Management of Haemophagocytic Lymphohistiocytosis (HLH) in Adults Guideline

Category:	Guideline
Summary:	This guideline aims to assist clinicians in the identification and immediate management of patients with haemophagocytic lymphohistiocytosis (HLH).
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Author(s):	Consultant Haematologist Lead Haematology Pharmacist
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Lead Director: Chief Medical Officer

Issue Date: August 2025

This document is uncontrolled once printed.

It is the responsibility of all users to this document to ensure that the correct and most current version is being used.
This document contains many hyperlinks to other related documents.
All users must check these documents are in date and have been ratified appropriately prior to use.

Document History

Date of revision	Version number	Author	Reason for review or update
April 2025	1.0	Consultant Haematologist Lead Haematology Pharmacist	New Document

Consultation Schedule

Who? Individuals or Committees	Rationale and/or Method of Involvement
HLH MDT	Review of documents and comments
Haematology Governance Committee (MOG)	Review of documents and comments
Rheumatology Governance Committee	Review of documents and comments
Microbiology and Infectious Diseases Governance Committee (OxMID)	Review of documents and comments

Endorsement

Endorsee Job Title
Medicines Management and Therapeutics Committee Chair
Clinical Lead – Haematology
Clinical Lead – Rheumatology
Clinical Lead – Microbiology & Infectious Diseases

Contents

Who should read this document?

1. This policy should be read by all clinical staff across the Trust who may come into contact with adult* patients with Haemophagocytic lymphohistiocytosis (HLH), such as emergency department, medical and surgical specialities, critical care and laboratory staff.

Key Standards/Messages

2. The guideline highlights the critical importance of early recognition, prompt investigation, timely treatment, and a multidisciplinary approach in managing HLH to improve patient outcomes.

Scope

3. Haemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome characterised by uncontrolled immune activation, leading to extensive tissue damage, multi-organ failure, and, if untreated, death. Despite advancements in treatment, HLH continues to have poor outcomes, with a UK one-year overall survival of 56%. The condition affects individuals of all ages and backgrounds and, while considered rare, its incidence appears to be increasing, suggesting it is likely under-diagnosed. Early identification, prompt investigation, and timely initiation of treatment are crucial to improving patient outcomes.

   This document applies to all adult patients who require diagnosis and/or treatment for HLH.

Aim

4. **Provide a Structured Framework** to recognise, diagnose and manage HLH.
5. **Enhance Early Detection:** Improve the ability to identify HLH promptly by utilising the HScore accurately, assess the probability of HLH and guide diagnostic evaluations.
6. **Streamline Management Strategies:** Outline evidence-based treatment protocols, tailored to patient response and disease severity.
7. **Promote Multidisciplinary Collaboration:** Encourage early and ongoing communication among relevant specialties to ensure comprehensive patient management.
8. **Improve Patient Outcomes:** By facilitating early recognition and appropriate management, the guideline aims to reduce morbidity and mortality associated with HLH.

Background

9. Haemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome driven by uncontrolled immune activation, leading to extensive tissue damage, multi-organ failure, and, if left untreated, death. Its presentation is often non-specific and can closely mimic sepsis, making early recognition particularly challenging. Patients may initially present to a wide range of medical and surgical specialties, further complicating timely diagnosis.
10. The underlying pathophysiology of HLH is characterised by a loss of immune regulation, due to persistently activated cytotoxic T cells and natural killer (NK) cells, which drives activation of macrophages and histiocytes, resulting in

excessive proinflammatory cytokine production, which fuels a self-perpetuating hyperinflammatory state and cytokine storm causing progressive organ dysfunction.

11. Primary HLH is caused by genetic defects affecting lymphocyte cytotoxicity, often via the function of T cells and NK cells or immune regulation, and occurs principally in children, although it is increasingly recognised in adults.

12. Secondary HLH is more frequent in adults and can be triggered by a variety of factors including infections, malignancies, autoimmune and autoinflammatory diseases, pregnancy, therapeutic interventions, and acquired immunodeficiency states, with incomplete understanding of the mechanisms involved.

13. Diagnosing HLH requires a high index of suspicion alongside the use of multi-faceted diagnostic criteria and readily available biomarkers to support clinical decision-making.

14. Despite advancements in treatment, HLH continues to have poor outcomes, with a UK one-year overall survival of 56%. The condition affects individuals of all ages and backgrounds and, while considered rare, its incidence appears to be increasing, suggesting it is likely under-diagnosed. Early identification, prompt investigation, and timely initiation of treatment are crucial to improving patient outcomes. Treatment priorities are to reduce hyperinflammation with immune suppression and identify and treat the trigger(s).

15. Given the complexity of its presentation, diagnosis, and management, HLH necessitates a coordinated, multidisciplinary approach. This guideline aims to equip clinicians with a structured framework to facilitate early recognition, streamline diagnosis, and optimise management strategies, ultimately improving outcomes in this rapidly progressive and life-threatening condition.

