Secondary hemophagocytic lymphohistiocytosis in children (Review)

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Abstract. Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening condition characterized by hyperinflammation in an uncontrolled and ineffective immune response. Despite great improvement in diagnosis and treatment, it still represents a challenge in clinical management, with poor prognosis in the absence of an aggressive therapeutic approach. The present literature review focuses on secondary HLH at pediatric age, which represents a heterogeneous group in terms of etiology and therapeutic approach. It summarizes the most recent evidence on epidemiology, pathophysiology, diagnosis, treatment and prognosis, and provides a detailed description and comparison of the major subtypes of secondary HLH. Finally, it addresses the open questions with a focus on diagnosis and new treatment insights.

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Abbreviations: carHLH, HLH following CAR-T infusion; CAR-T, chimeric antigen receptor T; CMV, cytomegalovirus; CNS, central nervous system; CRS, cytokine release syndrome; CSA, cyclosporine A; CTL, cytotoxic T lymphocyte; EBV, Epstein-Barr virus; FHL, familial HLH; FIRES, febrile infection-related epilepsy syndrome; FUO, fever of unknown origin; HAV, hepatitis A virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; IVIG, intravenous immunoglobulin; MAS, macrophage activation syndrome; MAS-HLH, HLH associated with defined rheumatologic conditions; M-HLH, malignancy-associated HLH; MIS-C, multisystemic inflammatory syndrome in children; NACHO, North American Consortium for Histiocytosis; pHLH, primary HLH; PT-HLH, Post-transplant HLH; sHLH, secondary HLH; WES, whole exome sequencing

Key words: HLH, secondary HLH, children

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening condition characterized by hyperinflammation in an uncontrolled and ineffective immune response (1). It was initially described in early infancy (2), but it may develop at any age, from childhood to adulthood. The spectrum of clinical symptoms of the disease is wide (3,4), ranging from fever, cytopenia and splenomegaly to shock, disseminated intravascular coagulation and multiple organ failure (5). Despite improvement in diagnosis and treatment, HLH represents a challenge in clinical management as it still results in a poor prognosis in the absence of an aggressive therapeutic approach (6,7).

The classical description of the disease distinguishes between primary forms due to a known genetic mutation [familial HLH (FHL), and HLH in the context of congenital immunodeficiency] and secondary forms triggered by an external stimulus [secondary HLH (sHLH)] (7). This classification, though widely accepted and used, is not fully effective in clinical practice (8). Often, due to the severity of the clinical picture, it is necessary to start an aggressive treatment before having clarified the primary or secondary nature of the syndrome (9).

The ongoing advances in genetic diagnosis and a deeper understanding of the molecular pathophysiology suggest new strategies in clinical management (10).

The present study focuses on sHLH at pediatric age and explored its pathogenetic and therapeutic peculiarities. To the best of our knowledge, the current review provided for the first time an extensive and exhaustive synopsis of all the known etiologies with an in-depth discussion of the individual aspects, a detailed overview of the most recent evidence and a summary of the remaining open questions.

2. Search/selection criteria

The present study reviewed the literature available on PubMed (https://pubmed-ncbi-nlm-nih-gov.bvsp.idm.oclc.org/) from 1950 to May 2022 to find all published works on sHLH at pediatric age, including case reports, meta-analyses, randomized controlled trials, reviews or systematic reviews and official guidelines. The PubMed search string was: 'Secondary HLH OR sHLH'. The PubMed age filter 'child: birth-18 years' was applied. Reference lists of all articles were manually searched for cross-references and additional articles were included, if relevant. The present study obtained the full text of each article. Exclusion criteria included: A text language other than English, a focus on adult patients and a focus on primary HLH forms. Each article was selected and analyzed for inclusion by two authors in parallel. If the authors disagreed, a third author was consulted, who was responsible for the final decision.

The website 'Clinical trial.gov' was searched for new trends in sHLH therapy. The research string was 'HLH, hemophagocytic lymphohistiocytoses and hemophagocytic syndrome'. The Clinical trial.gov age filter 'child: birth-17 years' was applied. Exclusion criteria included a focus on conditioning regimes for hematopoietic stem cell transplantation (HSCT).

3. Results of literature search

The Pubmed search found 283 articles, of which 199 were considered relevant and included. The manual search for cross references included nine more articles for a total of 204 articles. Clinical trial.gov search found 75 studies, 17 of which were included.

4. Epidemiology

HLH is rare and likely underestimated due to its difficult diagnosis. From the institution of the first international HLH registry in 1989 to the HLH-2004 therapeutic study, >700 patients have been formally evaluated worldwide (6). In Europe and Japan an HLH incidence of 1-2 per million was reported in 2005 (11), however, there is the possibility that the diagnosis is under-reported, especially in developing countries (12).

5. Clinical presentation

HLH should be suspected in all patients with prolonged high-grade fever associated with splenomegaly and multiple organ involvement (7). The clinical spectrum of the disease is wide, ranging from mild organ dysfunction to multiorgan failure requiring intensive care. Central nervous system (CNS) involvement is frequent and often severe, even though it is not included in the official diagnostic criteria (7). HLH is rare, and a high grade of suspicion is essential for diagnosis. Differentiation between primary and secondary forms is mandatory since they share the same clinical picture but often require different therapeutic approaches (10).

The typical patient is an infant under 1 year of age, ill-appearing (toxic aspect), occasionally with a critical sepsis-like aspect (8). A younger age at onset suggests an underlying genetic basis, as seen in FHL or in HLH forms arising from genetic primary immunodeficiencies; however, familial HLH can present at any age, including adulthood (13).

Progressive splenomegaly is typically observed in patients, and can be associated with hepatic involvement, neurological signs, respiratory and renal failure (14). Skin rashes, erythroderma, edema or petechiae have been reported (14). Lymphadenopathy is uncommon in patients and indicates a potential underlying lymphoma (15).

Typical laboratory findings include cytopenias (at least bilinear), hypertriglyceridemia, hypofibrinogenemia (suggestive of HLH in the context of general inflammation) and hyperferritinemia. Liver function tests are frequently altered (7). Leukocytosis is not typical of HLH [except in HLH-associated with defined rheumatological conditions/macrophage activation syndrome-HLH (MAS-HLH)] (7). Hemophagocytosis is frequently observed but is neither pathognomonic nor mandatory for diagnosis (7,16).

Atypical forms, usually seen in children older than 1 year, include isolated fever of unknown origin (FUOs), isolated CNS involvement (17) or isolated acute liver failure (18,19).

6. Pathophysiology

The pathogenesis of HLH has mostly been studied in FHL. An inherited defect in the perforin/granzyme pathway or in the fusion of cytotoxic lytic granules with the surface of natural killer (NK) cells causes, in the presence of an external trigger, an over-response by cytotoxic $CD8^+$ T lymphocytes. Viral infections are the most common triggers (20).

Cytotoxic $CD8^+$ T cells produce large amounts of INFγ, which in turn activates macrophages. Overstimulated macrophages release large amounts of inflammatory cytokines, such as IL-1β, IL-6, IL-12, IL-18 and TNFα. There is also an increased production of IL-10, with inhibitory activity, but not sufficient to limit the phenomenon. IL-12 and IL-18 produced by macrophages in turn stimulate $CD8^+$ T cells, amplifying the inflammatory response (1). The resulting tissue damage causes a release of IL-33 and IL1-β, which further activates the macrophages. Activated macrophages engulfblood cells and produce large amounts of ferritin. The 'cytokine storm' causes all the clinical manifestations of HLH, from endothelial damage to coagulopathy and multi-organ failure (1,13,21-23). The central role of INFgamma in the pathogenesis of FHL has been demonstrated in a perforin-deficient mouse model (24).

A similar pathogenesis of HLH can also be observed in patients with primary immunodeficiencies involving granule trafficking or exocytosis, such as Hermansky-Pudlak syndrome type 2, Griscelli syndrome type 2 and Chediak-Higashi syndrome II, all with reduced cy-totoxic T lymphocytes (CTL) cytotoxicity (3,4). Advances in genetic diagnosis suggest that cell killing by CTLs and NK cells can be affected from mildly to severely, thus explaining the different HLH phenotypes as a continuum (25). The known mutations in genes related to granule-mediated killing account for FHL and primary forms in general (7). Minor alterations of the CTL and NK activity, together with an external trigger, account for sHLH, severe sepsis, multi-organ failure and HLH in the context of rheumatologic diseases (25).

In all cases, a cytokine storm causing a devastating inflammation is the primal agent of the multiorgan failure, regardless of the underlying defect (24-29) and HLH should be considered a clinical syndrome of hyperinflammation with different phenotypes (10).

Moreover, this finding likely explains the numerous similarities and overlaps between HLH and other systemic inflammatory syndromes, such as septic shock, cytokine release syn-drome (CRS) following viral infections (29) and acute liver failure (30).

In 1994, the Histiocyte Society introduced an etoposide-based treatment protocol for HLH, which is still the gold standard in the therapy of the disease (31). Etoposide, dexamethasone and cyclosporine act on the pathogenetic mechanisms of HLH, inhibiting T cells and the release of inflammatory cytokines. In this respect, etoposide has a very high immunosuppressive activity (32).

Another treatment capable of acting on the pathogenesis of HLH is ATG-based immuno-therapy which has shown efficacy as a first-line therapy for FHL (33). Epstein-Barr virus (EBV)-associated HLH can occur in X-linked lymphoproliferative type (XLP)1 and XLP2, where it is caused by signaling lymphocytic activation molecule-associated protein (SAP) or X-linked inhibitor of apoptosis protein (XIAP) deficiency and by the subsequent uncontrolled EBV infection (34), or in individuals without obvious immune defects. In the latter case, activation of cytotoxic $CD8^+$ cells by EBV-infected B cells or a direct activation of $CD8^+$ cells or NK cells by the virus has been hypothesized (35,36). The addition of rituximab to an etoposide-based therapy is effective in the treatment of EBV-HLH, reducing the infected B lymphocyte population and EBV load (37).

The case of malignancy-associated HLH includes two completely heterogeneous mechanisms. Firstly, when HLH is a manifestation of the underlying malignancy, particularly in the case of lymphomas, the overproduction of inflammatory cytokines such as INF-γ and TNF-α is likely caused by neoplastic cells (1,38). Secondly, when HLH develops as the consequence of chemotherapy, the process is more likely to be caused by the association of drug-induced CTL suppression and infection (39).

7. Diagnosis

HLH was first described in the 1950s (2), and the first attempt to provide homogeneous diagnostic criteria by the International Histiocyte Society goes back to 1991 (40).The HLH 2004 international trial established a clear and small set of diagnostic criteria that is currently the most used (31). Those diagnostic criteria do not include frequent features of the disease such as CNS involvement, and their specificity remains unknown. Furthermore, they are often inconclusive in differentiating primary and secondary forms of HLH in intensive care settings (41).

In order to accelerate diagnosis, rapid screening by flow cytometry has been used to identify some forms of p-HLH through the assessment of expression of intracellular perforin, SAP, and XIAP protein in peripheral blood cells (42) while waiting for the results of the genetic tests. Moreover, some simplified clinical algorithms have been proposed, for example, the 'H score' (43,44) scoring system and the 'Minimal Parameter set' (45), but none of these scores are conclusive in differentiating secondary HLH forms that might benefit from a different treatment.

Another notable proposal came from the North American Consortium for Histiocytosis (NACHO) in 2019 (8): Patients fulfilling the HLH 2004 criteria should be diagnosed as having a 'HLH syndrome', while the subsequent diagnosis of 'HLH disease' should be restricted to the patients who additionally show distinctive immune dysregulation (FLH, HLH associated with immune compromise, rheumatological HLH/MAS) and are likely to benefit from deep immune suppression. Disorders leading to the HLH clinical symptoms, but not likely to benefit from immune suppression, should be diagnosed as 'HLH disease mimics' (such as infection-related HLH and iatrogenic HLH). This proposal clarifies diagnostic and therapeutic priorities, but some of the suggested categories still overlap (such as infection associated-HLH, malignancy-associated HLH and storage disorders) (41).

