

MANAGEMENT OF HYPERINFLAMMATORY DISEASES: HLH / MAS

- Hemophagocytic Lymphohistiocytosis (HLH) and Macrophage Activation Syndrome (MAS)
- Diagnosis of Primary and Secondary HLH
- Treatment and Outcome in HLH
- Treatment for MAS (HLH in Autoimmune Diseases)
- Summary of Treatment Options
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- References

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

Hemophagocytic lymphohistiocytosis (HLH) is a life threatening inflammatory emergency resulting from dysregulation of the immune system.¹ It can develop in children with healthy immune systems when exposed to certain virus such as EBV possibly at a susceptible state. However, more often an underlying systemic condition predisposes to HLH and can be identified. It is essential to conduct a rapid evaluation for an underlying condition since it will impact on the choice and order of therapies. HLH is often mistaken as culture-negative sepsis, and can be difficult to distinguish from critical care patients with MODS from other causes.² It may present with what appears to be isolated, severe organ dysfunction i.e. CNS.³

Primary HLH

Primary HLH is caused by defined genetic mutations coding for effector mechanisms of cytotoxic T- and natural killer (NK) cell killing. As a result, the weapons of T cells - cytolytic proteins, most commonly perforin, cannot be built, transported or secreted. The killer cell cannot kill (see [Figure 1](#)). Presentation is commonly early in life when exposed to the first virus. It often has a familial pattern (usually autosomal recessive, but can be X-linked). Consanguineous families are at higher risk for HLH.

Besides the so called "familial" causes, primary HLH is also well recognized to occur in some primary immunodeficiency syndromes (see [Figure 2](#)), some of which are not necessarily associated with an abnormality of NK cell function.^{4,5}

Secondary HLH

Secondary HLH also represents an inflammatory emergency; however it develops in a child with susceptibility to HLH due to systemic illness. The trigger can be a specific infection, most commonly viral infections (HSV, HHV6 and 8, CMV, VZV, and EBV). Susceptibility to HLH is now recognized in many systemic conditions including rheumatic diseases (systemic JIA, SLE), inflammatory bowel disease, immune dysregulations, metabolic-genetic diseases, acute leukemia and lymphatic malignancies, which occur more commonly in distinct native populations.

The line between primary and secondary HLH is now becoming blurred as secondary cases are now recognized to have heterogeneous genetic defects affecting immune regulation. Different genetic mutations and different triggers have been shown to impact the threshold for the development of HLH, whereas it is considered primary or secondary (see [Figure 3](#)).

For the purpose of this guideline, secondary HLH will describe those patients without a known “familial” mutation or primary immunodeficiency; and with a clear identified trigger such as viral illness, metabolic diseases, or malignancy. In the case of autoimmune disease, if HLH is secondary to a rheumatologic condition, it will then be referred to as macrophage activation syndrome (MAS).

Figure 1: Concept of HLH: T-cells can't kill (Ravelli et al., 2013)

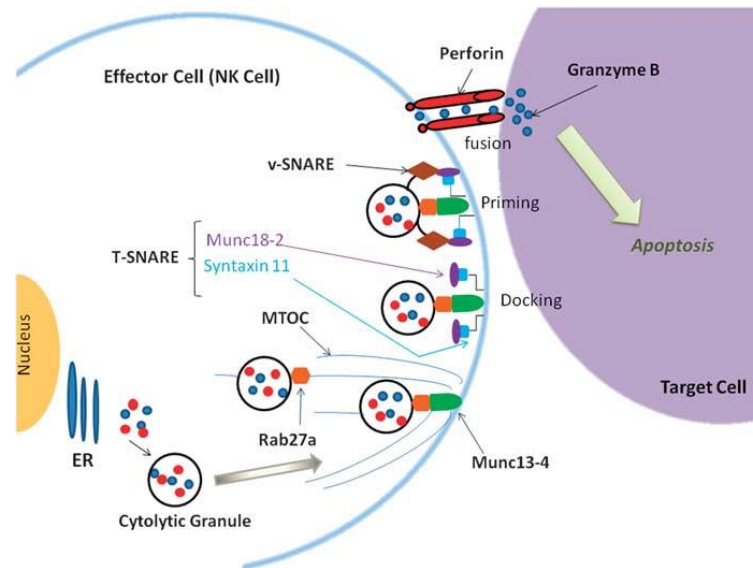


Figure 2. Cytolytic pathway proteins mutated in MAS. A diagram of the immunologic synapse between a cytolytic (to the left) lymphocyte and an APC (to the right) is portrayed. Proteins involved in the cytolytic pathway that can be found mutated in MAS and HLH include Rab27a, Munc13-4, Syntaxin 11, Munc18-2 and perforin.

