HEMOPHAGOCYTIC LYMPHOHISIOCYTOSIS

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· ***Hemophagocytic lymphohistiocytosis*** (HLH) is a hyperinflammatory syndrome due to aberrant activation of macrophages & cytotoxic T cells ⇢ cytokine storm, hyperinflammation and multi-organ failure. **Secondary HLH** can have many ***triggers*** (e.g. rheumatologic, infectious, malignant) and/or may have an underlying ***genetic susceptibility*** **(primary HLH)**.

· ***Macrophage Activation Syndrome (MAS):*** HLH secondary to a rheumatologic condition

HLH-2004 Diagnostic Criteria (5 of 8 criteria for diagnosis)*

	CRITERIA	PARAMETERS	DESCRIPTION
DIAGNOSTIC CRITERIA	FEVER	≥38.5°C	Present in >95% cases
	↑ FERRITIN	>=500 mg/L	Occurs in >95%, often markedly elevated (>5k) but non-specific
	SPLENOMEGALY		Occurs in >70%
	CYTOPENIA of >1 lineage	HgB <9 g/dL, PLT <100K, ANC <1000	Occurs in >95%
	↑ TRIGLYCERIDES and/or ↓ FIBRINOGEN	TG >265 mg/dL, fibrinogen <150 mg/dL	Occurs in 60-75%
	HEMOPHAGOCYTOSIS	In bone marrow, spleen, lymph node or liver	Neither sensitive nor *fully* specific; *absence does not rule out HLH*
	↑ SOLUBLE IL-2 RECEPTOR (sCD25)	>2400 U/mL or >2 SD above lab normal	sCD25 >10,000 is more specific (Sp 93%)
	↓ NK CELL ACTIVITY	low or absent NK cell activity	Highly specific (100% in one cohort)
SUPPORTING FEATURES	ESR/CRP discordance	Consumptive coagulopathy ⇢ low fibrinogen & low ESR; Low/normal ESR or falling ESR with high CRP may be seen with HLD	
	↑ AST/ALT, ↑ LDH Hepatomegaly	Hepatitis → coagulopathy, ↑ triglycerides, hypofibrinogenemia. LFT abnormalities are common (>95%) but ALF is rare (1%)	
	Coagulation Abnormalities	Due to impaired hepatic synthetic function and/or DIC; ↓ fibrinogen, ↑ D-dimer	
	Neurological symptoms	Present in >65%. Neuro sx may be the only sx. Altered mental status common; can also cause seizures, encephalitis, ataxia, PRES	
	Renal injury	Present in >50%. Oliguria, nephrotic Sd, ATN.	
	Rash	Present in 30%. Protean manifestations.	

* Genetic testing consistent with HLH can also establish primary (familial) HLH diagnosis

ETIOLOGY:

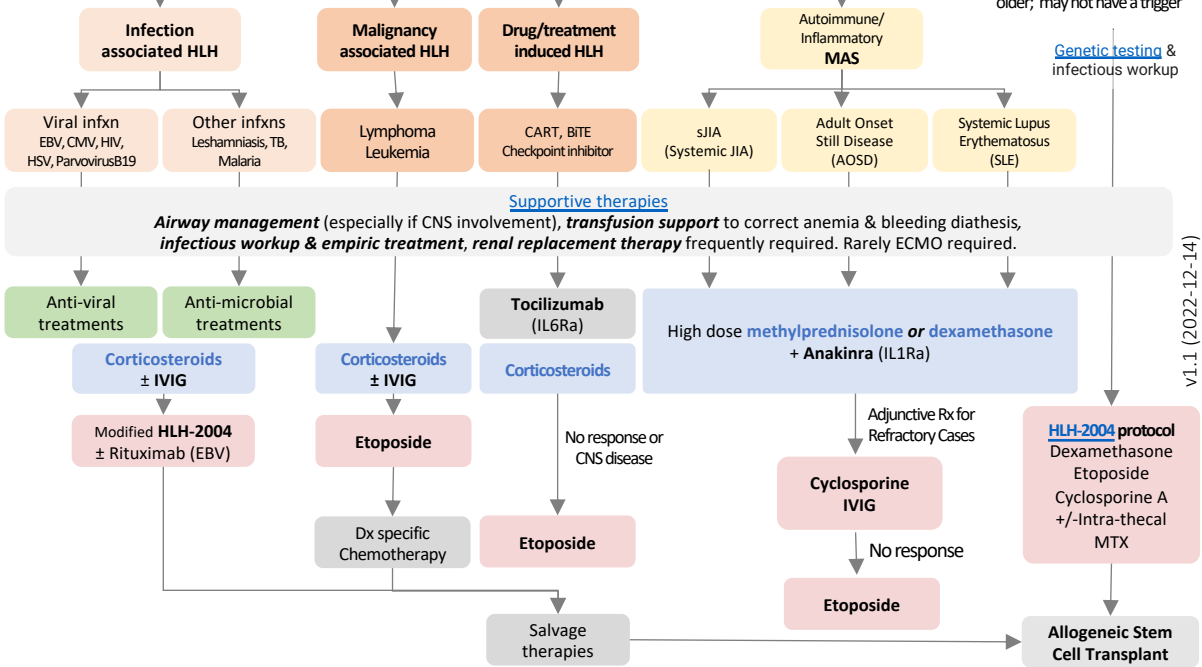
(Some adult onset HLH may have BOTH a trigger & an underlying genetic predisposition)

Secondary HLH

Excessive macrophage & T cell activation, due to a trigger such as infection, malignancy, medication/treatment, or rheumatic disease

Primary HLH

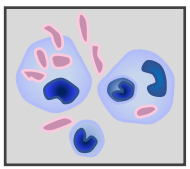
"Familial HLH" > rare, autosomal recessive disorders due to genetic mutations; often presents in 1st year of life but also older; may not have a trigger



v1.1 (2022-12-14)

PATHOPHYSIOLOGY:

· Uncontrolled immune activation of NK cells and/or cytotoxic T-cells. Activated cells fail to eliminate activated macrophages ⇢ excess macrophage activation ⇢ cytokine storm



· BM biopsy may show ***hemophagocytosis*** (consumption of RBCs & other cell precursors within histiocytes)

DIFFERENTIAL:

· sepsis with DIC (consider LP if neuro sx)
· TTP/aHUS
· Leukemia
· Liver failure
· ALPS
· Severe DRESS

DIAGNOSIS:

· No single lab or clinical feature can establish HLH diagnosis
· Diagnosis of HLH is established using the 2004 criteria, if at least 5 of 8 criteria are present. HSCORE can also be used.
· ↑ ferritin is a less specific finding in adults than children

Use the HSCORE calculator here.

· **H-SCORE** is helpful to *estimate* a patient's risk/probability of having a secondary HLH/MAS
· Promptly obtaining BM biopsy and sending Soluble IL-2 receptor and NK cell function (these are send out tests that can take >1 week to result)

MANAGEMENT:

· Treatment depends on etiology. Management is ***multi-disciplinary*** & requires collaboration between Rheumatology, Heme/Onc, ID, & critical care disciplines
· often require intubation due to multi-system organ failure & encephalopathy
· may require transfusions due to severe anemia & coagulopathy
· frequent trending of HLH labs is important to monitor for progression
· workup for infection (LP) & empiric treatment is often prudent
· **Corticosteroids** are the primary treatment, in conjunction with **antimicrobial treatment** (infectious), IL6 blockers (drug/treatment associated), **IL1R blockers** (rheumatic). **Etoposide + other chemotherapy** indicated in **primary HLH, malignancy associated** & **refractory HLH**.