British Society for Rheumatology

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GIRFT
GETTING IT RIGHT FIRST TIME

HISTIOUK
No-one should die of Histiocytosis

NHS IMPACT
Improving Patient Care Together

Haemophagocytic Lymphohistiocytosis (HLH)

Guidance on the diagnosis, treatment, management and governance.

July 2024

GIRFT is part of an aligned set of programmes within NHS England

Contents

We are proud to say this guide has been co-badged with:

British Society for Rheumatology

Histio UK

1. Introduction

Haemophagocytic Lymphohistiocytosis (HLH) is a devastating syndrome with uncontrolled activation of the immune system leading to hyperinflammation, tissue damage and multi-organ failure. HLH can be triggered by infection (including COVID-19), malignancy, autoimmune/autoinflammatory disease, pregnancy, therapeutic interventions including some drugs, CAR-T cell therapy and bone marrow transplant.

1.1 HLH – Key Information:

- Symptoms are non-specific (often mimicking sepsis) and can present to any medical or surgical speciality.
- If untreated, HLH leads to multi-organ failure and death.
- HLH affects people of all ages and from a broad demographic background.
- HLH is considered to be a rare disease, although incidence is increasing, and it is likely under-diagnosed.
- Even with treatment, recent UK data has shown a crude mortality rate of 50%: a nationwide study all cases of HLH diagnosed between 2003 and 2018 reported a crude one-year survival rate of 50%. This varied considerably by age, gender and associated comorbidity, highlighting the need for greater recognition and identification of underlying drivers of the condition.
- HLH requires cross-specialty management: the possible triggers of HLH span a range of specialities. Management can be nuanced and complex and patients often require critical care. Diagnosis is a challenge because there is no single test for HLH although there is increasing evidence that a combination of easily available biomarkers can be readily used in people at risk (those with fever and falling blood counts and uncertain precipitating illness or in at-risk groups e.g. with rheumatic disease) and a multi-disciplinary approach to management is advocated.

In 2018 Dr Rachel Tattersall (Sheffield) and Dr Jessica Manson (London), both rheumatologists, came together with the aim of trying to improve outcomes for patients with HLH, to standardise approaches to investigation and treatment as well as characterise HLH to improve research. The resulting network HiHASC (Hyperinflammation and HLH Across Specialty Collaboration) Across Speciality Collaboration www.hihasc.org) has 200 members across the UK from paediatric and adult medicine and disciplines including; rheumatology, haematology, neurology, critical care, infectious diseases, immunology, virology and acute/general medicine. London and North of England now have weekly national MDT provision, and have evidence to confirm that since formation, death rates have significantly reduced. A video showcasing patient experience can be found here: https://vimeo.com/906468560/5cf551d605?share=copy with the kind permission of the patients involved. The national framework has fostered new local/regional services but there remains inequity of access to care for people with HLH.

GIRFT is proud to release this best practice guidance in collaboration with Dr Rachel Tattersall and Dr Jessica Manson and would like to thank them for sharing their experience, expertise and clinical outcomes with fellow acute providers, via this guidance and the associated pathway.

This guide and the accompanying pathway are intended to showcase consensus recommendations and case studies for the diagnosis, management and treatment of HLH. These are shared with the assumption that the responsible clinician, leading the inpatient care, will retain responsibility for the patient, and that local guidelines will be followed on prescribing, bone and gastrointestinal prophylaxis and steroid stewardship.

It is important to recognise that patients can present with HLH in any part of acute medicine. Increasing awareness of HLH within an organisation leads to fewer missed cases, and reduces mortality rates shown in the case study section of this guide.
The intended audience of this guide is all clinicians, providers and ICBs involved in the delivery of acute care, however, patient information and support documents can be found here: https://www.histiouk.org/wp-content/uploads/2020/12/HLH-Adult-and-Adolesent-Patients-brochure_a5_1-002.pdf

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Paediatric HLH

We are pleased to have represented our colleagues in Paediatric Rheumatology by working together with multiple GIRFT workstreams (adult rheumatology, emergency medicine, adult critical care and pathology) and stakeholders from across the country to develop this pathway and guidance for the care of patients of all ages presenting with the symptoms of HLH.

Following this guide and pathway being shared with you all, we aim to capture data for children and young people with HLH to really help us to understand how many of these sick children are presenting across the country, who they are presenting to and what types of treatment they are responding to. Improving the depth of data available for this presentation will help us to shape future guidance and pathways.

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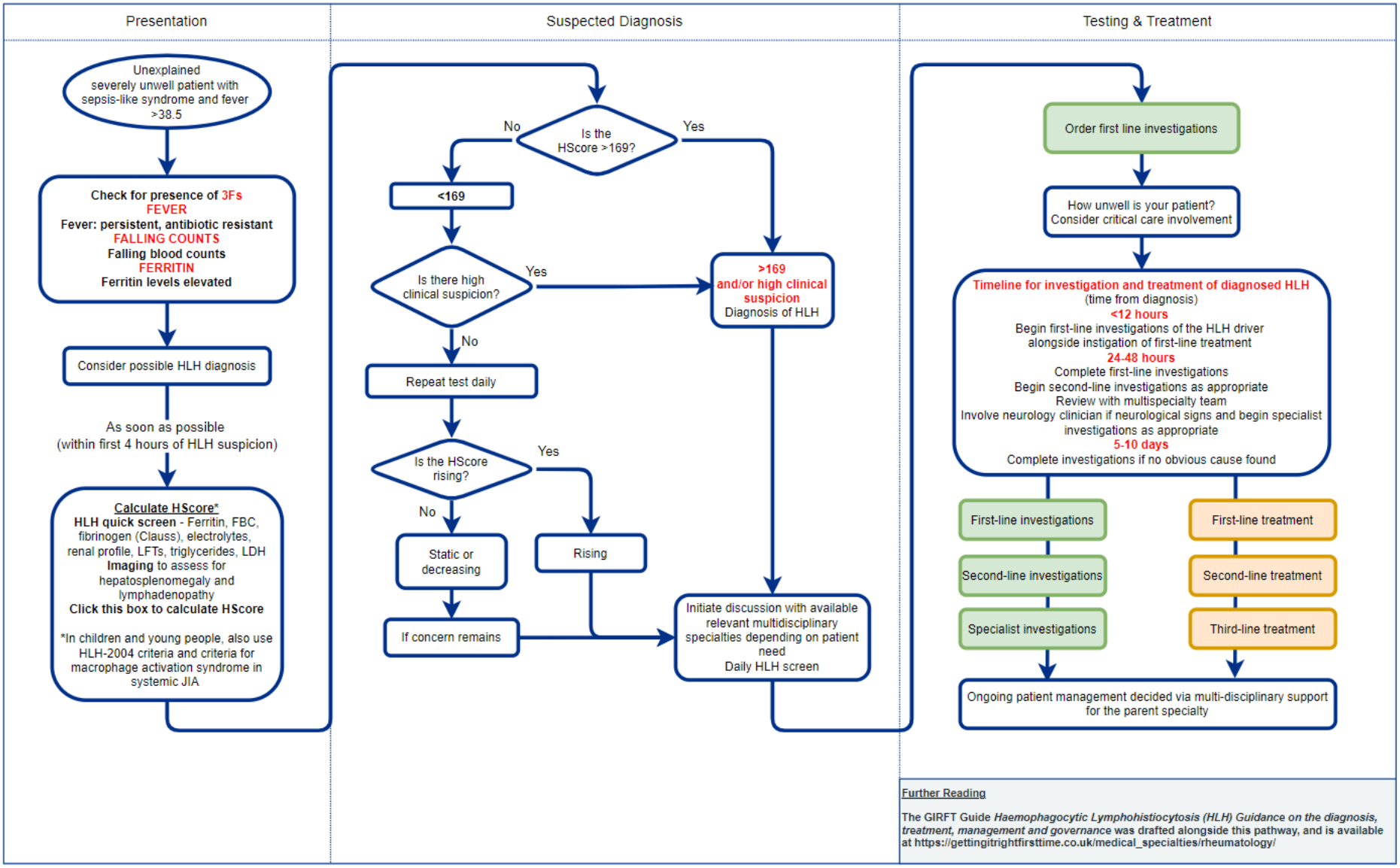
2. HLH pathway