Figure 2: Primary immunodeficiencies that can present with or develop HLH ⁴ (Faitelson Y et al., 2014)

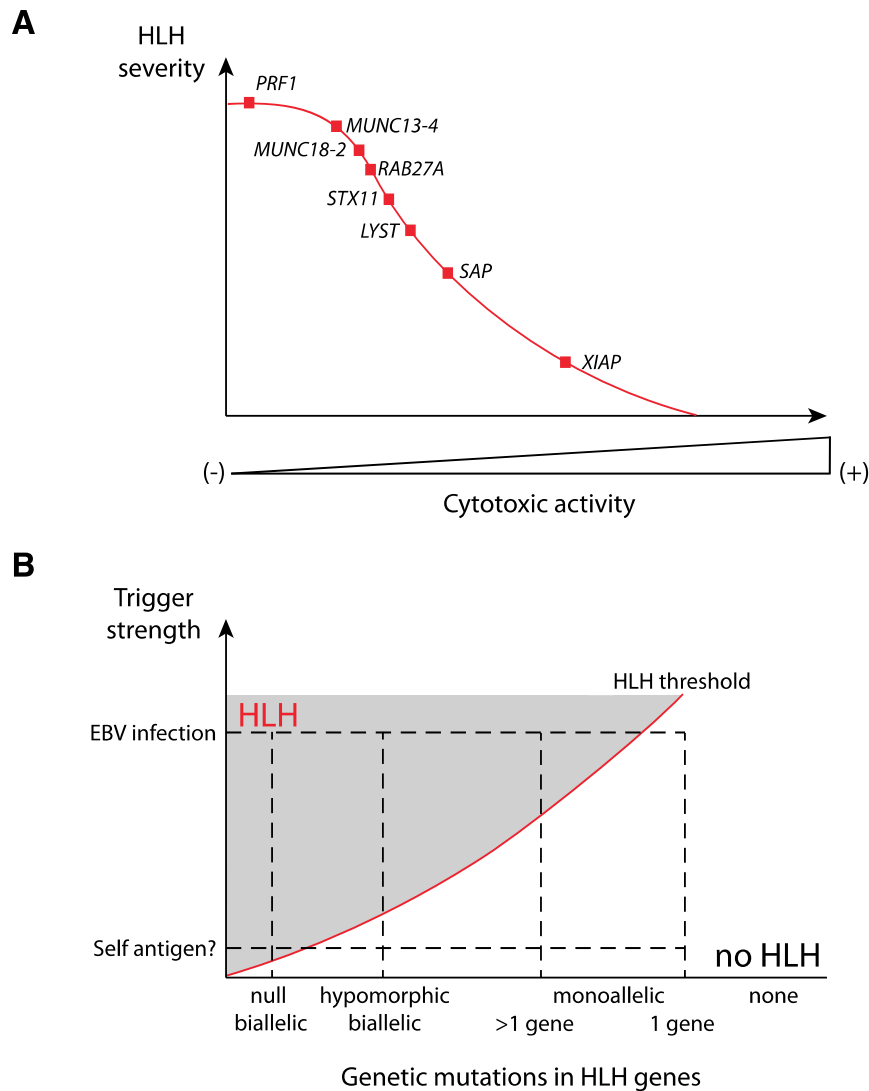
Table 2 Primary immune deficiency disorders associated with HLH.

HLH subtype	Gene/Protein defect	Function
<i>Isolated granule-mediated cytotoxic dysfunction of T cells and NK cells</i>		
Familial HLH type 1	Linked to chromosome 9q21.3-22/unknown	Unknown
Familial HLH type 2	PRF1/perforin	Pore formation
Familial HLH type 3	UNC13D/Munc13-4	Vesicle priming
Familial HLH type 4	STX11/syntaxin 11	Vesicle fusion
Familial HLH type 5	STXBP2/syntaxin-binding protein 2	Vesicle fusion
<i>Primary failure of biogenesis, function and trafficking of secretory lysosomes</i>		
Chediak-Higashi	LYST/lysosomal trafficking regulator	Regulate lysosomal size, trafficking exocytosis?
GrisCELLI type 2	RAB27A	GTPase which regulate vesicular fusion, trafficking and docking
Hermansky-Pudlak type 2	AP3B1/subunit of adapter protein 3	Trafficking of proteins from the Golgi apparatus to the lysosome
<i>Inherited T cell defects</i>		
X-linked lymphoproliferative syndrome (XLP)	XLP type 1 – SH2D1A/SAP XLP type 2 – XIAP/X-linked inhibitor of apoptosis protein	Regulating signal transduction through SLAM receptors. Suppression of apoptosis
IL2-inducible T cell kinase (ITK) deficiency	ITK/IL2-inducible T cell kinase	CD4 differentiation toward TH2 response
CD27 deficiency	CD27	Important for signal transduction in T and B cells
IL2 receptor gamma deficiency	Gamma common chain	Signaling from many interleukin receptors
Purine nucleoside phosphorylase (PNP) deficiency	PNP/purine nucleoside phosphorylase	Purine degradation
DiGeorge syndrome	22q11.2 deletion/unknown	Unknown
Wiskott-Aldrich syndrome	WAS/Wiskott-Aldrich syndrome protein	Essential for actin-regulating signals
Chronic mucocutaneous candidiasis	Signal transducer and activator of transcription 1	Activator of transcription
<i>Macrophage and B cell defects</i>		
Chronic granulomatous disease	PHOX(CYBB)/cytochrome b-245	Part of the NADPH oxidase complex, crucial for the microbicidal oxidase system of phagocytes
X linked agammaglobulinemia (XLA)	BTK/Bruton tyrosine kinase	Critical for B cells development from pre-B to immature B cell stage.



