Hemophagocytic Lymphohistiocytosis (HLH) in the Hospital Setting

Definition and Epidemiology

- Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome characterized by excessive immune activation, leading to cytokine storm, multi-organ dysfunction, and hemophagocytosis. It is classified as primary (genetic) or secondary (acquired, triggered by infections, malignancy, or autoimmune diseases). HLH requires urgent hospital management, often in the ICU.
- Prevalence:
  - Incidence is ~1-2 per million annually, with primary HLH more common in children (<0.1% of pediatric admissions) and secondary HLH in adults (1-2% of hematology/oncology admissions). Secondary HLH is associated with ~5-10% of severe sepsis cases.
- Risk Factors:
  - EBV infection, lymphoma, autoimmune diseases (e.g., SLE), immunosuppression, genetic mutations (e.g., PRF1).
- Rare Demographics:
  - Neonatal HLH (familial), elderly with malignancy-associated HLH, post-transplant HLH.

Pathophysiology

- Mechanisms:
  - HLH results from uncontrolled activation of T-cells and macrophages, driven by defects in cytotoxic function (primary) or excessive antigenic stimulation (secondary). This leads to a cytokine storm (IFN-γ, IL-6, IL-10), causing tissue damage, hemophagocytosis, and organ failure.
- Effects:
  - Hyperinflammation causes fever, cytopenias, hepatosplenomegaly, and coagulopathy. Hemophagocytosis in bone marrow, spleen, or lymph nodes leads to pancytopenia. Elevated ferritin and triglycerides reflect macrophage activation and lipid metabolism disruption.

- Molecular Pathways:
  - **Primary HLH:** Mutations (e.g., PRF1, UNC13D) impair perforin/granzyme-mediated cytotoxicity, preventing T-cell apoptosis. Secondary HLH: EBV or malignancy triggers TLR9/NF-κB, amplifying IL-12 and TNF-α. Soluble IL-2 receptor (sIL-2R) reflects T-cell activation.
- Key Pathway:
  - Immune hyperactivation → Cytokine storm → Hemophagocytosis → Multi-organ dysfunction.

Causes

Category	Common Causes	Rare Causes	Notes
Infectious	EBV, CMV, HSV	HIV, histoplasmosis, leishmaniasis	EBV in 50% of secondary HLH; viral PCR critical
Malignancy	T/NK-cell lymphoma, AML	Hodgkin lymphoma, solid tumors	Lymphoma in 30-40% of adult HLH; biopsy key
Autoimmune	SLE, Still's disease	RA, Kawasaki disease	Macrophage activation syndrome (MAS) in 10% of SLE
Primary (Genetic)	PRF1, UNC13D mutations	STX11, STXBP2 defects	Familial HLH (FHL) in children; genetic testing
Iatrogenic	Chemotherapy, immunosuppression	CAR-T therapy, transplant	Post-transplant HLH rare but severe
Other	None	Pregnancy, sarcoidosis	Pregnancy-associated HLH mimics preeclampsia

Clinical Presentation

- Symptoms:
  - Persistent fever (>38.5°C, >7 days)
  - Fatigue, weight loss, night sweats
  - Hepatosplenomegaly, jaundice
- Rare
  - Rash (erythematous, maculopapular), seizures (CNS involvement), respiratory distress
- Exam
  - Splenomegaly, hepatomegaly
  - Lymphadenopathy, pallor (anemia)
  - Petechiae, bruising (thrombocytopenia)
- Rare
  - Neurological deficits (CNS HLH), cyanosis (ARDS)

- Red Flags
  - Ferritin >10,000 ng/mL, cytopenias (2-3 cell lines), AMS, DIC signs

Labs and Studies

- Labs
  - CBC Cytopenias (Hb <9 g/dL, platelets <100K, ANC <1K)
  - Ferritin >500 ng/mL (severe >10,000)
  - Triglycerides >265 mg/dL, fibrinogen <150 mg/dL
  - LFTs Elevated AST/ALT, bilirubin
- Advanced
  - sIL-2R >2400 U/mL, IL-6, NK cell activity (low), genetic panel (PRF1)
- Imaging
  - CT Abdomen Splenomegaly, lymphadenopathy
  - MRI Brain CNS involvement (T2 hyperintensities)
  - PET-CT Malignancy workup (lymphoma)
- Advanced
  - Bone marrow biopsy (hemophagocytosis), liver biopsy (infiltration)
- Other
  - Bone Marrow Biopsy Hemophagocytosis (macrophages engulfing cells)
  - Viral PCR EBV, CMV, HIV
  - HLH-2004 Criteria
  - ≥5/8 (fever, splenomegaly, cytopenias, hypertriglyceridemia/ hypofibrinogenemia, hemophagocytosis, low NK activity, ferritin >500, sIL-2R >2400)
- Advanced
  - Flow cytometry (lymphoma), CSF analysis (CNS HLH)

Diagnosis

- Criteria
  - **HLH-2004:** ≥5/8 criteria met, or genetic confirmation (primary HLH). Secondary HLH diagnosed with clinical suspicion, triggers (e.g., EBV, lymphoma), and lab/imaging support.
- Differential
  - Sepsis, TTP, leukemia, MAS, multi-organ failure, acute liver failure.
- Flowsheet
  - **Step 1** History/Exam Fever, splenomegaly, cytopenias; assess triggers (infection, malignancy)
  - **Step 2** Labs CBC, ferritin, triglycerides, fibrinogen, sIL-2R, viral PCR
  - **Step 3** Imaging CT/PET-CT (lymphoma), MRI (CNS)

