HLH Diagnostic Strategy

Cincinnati Children's
changing the outcome together

Unexplained fevers, cytopenias, hepatitis or inflammatory central nervous system (CNS) disease

- **No** → **HLH Unlikely**
- **Yes** → **Evaluations for malignancies, infections, and rheumatologic diseases should be performed**

HPI: Fever, Rash, Bleeding or
PE: Hepatosplenomegaly
PMH: Prior HLH — like episodes or
FH: HLH or known genetic lesion

- **Yes**
- **No**

Inflammatory markers elevated? Ferritin, sIL2R (sCD25), CXCL9

- **Yes**
- **No** → **HLH unlikely except in cases of isolated CNS disease**

Diagnostic Work-up

1. Diagnose active HLH

- CBC
- Fibrinogen, Coags
- Triglycerides (fasting)
- ALT, biliruben
- Ferritin
- sIL2r, CXCL9, IL-18
- Marrow (or other) biopsy

2. Screening studies for genetic causes of HLH*

- Perforin/ granzyme B
- Degranulation (CD107a) or T cell degranulation
- SAP protein (for males)
- XIAP protein (for males)

3. Ancillary**

- Viral PCRs: EBV, CMV, Adenovirus, etc.
- CT of Chest/Abd/ Neck
- MRI of brain
- Consider testing for tick or mosquito-born diseases in your area
- Coonsider PET-CT to evaluate for lymphoma

Yes, HLH → **See additional treatment considerations (next page)**

Broad genetic panel for inborn errors of immunity

Or whole exome sequencing

CNS Work-up

LP and
Brain MRI

Follow-up Studies

To assess response to therapy

Daily (initially):

- CBC
- ALT
- Fibrinogen

Weekly:

- sIL2R
- Ferritin

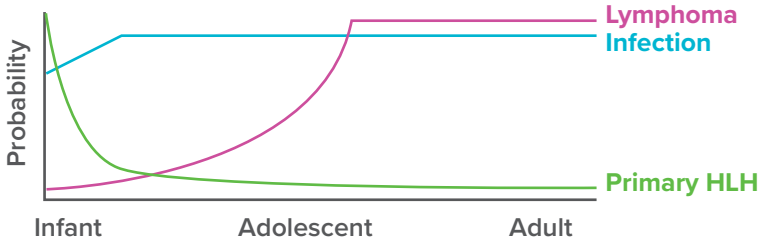
*These studies are helpful because they may rapidly confirm a clinical diagnosis by defining a potential immune/genetic etiology for HLH
**These studies may help eliminate other conditions in the differential diagnosis and/or define treatable underlying triggers for HLH.

HLH Treatment Paradigm

PAUSE

- **Before starting HLH therapy, consider how treatment may hinder diagnosis or treatment of unrecognized infections or malignancies!**
- **Hemophagocytosis, elevated ferritin, HLH-2004 diagnostic criteria, or Hscore are NOT specific to HLH**

sCD25 OR CXCL9 NORMAL, OR PROMINENT LYMPHADENOPATHY → **STOP** → **HLH less likely**



While considering HLH, primary HLH (green) is more likely in infants and young children, whereas lymphoma (pink) is more likely in teenagers and adults. Disseminated infections (blue) can manifest the features of HLH at any age.

Consider

- Malignancies: leukemia, lymphoma, other
- Infections: viral, fungal, protozoal
- MAS: Autoimmune or autoinflammatory disorders
- Primary HLH
- Inborn errors of immunity
- Drug reaction

Evaluate

- Standard and specialized testing for HLH
- Bone marrow for leukemia
- PET-CT and biopsy as needed
- Culture/PCR/antigen assays for infectious agents (EBV, adeno etc.)
- Comprehensive gene panel for IEIs, or whole exome sequencing

Treat

- Supportive care (transfusions etc.)
- Balance the need for urgent therapy with diagnostic uncertainties:
  - Rapid diagnosis and treatment is life-saving for primary HLH, but
  - Etoposide and steroids may obscure diagnosis, especially of lymphomas
  - In general, immune suppression may worsen infections while emapalumab may worsen specific atypical infections

Malignancy or infection based on imaging, biopsy, PCR etc.

Treat underlying malignancy or infection

Functional or genetic result consistent with primary HLH

Primary HLH likely; Confirm by genetic test Initiate therapy (HLH-94 or similar) based on clinical condition

Very high IL-18 (moderate elevations not specific)

MAS or inflammasome disorder; consult rheumatology for diagnostics and therapy

High EBV viral load

Evaluate NK/T-LPD by PCR on sorted cells, or EBER stain on marrow; NK/T-LPD often require lymphoma therapy. If EBV in B-cells, evaluate immune deficiencies by gene panel and consider rituximab

All tests normal

Reconsider occult infection, malignancy, or rheumatologic disorder if familial HLH not confirmed genetically or not responding to standard therapy

For more information please contact:
Cincinnati Children's HLH Center of Excellence: **hlh@cchmc.org** | **513-803-3872**

Cincinnati Children's
changing the outcome together

BRV802560