Clinical Commissioning Policy: Anakinra for Haemophagocytic Lymphohistiocytosis (HLH) for adults and children in all ages [210701P] (1924)

Publication date: October 2021 **Version number:** 1.0

Commissioning position

Summary

Anakinra is recommended to be available as a treatment option for adults and children of all ages through routine commissioning for HLH within the criteria set out in this document. In England services will be commissioned through Specialised Rheumatology Networks.

Executive summary

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain language summary

About haemophagocytic lymphohistiocytosis

Haemophagocytic lymphohistiocytosis (HLH) happens when the body's immune system responds abnormally to illness or some treatments which target the immune system. The illnesses include infections, cancers (particularly blood cancers) and some rheumatology conditions and treatments which can trigger HLH. Alternatively, primary HLH can be caused by an inherited genetic condition meaning the immune system cannot switch itself off once triggered. In HLH the body makes too many activated immune cells causing severe inflammation (known as hyperinflammation) throughout the body. This causes fever, damage to organs (including the liver, spleen brain and heart), and destroys blood-producing cells in the bone marrow. HLH can make people more at risk of infection. Without treatment many people die. With treatment, particularly if HLH is recognised and treated early, the outlook is much better. In addition to treating the HLH, the trigger needs to be found and treated too. The rapid, severe, progressive, multi-organ and life-threatening course of the illness results in admission to critical care. Its impact and experience on patients and their families has been described as catastrophic.

Treatment will usually include medicines that reduce the body's immune response such as steroid and immunosuppressants. Anakinra is a medicine which is given either by injection under the skin or as an infusion through a drip. It works by blocking the main driver of the hyperinflammation, interleukin1 (IL1). Anakinra in HLH is usually only needed for a short period of 3-14 days on average. Anakinra is licensed in the UK for other illnesses, including some

triggering conditions for HLH such as Stills disease, systemic juv enile idiopathic arthritis (SJIA), rheumatoid arthritis, cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), however it is not licensed for the treatment of HLH.

What we have decided

NHS England has carefully reviewed the evidence to treat HLH with anakinra. We have concluded that there is enough evidence to make the treatment available. Anakinra, when given early, stabilises the hyperinflammatory condition HLH and is usually a bridging treatment to allow diagnosis and treatment of the underlying triggering disease and is sometimes required longer-term.

Links and updates to other policies

NHS England Specialised commissioning policies already exist for the use of anakinra in patients with Systemic Juvenile Idiopathic Arthritis (SJIA) [E03X04] and Adult Onset Stills Disease (AOSD) [170056P] both of which are known to trigger HLH. It should be noted that the use of anakinra in these policies relates specifically to ongoing management of the trigger conditions themselves (SJIA and AOSD) rather than the treatment of HLH. It has led to a reduction in MAS related mortality in SJIA and AOSD. Therefore, these policies do not preclude the inclusion of patients with SJIA and AOSD in this HLH-focused policy.

A NICE TA for the use of anakinra for treating Stills Disease was published in March 2021. https://www.nice.org.uk/guidance/ta685

Committee discussion

Clinical Panel debated the evidence base and the decision was made to recommend the policy proposition progress as for routine commissioning, recognising the low evidence base in a rare condition.

See the committee papers (link) for full details of the evidence.

The condition

Haemophagocytic lymphohistiocytosis (HLH) is a rare condition and comprises a severe syndrome of, uncontrolled, self-perpetuating inflammation or hyperinflammation causing progression to multi-organ failure with a very high mortality rate. HLH may be triggered by rheumatic disease, malignancy (especially haematological malignancy) and infection (when it may be indistinguishable from sepsis) or by use of treatments such as chimeric antigen receptors cell Therapy (CAR T), Marrow Transplant (BMT), haematopoietic stem cell transplantation (HSCT) or stem cell transplant therapy for haematological malignancy. BMT may be used as a treatment for primary HLH, however it should be noted that HLH may also develop post BMT in a minority of patients.