The most recent consensus guidelines on recognition, diagnosis and management of HLH in critically ill children (46) stress the importance of a high suspicion rate for HLH in all patients admitted to intensive care units who show a disproportionate inflammatory response and/or rapid clinical deterioration. Those patients should be thoroughly investigated for possible triggers of sHLH and treated aggressively.

New diagnostic parameters. Imaging techniques, such as CT and 18F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) have been traditionally used in diagnosis to exclude an underlying malignancy. These imaging techniques can also be useful in raising HLH suspicion in the context of FUOs by showing an inflammatory disease involving bone marrow, lymph nodes and the spleen (47,48). Moreover, some 18F-FDG PET/CT metabolic parameters can help identify the etiology of sHLH in children (for example, malignancy and EBV-HLH), and provide directions for further inspection and information about the prognosis (47-49).

A high sCD25/ferritin ratio has been observed in malignancy-associated HLH (M-HLH) secondary to a lymphoma (50) and in HLH secondary to multisystem Langerhans cell histiocytosis (51), and may represent a novel useful marker for the malignancy-associated subset of sHLH (50,51).

A Chinese group suggested that using the T helper (Th)1/Th2 cytokine profile (dosage of sCD25/IFN-γ signature, TNF, IL-10, IL-6, IL-4 and IL-2 on cytometric bead array technique) for early quick diagnosis of HLH. This has demonstrated that a significant increase of IFN-γ and IL-10 and a slight increase of IL-6 is an early, specific and prognostic cytokine pattern for childhood HLH (52). More recently, to discriminate FHL from sHLH, lower IL-4 and IFN-γ levels have been demonstrated to more likely indicate primary HLH (53). This quick cytokine profile seems also useful in discriminating HLH vs. sepsis (54), and to identify EBV-HLH (55), so that a combined approach HLH2004 and Th1/Th2 profile is currently available.

Other new diagnostic tools are being developed, even though they are currently used in preclinical or research settings. Some relevant examples include studies on IFNγ and

its 'signature' (CXCL9 and CXCL10) as serum biomarkers of disease activity in both primary HLH (pHLH) and sHLH (56), or as predictors of predominant liver involvement in sHLH (57), or studies on soluble TNF-like weak inducer of apoptosis selective elevation in HLH patients (58) and studies on secretory sphingomyelinase upregulation in HLH, with the C16 ceramide:sphingosine ratio determining a poorer prognosis (59).

Genetic analysis of polymorphisms of the TNF-α promoter (60) or of the interferon regulatory factor 5 gene (61) have identified variants that increase susceptibility to sHLH/MAS-HLH.

Determination of the NK-cell dysfunction type (type 1-4) and of the underlying genetic defect has been used to guide HSCT indication (62) and to estimate the risk of progression to acute leukemia (63).

Finally, targeted sequencing of FHL genes appears to be insufficient to identify pathogenic mechanisms in the majority of patients with HLH, and whole exome sequencing (WES) is increasingly used. WES is rapidly expanding the range of causal mutations, with a double sided effect: It accelerates diagnosis in a subset of patients, but has redefined numerous other cases of secondary HLH as primary HLH (54). Furthermore,a proved mutation in HLH-related gene cannot exclude the coexistence of an underlying malignancy (41).

8. Classification

The most recent international classification of HLH is the one provided in 2016 by the Histiocyte Society in the 'revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages' (64). In 2019 the NACHO (8) introduced the concept of 'HLH syndrome' and proposed to categorize HLH subtypes by specific etiologic associations instead of classifying HLH as 'primary' or 'secondary'. The two classifications substantially overlap, so the present study referred to the 2016 Histiocyte Society classification because it is the most widely accepted and used to date (64).

Infection-associated HLH. Infection-associated HLH represents a challenge in classification. This is because infectious diseases can trigger HLH in both primary and secondary forms, and because septic shock can either be a presentation of HLH syndrome or may mime it, with great implications in therapeutic approach. A thorough infectious screening is thus highly recommended when facing an HLH syndrome (7,8).

Among the case reports the present study reviewed, the most frequent infectious triggers were viruses, such as the herpetic viruses, dengue virus, Crimean Congo hemorrhagic fever virus, Eastern equine encephalitis virus, hepatitis A virus (HAV), hepatitis B virus (HBV), human immunodeficiency virus (HIV), adenovirus, parvovirus B19, measles, influenza virus and severe acute respiratory syndrome coronavirus 2 (Sars-Cov2).

EBV has been frequently reported from all across the world, and especially from the Asian Countries (37,65-73). The reason for this geographical heterogeneity may involve a higher virulence in EBV viral strains circulating in Asia (74), or a different immune predisposition in the Asian patients, but this issue has not been clarified yet. EBV typically targets B cells, but in a subset of patients with EBV-HLH, of prevalent Asian origin again, it infects T or NK cells leading to oligoclonal or monoclonal proliferation and massive cytokine production (69,75). In extreme cases, EBV-HLH clinical picture can be difficult to differentiate from T cell lymphoproliferative disorder (69). EBV-HLH is usually quite aggressive, with a frequent involvement of CNS. Once EBV is demonstrated by serology tests or molecular biology methods, a targeted approach is recommended (74,76). Clinical scores to differentiate low risk vs. high-risk patients have been proposed (76), but have not achieved conclusive results yet. Targeted treatment is discussed later in this review.

Cytomegalovirus (CMV) is typical of newborns and immunocompromised patients (72,73,77-81) and so is the varicella zoster virus (82). Dengue virus plays a significant role in tropical countries (73,83-90). Tick-borne diseases include the Crimean-Congo hemorrhagic fever nairovirus (91,92) and the Eastern equine encephalitis virus (93). Sporadic case reports include HLH related to HAV (90,94), HBV (95), HIV (89,96), Adenovirus (72,89,97,98), Parvovirus B19 (72), Measles (88) and Influenza virus (99-101).

Sars-Cov2 infection, causative of the recent COVID19 pandemic, has been reported to also be a HLH trigger, mostly in adults (102,103). In 2021, a Mexican group reported the unusual case of a 7-years old boy that developed a severe inflammatory syndrome triggered by Sars-Cov-2 and Dengue virus coinfection (104). The authors diagnosed both multisystemic inflammatory syndrome in children (MIS-C) for the presence of coronary involvement and HLH for fulfilling the HLH 2004 criteria. The patient required mechanical ventilation and maximal support treatment for 2 weeks, but completely recovered. The authors agree that it is a very unusual presentation of HLH. In 2022, an Iranian group described the case of an 8-year-old boy who developed MIS-C with heart failure requiring heart transplantation (105). Liver and bone marrow biopsy, together with typical laboratory findings, fulfilled HLH04 diagnostic criteria. He was initially treated with intravenous immunoglobulins (IVIGs) and steroids, followed by heart transplantation and the consequent heavy immunosuppression. Unfortunately, the patient died 20 days after surgery. A third case, regarding a female newborn birthed from a SARS-CoV-2-positive mother via cesarean section at 35 weeks of gestation, was reported from Jordan in 2022 (106). The newborn tested positive for SARS-CoV-2 on the first day after birth and progressively developed typical HLH syndrome from the 6th day of life. The patient died on day 51 from severe respiratory failure.

Bacterial infections associated to HLH have frequently been reported in tropical countries and include *Brucella* (72,107-109), *Salmonella enteritidis* (73,90,110), *Tuberculosis* (88,90,111), sepsis by streptococcal infection [group B streptococcus (112) and *Streptococcus suis* (113)], by *Listeria* (72) or without identified pathogen (90). *Orientia tsutsugamushi*, the causing agent of scrub typhus, has been reported in India (73,89,90) and Korea (114-117). *Ehrlichia chaffeensis*, the agent of human monocytic ehrlichiosis, has been reported from the US (118-122). A case of *S. pneumoniae* 23A, serotype that is not included in the pneumococcal 13-valent conjugated vaccine (PCV-13) has been reported from Japan (123).

HLH in kidney transplant recipients has been associated with Ehrlichiosis in one case (121), and with *Bartonella henselae* in one other case (124). A case associated with *Serratia marcescens* has been reported in a preterm newborn (125).

Fungal infection-associated HLH has been reported in immunocompromised hosts (being treated for aplastic anemia and preB-acute lymphoblastic leukemia, respectively), caused by *Trichosporon asahii* (126).

Leishmania (71,72,127-135) and *Plasmodium* (90) [*falciparum* (136) and *vivax* (137)] have been reported as parasitic triggers of HLH.

M-HLH. M-HLH represents another challenging category, because it can be the initial manifestation of an underlying malignancy, it may develop during therapy as the consequence of chemotherapy or of treatment-induced mutations [treatment-induced HLH (Ch-HLH)], or it can develop as a consequence of an intercurrent infection (138-141).

HLH as a manifestation of underlying malignancy. The excess of proinflammatory cytokines produced by activated T cells infiltrating or surrounding the tumor or by the neoplastic T-cells in T/NK cell lymphoma is likely to cause M-HLH (1,38). In rare cases, the diagnosis of HLH anticipates that of malignancy by several weeks (138,142).

M-HLH is common in adults, where it accounts for ~50% of HLH cases (15), while it is significantly rarer in children, with a prevalence of 8-11% (138,143).

Lymphomas, though relatively uncommon at pediatric age, are frequently reported in association with HLH (138). Among the cases we reviewed in the present study, HLH has been associated with Hodgkin lymphoma (73,121,140,144), anaplastic large cell lymphoma (73,145,146), peripheral T-cell lymphoma (145,147), post-transplant lymphoproliferative disorder-lymphoma (148), subcutaneous panniculitis-like T-cell lymphoma (71) extranodal NK/T cell lymphoma, hepatosplenic T-cell lymphoma, systemic EBV-positive T-cell lymphoma of childhood (145). In addition, HLH and lymphoma can be alternative diagnoses as well (149), and extreme caution is required in differentiating the two conditions before starting steroid therapy.

Acute leukemia (both myeloblastic and lymphoblastic) presenting as HLH syndrome has also been reported (72,121,138-141,145).

Ch-HLH. Among the cases we reviewed in the present study, HLH developed on therapy or after treatment for juvenile myelomonocytic leukemia (150), acute monocytic leukemia (151), Langherhans cell histiocytosis (152) and solid tumors [Wilms tumor (153), neuroblastoma (72,154), rhabdomyosarcoma (140)]. Langerhans cell histiocytosis has been associated to HLH at presentation, during therapy or as a consequence of viral infection (140,142,155).

The immunosuppression induced by treatment frequently causes viral infections or reactivations, that in turn can trigger HLH. Among the cases reviewed, viral reactivation included EBV, CMV, respiratory syncytial virus, BK virus, human herpes virus 6, adenovirus and parvovirus B19 (141,156).

MAS-HLH. HLH syndrome occurring in the context of rheumatological disorders has been commonly referred to as MAS (157). While traditionally considered separate entities that share common features, it is now clear that they should be viewed as the same disease, regardless of differences in presentation and treatment (64). However, the detailed description of MAS-HLH is beyond the scope of the present work.

HLH associated with iatrogenic immune activation. Various emerging therapies, such as chimeric antigen receptor T cells (CAR-T cells) and Blinatumomab, have been associated with CRS (29). CRS shows major overlaps with HLH, so numerous authors classify it as a form of sHLH (158-160); some other authors, conversely, restrict the diagnosis of HLH following CAR-T infusion (carHLH) to the cases in which a severe CRS is associated to the typical HLH laboratory findings, often including hemophagocitosis (161,162).

CAR-T cells were officially licensed for use in children and young adults by the U.S. Food and Drug Administration in 2017 for the treatment of refractory B-cell acute lymphoblastic leukemia (163). CRS is a common severe adverse reaction following such therapies, especially in the acute phase (29). It probably results from the high amount of IFN-γ and IL-6 produced by the constitutionally activated CAR T cells (164) or by the subsequently activated macrophages (165-167) and by the targeted tumor cell lysis (168). Development of carHLH seems associated with pre-infusion NK lymphopenia (although it is not associated with impaired NK function) that is further amplified by treatment (161).

The St. Jude Children's Research Hospital group recently described a cohort of 27 pediatric patients treated with CD-19 CAR-T cells (162): 12/27 patients developed CRS alone, while four progressed to carHLH despite appropriate therapy. The carHLH subgroup showed higher and more sustained inflammation parameters and a poorer antileukemic response and survival. Blinatumomab, as well, has been associated with CRS and/or HLH in adults (29) and children (169).