Diagnosing HLH

16. HLH can present acutely in a non-specific manner with a sepsis like syndrome or with a prodrome of mild features that gradually evolve. The triad of **3Fs; fever, falling blood counts and raised ferritin** help identify potential HLH patients. Once HLH is suspected it is essential to establish the likelihood of HLH whilst also investigating possible triggers and assessing organ involvement and disease severity. Probability of HLH in adults is assessed using the validated **HScore probability calculator** which includes clinical, biological and morphological assessments.

17. The HScore should be calculated within 4 hours of suspecting HLH. A total score out of 337 is obtained, with probability ranges of 99% likelihood of HLH with a score >250.

18. A cut-off HScore of 169 has been shown to identify HLH with a 93% sensitivity and 86% specificity and a score of 169 or greater is considered diagnostic of HLH in people with a high pre-test probability because the probability of HLH is >50%.

19. If the initial score is less than 169 HScore should be checked daily, and a rising score increases the index of suspicion for HLH. Of note signs of central nervous system (CNS) dysfunction, cardiac compromise and liver dysfunction are poor prognostic features and add to clinical suspicion that HLH is either driving or

complicating the clinical presentation. Initial review should include an assessment of severity and consideration of higher levels of care and monitoring. Early identification of patients for admission to critical care is crucial.

20. The HScore should be recorded in the patient's medical notes each time it is calculated.

21. **The first point of contact for suspected HLH is the relevant specialty – see below. Contact should be made as soon as possible upon suspicion of HLH.**

- If underlying haematological condition – bleep 1836 or on call haematology*
- If underlying rheumatological condition – bleep 7187 or on call rheumatology*
- Patients who do not fulfil haematological or rheumatological criteria for HLH, and where there is an uncertain or infectious cause suspected or confirmed, should be managed on the John Warin Ward after discussion with the infection team (nominally bleep 5885). However, the final decision for admission should be on the discretion of the infection team on a case-by-case basis.

22. If there are ongoing concerns, the patient should be referred for urgent discussion at the local HLH multidisciplinary team (MDT) which occurs ad-hoc and consists of haematology, rheumatology, infectious disease, microbiology, biochemistry, immunology and critical care clinicians and specialist pharmacists from each area. (see qr code). Patients with suspected HLH can also be referred via email; **HLHMDTreferrals@ouh.nhs.uk** (but note that this inbox is not monitored constantly therefore patients that require urgent discussion should be highlighted directly to the relevant details (contacts detailed above).

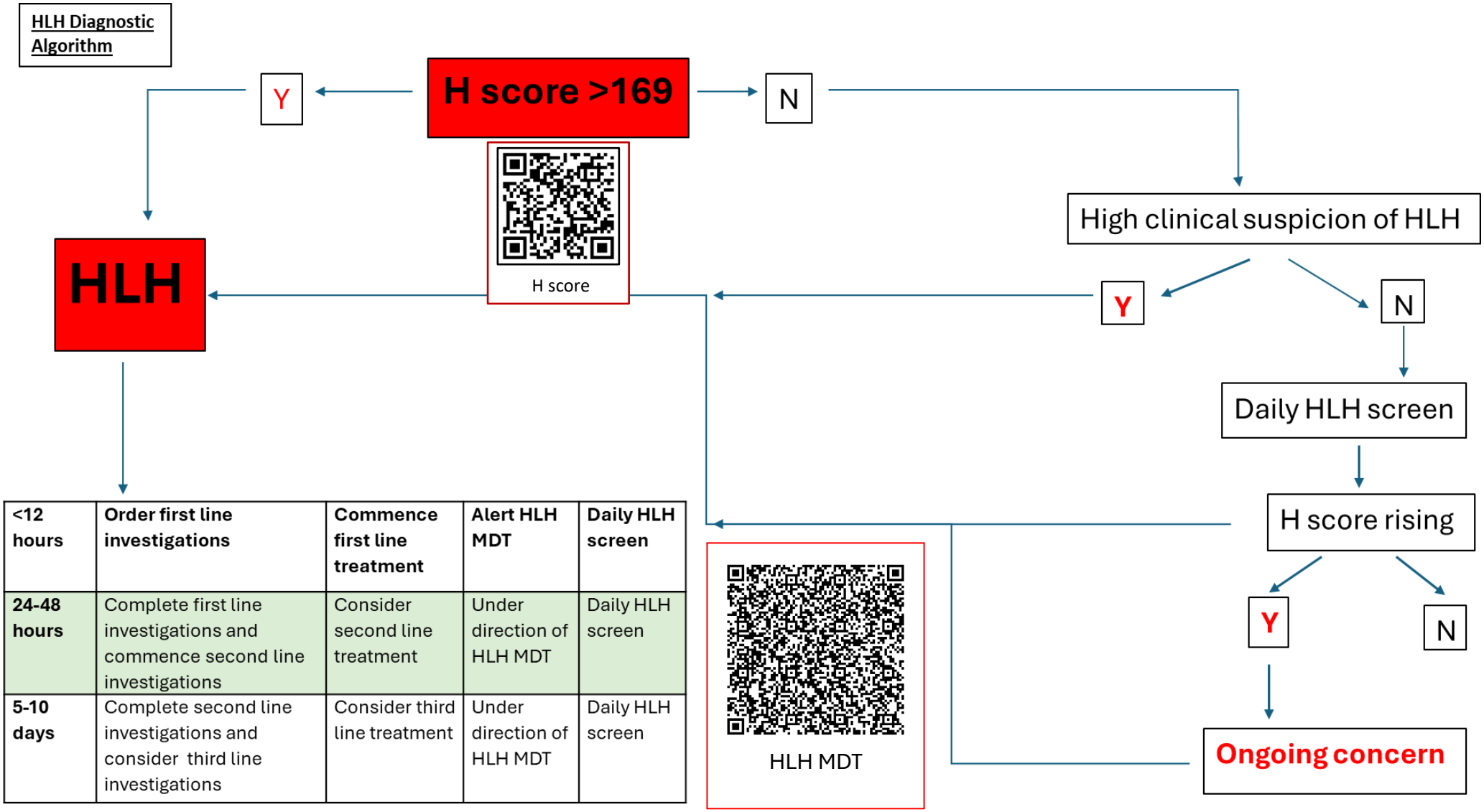
23. Some patients may require discussion at the fortnightly national HLH MDT, hosted by University College London Hospitals (UCLH) and the local MDT will guide which patients would require such a referral. Both MDT meetings are virtual and securely hosted on Microsoft Teams. Please see below for QR code link to Oxford HLH MDT Microsoft Teams meeting.

