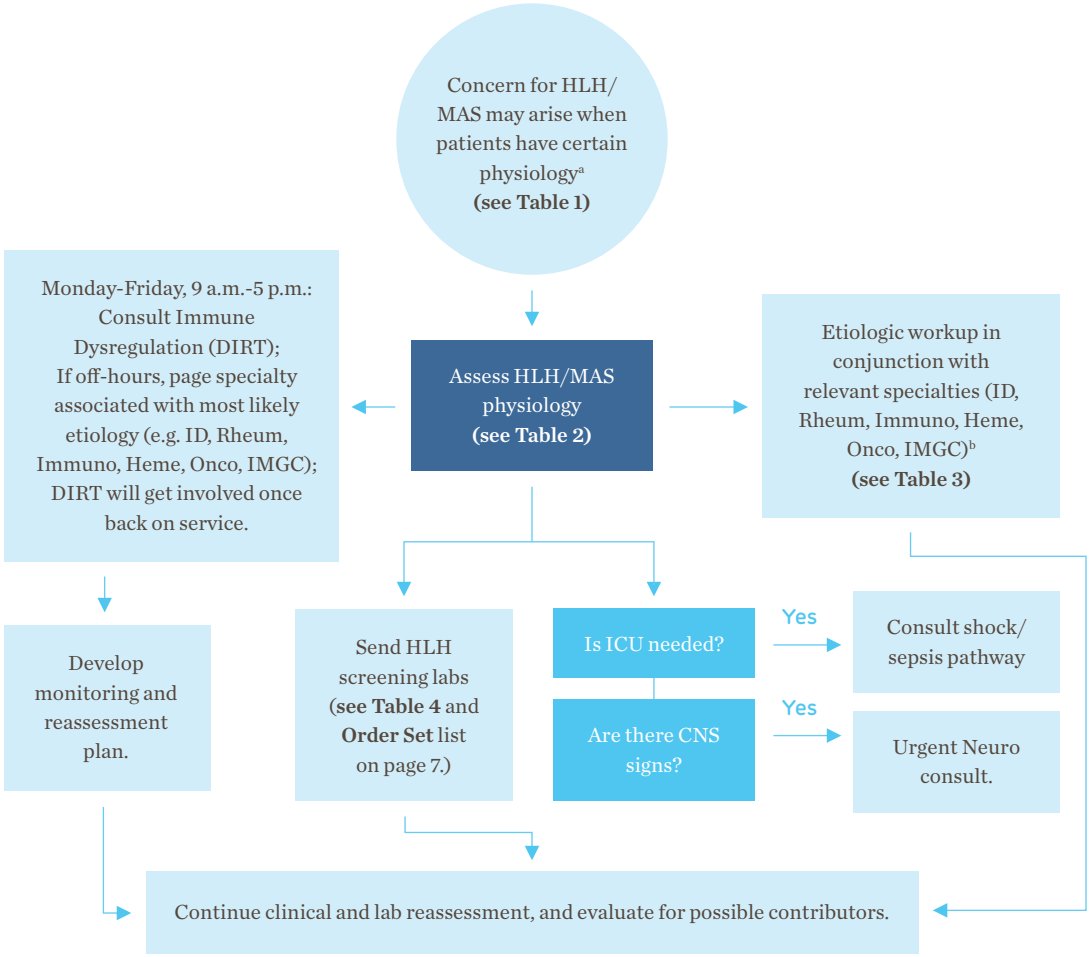
HLH DIAGNOSTIC GUIDELINES

(Updated October 2024)

Hemophagocytic Lymphohistiocytosis (HLH) and Macrophage Activation Syndrome (MAS) describe systemic hyperinflammatory syndromes that can develop in many inflammatory contexts. They can progress rapidly, and early identification and **management** are critical to prevent organ failure and mortality. **(see Table 3)**



[a]Physiology concerning for HLH/MAS may include:

- Pathologic processes, such as:
  - o Fever/SIRS/sepsis
  - o DIC
  - o Bi/pancytopenia
  - o Hepatitis
- Underlying diseases such as:
  - o Infections (EBV, Ehrlichia, Adenovirus, etc.)
  - o Rheumatic disease (Systemic JIA/Stills & SLE)
- Lab abnormalities, particularly:
  - o Very high ferritin

No individual test in **Table 4** on page 5 is specific for HLH/MAS of any form. The dynamics/trend/trajectory of many tests is often as valuable as any individual value.