Patients treated with T-activating therapies should be closely monitored for HLH, in order to optimize diagnosis and therapeutic approach.

Additional iatrogenic causes of cytokine storm include rituximab (170), gene therapies, immune checkpoint inhibitors, allogenic HSCT and heart transplantation (29).

Transplant-related HLH. HLH has been described in the context o HSCT (171,172) and, more rarely, in kidney (124,165) and liver (173-175) transplant recipients. Post-transplant HLH (PT-HLH) might be triggered by a combination of tissue damage, immunosuppressive therapy (176), alloimmune response, residual malignancies or by infections (171). Viral infections or reactivations, such as EBV and CMV but also gastrointestinal viruses, represent the most frequent trigger, but bacterial and fungal infections have also occasionally been described (124,165,172,177-179).

HLH post-HSCT (post-HSCT HLH) can occur within the first 30 days after transplantation (early onset) or later (late onset) (171). Late onset is usually related to infectious events, while for early onset the causes are not fully understood. In some cases the triggering factor may be the residual disease (171). PT-HLH diagnosis is extremely challenging because of the complex clinical and laboratory picture of the affected patients, for whom specific diagnostic criteria do not exist yet, and a high suspicion rate is essential (180).

In early onset post-HSCT HLH, aspects of differential diagnosis may occur with engraftment syndrome and acute graft-vs.-host disease (171). The treatment of PT-HLH is also particularly complex, since we are dealing with immunosuppressed patients, often with transplant-related toxicity (171). In EBV-related forms, the use of rituximab plays an important role (37,181).

HLH of unknown/uncertain origin. HLH has recently been described in the context of febrile infection related epilepsy syndrome (FIRES) (182), an epileptic encephalopathy characterized by refractory status epilepticus following unspecific febrile illnesses. The pathophysiology of FIRES has not been completely understood, but it likely to depend, once more, on dysfunctional activation of the innate immune system (182). Moreover, though rare, this association stresses the need of screening for patients with HLH presenting with severe CNS symptoms.

A curious case of HLH following spider bite (*Loxosceles reclusa*) has been reported from the US (183).

Drug reaction with eosinophilia and systemic symptoms induced by vancomycin, carbamazepine and levetiracetam has been described as an occasional trigger of HLH (72).

HLH and metabolic disorders. Among the cases reviewed in the present study, several patients were diagnosed with sHLH/HLH syndrome in the context of an inherited condition associated with metabolic diseases, such as Wolman's disease (184), galactosemia, Gaucher disease (185), Niemann-Pick disease, methylmalonic acidemia and propionic acidemia (186). Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (187), type 1 glycogen storage disease (188), lysosomal acid lipase deficiency (189), mucopolysaccharidosis-plus syndrome (190).

These patients fulfilled the HLH 2004 criteria, but it is possible that some HLH features, such as splenomegaly and cytopenias, were caused by the metabolic disease itself rather than by immune hyperactivation (184-190). On the other hand, it is possible that metabolites accumulation activated macrophages and triggered a proper sHLH. The link between metabolic disorders and HLH needs to be clarified, but an extensive screening for underlying metabolic diseases should be performed in patients presenting with HLH (184,185).

9. Treatment

The aim of HLH treatment is to suppress the life-threatening inflammation that leads to organ damage (23). The first goal invariably is to induce disease remission by controlling the hyper-activated T cells and the cytokine storm they generate (7,191). The second step, instead, may differ according to the underlying condition: in FHL and HLH cases, due to primary immunodeficiency, allogeneic HSCT is the only curative treatment that is currently known, while there is no consensus on sHLH best treatment. The present study agrees that, whenever possible, sHLH should be addressed according to the specific etiology, while the debate on whether treatment of the triggering disease may alone control sHLH or not is still open (7,191,192).

'Old but gold'-The HLH 94/04. Since a neat distinction between FHL and sHLH is often impossible in the clinical setting, the HLH 94/04 protocol (7,193) suggests a pragmatic approach to HSCT indication, which remains a mainstay of therapy.

HLH 94 induction chemotherapy is based on steroids and etoposide administration for 8 weeks with or without intrathecal methotrexate, followed by maintenance with cyclosporine A (CSA), etoposide and dexamethasone pulses while waiting for HSCT (193). Chemotherapy might be suspended after 8 weeks of treatment once clinical remission is obtained and a clear genetic base is excluded (193). Otherwise, if a clear genetic base is proved, or in case of reactivation, HSCT is recommended (193).

Treatment intensification was proposed in 2004, but failed to improve the outcome (6). The Histiocyte Society thus recommends HLH-94 as the standard of care (7).

New therapeutic frontiers. The heavy mortality rate before HSCT (7) and the significant toxicities of chemotherapy urge the clinicians to find new treatments (6). This is especially true in patients with sHLH, whose prognosis widely varies from a 55% survival at 3 years with the standard protocols (193) to 100% survival in specific conditions (such as Leishmania-triggered HLH when treated appropriately) (135).

The ongoing recognition of the central role played by cytokines suggests a treatment shift towards targeted therapies. Whether these drugs can eradicate HLH alone or require the addition of etoposide remains to be clarified, as well as how they are best used [including doses, drug combinations and use in adults/children (6).

Emapalumab (NI-0501; Novimmune SA), an anti-IFN-γ monoclonal antibody has been used successfully in pediatric patients with refractory or previously untreated pHLH (194,195).

The most recent clinical trials focus on hybrid immunotherapy (ATG + etoposide + dexamethasone; NCT01104025), monoclonal antibodies such as Alemtuzumab (196) (NCT02472054) and tyrosine-kinase inhibitors such as ruxolitinib (197) (NCT04999878; NCT04120090; NCT04551131; NCT03795909; ChiCTR2000029977) and zanubrutinib (NCT05320575). Studies on selectively cytokine-targeting molecules include Tocilizumab (198) (NCT02007239), Anakinra (NCT02780583) and Emapalumab/NI-0501 (195) (NCT05001737; NCT03311854; NCT03312751; NCT01818492). In the subset of EBV-HLH patients, the ongoing clinical trials focus on Rituximab (NCT05384743), anti CD20 monoclonal antibody Sintilimab and Lenalidomide (NCT05258136), Tabelecleucel (NCT04554914), programmed cell death protein 1 antibody alone (NCT05039580) or in association with Lenalidomide (NCT04084626).

In intensive care settings, nonspecific physical therapies showed interesting results, at least in the acute phase (199,200). If a massive release of cytokines/a cytokine storm is responsible for organ damage, blood purification techniques can blunt the process with a rapid non-selective effect, potentially translating into survival benefit (199). These techniques include plasma exchange, which has been successfully applied in medium resource contexts (such as Turkey and India) (201,202), and hemofiltration combined with highly

immune adsorbent cartridges (119,191,200). HLH recommendations have recognized blood purification as a potential salvage treatment in adults (203). Moreover, these non-specific therapies might be combined with targeted therapies (204), but do not replace appropriate treatment of the underlying trigger of HLH, especially in patients with refractory disease (205).

The most recent consensus guidelines on recognition, diagnosis and management of HLH in critically ill children (46) stress the importance of aggressive treatment. Steroids, in particular, should not be delayed as part of first-line treatment in different protocols (HLH-94 and ATG-based protocols) and are effective in both primary and secondary HLH.

A Canadian group reported nine cases of pediatric liver transplantation in acute liver failure secondary to sHLH, suggesting that HLH might not be an absolute contraindication to transplantation and instead play a role in a very restricted subgroup of patients (19).

Specific treatment considerations for infection-related HLH. Treatment of infection-associated HLH deserves specific considerations according to the underlying agent, since some forms respond to anti-infectious treatment [namely Leishmania (131-134), Ehrlichiosis (122), scrub typhus (89,90) and other tropical diseases-associated forms], while reaction to some other pathogens displays intermediate features and benefits of standard aggressive immunosuppression.

Several studies (131,132,134,206) have reported complete response of Leishmania-associated HLH to amphotericin B therapy +/- steroids, with an excellent prognosis [3 year overall survival rate 24% in pHLH vs. 100% in visceral leishmaniasis-associated HLH; P<0.001; 2021 Iranian cohort of 60 children (133)]. A Chinese retrospective study (135) reported good results with antiparasitic therapy associated with chemotherapy according to the HLH94 protocol in patients with visceral leishmaniosis-HLH; however, the cohort includes children and adults and it is impossible to discriminate whether treatment intensification depends on age.

Human monocytic ehrlichiosis, can also trigger an HLH form that has proved to respond to antimicrobial therapy alone (doxycycline) (122).

Scrub typhus, dengue fever and tropical infections in general respond to steroids alone or to regimens without cytotoxic drugs in cases with mild to moderate disease activity (89,90).

The hepatitis-associated HLH cases reviewed in the present study have experienced complete recovery on antiviral therapy and ruxolitinib in the case of a patient with HBV (95) and after IVIG-infusion in the cases of patients with HAV (94).

A patient developing HLH after HIV diagnosis has required both antiretroviral therapy and chemotherapy according to HLH94 protocol (96).

The Crimean Congo hemorrhagic fever-associated HLH has been resolved using antiviral therapy combined with IVIG therapy and plasma exchange (91).

The case of EBV-HLH is more complex. EBV-HLH standard treatment is by the HLH94 protocol, and early initiation of etoposide-based regimens improves survival in severe EBV-HLH (8,74,207). Chemotherapy can be combined with targeted therapies such as Rituximab (37,181) or Ruxolitinib (208). Treatment intensification with the L-DEP regimen (PEG-asparaginase in combination with liposomal doxorubicin, etoposide and high-dose methylprednisolone) has been reported as salvage therapy and bridge to alloHSCT for children with refractory disease (209). Blood purification techniques (plasma exchange and continuous renal replacement therapy) have proved to be safe and effective in addition to standard chemotherapy in severe cases (199). On the other hand, patients presenting with mild-to-moderate disease activity may only require immunomodulating therapies, such as IVIGs, CSA and steroids (69). A Japanese group (210) described a cohort of 22 patients aged 6 months to 41 years in which >60% recovered after immunotherapy (IVIG, CSA 6 mg/kg/day, prednisone); they suggest that early immunotherapy may modulate T-cell activation and reduce the chance of unnecessary chemotherapy. Sporadic cases of spontaneous resolution have been reported: An American group (68) reported the cases of two adolescents who fulfilled the HLH2004 diagnostic criteria in the context of an acute EBV infection. In both cases, treatment was planned according to HLH94 protocol, but the patients spontaneously improved before the initiation of therapy. The authors recommend caution in starting aggressive treatment, especially when patients experience mild-to-moderate symptoms. These differences in treatment approaches and outcomes underline the need for evidence-based risk stratification criteria in patients with EBV-HLH.

Specific treatment considerations for M-HLH. Malignancy-triggered forms should be distinguished from the forms that occur after chemotherapy (Ch-HLH) to optimize the therapeutic approach.

Ch-HLH. Ch-HLH is often caused by infections related to immunosuppression, and benefits of anti-infectious therapy, steroids and IVIGs.

HLH as a manifestation of underlying malignancy. M-HLH is associated with increased mortality and the early detection of malignancy can favorably influence the prognosis. Treatment is not homogeneous, and can address the underlying malignancy first, be focused on HLH or a combination of the two (41,138,145,211-213). The published series refer to small numbers and suggest an individualized therapeutic approach. Aggressive HLH-directed therapy at the onset of malignancy-associated HLH can delay or complicate anticancer treatment (39,41).

Specific treatment considerations for Rheumatologic HLH (MAS-HLH). MAS-HLH usually responds to steroid therapy or to anakinra (recombinant human IL-1 receptor antagonist), especially when given in the early course of therapy (214,215). The present study refers to specific international guidelines for more detailed considerations on MAS-HLH (157,216,217).

Specific treatment considerations for HLH associated with iatrogenic immune activation. The cytokine release syndrome following CAR-T or Blinatumomab administration usually responds to Tocilizumab, steroids, Anakinra or to a combination of such molecules (29,165-167,169). Whether carHLH should be differentiated from a severe form of CRS is still an open question, and a more precise definition of both conditions

is essential in order to guide therapeutic choices in the most complex cases (162,218).

