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Recognizing and managing HLH in the critical care setting:
Best practice for the multidisciplinary team

Practice aid for HLH

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Preliminary assessment before a full diagnosis work up[1]

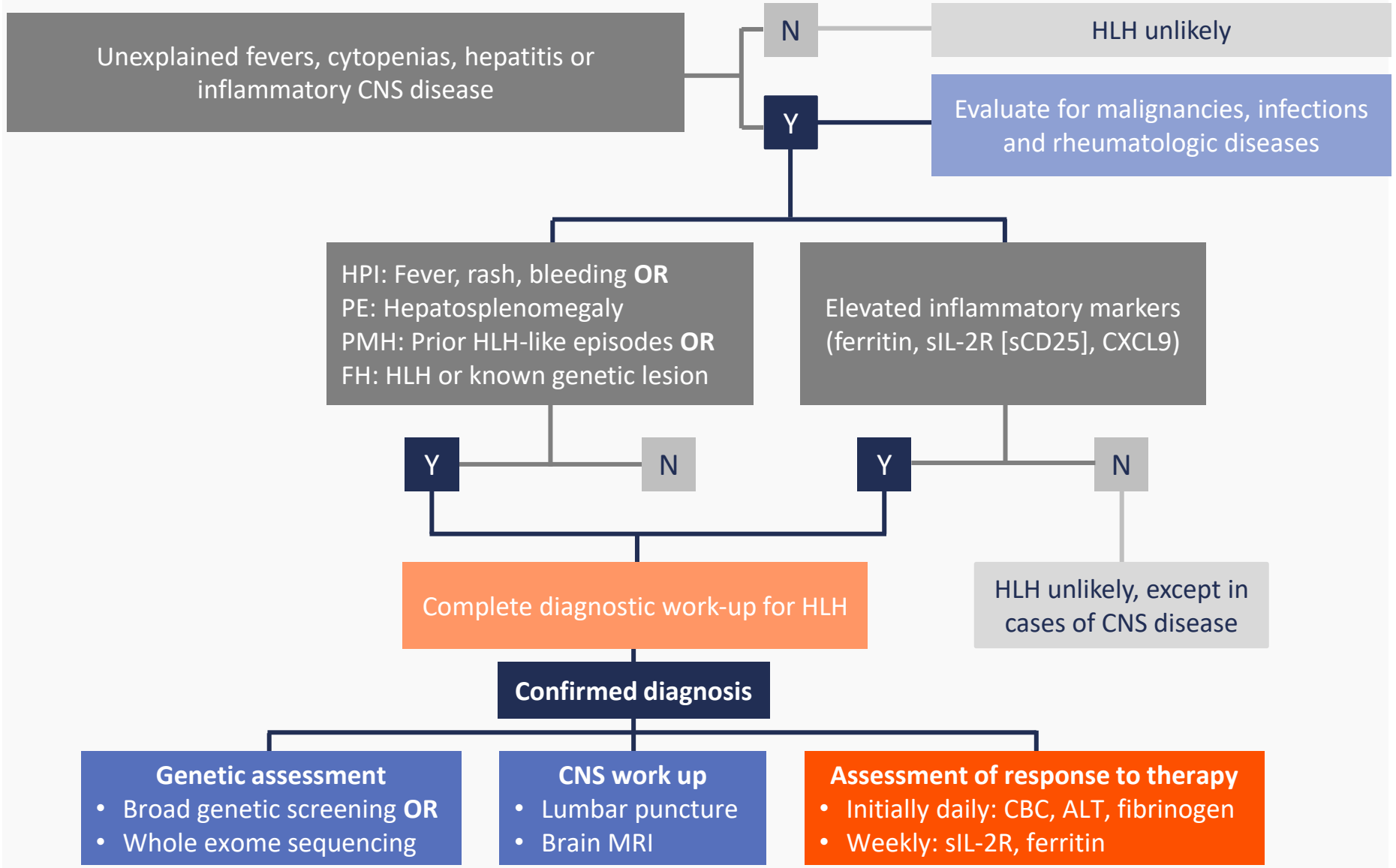

Figure adapted from Cincinnati Children's Hospital Medical Center. Available at: www.cincinnatichildrens.org/service/h/hlh/clinical/test (accessed 8 July 2024).

