Brief Reviews

Update in Hyperferritinemic Syndromes: Recognition and Management - A Scoping Review

Athanasios Vassilopoulos, MD[1], Winston McCormick[2], Alisha Lakhani, MD[3]

[1] Division of Infectious Diseases, Department of Medicine, Warren Alpert Medical School at Brown University; Co-first author, [2] Warren Alpert Medical School at Brown University; Co-first author, [3] Division of Rheumatology, Department of Medicine, Harvard University School of Medicine

Keywords: hyperferritinemic, hemophagocytic lymphohistiocytosis, macrophage activation syndrome, catastrophic antiphospholipid syndrome, septic shock, adult-onset Still's Disease, multi- inflammatory syndrome

https://doi.org/10.56305/001c.37667

Vol. 1, Issue 3, 2022

Elevated serum ferritin is a marker of macrophage activation and is associated with increased mortality. The hyperferritinemic syndromes which include hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), catastrophic antiphospholipid syndrome (CAPS), septic shock, adult-onset Still's Disease (AOSD), and multi-inflammatory syndrome related to COVID-19 (MIS-C/A) are characterized by intense inflammation and its sequalae. Prompt recognition and management of these heterogenous disorders is required to improve patient outcomes. We perform a scoping review of the existing literature on the key features of these rare syndromes.

INTRODUCTION

Ferritin is an iron storage shell protein composed of 24 light (FTL) or heavy (FTH) ferritin monomers synthesized and stored in hepatocytes.[1] Even though FTL is the most common monomer, the FTL to FTH ratio differs depending on tissue and is dynamic.[2] Serum ferritin is a well-known acute-phase reactant. Its levels reflect macrophage immune response and the degree of acute and chronic inflammation. In general, serum ferritin has a high ratio of FTL to FTH.[2–4]

Ferritin participates in host immune responses. FTH increases in inflammatory settings and has many immunomodulatory properties.[5,6] Its immunomodulatory effects include induction of the anti-inflammatory cytokine interleukin-10 (IL-10), suppression of lymphopoiesis type IV hypersensitivity reaction, induction of T-cell anergy and a decrease in antibody production.[7–10]

Normal ferritin levels range between 12 and 300 ng/mL for men and between 12 and 150 ng/mL for women. High levels of serum ferritin have been reported in various acute or chronic inflammatory conditions including infectious, rheumatologic, hematologic, and malignant diseases. Hyperferritinemia in general is considered a marker of macrophage activation and is associated with high mortality.[11] During the hyperferritinemic state, reticuloendothelial system activation, combined with elevated cytokine levels can lead to multiple organ dysfunction via induction of inflammatory pathways.[12–14]

Hyperferritinemia, defined as serum ferritin above 500 ng/mL, can be seen in hemophagocytic lymphohistiocytosis (HLH) and its secondary subcategory, macrophage activation syndrome (MAS), catastrophic antiphospholipid syndrome (CAPS), septic shock, adult-onset Still's Disease (AOSD), and more recently multi-inflammatory syndrome related to COVID-19 (MIS-C/A).[15–17]

Diagnosis and management of hyperferritinemic syndromes may be challenging due to their rarity, which may delay diagnosis. Therapeutic options are often empiric. In this review we outline key aspects of these conditions to aid clinicians in both recognition and management.

METHODS

This scoping review was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) checklist. We searched for English-language published studies in MEDLINE (up to July 31, 2022), discovered through multiple search queries specifying for "Macrophage activation syndrome" OR "MAS", "Hemophagocytic lymphohistiocytosis" OR "HLH", "Sepsis" OR "Shock" OR "Septic shock", "catastrophic antiphospholipid syndrome" OR "CAPS", "Still's Disease" OR "Adult Onset Still's Disease" OR "AOSD", "Multisystem inflammatory syndrome" OR "MIS-C" OR "MIS-A", and "Hyperferritinemia" OR "Hyperinflammatory syndrome" OR "Hyperinflammation" to capture remaining studies not discovered by searches specifying clinical conditions/syndromes.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) AND MACROPHAGE ACTIVATION SYNDROME (MAS)

HLH is a rare, life-threatening condition that is divided into primary and secondary subtypes. Genetic mutations which impair the function of natural killer (NK) and cytotoxic T cells cause primary HLH, a condition that typically presents in infancy and childhood.[18] Some mutations in gene loci that are associated with familial HLH can cause late-onset primary HLH in adults.[19] The most common causes of secondary HLH include infections, autoimmune diseases and malignancies.[20]

Regarding infections, certain viral, particularly Epstein–Barr virus (EBV), bacterial, fungal or parasitic infections can cause hyperferritinemia and secondary HLH.[21–28] Most commonly it is seen in children with the systemic form of juvenile idiopathic arthritis (sJIA), and its adult form, AOSD.[29–31] Other causes of MAS include systemic lupus erythematosus (SLE), Kawasaki disease, rheumatoid arthritis, and various rheumatologic diseases.[32–36] Malignancy-associated HLH is seen mainly in adults with hematologic malignancies such as T cell leukemias and lymphomas (0.9%-1.3%).[37,38] A higher rate has been reported in Japanese and Eastern Asian origin patients.[39]

Most of our understanding on the pathophysiology of HLH/MAS is derived from findings on primary HLH and familial subtypes. It is thought that NK cells and cytotoxic CD8 T cells become unable to lyse infected or otherwise activated antigen-presenting cells (APCs). Prolonged interactions between activated white blood cells thus lead to the amplification of the pro-inflammatory cytokine cascade. This loss-of-function of NK and cytotoxic T cells is further worsened under hypercytokinemic state.[18,40] TNF-α, IFN-γ, IL-1, IL-10, IL-12, IL-18, M-CSF and particularly IL-6 play a significant role.[12,13,41–45] Eventually, activated macrophages cause hemophagocytosis, resulting in multi-organ dysfunction.