Specific treatment considerations for transplant-related HLH. Post-transplant HLH requires prompt and aggressive treatment because of the high risk of graft failure, but no international consensus exists on treatment protocol. Reported therapeutic approaches range from corticosteroids, IVIGs and low-dose etoposide (219-221) to standard HLH94 protocol with eventual rescue HSCT (172). Ruxolitinib was recently reported as salvage therapy in 2 children, with alternating results (222). Outcome is unclear, usually compromised by graft failure.

10. Prognosis

The prognosis is related to the cause that induced sHLH, with the worst outcomes in M-HLH. In the 1980s, long-term survival in HLH was <5% (223). The HLH-94 protocol improved life expectancy up to 54% of 5-year survival, with similar results in FHL and sHLH patients. Unfortunately, the subsequent 2004 revision failed to further improve the outcome (6).

An alternative therapeutic approach consisting of steroids, antithymocyte globulin and cyclosporin has obtained satisfactory results, with a 70% remission rate (33). In general, in HLH the highest mortality is in the first weeks of therapy. In patients with pHLH who underwent hematopoietic stem cell transplantation, a 5-year probability of overall survival of ~70% has been observed (224). Overall, HLH still carries a heavy burden of mortality up to the present day.

11. Conclusions

HLH is a rare disease that may develop from childhood to adult life, but HLH subtypes spread with different frequency according to the age of the patient. In early infancy, FLH forms are most typical. They are linked to genetic defects affecting the cytotoxic activity of T lymphocytes and NK cells, and invariably require allogeneic HSCT.

Secondary forms become more frequent with increasing age. They represent a heterogeneous group in terms of etiology and therapeutic approach. The severity of the clinical picture often requires heavy immunosuppression and the use of etoposide while trying to define the etiology. Some significant exceptions exist: i) Less aggressive therapeutic approaches proved to have efficacy in MAS-HLH and in the majority of infection-triggered HLH forms; and ii) anti-tumor therapy, alone or in combination with corticosteroids, can usually control M-HLH when hyperinflammation is triggered by the tumor itself.

Various viruses and EBV can trigger FHL or cause a HLH syndrome in the absence of known genetic alterations. The improvement of genetic investigations will probably clarify the genetic background of several patients with 'secondary' forms of HLH.

The future goal in addressing this rare and potentially fatal condition will be to provide a tailored therapy for each patient, based on its genetic and biological characteristics.

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Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

References

1. Griffin G, Shenoi S and Hughes GC: Hemophagocytic lymphohistiocytosis: An update on pathogenesis, diagnosis, and therapy. Best Pract Res Clin Rheumatol 34: 101515, 2020.
2. Farquhar JW and Claireaux AE: Familial haemophagocytic reticulosis. Arch Dis Child 27: 519-525, 1952.
3. Brisse E, Wouters CH and Matthys P: Advances in the pathogenesis of primary and secondary haemophagocytic lymphohistiocytosis: Differences and similarities. Br J Haematol 174: 203-217, 2016.
4. Brisse E, Matthys P and Wouters CH: Understanding the spectrum of haemophagocytic lymphohistiocytosis: Update on diagnostic challenges and therapeutic options. Br J Haematol 174: 175-187, 2016.
5. Price B, Lines J, Lewis D and Holland N: Haemophagocytic lymphohistiocytosis: A fulminant syndrome associated with multiorgan failure and high mortality that frequently masquerades as sepsis and shock. S Afr Med J 104: 401-406, 2014.
6. Bergsten E, Horne A, Aricó M, Astigarraga I, Egeler RM, Filipovich AH, Ishii E, Janka G, Ladisch S, Lehmberg K, *et al*: Confirmed efficacy of etoposide and dexamethasone in HLH treatment: Long-term results of the cooperative HLH-2004 study. Blood 130: 2728-2738, 2017.
7. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J and Janka G: HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 48: 124-131, 2007.

8. Jordan MB, Allen CE, Greenberg J, Henry M, Hermiston ML, Kumar A, Hines M, Eckstein O, Ladisch S, Nichols KE, *et al*: Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: Recommendations from the North American consortium for histiocytosis (NACHO). Pediatr Blood Cancer 66: e27929, 2019.
9. Ehl S, Astigarraga I, von Bahr Greenwood T, Hines M, Horne A, Ishii E, Janka G, Jordan MB, La Rosée P, Lehmberg K, *et al*: Recommendations for the use of etoposide-based therapy and bone marrow transplantation for the treatment of HLH: Consensus statements by the HLH steering committee of the histiocyte society. J Allergy Clin Immunol Pract 6: 1508-1517, 2018.
10. Freeman HR and Ramanan AV: Review of haemophagocytic lymphohistiocytosis. Arch Dis Child 96: 688-693, 2011.
11. Ishii E, Ohga S, Imashuku S, Yasukawa M, Tsuda H, Miura I, Yamamoto K, Horiuchi H, Takada K, Ohshima K, *et al*: Nationwide survey of hemophagocytic lymphohistiocytosis in Japan. Int J Hematol 86: 58-65, 2007.
12. Cleves D, Lotero V, Medina D, Perez PM, Patiño JA, Torres-Canchala L and Olaya M: Pediatric hemophagocytic lymphohistiocytosis: A rarely diagnosed entity in a developing country. BMC Pediatr 21: 411, 2021.
13. Sieni E, Cetica V, Piccin A, Gherlinzoni F, Sasso FC, Rabusin M, Attard L, Bosi A, Pende D, Moretta L and Aricò M: Familial hemophagocytic lymphohistiocytosis may present during adulthood: Clinical and genetic features of a small series. PLoS One 7: e44649, 2012.
14. Malinowska I, Machaczka M, Popko K, Siwicka A, Salamonowicz M and Nasiłowska-Adamska B: Hemophagocytic syndrome in children and adults. Arch Immunol Ther Exp (Warsz) 62: 385-394, 2014.
15. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA and Bosch X: Adult haemophagocytic syndrome. Lancet 383: 1503-1516, 2014.
16. Macheta M, Will AM, Houghton JB and Wynn RF: Prominent dyserythropoiesis in four cases of haemophagocytic lymphohistiocytosis. J Clin Pathol 54: 961-963, 2001.
17. Benson LA, Li H, Henderson LA, Solomon IH, Soldatos A, Murphy J, Bielekova B, Kennedy AL, Rivkin MJ, Davies KJ, *et al*: Pediatric CNS-isolated hemophagocytic lymphohistiocytosis. Neurol Neuroimmunol Neuroinflamm 6: e560, 2019.
18. de Kerguenec C, Hillaire S, Molinié V, Gardin C, Degott C, Erlinger S and Valla D: Hepatic manifestations of hemophagocytic syndrome: A study of 30 cases. Am J Gastroenterol 96: 852-857, 2001.
19. Amir AZ, Ling SC, Naqvi A, Weitzman S, Fecteau A, Grant D, Ghanekar A, Cattral M, Nalli N, Cutz E, *et al*: Liver transplantation for children with acute liver failure associated with secondary hemophagocytic lymphohistiocytosis. Liver Transpl 22: 1245-1253, 2016.
20. Al-Samkari H and Berliner N: Hemophagocytic lymphohistiocytosis. Annu Rev Pathol 13: 27-49, 2018.
21. Ishii E: Hemophagocytic lymphohistiocytosis in children: Pathogenesis and treatment. Front Pediatr 4: 47, 2016.
22. Skinner J, Yankey B and Shelton BK: Hemophagocytic lymphohistiocytosis. AACN Adv Crit Care 30: 151-164, 2019.
23. Morimoto A, Nakazawa Y and Ishii E: Hemophagocytic lymphohistiocytosis: Pathogenesis, diagnosis, and management. Pediatr Int 58: 817-825, 2016.
24. Jordan MB, Hildeman D, Kappler J and Marrack P: An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. Blood 104: 735-743, 2004.
25. Castillo L and 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 10: 387-392, 2009.
26. Grom AA, Horne A and De Benedetti F: Macrophage activation syndrome in the era of biologic therapy. Nat Rev Rheumatol 12: 259-268, 2016.
27. Canna SW and Behrens EM: Making sense of the cytokine storm: A conceptual framework for understanding, diagnosing, and treating hemophagocytic syndromes. Pediatr Clin North Am 59: 329-344, 2012.
28. Jordan MB: Emergence of targeted therapy for hemophagocytic lymphohistiocytosis. Hematologist 15, 2018.
29. Fajgenbaum DC and June CH: Cytokine storm. N Engl J Med 383: 2255-2273, 2020.
30. Alonso EM, Horslen SP, Behrens EM and Doo E: Pediatric acute liver failure of undetermined cause: A research workshop. Hepatology 65: 1026-1037, 2017.
31. Henter JI, Aricò M, Egeler RM, Elinder G, Favara BE, Filipovich AH, Gadner H, Imashuku S, Janka-Schaub G, Komp D, *et al*: HLH-94: A treatment protocol for hemophagocytic lymphohistiocytosis. HLH study group of the histiocyte society. Med Pediatr Oncol 28: 342-347, 1997.
32. Johnson TS, Terrell CE, Millen SH, Katz JD, Hildeman DA and Jordan MB: Etoposide selectively ablates activated T cells to control the immunoregulatory disorder hemophagocytic lymphohistiocytosis. J Immunol 192: 84-91, 2014.
33. Mahlaoui N, Ouachée-Chardin M, de Saint Basile G, Neven B, Picard C, Blanche S and Fischer A: Immunotherapy of familial hemophagocytic lymphohistiocytosis with antithymocyte globulins: A single-center retrospective report of 38 patients. Pediatrics 120: e622-e628, 2007.
34. Latour S and Fischer A: Signaling pathways involved in the T-cell-mediated immunity against Epstein-Barr virus: Lessons from genetic diseases. Immunol Rev 291: 174-189, 2019.
35. Moss DJ, Burrows SR, Khanna R, Misko IS and Sculley TB: Immune surveillance against Epstein-Barr virus. Semin Immunol 4: 97-104, 1992.
36. Kasahara Y and Yachie A: Cell type specific infection of Epstein-Barr virus (EBV) in EBV-associated hemophagocytic lymphohistiocytosis and chronic active EBV infection. Crit Rev Oncol Hematol 44: 283-294, 2002.
37. Balamuth NJ, Nichols KE, Paessler M and Teachey DT: Use of rituximab in conjunction with immunosuppressive chemotherapy as a novel therapy for Epstein Barr virus-associated hemophagocytic lymphohistiocytosis. J Pediatr Hematol Oncol 29: 569-573, 2007.
38. Daver N, McClain K, Allen CE, Parikh SA, Otrock Z, Rojas-Hernandez C, Blechacz B, Wang S, Minkov M, Jordan MB, *et al*: A consensus review on malignancy-associated hemophagocytic lymphohistiocytosis in adults. Cancer 123: 3229-3240, 2017.
39. Lehmberg K, Nichols KE, Henter JI, Girschikofsky M, Greenwood T, Jordan M, Kumar A, Minkov M, La Rosée P and Weitzman S; Study Group on Hemophagocytic Lymphohistiocytosis Subtypes of the Histiocyte Society: Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. Haematologica 100: 997-1004, 2015.
40. Henter JI, Elinder G and Ost A: Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL study group of the histiocyte society. Semin Oncol 18: 29-33, 1991.
41. Gurunathan A, Boucher AA, Mark M, Prus KM, O'Brien MM, Breese EH, Mizukawa BE, Absalon MJ, Nelson AS, Jordan MB, *et al*: Limitations of HLH-2004 criteria in distinguishing malignancy-associated hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 65: e27400, 2018.
42. Gifford CE, Weingartner E, Villanueva J, Johnson J, Zhang K, Filipovich AH, Bleesing JJ and Marsh RA: Clinical flow cytometric screening of SAP and XIAP expression accurately identifies patients with SH2D1A and XIAP/BIRC4 mutations. Cytometry B Clin Cytom 86: 263-271, 2014.
43. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, Coppo P and Hejblum G: Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol 66: 2613-2620, 2014.
44. Debaugnies F, Mahadeb B, Ferster A, Meuleman N, Rozen L, Demulder A and Corazza F: Performances of the H-score for diagnosis of hemophagocytic lymphohistiocytosis in adult and pediatric patients. Am J Clin Pathol 145: 862-870, 2016.
45. Nakashima Y and Koga H: Using a Minimal Parameter Set for Early Diagnosis of Hemophagocytic lymphohistiocytosis in non-European children. Am J Case Rep 23: e934037, 2022.
46. Hines MR, von Bahr Greenwood T, Beutel G, Beutel K, Hays JA, Horne A, Janka G, Jordan MB, van Laar JAM, Lachmann G, *et al*: Consensus-based guidelines for the recognition, diagnosis, and management of hemophagocytic lymphohistiocytosis in critically Ill children and adults. Crit Care Med 50: 860-872, 2022.
47. Koç ZP, Akarsu S, Balci T and Unal K: PET/CT images of a patient with haemophagocytic lymphohistiocytosis. BMJ Case Rep 2012: bcr0320126026, 2012.

