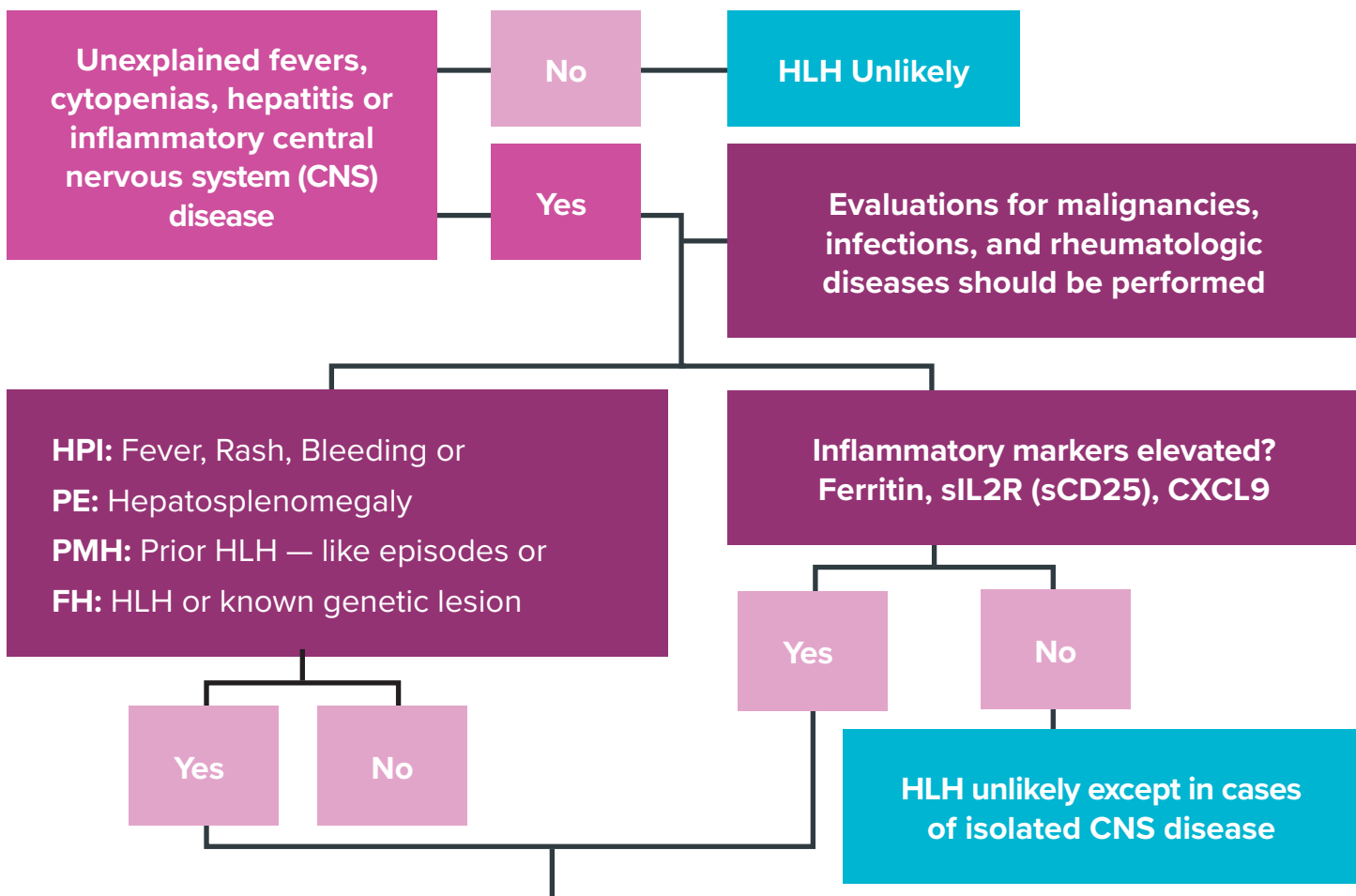
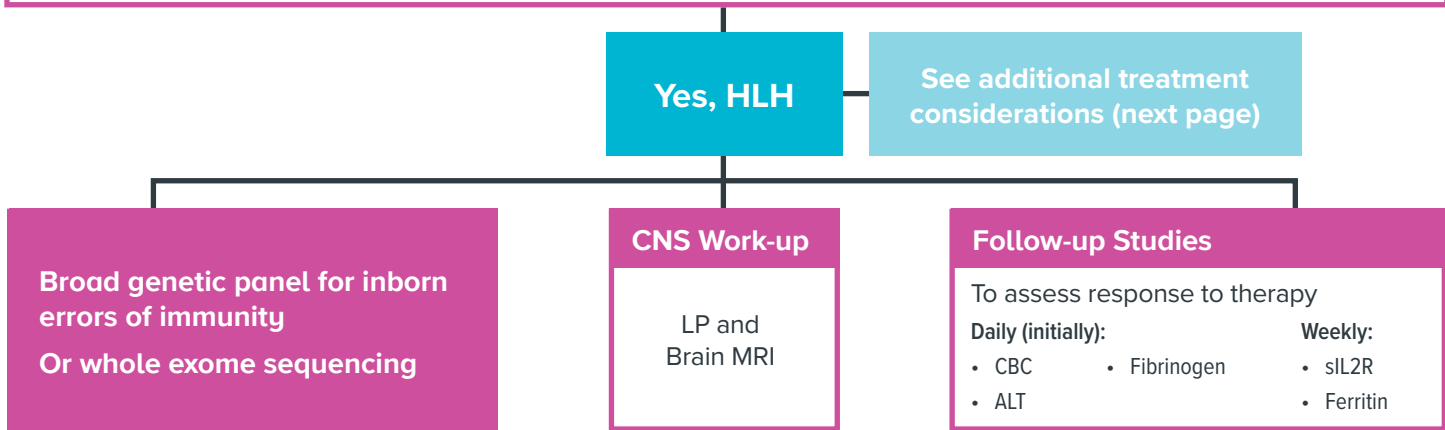