UPDATE

Figure 3: Impact of various genetic and environmental risk factors on threshold of hemophagocytic lymphohistiocytosis (HLH) development (de Saint Basile et al, 2015).



Macrophage Activation Syndrome (MAS)

MAS, as mentioned above, is simply the name given to secondary HLH in children with rheumatic diseases, most commonly systemic juvenile idiopathic arthritis (Still's disease), SLE, Kawasaki disease and Crohn's disease, less commonly in dermatomyositis and other forms of vasculitis.⁶

DIAGNOSIS OF PRIMARY AND SECONDARY HLH

The true incidence of HLH is unknown since the diagnosis is problematic as no true diagnostic test is available beyond expensive and time consuming genetic testing. Lack of awareness of the condition is common; HLH mimics many other illnesses such as sepsis. It is now more commonly diagnosed due to increasing awareness.

Diagnosing HLH often means putting the pieces of the puzzle together. A family history of HLH possibly including genetic confirmation is strongly suggestive of the diagnosis. However a family history is frequently not present.

Therefore, a combination of clinical and laboratory criteria serve as the framework for the diagnosis of primary and secondary HLH (see [Table 1](#)).

An international group of rheumatologists and hematologists with strong HLH/MAS expertise compared clinical and laboratory findings of groups of children with sJIA with and without MAS and paediatric patients with infection (see [Table 2](#)).

Classically children with HLH present with fever, cytopenias, signs of multiple organ dysfunction secondary to severe inflammation and cytokine storm. Splenomegaly, hepatomegaly, signs of CNS inflammation such as irritability and seizures, very elevated ferritin, LDH and D-dimers with decreased fibrinogen help distinguish HLH from sepsis.⁷ Liver dysfunction is also common. In fact, HLH is an increasingly recognized cause of severe liver failure in children.^{8,9} Myocarditis, pneumonitis and serositis can also occur.

Table 1: Diagnostic criteria for HLH used in the HLH-2004 trial¹⁰

The diagnosis of HLH may be established:
<ul style="list-style-type: none"> ▪ Molecular diagnosis consistent with HLH: e.g. pathologic mutations of PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4 OR ▪ Five of the 8 criteria listed below are fulfilled: <ul style="list-style-type: none"> ○ Fever $\geq 38.5^{\circ}\text{C}$ (note fever only occurs in 80-90% of cases) ○ Splenomegaly ○ Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood) <ul style="list-style-type: none"> ◆ Hemoglobin $< 90\text{ g/L}$ (in infants < 4 weeks: hemoglobin $< 100\text{ g/L}$) ◆ Platelets $< 100 \times 10^3/\text{mL}$ ◆ Neutrophils $< 1 \times 10^3/\text{mL}$ ○ Hypertriglyceridemia (fasting, $> 3\text{ mmol/L}$) and/or hypofibrinogenemia ($< 1.50\text{ g/L}$) ○ Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver ○ Low or absent NK-cell activity (which can be impacted by recent steroid therapy) ○ Ferritin $> 500\text{ ng/mL}$ ○ Elevated sCD25 (α-chain of sIL-2 receptor) $> 2400\text{ U/mL}$

Table 2: Comparison of clinical and laboratory features of systemic JIA with and without MAS and systemic infection.

Table 1. Demographic, clinical, and histopathologic features of the patients with systemic JIA-associated MAS and control patients*

Feature	Systemic JIA with MAS (n = 362)	Systemic JIA without MAS (n = 404)	Systemic infection (n = 345)	P†	P‡
Female	208 (57.5)	203 (50.2)	172 (49.9)	0.13	0.12
Age at onset of systemic JIA, median (IQR) years	5.3 (2.7–10.1)	5.5 (2.5–9.5)	–	0.80§	–
Age at onset of systemic infection, median (IQR) years	–	–	3.8 (1.5–8.6)	–	–
Fever	341/355 (96.1)	382/403 (94.8)	345 (100)	0.79	<0.0006
Hepatomegaly	245/350 (70)	123/400 (30.8)	39/344 (11.3)	<0.0001	<0.0001
Splenomegaly	201/347 (57.9)	95/399 (23.8)	23/344 (6.7)	<0.0001	<0.0001
Lymphadenopathy	178/346 (51.4)	115/396 (29)	29/344 (8.4)	<0.0001	<0.0001
Active arthritis	230/354 (65)	382/401 (95.3)	22 (6.4)	<0.0001	<0.0001
Central nervous system disease	122/349 (35)	7/400 (1.8)	34/344 (9.9)	<0.0001	<0.0001
Hemorrhagic manifestations	71/348 (20.4)	5/402 (1.2)	22/345 (6.4)	<0.0001	<0.0001
Bone marrow hemophagocytosis	149/249 (59.8)	–	–	–	–