48. Wei A, Lu X, Ma H, Lian H, Yang X, Zhang L, Wang D, Chen S, Zhang Q, Li Z, *et al*: ^{18}F-FDG PET/CT for identifying the potential primary diseases and predicting prognosis of secondary hemophagocytic lymphohistiocytosis in children. Contrast Media Mol Imaging 2022: 4849081, 2022.
49. Yang X, Lu X, Liu J, Kan Y, Wang W, Zhang S, Liu L, Li J and Yang J: Development and validation of ^{18}F-FDG PET/CT-based multivariable clinical prediction models for the identification of malignancy-associated hemophagocytic lymphohistiocytosis. Korean J Radiol 23: 466-478, 2022.
50. Tabata C and Tabata R: Possible prediction of underlying lymphoma by high sIL-2R/ferritin ratio in hemophagocytic syndrome. Ann Hematol 91: 63-71, 2012.
51. Tsuji T, Hirano T, Yamasaki H, Tsuji M and Tsuda H: A high sIL-2R/ferritin ratio is a useful marker for the diagnosis of lymphoma-associated hemophagocytic syndrome. Ann Hematol 93: 821-826, 2014.
52. Tang Y, Xu X, Song H, Yang S, Shi S, Wei J, Pan B, Zhao F, Liao C and Luo C: Early diagnostic and prognostic significance of a specific Th1/Th2 cytokine pattern in children with haemophagocytic syndrome. Br J Haematol 143: 84-91, 2008.
53. Chen Y, Wang Z, Luo Z, Zhao N, Yang S and Tang Y: Comparison of Th1/Th2 cytokine profiles between primary and secondary haemophagocytic lymphohistiocytosis. Ital J Pediatr 42: 50, 2016.
54. Xu XJ and Tang YM: Dilemmas in diagnosis and management of hemophagocytic lymphohistiocytosis in children. World J Pediatr 16: 333-340, 2020.
55. Han XC, Ye Q, Zhang WY, Tang YM, Xu XJ and Zhang T: Cytokine profiles as novel diagnostic markers of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in children. J Crit Care 39: 72-77, 2017.
56. Buatois V, Chatel L, Cons L, Lory S, Richard F, Guilhot F, Johnson Z, Bracaglia C, De Benedetti F, de Min C, *et al*: Use of a mouse model to identify a blood biomarker for IFNγ activity in pediatric secondary hemophagocytic lymphohistiocytosis. Transl Res 180: 37-52.e2, 2017.
57. Prencipe G, Bracaglia C, Caiello I, Pascarella A, Francalanci P, Pardeo M, Meneghel A, Martini G, Rossi MN, Insalaco A, *et al*: The interferon-gamma pathway is selectively up-regulated in the liver of patients with secondary hemophagocytic lymphohistiocytosis. PLoS One 14: e0226043, 2019.
58. Nagasawa M, Yi Z, Imashuku S, Nonoyama S, Ogawa K, Okumura K and Mizutani S: Soluble TWEAK is markedly elevated in hemophagocytic lymphohistiocytosis. Am J Hematol 83: 222-225, 2008.
59. Jenkins RW, Clarke CJ, Lucas JT Jr, Shabbir M, Wu BX, Simbari F, Mueller J, Hannun YA, Lazarchick J and Shirai K: Evaluation of the role of secretory sphingomyelinase and bioactive sphingolipids as biomarkers in hemophagocytic lymphohistiocytosis. Am J Hematol 88: E265-E272, 2013.
60. Chang YH, Lee DS, Jo HS, Cho SI, Yoon HJ, Shin S, Yoon JH, Kim HY, Hong YJ, Hong SI and Cho HI: Tumor necrosis factor alpha promoter polymorphism associated with increased susceptibility to secondary hemophagocytic lymphohistiocytosis in the Korean population. Cytokine 36: 45-50, 2006.
61. Yanagimachi M, Goto H, Miyamae T, Kadota K, Imagawa T, Mori M, Sato H, Yanagisawa R, Kaneko T, Morita S, *et al*: Association of IRF5 polymorphisms with susceptibility to hemophagocytic lymphohistiocytosis in children. J Clin Immunol 31: 946-951, 2011.
62. Horne A, Zheng C, Lorenz I, Löfstedt M, Montgomery SM, Janka G, Henter JI and Marion Schneider E: Subtyping of natural killer cell cytotoxicity deficiencies in haemophagocytic lymphohistocytosis provides therapeutic guidance. Br J Haematol 129: 658-666, 2005.
63. Chang TY, Jaffray J, Woda B, Newburger PE and Usmani GN: Hemophagocytic lymphohistiocytosis with MUNC13-4 gene mutation or reduced natural killer cell function prior to onset of childhood leukemia. Pediatr Blood Cancer 56: 856-858, 2011.
64. Emile JF, Abla O, Fraitag S, Horne A, Haroche J, Donadieu J, Requena-Caballero L, Jordan MB, Abdel-Wahab O, Allen CE, *et al*: Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood 127: 2672-2681, 2016.
65. Mărginean MO, Molnar E and Chinceşan MI: Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in a small child: A case report. Medicine (Baltimore) 99: e18759, 2020.
66. Fałkowska A, Prądzyńska K and Drabko K: Difficult balance between EBV treatment and posttransplant immunosuppression: A successful transplant in a child with recurrent Epstein-Barr virus-induced hemophagocytic lymphohistiocytosis. Transplant Proc 53: 2035-2039, 2021.
67. Pan H, Feng DN, Song L and Sun LR: Acute myeloid leukemia following etoposide therapy for EBV-associated hemophagocytic lymphohistiocytosis: A case report and a brief review of the literature. BMC Pediatr 16: 116, 2016.
68. Belyea B, Hinson A, Moran C, Hwang E, Heath J and Barfield R: Spontaneous resolution of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 55: 754-756, 2010.
69. Lin MT, Chang HM, Huang CJ, Chen WL, Lin CY, Lin CY and Chuang SS: Massive expansion of EBV+ monoclonal T cells with CD5 down regulation in EBV-associated haemophagocytic lymphohistiocytosis. J Clin Pathol 60: 101-103, 2007.
70. DomInguez-Pinilla N, Baro-Fernández M and González-Granado LI: Hemophagocytic lymphohistiocytosis secondary to Epstein Barr virus and Leishmania co-infection in a toddler. J Postgrad Med 61: 44-45, 2015.
71. Gera A, Misra A, Tiwari A, Singh A and Mehndiratta S: A hungry Histiocyte, altered immunity and myriad of problems: Diagnostic challenges for Pediatric HLH. Int J Lab Hematol 43: 1443-1450, 2021.
72. Oguz MM, Sahin G, Altinel Acoglu E, Polat E, Yucel H, Oztek Celebi FZ, Unsal H, Akcaboy M, Sari E and Senel S: Secondary hemophagocytic lymphohistiocytosis in pediatric patients: A single center experience and factors that influenced patient prognosis. Pediatr Hematol Oncol 36: 1-16, 2019.
73. Paul T, Kalra M, Danewa A, Sachdeva P, Thatikonda KB, Sachdeva D and Sachdeva A: Pediatric hemophagocytic lymphohistiocytosis-a single center study. Indian Pediatr 59: 283-286, 2022.
74. Imashuku S, Tabata Y, Teramura T and Hibi S: Treatment strategies for Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH). Leuk Lymphoma 39: 37-49, 2000.
75. Kawaguchi H, Miyashita T, Herbst H, Niedobitek G, Asada M, Tsuchida M, Hanada R, Kinoshita A, Sakurai M, Kobayashi N, *et al*: Epstein-Barr virus-infected T lymphocytes in Epstein-Barr virus-associated hemophagocytic syndrome. J Clin Invest 92: 1444-1450, 1993.
76. Imashuku S: Clinical features and treatment strategies of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Crit Rev Oncol Hematol 44: 259-272, 2002.
77. Lohana C, Jhatial MA and Bokhari SWI: A challenging case of haemophagocytic lymphohistiocytosis (HLH) secondary to CMV infection in an adolescent with B-acute lymphoblastic leukemia. J Coll Physicians Surg Pak 31: 1011-1012, 2021.
78. Pessoa FS, Gonçalves VC and Lacerda EMDCB: Haemophagocytic lymphohistiocytosis secondary to intrauterine cytomegalovirus infection. Rev Inst Med Trop Sao Paulo 63: e15, 2021.
79. Eldem İ, Al-Rahawan MM and Levent F: How to treat cytomegalovirus-induced hemophagocytic lymphohistiocytosis in a child with leukemia. J Pediatr Hematol Oncol 42: 313-315, 2020.
80. Silwedel C, Frieauff E, Thomas W, Liese JG and Speer CP: Secondary haemophagocytic lymphohistiocytosis triggered by postnatally acquired cytomegalovirus infection in a late preterm infant. Infection 45: 355-359, 2017.
81. Hasan MR, Sundaram MS, Sundararaju S, Tsui KM, Karim MY, Roscoe D, Imam O, Janahi MA, Thomas E, Dobson S, *et al*: Unusual accumulation of a wide array of antimicrobial resistance mechanisms in a patient with cytomegalovirus-associated hemophagocytic lymphohistiocytosis: A case report. BMC Infect Dis 20: 237, 2020.
82. Gur G, Cakar N, Uncu N, Ayar G, Basaran O, Taktak A, Koksoy AY, Acar B and Caycı FS: Hemophagocytic lymphohistiocytosis secondary to Varicella zoster infection in a child with Henoch-Schönlein purpura. Pediatr Int 57: e37-e38, 2015.
83. Krishnappa A, Munusamy J, Ray S, Rameshbabu M, Bhatia P, Roy PS, Sundaram V and Kumar P: Neonatal dengue with HLH: Perks of early diagnosis and management. J Pediatr Hematol Oncol 43: e770-e773, 2021.
84. Agrawal G, Wazir S, Sachdeva A and Kumar S: Primary dengue infection triggered haemophagocytic lymphohistiocytosis in a neonate. BMJ Case Rep 13: e236881, 2020.
85. Krithika MV, Amboiram P, Latha SM, Ninan B, Suman FR and Scott J: Neonate with haemophagocytic lymphohistiocytosis secondary to dengue infection: A case report. Trop Doct 47: 253-255, 2017.
86. Jasmine YSY, Lee SL and Kan FK: Infection associated haemophagocytic syndrome in severe dengue infection-a case series in a district hospital. Med J Malaysia 72: 62-64, 2017.