SCAN ME

Calculation of HScore

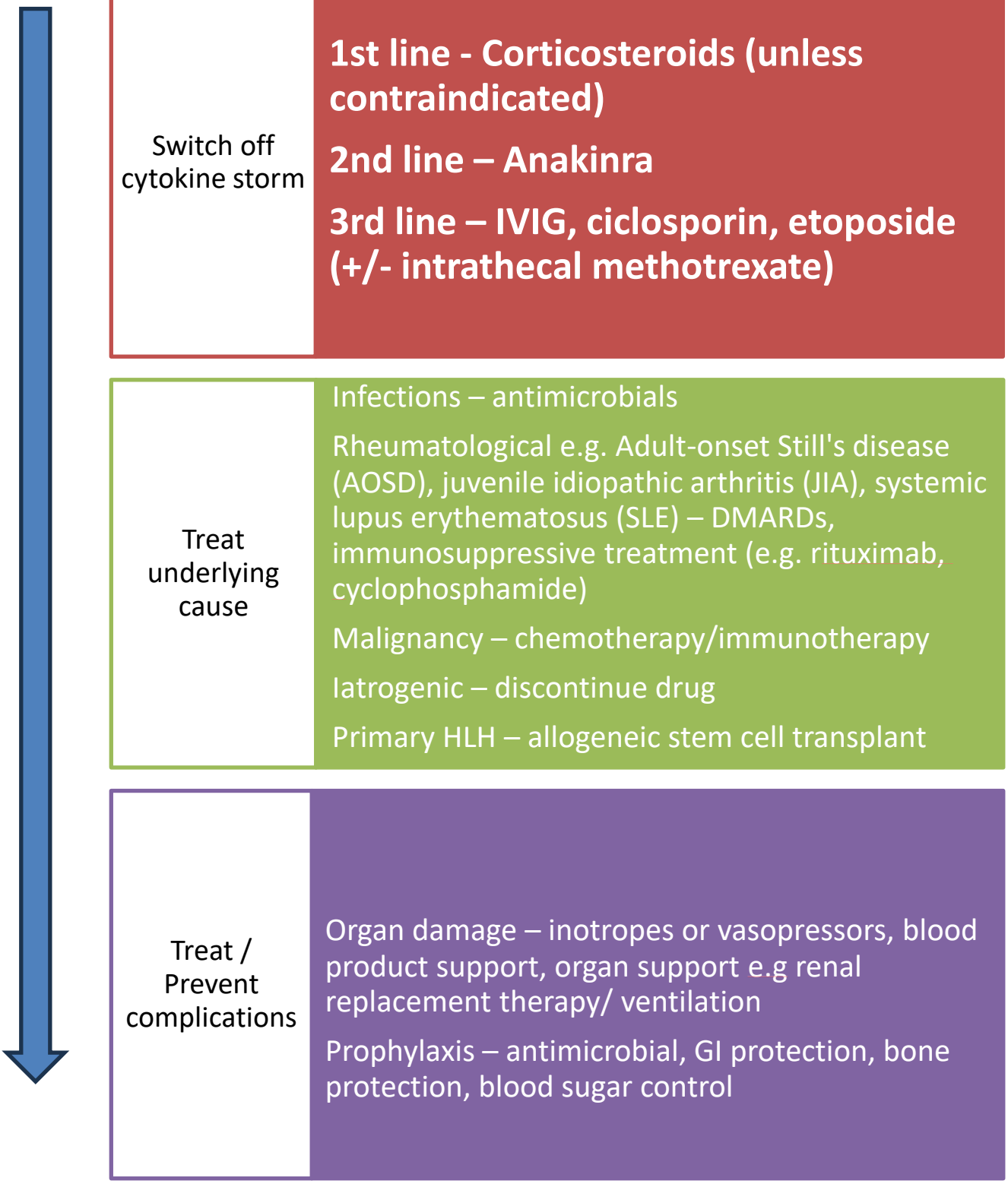
24. Given the complexity of the scoring system, a validated online calculator should be used. The below table is for reference only.