[b]The most common underlying causes of HLH/MAS are:

- Infection
  - o This is the most common trigger in older teens.
- Malignancy
- Rheumatic disease
- Genetic inborn error of immunity (primary HLH)
  - o Particularly in younger children
  - o Familial HLH – cytotoxicity defects
  - o Other inborn errors of immunity

Often, multiple causes combine to drive HLH/MAS.

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TABLE 1: OVERARCHING PRINCIPLES OF HLH/MAS	
A	Systemic hyperinflammation is an immunopathological continuum; the characteristic clinical and laboratory findings are individually non-specific but when viewed collectively and longitudinally are recognizable. Diagnostic evaluation is warranted, and therapeutic intervention may be needed even if diagnostic criteria for HLH/MAS are not met.
B	Systemic hyperinflammation can be associated with hyperferritinemia and can progress to life-threatening HLH/MAS.
C	Systemic hyperinflammation and HLH/MAS can occur in nearly any inflammatory state, but certain predisposing conditions and/or inflammatory triggers warrant a high index of suspicion.
D	Investigating and treating modifiable contributors to systemic hyperinflammation and HLH/MAS are essential in the management of every patient.
E	HLH/MAS should be treated with an urgency based on both the degree of inflammation and extent of organ dysfunction; the goals of therapy are to prevent/limit immunopathology, preserve integrity of the ongoing diagnostic workup and minimize toxicity.
F	The evaluation and management of patients with systemic hyperinflammation suspected of having or progressing to HLH/MAS may benefit from consultation with experts in these disorders.

Source: *Shakoory B, Geerlinks A, Wilejto M, et al. Ann Rheum Dis, doi:10.1136/, ard-2023-224123*

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TABLE 2: RECOGNIZABLE CLINICAL FEATURES/PATTERNS IN HLH/MAS		
	FEATURE	**CRITERIA***
1	Systemic inflammation (elevated or rising)	
	Fever	All
	CRP	None
	LDH	None
2	Hyperferritinemia (elevating or rising)	All
3	Cytopenias (low or dropping)	
	Platelet count	All
	Leucocyte count (particularly neutrophil count)	HLH04, HScore
	Hemoglobin	HLH04, HScore
4	Disseminated intravascular coagulopathy	
	Increased D-dimer	None
	Low/dropping fibrinogen	All
	Prolonged PT/INR, PTT	None
5	Liver dysfunction	
	Hepatomegaly	HScore
	Increased ALT, AST, bilirubin	HLH04, HScore
	Increased triglycerides	All
6	Splenomegaly	HLH04, HScore
7	CNS dysfunction	
	Encephalitis, encephalopathy, altered mental status, seizure	None
	CSF pleocytosis, elevated CSF protein, increased ICP	None
	Radiologic evidence of CNS inflammation	None

Source: *Shakoory B, Geerlinks A, Wilejto M, et al. Ann Rheum Dis, doi:10.1136/, ard-2023-224123*

*Criteria

- HLH04 (revised): Developed to classify infants and children for treatment trials targeting pediatric patients with genetic causes of HLH/MAS (Henter et al., Pediatr Blood Ca 2007)
- MAS16: Developed to classify MAS in patients with known or strongly suspected Systemic Juvenile Idiopathic Arthritis (sJIA). (Ravelli et al., Arthritis Rheumatol 2016)
- Hscore: Developed in adults with primarily malignancy or infection-associated HLH. (Fardet, Arthritis Rheumatol 2014)

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HLH Diagnostic Guidelines (continued from page 3)

TABLE 3: PROPORTION OF ATTRIBUTABLE HLH/MAS CASES BY PRIMARY CONTRIBUTOR

		Median % (min, max)	
		Pediatric	Adult
Genetic cause			
	Genetic HLH disorders	12% (3-46)	Rare
	Other inborn errors of immunity	6% (2-18)	Rare
Predisposing conditions			
	Rheumatological	10% (2-26)	8% (2-26)
	Malignancies	5% (2-19)	46% (26-73)
Acute triggers			
	All-cause infections	57% (9-88)	27% (9-75)
	Viral infections	57% (18-80)	14% (2-33)
	Bacterial infections	10% (3-58)	14% (2-45)
Idiopathic			
	Unknown etiology	42% (17-49)	18% (4-40)