Patient assessment and critical care following presentation in the ED[1]

Consider

- Infections: bacterial,[2] fungal, protozoal and viral (EBV)[2]
- Malignant neoplasms:[3] leukaemia, lymphoma, other
  MAS: autoimmune (e.g. Kawasaki disease or rheumatologic conditions [sJIA or SLE])[2] or autoinflammatory disorders
- Primary HLH
- IEIs
- Drug reaction

Evaluate

- Standard and specialized testing for HLH
- Bone marrow for leukaemia
- PET-CT and biopsy, as needed
- Culture/PCR/antigen assays for infectious agents
- Comprehensive gene panel for IEIs, or whole exome sequencing

Treat

- Supportive care
- Urgent therapy provision vs diagnostic uncertainties:
  - Treatment may obscure diagnosis, especially of lymphomas
  - Immune suppression may worsen infections

Haemophagocytosis and diagnostic considerations for establishing HLH[1]

Diagnostic work-up

Tests for active HLH

- CBC
- Fibrinogen, coagulation factor tests
- Triglycerides (fasting)
- Liver function: ALT, bilirubin
- Ferritin
- Inflammation markers:
  CRP,[2] CXCL9, IL-18, sIL-2R
- Marrow (or other) biopsy

Tests for genetic causes of HLH

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

Ancillary tests

- Viral PCRs: EBV, CMV, adenovirus, etc.
- CT of chest/abdomen/neck
- Brain MRI
- Tick- or mosquito-borne diseases (as relevant locally)
- PET-CT (evaluation for lymphoma)

- ^{18}F-FDG PET/CT metabolic parameters can help identify the aetiology of secondary HLH[4]
- A high sCD25/ferritin ratio is associated with M-HLH secondary to a lymphoma[4]
- Cytokine profiling can help distinguish between primary and secondary HLH[4]

The histological corollary to clinical HLH – haemophagocytosis – is neither necessary nor sufficient for the diagnosis of HLH; it may be absent in true HLH[5]

Potential triggers for secondary HLH[6]

Children

- Infections
- Autoimmune/autoinflammatory conditions
- Malignant neoplasms
- Immunodeficiencies
- Inborn metabolic diseases

Adults

- Infections
- Malignant neoplasms
  - Occult malignancies e.g. lymphoma
- Autoimmune/autoinflammatory conditions

A thorough investigation of the underlying triggers of HLH is mandatory for optimal treatment of HLH.
Certain tiggers may influence treatment choice and/or prognosis.[6]

The treatment paradigm for HLH: First-line[6]

HLH type	Severity	Therapy
Primary and familial	• All	**HLH-94 regimen**: Induction (etoposide + dexamethasone for 8 weeks) + continuation (dexamethasone or etoposide alternating every second week + daily cyclosporine A)[7]
Secondary	• Mild • Moderate • Severe, progressive or refractory	**Treat underlying trigger**, and: • Consider corticosteroids • Dexamethasone or methyprednisolone ± anakinra • Dexamethasone or methyprednisolone ± anakinra + etoposide (with age appropriate dose reductions)
Macrophage activation syndrome	• Mild • Moderate • Severe, progressive or refractory	• Corticosteroids ± IVIg • Corticosteroids ± IVIg ± anakinra ± cyclosporine A ± tocilizumab • Corticosteroids ± IVIg ± anakinra ± cyclosporine A ± tocilizumab ± etoposide or cyclophosphamide
Malignancy-associated	• HLH-triggered organ damage (e.g. cytopenias, cholestatic icterus, encephalopathy, pulmonary infiltrates, or renal failure)	**Two-step approach** • Etoposide + corticosteroids + IVIg • Cancer-directed therapy following stabilization of HLH symptoms

The treatment paradigm for HLH: Second-line[6]

HLH type	Indication	Therapy
Primary and familial	• Adult and paediatric (newborn and older) patients • Refractory, recurrent or progressive disease or intolerance to conventional HLH therapy	• Emapalumab + dexamethasone[8]
Other (off label)		• Alemtuzumab • Tocilizumab • Ruxolitinib

Early and aggressive intensive interventions, such as broad-spectrum antibiotics, vasopressors, renal replacement therapy, mechanical ventilation, blood product replacement, and management of coagulopathy, are often required in HLH/MAS-HLH.[6]

Abbreviations

2R, 2-receptor; ALT, alanine transaminase; CBC, complete blood count; CD, cluster of differentiation; CMV, cytomegalovirus; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; CXCL9, C-X-C motif chemokine ligand 9; EBV, Epstein-Barr virus; ED, emergency department; ^{18}F-FDG, 2-deoxy-2-[fluorine-18]fluoro-D-glucose; FH, family history; HLH, haemophagocytic lymphohistiocytosis; HPI, history of present illness; IEI, inborn errors of immunity; IL, interleukin; IVIg, intravenous immunoglobulin; M-, malignancy associated; MAS, macrophage activation syndrome; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PE, physical exam; PET, positron emission tomography; PMH, prior medical history; s-, soluble; SAP, signalling lymphocytic activation molecule-associated protein; sJIA, systemic juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; XIAP, X-linked inhibitor of apoptosis protein.

References

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