Metric	Result	Score
Known underlying immunosuppression (HIV positive or receiving long-term immunosuppressive therapy i.e. corticosteroids, ciclosporin, azathioprine)	No	0
	Yes	18
Maximal Temperature (°C)	Below 38.4	0
	38.4 – 39.4	33
	Greater than 39.4	49
Organomegaly	No	0
	Either Hepatomegaly **OR** Splenomegaly	23
	Hepatomegaly **AND** Splenomegaly	38
Number of Cytopenias - Haemoglobin under 92g/L - WBC 5 x 10^9/L or lower - Platelets 110 x 10^9/L or lower	0-1	0
	2	24
	3	34
Ferritin (microgram/L)	Less than 2000	0
	2000 – 6000	35
	Greater than 6000	50
Triglyceride (mmol/L)	Less than 1.5	0
	1.5 – 4	44
	Greater than 4	64
Fibrinogen (g/L)	Greater than 2.5	0
	2.5 or less	30
Aspartate Transferase (AST) (units/L)	Less than 30	0
	30 or greater	19
Haemophagocytosis features on bone marrow aspirate	No	0
	Yes	35
Total Score	**Unlikely to be HLH**	**0-168**
	Likely to be HLH (in conjunction with clinical signs & symptoms)	**169 or greater**



<12 hours	Order first line investigations	Commence first line treatment	Alert HLH MDT	Daily HLH screen
24-48 hours	Complete first line investigations and commence second line investigations	Consider second line treatment	Under direction of HLH MDT	Daily HLH screen
5-10 days	Complete second line investigations and consider third line investigations	Consider third line treatment	Under direction of HLH MDT	Daily HLH screen

HLH Treatment Priorities (see text below for further details)



Investigations and Treatment of HLH

25. In patients exhibiting features indicative of HLH, it is imperative to initiate investigations and treatment concurrently and without delay. Early notification of the Oxford Critical Care Unit (OCCU) or Churchill Intensive Care Unit (CICUAd) team is prudent, as patients can deteriorate rapidly. Investigations should focus on identifying potential triggers and assessing organ damage. Treatment aims to halt the cytokine storm, address the underlying cause, and manage or prevent complications.

Within the first 12 hours of diagnosis:

26. Order first-line investigations via EPR HLH careset (Table 1a) and commence treatment (Table 1b) promptly to prevent disease progression, with support of relevant teams (infection, rheumatology, haematology).

27. Alert the HLH MDT to the patient's condition

28. Administer corticosteroids unless clearly contraindicated.

    28.1. Contraindications may exist in individuals with profound immunosuppression, where steroids could pose an unacceptable risk of further infection, with a history of neuropsychiatric disorders or previous unacceptable steroid side-effects.

29. If the driver of HLH is unclear, make every effort to rapidly exclude lymphoma, typically through CT imaging and biopsy of an enlarged node or bone marrow.

    29.1. Consider rheumatology referral.

    29.2. Steroids may mask the presence of lymphoma; therefore, obtain imaging and biopsy investigations urgently.

    29.3. Consult with Haematology if lymphoma is suspected as the driver before initiating steroids.

Within 24-48 hours:

30. Complete first line investigations

31. If first-line investigations do not identify the trigger, proceed to second-line investigations in consultation with the HLH MDT/relevant specialty (Table 2a).

32. Consider administering second-line treatment (Table 2b) under the direction of the HLH MDT.

Between 5-10 days:

33. If HLH persists, consider expert-directed third-line investigations (Table 3a).

34. Initiate third-line treatment (Table 3b) under the guidance of the HLH MDT.

35. Throughout treatment, daily HLH screening remains essential to detect complications and guide therapy modifications. This stepwise approach ensures prompt intervention, continuous monitoring, and timely escalation of treatment to optimise patient outcomes. Management decisions should be made in collaboration with the HLH MDT to ensure best practice and individualised patient care.

Table 1a: First Line Investigations

FIRST LINE INVESTIGATIONS	
Haematology	FBC, Coagulation screen including Clauss fibrinogen, blood film, ESR, reticulocyte count, consider D-dimer and bone marrow biopsy
Biochemistry	U+Es, LFTs including AST, LDH, Triglycerides, CRP, Immunoglobulins, Serum protein electrophoresis, Ferritin, Iron profile, B12, Folate, Troponin, BNP, Urine protein-creatinine ratio
Immunology	C3, C4, ANA, ANCA, ENA screen, dsDNA Ab,
Microbiology	Bacterial blood cultures x3 (ideally prior to antibiotic administration), consider tuberculosis and test with Mycobacterial culture of sputum or urine.
Virology	Serum save (ideally before blood products) Serology for Epstein-Barr virus; cytomegalovirus; HIV; hepatitis viruses A, B, C, and E; parvovirus B19; and human T-lymphotropic virus 1 (ideally before blood products) Epstein-Barr virus and cytomegalovirus PCR Respiratory viral throat swab PCR Influenza A and B, enterovirus, and SARS-CoV-2
Imaging	CXR, CT neck, chest, abdo, pelvis with contrast or whole body PET-CT, ECG, Echo