87. Phuakpet K, Sanpakit K, Vathana N, Takpradit C, Chokephaibulkit K and Viprakasit V: Hemophagocytic lymphohistiocytosis following dengue hemorrhagic fever in Hb H/Hb Constant Spring patient. Pediatr Int 57: 763-765, 2015.
88. Joshi R, Phatarpekar A, Currimbhoy Z and Desai M: Haemophagocytic lymphohistiocytosis: A case series from Mumbai. Ann Trop Paediatr 31: 135-140, 2011.
89. Nandhakumar D, Loganatha A, Sivasankaran M, Sivabalan S and Munirathnam D: Hemophagocytic lymphohistiocytosis in children. Indian J Pediatr 87: 526-531, 2020.
90. Simon AC, Delhi Kumar CG, Basu D and Ramesh Kumar R: Hemophagocytic lymphohistiocytosis in children: Clinical profile and outcome. J Pediatr Hematol Oncol 42: e281-e285, 2020.
91. Gayretli Aydin ZG, Yesilbas O, Reis GP and Guven B: The first pediatric case of hemophagocytic lymphohistiocytosis secondary to Crimean-Congo haemorrhagic fever successfully treated with therapeutic plasma exchange accompanying ribavirin and intravenous immunoglobulin. J Clin Apher 36: 780-784, 2021.
92. Bıçakçı Z, Tavil B, Tezer H and Olcay L: Hemophagocytosis in a case with Crimean-Congo hemorrhagic fever and an overview of possible pathogenesis with current evidence. Turk J Pediatr 55: 344-348, 2013.
93. Mancao MY, Imran H, Chandra S, Estrada B, Figarola M, Sosnowski J and Vidal R: Eastern equine encephalitis virus infection and hemophagocytic lymphohistiocytosis in a 5-month-old infant. Pediatr Infect Dis J 28: 543-545, 2009.
94. Bay A, Bosnak V, Leblebisatan G, Yavuz S, Yilmaz F and Hizli S: Hemophagocytic lymphohistiocytosis in 2 pediatric patients secondary to hepatitis A virus infection. Pediatr Hematol Oncol 29: 211-214, 2012.
95. Jianguo L, Zhixuan Z, Rong L and Xiaodong S: Ruxolitinib in alleviating the cytokine storm of hemophagocytic lymphohistiocytosis. Pediatrics 146: e20191301, 2020.
96. Chiperi LE, Ionescu AD, Marcu CT, Itu-Mureşan C and Pantelemon C: Hemophagocytic lymphohistiocytosis in a child with human immunodeficiency virus infection-a case report. Rom J Morphol Embryol 62: 279-282, 2021.
97. Censoplano N, Gorga S, Waldeck K, Stillwell T, Rabah-Hammad R and Flori H: Neonatal adenovirus infection complicated by hemophagocytic lymphohistiocytosis syndrome. Pediatrics 141 (Suppl 5): S475-S480, 2018.
98. Otto WR, Behrens EM, Teachey DT, Lamson DM, Barrett DM, Bassiri H, Lambert MP, Mount S, Petrosa WL, Romberg N, *et al*: Human adenovirus 7-associated hemophagocytic lymphohistiocytosis-like illness: Clinical and virological characteristics in a cluster of five pediatric cases. Clin Infect Dis 73: e1532-e1538, 2021.
99. Zhang XY, Ye XW, Feng DX, Han J, Li D and Zhang C: Hemophagocytic lymphohistiocytosis induced by severe pandemic influenza A (H1N1) 2009 virus infection: A case report. Case Rep Med 2011: 951910, 2011.
100. Shrestha B, Omran A, Rong P and Wang W: Report of a fatal pediatric case of hemophagocytic lymphohistiocytosis associated with pandemic influenza A (H1N1) infection in 2009. Pediatr Neonatol 56: 189-192, 2015.
101. Ozdemir H, Çiftçi E, Ince EU, Ertem M, Ince E and Doğru U: Hemophagocytic lymphohistiocytosis associated with 2009 pandemic influenza A (H1N1) virus infection. J Pediatr Hematol Oncol 33: 135-137, 2011.
102. Tholin B, Hauge MT, Aukrust P, Fehrle L and Tvedt TH: Hemophagocytic lymphohistiocytosis in a patient with COVID-19 treated with tocilizumab: A case report. J Med Case Rep 14: 187, 2020.
103. Hakim NN, Chi J, Olazagasti C and Liu JM: Secondary hemophagocytic lymphohistiocytosis versus cytokine release syndrome in severe COVID-19 patients. Exp Biol Med (Maywood) 246: 5-9, 2021.
104. Jose PMM, Paola ZS, Eduardo DG, Arturo SMMO and Fernando BG: A case of coinfection of a pediatric patient with acute SARS-COV-2 with MIS-C and severe DENV-2 in Mexico: A case report. BMC Infect Dis 21: 1072, 2021.
105. Mahdavi M, Hejri GM, Pouraliakbar H, Shahzadi H, Hesami M and Houshmand G: Cytokine storm after heart transplantation in COVID-19-related haemophagocytic lymphohistiocytosis (HLH). ESC Heart Fail 9: 219-223, 2022.
106. El-Isa HZ, Khader OA, Khader M, Ashour BA, Azzam MI and Badran EF: Secondary hemophagocytic lymphohistiocytosis in a neonate with SARS-CoV-2 infection. Am J Case Rep 23: e934839, 2022.
107. Mittal J, Kumar P, Goyal JP and Purohit A: Haemophagocytic lymphohistiocytosis secondary to brucellosis in a young child. BMJ Case Rep 14: e240759, 2021.
108. Pekpak E and Sirvan Cetin B: Secondary hemophagocytic lymphohistocytosis in a child with brucellosis. J Pediatr Hematol Oncol 39: e501-e503, 2017.
109. Yaman Y, Gözmen S, Özkaya AK, Oymak Y, Apa H, Vergin C and Devrim İ: Secondary hemophagocytic lymphohistiocytosis in children with brucellosis: Report of three cases. J Infect Dev Ctries 9: 1172-1176, 2015.
110. Banday AZ, Mehta R, Vignesh P, Kanaujia R, Durgadevi S, Angrup A, Kumar N, Ray P and Suri D: Case Report: Ceftriaxone-resistant invasive *Salmonella enteritidis* infection with secondary hemophagocytic lymphohistiocytosis: A contrast with enteric fever. Am J Trop Med Hyg 103: 2515-2517, 2020.
111. Maheshwari P, Chhabra R and Yadav P: Perinatal tuberculosis associated hemophagocytic lymphohistiocytosis. Indian J Pediatr 79: 1228-1229, 2012.
112. Choi YB and Yi DY: Fatal case of hemophagocytic lymphohistiocytosis associated with group B streptococcus sepsis: A case report. Medicine (Baltimore) 97: e12210, 2018.
113. Liu SS, Wang Y, Xue L, Ma C and Li CH: Hemophagocytic lymphohistiocytosis due to *Streptococcus suis* in a 12-year-old girl: A case report. Medicine (Baltimore) 98: e15136, 2019.
114. Sahu SK, Behera JR and Yadav SK: Scrub typhus with secondary hemophagocytic lymphohistiocytosis in a 3-month-old child from a tertiary care hospital of Odisha. Indian J Public Health 65: 85-86, 2021.
115. Han DK, Baek HJ, Shin MG, Kim JW, Kook H and Hwang TJ: Scrub typhus-associated severe hemophagocytic lymphohistiocytosis with encephalomyelitis leading to permanent sequelae: A case report and review of the literature. J Pediatr Hematol Oncol 34: 531-533, 2012.
116. Agrwal S, Dabas A, Mantan M and Yadav S: Hemophagocytic lymphohistiocytosis with neurological manifestations in an infant with scrub typhus: A rare fatal occurrence. Trop Doct 49: 52-53, 2019.
117. Pazhaniyandi S, Lenin R and Sivathanu S: Hemophagocytic lymphohistiocytosis with a leukemoid reaction in an infant with scrub typhus. J Infect Public Health 8: 626-629, 2015.
118. Otrock ZK, Gonzalez MD and Eby CS: Ehrlichia-induced hemophagocytic lymphohistiocytosis: A case series and review of literature. Blood Cells Mol Dis 55: 191-193, 2015.
119. Cheng A, Williams F, Fortenberry J, Preissig C, Salinas S and Kamat P: Use of extracorporeal support in hemophagocytic lymphohistiocytosis secondary to ehrlichiosis. Pediatrics 138: e20154176, 2016.
120. Burns S, Saylors R and Mian A: Hemophagocytic lymphohistiocytosis secondary to *Ehrlichia chaffeensis* infection: A case report. J Pediatr Hematol Oncol 32: e142-143, 2010.
121. Singh NS, Pagano AL, Hays AJ, Kats A, Dahl SM, Warady BA, Beins NT and Yin DE: Ehrlichia-induced hemophagocytic lymphohistiocytosis in a pediatric kidney transplant recipient. Pediatr Transplant 26: e14134, 2022.
122. Cabler SS, Hogan PG, Fritz SA, Bednarski JJ and Hunstad DA: Incidence and treatment of hemophagocytic lymphohistiocytosis in hospitalized children with Ehrlichia infection. Pediatr Blood Cancer 67: e28436, 2020.
123. Tsuge M, Miyamoto M, Miyawaki R, Kondo Y and Tsukahara H: Hemophagocytic lymphohistiocytosis complicating invasive pneumococcal disease: A pediatric case report. BMC Pediatr 20: 15, 2020.
124. Poudel A, Lew J, Slayton W and Dharnidharka VR: *Bartonella henselae* infection inducing hemophagocytic lymphohistiocytosis in a kidney transplant recipient. Pediatr Transplant 18: E83-E87, 2014.
125. Edner J, Rudd E, Zheng C, Dahlander A, Eksborg S, Schneider EM, Edner A and Henter JI: Severe bacteria-associated hemophagocytic lymphohistiocytosis in an extremely premature infant. Acta Paediatr 96: 1703-1706, 2007.
126. Karapinar DY, Karadaş N, Yazici P, Polat SH and Karapinar B: *Trichosporon asahii*, sepsis, and secondary hemophagocytic lymphohistiocytosis in children with hematologic malignancy. Pediatr Hematol Oncol 31: 282-284, 2014.
127. Guo F, Kang L and Xu M: A case of pediatric visceral leishmaniasis-related hemophagocytic lymphohistiocytosis diagnosed by mNGS. Int J Infect Dis 97: 27-29, 2020.