There are limited epidemiological data on the incidence of HLH/MAS. The annual incidence of HLH in children and adults was determined to be 1 per 800,000 at a nationwide survey in Japan.[46] HLH diagnosis in pediatric patients is close to 1 case per 3000 admissions.[47]

As a result of immune dysregulation, HLH/MAS usually presents with a wide spectrum of clinical features.[48] Diagnostic criteria for HLH diagnosis in children were developed per the HLH-2004 protocol, and are shown in **Table 1**.[48] These criteria are also commonly used for HLH diagnosis in adults. Notably, some clinical manifestations that are regularly observed in adults are excluded from these criteria, such as elevated transaminases, especially AST (aspartate aminotransferase), elevated serum D-dimer and abnormal coagulation labs, elevated LDH (lactate dehydrogenase) and CRP (C-reactive protein) levels, hyponatremia, maculopapular rash, and neurologic abnormalities. Neurologic manifestations can be seen in one-third of patients including seizures, altered mental status, ataxia, and posterior reversible encephalopathy syndrome (PRES).[49–51]

Results of sIL2r (soluble CD-25) levels and NK cell activity are not usually available expeditiously, and assays of heterozygous allele mutation do not always have specific or measurable clinical significance. In contrast to these shortcomings, the Hscore shown in **Table 2**, generates a probability for an HLH diagnosis without considering the sIL2r levels and NK cell activity. By setting a cutoff of 168, Hscore appears to have slightly superior diagnostic accuracy (100% sensitivity, 94.1% specificity) compared to the HLH-2004 diagnostic criteria in adults (95% sensitivity, 93.6% specificity).[52]

It is more challenging to diagnose MAS in rheumatologic diseases, as there is a high rate of overlap between clinical features of underlying disease and MAS. Especially, acute sJIA is difficult to differentiate from MAS.[53] In such cases, the newer 2016 classification criteria for MAS in sJIA (**Table 3**) is used for assisting in the diagnosis.

The role of ferritin levels in the diagnosis of primary or secondary HLH is crucial. In children with primary HLH, ferritin levels greater than 500, 5,000, and 10,000 ng/mL were seen in 93%, 42%, and 25% of patients, respectively.[54,55] Ferritin levels >3,000 ng/mL should raise high clinical suspicion of HLH/MAS.[47,56]

Treatment guidelines for HLH/MAS are mainly based on the HLH-94 protocol and its modified recommendations, the HLH-2004 protocol.[48,54,55,57] Generally, in cases of mild severity the first therapeutic step is high-dose glucocorticoids and treatment of the underlying condition.[48,55,57] This is particularly important for infectious causes since an early diagnosis of infection and empirical initiation of ap-

Table 1. HLH-2004 diagnostic criteria

Diagnostic criteria (5 out of 8 required)
Cytopenias (affecting ≥2 of 3 lineages in peripheral blood) *
Fever ≥38.5°C
Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides >265 mg/dL, fibrinogen <150 mg/dL
Ferritin >500 ng/mL
Splenomegaly
Low or absent NK cell activity
Elevated soluble CD25 sIL2R (>2,400 U/mL)
Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver

*hemoglobin <9 g/dL (for infants <4 weeks, hemoglobin <10 g/dL); platelets <100,000/microL; absolute neutrophil count <1000/microL

Table 2. Elements of the H Score

Known underlying immunosuppression	Yes/No
Temperature	<38.4°C 38.4-39.4°C ≥39.5°C
Organomegaly	None Hepatomegaly OR splenomegaly Hepatomegaly AND splenomegaly
Cytopenia	of 1 lineage of 2 lineages of 3 lineages
Ferritin	<2000 ng/mL 2000-6000 ng/mL >6000 ng/mL
Triglycerides	<1.5 mmol/L 1.5-4.0 mmol/L >4.0 mmol/L
Fibrinogen	>2.5 g/L ≤2.5 g/L
AST	<30 IU/L ≥30 IU/L

AST - aspartate aminotransferase

Table 3. 2016 Classification criteria for MAS in sJIA patients

Fever	
Ferritin	>684 ng/mL
2 of the following:	
Thrombocytopenia	≤181 x 10^9/L
AST	>48 IU/L
Triglycerides	>156 mg/dL
Fibrinogen	≤360 mg/dL

AST - aspartate aminotransferase, MAS – macrophage activation syndrome, sJIA – juvenile rheumatoid arthritis

propriate antimicrobial treatment may reverse the disease course. In active EBV infection, treatment with rituximab is also an option.[58] Increased immunosuppression for the underlying disease may be useful for rheumatologic patients with MAS.

For acutely ill patients, induction therapy consists of a series of weekly treatments with dexamethasone and etoposide and, possibly, the addition of cyclosporine.[48,55,57] In patients with liver failure, treatment with alemtuzumab rather than etoposide may be preferable due to concerns of hepatotoxicity. Patients with central nervous system manifestations after 2 weeks of treatment might be eligible for intrathecal methotrexate and hydrocortisone treatment. Patients with lymphoma-associated HLH may benefit from cyclophosphamide, adriamycin, vincristine, and prednisolone (CHOP) chemotherapy in addition to etoposide.[59]

Etoposide use is a risk factor for development of acute myeloid leukemia and myelodysplastic syndromes in later life. To avoid these adverse effects, an alternative treatment option is intravenous immunoglobulin (IVIG) with or without glucocorticoids especially in patients with underlying rheumatologic diseases.[60] In critically ill patients with autoimmune diseases who develop MAS, cyclosporine and other immunosuppresants (e.g. anakinra) along with glucocorticoids are regularly chosen and etoposide is avoided. Anakinra an interleukin-1 antagonist, can also be used in those with sJIA-associated MAS.[61] There is also an ongoing phase II trial evaluating emapalumab (IFNγ blocking antibody) for MAS associated with sJIA.[62]

Guidelines do not exist for relapsed or refractory HLH. Patients with relapse, refractory, central nervous system disease or primary HLH are usually continued on standard protocol therapy until allogeneic hematopoietic cell transplantation is undertaken. The only available treatment option, other than clinical trials, is emapalumab plus dexamethasone with favorable efficacy and toxicity aspects.[63] Promising treatment options include a combination of doxorubicin, etoposide and glucocorticoids (DEP) as salvage therapy, the JAK2 inhibitor ruxolitinib and IL-6 blockade in patients with cytokine release syndrome (CRS), plasma exchange and splenectomy in patients with splenomegaly.[64–67] HLH remains a rare syndrome with poor prognosis despite early intervention. The reported overall mortality of HLH ranges from 20.4% to 88% in treated populations with variable baseline characteristics and length of follow up.[68] Survival is worse in patients with malignancy-associated HLH compared with patients with non–malignancy-associated HLH. Ferritin level > 50,000 is a poor predictor for 30-day mortality.[69] Of note, slower rates of decline in serum ferritin during treatment are a poor prognostic factor. Less than a 50% decrease during the first three weeks of therapy is associated with a higher mortality than a ferritin decrease ≥96%.[70]

Table 4. CAPS diagnostic criteria (All 4 required)

Multiorgan involvement (>3 organs/tissues/systems)
Synchronous clinical manifestations or within a week
Histopathological confirmation of small-vessel occlusion
Positive antiphospholipid antibodies

CAPS- catastrophic antiphospholipid syndrome

CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME (CAPS)

CAPS is characterized by disseminated thrombotic vascular events in multiple organs in patients with underlying antiphospholipid syndrome (APS) leading to acute multi-organ failure.[71] Its prevalence in patients with APS is <1%, and it affects mainly women (72%) with a mean age of 39 years.[72] Recent surgery and infections are usual triggers in genetically predisposed patients. This condition has high morbidity and mortality (30-50%).