Table 1b: First Line Treatment

FIRST LINE TREATMENT	
Initial dosing	**Methylprednisolone 10-20mg/kg (maximum of 1g) IV OD or Dexamethasone phosphate 10mg/m^2 IV OD** (Dexamethasone phosphate 4mg is equivalent to 3.3mg dexamethasone base) *Consider higher dose dexamethasone (10mg QDS IV) in cases with CNS involvement* Step down to 1mg/kg prednisolone or equivalent after 1-5 days and if possible, aim to curtail steroids in selected appropriate cases with direction of HLH MDT. If steroids contraindicated discuss with HLH MDT urgently to consider anakinra first-line. Document in handover and discharge summary that adrenal suppression is possible and steroid card should be given along with advice on sick day rules for 3 months after stopping steroids. Ensure this is discussed with patient at discharge.
Infections	Commence antibiotics in line with antibiotic guidelines if bacterial infection suspected and continue for 7 days or until bacterial infection excluded. Consider antimicrobial prophylaxis with immunosuppression in consultation with ID/micro.
GI prophylaxis	Omeprazole 20mg daily. Start with first dose of steroids.
Bone protection	Oral bisphosphonates e.g. alendronic acid 70mg once a week ***PLUS*** Adcal D3 chewable, one twice a day. Start with first dose if steroids, if possible.
Monitor blood glucose levels	D/w diabetic team for diabetic patients

Table 2a: Second Line Investigations

SECOND LINE INVESTIGATIONS	
Infection screen – depending on travel history/ID advice	Parasites – malaria film and rapid diagnostic test Serology for Toxoplasma and Leishmania Syphilis, Coxiella, Brucella, endemic mycoses and Rickettsia. Consider QuantiFERON test (unreliable for diagnosing active tuberculosis). If Epstein-Barr virus viraemia, consider investigating which lymphocyte compartments are harbouring Epstein-Barr virus Tissue biopsy infection tests: tuberculosis and leishmaniasis Tests to ensure no potential adverse effects of immune suppression (depending on travel history), consider: strongyloides serology trypanosoma cruzi serology If immunocompromised – Swab of urogenital ulcers for herpes simplex virus PCR PCR for adenovirus, hepatitis C virus, human herpes virus 6 (if history of HIV, allogenic bone marrow transplant, chimeric antigen receptor therapy and solid organ transplant) and parvovirus Consider: Human herpes virus 8 PCR, hepatitis E virus PCR, cryptococcal antigen, betaD-glucan (possible false positive after intravenous immunoglobulin) Stool microscopy for ova, cysts and parasites
Malignancy	Based on clinical findings/imaging consider core or excision biopsy (not FNA) Bone marrow following d/w haematology team – aspirate, flow, cytogenetics, molecular, trephine Consider deep skin biopsy
Neurological	If neurological signs/symptoms for MRI brain with contrast followed by lumbar puncture (opening pressure, MCS, protein, paired glucose, paired oligoclonal bands, cytospin, flow cytometry, cytology, viral PCR panel)

Table 2b: Second Line Treatment

SECOND LINE TREATMENT	
ANAKINRA	• Recombinant IL-1 receptor blocker • For patients who are steroid refractory or when steroids are contraindicated • Funded by NHSE, prior approval (Blueteq®) form must be completed (see NHSE commissioning policy) • Request supply from pharmacist immediately as administration must not be delayed • Use in HLH is off-label but is a recognised indication
Dose	4mg/kg (rounded to nearest 100mg in 2 divided doses, maximum of 8mg/kg/day)
Administration route	Subcutaneous preferred unless contraindicated due to low platelets or oedema Intravenous is the same dose and can be considered in critical illness to achieve higher and faster maximal plasma concentration.
Renal impairment	CrCl less than30mL/min or on renal replacement therapy - consider administration every 48 hours
Response criteria	Reduction in level of organ support Serial reduction in Hscore Ferritin level reduced by 10% within 7 days If applicable – reduction in corticosteroid dose by at least 25% in 14 days
Stopping criteria	Serious adverse events e.g. anaphylaxis No evidence of clinical response according to the response criteria within 14 days Resolution of HLH defined by local/national MDT discussion

Subcutaneous Administration:

36. Anakinra pre-filled syringes are sterile unpreserved solutions and for single use only.

37. Do not shake. Allow the pre-filled syringe to reach room temperature before injecting.

38. Before administration, visually inspect the solution for particulate matter and discolouration. Only clear, colourless-to-white solutions that may contain some product-related translucent-to-white amorphous particles should be injected. The presence of these particles does not affect the quality of the product

39. To be administered subcutaneously to any of the following sites: abdomen except for the area around the navel, top of thighs, upper outer areas of buttocks, outer area of the upper arms

Intravenous Administration:

40. Intravenous bolus administration is reserved for patients for whom subcutaneous injections of anakinra is unsuitable (e.g. platelets less than 20 x 10^9/L) or those who are critically unwell and have significant subcutaneous oedema. Recommended dose remains as above.