HLH Diagnostic Strategy



Diagnostic Work-up

1. Diagnose active HLH <ul style="list-style-type: none"> CBC Fibrinogen, Coags Triglycerides (fasting) ALT, bilirubin Ferritin sIL2r, CXCL9, IL-18 Marrow (or other) biopsy 	2. Screening studies for genetic causes of HLH* <ul style="list-style-type: none"> Perforin/granzyme B Degranulation (CD107a) or T cell degranulation SAP protein (for males) XIAP protein (for males) 	3. Ancillary** <ul style="list-style-type: none"> Viral PCRs: EBV, CMV, Adenovirus, etc. CT of Chest/Abd/Neck MRI of brain Consider testing for tick or mosquito-borne diseases in your area Consider PET-CT to evaluate for lymphoma
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*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

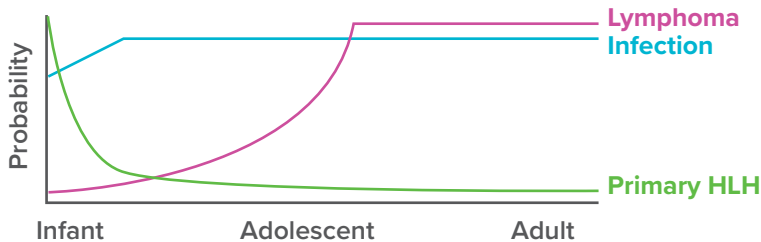


- Before starting HLH therapy, consider how treatment may hinder diagnosis or treatment of unrecognized infections or malignancies!
- Hemophagocytosis, elevated ferritin, HLH-2004 diagnostic criteria, or HScore are NOT specific to HLH

sCD25 OR CXCL9 NORMAL, OR PROMINENT LYMPHADENOPATHY



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 IELs, 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:

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