Patients present with almost simultaneous (within a week) multiple organ involvement and positive antiphospholipid antibodies. The clinical presentation depends on the affected organs and systems.[72] These include renal insufficiency and hypertension (kidney), ischemic ulcers, gangrene or livedo reticularis (skin), ischemic cerebrovascular events (brain), ischemic hepatitis (liver), acute respiratory failure from hemorrhage, pulmonary embolism or ARDS (lungs), myocardial infarction (heart). Typical laboratory findings include thrombocytopenia, hemolytic anemia and increased creatinine levels in the presence of antiphospholipid antibodies. Biopsy confirmation of thrombotic microangiopathy is required.

The diagnostic criteria for CAPS, as shown in **Table 4**, require the exclusion of other causes of multiple microthromboses.[73] The differential diagnosis includes disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), heparin-induced thrombocytopenia (HIT), sepsis, or systemic vasculitis.[73] CAPS should also be differentiated from HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets syndrome) in pregnant patients.

Hyperferritinemia was present in 71% of CAPS patients with mean levels higher than those seen in patients with APS alone (816 *vs.* 120 ng/mL). Approximately one third of CAPS patients had very high levels of ferritin (>1000 ng/mL).[74] Release of many pro-inflammatory cytokines, mainly IL-1, IL-6 and TNF from occluded micro-vessels during CAPS is the presumed pathogenetic mechanism leading to non-thrombotic manifestations such as ARDS.

Treatment of CAPS is directed at preventing further thrombosis with anticoagulation (heparin), removal of

pathogenic anti-phospholipid antibodies with plasma exchange and cytokine cascade suppression with immunemodulatory/suppressive therapies such as systemic glucocorticoids, cyclophosphamide or IVIG.[75] When suspecting acute infection, appropriate antibiotics should be given.

In patients with CAPS resistant to first-line therapy, treatment with rituximab or eculizumab may have positive outcomes.[72,76,77] It has been shown that activation of complement is required for APS to develop in mouse models.[78] C5a interaction with its receptor results in inflammation, placental insufficiency, and thrombosis. Moreover, in these models, anti-C5 antibody (same mechanism of action as eculizumab) prevent pregnancy loss and thrombosis.

In terms of prognosis, triple therapy with therapeutic anticoagulation, glucocorticoids, plasma exchange and/or IVIG resulted in a higher chance of survival compared with no treatment or treatment with other regimens (adjusted OR = 9.7 and 1.7 respectively).[79]

SEPTIC SHOCK

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.[80] Immune activation in response to infection causes the release of both pro-inflammatory and anti-inflammatory cytokines with variable clinical significance of both.

The clinical presentation of sepsis depends on the infectious cause, primary site of infection and the clinical features of immune response. Non-specific findings, such as abnormal vital signs, and altered mental status are common. In the skin, livedo reticularis can be observed. Regarding laboratory findings, elevated lactate levels (especially in septic shock), leukocytosis or leukopenia, elevated CRP and abnormal urinary and liver function tests can be seen.

Sepsis and septic shock with increased serum ferritin levels is observed more commonly in patients infected with DNA viruses, parasites, intracellular bacteria, fungi or in patients that have undergone transfusions or have suffered from hemolysis. Therefore, workup should be oriented more towards these causes. During infection, ferritin is produced by macrophages as a result of interleukin IL–1 and TNF-α induced nuclear factor kappa B (NF-κβ) activation.[81] As a result, further immune dysregulation is expected. Ferritin levels above 4420 ng/mL have been associated with an increase of IL-6, IL-18, INF-γ, and sCD163 and a decrease of the IL-10/TNF-α ratio, indicating a heightened pro-inflammatory response.[82]

Median serum ferritin levels of 371.5 ng/mL, 892.2 ng/mL, and 1784.9 ng/mL during the stages of sepsis, severe sepsis or septic shock, and multiple organ dysfunction syndrome (MODS), respectively, have been reported.[83] Ferritin levels have also been associated with higher mortality rate in pediatric patients with severe sepsis or septic shock.[84] Additionally, ferritin levels of septic pediatric patients in need of mechanical intubation for >48 hours were associated with disease severity.[85] Patients with elevated levels (⩾300 ng/mL) had fewer hours off ventilation and required more inotropic medications.

In patients with influenza A infection, ferritin levels demonstrate a negative predictive value that might be useful in excluding the chance of developing serious complications. Levels ≥500 ng/mL show sensitivity of 57% and specificity of 83%, which could go up to 95% if the ferritin level cut-off was >955 ng/mL, for serious complications.[86]

Sepsis and septic shock treatment in general, consists of resuscitation measures with the use of intravenous fluids, vasopressors, oxygen therapy, possibly mechanical ventilation, and appropriate empirical antimicrobial therapy as well as rapid source control. However, in a state of elevated pro-inflammatory response, like the one in hyperferritinemic patients, further medications may be needed.[82] There remains uncertainty regarding the use of glucocorticoids in sepsis and septic shock. Glucocorticoids may counteract the excessive pro-inflammatory response present in sepsis. Part of the immune dysregulation in sepsis is also the dysfunction of the hypothalamic–pituitary–adrenal axis and glucocorticoid resistance in tissue.[87] Trials of glucocorticoid treatment have reported contradicting data regarding 90-day mortality.[88] For hyperferritinemic sepsis, however, increased survival rates are seen in patients with septic shock treated with glucocorticoids (methylprednisolone), IVIG, plasma exchange.[89] Anakinra has been tested in septic patients with features of MAS.[61] Treatment with anakinra was associated with a higher rate of 28-day survival (65.4%) compared with placebo (35.3%).

