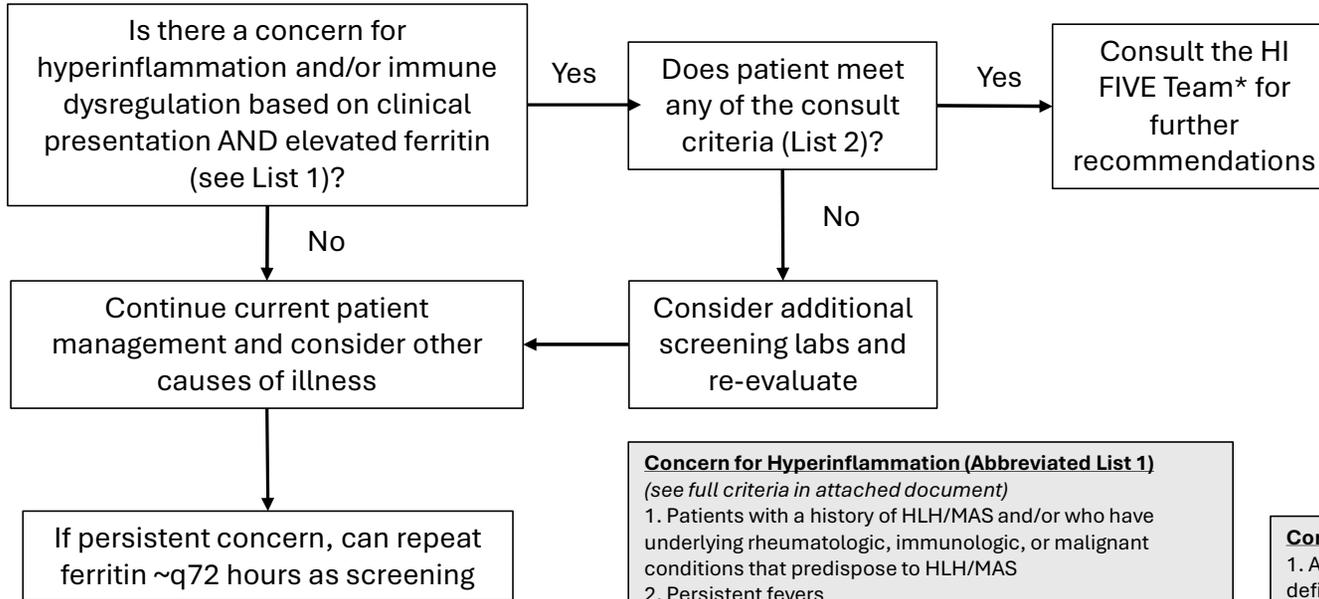


## Hyperinflammation/Immune Dysregulation Pathway and HI FIVE Consults



**HyperInFlammatory Interdisciplinary Visits and Evaluation Team**  
The HI FIVE team has expertise in immune dysregulation and will provide a coordinated multidisciplinary consult on inpatients with a concern or diagnosis of hyperinflammation .

*\*The HI FIVE contact can be reach through the Synergy call system under the "HI FIVE" call number. Upon choosing the HI FIVE contact, Synergy will list which service is acting as the primary contact team. You should then contact the service listed and specifically request a "HI FIVE" consult.*

**Concern for Hyperinflammation (Abbreviated List 1)**  
*(see full criteria in attached document)*

1. Patients with a history of HLH/MAS and/or who have underlying rheumatologic, immunologic, or malignant conditions that predispose to HLH/MAS
2. Persistent fevers
3. Hepatosplenomegaly and/or diffuse lymphadenopathy
4. At least 2 cytopenias
5. Severe hyperinflammation related to infection
6. Neurologic symptoms
7. Hepatobiliary dysfunction
8. Hemophagocytosis on tissue biopsy
9. Additional lab abnormalities associated with immune dysregulation
  - a. Albumin < 3.5 g/dL
  - b. Lactate Dehydrogenase (LDH) > 450 IU/L
  - c. Fibrinogen < 150 mg/dL
  - d. Fasting triglycerides > 265 mg/dL