41. Uncap the desired number of pre-filled anakinra syringe(s)
42. Add the appropriate dose to a 50ml syringe, making up the total volume of 50ml with sodium chloride 0.9%
43. Infuse over 30 minutes via syringe pump.
44. **Note**: Anakinra should not be administered concomitantly via Y-site or mixed with any other medications due to lack of compatibility information.

Table 3a: Third Line Investigations

THIRD LINE INVESTIGATIONS	
Immunology	Soluble CD25, Cytokine testing Lymphocyte subsets Natural killer cell activity
Primary HLH	CD107a granule release assay - if abnormal, send an R15 genetic analysis to commissioned genetic service: nhs england genetic screening eligibility criteria Protein expression - perforin, SH2D1A, or XIAP - if abnormal, send for genetic analysis
Lymphoma	Deep skin biopsy if PET negative
Immunosuppressed	Fungal and tuberculosis cultures, and bone marrow aspirate blood sample for TB

Table 3b: Third Line Treatments

THIRD LINE TREATMENT	
Intravenous Immunoglobulin (IVIG)	Steroid/anakinra refractory HLH, consider if CNS or cardiac involvement or in relapse if recommended by local/national MDT Will require prior approval from IVIG panel or Immunology consultant (see NHSE commissioning policy). Submit application on the national database Check with pharmacy for available brand **Dose**: 1g/kg/day for 2 days Consider repeating the same dose after 14 days following discussion with MDT if HLH relapses or remains steroid dependent, and for a 2nd relapse, where alternative therapies are not indicated or are contraindicated. IVIG is contraindicated where hyperviscosity is a risk (paraprotein >40g/L or known IgM paraprotein) and in this case urgent discussion with haematology on call team is required.
Ciclosporin	If recommended by rheumatology to treat HLH triggered by rheumatological disease or to prevent relapse. **Dose**: 1-2.5mg/kg bd po/iv (target trough level is 150-300ng/ml taken 10-12 hours post dose)

	IV brand: Sandimmun PO brand: Capimune Steady state will not have been reached until 72 hours.
Etoposide	If recommended by haematology. Chemotherapeutic agent will require haematologist prescription. 150mg/m^2 IV twice weekly for two weeks, then 150mg/m^2 IV weekly for 6 weeks, may require dose reduction with liver dysfunction Consider intrathecal methotrexate if lymphoma driven CNS involvement All doses to be screened & ordered by haematology-trained pharmacist (see NSSG protocol)

Additional Considerations

Patients with refractory HLH or intolerance to standard agents: There is a precedent for using alternative agents such as JAK inhibitors or canakinumab. This can only be accessed following approval from the Medicines Management and Therapeutics Committee (MMTC) chair. Financial processes for approval of high-cost drugs should be followed.

Review

45. An initial review will be conducted in 2 years based on local MDT data and new guidance. Following this review, this policy will be reviewed every 3 years, as set out in the Policy for the Development and Implementation of Procedural Documents.

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Further Information

55. Hyperinflammation and HLH Across Specialty Collaboration (HiHASC): https://www.hihasc.org/

Appendix 1: Responsibilities

1. The **patient's primary team** are responsible for:
    1.1. Sending appropriate screening investigations for HLH
    1.2. Contacting the local HLH MDT if HLH suspected
    1.3. Liaising with appropriate teams to assist in the diagnosis of the likely HLH trigger
    1.4. Initiating treatment of HLH with guidance from the HLH MDT (with the exception of etoposide, which must be prescribed by a haematologist)
    1.5. Following up results of investigations and calculating daily Hscore as needed
2. The **HLH MDT** are responsible for:
    2.1. Providing support for the diagnosis and management of HLH via discussion at the weekly MDT
    2.2. Review list of patients from biochemistry with ferritin over 6000 mcg/L to identify any undiagnosed cases
    2.3. Refer and discuss complex cases with the national HLH MDT with input from the primary team

Appendix 2: Definitions

Haemophagocytic Lymphohistocytosis (HLH) is an immune disorder characterised by hyperinflammation, hyperferritinaemia and cytopenias.

Intravenous immunoglobulin (IVIG) is a blood-based treatment made from plasma separated out from donated blood, leaving a type of immunoglobulin called immunoglobulin G (IgG). IVIG is used in a variety of immunodeficiency or autoimmune conditions.

*Adult patients may include those over 16 years. Different specialties may consider patients over the age of 16 or 18 as adult patients. This guideline applies to any patients considered as adults in their primary specialty.