ADULT-ONSET STILL'S DISEASE (AOSD)

AOSD is a rare inflammatory condition that is considered to be autoimmune in origin, although the true pathophysiology remains elusive.[90] Current suggestions towards the etiology include macrophage activation and Th1 cytokines.[90] The incidence is estimated to be less than 1:100,000 individuals in the United States.[91] A rare clinical diagnosis of exclusion, the hallmarks of AOSD include quotidian fever, polyarthritis, and a mixed erythematous or salmon-colored maculopapular, patchy rash that covers the extremities and trunk.[90–92] Although not universal, sore throat and general arthralgias are extremely common. Systemic symptoms, particularly fever, are typically found.[91] AOSD accounts for up to 20% of fevers of unknown origin.[91,92] Lymphadenopathy, particularly cervical lymphadenopathy, is common. Lymph nodes in AOSD are often avidly enhancing on 18FDG-PET scans. A clinician might expect to find hepatosplenomegaly.[90–92]

In addition, on laboratory studies, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are uniformly elevated. LFT abnormalities and anemia of inflammation are common findings. Significant leukocytosis (e.g., >15,000/mm^3) may be found with neutrophilic predominance. AOSD will often present with negative ANA and RF labs, if obtained. Ferritin is typically elevated as well; one retrospective review of 57 patients revealed a mean ferritin of 8745 (range 84-130,000). Elevated serum ferritin levels higher than five times the upper limits of normal if combined w/ a decrease in the proportion of glycostylated ferritin (<20%) increase the specificity of AOSD to 93%.[90–92]

The Yamaguchi criteria are the most commonly used criteria for diagnosis (**Table 5**).[93] Notably, hyperferritinemia is absent. In addition, the disease is further classified among the three following categories: a monocyclic pattern, a

Table 5. Yamaguchi criteria. (To diagnose AOSD, at least five (5) of the criteria must be met, with at least two (2) coming from the major criteria)

Major Criteria	Minor Criteria
Fever >39C for >1 week	Sore throat
Arthralgia/arthritis >2 weeks	Recent onset lymphadenopathy
Typical salmon evanescent rash	Hepatosplenomegaly
Leukocytosis >10,000/mm^3 with >80% polymorphonuclear cells	Negative serum ANA or RF
	Abnormal liver function tests

ANA – antinuclear antigen, RF – rheumatoid factor

polycyclic pattern where flares last < 1 year each, and a chronic pattern.[90]

Despite multiple complications from AOSD flares, prognosis is generally good, with an estimated mortality from AOSD itself being approximately 16% of affected individuals, typically due to transformation to the MAS.[90,92] First-line treatments remain empiric and consist primarily of glucocorticoids.[90–92] Methotrexate is a second-line treatment. Multiple trials are ongoing to examine the role of individual biologic anti-cytokine therapies, in particular IL-1, IL-18, and TNF-a.[90] In 2020, the FDA approved canakinumab, an IL-1 inhibitor, and the first agent approved specifically to treat AOSD.[94]

MULTI-SYSTEM INFLAMMATORY SYNDROME OF COVID-19 (MIS)

The COVID-19 pandemic has demonstrated the appearance of MIS, a new Kawasaki-like syndrome that affects primarily children and adolescents exposed to SARS-CoV-2, the virus that causes COVID-19, and who have typically resolved infection, up to several weeks after exposure. Its exact etiology is unknown, but it is hypothesized that it represents a hyper-immune response by the immature immune systems of these individuals to SARS-CoV-2 antigens.[95,96] Due to the novelty of this condition, its incidence is unknown.[96]

MIS-A, occuring in adults, is assumed to be a distinct clinical entity with increased severity and co-morbidities, but it is otherwise similar in presentation, management, and laboratory studies to MIS-C.[96] For example, diagnostic criteria for MIS-A include severe acute cardiac illness or dysfunction and encephalopathy, which may be seen in MIS-C with less severity.

Patient presentation for MIS-C/A uniformly includes fever. Exposure to SARS-CoV-2 might not be evident by history alone, and patients very often have positive antibodies to this virus. Cardiac involvement at presentation is typical, with tachycardia and hypotension being the most common presenting pathophysiologic manifestations.[97] Respiratory distress may occur as the disease progresses but has not been found to be the primary initial manifestation in most cases. Patients often present with acute gastrointestinal symptoms, rash and mucocutaneous injection, including the conjunctiva as seen in Kawasaki's disease.

Laboratory findings for MIS-C/A include elevated CRP and often elevated ESR. The patient will usually have a mild hyponatremia and leukopenia. Signs of coagulopathy (specifically elevated D-dimer and increased PT/INR, PTT) will be seen. Other inflammatory markers, such as procalcitonin and ferritin, are elevated in a majority of cases.[95–97] Cases typically present with a serum ferritin >10,000 ng/dL, but the prognostic value is unclear.[98]

MIS-C/A typically requires ICU admission. IVIG is the treatment of choice, and glucocorticoids are often used in conjunction. Infliximab (TNFa), anakinra (IL-1), and IL-6 inhibitors have also been used with less frequency and less success.[96] Despite the severity of the condition, with treatment the mortality of MIS-C is approximately 1.5%.[95] Cardiology follow-up is warranted when cardiac involvement is present.[97]

OTHER CAUSES OF HYPERFERRITINEMIA

As ferritin is a marker of acute inflammation, markedly elevated ferritin levels >1000 ng/dL may be seen, occasionally and intermittently, in a variety of other conditions, particularly in acute phases. However, and by contrast to the aforementioned syndromes, conditions where hyperferritinemia might be found are not characterized as hyperferritinemic syndromes.

Lymphomas might demonstrate hyperferritinemia, and some research has indicated that higher levels of ferritin at diagnosis correlate with worse prognosis.[99] Hyperferritinemia may be seen in liver disease.[100,101] Ferritin is stored in hepatocytes, and as such, elevated ferritin might be considered a marker of hepatic necrosis. In addition to diseases of hepatocyte injury and destruction, hereditary hemochromatosis, the familial disease of iron overload, can be characterized by ferritin levels >1000 ng/dL when not regularly treated with phlebotomy.[101]

DISCUSSION

The hyperferritinemic syndromes are characterized by definition as having serum ferritin levels elevated to >500 ng/dL being a reliable, characteristic finding of the syndrome.[15] Though limited in number, the hyperferritinemic syndromes represent diseases across a wide swath of medical and pediatric specialties. The central tenet is that hyperferritinemic syndromes are syndromes of intense systemic inflammation. Hence, the serum ferritin is often elevated above 1,000 ng/dL in these syndromes and may occasionally be elevated above 10,000 ng/dL.[47]

The unifying thread is that each syndrome is marked by severe inflammation and that treatment is based upon addressing the underlying cause or when that is unknown, targeting the immune system through various treatment modalities.