HLH affects people of all ages (children, adolescents, adults). There are two types:

- a genetic immune system defect usually identified in infants or childhood termed primary HLH (pHLH) leading to a failure of immune regulation and hyperinflammation, or associated with Primary Immunodeficiency or

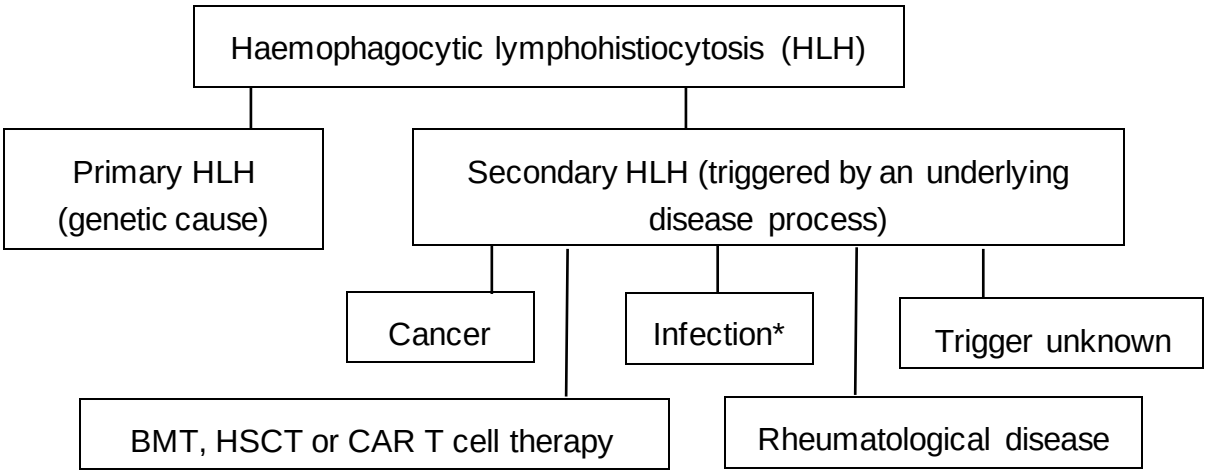
- resulting from a trigger from another disease process leading to uncontrolled, pathological inflammation (hyperinflammation) termed secondary HLH (sHLH). Most commonly this is cancer (malignancy), infection (caused most commonly by viruses, including Sars-Cov-2), metabolic disorders or rheumatological disease and is termed secondary HLH (sHLH). Viral infections are the leading cause of secondary HLH (Carter

et al 2019, Mehta et al 2020). HLH can be thought of as an umbrella term for a group of hyperinflammatory syndromes, characterised by similar pathophysiology and clinical presentation.

Increasingly atypical HLH presentations are being recognised, such as isolated central nervous system (CNS) HLH. The lack of systemic inflammation makes the use of long courses of high dose steroids problematic. Anakinra has an important role in these rare cases, as determination of diagnosis and optimal management can be protracted.

Figure 1 below summarises the types and triggers of HLH.

Figure 1. Types and triggers of HLH



* including viruses such as SARS-CoV-2.

There are several terms used to describe HLH in the literature, depending on the underlying trigger (Table 1).

Table 1. Terminology used to describe HLH.

Term	**Definition/Comment**
Macrophage Activation Syndrome (MAS)	sHLH triggered by rheumatic disease
Macrophage Activation Like Syndrome in Sepsis (MALS)	sHLH triggered by sepsis
Cytokine storm syndrome (CSS)	This term includes, but is not limited to, HLH (e.g., may also refer to MALS, CRS, MAS)
Cytokine release syndrome (CRS)	sHLH triggered by CAR T cell therapy
Hyperferritinaemic syndrome	Synonym for any cause of HLH

Symptoms at the beginning of the illness are non-specific and are very similar to sepsis.

Patients may present to multiple medical specialties. Unless diagnosed and treated early, patients will become progressively and critically unwell with persistent fever, low blood counts (cytopaenias), splenomegaly and multiple organ failure. Untreated, continuing HLH from all causes is fatal.

Lack of recognition and delay in diagnosis are barriers to timely treatment. This is being addressed in the UK by the formation of the Hyperinflammation and HLH Across Speciality Collaboration (HiHASC) hosted by the charity HistioUK (http://www.histiouk.org). Some centres host HLH Multidisciplinary Teams (MDTs) to better facilitate recognition, treatment and management of cases and new MDTs will be considered with advice from the Histio UK Haemophagocytic Lymphohistiocytosis across specialty collaboration (HASC) network. In England services will be commissioned through Specialised Rheumatology Networks.

Current treatments

Current treatment pathways are summarised here:

- pHLH – HLH-2004 protocol (dexamethasone, intravenous immunoglobulin (IVIg), methotrexate, ciclosporin, etoposide, emapalumab).

