Management of the critically ill child with the sepsis/hemophagocytic lymphohistiocytosis/macrophage activation syndrome overlap syndrome

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Abstract. Hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS) is a frequently fatal disease, which can result in end-organ damage and death. This condition shares features with sepsis and systemic inflammatory response syndrome. Making a diagnosis of HLH can be challenging since most of the clinical and laboratory features of HLH are quite nonspecific. Timely diagnosis is critical to start therapy before damage by hypercytokinemia becomes irreversible. The treatment for patients with suspected acquired HLH/sepsis/systemic inflammatory response syndrome/multi organ dysfunction syndrome/MAS overlap syndrome should be guided primarily by the severity of signs and symptoms, age of the patient, and underlying conditions. It is critical that the risks of treatment or non-treatment be weighed according to the clinical presentation of each patient. In this article, the authors discuss the diagnostic similarities between sepsis/HLH/MAS and management of the critically ill child with sepsis/HLH/MAS overlap syndrome.

Keywords: Hemophagocytic lymphohistiocytosis, macrophage activation syndrome, sepsis, multiple organ dysfunction syndrome, hyperferritinemia, hypercytokinemia

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS) is a frequently fatal and likely under diagnosed disease involving a final common pathway of hypercytokinemia, which can result in end-organ damage and

death. HLH is not a single disease, but rather a clinical syndrome caused by excessive activation of lymphocytes and macrophages that produce high levels of cytokines. This condition shares features with sepsis and systemic inflammatory response syndrome (SIRS), and the diagnosis is challenging because of the relatively nonspecific nature of the clinical signs and symptoms.

In this article, the authors discuss the diagnostic similarities between sepsis/HLH/MAS and management of the critically ill child with sepsis/HLH/MAS overlap syndrome.

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2. Definition of HLH

One of the earliest descriptions of the disease was in 1939 when Scott and Robb-Smith [1] described a disorder featuring erythrophagocytosis by proliferating histiocytes in the lymphoreticular system and called it “histiocytic medullary reticulosis”. Later in 1952, the familial form of HLH was more fully described by Farquhar and Claireaux [2, 3] with two siblings who succumbed to HLH, and later in 1958, another sibling from this same family presented in the same manner. Risdall et al. [4] was among the first to describe a viral association with HLH and proposed that the condition be called virus-associated HLH, distinct from malignant histiocytosis. In the years since, researches have recognized the wide scope of this disease.

HLH has been traditionally divided into a primary form, which typically manifest in infancy with documented genetic abnormalities of the cytotoxic function of natural killer (NK) cells and T cells, and a secondary form that tends to occur at older ages in the setting of associated conditions without an identifiable genetic abnormality. Upon the realization that genetic defects of HLH can occur at any age and that these defects are uncommonly present even in children and adults, the designations primary and secondary have been changed to genetic and acquired HLH (Table 1) [5–8].

Genetic HLH currently encompasses the cases associated with discrete genetic abnormalities. These patients will show a predisposition to the recurrence of HLH that manifests within the first yr of life in 70% to 80% of cases [9, 10]. In acquired HLH, which makes up majority of HLH both in children, and adults and is by definition not associated with a known genetic defect, the hyperinflammatory state is triggered by infectious, autoimmune, or neoplastic conditions (Table 1). HLH occurring in a setting of rheumatologic illness is commonly referred to MAS [11].

Infection associated HLH is the most common. The most common infectious triggers associated with acquired HLH include viral infections, such as Epstein Barr virus, cytomegalovirus, parvovirus, herpes simplex virus, varicella zoster virus, human herpes virus 8, human immunodeficiency virus, influenza, and hepatitis viruses, among others [12–14]. A number of bacterial infections (Gram-negative rods, *Mycoplasma* species and *Mycobacterium tuberculosis*), parasitic and fungal infections have also been implicated [12, 15, 16]. Malignancy, especially hematologic malignancy,

has been a long appreciated trigger of acquired HLH [14, 17, 18]. An incidence of 20% has been reported in the pediatric population [19]. Malignancies may be the part of the initial clinical presentation or may arise from cancer progression or treatment. A number of autoimmune diseases, especially rheumatologic illnesses, have been linked to an HLH-like syndrome (MAS). Among these, systemic onset juvenile inflammatory arthritis leads the way, followed by systemic lupus erythematosus, Still disease, rheumatoid arthritis, Kawasaki disease [8, 20]. The estimated prevalence of MAS ranges from 7–13% of children with systemic onset juvenile inflammatory arthritis or Still disease [20]. Drug-induced hypersensitivity syndromes, such as drug reaction with eosinophilia and systemic symptoms have been linked to HLH as well [21].