A new hyperferritinemic syndrome has emerged in the COVID-19 pandemic, MIS-C/A, and in must be considered in the context of the other hyperferritinemic syndromes: HLH, cAPS, AOSD, and septic shock. Significant advancement has been made in the development of disease-directed therapy in the last decade, but curative disease-specific

treatment remains elusive.[62,63,72] What's more, it has been suggested that high levels of ferritin may play a role in disease pathogenesis, thus understanding the pathologic response to one syndrome may lead to better management of all.[15]

More studies are needed to elucidate the common role of ferritin in the pathogenesis of these syndromes or as a prognostic indicator for these syndromes, if any such role exists. Furthermore, clinicians should remember that ferritin is an acute phase reactant and should consider it alongside ESR and CRP to both diagnose and monitor response to treatment in specific inflammatory syndromes.

CONCLUSION

Hyperferritinemic syndromes are rare diseases that are challenging to diagnose and treat. MIS-A/C, hyperinflammatory complications of COVID-19 should be added to the hyperferritinemic syndromes. High levels of ferritin help with diagnosis and provide information about prognosis. Immunomodulatory treatment, including corticosteroids, are useful in all hyperferritinemic syndromes because of the noted heightened pro-inflammatory response. Additional treatment regimens depend on the underlying cause and disease severity. The proposed association of high levels of ferritin with disease pathogenesis needs further assessment in order to improve patient outcomes.

DISCLOSURES/CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

FUNDING

None

CORRESPONDING AUTHOR

Athanasios Vassilopoulos
Division of Infectious Diseases, Department of Medicine, Warren Alpert Medical School of Brown University, Providence, RI
The Miriam Hospital
164 Summit Avenue, Providence, RI
Email: avassilopoulos@lifespan.org
ORCID: 0000-0002-5859-1232

Submitted: July 12, 2022 EDT, Accepted: August 15, 2022 EDT

REFERENCES

1. Harrison PM, Arosio P. The ferritins: molecular properties, iron storage function and cellular regulation. *Biochim Biophys Acta*. 1996;1275(3):161-203. doi:10.1016/0005-2728(96)00022-9

2. Cragg SJ, Wagstaff M, Worwood M. Detection of a glycosylated subunit in human serum ferritin. *Biochem J*. 1981;199(3):565-571. doi:10.1042/bj1990565

3. Vignes S, Le Moël G, Fautrel B, Wechsler B, Godeau P, Piette JC. Percentage of glycosylated serum ferritin remains low throughout the course of adult onset Still's disease. *Ann Rheum Dis*. 2000;59(5):347-350. doi:10.1136/ard.59.5.347

4. Lambotte O, Cacoub P, Costedoat N, Le Moel G, Amoura Z, Piette JC. High ferritin and low glycosylated ferritin may also be a marker of excessive macrophage activation. *J Rheumatol*. 30(5):1027-1028.

5. Weis S, Carlos AR, Moita MR, et al. Metabolic Adaptation Establishes Disease Tolerance to Sepsis. *Cell*. 2017;169(7):1263-1275.e14. doi:10.1016/j.cell.2017.05.031

6. Ruscitti P, Cipriani P, Di Benedetto P, et al. H-ferritin and proinflammatory cytokines are increased in the bone marrow of patients affected by macrophage activation syndrome. *Clin Exp Immunol*. 2018;191(2):220-228. doi:10.1111/cei.13057

7. Gray CP, Arosio P, Hersey P. Heavy chain ferritin activates regulatory T cells by induction of changes in dendritic cells. *Blood*. 2002;99(9):3326-3334. doi:10.1182/blood.v99.9.3326

8. Broxmeyer HE, Mantel C, Gentile P, et al. Actions of H-subunit ferritin and lactoferrin as suppressor molecules of myelopoiesis in vitro and in vivo. *Curr Stud Hematol Blood Transfus*. 1991;(58):178-181. doi:10.1159/000419358

9. Li R, Luo C, Mines M, Zhang J, Fan GH. Chemokine CXCL12 induces binding of ferritin heavy chain to the chemokine receptor CXCR4, alters CXCR4 signaling, and induces phosphorylation and nuclear translocation of ferritin heavy chain. *J Biol Chem*. 2006;281(49):37616-37627. doi:10.1074/jbc.m607266200

10. Hann HW, Stahlhut MW, Lee S, London WT, Hann RS. Effects of isoferritins on human granulocytes. *Cancer*. 1989;63(12):2492-2496. doi:10.1002/1097-0142(19890615)63:12

11. Bennett TD, Hayward KN, Farris RWD, Ringold S, Wallace CA, Brogan TV. Very high serum ferritin levels are associated with increased mortality and critical care in pediatric patients. *Pediatr Crit Care Med*. 2011;12(6):e233-e236. doi:10.1097/pcc.0b013e31820abca8

12. Maruyama J, Inokuma S. Cytokine profiles of macrophage activation syndrome associated with rheumatic diseases. *J Rheumatol*. 2010;37(5):967-973. doi:10.3899/jrheum.090662

13. Girard-Guyonvarc'h C, Palomo J, Martin P, et al. Unopposed IL-18 signaling leads to severe TLR9-induced macrophage activation syndrome in mice. *Blood*. 2018;131(13):1430-1441. doi:10.1182/blood-2017-06-789552

14. Weiss ES, Girard-Guyonvarc'h C, Holzinger D, et al. Interleukin-18 diagnostically distinguishes and pathogenically promotes human and murine macrophage activation syndrome. *Blood*. 2018;131(13):1442-1455. doi:10.1182/blood-2017-12-820852

15. Rosário C, Zandman-Goddard G, Meyron-Holtz EG, D'Cruz DP, Shoenfeld Y. Shoenfeld Y. The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. *BMC Med*. 2013;11(1):185. doi:10.1186/1741-7015-11-185

16. Abrams JY, Oster ME, Godfred-Cato SE, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. *Lancet Child Adolesc Health*. 2021;5(5):323-331. doi:10.1016/s2352-4642(21)00050-x

17. Patel P, DeCuir J, Abrams J, Campbell AP, Godfred-Cato S, Belay ED. Clinical Characteristics of Multisystem Inflammatory Syndrome in Adults: A Systematic Review. *JAMA Netw Open*. 2021;4(9):e2126456. doi:10.1001/jamanetworkopen.2021.26456

18. Jenkins MR, Rudd-Schmidt JA, Lopez JA, et al. Failed CTL/NK cell killing and cytokine hypersecretion are directly linked through prolonged synapse time. *J Exp Med*. 2015;212(3):307-317. doi:10.1084/jem.20140964

19. Zhang K, Jordan MB, Marsh RA, et al. Hypomorphic mutations in PRF1, MUNC13-4, and STXBP2 are associated with adult-onset familial HLH. *Blood*. 2011;118(22):5794-5798. doi:10.1182/blood-2011-07-370148

20. Lehmberg K, Sprekels B, Nichols KE, et al. Malignancy-associated haemophagocytic lymphohistiocytosis in children and adolescents. *Br J Haematol*. 2015;170(4):539-549. doi:10.1111/bjh.13462

21. Smith MC, Cohen DN, Greig B, et al. The ambiguous boundary between EBV-related hemophagocytic lymphohistiocytosis and systemic EBV-driven T cell lymphoproliferative disorder. *Int J Clin Exp Pathol*. 2014;7(9):5738-5749.