2.1 Pathway overview

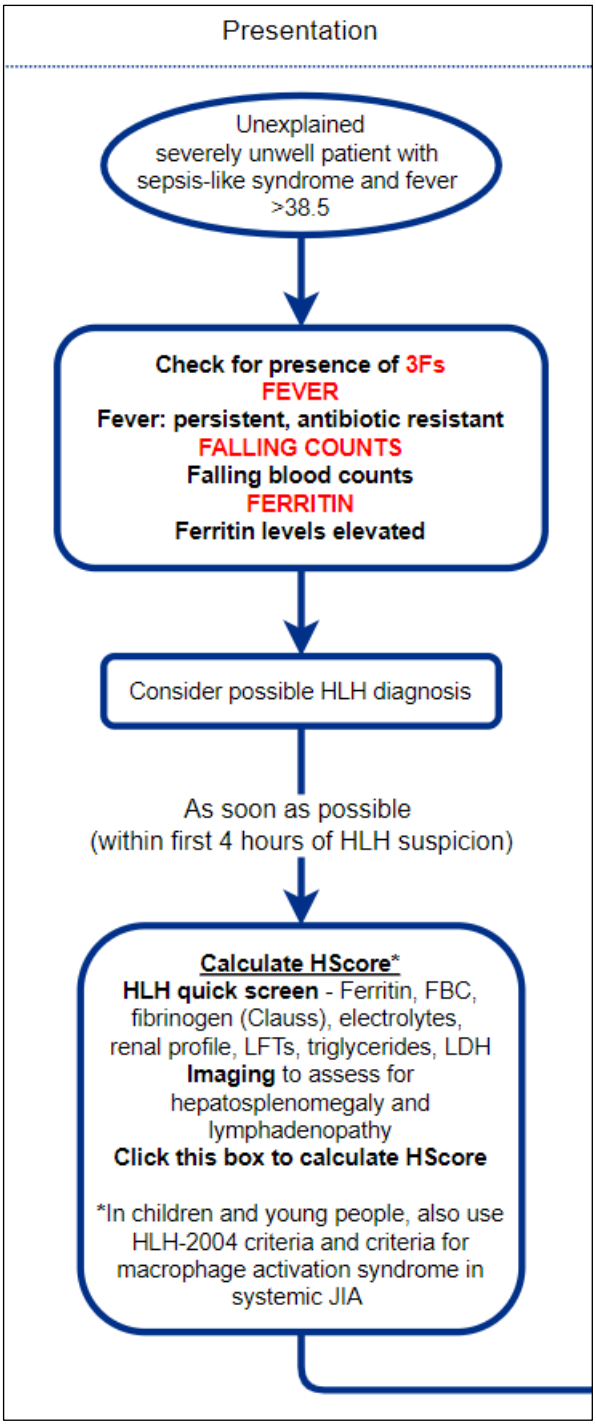
Available at: https://gettingitrightfirsttime.co.uk/wp-content/uploads/2024/07/HLH-Pathway-FINAL-V1-July-2024.html



2.1.1 Presentation

People may present in two ways with HLH;

1. With a known diagnosis e.g. sepsis or autoimmune disease that becomes complicated by HLH – sometimes treatment of underlying condition will switch off HLH but usually the HLH needs treatment in its own right.
2. HLH as presenting feature e.g. pyrexia of unknown origin (PUO) or illness characterised by cytopaenia. The priority is recognition and treatment of HLH with parallel investigation of the underlying driver and its appropriate treatment.



Above: Presentation column from HLH pathway shared on page 5 of this guide

Presentations of HLH can occur in any acute medical setting. Supportive muti-disciplinary advice for suspected cases of HLH should be available for all clinicians working in the acute medical setting. The **case study** section of this guide explores how this has worked in practice for providers of adult and paediatric acute care.

2.1.2 Aetiopathogenesis of HLH

Under normal circumstances, macrophages and dendritic cells are activated to phagocytose pathogens, present antigens and activate the adaptive immune system (NK cells and cytotoxic CD8 T lymphocytes/CTL). NK cells and CTL recognise and destroy pathogen-infected cells by release of cytolytic granules (containing perforin and granzymes) and production of pro-inflammatory cytokines. NK cells and CTL also play a role in removing the antigen-presenting cells by inducing apoptosis acting with a negative feedback loop which eventually terminates the immune response. The clinical features of HLH occur due to loss of this negative feedback loop and subsequent hyper-activation of CTLs and macrophages. This leads to hypercytokinaemia with persistently elevated levels of multiple proinflammatory cytokines ((IFN γ, IL-1, IL-6, IL-18) resulting in progressive organ dysfunction (cytokine storm).

Genetic lesions in the cytolytic pathways are a cause of (primary) HLH, and the discovery of these mutations has provided the evidence that it is aberrations of activation and function of mainly CD8 T cells

and NK cells that is the underlying aetiology of HLH. Exactly how or why this occurs in secondary HLH is less clear.