3. Pathophysiology

In the normal physiologic context, granule mediated toxic function of natural killer (NK) cells and cytotoxic T lymphocyte (CTL) is required for clearance of viral infection as well as regulation and termination of the inflammatory response. Cytotoxic cells exert their effect by releasing cytotoxic granules. This is a multistage process involving trafficking of cytotoxic granules containing perforin and granzyme toward the immune synapse, anchoring and connecting granules with the cell membrane, releasing contents of granules and ultimately leading to death of target cell through apoptosis [22, 23]. Patients with genetic HLH have genetic defects of the genes involved in cytotoxic granule exocytosis and function (Table 1). Defects in NK cell and CTL granule mediated cytotoxicity result in ineffective clearance of infection and defective suppression of antigen presentation, leading to persistent antigen exposure and prolonged cytotoxic T-cell activation [24].

Mechanisms in acquired HLH are probably diverse and may have to act in combination. Some patients with acquired HLH are immunosuppressed, which may result in the inability to cope with an infectious trigger, thus leading to HLH. In patients with autoinflammatory and autoimmune diseases, non-antigen-specific stimulation of innate immunity may be trigger for HLH [25]. The finding of HLH/MAS like condition from repeated Toll-like receptor 9 stimulation in genetically normal mice could explain the potential mechanism of acquired HLH with

Table 1
Classification of hemophagocytic lymphohistiocytosis

Type	Gene	Protein	Gene function
FHLH-1	Unknown	Unknown	Unknown
FHLH-2	<i>PFRI</i>	Perforin	Induction of apoptosis
FHLH-3	<i>UNC13D</i>	Munc13-4	Vesicle priming
FHLH-4	<i>STXII</i>	SyntaxinII	Vesicle transport
FHLH-5	<i>STXBP2</i>	Munc18-2	Vesicle transport
Chédiak-Higashi syndrome 1	<i>LYST</i>	Lyst	Vesicle transport
Griselli syndrome type 2	<i>RAB27A</i>	Rab27a	Vesicle transport
XLP-1	<i>SHDIA</i>	SAP	Signal transduction and activation of lymphocytes
XLP-2	<i>BIRC4</i>	XIAP	Various signaling pathways
Acquired hemophagocytic lymphohistiocytosis			
Infectious agents	Viral, bacterial, fungal, parasitic		
Autoinflammatory and autoimmune diseases	Systemic-onset juvenile idiopathic arthritis, Kawasaki disease, systemic lupus erythematosus, seronegative spondyloarthropathies		
Malignant diseases	Peripheral T-cell/natural killer -cell lymphomas, anaplastic large-cell lymphoma, acute lymphocytic leukemia, Hodgkin lymphoma		
Immunosuppression	Hematopoietic stem cell transplantation, solid organ transplantation		
Metabolic diseases	Lysinuric protein intolerance		

FHLH = Familial hemophagocytic lymphohistiocytosis; XLP = X-linked proliferative syndrome.

normal T-cell cytotoxicity [26]. Overwhelming T-cell and macrophage activation results in the “cytokine storm” characterized by marked elevations of cytokine, such as interferon (IFN)- γ , tumor necrosis factor- α , interleukin (IL)-6, IL-8, IL-10, IL-12, IL-18 and macrophage colony stimulating factor [27]. Gene expression studies on peripheral blood mononuclear cells in patients with active HLH have revealed down-regulation of genes involved in innate and adaptive immune systems, including Toll-like receptor expression and B-cell and T-cell function [28, 29]. Other mechanisms may involve single nucleotide polymorphism in genes important in the immune response and imbalance between infected cells and immune effector cells. Finally, some of these patients may have hypomorphic mono- or biallelic mutation in FHL (familial hemophagocytic lymphohistiocytosis) genes [30].