22. Drori A, Ribak Y, van Heerden PV, Meir K, Wolf D, Safadi R. Hemophagocytic lymphohistiocytosis due to acute primary herpes simplex virus 1 infection. *J Clin Virol*. 2015;68:6-10. doi:10.1016/j.jcv.2015.04.013

23. van der Ven AJAM, Netea MG, van der Meer JWM, de Mast Q. Ebola Virus Disease has Features of Hemophagocytic Lymphohistiocytosis Syndrome. *Front Med*. 2015;2(4). doi:10.3389/fmed.2015.00004

24. Hui YMT, Pillinger T, Luqmani A, Cooper N. Haemophagocytic lymphohistiocytosis associated with Mycobacterium tuberculosis infection. *BMJ Case Rep*. 2015;2015. doi:10.1136/bcr-2014-208220

25. Naoi T, Morita M, Kawakami T, Fujimoto S. Hemophagocytic Lymphohistiocytosis Associated with Scrub Typhus: Systematic Review and Comparison between Pediatric and Adult Cases. *Trop Med Infect Dis*. 2018;3(1):19. doi:10.3390/tropicalmed3010019

26. Untanu RV, Akbar S, Graziano S, Vajpayee N. Histoplasmosis-Induced Hemophagocytic Lymphohistiocytosis in an Adult Patient: A Case Report and Review of the Literature. *Case Rep Infect Dis*. 2016;2016(1358742):1-5. doi:10.1155/2016/1358742

27. Sung PS, Kim IH, Lee JH, Park JW. Hemophagocytic Lymphohistiocytosis (HLH) Associated with*Plasmodium vivax*Infection: Case Report and Review of the Literature. *Chonnam Med J*. 2011;47(3):173. doi:10.4068/cmj.2011.47.3.173

28. Colomba C, Di Carlo P, Scarlata F, et al. Visceral leishmaniasis, hypertriglyceridemia and secondary hemophagocytic lymphohistiocytosis. *Infection*. 2016;44(3):391-392. doi:10.1007/s15010-016-0881-3

29. Behrens EM, Beukelman T, Paessler M, Cron RQ. Occult macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis. *J Rheumatol*. 2007;34(5):1133-1138.

30. Moradinejad MH, Ziaee V. The incidence of macrophage activation syndrome in children with rheumatic disorders. *Minerva Pediatr Dec*. 2011;63(6):459-466.

31. Lenert A, Yao Q. Macrophage activation syndrome complicating adult onset Still's disease: A single center case series and comparison with literature. *Semin Arthritis Rheum*. 2016;45(6):711-716. doi:10.1016/j.semarthrit.2015.11.002

32. Gavand PE, Serio I, Arnaud L, et al. Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: A study of 103 episodes in 89 adult patients. *Autoimmun Rev*. 2017;16(7):743-749. doi:10.1016/j.autrev.2017.05.010

33. Wafa A, Hicham H, Naoufal R, et al. Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: a study of 20 Moroccan adult patients. *Clin Rheumatol*. 2022;41(7):2021-2033. doi:10.1007/s10067-022-06055-9

34. Latino GA, Manlhiot C, Yeung RSM, Chahal N, McCrindle BW. Macrophage activation syndrome in the acute phase of Kawasaki disease. *J Pediatr Hematol Oncol*. 2010;32(7):527-531. doi:10.1097/mph.0b013e3181dccbf4

35. Oda Y, Urushidani Y, Ooi S, et al. Hemophagocytic lymphohistiocytosis in a rheumatoid arthritis patient treated with infliximab. *Intern Med*. 2012;51(6):655-657. doi:10.2169/internalmedicine.51.5687

36. Kishida D, Sakaguchi N, Ueno KI, et al. Macrophage activation syndrome in adult dermatomyositis: a case-based review. *Rheumatol Int*. 2020;40(7):1151-1162. doi:10.1007/s00296-020-04590-9

37. Machaczka M, Vaktnäs J, Klimkowska M, Hägglund H. Malignancy-associated hemophagocytic lymphohistiocytosis in adults: a retrospective population-based analysis from a single center. *Leuk Lymphoma*. 2011;52(4):613-619. doi:10.3109/10428194.2010.551153

38. Strenger V, Merth G, Lackner H, et al. Malignancy and chemotherapy induced haemophagocytic lymphohistiocytosis in children and adolescents—a single centre experience of 20 years. *Ann Hematol*. 2018;97(6):989-998. doi:10.1007/s00277-018-3254-4

39. Ferreri AJM, Dognini GP, Campo E, et al. Variations in clinical presentation, frequency of hemophagocytosis and clinical behavior of intravascular lymphoma diagnosed in different geographical regions. *Haematologica*. 2007;92(4):486-492. doi:10.3324/haematol.10829

40. Ruddell RG, Hoang-Le D, Barwood JM, et al. Ferritin functions as a proinflammatory cytokine via iron-independent protein kinase C zeta/nuclear factor kappaB-regulated signaling in rat hepatic stellate cells. *Hepatology*. 2009;49(3):887-900. doi:10.1002/hep.22716

41. Billiau AD, Roskams T, Van Damme-Lombaerts R, Matthys P, Wouters C. Macrophage activation syndrome: characteristic findings on liver biopsy illustrating the key role of activated, IFN-gamma-producing lymphocytes and IL-6- and TNF-alpha-producing macrophages. *Blood*. 2005;105(4):1648-1651. doi:10.1182/blood-2004-08-2997

42. Strippoli R, Carvello F, Scianaro R, et al. Amplification of the response to Toll-like receptor ligands by prolonged exposure to interleukin-6 in mice: implication for the pathogenesis of macrophage activation syndrome. *Arthritis Rheum*. 2012;64(5):1680-1688. doi:10.1002/art.33496

43. Behrens EM, Canna SW, Slade K, et al. Repeated TLR9 stimulation results in macrophage activation syndrome–like disease in mice. *J Clin Invest*. 2011;121(6):2264-2277. doi:10.1172/jci43157