- sHLH (extrapolated from HLH-2004) – high dose steroids followed by IVIG plus consideration of ciclosporin. In refractory HLH, further high-dose steroids and etoposide. The dose of IVIG is different between children and adults, initially being given as replacement dose in children (0.5g/kg 4 weekly) in contrast to a higher immunomodulatory dose in adults (1g/kg for 2 days and repeated at 14 days if needed).

Current definitive treatment for pHLH once diagnosed is based on the HLH 2004 protocol (Henter et al 2007). However, during the initial presentation of pHLH or sHLH, intensive treatment of HLH regardless of cause is needed before those ultimately diagnosed with pHLH can be put forward for the HLH 2004 protocol and curative bone marrow transplant. The medicines used in this protocol include steroids and chemotherapies with a range of very significant side effects. The protocol is designed to be a limited treatment to get children and young people well enough to proceed to a BMT which cures their inherited genetic abnormality.

The HLH-2004 protocol is extrapolated for use in sHLH but is associated with several risks. The use of 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. Both steroids and chemotherapies can worsen infection in patients in whom the underlying disease process is infection. For these reasons there may be variation in the specific treatments that are used depending on the underlying trigger of HLH. Finally, there are high costs associated with the use of scarce IVIG, depending on frequency of fortnightly usage.

The aim of early and intensive treatment of HLH is to achieve stabilisation and prevent rapid progression to multi-organ failure, and to enable specific treatment of the underlying disease triggers.

The new treatment

Anakinra is a very short-acting medicine given either by its licensed route as a subcutaneous injection or (unlicensed) as an intravenous infusion through a drip – the latter route often being necessary in critically unwell patients. Dysfunction of the innate immune system involving interleukin1 (IL1) is central to disease pathogenesis and anakinra blocks this main driver of hyperinflammation.

Anakinra is needed in the acute phase of HLH (during which managing clinicians will diagnose the trigger and identify those with genetic pHLH or sHLH) for 3-14 days on average and is generally not continued long term. Anakinra is not a curative treatment but rather dampens the pathological, hyperinflammatory response to allow the underlying disease to be diagnosed and

treated, or genetic error to be discerned in the case of pHLH. It enables down-regulation of the immune overdrive and consequent hyperinflammation, tissue damage, multi-organ failure and circulatory collapse requiring critical care. Hence it assists the patient with HLH, by limiting progression and to survive the critical episode in order to enable treatment of the underlying disease. It is important to recognise that, once HLH is established, both the trigger of HLH and the HLH itself need treatment. Outside of rheumatological diseases such as AOSD and SJIA where anakinra is a treatment for the underlying disease as well as HLH, anakinra is used as a "bridging treatment". While anakinra stabilises the patient, diagnostic imaging and tissue testing can be organised for confirmation of the triggering disease.

Anakinra has a good safety profile in contrast to the toxicity of other treatments for HLH. First line treatment with corticosteroids often requires large doses which are profoundly immune suppressive and lead to significant risk of secondary infection. In haematological malignancy, steroids can temporarily obscure the malignant disease. The other first line treatment, ciclosporin, can be neurotoxic and may cause posterior reversible encephalopathic syndrome. Anakinra has a role as a therapeutic adjuvant where ciclosporin toxicity prevents its ongoing use, and inflammation remains poorly controlled.

Etoposide is a chemotherapeutic agent used second line in HLH and is both profoundly bone marrow suppressant and very long acting; again, leading to significant morbidity from secondary infection and often contra-indicated in those who are critically ill.

Epidemiology and needs assessment

There can be an overlap between pHLH and sHLH, as genetic predisposition with variable penetration in the "secondary HLH" and infectious and other triggers playing an important role in Primary HLH. It is therefore important that the same treatments are available to all patients with HLH and overlapping hyperinflammatory disorders.

The HASC network and MDT experience confirm the rarity of sHLH so this policy would be relevant to a very small number of patients in tertiary centres and secondary care. Reports from centres for which MDT data is available identified 91 cases of sHLH (42 adults and 49 children) in 2018 excluding patients with SJIA/AOSD (HASC network). SJIA/AOSD affects around 1,600 patients in England, 10% of whom either present with or experience sHLH secondary to their disease but rheumatologists looking after this group are usually aware of the potential for sHLH and proactively screen for the condition (Gurion et al 2012).