Source: *Shakoory B, Geerlinks A, Wilejto M, et al. Ann Rheum Dis, doi:10.1136/, ard-2023-224123*

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HLH Diagnostic Guidelines (continued from page 4)

Monitoring key: F: Frequent (e.g., daily) I: Intermittent (e.g., weekly) R: Rarely (e.g., monthly) PRN: As needed

TABLE 4: LABORATORY AND BIOMARKER TESTING IN HLH/MAS

TEST	TREND IN HLH/MAS	BIOLOGY	MONITORING	CAVEATS
CBC				
Neutrophil count	↓	Affected by marrow production, proliferation, tissue sequestration and consumption	F	Glucocorticoid demargination
Lymphocyte count	↓		F	
Hemoglobin	↓		F	
Platelet count	↓		F	
INFLAMMATORY BIOMARKERS				
CRP	↑	Hepatic release in response to IL-6	F	Blunted by IL-6 blocking drugs
Ferritin	↑	Macrophage/ Hepatocyte activation	F	↑ by iron overload and hepatic failure
ESR	↑↓	Falls with fibrinogen consumption	I	↑ by IVIg, dialysis
LDH	↑	Cellular death/injury	I	↑ with hemolysis, TMA
Soluble IL-2Ra	↑	T-cell activation	I, R	
CXCL9	↑	Chemokine induced by IFNy	I, R	
IL-18	↑	Inflammasome-activated, induces IFNy	PRN	
LIVER FUNCTION TESTS				
ALT, AST, bilirubin	↑	Hepatocyte injury	F	
Triglycerides	↓	Cytokine inhibition of lipoprotein lipase	R, PRN	Fasting
Albumin	↓	Vascular leak /third spacing	F	

Source: *Shakoory B, Geerlinks A, Wilejto M, et al. Ann Rheum Dis, doi:10.1136/, ard-2023-224123*

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TABLE 4: LABORATORY AND BIOMARKER TESTING IN HLH/MAS (continued)

COAGULOPATHY TESTS				
Fibrinogen	↓	Fibrinogen consumption/fibrin degradation	F	
D-dimer	↑		F, I	
PT/INR/PTT	↑	Factor consumption	F	Heparin effects
CNS TESTS				
Brain imaging	abnormal	Inflammation of white or gray matter, meninges, hypoxia	PRN	
CSF studies	↑	Pleocytosis and/or high protein > CNS inflammation	PRN	

Source: *Shakoory B, Geerlinks A, Wilejto M, et al. Ann Rheum Dis, doi:10.1136/, ard-2023-224123*

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HLH Diagnostic Guidelines (continued from page 6)

SCREENING FOR HLH AND PROPOSED ORDER SET

HLH/Hyperinflammatory screening and monitoring

CBC with Diff
CRP
ESR
Comprehensive metabolic panel
Ferritin
Fibrinogen
Triglycerides
Proinflammatory cytokine panel (CHOP)
D-Dimer
LDH
Soluble Interleukin-2 Receptor alpha (IL-2) Ra (aka CD25)
PT/INR
PTT
IL-18
CXCL9
Consult to Immune Dysregulation IP team.

TMA labs: sC5B9, ADAMTS-13 activity w/reflex to inhibitor & Ab (Machaon)

To learn more, contact the Immune Dysregulation Program at **215-590-6706** or visit **chop.edu/immune-dysregulation**.

HLH/Hyperinflammation etiology (select)

CD107a mobilization
Perforin/Granzyme B flow cytometry
SAP/XIAP flow cytometry
Adenovirus PCR
EBV PCR
Sorted EBV PCR
- o To determine if EBV is present in B-cells, T-cells, and/or NK cells sorted from the same sample.
- o Check all subsets you're interested in sending.
- o Call the immunogenetics lab at ext. 45648 to let them know.

EBV serology
CMV PCR
CMV serology
HSV if neonate
HLH molecular genetic panel (collapsible)
- o Machaon
- o CHOP
- o Invitae

Save our specimen.
- o Rainbow tube = small volume (all of the tubes saved 24-48 hours):
  - Serum separator
  - EDTA
  - Sodium heparin
  - Lithium plasma ■