4. Symptoms of HLH reflect hypercytokinemia

The official diagnostic criteria for HLH was established by the Histiocyte Society in 1991 and updated in 2004 (Table 2) and based on a number of clinical and laboratory findings [22, 23]. According to these guidelines, at least five of eight diagnostic criteria must be fulfilled for diagnosis. The cardinal symptoms and signs of HLH are prolonged fever,

hepatosplenomegaly, and cytopenias. Characteristic laboratory abnormalities included elevated ferritin, triglycerides, transaminases, bilirubin, lactate dehydrogenase, low fibrinogen and hemophagocytosis.

Activated lymphocytes and macrophages secrete high levels of pro- and anti-inflammatory cytokines and chemokines, which lead to characteristic clinical and laboratory findings. High levels of cytokines cause fever. Cytopenia can probably be attributed primarily to high concentrations of TNF- α and INF- γ , and hemophagocytosis [31]. Low fibrinogen can be explained by secretion of high levels of plasminogen activator by macrophages leading to decreased concentrations of plasmin, which in turn cleaves fibrinogen [32]. High concentrations of the alpha chain of the soluble IL-2 receptor and of beta 2-microglobulin are produced by activated lymphocytes [10]. The mechanisms leading to the hyperferritinemia seen in HLH remain elusive, even more considering that ferritin levels can increase dramatically within hours. The expression of cytoplasmic ferritin is under delicate control. The amount of cytoplasmic ferritin is regulated by the translation ferritin mRNAs in response to an intracellular pool of cheatable or labile iron. In addition to iron, ferritin synthesis is regulated by cytokines at various levels (transcriptional, post-transcriptional and translational) during development, cellular differentiation, proliferation and inflammation [33]. Oxidative stress, hormones, growth factors, second messengers, and hypoxia-ischemia and hyperoxia also regulate

Table 2
Diagnostic criteria for hemophagocytic lymphohistiocytosis*

The diagnosis HLH can be established if either I or II is fulfilled**
(I) A molecular diagnosis consistent with HLH
(II) Diagnostic criteria for HLH fulfilled (five of the eight criteria below)
(A) Initial diagnostic criteria (to be evaluated in all patients with HLH)
1. Fever
2. Splenomegaly
3. Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood): Hemoglobin < 9 g/dL (in infants < 4 wk < 10 g/dL) Platelets $< 100 \times 10^9/L$ Neutrophils $< 1 \times 10^9/L$
4. Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides ≥ 265 mg/dL or ≥ 3.0 mmol/L Fibrinogen ≤ 1.5 g/L
5. Hemophagocytosis in bone marrow or spleen or lymph nodes No evidence of malignancy
(B) New diagnostic criteria
6. Low or absent natural killer-cell activity (according to local laboratory reference)
7. Ferritin ≥ 500 $\mu\text{g/L}$
8. Soluble CD25 (i.e., soluble IL-2 receptor) $\geq 2,400$ U/mL

*Adopted from reference 35. HLH = Hemophagocytic lymphohistiocytosis. **Comments: 1) If hemophagocytic activity is not proven at the time of presentation, further search for hemophagocytic activity is encouraged. If the bone marrow specimen is not conclusive, material may be obtained from other organs. Serial marrow aspirates may also be helpful. 2) The following findings may provide strong supportive evidence for the diagnosis: (a) spinal fluid pleocytosis and/or elevated spinal fluid protein, (b) histological picture in the liver resembling chronic persistent hepatitis. 3) Other abnormal clinical and laboratory findings consistent with the diagnosis are as follows: cerebromeningeal symptoms, lymph node enlargement, jaundice, edema, skin rash. Hepatic enzyme abnormalities, hypoproteinemia, hyponatremia, very low-density lipoprotein, high-density lipoprotein.

expression of ferritin. Lipopolysaccharide, elicits a variety of reactions that involve ferritin; in animal models, the administration of lipopolysaccharide can increase ferritin expression. Also, cyclopentenone prostaglandins, which are involved in inflammatory and febrile responses as well as viral replication, induced ferritin in human monocytes [33]. In the bone marrow, hemophagocytosis of mature and immature hematopoietic cells is characteristic, in addition to myeloid and erythroid hypoplasia, as well as variable megakaryocytic hyperplasia. The triggers, the mechanism by which hemophagocytic macrophages consume blood cells, and the consequences are all unknown.

