary HLH, treatment is adapted to the underlying condition and the severity of the HLH (i.e., graded treatment intensity and duration). In addition to etoposide and glucocorticoids, common drugs directed at secondary HLH include inhibitors of interleukin-1 (e.g., anakinra),[61] interferon-γ (e.g., emapalumab),[33] and Janus kinases (e.g., ruxolitinib),[62] as well as intravenous immune globulin.[22]

In patients with moderate secondary HLH, glucocorticoids with or without intravenous immune globulin may be sufficient, and adding anakinra (2 to 10 mg per kilogram of body weight per day) can be considered.[63] Cyclosporine is not often used in adults, except in those with MAS-HLH. In patients with severe, nonresponsive, or progressive secondary HLH, particularly those with CNS involvement, imminent organ failure, or both, prompt addition of weekly treatment with etoposide is often recommended, at an age-adjusted dose, such as 100 mg per square meter of body-surface area in adolescents and young adults, 75 mg per square meter in adults, and 50 mg per square meter in older adults.[64] The duration of treatment should be determined weekly by evaluating the response.

Infection-Associated HLH

In studies pioneered by Imashuku and colleagues in Japan, the risk of death among patients with severe EBV infection was markedly reduced by means of HLH-directed therapy with etoposide and glucocorticoids. More recently, a therapeutic step-up strategy based on clinical and laboratory findings has been suggested.[65] Chronic, active EBV infection is a progressive, fatal disease characterized by organ failure, hypercytokinemia, HLH, and overt lymphomatous or leukemic changes, for which allogeneic HSCT is recommended.[66]

Since secondary HLH develops in approximately 10% of patients with severe dengue fever, with high associated mortality, HLH-directed therapy is worth considering in selected cases. Virus-associated HLH caused by neonatal herpes simplex virus, enteroviruses, or human immunodeficiency virus rarely requires extensive HLH-directed therapy.[67] Treatment of severe influenza-associated HLH has not been well studied. Severe coronavirus disease 2019 (Covid-19) only rarely induces full-blown systemic HLH.[67] HLH induced by intracellular infections, such as tuberculosis, leishmaniasis, or rickettsial disease, usually responds to specific antimicrobial treatment, and therapy based on the HLH-94 or HLH-2004 protocols should typically be avoided.[63]

It is important to consider HLH in patients with sepsislike critical illness that does not respond to sepsis-directed therapy. In sepsis-associated HLH, treatment with anakinra, in addition to sepsis-directed therapy, has been associated with improved survival.[61] Further studies on the frequency and treatment of sepsis-associated HLH are needed.

Malignancy-Associated HLH

HLH associated with cancer has two forms: "malignancy-triggered HLH" (HLH identified at diagnosis or relapse of cancer) and "HLH during chemotherapy." The latter form often has an infectious trigger and may develop years after the initiation of chemotherapy. Malignancy-associated HLH is the form of secondary HLH with the worst prognosis, with 20 to 30% survival at 2 years, in part because of poor survival associated with the underlying cancer. It is most common in young men, affecting approximately 2.5% of young men with hematologic cancers.[16]

A consensus review has suggested a two-step therapeutic approach to organ damage from malignancy-associated HLH. First, target the cytokine storm and T-cell proliferation with etoposide at a moderate dose (75 to 100 mg per square meter), glucocorticoids, and possibly intravenous immune globulin, and then, when organ function has improved sufficiently, target the neoplastic disease.[68] Other HLH-directed immunomodulatory agents, such as anakinra, are also likely to be valuable, but data from studies of such agents are still limited.

Macrophage Activation Syndrome–Associated HLH

MAS is a life-threatening hyperinflammatory complication of rheumatic diseases and other autoimmune diseases that is classified as secondary HLH because it shares many clinical and laboratory features with HLH; hence, the term MAS-HLH. In patients with systemic juvenile idiopathic arthritis, MAS-HLH is defined by the presence of a fever, a ferritin level exceeding 684 μg per liter, and any two of the following signs: a platelet count of 181×10^9 per liter or lower, an aspartate aminotransferase level higher than 48 U per liter, a fasting triglyceride level exceeding 1.76 mmol per liter (156 mg per deciliter), and a fibrinogen level of 3.6 g per liter or lower.[69] Fibrinogen and platelet levels are often higher in MAS-HLH than in other forms of HLH because of the inflammatory nature of this form.

Mortality associated with MAS-HLH is approximately 5 to 10% among children and 10 to 15% among adults. CNS involvement may lead to irreversible neurologic damage. Severe pulmonary disease with a high risk of death may also develop, but the best prevention and treatment are still unknown.

A common first-line approach is the use of high-dose glucocorticoid therapy, such as intravenous pulse methylprednisolone, administered at 30 mg per kilogram per dose (maximum, 1000 mg per dose) once daily for 3 to 5 days, followed by oral or intravenous glucocorticoids. Cyclosporine, given at a dose of 2 to 7 mg per kilogram per day (trough value, 100 to 150 μg per liter), can be added. Interleukin-1–blocking therapy is increasingly used (e.g., anakinra at a dose of 2 to 10 mg per kilogram per day).[63]

In patients with severe disease or CNS involvement despite glucocorticoid therapy and therapy with cyclosporine or anakinra (or both), one or a few moderate weekly doses of etoposide (50 to 100 mg per square meter) can be effective.[63] Emapalumab, Janus kinase inhibitors, and interleukin-6 inhibitors have also been reported to be effective as salvage therapy.[33,70,71]

Transplantation-Associated HLH and Immune Effector Cell–Associated HLH

Other causes of secondary HLH include transplantation, particularly kidney transplantation and allogeneic HSCT, and new types of therapy, such as chimeric antigen receptor (CAR) T cells, bispecific T-cell engagers, and checkpoint inhibitors.[2] Transplantation-associated HLH with an onset more than 30 days after HSCT is often comparable to infection-associated HLH.[72]

CAR T-cell therapy, as well as other immune effector cell–based therapies, may cause a complication that resembles secondary HLH and is distinct from — and typically occurs later after CAR T-cell infusion than — cytokine release syndrome. This HLH-like complication is common when CD22 CAR T cells are used, affecting approximately one third of patients receiving this treatment.[73] Published data on treatment results are limited, but anakinra with or without glucocorticoids has been suggested as first-line therapy, with ruxolitinib, emapalumab, and low-dose

etoposide as second-line and third-line treatments.[74]

HLH with CNS Involvement and Refractory or Relapsing HLH

CNS involvement should be treated promptly; potential treatments include high doses of dexamethasone (or methylprednisolone pulses) and etoposide (at a dose adapted to the disease severity). These drugs are highly effective in HLH and easily pass the blood–brain barrier. Anakinra also passes the blood–brain barrier well and may be considered as a complementary drug.

In primary HLH, refractory disease should not preclude HSCT, but haploidentical donors should then be avoided. Relapsing HLH often responds to the same therapy that previously induced remission.

Future Directions

Although life-threatening and treatable, HLH, particularly secondary HLH, is still underdiagnosed. Numerous lives could be saved with increased awareness of the disorder. The pathophysiology of secondary HLH is not yet fully understood, and best practices for diagnosis and treatment of the various forms of secondary HLH deserve further attention. Gene therapy is effective for *PRF1* and *UNC13D* defects in murine models, and the hope is that the role of gene therapy will be clarified in phase 1–2 clinical trials.[75] Finally, the identification of additional medical conditions that can cause secondary HLH may improve our capacity for early detection and intervention.

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