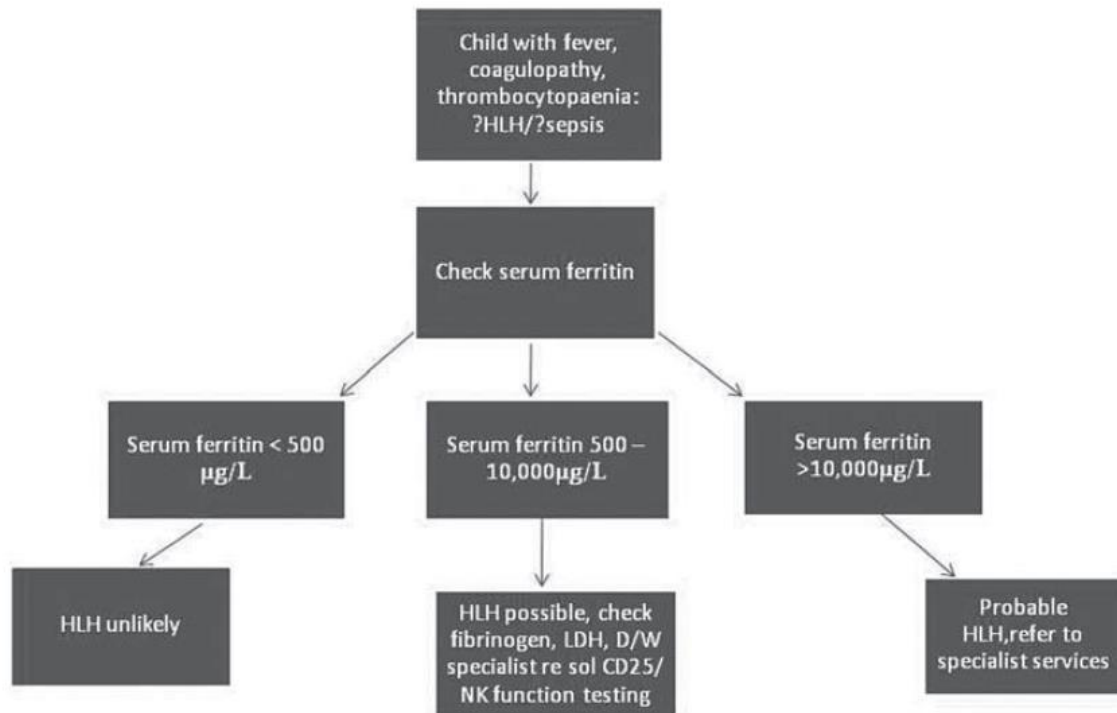
Table 2. Laboratory findings in the patients with systemic JIA-associated MAS and control patients*

Laboratory test	Systemic JIA with MAS (n = 362)	Systemic JIA without MAS (n = 404)	Systemic infection (n = 345)	P†	P‡
White blood cell count, × 10 ⁹ /liter	9.9 (4.6–16.3)	16.8 (12.1–21.9)	12.2 (8–18.3)	<0.0001	<0.0001
Neutrophil count, × 10 ⁹ /liter	5.4 (2.3–11.5)	11.9 (7.7–17.8)	6.8 (3.7–11.8)	<0.0001	0.002
Hemoglobin, gm/liter	9.8 (8.3–11.1)	10.1 (9.1–11.2)	11.8 (10.8–12.7)	0.019	<0.0001
Platelet count, × 10 ⁹ /liter	144 (86–269)	498 (377–615)	340 (257–443)	<0.0001	<0.0001
Aspartate aminotransferase, units/liter	134 (58–338)	28 (20–39)	33 (25–44)	<0.0001	<0.0001
Alanine aminotransferase, units/liter	96 (37–234)	18 (11–34)	20 (13–32)	<0.0001	<0.0001
Lactate dehydrogenase, units/liter	1,203 (666–2,345)	438 (291–611)	507 (391–652)	<0.0001	<0.0001
Triglycerides, mg/dl	234 (151–318)	124 (91–142)	133 (100–192)	<0.0001	<0.0001
Albumin, gm/dl	3.1 (2.6–3.5)	3.5 (3–4)	3.8 (3.4–4.2)	<0.0001	<0.0001
Serum sodium, mmoles/liter	136 (132–138)	138 (135–140)	135 (133–138)	<0.0001	0.99
Fibrinogen, mg/dl	267 (152–437)	559 (463–720)	411 (293–559)	<0.0001	<0.0001
D-dimer, ng/ml	2,996 (1,094–7,550)	2,050 (501–4,064)	417 (135–972)	0.004	<0.0001
Ferritin, ng/ml	5,353 (1,500–13,040)	502 (158–1,627)	68 (33–133)	<0.0001	<0.0001
Erythrocyte sedimentation rate, mm/hour	48 (19–84)	78 (56–100)	40 (24–64)	<0.0001	0.47
C-reactive protein, mg/dl	9.2 (3.5–17.7)	8.9 (4.8–15.3)	3.8 (0.8–10)	0.99	<0.0001

Hyperferritinemia

Elevated serum ferritin level is the most characteristic laboratory feature of HLH/MAS. Ferritin levels are frequently very high.¹¹ This finding in isolation is not sufficiently specific for HLH.^{12 13 14 15} However, ferritin level is helpful to distinguish HLH from severe sepsis.¹⁶ (see [Figure 4](#))