5. Acquired HLH and sepsis/SIRS/ multi organ dysfunction syndrome and MAS

Timely diagnosis is critical to start therapy before damage by hypercytokinemia becomes irreversible [34, 35]. Making a diagnosis of HLH can be challenging since most of the clinical and laboratory features of HLH are quite nonspecific. This is particularly the case

in the setting of pediatric intensive care unit, where distinguishing critically ill pediatric patients with sepsis or multi organ dysfunction syndrome (MODS) from those with or without HLH is a major challenge. The inflammatory state of sepsis, similar to HLH is characterized by a cytokine storm [36]. All symptoms and laboratory changes in HLH can also be found to some extent in patients who can cope with an infectious trigger by mounting an adequate and effective inflammatory response. HLH represents the extreme end of the spectrum of inflammatory reactions and is characterized by the magnitude of the clinical and laboratory abnormalities and progressive symptoms.

The International Histiocyte Society guidelines for the diagnosis of HLH can result in many patients with severe sepsis, SIRS and MODS as well as those with MAS meeting diagnostic criteria for HLH. This lack of clarity has led to diverse therapeutic options and outcomes. As given in table 3 the eight nonspecific criteria for HLH can also be present in patients with severe sepsis, SIRS, MODS as well as those with MAS. Fever and cytopenia that are frequently seen in HLH patients are also common features of severe sepsis/SIRS/ MODS as well as MAS [37, 38]. Other criteria for HLH, includ-

ing hypertriglyceridemia or hypofibrinogenemia, are also common in severe sepsis/SIRS/MODS as well as MAS [37, 39]. Hyperferritinemia and hemophagocytosis in bone marrow and other locations are closely related and are present in critically ill patients with severe sepsis/SIRS/MODS and MAS. In one report, hemophagocytosis was demonstrable in up to 60% of patients with severe sepsis who do not fulfill criteria for HLH, whereas another report found microscopic evidence for HLH in one-third of the patients who died in the intensive care unit with sepsis and MODS [40, 41]. The explanation for this recurrence lies in the suppression of the function of NK cells that occurs in severe sepsis [42, 43]. Elevated sCD25/sIL-2R was also detected in those patients. In another study, Stephan et al. [44] found evidence of hemophagocytosis in bone marrow aspirates of 12/20 mechanically ventilated patients with sepsis or septic shock and thrombocytopenia with various surgical ($n=15$) and medical ($n=5$) conditions, but without pre-existing immunodeficiency.

Serum ferritin measurements are simple, cheap and reasonably specific screening strategy for the diagnosis of HLH. However, high level of ferritin has been associated with multiple inflammatory conditions frequently seen in the intensive care unit, from trauma patients, to viral and bacterial infection, septic shock, autoimmune processes, liver, renal and pulmonary disease, solid organ transplant recipients, as well as premature infants and with MAS [37, 45–48]. Hyperferritinemia is associated with the severity of the underlying disease [49–51]. In one study, very high levels of ferritin ($>3,000 \mu\text{g/L}$) were associated with increased mortality in a dose-response fashion [49]. Because of great overlap with other diseases, the appropriate cut-off level for ferritin in the diagnosis of patients with HLH has been a topic of debate. The cut-off of ferritin $>500 \mu\text{g/L}$ was included in the original 1991 HLH diagnostic criteria and carried over in the updated 2004 guidelines, with the caveat that the sensitivity of this test is only 84% based on the results of the HLH-94 study [34, 52]. A review of ferritin levels in pediatric patients found a cut-off of $10,000 \mu\text{g/L}$ to be 90% sensitive and 96% specific for HLH [46].

Elevated soluble IL-2 receptor has been reported in sepsis/SIRS/MODS/MAS patients [53–56]. Decreased NK-cell activity is also found in septic and MAS patients, as well as in the thermal and traumatic injury [42, 57–59]. Anomalies of the perforin/granzyme system have also been described

in septic patients [42, 37, 39, 60]. Granzymes of various molecular weights are increased in patients suspected of having sepsis seen in the emergency room, but granzyme K is decreased in septic intensive care unit patients [58]. Finally decreased NK activity in sepsis is found related to acutely reduced numbers of NK cells leading to decreased NK-cell activity per peripheral blood mononuclear cell [42].