44. Canna SW, Wrobel J, Chu N, Kreiger PA, Paessler M, Behrens EM. Interferon-γ mediates anemia but is dispensable for fulminant toll-like receptor 9-induced macrophage activation syndrome and hemophagocytosis in mice. *Arthritis Rheum*. 2013;65(7):1764-1775. doi:10.1002/art.37958

45. Yasin S, Fall N, Brown RA, et al. IL-18 as a biomarker linking systemic juvenile idiopathic arthritis and macrophage activation syndrome. *Rheumatology*. 2020;59(2):361-366. doi:10.1093/rheumatology/kez282

46. Ishii E, Ohga S, Imashuku S, et al. Nationwide survey of hemophagocytic lymphohistiocytosis in Japan. *Int J Hematol*. 2007;86(1):58-65. doi:10.1532/ijh97.07012

47. Allen CE, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2008;50(6):1227-1235. doi:10.1002/pbc.21423

48. Bergsten E, Horne A, Aricó M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. *Blood*. 2017;130(25):2728-2738. doi:10.1182/blood-2017-06-788349

49. Deiva K, Mahlaoui N, Beaudonnet F, et al. CNS involvement at the onset of primary hemophagocytic lymphohistiocytosis. *Neurology*. 2012;78(15):1150-1156. doi:10.1212/wnl.0b013e31824f800a

50. Horne A, Trottestam H, Aricò M, et al. Frequency and spectrum of central nervous system involvement in 193 children with haemophagocytic lymphohistiocytosis. *Br J Haematol*. 2008;140(3):327-335. doi:10.1111/j.1365-2141.2007.06922.x

51. Thompson PA, Allen CE, Horton T, Jones JY, Vinks AA, McClain KL. Severe neurologic side effects in patients being treated for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2009;52(5):621-625. doi:10.1002/pbc.21838

52. Knaak C, Nyvlt P, Schuster FS, et al. Hemophagocytic lymphohistiocytosis in critically ill patients: diagnostic reliability of HLH-2004 criteria and HScore. *Crit Care*. 2020;24(1):244. doi:10.1186/s13054-020-02941-3

53. Davì S, Minoia F, Pistorio A, et al. Performance of current guidelines for diagnosis of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. *Arthritis Rheumatol*. 2014;66(10):2871-2880. doi:10.1002/art.38769

54. Henter JI, Samuelsson-Horne A, Aricò M, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood*. 2002;100(7):2367-2373. doi:10.1182/blood-2002-01-0172

55. Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124-131. doi:10.1002/pbc.21039

56. Schram AM, Campigotto F, Mullally A, et al. Marked hyperferritinemia does not predict for HLH in the adult population. *Blood*. 2015;125(10):1548-1552. doi:10.1182/blood-2014-10-602607

57. La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood*. 2019;133(23):2465-2477. doi:10.1182/blood.2018894618

58. Chellapandian D, Das R, Zelley K, et al. Treatment of Epstein Barr virus-induced haemophagocytic lymphohistiocytosis with rituximab-containing chemo-immunotherapeutic regimens. *Br J Haematol*. 2013;162(3):376-382. doi:10.1111/bjh.12386

59. Shin HJ, Chung JS, Lee JJ, et al. Treatment outcomes with CHOP chemotherapy in adult patients with hemophagocytic lymphohistiocytosis. *J Korean Med Sci*. 2008;23(3):439-444. doi:10.3346/jkms.2008.23.3.439

60. Wohlfarth P, Agis H, Gualdoni GA, et al. Interleukin 1 Receptor Antagonist Anakinra, Intravenous Immunoglobulin, and Corticosteroids in the Management of Critically Ill Adult Patients With Hemophagocytic Lymphohistiocytosis. *J Intensive Care Med*. 2019;34(9):723-731. doi:10.1177/0885066617711386

61. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. *Crit Care Med*. 2016;44(2):275-281. doi:10.1097/ccm.0000000000001402

62. De Benedetti F, Grom AA, Brogan P, et al. Macrophage Activation Syndrome (MAS) in Systemic Juvenile Idiopathic Arthritis (sJIA): Treatment with Emapalumab, an Anti-Interferon Gamma (IFNγ) Monoclonal Antibody. *Blood*. 2021;138:2058. doi:10.1182/blood-2021-147596

63. Locatelli F, Jordan MB, Allen C, et al. Emapalumab in Children with Primary Hemophagocytic Lymphohistiocytosis. *N Engl J Med*. 2020;382(19):1811-1822. doi:10.1056/nejmoa1911326

64. Wang Y, Huang W, Hu L, et al. Multicenter study of combination DEP regimen as a salvage therapy for adult refractory hemophagocytic lymphohistiocytosis. *Blood*. 2015;126(19):2186-2192. doi:10.1182/blood-2015-05-644914

65. Ahmed A, Merrill SA, Alsawah F, et al. Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-centre, pilot trial. *Lancet Haematol*. 2019;6(12):e630-e637. doi:10.1016/s2352-3026(19)30156-5

66. Major A, Collins J, Craney C, et al. Management of hemophagocytic lymphohistiocytosis (HLH) associated with chimeric antigen receptor T-cell (CAR-T) therapy using anti-cytokine therapy: an illustrative case and review of the literature. *Leuk Lymphoma*. 2021;62(7):1765-1769. doi:10.1080/10428194.2021.1881507

67. Teachey DT, Rheingold SR, Maude SL, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. *Blood*. 2013;121(26):5154-5157. doi:10.1182/blood-2013-02-485623

68. Hayden A, Park S, Giustini D, Lee AYY, Chen LYC. Hemophagocytic syndromes (HPSs) including hemophagocytic lymphohistiocytosis (HLH) in adults: A systematic scoping review. *Blood Rev*. 2016;30(6):411-420. doi:10.1016/j.blre.2016.05.001

69. Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. *Am J Hematol*. 2015;90(3):220-224. doi:10.1002/ajh.23911

70. Lin TF, Ferlic-Stark LL, Allen CE, Kozinetz CA, McClain KL. Rate of decline of ferritin in patients with hemophagocytic lymphohistiocytosis as a prognostic variable for mortality. *Pediatr Blood Cancer*. 2011;56(1):154-155. doi:10.1002/pbc.22774

71. Rodríguez-Pintó I, Moitinho M, Santacreu I, et al. Catastrophic antiphospholipid syndrome (CAPS): Descriptive analysis of 500 patients from the International CAPS Registry. *Autoimmun Rev*. 2016;15(12):1120-1124. doi:10.1016/j.autrev.2016.09.010