Figure 4: Serum ferritin in the assessment of HLH



Diagnostic evaluation should include these considerations:

Primary HLH

- **Early age at diagnosis of <2 years** of age and/or recurrent disease is suggestive of primary familial HLH (types 1 through 5) or an underlying primary immunodeficiency. This would be strongly supported by a history of a family member who died at an early age in multi-organ failure/sepsis. However, older children and adults can have primary HLH and can remain well for many years until triggered by a virus such as EBV or other immune dysregulation later in life.
- **Boys with X-linked lymphoproliferative disease (XLP)**, an example of a primary immunodeficiency, can develop HLH when contracting EBV infection. They commonly have been well despite previous viral illnesses. They may or may not have associated symptoms.
- **Children with abnormal pigmentation of their hair** (silvery body and head hair) may suffer from Chediak Higashi, Griscelli, or Hermansky-Pudlak syndromes and can develop HLH when triggered by infections and other triggers.
- **Besides XLP and the pigmentation disorders mentioned above, keep in mind that other primary immunodeficiency disorders can present with or develop HLH at any point in their lifetimes** (see [Figure 2](#)).

Secondary HLH:

- Children with any hematologic or lymphatic malignancy, post allogeneic HSCT or defined immune dysregulation are at risk for HLH

- Children with rheumatic or inflammatory disease are at risk for HLH. Children with sJIA have a 20% risk of developing HLH/MAS; children with SLE are also at risk, less commonly those with other rheumatic or inflammatory diseases such as IBD.
- Children with recalcitrant Kawasaki disease can develop MAS/HLH.
- EBV, *Leishmania* and other infections can result in secondary HLH. (see [Table 3](#))
 - Important note: Some infectious disease etiologies (i.e. Leishmaniasis), when appropriately treated, can negate the need for direct treatment of HLH/MAS with immunosuppression.
- Some genetic-metabolic diseases carry a risk of secondary HLH. Examples include: lysinuric protein intolerance, multiple sulfatase deficiency, galactosemia, Gaucher disease, Pearson syndrome, galactosialidosis, methylmalonic and propionic acidemias.¹⁷

Table 3: Infections associated with secondary HLH¹⁸ (Cascio A et al. 2012)

Infections Associated with Secondary HLH	
Virus	EBV, CMV, HSV, VZV, HIV, HAV, HBV, HEV, HHV6, Parvovirus, Influenza, Parainfluenza, Rotavirus, Dengue, Hanta, SARS
Bacteria	<i>Brucella, Mycoplasma, Mycobacterium, Chlamydia, Salmonella, Bartonella, Borrelia, Campylobacter, Clostridium, Listeria, Leptospira</i>
Fungi	<i>Histoplasma, Candida, Aspergillus, Cryptococcus</i>
Parasites	<i>Leishmania, Toxoplasma, Coccidia, Plasmodium, Babesia</i>

In bold: infections with the most number of cases reported

Proposed Investigations in Suspected Cases

- CBC/differential/ reticulocytes
- CRP, ESR
- Ferritin, LDH, AST, ALT, bilirubin (total and direct), albumin, total protein, fasting triglycerides
- INR, PTT, Fibrinogen, D-dimer
- **HLH/MAS specific investigations (see Appendix for instructions, special requisitions/send out tests):**
 - Bone marrow aspirate +/- biopsy and biopsies of other organs, if indicated - assessing for hemophagocytosis and to rule out malignancy +/- infection.
 - ◆ **Note:** It is important to note that the finding of hemophagocytosis in the bone marrow and/or other organs is not pathognomonic for HLH and may be found in other conditions. Therefore, biopsies are not necessarily required to make a provisional diagnosis of HLH.
 - ◆ Also hemophagocytosis is often a late finding in true HLH.
 - sCD25 (sIL2R) - send "Soluble cytokine receptor 14-Plex" panel to Mitogen Advanced Diagnostics Laboratory (Calgary).
 - ◆ Needs CLS approval (see [Appendix](#))
 - Perforin/Granzyme B levels by flow cytometry to CLS Flow cytometry lab.
 - NK cell function - CD107a flow cytometry degranulation assay +/- NK cell function testing (lytic assay) - send to SickKids as first option
 - ◆ Needs CLS approval. See [Appendix](#)
 - ◆ Sickkids will run lytic assay only if CD107a degranulation assay is abnormal.
 - ◆ Second option (more expensive): Cincinnati Children's Hospital HLH lab, Can only be sent before noon, Mon-Wed. Discuss with Rheumatology/Immunology
 - HLH genetics - discussion with Genetics and Immunology; requires funding approval. Results take minimum 6-8 weeks.
 - Cytokine assays - see **Mitogen Immune Biomarker requisition in [Appendix](#)**

- MRI assessing for evidence of CNS involvement and/or CSF for cell count and differential, pathology, protein, glucose, culture and viral testing and autoimmune. Assess for pleocytosis and increased protein. Discuss with Rheumatology

Note: biopsies, LP and imaging may need to be deferred if the patient is too unstable; these should be considered once the patient has stabilized)