Based on two childhood HLH cases, Gauvin et al. [60] concluded that HLH and MODS share pathophysiological traits and might be related to each other. Finally Castillo and Carcillo [61] proposed that given the clinical similarities between HLH, severe sepsis, SIRS, MODS and MAS that these entities are intermediate phenotypes of the same inflammatory processes. The term “cytokine storm syndrome” was developed to accommodate the observation that multiple inflammatory causes can result in a disease that appears very similar to sepsis [62]. The relevance of this overlap lies in the treatment and outcomes of acquired HLH versus those of sepsis/SIRS/MODS and MAS.

6. Treatment

The observation that sepsis/SIRS/MODS/MAS and acquired HLH involve similar triggers and overlap in molecular mechanisms and clinical and laboratory characteristics raises interesting questions and leads to a therapeutic dilemma. According to the International Histiocyte guidelines, the treatment for HLH, whether genetic or acquired, involves an initial eight weeks of chemoimmune therapy with dexamethasone, etoposide, and cyclosporine. Further, if the disease is severe, recurrent, or persistent, etoposide and cyclosporine are continued for 40 wk and hematopoietic bone marrow transplantation is recommended as soon as possible [63]. Without therapy, survival of patients with genetic HLH is approximately 2 mo and with HLH treatment protocol the survival increased to 55% [63]. Compared to historical controls, the HLH-94 treatment protocol has dramatically changed the outcome of children with genetic HLH. It allows in most instances to stabilize disease activity in genetic HLH. This permits performing allogeneic stem cell transplantation, which is the only curative option in the case of genetic HLH.

However, acquired HLH patients treated with this protocol have 55% survival at 3 yr also [63]. Patients treated supportively for sepsis, SIRS, and MODS have better survival rates than patients treated for acquired

Table 3
Diagnostic criteria of HLH according to the International Histiocyte Guidelines and clinical and laboratory manifestations of sepsis/SIRS/MODS/MAS*

HLH [35]	Sepsis/SIRS/MODS/MAS
Differences	
Molecular diagnosis: Present	Molecular diagnosis: Absent
Splenomegaly: Present	Visceromegaly: May be present or absent
Similarities	
Fever	
Cytopenia of 2 of 3 lineage [37,38]	
Hemoglobin < 9 g/dL, platelets, 100×10^9 /L, neutrophils $< 1 \times 10^9$ /L	
Hypertriglyceridemia (fasting triglycerides ≥ 265 mg/dL) or hypofibrinogenemia < 1.5 g/L [37,38]	
Hemophagocytosis in bone marrow, spleen or lymph nodes [37, 40, 41]	
Ferritin ≥ 500 μ g/ [37, 45–51]	
Low or absent NK cell activity (according to local laboratory reference) [42, 57, 58]	
Soluble CD25 (soluble interleukin –2 receptor) $\geq 2,400$ U/mL [37, 53–56]	

*Adopted from Reference 61. HLH=Hemophagocytic lymphohistiocytosis; SIRS=Systemic inflammatory response syndrome; MODS=Multiorgan dysfunction syndrome; MAS=Macrophage activation syndrome.

HLH with chemotherapy. Mortality of pediatric sepsis and SIRS is about 13.5% and MODS is 18% [64]. MAS is treated with steroids and cyclosporine A and carries a mortality rate ranging between 8% and 22% depending on the case series [65]. However, applying any HLH targeted therapies to children with sepsis/SIRS/MODS/MAS has the potential to cause harm, with early mortality related to infection and hemorrhage. In septic patients who often have reduced number of NK cells, the use chemotherapeutic agents may prevent recovery of NK cell and CTL numbers leading to immunoparalysis and opportunistic secondary infections [66]. Prolonged immunosuppressive treatment in acquired HLH can not only lead to reactivation of the original trigger and of other dormant infectious agents, but also to increase susceptibility toward a new triggering agent. An HLH series of 20 patients showed a mortality rate of 60%, and deaths were attributed to invasive infections in eight cases [67]. Karapinar et al. [68] reported 43% survival in critically ill pediatric patients whose HLH and MODS were treated with HLH-2004 protocol. An adult study showed 89% mortality in patients with virus associated hemophagocytic syndrome treated with chemoimmune therapy [69]. Buyse et al. [70] reported 51.8% mortality with etoposide-based therapy in intensive care unit patients with acquired HLH. These facts raise a major question: how should we treat cytokine storm syndrome or hyperferritinemic syndromes? The authors opinion is that hyperferritinemia-associated acquired HLH/sepsis/MODS/MAS should be treated with a less immunosuppressive approach than is recommended for genetic HLH.

