

*Distinguishing critical conditions with similar presentations:
primary hemophagocytic lymphohistiocytosis (pHLH) and sepsis*



4 signs that may suggest pHLH

Despite distinct etiologies, pHLH and sepsis both involve a dysregulated immune response that results in hyperinflammation and multiorgan dysfunction. Because they can share similar signs and symptoms, it can be difficult to identify a patient with pHLH before it's too late.¹

Including pHLH in your differential diagnosis when you suspect sepsis can help ensure timely and accurate identification.

Use these 4 signs to help you know when to suspect pHLH.

The signs are listed from most to least prevalent in patients with sepsis.¹

pHLH: A rare, rapidly progressive, life-threatening genetic condition⁴

sepsis: A common, but extreme, life-threatening complication of infection^{2,5}

1. Prolonged fever

Fever is common in both pHLH and sepsis and tends to persist until inflammation is subdued. If a patient has sepsis, fever should subside with antibiotic treatment of the source of infection. Fever that persists despite antibiotic treatment may indicate pHLH.^{1,2}

2. Hyperferritinemia

Ferritin may be elevated in patients with sepsis, but dramatically increased ferritin levels are characteristic of patients with pHLH. While HLH-2004 diagnostic criteria include ferritin ≥ 500 $\mu\text{g/L}$, ferritin $>10,000$ $\mu\text{g/L}$ is likely a better indicator of pHLH.^{1,2}

3. High sCD25

Though uncommon in sepsis, elevated sCD25 (soluble interleukin-2 receptor) is a diagnostic indicator for patients with pHLH. sCD25 activity ≥ 2400 U/mL may indicate pHLH.^{1,2}

4. Hypofibrinogenemia

Also uncommon in sepsis, hypofibrinogenemia is often observed in patients with pHLH. Fibrinogen levels ≤ 1.5 g/L may indicate pHLH.¹⁻³

Please note that this guidance may not apply to all cases since the signs and symptoms of pHLH and sepsis present across a spectrum and may vary between patients.



If you suspect your patient may have pHLH, consult a hematologist/oncologist who may be able to help.

HLH-2004 diagnostic criteria

If you suspect pHLH, there's no time to wait to consult a hematologist/oncologist for further guidance. Fulfillment of 5 of the 8 HLH-2004 criteria listed below can be used to suspect a diagnosis in the absence of an underlying cause, such as malignancies.^{3,4}

- Fever $\geq 38.5^{\circ}\text{C}$ ⁴**
- Hemophagocytosis* in bone marrow, spleen, or lymph nodes**
- Low or absent natural killer-cell activity**
- Hypofibrinogenemia (≤ 1.5 g/L) and/or hypertriglyceridemia (≥ 265 mg/dL)[†]**
- Splenomegaly**
- Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood):**
 - Hemoglobin < 90 g/L[‡]
 - Platelets $< 100 \times 10^9$ /L
 - Neutrophils $< 1 \times 10^9$ /L
- Ferritin (≥ 500 $\mu\text{g/L}$)**
- sCD25 ≥ 2400 U/mL**

*Note that hemophagocytosis is not specific nor always present in early stages of the disease.⁴

[†]Fasting triglycerides.³

[‡]In infants < 4 weeks old: hemoglobin < 100 g/L.³



If you suspect pHLH, consult a hematologist/oncologist for further guidance.

Ask your local Sobi Health Systems Director how they can help connect you with a pHLH expert.

References: **1.** Bursa D, Bednarska A, Pihowicz A, Paciorek M, Horban A. Analysis of the occurrence of hemophagocytic lymphohistiocytosis (HLH) features in patients with sepsis: a prospective study. *Sci Rep.* 2021;11(1):10529. Published online May 18, 2021. doi:10.1038/s41598-021-90046-4 **2.** Machowicz R, Janka G, Wiktor-Jedrzejczak W. Similar but not the same: differential diagnosis of HLH and sepsis. *Crit Rev Oncol Hematol.* 2017;114:1-12. doi:10.1016/j.critrevonc.2017.03.023 **3.** Henter J-I, Horne AC, Aricó M, et al; Histiocyte Society. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007;48(2):124-131. doi:10.1002/xbc.21039 **4.** Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood.* 2011;118(15):4041-4052. doi:10.1182/blood-2011-03-278127 **5.** What is sepsis. Sepsis Alliance. Updated August 2, 2021. Accessed October 18, 2021. <https://www.sepsis.org/sepsis-basics/what-is-sepsis>