2.1.3 Clinical Feature and Diagnosis of HLH

HLH is a syndrome of hyperinflammation driven by an underlying trigger or triggers. Especially in the early stages, features are non-specific. Patients have often been treated for sepsis with no apparent benefit, see multiple specialists with no clear diagnosis or present critically unwell. There is an important clinical triad to recognise – the 3 Fs: Fever, Falling blood counts, Ferritin;

1) Fever – persistent and antibiotic resistant
2) Falling blood counts - especially platelets
3) Ferritin - a marker of macrophage activation (and in the HScore values of over 2000 are suggestive of hyperinflammation).

These features (especially hyperferritinaemia) define a patient group who are 'at risk' of HLH and in whom HLH should be actively excluded. 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.

Once HLH is suspected or diagnosed, the aims of treatment are twofold:

1) reducing hyperinflammation with immune suppression
2) identifying and treating the trigger(s) – where infection is/may be the trigger for HLH it is important to treat infection and HLH. There are other precedents in medicine for treating infection with immunosuppression and antibiotics e.g. neurosepsis, some tuberculosis.

There are no evidence-based diagnostic criteria in secondary HLH and it is not the province of any particular speciality but often presents to acute medicine, rheumatology, haematology or critical care. The probability that HLH is present can be assessed by applying the HScore probability calculator. This is validated in adults on general medical wards or critical care. The HLH2004 score is validated in children where primary HLH is the more common cause, and there are disease specific scores for systemic juvenile idiopathic arthritis, or JIA (where HLH is termed macrophage activation syndrome – MAS) as well as in malignancy. Clinical scoring systems should be used in the context of clinical presentations and patterns of biomarkers.

2.1.4 HScore

HScore is an online probability calculator of HLH, which uses nine variables. Advantages of the HScore include that it is validated in adult populations, uses widely available laboratory markers and offers a dynamic prediction of probability of HLH. The score is done on the assumption of a high pre-test probability. The HScore need to be interpreted with caution where known liver failure where ferritin levels can be very high and associated cytopenias; in those patients with pre-existing cytopenias due to chemotherapy/post BMT; and reactions to intravenous iron.

Three clinical:

1) underlying immunosuppression

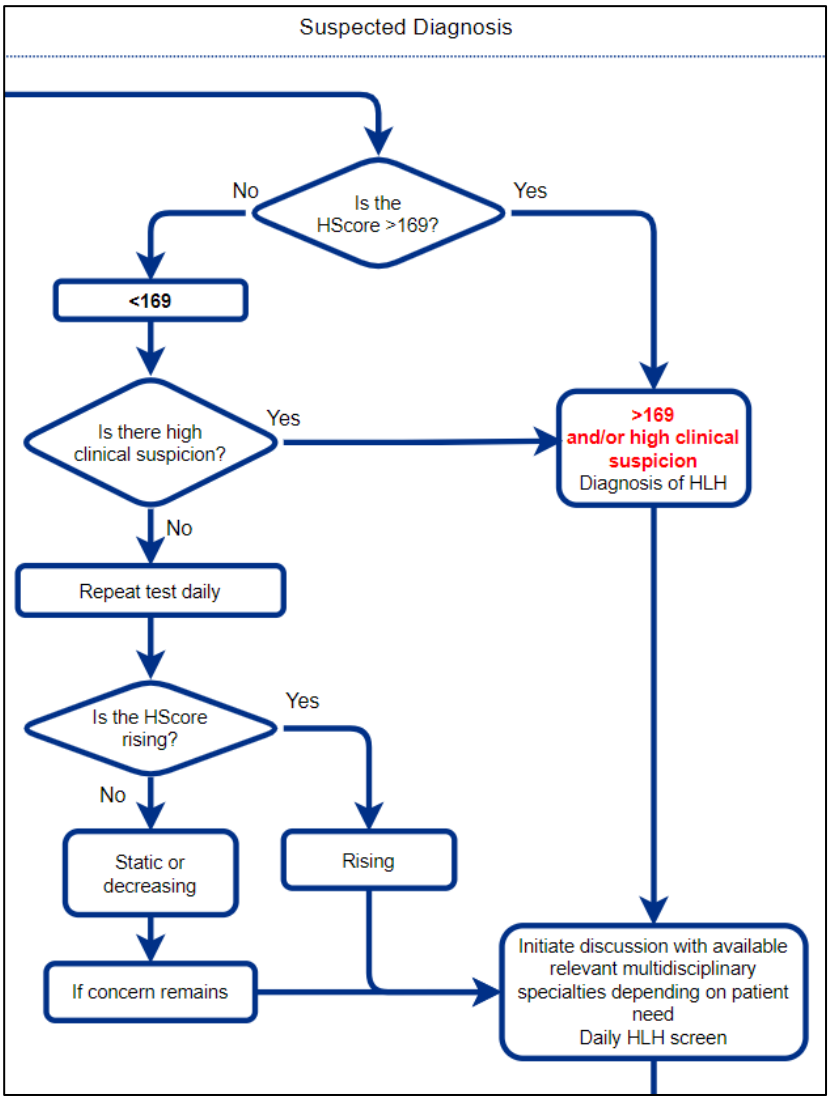
2) fever
3) organomegaly

Five biological:

4) ferritin
5) triglycerides
6) aspartate aminotransferase
7) fibrinogen (Clauss)
8) cytopenia

One morphological:

9) haemophagocytosis



Above: Suspected Diagnosis column from HLH pathway shared on page 5 of this guide

A total score out of 337 is obtained, with probability ranges of <1% likelihood of HLH if the score is <90 to >99% likelihood of HLH with a score >250. A cut-off HScore of 169 has been shown to identify HLH with a 93% sensitivity and 86% specificity.

http://saintantoine.aphp.fr/score/

Score 169 or above is considered diagnostic of HLH in people with a high pre-test probability. If the initial score is <169, the HScore should be checked daily and a rising trend in HScore should increase index of suspicion for HLH.

HScore is validated in adults but can be useful at any age.

In children and young people, also use HLH-2004 criteria and criteria for macrophage activation syndrome in systemic JIA.