- **Infectious Diseases investigations:** It is mandatory to consult ID prior to starting of treatment as the specific investigations require consideration on a case by case basis.
 - **Important: All serologies must be drawn prior to administering IVIG**
 - See [Table 3](#) for possible etiologies and send investigations accordingly and in discussion with ID:
 - ◆ Most common tests:
 - NPA, blood culture, urine culture, stool studies if diarrhea (C&S, O&P, C. diff, GI viral panel)
 - Serologies for: EBV, CMV, HSV, VZV, HIV (Ag/Ab combo), Parvovirus (serology +/- PCR)
 - ◆ Please send an extra tube of serum (gold top tube) and plasma (mint tube) to Provincial Lab prior to IVIG administration for serology investigations.
 - ◆ Special tests to consider (in discussion with ID) are :
 - Leishmaniasis (rk39, BMT sample requires special media)
 - TB testing (gene Xpert, IGRA)
- **Immunology investigations:** Consult Immunology if a primary immunodeficiency is suspected
 - **To be drawn prior to administering IVIG:**
 - ◆ IgG, IgA, IgM, IgE, vaccination IgG titers (tetanus and diphtheria, measles, mumps, rubella if vaccinated)
 - **To be done before any immunosuppression is started:**
 - ◆ Immunodeficiency panel, mitogen stimulation assay
 - Note: Mitogen stimulation assay can only be sent on Thursdays (except under special circumstances, discuss with Immunology); Important: do not delay start of immunosuppression to obtain mitogen testing
 - ◆ Immunology may suggest additional tests depending on the case: flow cytometry for SAP and XIAP proteins, NOBI, WASP panel, TCRVbeta, etc.
- **Imaging**
 - Consider abdominal U/S to assess hepatosplenomegaly and adenopathy if difficult clinical exam

TREATMENT AND OUTCOME IN HLH

When a patient with HLH/MAS presents, they are often unstable and treatment may need to be initiated before results of investigations to determine underlying cause are available. It is reasonable to initiate therapy with IVIG and steroids (after the proper samples are drawn, see above) while investigations for underlying cause are completed. For patients under 2 years of age, primary HLH should be presumed, even if an infectious trigger is identified, and patients should be treated as such. It will be very important, however, to differentiate primary and secondary HLH, as hematopoietic stem cell transplant will be the definite treatment for the former.

Role of subspecialties

Primary HLH

- For patients with familial HLH, the primary subspecialty managing the patient should be **Hematology**. Hematology should be responsible for final decisions regarding therapy and long term follow up.
- **Immunology** consult should be considered to rule out primary immunodeficiency as an underlying cause. If a primary immunodeficiency is found, Immunology should then become the primary subspecialty.
- **Infectious Diseases, Rheumatology, and Oncology** consults should always be considered if there is any possibility of secondary HLH

Secondary HLH

- The primary subspecialist managing the patient should be identified based on underlying cause
 - E.g. If secondary to malignancy, the primary service may be **Oncology** with consultation with the other services. This service would be responsible for final decisions regarding therapy and long term follow up.
- For patients with MAS, the primary subspecialty managing the patient should be **Rheumatology**. Rheumatology should be responsible for final decisions regarding therapy and long term follow up.
 - **Immunology** consult can be considered if there is a concern regarding underlying immune dysregulation. Hematology consult should be considered for assistance in ruling out primary HLH, managing cytopenias and bleeding complications, or if a bone marrow aspirate and biopsy are required.

Primary HLH:

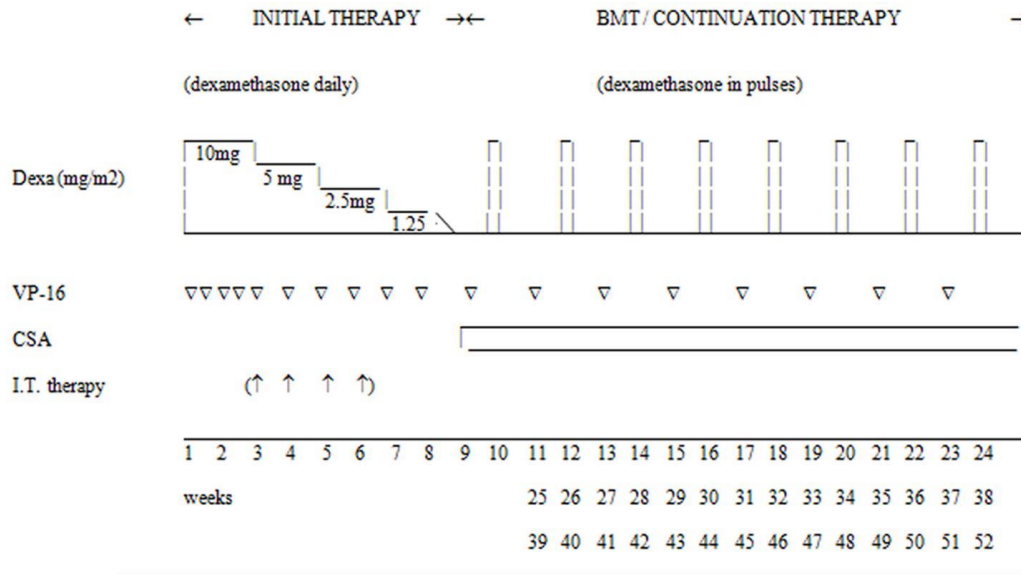
Primary HLH continues to have a significant mortality. The results of the Histiocyte Society multi-center HLH-94 trial with SCT have been published.¹⁹ It demonstrated an overall 56% survival; 51% for familial cases, and 66% after HSCT at 5 yrs. These outcomes are thought to be better than the previously reported outcomes.