Appendix 3: Education and Training

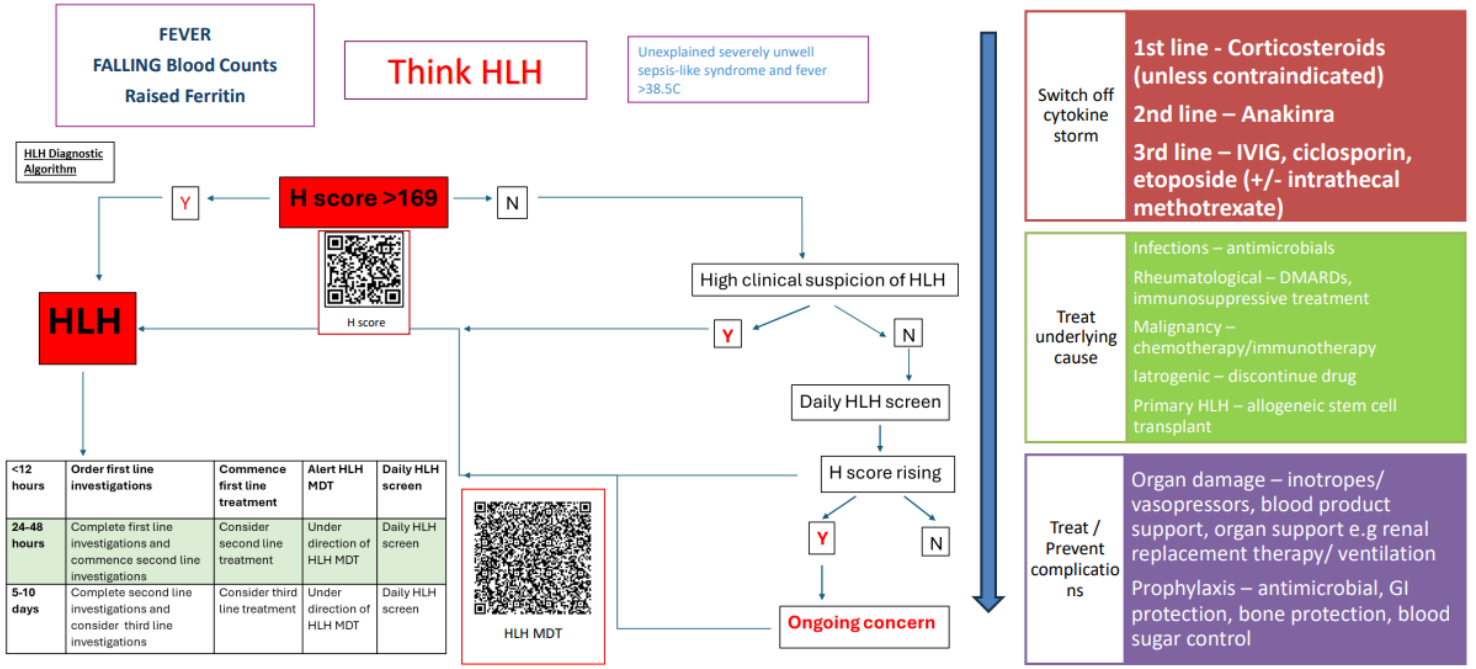
1. There is no mandatory training associated with this policy. Individuals' training needs will be identified through annual appraisal and supervision.

Appendix 4: Monitoring Compliance

1. Use the following statement and mandatory table to list specifically what will be monitored to ensure that the policy is effective, including the minimum standards for compliance or non-compliance.
2. Compliance with the document will be monitored in the following ways.

What is being monitored:	How is it monitored:	By who, and when:	Minimum standard	Reporting to:
Number and survival of HLH patients	*Patients flagged by biochemistry with high ferritin over 6000 mcg/L and have a Hscore of >169 are referred to the HLH MDT*	*HLH MDT*	*First line investigations are sent off within 12 hours of suspecting HLH. 100% of HLH patients are recognised and referred to HLH MDT for appropriate management.*	*HLH MDT, HiHASC registry*

Appendix 5: HLH guideline summary



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Immunology	C3, C4, ANA, ANCA, ENA screen, dsDNA Ab
Microbiology	Bacterial blood cultures x3 (ideally prior to antibiotic administration), consider tuberculosis and test with Mycobacterial culture of sputum or urine.
Virology	Serum save (ideally before blood products) Serology for Epstein-Barr virus; cytomegalovirus; HIV; hepatitis viruses A, B, C, and E; parvovirus B19; and human T-lymphotropic virus 1 (ideally before blood products) Epstein-Barr virus and cytomegalovirus PCR Respiratory viral throat swab PCR Influenza A and B, enterovirus, and SARS-CoV-2
Imaging	CXR, CT neck, chest, abdo, pelvis with contrast or whole body PET-CT, ECG, Echo

FIRST LINE TREATMENT	
Initial dosing	**Methylprednisolone 10-20mg/kg (maximum of 1g) IV OD or Dexamethasone phosphate 10mg/m² IV OD** *Consider higher dose dexamethasone in cases with CNS involvement* Step down to 1mg/kg prednisolone or equivalent after 1-5 days and aim to curtail steroids in appropriate cases under direction of HLH MDT. If steroids contraindicated discuss with HLH MDT urgently to consider anakinra first-line.
Infections	Commence antibiotics in line with antibiotic guidelines if bacterial infection suspected and continue for 7 days or until bacterial infection excluded. Consider antimicrobial prophylaxis with immunosuppression in consultation with ID/micro.
GI prophylaxis	Omeprazole 20mg od
Bone protection	Oral bisphosphonates e.g. alendronic acid 70mg weekly ***PLUS*** Adcal D3 chewable T bd
Monitor blood glucose levels	D/w diabetic team for diabetic patients