72. López-Benjume B, Rodríguez-Pintó I, Amigo MC, et al. Eculizumab use in catastrophic antiphospholipid syndrome (CAPS): Descriptive analysis from the "CAPS Registry." *Autoimmun Rev*. 2022;21(4):103055. doi:10.1016/j.autrev.2022.103055

73. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med*. 2014;371(7):654-666. doi:10.1056/nejmra1312353

74. Agmon-Levin N, Rosário C, Katz BSP, et al. Ferritin in the antiphospholipid syndrome and its catastrophic variant (cAPS). *Lupus*. 2013;22(13):1327-1335. doi:10.1177/0961203313504633

75. Cervera R, Rodríguez-Pintó I, Legault K, Erkan D. 16th International Congress on Antiphospholipid Antibodies Task Force Report on Catastrophic Antiphospholipid Syndrome. *Lupus*. 2020;29(12):1594-1600. doi:10.1177/0961203320951260

76. Berman H, Rodríguez-Pintó I, Cervera R, et al. Rituximab use in the catastrophic antiphospholipid syndrome: descriptive analysis of the CAPS registry patients receiving rituximab. *Autoimmun Rev*. 2013;12(11):1085-1090. doi:10.1016/j.autrev.2013.05.004

77. Lonze BE, Singer AL, Montgomery RA. Eculizumab and renal transplantation in a patient with CAPS. *N Engl J Med*. 2010;362(18):1744-1745. doi:10.1056/nejmc0910965

78. Chaturvedi S, Braunstein EM, Yuan X, et al. Complement activity and complement regulatory gene mutations are associated with thrombosis in APS and CAPS. *Blood*. 2020;135(4):239-251. doi:10.1182/blood.2019003863

79. Rodríguez-Pintó I, Espinosa G, Erkan D, et al. The effect of triple therapy on the mortality of catastrophic anti-phospholipid syndrome patients. *Rheumatology*. 2018;57(7):1264-1270. doi:10.1093/rheumatology/key082

80. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801. doi:10.1001/jama.2016.0287

81. Simon DW, Halstead ES, Davila S, et al. DNA Viremia Is Associated with Hyperferritinemia in Pediatric Sepsis. *J Pediatr*. 2019;213:82-87.e2. doi:10.1016/j.jpeds.2019.06.033

82. Kyriazopoulou E, Leventogiannis K, Norrby-Teglund A, et al. Macrophage activation-like syndrome: an immunological entity associated with rapid progression to death in sepsis. *BMC Med*. 2017;15(1):172. doi:10.1186/s12916-017-0930-5

83. Nandy A, Mondal T, Datta D, et al. Serum Ferritin as a Diagnostic Biomarker for Severity of Childhood Sepsis. *Indian Pediatr*. 2021;58(12):1143-1146. doi:10.1007/s13312-021-2396-y

84. Garcia PCR, Longhi F, Branco RG, Piva JP, Lacks D, Tasker RC. Ferritin levels in children with severe sepsis and septic shock. *Acta Paediatr*. 2007;96(12):1829-1831. doi:10.1111/j.1651-2227.2007.00564.x

85. Tonial CT, Garcia PCR, Schweitzer LC, et al. Cardiac dysfunction and ferritin as early markers of severity in pediatric sepsis. *J Pediatr (Rio J)*. 2017;93(3):301-307. doi:10.1016/j.jped.2016.08.006

86. Lalueza A, Ayuso B, Arrieta E, et al. Elevation of serum ferritin levels for predicting a poor outcome in hospitalized patients with influenza infection. *Clin Microbiol Infect*. 2020;26(11):1557.e9-1557.e15. doi:10.1016/j.cmi.2020.02.018

87. Annane D, Pastores SM, Arlt W, et al. Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). *Intensive Care Med*. 2017;43(12):1781-1792. doi:10.1007/s00134-017-4914-x

88. Marik PE. The role of glucocorticoids as adjunctive treatment for sepsis in the modern era. *Lancet Respir Med*. 2018;6(10):793-800. doi:10.1016/s2213-2600(18)30265-0

89. Demirkol D, Yildizdas D, Bayrakci B, 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*. 2012;16(2):R52. doi:10.1186/cc11256

90. Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset Still's disease. *J Autoimmun*. 2018;93:24-36. doi:10.1016/j.jaut.2018.07.018

91. Mahroum N, Mahagna H, Amital H. Diagnosis and classification of adult Still's disease. *J Autoimmun*. 2014;48-49:34-37. doi:10.1016/j.jaut.2014.01.011

92. Gerfaud-Valentin M, Maucort-Boulch D, Hot A, et al. Adult-onset still disease: manifestations, treatment, outcome, and prognostic factors in 57 patients. *Medicine*. 2014;93(2):91-99. doi:10.1097/md.0000000000000021

93. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. *J Rheumatol*. 1992;19(3):424-430.

94. FDA Approves First Treatment for Adult Onset Still's Disease, a Severe and Rare Disease. 2020.

95. Radia T, Williams N, Agrawal P, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): A systematic review of clinical features and presentation. *Paediatr Respir Rev*. 2021;38:51-57. doi:10.1016/j.prrv.2020.08.001

96. Vogel TP, Top KA, Karatzios C, et al. Multisystem inflammatory syndrome in children and adults (MIS-C/A): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2021;39(22):3037-3049. doi:10.1016/j.vaccine.2021.01.054

97. Bukulmez H. Current Understanding of Multisystem Inflammatory Syndrome (MIS-C) Following COVID-19 and Its Distinction from Kawasaki Disease. *Curr Rheumatol Rep*. 2021;23(8):58. doi:10.1007/s11926-021-01028-4

98. Saha S, Pal P, Mukherjee D. Neonatal MIS-C: Managing the Cytokine Storm. *Pediatrics*. 2021;148(5). doi:10.1542/peds.2020-042093

99. Das S, Kashyap A, Chopra N, Aggarwal KC, Misra A, Singh A. Ferritin as an indicator of disease activity in Hodgkin lymphoma in pediatric patients. *Am J Blood Res*. 2022;12(1):11-16.

100. Sackett K, Cunderlik M, Sahni N, Killeen AA, Olson APJ. Extreme Hyperferritinemia: Causes and Impact on Diagnostic Reasoning. *Am J Clin Pathol*. 2016;145(5):646-650. doi:10.1093/ajcp/aqw053

101. Waalen J, Felitti VJ, Gelbart T, Beutler E. Screening for hemochromatosis by measuring ferritin levels: a more effective approach. *Blood*. 2008;111(7):3373-3376. doi:10.1182/blood-2007-07-102673