2.1.5 Hyperinflammatory biomarkers and scores

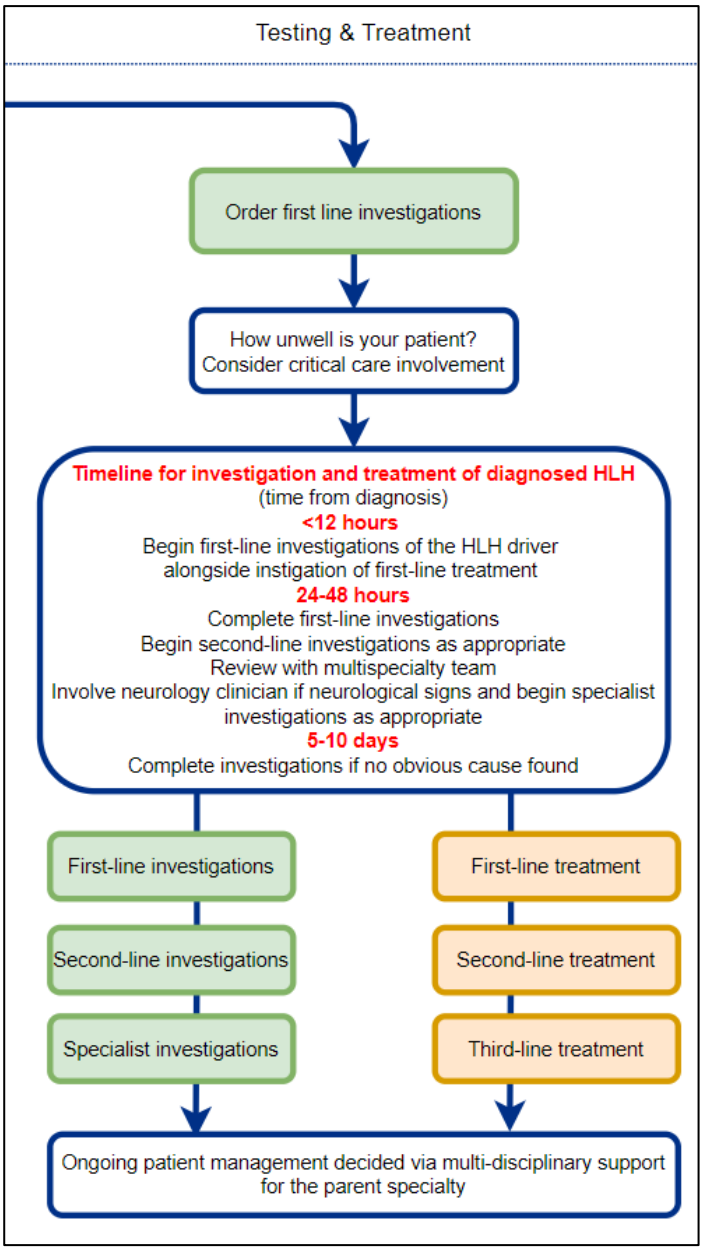
Marker	HLH-2004	HScore adults	MAS criteria HLH in SJIA	OH index malignancy associated HLH
Fever	✓	✓		
Hyperferritinaemia	>500ng/ml	>2000ng/ml	>684ng/ml	>1000ng/ml
Organomegaly	✓	✓		
Cytopaenia	✓	✓	✓	
Hypertriglycerides	✓	✓	✓	
Hypofibrinogen	✓	✓	✓	
ALT/LDH		✓	✓	

Haemophagocytosis	✓	(✓)		
Soluble CD25	✓			✓
NK cell activity	✓			
Link to document	*Link*	*Link*	*Link*	*Link*

2.1.6 Treatment

Do not delay first line treatment if HLH is diagnosed/suspected with high HScore in a patient with at-risk clinical features (fever, cytopaenia, hyperferritinaemia).

First line treatment is usually with corticosteroids. Where there is concern about concomitant infection +/- infection driving HLH, cover with appropriate antimicrobials. Do not delay treatment with steroids unless there are definitely contraindicated.



Above: Testing & Treatment column from HLH pathway shared on page 5 of this guide

2.1.6.1 First line treatment - Corticosteroids

Treatment	Adult	Child
Corticosteroids initial dosing	Methylprednisolone 1g IV OD or dexamethasone 10mg/m2 IV OD Consider higher dose dexamethasone in cases with CNS involvement	Methylprednisolone IV 30mg/kg (maximum 1g) OD or equivalent in dexamethasone Consider higher dose dexamethasone in cases with CNS involvement
Corticosteroids step-down dosing	Step down to 1mg/kg prednisolone or equivalent after 3-5 days	Step down to 10mg/kg prednisolone or equivalent after 3-5 days

- Start bone and gastrointestinal prophylaxis in line with local guidelines.
- 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, in line with local guidelines.
- Try to limit dose and duration of steroids if driver unclear (may mask lymphoma diagnosis) but do not allow this concern to delay corticosteroid therapy

2.1.6.2 Second line treatment - Anakinra

Anakinra is a recombinant IL-1 receptor blocker. Since Il-1 is an important initiating agent in the cytokine cascade, blocking its activity is a logical therapeutic strategy.

Anakinra is indicated for steroid refractory HLH due to all causes presenting in people of any ages in whom first line therapy with corticosteroids has not been effective or would obscure the diagnosis of the underlying condition – see https://www.england.nhs.uk/wp-content/uploads/2021/12/ccp-for-the-use-of-therapeutic-immunoglobulin-england-2024-v4.pdf.

Use is commissioned through Specialised Rheumatology Commissioning and use by providers must be registered through the appropriate prescribing system.

- Use of anakinra for HLH is off-label, as is administration by the intravenous route. In critical illness, intravenous dosing is often used to achieve a higher and faster maximal plasma concentration.
- Dosing involves starting with at least 1-2 mg/kg/day, increasing to a maximum of 8mg/kg/day in both adults and children. If there is an inadequate therapeutic response, advice from specialist centres which regularly manage HLH.
- In practice, starting dose is often 2-4mg/kg IV rounded up to nearest 100mg in 2-3 divided doses. This can be titrated to a maximum of 8mg/kg/day in divided doses (if >100kg, dose should not exceed 800mg daily).
- In cases involving severe renal impairment (CrCl <30ml/min) consider administration every 48 hours
- Anakinra is a critical medicine and doses should not be delayed or omitted

- Anakinra is not stocked on the wards and is supplied via the ward pharmacist. Anakinra may not be stocked routinely and there should be a local protocol in place for ensuring availability.
- Anakinra is stored in the fridge (2℃ to 8℃).