HLH-2004²⁰ trial added cyclosporine A to induction therapy which resulted in increased neurotoxicity (seizures and PRES) without improved outcomes, therefore we discourage the use of cyclosporine in up front treatment of primary HLH. (Personal communication, unpublished data).

Therefore, HLH-94 protocol should be considered the gold standard for the treatment of primary HLH and the treatment protocol to follow here at ACH (see [Figure 5](#)).

Patients with primary HLH should proceed to HSCT. Relapsed secondary HLH also warrants consideration for BMT.

Figure 5: HLH-94 protocol treatment flow chart (Trottestam H et al. Blood 2011)¹⁹



Daily dexamethasone (10 mg/m² for 2 weeks followed by 5 mg/m² for 2 weeks, 2.5 mg/m² for 2 weeks, 1.25 mg/m² for 1 week, and 1 week of tapering; pulses were 3 days, 10 mg/m² daily).
VP-16: Etoposide 150 mg/m² IV.

IT therapy: Intrathecal methotrexate in patients with progressive neurological symptoms and/or persisting abnormal cerebrospinal fluid findings.

CSA: will not be used in our Institution, as mentioned before.

Secondary HLH:

The mainstay of treatment in secondary HLH will be directing it at the underlying cause whereas it is triggered by infection, autoimmunity, or malignancy.

Of note, in some circumstances e.g. Leishmaniasis, treatment of the underlying infection (L-AmphB) alone is often all that is required.²¹

There are several excellent reviews from major institutions discussing their approach to secondary HLH. In adults, a steroid and etoposide (VP-16) based regime is commonly used.^{22 23}

In malignancy triggered HLH in children (usually T or B cell malignancies and often EBV triggered) an etoposide based regime should be considered in combination with therapy directed at the underlying leukemia/lymphoma.²⁴

In sepsis triggered HLH, mortality may be reduced by using interleukin-1 receptor antagonist (anakinra).²⁵ Post hoc analysis of the adult trial in severe sepsis²⁶ showed mortality reduction from 65% to 35% in cases classified as possible hemophagocytic syndrome (HPS) cases.²⁷ The classification of cases as HPS in this study (an older term for HLH/MAS) can be disputed.

Very good results have been reported in a recent series of 40 cases of presumed HLH in children from India using dexamethasone and IVIG when compared to HLH-94 protocol (85% vs. 83% survival respectively). The age of children was older (mean 4.3 yrs.), familial HLH cases were excluded and HSCT was not used.²⁸

In another recent Turkish series of 23 children admitted to intensive care, the best survival was associated with the use of plasmapheresis with IVIG or methyl prednisone 17/17 (100%), vs. plasmapheresis combined with more immunosuppressive therapy that included cyclosporine and/or VP-16 (etoposide) 3/6 (50%, P 0.002).²⁹

Thus, some expert pediatric commentators are suggesting children be treated with plasmapheresis, methylprednisolone and IVIG plus anakinra.^{30 31}

Rituximab (monoclonal B-cell antibody) is effective in EBV related HLH³², commonly it is added to a HLH-2004 regime.³³

Use of rituximab may be associated with improved survival in B cell lymphoma associated HLH.³⁴

Alemtuzumab (monoclonal T-cell antibody) has been reported to be effective in refractory HLH after rituximab has failed and when used outside the context of EBV/B cell lymphoma related HLH.³⁵

TREATMENT FOR MAS

The treatment regimens used around the world vary widely and diagnostic criteria are not clear cut and the optimal strategy is unknown.^{36,37}

In secondary HLH in the context of rheumatologic diseases (often called MAS), anakinra has been reported to have dramatic results.^{38,39,40, 41}

Also pulse steroid therapy and IVIG has been reported to be effective with 12.5% mortality in pediatric MAS cases with autoimmune diseases.⁴²

In adults with autoimmune disease, cyclophosphamide is described as being more effective than cyclosporine or IVIG, with an overall mortality of 12.9%.⁴³

Etanercept (TNF inhibitor) has been reported to be effective when other therapies have failed.⁴⁴ Plasmapheresis has also been reported to be useful in autoimmune induced HLH.⁴⁵

Rituximab has also been reported to be useful in SLE associated HLH when most other options have failed.⁴⁶

SUMMARY OF TREATMENT OPTIONS

There is no known ideal treatment strategy.⁴⁷

Primary HLH:

For primary HLH cases the HLH-94 protocol will be the standard in our institution.