**Consult Criteria (List 2)**

1. Any patient with temperature derangement during the admission, defined as hyperthermia (temperature >38.5 ° C) or hypothermia (temperature < 36.0 ° C), and a ferritin > 500 ng/mL that is **NOT** explained by conditions associated with iron overload.
2. Patients who have condition(s) in **List 1** that are not explained by the degree of underlying illness and/or medications AND a ferritin > 500 ng/mL.
3. Concern that the patient is at high risk for the development of immune dysregulation despite not currently meeting typical clinical and laboratory findings in **List 1**.

## HI FIVE Guidance Document for Inpatient Teams

### 1. Who is the HI FIVE Team?

The HyperInflammatory/ Interdisciplinary Visits and Evaluation Team is a multi-disciplinary team of sub-specialists with clinical expertise in immune dysregulation that serves as the primary consulting group for admitted patients at Vanderbilt Children's Hospital with concern for hyperinflammation.

### 2. What is the difference between hyperinflammation, immune dysregulation, and hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS)?

- a. **Hyperinflammation** refers to "excessive activity of the immune system with current or high likelihood of developing severe pathology related to this immune activity." Hyperinflammation may be localized to a single organ, or systemic and involve 2 or more organ systems.
- b. **Immune dysregulation:** During hyperinflammation, the immune response may be controlled and regulated, meaning the intensity of the immune response is appropriate for the trigger to the immune system. In other situations, the immune activity may be dysregulated or uncontrolled and inappropriate relative to the immune trigger. **Although immune modulation may be beneficial in a minority of patients with regulated hyperinflammation, it is much more likely to be required in the setting of immune dysregulation.**
- c. **HLH and MAS** are systemic forms of a dysregulated, hyperinflammatory state that pose a significant mortality risk from the immune pathology and require immune modulation to prevent severe outcomes.

### 3. Does the HI FIVE Team want to know about all hyperinflammatory patients or just patients with immune dysregulation?

The HI FIVE Team should be notified for any patient with hyperinflammation with evidence or concern for development of immune dysregulation. Upon review of each patient, the HI FIVE Team may determine that the inflammatory response is regulated and appropriate and no additional work-up is necessary or suggest additional evaluation and possible treatment options.

### 4. How do I identify admitted patients with hyperinflammation and/or immune dysregulation?

Patients with hyperinflammation and/or immune dysregulation can have a variable presentation, and, therefore, may be difficult to identify amongst a sick population of admitted pediatric patients. Clinical features that are associated with immune dysregulation may include features in the following List 1:

**List 1: Clinical features associated with immune dysregulation:**

1. Patients with a history of HLH/MAS and/or who have underlying rheumatologic, immunologic, or malignant conditions that predispose to HLH/MAS.
  - a. Disorders include but not limited to systemic juvenile idiopathic arthritis/Still's disease, systemic lupus erythematosus, Kawasaki Disease, familial HLH, Chediak Higashi Syndrome, Griscelli Syndrome type 2, Hermansky-Pudlak Syndrome type 2, X-linked lymphoproliferative disease 1 and 2, XMEN (MAGT1 deficiency), NOCARH (CDC42 dysfunction), severe combined immunodeficiency, chronic granulomatous disease, Wiskott-Aldrich syndrome, 22q11.2 deletion (DiGeorge) syndrome, lymphoma
2. Persistent fevers
3. Hepatosplenomegaly and/or diffuse lymphadenopathy
4. At least 2 cytopenias
  - a. Hemoglobin < 9 g/dL, platelets <  $100 \times 10^9/L$ , absolute neutrophil count < 1000 cells/mm<sup>3</sup>
5. Severe hyperinflammation related to infection
  - a. Development of disseminated intravascular coagulation (DIC)
  - b. Requirement for prolonged (>24 hours) vasopressor support
  - c. Admission required secondary to complications of EBV, CMV, HSV, or adenovirus
6. Neurologic symptoms
  - a. Headaches, cognitive changes, focal examination findings, seizures
  - b. MRI with diffuse or focal white matter changes in the cerebrum and cerebellum
  - c. CSF with elevated intracranial pressure, protein, and/or white blood cells
7. Hepatobiliary dysfunction
  - a. Elevated AST, ALT, and/or bilirubin
  - b. Elevated coagulation studies (PT, PTT)
  - c. Acute liver failure
8. Hemophagocytosis on tissue biopsy
9. Additional lab abnormalities associated with immune dysregulation
  - a. Low albumin < 3.5 g/dL
  - b. Elevated lactate dehydrogenase (LDH) > 450 IU/L
  - c. Low fibrinogen < 150 mg/dL
  - d. Fasting high triglycerides > 265 mg/dL