2.1.6.2.1 Subcutaneous injection of Anakinra:

- Anakinra is given subcutaneously unless contraindicated/unsuitable (e.g. low platelets, significant subcutaneous oedema).
- Anakinra pre-filled syringes are sterile unpreserved solutions and for single use only.
- Do not shake. Allow the pre-filled syringe to reach room temperature before injecting.
- 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
- To be administered subcutaneously to:
    - the abdomen (except for the area around the navel)
    - the top of the thighs
    - the upper outer areas of the buttocks; and
    - the outer area of the upper arms

2.1.6.2.2 Intravenous bolus of Anakinra:

- Intravenous bolus administration is reserved for patients for whom subcutaneous injections of anakinra is unsuitable (e.g. platelets <20x109/L) or who are critically unwell and have significant subcutaneous oedema.
- Recommended dose remains as above:
    - Uncap the desired number of pre-filled anakinra syringe(s);
    - Add the appropriate dose to a 50ml syringe, making up the total volume of 50ml with sodium chloride 0.9%;
    - Infuse over 30 minutes via syringe pump.

Note: Anakinra should not be administered concomitantly via Y-site or mixed with any other medications due to lack of compatibility information.

2.1.6.2.3 Response criteria when using anakinra

This is in line with the NHS England commissioning policy: https://www.england.nhs.uk/publication/commissioning-criteria-policy-for-the-use-of-therapeutic-immunoglobulin-ig-in-england-2021/

At least one of the following:

- Reduction in level of organ support (such as vasopressor dose, renal replacement therapy and ventilation)
- Serial reduction in the HScore

- Reduction of ferritin level by at least 10% within 7 days
- Where applicable, a reduction of corticosteroid dose by at least 25% within 14 days

2.1.6.2.4 Stopping criteria

1) Serious adverse events e.g., anaphylaxis
2) No evidence of clinical response according to the response criteria above within 14 days
3) Resolution of HLH defined by local/national MDT discussion

2.1.6.3 Third line treatment for steroid/anakinra refractory HLH

Third line treatments should be considered in line with MDT discussion

Intravenous Immunoglobulin

Intravenous Immunoglobulin (IVIG) may be considered in refractory HLH particularly if there is cardiac or CNS involvement. IVIG is an expensive therapy, in short supply and use is therefore controlled by NHS England guidelines.

In HLH, IVIG use should only be considered after local/national MDT discussion and in the context of steroid/anakinra refractory HLH. IVIG can be given in an emergency situation and permission sought from the IVIG panel retrospectively – liaise with ward pharmacist to ensure this is done. 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 required. IVIG Dosing is 1g/kg/day for 2 days; consider repeating same dose on day 14 after discussion with MDT if HLH relapses or remains steroid dependent. Usage should be reported on the national database https://igd.mdsas.com/

Ciclosporin

Ciclosporin is useful particularly in HLH triggered by rheumatic disease as well as in preventing relapse HLH more generally. Usual dose is 1mg/kg BD either PO or IV.

Etoposide

Etoposide is chemotherapeutic agent and prescribed by haematologists only. Etoposide may be considered in steroid/anakinra refractory HLH in discussion with haematology consultant. Usual dose for HLH is 150mg/m2 intravenous twice weekly for two weeks in the first instance but dose reduction is often needed because of liver dysfunction. Etoposide may be available as an oral medication depending on local prescribing arrangements, and should be discussed with a local Haematologist.

2.1.7 Support with treatment/management decisions

Particularly when recognised and treated early and in the absence of a malignant driver, HLH can be successfully treated with relatively modest treatment e.g. steroids and short course of anakinra. In these cases tapering of treatment is often a question for clinicians. There are no evidence-based guidelines but general principles include risk assessing treatment morbidity and weaning the treatment with highest risk first – often this is corticosteroids.

Referral to national MDT is suggested in cases where:

- HLH has been refractory;
- the diagnosis is unclear;
- patient is critically unwell; or
- treatment is increasingly complex.

2.1.8 Investigating HLH

Daily HLH screen:

- FBC
- U&E
- LFT
- CRP/ESR (ESR disproportionately low or falling, despite clinical deterioration in the patient)
- Ferritin
- Coagulation screen including fibrinogen (Clauss)
- Triglycerides
- Calculate daily HScore using https://saintantoine.aphp.fr/score/

2.1.8.1 First line investigations – tests to consider for the patient with suspected HLH of unknown driver	
Haematology	Coagulation screening including Clauss Blood film Erythrocyte sedimentation rate Reticulocytes Consider: D-dimer Bone marrow biopsy
Biochemistry	Renal profile LFTs including AST LDH Triglycerides CRP Iron profile Troponin NT-proBNP Urine protein-creatinine ratio
Rheumatology	Complement C3 and C4, antinuclear antibodies, antineutrophilic cytoplasmic antibodies, antibodies to extractable nuclear antigens, anti-double-stranded DNA antibodies

Microbiology	Bacterial blood cultures x 3 Ideally before 1st antibiotic administration
Virology	Blood 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	Chest x-ray CT of neck, chest abdomen and pelvis with contrast Whole body PET / CT (if available – cross sectional imaging should be sought within 48 hours, PET-CT as gold standard for adults) Ultrasound if delay for cross-sectional imaging (often preferred in children) In children, consider whole body MRI or ultrasound depending on availability Electrocardiogram Echocardiogram
2.1.8.2 Second line investigations – tests to further investigate the HLH driver of trigger	
Evaluating for infection	Depending on infectious diseases consult or travel history, consider: Parasites: Malaria film or rapid diagnostic test Toxoplasma and Leishmania serology Other: 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 leishmaniasis Tests to ensure no adverse effects of immune suppression (depending on travel history), consider: strongyloides serology trypanosoma cruzi serology Virology: Human T-lymphotropic virus 1 (ideally before blood products)

Additional tests in immunocompromised people	Recommended: 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, beta-D-glucan (possible false positive after intravenous immunoglobulin) Stool microscopy for ova, cysts and parasites
Evaluation for malignancy	Early biopsy is recommended; steroids might mask lymphoma. Bone marrow biopsy: Aspirate smear Flow cytometry Cytogenetics if lymphoma or other malignancy Other biopsy sites as determined by imaging: Lymph node (core or excision), Deep skin (for intravascular or cutaneous lymphoma), Liver, spleen or any fluorodeoxyglucose avid site
Additional imaging if neurological features	Brain MRI with gadolinium (before lumbar puncture to avoid false-positive meningeal enhancement)

2.1.8.3 Specialist investigations

Immunology	Soluble CD25 Cytokine testing Lymphocyte subsets Natural killer cell activity (these may not be routinely available on all sites)
Evaluating for Primary HLH	If considering primary HLH : CD107a granule release assay - if abnormal, send an R15 genetic analysis to your commissioned genetic service: https://www.england.nhs.uk/wp-content/uploads/2018/08/rare-and-inherited-disease-eligibility-criteria-v2.pdf Protein expression - perforin, SH2D1A, or XIAP - if abnormal, send for genetic analysis Consider: Flow cytometry-based assays
Lumbar puncture	Cell count