SECOND LINE INVESTIGATIONS	
Infection screen – depending on travel history/ID advice	Parasites – malaria film and rapid diagnostic test Serology for Toxoplasma and Leishmania Syphilis, Coxiella, Brucella, endemic mycoses and Rickettsia. Consider QuantiFERON test (unreliable for diagnosing active tuberculosis). If Epstein-Barr virus viraemia, consider investigating which lymphocyte compartments are harbouring Epstein-Barr virus Tissue biopsy infection tests: tuberculosis and leishmaniasis Tests to ensure no potential adverse effects of immune suppression (depending on travel history), consider: strongyloides serology trypanosoma cruzi serology If immunocompromised – Swab of urogenital ulcers for herpes simplex virus PCR PCR for adenovirus, hepatitis C virus, human herpes virus 6 (if history of HIV, allogenic bone marrow transplant, chimeric antigen receptor therapy and solid organ transplant) and parvovirus Consider: Human herpes virus 8 PCR, hepatitis E virus PCR, cryptococcal antigen, betaD-glucan (possible false positive after intravenous immunoglobulin) Stool microscopy for ova, cysts and parasites
Malignancy	Based on clinical findings/imaging consider core or excision biopsy (not FNA) Bone marrow following d/w haematology team – aspirate, flow, cytogenetics, molecular, trephine Consider deep skin biopsy
Neurological	If neurological signs/symptoms for MRI brain with contrast followed by lumbar puncture (opening pressure, mcs, protein, paired glucose, paired oligoclonal bands, cytospin, flow cytometry, cytology, viral PCR panel)

SECOND LINE TREATMENT	
ANAKINRA	• Recombinant IL-1 receptor blocker • For patients who are steroid refractory or when steroids are contraindicated
Dose	4mg/kg (rounded to nearest 100mg in 2 divided doses, maximum of 8mg/kg/day)
Administration route	Subcutaneous preferred unless contraindicated due to low platelets or oedema Intravenous is same dose and can be considered in critical illness to achieve higher and faster maximal plasma concentration.
Renal impairment	CrCl<30ml/min administer every 48 hours
Response criteria	Reduction in level of organ support Serial reduction in Hscore Ferritin level reduced by 10% within 7 days If applicable – reduction in corticosteroid dose by at least 25% in 14 days
Stopping criteria	Serious adverse events e.g., anaphylaxis No evidence of clinical response according to the response criteria within 14 days Resolution of HLH defined by local/national MDT discussion

THIRD LINE INVESTIGATIONS	
Immunology	Soluble CD25, Cytokine testing Lymphocyte subsets Natural killer cell activity
Primary HLH	CD107a granule release assay - if abnormal, send an R15 genetic analysis to commissioned genetic service: https://www.england.nhs.uk/wp-content/uploads/2018/08/rare-and-inheriteddisease-eligibility-criteria-v2.pdf Protein expression - perforin, SH2D1A, or XIAP - if abnormal, send for genetic analysis
Lymphoma	Deep skin biopsy if PET negative
Immunosuppressed	Fungal and tuberculosis cultures, and bone marrow aspirate blood sample for TB

THIRD LINE TREATMENT	
IVIG	Steroid/anakinra refractory HLH, consider if CNS or cardiac involvement or in relapse if recommended by local/national MDT 1g/kg/day for 2 days Consider repeating after 14 days
Ciclosporin	If recommended by rheumatology to treat HLH triggered by rheumatological disease or to prevent relapse. **Dose**: 1-2.5mg/kg bd po/iv (target trough level is 150-300ng/ml taken 10-12 hours post dose)
Etoposide	If recommended by haematology. Chemotherapeutic agent will require haematologist prescription. 150mg/m2 twice weekly for two weeks, then 150mg/m2 weekly for 6 weeks, may require dose reduction with liver dysfunction Consider intrathecal methotrexate if lymphoma driven CNS involvement

Appendix 6: Equality Impact Assessment

1. Information about the policy, service or function

What is being assessed	New Policy
Job title of staff member completing assessment	Lymphoma and CAR-T Consultant
Name of policy / service / function:	Management of Haemophagocytic Lymphohistiocytosis (HLH) in Adults Guideline
Details about the policy / service / function	The guideline highlights the critical importance of early recognition, prompt investigation, timely treatment, and a multidisciplinary approach in managing HLH to improve patient outcomes.
Is this document compliant with the Web Content Accessibility Guidelines?	Yes
Review Date	April 2028
Date assessment completed	04/04/25
Signature of staff member completing assessment	
Signature of staff member approving assessment	

2. Screening Stage

Who benefits from this policy, service or function? Who is the target audience?

- Patients
- Staff

Does the policy, service or function involve direct engagement with the target audience?
No - *full equality impact assessment not required*