An initial laboratory screening with a ferritin level in addition to the clinical presentation can be valuable in deciding whether to consult the HI FIVE Team. If ferritin is normal, consider repeating ferritin every 72 hours for continued screening for immune dysregulation and additional testing as outlined in List 1.

**5. What are patient indications for contacting the HI FIVE Team?**

General guidelines for contacting the HI FIVE Team regarding a patient are listed below, but as early identification and treatment initiation is critical for patient outcomes, you should contact the HI FIVE team for any concerns of hyperinflammation that could lead to immune dysregulation.

**List 2: Patient Indications for Contacting the HI FIVE Team**

1. Any patient with temperature derangement during the admission, defined as hyperthermia (temperature  $\geq 38.5$ ) OR hypothermia (temperature  $< 36.0$ ), and a ferritin greater than 500 ng/mL that is **NOT** explained by conditions associated with iron overload.
2. Patients who have condition(s) in **List 1** that are not explained by the degree of underlying illness and/or medications AND a ferritin  $> 500$  ng/mL.
3. Concern that the patient is at high risk for the development of immune dysregulation despite not currently meeting typical clinical and laboratory findings in **List 1**.

Another way to think about your patient is to determine if the degree of inflammation were to continue for the next 2-3 days without improvement, the patient would be at high risk of severe complications. If this is the case, the patient should be considered for consultation with the HI FIVE team.

**6. How do I contact the HI FIVE Team?**

The HI FIVE contact can be reached through the Synergy call system under the "HI FIVE" call number. Upon choosing the HI FIVE contact, Synergy will list which service is acting as the primary contact team. You should then contact the service listed and specifically request a "HI FIVE" consult.

**7. If I consult the HI FIVE Team, do I need to consult other sub-specialty teams to help care for the patient?**

Yes, you should consult sub-specialty teams that you deem important to help diagnose and care for the patient in addition to the HI FIVE Team. The HI FIVE Team may suggest additional consult teams to help you with care for your patient.

**8. How will the HI FIVE Team communicate and document the recommendations for the patient?**

Once consulted, the on-call HI FIVE contact service will review the case and if concerned for immune dysregulation, will contact all members of the HI FIVE team to urgently discuss the case. Additional members of the patient's care team will also be included in discussions about the patient to consolidate information on the case and facilitate communication. Once consensus is reached on recommendations for the patient, the HI FIVE attending and/or supervised fellow will communicate the HI FIVE recommendations to the primary team and document the assessment and plan in a multispecialty EPIC document. The HI FIVE contact service will continue to follow the patient and update the HI FIVE Team as necessary for important updates on the patient course with appropriate documentation and communication to the primary team.

**9. Will the HI FIVE team follow the patient at discharge, and can I consult the HI FIVE Team for outpatient care?**

No, currently the HI FIVE team is an inpatient only service. If follow-up is required as an outpatient, the patient should be followed by an appropriate sub-specialty service(s). If a new patient is being seen as an outpatient, we recommend referring the patient to an appropriate sub-specialty service with expertise in the suspected immune defect.