128. Guo X, Chen N, Wang TY, Zhou YC, Li Q and Gao J: Visceral leishmaniasis associated hemophagocytic lymphohistiocytosis: Report of four childhood cases. Zhonghua Er Ke Za Zhi 49: 550-553, 2011 (In Chinese).
129. Bouguila J, Chabchoub I, Moncef Y, Mlika A, Saghrouni F, Boughamoura L and Essoussi AS: Treatment of severe hemophagocytic syndrome associated with visceral leishmaniasis. Arch Pediatr 17: 1566-1570, 2010 (In French).
130. Castberg FC, Poulsen A, Petersen BL and Lausen B: Visceral leishmaniasis in two children after vacation in Southern Europe. Ugeskr Laeger 175: 2193-2194, 2013 (In Danish).
131. Rajagopala S, Dutta U, Chandra KSP, Bhatia P, Varma N and Kochhar R: Visceral leishmaniasis associated hemophagocytic lymphohistiocytosis-case report and systematic review. J Infect 56: 381-388, 2008.
132. Ay Y, Yildiz B, Unver H, Karapinar DY and Vardar F: Hemophagocytic lymphohistiocytosis associated with H1N1 virus infection and visceral leishmaniasis in a 4.5-month-old infant. Rev Soc Bras Med Trop 45: 407-409, 2012.
133. Mottaghipisheh H, Kalantar K, Amanati A, Shokripour M, Shahriari M, Zekavat OR, Zareifar S, Karimi M, Haghpanah S and Bordbar M: Comparison of the clinical features and outcome of children with hemophagocytic lymphohistiocytosis (HLH) secondary to visceral leishmaniasis and primary HLH: A single-center study. BMC Infect Dis 21: 732, 2021.
134. de Carvalho FHG, Lula JF, Teles LF, Caldeira AP and de Carvalho SFG: Hemophagocytic lymphohistiocytosis secondary to visceral leishmaniasis in an endemic area in the north of Minas Gerais, Brazil. Rev Soc Bras Med Trop 53: e20190491, 2020.
135. Shi Q, Huang M, Li X, Zheng X, Wang F, Zou Y, Wang L and Jia J: Clinical and laboratory characteristics of hemophagocytic lymphohistiocytosis induced by Leishmania infantum infection. PLoS Negl Trop Dis 15: e0009944, 2021.
136. Srivatsav S, Mahalingam S, Ramineni P and Manya S: Dengue and *Plasmodium* falciparum coinfection with secondary hemophagocytic lymphohistiocytosis in a 3-year-old boy: A clinical conundrum. J Pediatr Hematol Oncol 44: e253-e254, 2022.
137. Padhi S, Varghese RGB, Ramdas A, Phansalkar MD and Sarangi R: Hemophagocytic lymphohistiocytosis: Critical reappraisal of a potentially under-recognized condition. Front Med 7: 492-498, 2013.
138. Lehmberg K, Sprekels B, Nichols KE, Woessmann W, Müller I, Suttorp M, Bernig T, Beutel K, Bode SF, Kentouche K, *et al*: Malignancy-associated haemophagocytic lymphohistiocytosis in children and adolescents. Br J Haematol 170: 539-549, 2015.
139. O'Brien MM, Lee-Kim Y, George TI, McClain KL, Twist CJ and Jeng M: Precursor B-cell acute lymphoblastic leukemia presenting with hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 50: 381-383, 2008.
140. Celkan T, Berrak S, Kazanci E, Ozyürek E, Unal S, Uçar C, Yilmaz S and Gürgey A: Malignancy-associated hemophagocytic lymphohistiocytosis in pediatric cases: A multicenter study from Turkey. Turk J Pediatr 51: 207-213, 2009.
141. Strenger V, Merth G, Lackner H, Aberle SW, Kessler HH, Seidel MG, Schwinger W, Sperl D, Sovinz P, Karastaneva A, *et al*: Malignancy and chemotherapy induced haemophagocytic lymphohistiocytosis in children and adolescents-a single centre experience of 20 years. Ann Hematol 97: 989-998, 2018.
142. Chellapandian D, Hines MR, Zhang R, Jeng M, van den Bos C, Santa-María López V, Lehmberg K, Sieni E, Wang Y, Nakano T, *et al*: A multicenter study of patients with multisystem Langerhans cell histiocytosis who develop secondary hemophagocytic lymphohistiocytosis. Cancer 125: 963-971, 2019.
143. Chinn IK, Eckstein OS, Peckham-Gregory EC, Goldberg BR, Forbes LR, Nicholas SK, Mace EM, Vogel TP, Abhyankar HA, Diaz MI, *et al*: Genetic and mechanistic diversity in pediatric hemophagocytic lymphohistiocytosis. Blood 132: 89-100, 2018.
144. Cader FZ, Colmenero I and Mussai F: Hemophagocytic lymphohistiocytosis associated with 2 cases of pediatric lymphocyte-depleted classic hodgkin lymphoma. J Pediatr Hematol Oncol 41: e341-e345, 2019.
145. Huang Z, Jia Y, Zuo Y, Wu J, Lu A and Zhang L: Malignancy-associated hemophagocytic lymphohistiocytosis in children: A 10-year experience of a single pediatric hematology center. Hematology 25: 389-399, 2020.
146. Sakamoto K, Osumi T, Yoshimura S, Shimizu S, Kato M, Tomizawa D, Fukuda A, Sakamoto S, Nakano N, Yoshioka T, *et al*: Living-donor liver transplantation providing an adequate chemotherapy for a pediatric patient with anaplastic large cell lymphoma complicated with liver failure due to the aggravation of biliary hepatopathy by secondary hemophagocytic lymphohistiocytosis. Int J Hematol 112: 900-905, 2020.
147. Teshigawara S, Katada Y, Maeda Y, Yoshimura M, Kudo-Tanaka E, Tsuji S, Harada Y, Matsushita M, Ohshima S, Watanabe K, *et al*: Hemophagocytic lymphohistiocytosis with leukoencephalopathy in a patient with dermatomyositis accompanied with peripheral T-cell lymphoma: A case report. J Med Case Rep 10: 212, 2016.
148. Sinno MG, Rosen D and Wittler R: Concomitant presentation of hemophagocytic lymphohistiocytosis and posttransplant lymphoproliferative disease-like lymphoma in a mildly immunosuppressed leukemia patient: An unusual association. Pediatr Blood Cancer 63: 1474-1476, 2016.
149. McCall CM, Mudali S, Arceci RJ, Small D, Fuller S, Gocke CD, Vuica-Ross M, Burns KH, Borowitz MJ and Duffield AS: Flow cytometric findings in hemophagocytic lymphohistiocytosis. Am J Clin Pathol 137: 786-794, 2012.
150. Zheng F, Jia Y, Zhang L and Qin J: Hemophagocytic lymphohistiocytosis secondary to juvenile myelomonocytic leukemia: A case report and review of the literature. J Pediatr Hematol Oncol 44: e580-e584, 2022.
151. Farias MG, Freitas PAC, Spagnol F, Souza MV, Alegretti AP, Riegel M, Taniguchi ANR and Daudt LE: Hemophagocytosis by blasts in a child with acute monocytic leukemia after chemotherapy. Rev Paul Pediatr 39: e2019290, 2021 (In Portuguese, English).
152. Dokmanovic L, Krstovski N, Jankovic S and Janic D: Hemophagocytic lymphohistiocytosis arising in a child with Langerhans cell histiocytosis. Turk J Pediatr 56: 452-457, 2014.
153. Murphy EP, Mo J and Yoon JM: Secondary hemophagocytic lymphohistiocytosis in a patient with favorable histology wilms tumor. J Pediatr Hematol Oncol 37: e494-e496, 2015.
154. Nascimento FA, Nery J, Trennepohl J and Pianovski MAD: Hemophagocytic lymphohistiocytosis after initiation of chemotherapy for bilateral adrenal neuroblastoma. J Pediatr Hematol Oncol 38: e13-e15, 2016.
155. Tang X, Guo X, Gao J, Sun JJ and Wan Z: Hemophagocytic lymphohistiocytosis in langerhans cell histiocytosis: A case series and literature review. J Pediatr Hematol Oncol 44: e20-e25, 2022.
156. Devecioglu O, Anak S, Atay D, Aktan P, Devecioglu E, Ozalp B and Saribeyoglu E: Pediatric acute lymphoblastic leukemia complicated by secondary hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 53: 491-492, 2009.
157. Henderson LA and Cron RQ: Macrophage activation syndrome and secondary hemophagocytic lymphohistiocytosis in childhood inflammatory disorders: Diagnosis and management. Paediatr Drugs 22: 29-44, 2020.
158. Sandler RD, Tattersall RS, Schoemans H, Greco R, Badoglio M, Labopin M, Alexander T, Kirgizov K, Rovira M, Saif M, *et al*: Diagnosis and management of secondary HLH/MAS following HSCT and CAR-T cell therapy in adults; A review of the literature and a survey of practice within EBMT centres on behalf of the autoimmune diseases working party (ADWP) and transplant complications working party (TCWP). Front Immunol 11: 524, 2020.
159. Teachey DT, Lacey SF, Shaw PA, Melenhorst JJ, Maude SL, Frey N, Pequignot E, Gonzalez VE, Chen F, Finklestein J, *et al*: Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Cancer Discov 6: 664-679, 2016.
160. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, Komanduri KV, Lin Y, Jain N, Daver N, *et al*: Chimeric antigen receptor T-cell therapy-assessment and management of toxicities. Nat Rev Clin Oncol 15: 47-62, 2018.
161. Lichtenstein DA, Schischlik F, Shao L, Steinberg SM, Yates B, Wang HW, Wang Y, Inglefield J, Dulau-Florea A, Ceppi F, *et al*: Characterization of HLH-like manifestations as a CRS variant in patients receiving CD22 CAR T cells. Blood 138: 2469-2484, 2021.
162. Hines MR, Keenan C, Maron Alfaro G, Cheng C, Zhou Y, Sharma A, Hurley C, Nichols KE, Gottschalk S, Triplett BM and Talleur AC: Hemophagocytic lymphohistiocytosis-like toxicity (carHLH) after CD19-specific CAR T-cell therapy. Br J Haematol 194: 701-707, 2021.

163. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, Bader P, Verneris MR, Stefanski HE, Myers GD, *et al*: Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 378: 439-448, 2018.
164. Xu XJ and Tang YM: Cytokine release syndrome in cancer immunotherapy with chimeric antigen receptor engineered T cells. Cancer Lett 343: 172-178, 2014.
165. Singh N, Hofmann TJ, Gershenson Z, Levine BL, Grupp SA, Teachey DT and Barrett DM: Monocyte lineage-derived IL-6 does not affect chimeric antigen receptor T-cell function. Cytotherapy 19: 867-880, 2017.
166. Giavridis T, van der Stegen SJC, Eyquem J, Hamieh M, Piersigilli A and Sadelain M: CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. Nat Med 24: 731-738, 2018.
167. Norelli M, Camisa B, Barbiera G, Falcone L, Purevdorj A, Genua M, Sanvito F, Ponzoni M, Doglioni C, Cristofori P, *et al*: Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. Nat Med 24: 739-748, 2018.
168. Liu Y, Fang Y, Chen X, Wang Z, Liang X, Zhang T, Liu M, Zhou N, Lv J, Tang K, *et al*: Gasdermin E-mediated target cell pyroptosis by CAR T cells triggers cytokine release syndrome. Sci Immunol 5: eaax7969, 2020.
169. Teachey DT, Rheingold SR, Maude SL, Zugmaier G, Barrett DM, Seif AE, Nichols KE, Suppa EK, Kalos M, Berg RA, *et al*: Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. Blood 121: 5154-5157, 2013.
170. Winkler U, Jensen M, Manzke O, Schulz H, Diehl V and Engert A: Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). Blood 94: 2217-2224, 1999.
171. Asano T, Kogawa K, Morimoto A, Ishida Y, Suzuki N, Ohga S, Kudo K, Ohta S, Wakiguchi H, Tabuchi K, *et al*: Hemophagocytic lymphohistiocytosis after hematopoietic stem cell transplantation in children: A nationwide survey in Japan. Pediatr Blood Cancer 59: 110-114, 2012.
172. Noguchi M and Inagaki J: Hemophagocytic lymphohistiocytosis and graft failure following unrelated umbilical cord blood transplantation in children. J Pediatr Hematol Oncol 42: e440-e444, 2020.
173. Jarchin L, Chu J, Januska M, Merola P and Arnon R: Autoimmune hemolytic anemia: An unusual presentation of hemophagocytic lymphohistiocytosis in a pediatric post-liver transplant patient. Pediatr Transplant 22: e13281, 2018.
174. Nakajima K, Hiejima E, Nihira H, Kato K, Honda Y, Izawa K, Kawabata N, Kato I, Ogawa E, Sonoda M, *et al*: Case report: A case of Epstein-Barr virus-associated acute liver failure requiring hematopoietic cell transplantation after emergent liver transplantation. Front Immunol 13: 825806, 2022.
175. Jha B, Mohan N, Gajendra S, Sachdev R, Goel S, Sahni T, Raina V and Soin A: Prompt diagnosis and management of Epstein-Barr virus-associated post-transplant lymphoproliferative disorder and hemophagocytosis: A dreaded complication in a post-liver transplant child. Pediatr Transplant 19: E177-E180, 2015.
176. Matsuda K, Toyama K, Toya T, Ikemura M, Nakamura F and Kurokawa M: Reactivation of hemophagocytic lymphohistiocytosis triggered by antithymocyte globulin. Intern Med 57: 583-586, 2018.
177. Ali S, AlThubaiti S, Renzi S, Krueger J, Chiang KY, Naqvi A, Schechter T, Punnett A and Ali M: Hemophagocytic lymphohistiocytosis is a sign of poor outcome in pediatric Epstein-Barr virus-associated post-transplant lymphoproliferative disease after allogeneic hematopoietic stem cell transplantation. Pediatr Transplant 23: e13319, 2019.
178. Park M, Yun YJ, Woo SI, Lee JW, Chung NG and Cho B: Rotavirus-associated hemophagocytic lymphohistiocytosis (HLH) after hematopoietic stem cell transplantation for familial HLH. Pediatr Int 57: e77-e80, 2015.
179. Salvador C, Meister B, Larcher H, Crazzolara R and Kropshofer G: Hemophagocytic lymphohistiocytosis after allogeneic bone marrow transplantation during chronic norovirus infection. Hematol Oncol 32: 102-106, 2014.
180. Hattori N, Sato M, Uesugi Y, Nakata A, Sasaki Y, Shimada S, Watanuki M, Fujiwara S, Kawaguchi Y, Arai N, *et al*: Characteristics and predictors of post-transplant-associated hemophagocytic lymphohistiocytosis in adults. Int J Hematol 113: 693-702, 2021.
181. Stefanou C, Tzortzi C, Georgiou F and Timiliotou C: Combining an antiviral with rituximab in EBV-related haemophagocytic lymphohistiocytosis led to rapid viral clearance; and a comprehensive review. BMJ Case Rep 2016: bcr2016216488, 2016.
182. Farias-Moeller R, LaFrance-Corey R, Bartolini L, Wells EM, Baker M, Doslea A, Suslovic W, Greenberg J, Carpenter JL and Howe CL: Fueling the FIRES: Hemophagocytic lymphohistiocytosis in febrile infection-related epilepsy syndrome. Epilepsia 59: 1753-1763, 2018.
183. Dandoy C and Grimley M: Secondary hemophagocytic lymphohistiocytosis (HLH) from a presumed brown recluse spider bite. J Clin Immunol 34: 544-547, 2014.
184. Alabbas F, Elyamany G, Alanzi T, Ali TB, Albatniji F and Alfaraidi H: Wolman's disease presenting with secondary hemophagocytic lymphohistiocytosis: A case report from Saudi Arabia and literature review. BMC Pediatr 21: 72, 2021.
185. Schüller S, Attarbaschi A, Berger A, Hutter C, Klebermass-Schrehof K and Steiner M: Hemophagocytic lymphohistiocytosis triggered by Gaucher disease in a preterm neonate. Pediatr Hematol Oncol 33: 462-467, 2016.
186. Gokce M, Unal O, Hismi B, Gumruk F, Coskun T, Balta G, Unal S, Cetin M, Kalkanoglu-Sivri HS, Dursun A and Tokatlı A: Secondary hemophagocytosis in 3 patients with organic acidemia involving propionate metabolism. Pediatr Hematol Oncol 29: 92-98, 2012.
187. Erdol S, Ture M, Baytan B, Yakut T and Saglam H: An unusual case of LCHAD deficiency presenting with a clinical picture of hemophagocytic lymphohistiocytosis: Secondary HLH or coincidence? J Pediatr Hematol Oncol 38: 661-662, 2016.
188. Düzenli Kar Y, Özdemir ZC, Kiral E, Kiliç Yildirim G, Dinleyici EÇ and Bör Ö: Hemophagocytic lymphohystiocytosis associated with type Ia glycogen storage disease. J Pediatr Hematol Oncol 41: e260-e262, 2019.
189. Santos Silva E, Klaudel-Dreszler M, Bakuła A, Oliva T, Sousa T, Fernandes PC, Tylki-Szymańska A, Kamenets E, Martins E and Socha P: Early onset lysosomal acid lipase deficiency presenting as secondary hemophagocytic lymphohistiocytosis: Two infants treated with sebelipase alfa. Clin Res Hepatol Gastroenterol 42: e77-e82, 2018.
190. Faraguna MC, Musto F, Crescitelli V, Iascone M, Spaccini L, Tonduti D, Fedeli T, Kullmann G, Canonico F, Cattoni A, *et al*: Mucopolysaccharidosis-plus syndrome, a rapidly progressive disease: Favorable impact of a very prolonged steroid treatment on the clinical course in a child. Genes (Basel) 13: 442, 2022.
191. Merli P, Quintarelli C, Strocchio L and Locatelli F: The role of interferon-gamma and its signaling pathway in pediatric hematological disorders. Pediatr Blood Cancer 68: e28900, 2021.
192. George MR: Hemophagocytic lymphohistiocytosis: Review of etiologies and management. J Blood Med 5: 69-86, 2014.
193. Henter JI, Samuelsson-Horne A, Aricò M, Egeler RM, Elinder G, Filipovich AH, Gadner H, Imashuku S, Komp D, Ladisch S, *et al*: Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood 100: 2367-2373, 2002.
194. Jordan M, Prof FL, Allen C, De Benedetti F, Grom AA, Ballabio M, Ferlin WG and De Min C: A novel targeted approach to the treatment of hemophagocytic lymphohistiocytosis (HLH) with an anti-interferon gamma (IFNγ) monoclonal antibody (mAb), NI-0501: First results from a pilot phase 2 study in children with primary HLH. Blood 126: LBA-3, 2015.
195. Locatelli F, Jordan MB, Allen C, Cesaro S, Rizzari C, Rao A, Degar B, Garrington TP, Sevilla J, Putti MC, *et al*: Emapalumab in children with primary hemophagocytic lymphohistiocytosis. N Engl J Med 382: 1811-1822, 2020.
196. Marsh RA, Allen CE, McClain KL, Weinstein JL, Kanter J, Skiles J, Lee ND, Khan SP, Lawrence J, Mo JQ, *et al*: Salvage therapy of refractory hemophagocytic lymphohistiocytosis with alemtuzumab. Pediatr Blood Cancer 60: 101-109, 2013.
197. Das R, Guan P, Sprague L, Verbist K, Tedrick P, An QA, Cheng C, Kurachi M, Levine R, Wherry EJ, *et al*: Janus kinase inhibition lessens inflammation and ameliorates disease in murine models of hemophagocytic lymphohistiocytosis. Blood 127: 1666-1675, 2016.

198. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, Cuttica R, Ravelli A, Schneider R, Woo P, *et al*: Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med 367: 2385-2395, 2012.
199. Huang P, Huang C, Xu H, Lu J, Tian R, Wang Z and Chen Y: Early use of blood purification in severe Epstein-Barr virus-associated hemophagocytic syndrome. Pediatrics 145: e20193197, 2020.
200. Bottari G, Murciano M, Merli P, Bracaglia C, Guzzo I, Stoppa F, Pardeo M, Nunziata J, Bufalo FD, Genuini L, *et al*: Hemoperfusion with cytosorb to manage multiorgan dysfunction in the spectrum of hemophagocytic lymphohistiocytosis syndrome in critically Ill children. Blood Purif 51: 417-424, 2022.
201. Matsumoto Y, Naniwa D, Banno S and Sugiura Y: The efficacy of therapeutic plasmapheresis for the treatment of fatal hemophagocytic syndrome: Two case reports. Ther Apher 2: 300-304, 1998.
202. Demirkol D, Yildizdas D, Bayrakci B, Karapinar B, Kendirli T, Koroglu TF, Dursun O, Erkek N, Gedik H, Citak A, *et al*: Hyperferritinemia in the critically ill child with secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction syndrome/macrophage activation syndrome: What is the treatment? Crit Care 16: R52, 2012.
203. La Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, Birndt S, Gil-Herrera J, Girschikofsky M, Jordan MB, *et al*: Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 133: 2465-2477, 2019.
204. Yan WL, Yang SL, Zhao FY and Xu XJ: Ruxolitinib is an alternative to etoposide for patient with hemophagocytic lymphohistiocytosis complicated by acute renal injury: A case report. J Oncol Pharm Pract 28: 222-227, 2022.
205. Broglie L, Pommert L, Rao S, Thakar M, Phelan R, Margolis D and Talano J: Ruxolitinib for treatment of refractory hemophagocytic lymphohistiocytosis. Blood Adv 1: 1533-1536, 2017.
206. Cançado GGL, Freitas GG, Faria FHF, de Macedo AV and Nobre V: Hemophagocytic lymphohistiocytosis associated with visceral leishmaniasis in late adulthood. Am J Trop Med Hyg 88: 575-577, 2013.
207. Imashuku S, Kuriyama K, Teramura T, Ishii E, Kinugawa N, Kato M, Sako M and Hibi S: Requirement for etoposide in the treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. J Clin Oncol 19: 2665-2673, 2001.
208. Huang Z and Xie J: Ruxolitinib in conjunction with the HLH-94 protocol for Epstein-Barr virus-related hemophagocytic lymphohistiocytosis in the intensive care unit: A case report. Medicine (Baltimore) 100: e25188, 2021.
209. Zhao Y, Li Z, Zhang L, Lian H, Ma H, Wang D, Zhao X, Zhang Q, Wang T and Zhang R: L-DEP regimen salvage therapy for paediatric patients with refractory Epstein-Barr virus-associated haemophagocytic lymphohistiocytosis. Br J Haematol 191: 453-459, 2020.
210. Shiraishi A, Ohga S, Doi T, Ishimura M, Takimoto T, Takada H, Miyamoto T, Abe Y and Hara T: Treatment choice of immunotherapy or further chemotherapy for Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 59: 265-270, 2012.
211. Lackner H, Seidel MG, Strenger V, Sovinz P, Schwinger W, Benesch M, Sperl D and Urban C: Hemophagocytic syndrome in children with acute monoblastic leukemia-another cause of fever of unknown origin. Support Care Cancer 21: 3519-3523, 2013.
212. Chi MS, Chang YC and Chi KH: In reply to roos *et al*. Int J Radiat Oncol Biol Phys 101: 1003, 2018.
213. Han L, Li L, Wu J, Li X, Zhang L, Wang X, Fu X, Ma W, Sun Z, Zhang X, *et al*: Clinical features and treatment of natural killer/T cell lymphoma associated with hemophagocytic syndrome: comparison with other T cell lymphoma associated with hemophagocytic syndrome. Leuk Lymphoma 55: 2048-2055, 2014.
214. Eloseily EM, Weiser P, Crayne CB, Haines H, Mannion ML, Stoll ML, Beukelman T, Atkinson TP and Cron RQ: Benefit of anakinra in treating pediatric secondary hemophagocytic lymphohistiocytosis. Arthritis Rheumatol 72: 326-334, 2020.
215. Bami S, Vagrecha A, Soberman D, Badawi M, Cannone D, Lipton JM, Cron RQ and Levy CF: The use of anakinra in the treatment of secondary hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 67: e28581, 2020.
216. Bagri NK, Gupta L, Sen ES and Ramanan AV: Macrophage activation syndrome in children: Diagnosis and management. Indian Pediatr 58: 1155-1161, 2021.
217. Ravelli A, Minoia F, Davì S, Horne A, Bovis F, Pistorio A, Aricò M, Avcin T, Behrens EM, De Benedetti F, *et al*: 2016 Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: A European league against rheumatism/American college of rheumatology/paediatric rheumatology international trials organisation collaborative initiative. Arthritis Rheumatol 68: 566-576, 2016.
218. Shalabi H, Gust J, Taraseviciute A, Wolters PL, Leahy AB, Sandi C, Laetsch TW, Wiener L, Gardner RA, Nussenblatt V, *et al*: Beyond the storm-subacute toxicities and late effects in children receiving CAR T cells. Nat Rev Clin Oncol 18: 363-378, 2021.
219. Ishida H, Yoshida H, Yoshihara T, Ito M and Morimoto A: Origin of macrophages involved in the development of allogeneic hematopoietic stem cell transplantation-associated hemophagocytic syndrome: Observations on a patient with juvenile myelomonocytic leukemia. Bone Marrow Transplant 40: 701-703, 2007.
220. Ostronoff M, Ostronoff F, Coutinho M, Calixto R, Souto Maior AP, Sucupira A, Florencio R and Tagliari C: Hemophagocytic syndrome after autologous peripheral blood stem cell transplantation for multiple myeloma; successful treatment with high-dose intravenous immunoglobulin. Bone Marrow Transplant 37: 797-798, 2006.
221. Koyama M, Sawada A, Yasui M, Inoue M and Kawa K: Encouraging results of low-dose etoposide in the treatment of early-onset hemophagocytic syndrome following allogeneic hematopoietic stem cell transplantation. Int J Hematol 86: 466-467, 2007.
222. Ono R, Ashiarai M, Hirabayashi S, Mizuki K, Hosoya Y, Yoshihara H, Ohtake J, Mori S, Manabe A and Hasegawa D: Ruxolitinib for hematopoietic cell transplantation-associated hemophagocytic lymphohistiocytosis. Int J Hematol 113: 297-301, 2021.
223. Janka GE: Familial hemophagocytic lymphohistiocytosis. Eur J Pediatr 140: 221-230, 1983.
224. Messina C, Zecca M, Fagioli F, Rovelli A, Giardino S, Merli P, Porta F, Aricò M, Sieni E, Basso G, *et al*: Outcomes of children with hemophagocytic lymphohistiocytosis given allogeneic hematopoietic stem cell transplantation in italy. Biol Blood Marrow Transplant 24: 1223-1231, 2018.