7. Etiology based treatment

As with diagnosis, treatment of hyperferritinemic syndromes must begin by addressing the final common pathway: intensive care of hemodynamic stability, support of specific organ dysfunction, and correction of coagulopathy. However, such supportive measures are unlikely to be sufficient to re-establish homeostasis without also addressing the factors driving cytokine production and effect.

7.1. Altering the environment

Although suppression of hyperinflammation usually requires immediate action and should not be postponed, the search for a treatable trigger is mandatory. Elimination of the offending microbe, allergen or cytotoxic is mandatory. Empiric antimicrobial use is indicated in any hyperferritinemic syndromes for possible sepsis.

7.2. Managing cytokine production and/or elimination

The principal goal of therapy in hyperferritinemic syndromes is to suppress the life-threatening inflammatory process. Hyperferritinemic syndromes (acquired HLH/sepsis/ MODS/MAS) have been successfully treated with intravenous immunoglobulin (IVIg), methylprednisolone, plasma exchange and anakinra [51, 71–73]. Indeed, these therapies can be effective modalities, individually or in combination.

7.2.1. Corticosteroids

Corticosteroids are one of the cornerstones of therapy for hyperferritinemic syndromes. Corticosteroids harbor anti-inflammatory effects that rely on their ability to repress the activity of immunomodulatory transcription factors [74]. They are cytotoxic for lymphocytes and inhibit expression of cytokines and differentiation of dendritic cells [22]. In MAS, high-dose corticosteroids are often used with good response [22]. Although the utilization of corticosteroids in the treatment of sepsis remains controversial [75], Demirkol et al. [51] used high dose steroids in combination with plasma exchange in hyperferritinemic MODS patients (65% of whom had an underlying active infection) and achieved 100% survival. In hyperferritinemic syndromes, corticosteroids may be considered in all patients.

7.2.2. IVIg

IVIg therapy is beneficial in a large number of autoantibody-mediated or self-reactive T cell-associated autoimmune diseases [22, 76]. IVIg is indicated at least theoretically in the view of many mechanisms of actions: Fc-receptor blockade, activation of the inhibitory Fcγ-receptor IIB, inhibition of complement activation, down regulation of T/B-cell functions, anti-idiotypic suppression, neutralization of superantigens or infectious agents, neutralization of cytokines, enhanced clearance of pathogenic antibodies [77–80]. The administration of IVIg alone or in combination with other treatment modalities has been described in hyperferritinemic syndromes [71, 72]. Variable efficacy is demonstrated, which is not astonishing given the heterogeneity of hyperferritinemic syndromes, the different IVIg preparations on the market, the inherent batch variability, the different dosing schedules, and variability of administration time points used. Two larger series of adults with HLH treated with IVIg showed promising results. Larroche et al. [71] describe a global response rate of 59% in a mixed population of infection, malignancy and systemic lupus erythematosus associated HLH. However, IVIg seems to be largely ineffective in malignancy-associated HLH. Infection-associated HLH patients seem to benefit most. The main predictive factor for response was the early-within 2 days of the ferritin peak-administration of IVIg [71]. Finally, Rajaje et al. [72] compared IVIg and HLH-2004 protocol in 40 pediatric acquired HLH patients and they found similar efficacy.

7.2.3. Plasma exchange

Plasma exchange (PE) is an extracorporeal blood purification technique designed to remove various toxic and inflammatory mediators and to replenish essential compounds via the replacement plasma. MAS is a prototype of a major immune system activation characterized by enormous levels of ferritin and severe hypercytokinemia: IL-1β, IFN-γ, TNF-α, IL-10, IL-18, IL-2, IL-12 [81]. In Still's disease, recent studies revealed a pivotal role of several pro-inflammatory cytokines such as IL-1, IL-6, TNF-α and IL-18 in disease pathogenesis [82]. Finally, pro- and anti-inflammatory hypercytokinemia play a pivotal role also in the pathophysiology of sepsis contributing to the dysregulation of the host immune and inflammatory responses and coagulation system. [83]. The overall concept of PE is in these diseases, therefore, is to attenuate the overwhelming systemic overflow of pro- and anti-inflammatory mediators released at the early phase of disease and to restore a broad-based humoral homeostasis. PE was found as a successful therapy in MAS, Still's disease, catastrophic antiphospholipid syndrome and sepsis [84–88]. Demirkol et al. [51] investigated the efficacy of PE treatment in hyperferritinemia associated acquired HLH/SIRS/MODS/ MAS patients. The patients had severe disease with median five organ involvements. The overall mortality was 13%. The authors concluded that PE might be important therapeutic tool in the pediatric field for the treatment of acquired HLH/MAS with MODS. Furthermore, PE is also beneficial for controlling coagulopathy that was commonly seen in HLH/SIRS/MODS patients. Several studies favor the use of PE in severely ill septic patients with MODS and thrombocytopenia-associated MOF [89–95]. Stegmayr et al. [89] reported a beneficial effect of PE as supportive therapy in patients with progressive disseminated intravascular coagulation and MODS, especially if septic shock was present.