	Opening pressure Glucose Protein and matched oligoclonal bands with or without cytospin (≥10ml) Bacterial culture Viral PCR Consider: Cytology Flow cytometry
Further tests for targeted populations	Immunoglobulins Syphilis serology Fungal and tuberculosis cultures Neurophysiology Targeted CNS biopsy

3. Case studies

The aim of the GIRFT pathway is to enable and support an England-wide approach to suspected HLH in any Trust. These case studies represent secondary, tertiary and quaternary approaches to HLH management, and include paediatric, adolescent and adult services. We present these case studies to demonstrate the impact of having a standardised approach to the diagnosis and management of HLH upon outcomes for patients with this life-threatening condition.

3.1 Case Study 1 – Sheffield Teaching Hospitals NHS Foundation Trust (STH)

Available at: https://future.nhs.uk/GIRFTNational/view?objectID=212515429

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Sheffield improves in-hospital mortality rate for HLH through MDT working

Sheffield Teaching Hospitals NHS Foundation Trust

Summary

Sheffield Teaching Hospitals (STH) is a large University hospital trust and offers support to other providers caring for suspected and diagnosed Haemophagocytic Lymphohistiocytosis (HLH) patients.
Dr Rachel Tattersall from STH is co-chair of HLH Across Specialty Collaboration (HiHASC), a professional network for HLH and hyperinflammatory medicine, established in 2018.
At STH, a collaborative and coordinated approach to HLH care has increased the identification rate, and successfully reduced in-hospital mortality from 72% to 31%.

Contextual clinical challenges

HLH is a devastating syndrome with uncontrolled activation of the immune system leading to hyperinflammation, tissue damage and multi-organ failure. It can be triggered by infection, malignancy, autoimmune/ autoinflammatory disease and therapeutic interventions including drugs, CAR-T cell therapy and bone marrow transplant.
It is a rare disease and although diagnosis rates are increasing, it is likely under-diagnosed. One-year survival varies significantly and is poorest in patients over 75 with haematological malignancy.

Retrospective evaluation of MDT patients from 1st Oct 2016 to 30th Sept 2021

Demographics & Outcomes	All (n=79)	Pre 1st March 2020 (n=43)	Post 1st March 2020 (n=36)
Mean age (years)	52	53	50
Female n (%)	28 (35%)	18 (42%)	10 (28%)
In-hospital mortality n (%)	42 (53%)	31 (72%)	11 (31%)
If discharged, length of stay	33	34	32
Cause of HLH n (%)			
Haematological malignancy	28 (35%)	20 (47%)	8 (22%)
Infection (bacterial + viral)	35 (44%)	12 (28%)	23 (64%)
of which, COVID-19	15 (19%	0 (0%)	12 (42%)
Rheumatological	10 (13%)	7 (16%)	3 (8%)
Other	6 (8%)	4 (9%)	2 (6%)

Approach

- In 2010 an MDT between haematology, rheumatology, infectious diseases and critical care began caring for people with HLH.
- In 2018, STH joined up with the UCLH team led by Dr Jessica Manson to agree an evidence-based approach.
- In 2002, within STH a guideline was agreed and ferritin auto-flagging to increase diagnosis was implemented.

In-hospital HLH mortality rate has fallen from 72% to 31%

Resource links

Lancet Rheum: Cox et al (2023) Diagnosis and investigation of suspected HLH in adults 2023 HiHASC consensus guideline

https://www.HiHASC.org

Dr Rachel Tattersall
"HLH can present to any speciality, early diagnosis and treatment is key. Getting a team of champions together across different disciplines, including laboratory medicine, enabled a guideline to be agreed. Coupled with an educational programme going into departments and helping teams to understand their role in HLH, the profile of HLH was raised. Colleague feedback about support and education has been positive. Ferritin (HLH biomarker) was auto-flagged and when highly elevated, phoned through to the requesting clinician, with a hyperlink to the result guideline. This has improved early diagnosis and treatment of HLH with demonstrable mortality reduction."

Future considerations and learning

Dr Tattersall is working with the GIRFT clinical leads for Rheumatology to develop content intended to spread awareness among clinicians of this condition.

Contacts for further information

Dr Rachel Tattersall, Adolescent and Adult rheumatology consultant at STH and Co-chair of HiHASC
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Scalable
Best Practice

3.2 Case Study 2 – University College London Hospitals NHS Foundation Trust (UCLH)

Available at: https://future.nhs.uk/GIRFTNational/view?objectId=216084581

GIRFT GETTING IT RIGHT FIRST TIME | NHS IMPACT Improving Patient Care Together | NHS England

UCLH supports HLH cases across England through MDT working

NHS University College London Hospitals NHS Foundation Trust

Summary

University College London Hospitals (UCLH) is a large teaching hospital trust and offers support to providers all over England caring for suspected and diagnosed Haemophagocytic Lymphohistiocytosis (HLH) patients.
Dr Jessica Manson from UCLH is co-chair of HLH Across Specialty Collaboration (HiHASC), a professional network for HLH and hyperinflammatory medicine, established in 2018.
A collaborative and coordinated approach to HLH care has increased the identification and treatments rates, with inpatient numbers tripling over the last 5 years. This work has been associated with a reduction in mortality from 55% to 36%.

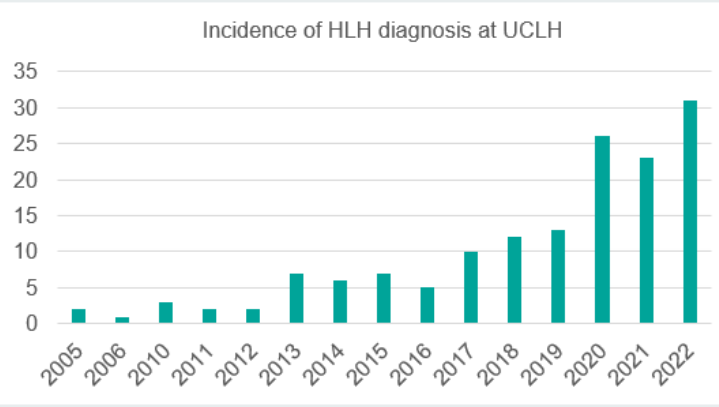
Contextual challenges

HLH is a devastating syndrome with uncontrolled activation of the immune system leading to hyperinflammation, tissue damage and multi-organ failure. It can be triggered by infection, malignancy, autoimmune/autoinflammatory disease and therapeutic interventions including drugs, CAR-T cell therapy and bone marrow transplant.
It is a rare disease and although diagnosis rates are increasing, it is likely under-diagnosed. One-year survival varies significantly and is poorest in patients over 75 with haematological malignancy.

