FEVER
FALLING Blood Counts
Raised Ferritin

Think HLH

Unexplained severely unwell sepsis-like syndrome and fever >38.5C

HLH Diagnostic Algorithm

H score >169

Y

N

H score

HLH

High clinical suspicion of HLH

Y

N

Daily HLH screen

H score rising

Y

N

Ongoing concern

HLH MDT

<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

Switch off cytokine storm	**1st line - Corticosteroids (unless contraindicated)** **2nd line – Anakinra** **3rd line – IVIG, ciclosporin, etoposide (+/- intrathecal methotrexate)**
Treat underlying cause	Infections – antimicrobials Rheumatological – DMARDs, immunosuppressive treatment Malignancy – chemotherapy/immunotherapy Iatrogenic – discontinue drug Primary HLH – allogeneic stem cell transplant
Treat / Prevent complications	Organ damage – inotropes/ vasopressors, blood product support, organ support e.g renal replacement therapy/ ventilation Prophylaxis – antimicrobial, GI protection, bone protection, blood sugar control

FIRST LINE INVESTIGATIONS	
Haematology	FBC, Coagulation screen including clauss fibrinogen, blood film, ESR, reticulocyte count, consider D-dimer and bone marrow
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

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

Oxford University Hospitals NHS Foundation Trust. Management of Haemophagocytic Lymphohistiocytosis (HLH) in Adults Guideline
Version 1.0 – August 2025

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