- **Step 4** Biopsy Bone marrow, lymph node; confirm hemophagocytosis
- **Step 5** HLH-2004 Criteria Apply criteria; rule out mimics (sepsis, TTP)

Treatment

- **General Principles**
  - Suppress hyperinflammation, treat triggers, and support organ function, often requiring ICU care. HLH-94 protocol is standard for severe cases.
- **Supportive Care**
  - Transfusions: PRBCs (Hgb <7 g/dL), platelets (<20K)
  - Antibiotics: Broad-spectrum (e.g., ceftriaxone 2 g IV q24h) for suspected infection
  - Monitoring: Vitals q2h, CMP/CBC q12h, ferritin q48h
- **Specific Therapies**
  - HLH-94 Protocol
  - Dexamethasone 10 mg/m²/day (taper), etoposide 150 mg/m² IV qweek x 8 weeks
- **Infections**
  - Ganciclovir 5 mg/kg IV q12h (CMV), voriconazole (fungal), rituximab (EBV)
- **Malignancy**
  - Chemotherapy (e.g., CHOP for lymphoma), transplant (refractory)
- **Autoimmune**
  - Pulse steroids (methylprednisolone 1 g IV q24h x 3d), anakinra 100 mg SC daily
- **Primary HLH**
  - HSCT (curative), alemtuzumab 0.2 mg/kg/day (bridge to transplant)
- **Advanced**
  - Emapalumab (anti-IFN-γ) 1 mg/kg IV q3d, ruxolitinib 25 mg PO BID (refractory)
- **Monitoring**
  - Ferritin, sIL-2R q48h (response)
  - Bone marrow repeat at 8 weeks
- **Transplant consult for primary/refractory HLH**

Complications

- Acute
  - Multi-Organ Failure
  - Sepsis, ARDS, AKI (30-50% mortality)
  - DIC
  - Bleeding, thrombosis (20-30%)

    - CNS Involvement
    - Seizures, coma (10-15%)
- Long-Term
    - Relapse
    - 20-30% without HSCT (primary HLH)
    - Chronic Organ Damage
    - Liver fibrosis, CKD
- Rare
    - Secondary malignancies (post-chemotherapy), amyloidosis

Clinical Scenarios

Case 1 Secondary HLH (EBV)

- Presentation: 30 y/o M with fever, fatigue, splenomegaly for 2 weeks. Vitals BP 110/70, HR 100, SpO2 96%, RR 18. Exam Jaundice, lymphadenopathy.
- Labs/Studies; Ferritin 15,000 ng/mL, Hb 8 g/dL, platelets 80K, EBV PCR 50,000 IU/mL. Bone marrow Hemophagocytosis.
- Interpretation: Secondary HLH, EBV-triggered.
- Management: HLH-94 (dexamethasone, etoposide), rituximab 375 mg/m² IV qweek. ICU monitoring. Ferritin drops to 2000 ng/mL by week 4.

Case 2 Primary HLH (Pediatric)

- Presentation: 2 y/o F with fever, rash, hepatomegaly. Vitals BP 90/60, HR 120, SpO2 94%, RR 20. Exam Pallor, petechiae.
- Labs/Studies: Ferritin 8000 ng/mL, sIL-2R 5000 U/mL, PRF1 mutation. Biopsy Hemophagocytosis.
- Interpretation: Primary HLH, familial.
- Management: HLH-94, alemtuzumab 0.2 mg/kg/day. HSCT planned. Stable by week 6.

Case 3 Malignancy-Associated HLH

- Presentation: 65 y/o M with weight loss, fever, lymphadenopathy. Vitals BP 100/60, HR 110, SpO2 92%, RR 22. Exam Splenomegaly.
- Labs/Studies: Ferritin 20,000 ng/mL, triglycerides 300 mg/dL, PET-CT Lymphadenopathy. Biopsy T-cell lymphoma.
- Interpretation: Secondary HLH, lymphoma-driven.
- Management: CHOP chemotherapy, dexamethasone 10 mg/m²/day. Oncology consult. Partial response by week 3.

Expert Tips

- Check ferritin, sIL-2R early; >10,000 ng/mL or rising suggests HLH
- Use EBV PCR, PET-CT to identify triggers; biopsy confirms diagnosis
- Start HLH-94 within 24h of diagnosis; steroids first-line
- Monitor DIC (D-dimer, fibrinogen); transfuse for bleeding
- Consider emapalumab in refractory HLH; HSCT for primary
- Pitfall
    - Missing lymphoma; PET-CT, flow cytometry critical
- Advanced
    - Anakinra for MAS; genetic panel (PRF1, UNC13D) for familial HLH

Key Pearls

- HLH-2004 criteria (≥5/8) diagnose HLH; ferritin >500 key marker
- EBV, lymphoma common triggers; viral PCR, PET-CT guide workup
- HLH-94 (dexamethasone, etoposide) is standard; HSCT for primary
- Infections (CMV, PCP) need urgent antimicrobials, prophylaxis
- Multi-organ failure, DIC are major risks; ICU care often required

References

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