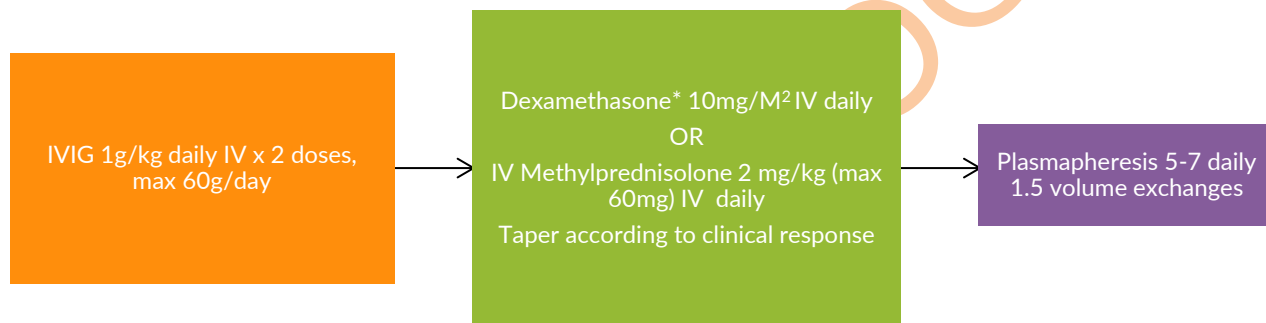
- HLH-94 Protocol with dexamethasone and VP-16 ± IT methotrexate and prednisolone (see above)

Secondary HLH:

For secondary HLH/MAS the treatment plan should be individualized, weighing carefully the balance between treating the underlying cause e.g. leukemia/lymphoma or infection and controlling the hyperinflammation.⁴⁸ A step-wise approach is warranted, depending on the severity of illness and response to treatment.

The main concerns relate to an underlying malignancy or infection where corticosteroids may make the diagnosis more difficult and/or worsen the outcome or worsen severe infection. Thus a rapid evaluation for possible malignancy and infection is required before corticosteroid treatment is started.

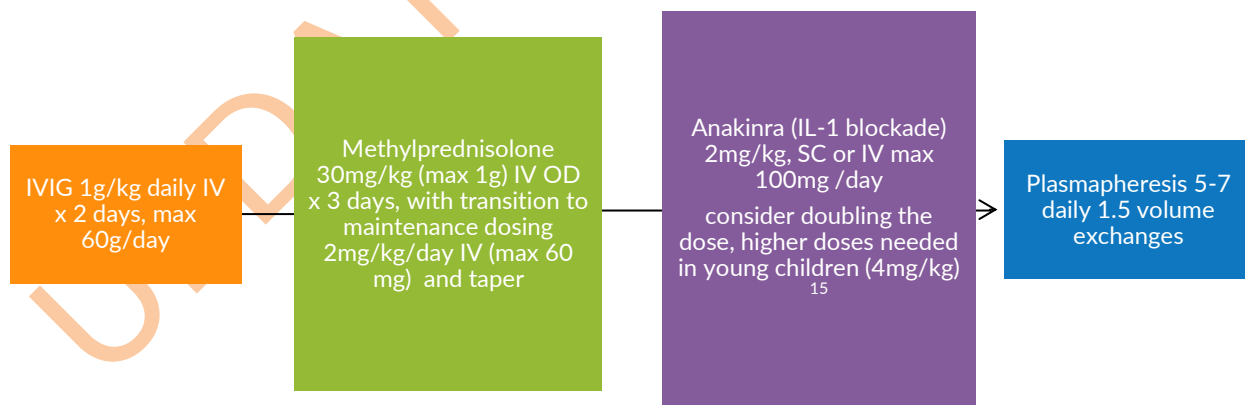
- Malignancy triggered HLH:
 - Treat the underlying malignancy. Therapy should be individualized. Some cases of HLH secondary to malignancy will likely be treated with etoposide (VP-16) and steroids. For EBV-induced malignancies, Rituximab may be a consideration. Oncology service should decide on the best management for each patient.
- Infection triggered:
 - Treat underlying infection (e.g. antivirals, antibiotics, and/or antifungals as appropriate).
 - Consider Rituximab for EBV induced HLH.



*Discuss Steroid use with

*May be specifically considered if evidence of CNS disease.

- HLH in autoimmune disease:



Fourth Line Therapies:

- Etanercept (TNF inhibitor) 0.8 mg/kg (MAX dose 50 mg) SC weekly
- Rituximab (monoclonal B-cell antibody) 375 mg/m² (MAX dose 1000 mg) IV weekly, particularly useful in cases of EBV-driven HLH

- Alemtuzumab (monoclonal T-cell antibody) adult dosing 3 mg IV daily over 2 hrs, increasing to 30 mg IV 3 x per week, pediatric dosing consult Hematology
- Cyclosporin A
- Cyclophosphamide

Note: Some of these agents require dosage adjustment for liver and renal dysfunction.

APPENDIX

- Instructions for arranging send out labs
- Mitogen Immune Biomarker Test requisition
- HLH Cincinnati requisition
- HLH CLS Flow Cytometry requisition
- HLH Test information; Sickkids
- HLH send out format to Sickkids
- CLS Billing information
- Cincinnati prices

REFERENCES

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