During the impact assessment stage of policy development, it was identified that around 155 patients in total would be eligible for treatment.; 15 children with pHLH, and 140 people with sHLH (40 children and 100 adults).

In addition, published estimates for the incidence of confirmed pHLH in people aged 15 years and under range from 1.2 to 1.5 per million people per year (Meeths et al 2014), suggesting there are approximately 13 to 15 people with confirmed pHLH in England each year. Rarely, HLH is an indication for allogeneic BMT/HSCT, in which case patients need stabilising as effectively as possible before a high-risk procedure. JACIE accredited BMT/CAR T centres will have agreed local pathways and therapeutic treatment protocols.

Evidence summary

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of this treatment for the indication.

Six papers were included in this review (Eloseily et al 2019, Gregory et al 2019, Kumar et al 2017, Shakoory et al 2016, Sonmez et al 2018 and Wohlfarth et al 2019).

The paper by Shakhoory et al (2016) was a comparative cohort study based on a subgroup analysis of adults recruited to an earlier phase III randomised controlled trial (RCT) (Opal et al 1997)[1]. The other five papers were single centre, retrospective case series of paediatric patients (Eloseily et al 2019, Gregory et al 2019, Sonmez et al 2018) and adults (Kumar et al 2017, Wohlfarth et al 2019). None of these studies were undertaken in the UK.

In adults and children with HLH, what is the clinical effectiveness of anakinra compared with standard treatment?

Critical Outcomes

The critical outcomes for decision making are in hospital and 30-day mortality and intensive care unit (ICU) duration of stay. Acquired infection and adverse events are also critical outcomes. These are reported in the question on safety below. Certainty in the quality of the evidence for the critical outcomes was very low when assessed using modified GRADE.

In-hospital and 30-day mortality

In total, five studies (one comparative cohort analysis using subgroup data from an earlier RCT (Opal et al 1997) and four case series) provided evidence relating to in hospital and 30-day mortality.

For adults with macrophage activation syndrome (MAS - defined as the presence of hepatobiliary dysfunction (HBD) and disseminated intravascular coagulation (DIC)), one comparative cohort analysis (n=43) reported statistically significantly lower 28-day mortality in patients treated with anakinra (n=26) compared to placebo (n=17) (34.6% vs 64.7%, p=0.0006) with a lower risk of death (HR 0.28 (95%CI 0.11 to 0.71), p=0.007) (Shakhoory et al 2016). This study provided very low certainty evidence that compared to standard treatment, anakinra reduced 28-day mortality.

In patients receiving anakinra for HLH, in hospital mortality at undefined timepoints reported in four case series (total n=81) ranged from 27% to 50% (Eloseily et al 2019, Gregory et al 2019, Wohlfarth et al 2019, Kumar et al 2017). The certainty of the evidence was very low.

ICU duration of stay

In adults who received anakinra for HLH, non-comparative evidence from one case series (n=8) reported that the mean ICU duration of stay was 36 days (range 3 to 118 days). For the 5/8 (63%) patients who survived to discharge from ICU, the mean length of stay was 43.6 days (range 6 to 118 days). This single centre, case series (Wohlfarth et al 2019) provided no evidence about ICU duration of stay for patients with HLH treated with anakinra compared to standard treatment. The certainty of the evidence was very low.

[1] 763 patients (out of 906 originally recruited) completed the original RCT for anakinra for severe sepsis. This study is an analysis of 43 adults who had hepatobiliary dysfunction/ disseminated intravascular coagulation.

Important Outcomes

The outcomes important to decision making are abolition of fever, hyperferritinaemia – reduction in serum ferritin levels of 20-50% or more, length of hospital stay, complications such as multiorgan failure, severe cognitive impairment with consequent learning disabilities, nerve paresis, renal impairment and obstructive bronchiolitis, use or change in dose of IVIG, steroids, etoposide or ciclosporin., Complications are reported in the question on safety below. Certainty in the quality of the evidence for the important outcomes was very low when assessed using modified GRADE.

Abolition of fever

In paediatric patients who received anakinra for HLH, non-comparative evidence from two case series (total n=59) reported time to abolition of fever of approximately two days. The mean time for reduction in fever reported by Eloseily et al 2019 was 1.7 (SD±1.11) days and the median time to resolution of fever reported by Sonmez et al 2018 was 2 (range 1 to 4) days. These studies provide no evidence about the abolition of fever with anakinra compared to standard treatment in patients with HLH. The certainty of the evidence was very low.

