មន្ទីរពេទ្យ កាល់ម៉ែត HOPITAL Calmette	**SOP for Management of Secondary Hemophagocytic Lymphohistiocytosis (sHLH) in Adult**	Date/Place April 2024/PP	Number of page

OBJECTIVES

To provide guidelines for Physicians and Nurses for the management of secondary hemophagocytic lymphohistiocytosis (sHLH) in haemato-oncology patients.

SCOPE

This document outlines the indication for treatment and management for all those patients presumed or diagnosed with secondary hemophagocytic lymphohistiocytosis (sHLH) .

REFERENCE TEAM

REFERENCES

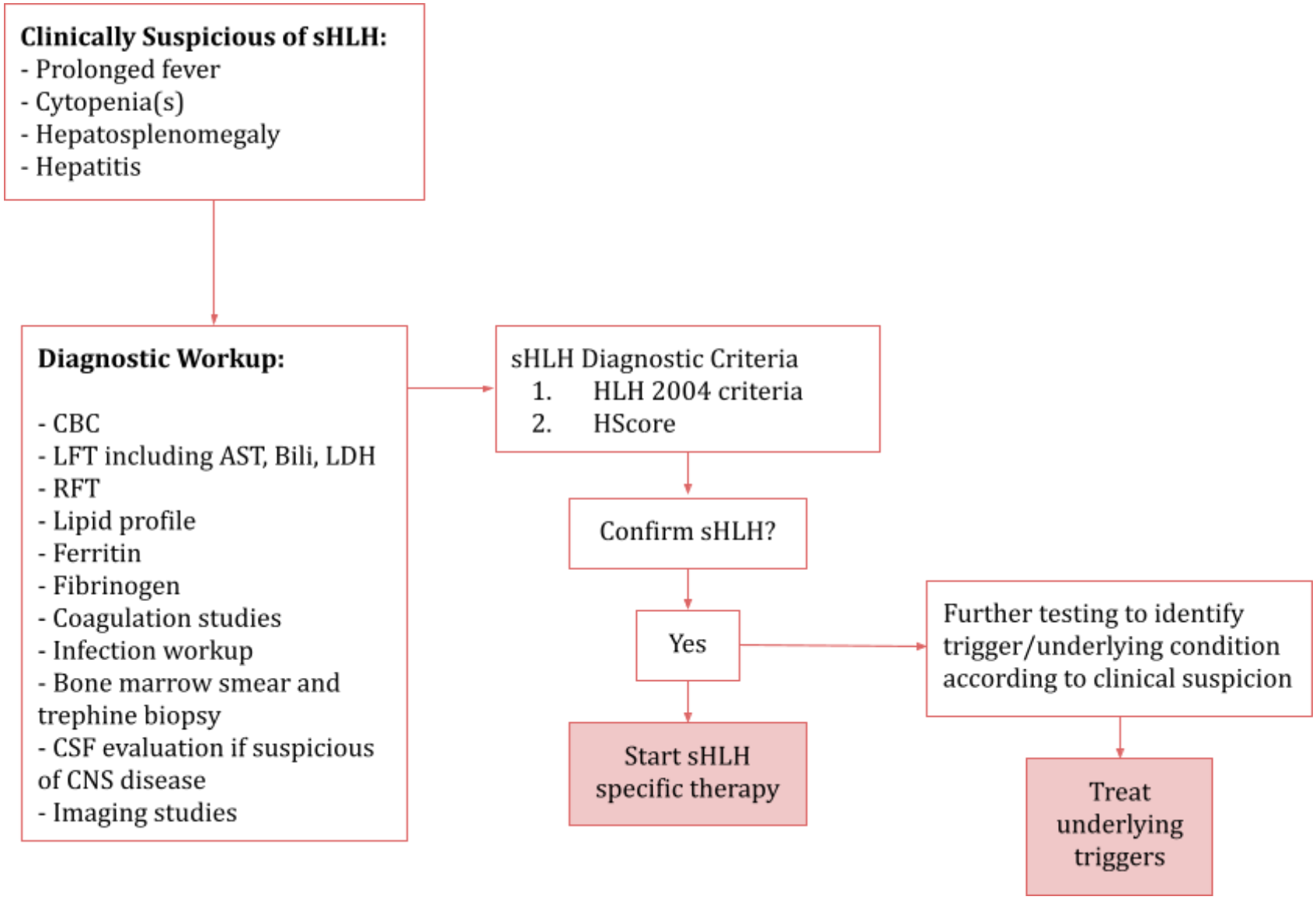
Hospital Director	Head of Technical Bureau	Representative of Compilation Team

Definition	Hemophagocytic lymphohistiocytosis (HLH) is a condition of hyperinflammation leading to cytokine storm due to immune system dysregulation. The primary (genetic) form is most common in children (pHLH), whereas the secondary (acquired) form is most frequent in adults (sHLH).
Clinical manifestation	- Prolonged unexplained fever unresponsive to antibiotics - Bone marrow failure syndrome i.e. persistent cytopenia - Severe hepatitis - Skin manifestations i.e. erythroderma, petechiae and generalized purpura - Neurological manifestations i.e. mild cognitive impairment, delirium, seizures, and coma - Hepatomegaly or splenomegaly
Laboratory findings	- Cytopenia(s) (usually 2 or more lineages) - Elevated AST, ALT, Bilirubin, LDH, Trigliceride, D-Dimer - Marked elevation of Ferritin - Abnormal coagulation studies: prolonged PT and low fibrinogen - Presence of hemophagocytosis in bone marrow smear

sHLH can be triggered by infection, malignancy, metabolic disorders and rheumatological disease and has a high acute mortality rate of 30-60%. Early recognition and treatment of sHLH potentially improves outcomes.