Approach

- Terms of reference agreed
- Attendance – clinicians from Rheumatology, Haematology, and Infectious Disease are core attendees, with optional attendance from Critical Care, Virology and Neurology
- Patients are referred into the MDT via proforma into a generic inbox

Diagnosis of HLH



Following establishment of the MDT, mortality fell from 55% to 36%

3x **Patient numbers in the UCLH inpatient service for HLH have tripled over the last 5 years**

Service Provision

- In-patient cross-specialty care for HLH cases across the UCLH sites
- Advice via multidisciplinary meetings for suspected and confirmed cases of HLH across the 4 united nations.
- MDT was established in 2019, meeting once per month
- In 2023, over 100 different patients were discussed via the MDT meetings
- In 2024, there are now 6 meetings per month due to demand

Dr Jessica Manson
"*The UCLH HLH service has grown exponentially, as HLH is identified in more and more patients. The service has had to adapt with this demand with colleagues having time recognised in job plans, and formalised support from the admin team.*"

Future considerations and learning

Dr Manson is working with the GIRFT clinical leads for Rheumatology to develop content intended to spread awareness among clinicians of this condition.

Resource links

- UCLH HLH Service website
- Lancet Rheum: Cox et al (2023)
- https://www.HiHASC.org

Contacts for further information

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Best Practice
Scalable

3.3 Case study 3 – Kent & Medway HLH MDT

Available at: https://future.nhs.uk/GIRFTNational/view?objectId=216084613

GIRFT GETTING IT RIGHT FIRST TIME | NHS IMPACT Improving Patient Care Together

HLH: Kent & Medway increase diagnosis numbers and reduce mortality

NHS England

NHS Kent and Medway

Summary

NHS Kent and Medway (K&M) is the NHS organisation that plans and commissions healthcare services to meet the needs of their population of 1.9million people. Within the system there are 3 acute care providers, with East Kent Hospitals as the specialist centre for rheumatology. Clinical teams across the system came together as a regional MDT, to plan a collaborative pathway for their patients with suspected Haemophagocytic Lymphohistiocytosis (HLH).

Background

In 2022, the clinical teams in K&M diagnosed and treated approximately 1-2 HLH cases per month. It was acknowledged, though, that there was limited regional expertise, and all referrals were taken to the MDT at University College London Hospitals (UCLH) for discussion and planning.
2 Rheumatologists within the system were members of HiHASC (Hyper inflammation and HLH across specialty collaboration).

Resource links

GIRFT HLH Guidance

Approach

1. UCLH clinicians were available for discussion and advice
2. Referral forms shared by UCLH and adapted for use in K&M
3. Expressions of interest for staff to join K&M multidisciplinary approach
4. Network established in February 2023 in collaboration with UCLH
5. Trust pharmacists ensure pharmaceutical stocks to treat HLH are available at all Trusts within K&M
6. Managed within existing clinical and operational capacity

MDT membership

3 x Rheumatology clinicians
1 x Rheumatology specialist nurse
2 x Haematology clinicians
1 x Virology/infection clinician
1 x Trust Pharmacist
1 x MDT Co-Ordinator

Factors in sustainability

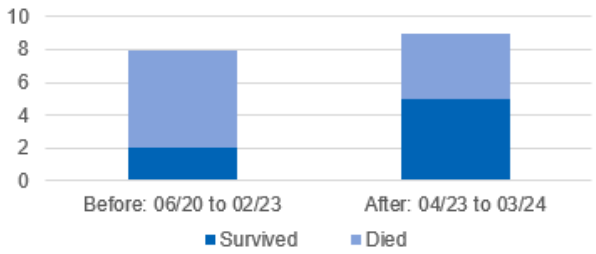
- Committed and enthusiastic multidisciplinary group
- Education of clinical teams
- Raising awareness
- Job planning

Achievements

For patients
- Quick, responsive and improved local care
- Reduced requirement for transfer to UCLH
- Biopsies expedited

For clinicians
- Development of individual clinician skill set
- MDT clinicians find the process motivational
- Raised awareness of HLH and local MDT
- Early detection and referral encouraged
- Ferritin flag agreed across region
- MDT discussions within 1 working day of referral
- 6 members have joined HiHASC

HLH Patient diagnosis and survival before and after introduction of MDT working



28-day mortality taken from 75% to 44%

Median days to Anakinra reduced from 13 to 3 days

Outcomes

- Median days from admission to treatment with Anakinra reduced from 13 days to 3 days
- 28-day mortality decreased from 75% to 44% following introduction of K&M MDT
- Diagnosis numbers of preceding 32 months met within 11 months of introducing MDT

Issues and opportunities for learning

- Communication between members of the MDT in OOH/evening times is out of the remit
- Importance of early bone marrow/LN biopsy
- Responsible ward clinician to attend MDT, arrange prescription, and daily HLH blood tests
- Referral form continually reviewed and updated

Future developments

- Grand Round presentations
- Teaching acute medicine regional SpR
- HLH scenario development in process
- MDT member to present at Society for Acute Medicine conference Oct 2024
- Infectious disease and Immunology clinicians have joined the MDT