7.2.4. IL-1 receptor antagonist

IL-1 is (referring IL-1α and IL-1β) is a prototypic proinflammatory cytokine that plays a critical role in acute and chronic inflammation. IL-1β is released by activated macrophages and neutrophils and contributes to systemic inflammatory manifestations, whereas IL-1α remains primarily cell associated. The biological effects of IL-1β are tightly controlled at the level of its production and then, by different natural inhibitors,

including membrane bound and soluble receptors, and IL-1R antagonist (IL-1Ra). IL-1Ra binds to IL-1Rs but does not induce any intracellular signals and competitively inhibits the biological activity of IL-1 with its receptors. Evidence derived from animal studies and human patients indicates that the balance between IL-1 and IL-1Ra is critical to avoid excessive inflammatory responses [96]. IL-1 has been proposed as an important mediator of sepsis and septic shock [97]. A significant increase in circulating IL-1 β levels was detected in patients with septic shock [98]. The previous studies showed that mice lacking IL-1-converting enzyme or IL-1R type I were resistant to endotoxic shock [99, 100].

Anakinra (Kineret; Amgen, Thousand Oaks, CA), a recombinant IL-1 receptor antagonist, has been shown control inflammation in multiple

disease process, including hemophagocytic syndromes [101–104]. Rajasekaran et al. [73] presented a single center retrospective case series of eight critically ill patients with hyperferritinemia-associated sepsis/MODS/MAS/acquired HLH treated with anakinra. The patients had median three organ involvements. Several children additionally received IVIg and/or corticosteroids. Overall mortality was 12%. *Post hoc* analysis by Shakoory et al. [105] of the randomized placebo-controlled trial of anakinra in adults with severe sepsis finds anakinra infusion for 72 hr reduced mortality two-fold with severe sepsis and MAS/hemophagocytic syndrome.

Additional reports of anti-inflammatory management of acquired HLH/MAS include the following: successful treatment of acquired HLH with IL-6

Fig. 1. Proposed treatment algorithm for clinical suspicion of hemophagocytic lymphohistiocytosis. CNS = Central nervous system; HLH = Hemophagocytic lymphohistiocytosis; IVIG = Intravenous immunoglobuline; PE = Plasma exchange.

receptor- directed therapy and successful treatment of two reactive HLH patients with IFN- γ [106, 107].

8. Conclusions

In conclusion, treatment for patients with suspected acquired HLH/sepsis/SIRS/MODS/MAS overlap syndrome should be guided primarily by the severity of signs and symptoms, age of the patient, and underlying conditions. It is critical that the risks of treatment or non-treatment be weighed according to the clinical presentation of each patient. For patients meeting at least five of eight HLH-2004 criteria, the physicians should consider the following factors as high risk for genetic HLH: 2-year-old and younger, consanguinity, death of a family member due to unspecified febrile illness, or a primary cerebral nervous system disease. Equipoise in the treatment of hyperferritinemia-associated sepsis/MAS/MODS/acquired HLH is prudent until randomized clinical trials to guide therapy are evident. However, the authors suggest using the treatment algorithm in Fig. 1 until more data become available. Elimination the offending microbe, allergen or cytotoxic is mandatory. Genetic HLH patients should be treated with HLH-94 protocol. In infection associated HLH cases, IVIg may be enough as a first line treatment if the patient has no organ dysfunction; if there is no response or progression of the disease, then PE and/or anakinra with high dose corticosteroids should be added to the therapy. In severe cases with MODS, PE and/or anakinra with high dose corticosteroids should be started as soon as possible.

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