HLH Diagnostic Strategy

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

- No
- Yes

HLH Unlikely

Evaluations for malignancies, infections, and rheumatologic diseases should be performed

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

Inflammatory markers elevated? Ferritin or siL2R

- Yes
- No

HLH unlikely except in cases of isolated CNS disease

Diagnostic Work-up

1. Diagnose active HLH
   - CBC
   - Fibrinogen, Coags
   - Triglycerides (fasting)
   - ALT, bilirubin
   - 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 Studies**
   - CT of Chest/Abd/Neck
   - MRI of brain
   - Consider testing for tick or mosquito-born diseases in your area
   - Viral PCRs:
     EBV, CMV, Adenovirus, etc.
   - Consider PET-CT to evaluate for lymphoma

Cincinnati Children’s HLH Genetic Panel (NGS)

- See genetic algorithm on the next page

CNS Work-up

- LP and Brain MRI

Follow-up Studies

To assess response to therapy

- Daily (initially):
  - CBC
  - Fibrinogen
  - ALT

- 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.
Genetic HLH Screening

History and physical are consistent with HLH

Flow Cytometry Screening
All patients: Perforin, CD107a
Male patients: SAP, XIAP^  

HLH Panel by Next Generation Sequencing (NGS)
AP3B1, BLOC1S6, CD27, ITK, LYST, MAGT1, PRF1, RAB27A, SH2D1A, SLC7A7, STX11, STXB2, UNC13D (MUNC13-4), XIAP (BIRC4)

If negative, consider autoinflammatory genes, particularly NLRC4 and enteropathy genes.
Consider also testing for lysinuric protein intolerance or other metabolic diseases.

Immunology Testing
Molecular Genetics Testing

If absolute lymphocyte count <300 cells/μL, proceed to sequencing in lieu of flow cytometry testing.
Saliva is preferred method of sample collection in patients with blood cell counts <2000 cells/μL.

*If single gene testing is normal, recommend additional genetic testing
^Consider XIAP testing in female patients who lack another genetic cause of HLH

Visit the Diagnostic Center for Heritable Immunodeficiencies at www.cincinnatichildrens.org/dchi or call 513-636-4474.