Contacts for further information

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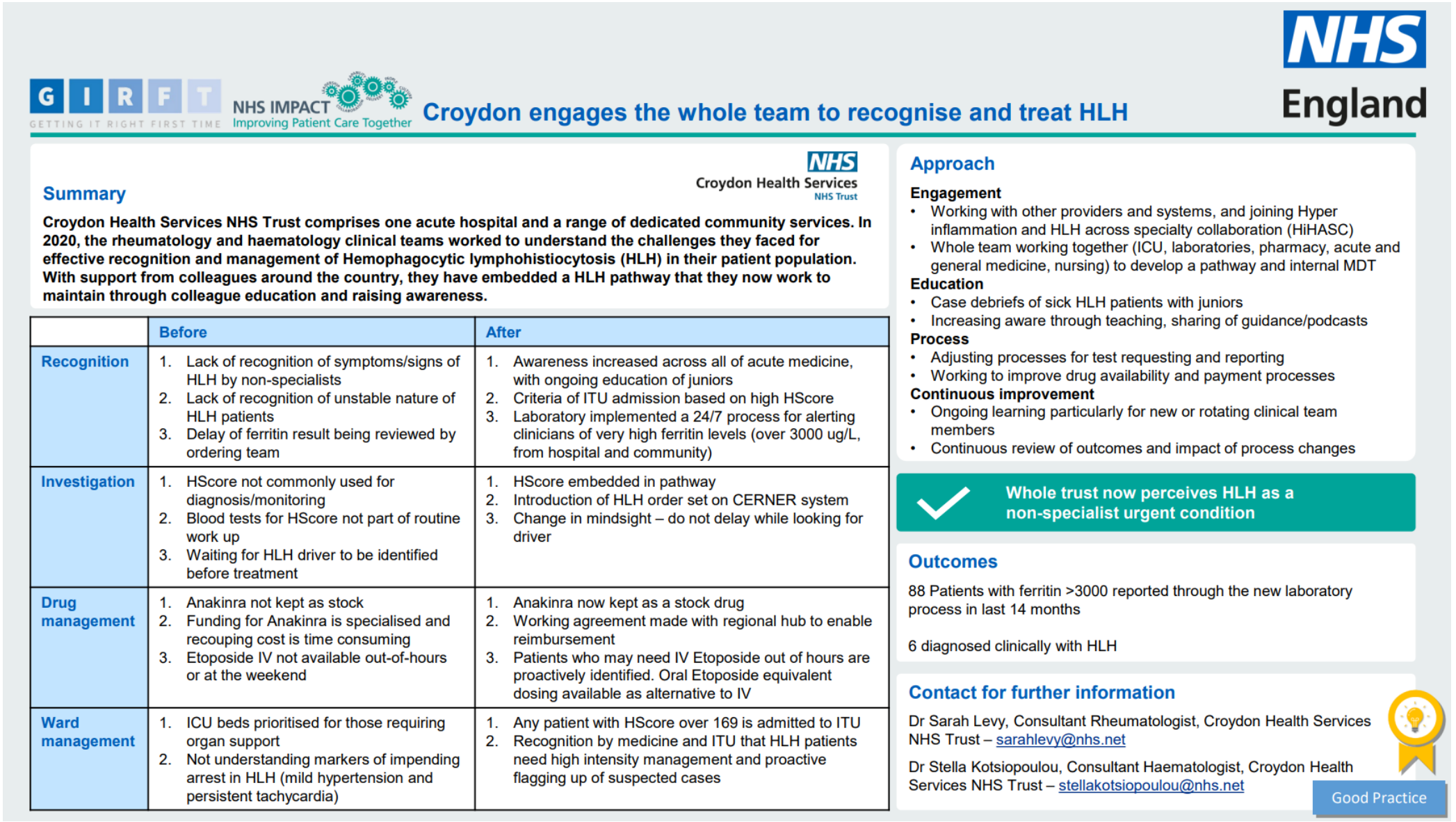
Good Practice

3.4 Case Study 5 – HLH at Croydon

Available at: https://future.nhs.uk/GIRFTNational/view?objectID=212517541



GIRFT GETTING IT RIGHT FIRST TIME | NHS IMPACT Improving Patient Care Together

Croydon engages the whole team to recognise and treat HLH

NHS England

NHS Croydon Health Services NHS Trust

Summary

Croydon Health Services NHS Trust comprises one acute hospital and a range of dedicated community services. In 2020, the rheumatology and haematology clinical teams worked to understand the challenges they faced for effective recognition and management of Hemophagocytic lymphohistiocytosis (HLH) in their patient population. With support from colleagues around the country, they have embedded a HLH pathway that they now work to maintain through colleague education and raising awareness.

	Before	After
Recognition	1. Lack of recognition of symptoms/signs of HLH by non-specialists 2. Lack of recognition of unstable nature of HLH patients 3. Delay of ferritin result being reviewed by ordering team	1. Awareness increased across all of acute medicine, with ongoing education of juniors 2. Criteria of ITU admission based on high HScore 3. Laboratory implemented a 24/7 process for alerting clinicians of very high ferritin levels (over 3000 ug/L, from hospital and community)
Investigation	1. HScore not commonly used for diagnosis/monitoring 2. Blood tests for HScore not part of routine work up 3. Waiting for HLH driver to be identified before treatment	1. HScore embedded in pathway 2. Introduction of HLH order set on CERNER system 3. Change in mindsight – do not delay while looking for driver
Drug management	1. Anakinra not kept as stock 2. Funding for Anakinra is specialised and recouping cost is time consuming 3. Etoposide IV not available out-of-hours or at the weekend	1. Anakinra now kept as a stock drug 2. Working agreement made with regional hub to enable reimbursement 3. Patients who may need IV Etoposide out of hours are proactively identified. Oral Etoposide equivalent dosing available as alternative to IV
Ward management	1. ICU beds prioritised for those requiring organ support 2. Not understanding markers of impending arrest in HLH (mild hypertension and persistent tachycardia)	1. Any patient with HScore over 169 is admitted to ITU 2. Recognition by medicine and ITU that HLH patients need high intensity management and proactive flagging up of suspected cases

Approach

Engagement
- Working with other providers and systems, and joining Hyper inflammation and HLH across specialty collaboration (HiHASC)
- Whole team working together (ICU, laboratories, pharmacy, acute and general medicine, nursing) to develop a pathway and internal MDT

Education
- Case debriefs of sick HLH patients with juniors
- Increasing aware through teaching, sharing of guidance/podcasts

Process
- Adjusting processes for test requesting and reporting
- Working to improve drug availability and payment processes

Continuous improvement
- Ongoing learning particularly for new or rotating clinical team members
- Continuous review of outcomes and impact of process changes

Whole trust now perceives HLH as a non-specialist urgent condition

Outcomes

88 Patients with ferritin >3000 reported through the new laboratory process in last 14 months

6 diagnosed clinically with HLH

Contact for further information

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Good Practice

4. Further information

NHS England https://www.england.nhs.uk/publication/commissioning-criteria-policy-for-the-use-of-therapeutic-immunoglobulin-ig-in-england-2021/

NICE Guidance Key messages | COVID 19 rapid evidence summary: Anakinra for COVID-19 associated secondary haemophagocytic lymphohistiocytosis | Advice | NICE

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5.3 Contributing Organisations

Histio UK https://www.histiouk.org/

BSR - British Society for Rheumatology https://www.rheumatology.org.uk/

ARMA – Arthritis and Musculoskeletal Alliance https://arma.uk.net/msk-health-inequalities-equality/