Possible triggers or underlying cause of sHLH	
Infectious	EBV, CMV, HIV, Leishmania, COVID-19, hepatitis A, B or C, HHV-6, HIV-1, H1N1 influenza, Parvovirus B19, Bacterial sepsis
Inflammatory	sJIA, AOSD, SLE, Kawasaki disease, spondyloarthritis, rheumatoid arthritis, ALPS, Sarcoidosis
Malignant	BCL, HL, TCL, CLL, MDS, AML, ALL, CML, HCC
Iatrogenic	Haematopoietic stem cell transplantation, CAR-T therapies

** Further investigations for sHLH triggers must be done according to clinical suspicion for prompt and appropriate treatment of the underlying cause.


Clinically Suspicious of sHLH:
- Prolonged fever
- Cytopenia(s)
- Hepatosplenomegaly
- Hepatitis
Diagnostic Workup:
- CBC
- LFT including AST, Bili, LDH
- RFT
- Lipid profile
- Ferritin
- Fibrinogen
- Coagulation studies
- Infection workup
- Bone marrow smear and trephine biopsy
- CSF evaluation if suspicious of CNS disease
- Imaging studies
sHLH Diagnostic Criteria
1. HLH 2004 criteria
2. HScore
Confirm sHLH?
Yes
Start sHLH specific therapy
Further testing to identify trigger/underlying condition according to clinical suspicion
Treat underlying triggers

Diagnosis of sHLH is based on either HLH 2004 Criteria or HScore

1. HLH 2004 Criteria (requires 5 out of 8 criteria)

    a. Fever ≥ 38.5°C
    b. Splenomegaly
    c. Cytopenias affecting at least two of three lineages in the peripheral blood
    d. Hypertriglyceridemia and/or hypofibrinogenemia
    e. Hemophagocytosis in bone marrow, spleen, or lymph nodes
    f. Low or absent NK-cell activity
    g. Hyperferritinemia (>500 ng/mL)
    h. Elevated sCD25

2. HScore

Parameter	Criteria for scoring		
Known immunosuppression	0 (no)	18 (yes)	
Temperature (°C)	0 (< 38.4)	33 (38.4–39.4)	49 (> 39.4)
Organomegaly	0 (no)	23 (hepatomegaly or splenomegaly)	38 (hepatomegaly & splenomegaly)
No of cytopenia	0 (1 lineage)	24 (2 lineages)	34 (3 lineages)
Ferritin (ng/ml)	0 (< 2,000)	35 (2,000–6,000)	50 (> 6,000)
Triglyceride (mmol/L)	0 (< 1.5)	44 (1.5–4)	64 (> 4)
Fibrinogen (gm/liter)	0 (> 2.5)	30 (≤ 2.5)	
Serum AST (IU/liter)	0 (< 30)	19 (≥ 30)	
Hemophagocytosis features on bone marrow aspirate	0 (no)	35 (yes)	

HScore	Probability of HLH	HScore	Probability of HLH
90	<1	180	70
100	1	190	80
110	3	200	88
120	5	210	93
130	9	220	96
140	16	230	98
150	25	240	99
160	40	250	>99
170	54		

* Online calculator: https://saintantoine.aphp.fr/score/

Management of sHLH

1st line - Corticosteroid
Dexamethasone 10 mg/m2 IV daily for at least 3 days or Methylprednisolone 250-1000 mg IV once daily for at least 3 days ** Switch to oral prednisolone (minimum dose 1mg/kg/day) ** Slowly taper off only once sHLH is in remission ** Steroids can hinder the diagnosis of certain malignancies (e.g. lymphoma) which is of concern in patients in whom the underlying disease process is cancer. Definitive testing for malignancy (typically biopsy/aspirate of bone marrow, lymph node and/or other indicated tissues) should be attempted prior to corticosteroid administration where possible

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2nd line - Cyclosporine
5 mg/kg/day oral in two divided doses; can increase up to 7mg/kg/day ** Blood cyclosporine levels: 150-300 ng/ml ** Use in association with 1st line

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3rd line - Etoposide
Week 1 & 2: 150 mg/m^2 intravenously twice a week (on day 1 and day 4) Week 3 to 9: 150 mg/m^2 intravenously once a week ** Lower dose of 50 to 100 mg/m^2 may be used based on the clinical status of the patient. ** Use in association with 1st line and 2nd line

Note:

1. When to escalate treatment?
    - Lack of improvement, persistent fever, worsening lab, increasing ferritin despites multiple days of treatment initiation
2. CNS involvement: Intrathecal therapy with methotrexate 12 mg weekly until normal CSF

Treatment of Underlying Cause
• EBV triggered HLH: Rituximab • Other viral cause: antiviral as appropriate • Leishmania: Amphotericin B • Autoimmune triggered HLH (i.e. SLE): Rituximab or cyclophosphamide • Malignancy triggered HLH: disease specific treatments

Supportive Care
• Antibiotic/fungal/viral prophylaxis alongside immunosuppressive therapy • Blood product support (maintain platelet count above 20 Giga/L) • Gastric protection (when appropriate) • Bone protection (when appropriate)