Hyperferritinaemia – reduction in serum ferritin levels of 20-50% or more

In patients who received anakinra for HLH, non-comparative evidence from two case series (total n=52) reported a reduction in serum ferritin levels. At 15 days after treatment initiation, one case series (n=44) reported a mean change in ferritin levels of 19,256 (SD 66,334) ng/mL corresponding to a mean decrease of 72% (SD 62) (Eloseily et al 2019).

At 14 days after treatment initiation with anakinra, one case series reported a median ferritin level of 2,754 (489-9036) µg/L for seven patients compared to the median baseline for all eight patients of 32,419 (946-79,586) µg/L (Wohlfarth et al 2019). This was an eight-fold reduction. These studies provide no evidence about reduction in serum ferritin levels of 20 to 50% or more with anakinra compared to standard treatment in patients with HLH. The certainty of the evidence was very low.

Length of hospital stay (LOS)

In patients who received anakinra for HLH, non-comparative evidence from three case series (total n=67) reported length of hospital stay which ranged from an average of approximately 12 to 66 days for all patients. Eloseily et al 2019 reported a mean (±SD) duration of hospitalisation of 30 (±40) days for 44 paediatric patients treated with anakinra. LOS was significantly longer for the 12 patients who did not survive to discharge (62.0 (±62) days) compared to those who survived (18.6 (±16) days, p=0.0005). Conversely, Wohlfarth et al 2019 reported a longer mean LOS for four patients who survived to discharge (99.25 days (range 32 to 190 days) compared to the mean LOS for all 8 adults included in the study (65.75 days (range 5 to 190 days).

Sonmez et al 2018 reported the median time of discharge after anakinra initiation was 12 (range 8 to 21) days (n=15 paediatric patients). These studies provide no evidence about length of hospital stay with anakinra compared to standard treatment in patients with HLH. The certainty of the evidence was very low.

Use or change in dose of IVIg

No evidence was identified for this outcome.

Use of or change in dose of steroids

In paediatric patients who received anakinra for HLH, non-comparative evidence from one case series (n=15) reported that the median cessation time of steroids after anakinra initiation was 10 (range 4 to 13) weeks (Sonmez et al 2018). This study provides no evidence on the use or change in dose of steroid medication with anakinra compared to standard treatment in patients with HLH. The certainty of the evidence was very low.

Use of or change in dose of etoposide

No evidence was identified for this outcome.

Use of or change in dose of ciclosporin

No evidence was identified for this outcome.

In adults and children with HLH, what is the safety of anakinra compared with standard treatment?

Acquired infection (Critical for decision making)

In paediatric patients who received anakinra for HLH, non-comparative evidence from one case series (n=44) reported that 6/12 (50%) patients who died had systemic infections (5 had positive fungal cultures) although the authors stated that *'there was no association with the timing of anakinra administration and infection' (*Eloseily et al 2019). This study provided no evidence about acquired infection for patients with HLH treated with anakinra compared to standard treatment. The certainty of the evidence was very low.

Adverse events (Critical for decision making)

In patients who received anakinra for HLH, non-comparative evidence from two case series (total n=23) provided information on adverse events. One patient developed vitiligo causing the cessation of treatment with anakinra (timepoint not reported) (Sonmez et al 2018). Wohlfarth et al 2019 reported no unscheduled treatment discontinuations or adverse events considered attributable to the administration of anakinra. These studies provide no evidence about adverse events with anakinra compared to standard treatment in patients with HLH. The number of adverse events reported with anakinra was low. The certainty of the evidence was very low.

Complications (Important for decision making) - multiorgan failure, severe cognitive impairment with consequent learning disabilities, nerve paresis, renal impairment and obstructive bronchiolitis etc

No evidence was identified for this outcome.

In adults and children with HLH, what is the cost effectiveness of anakinra compared with standard treatment?

No cost effectiveness studies were available for inclusion in this review.

From the evidence selected, are there any subgroups of patients that may benefit from anakinra more than the wider population of interest?

One, single centre, case series (Eloseily et al 2019, n=44) identified two subgroups of paediatric patients treated with anakinra for HLH that experienced a lower rate of in hospital mortality. The survival rate in patients with rheumatic/autoimmune diseases was 86% (100% for sJIA and 70% for SLE and related conditions), compared to 50% for all other patients with secondary

haemophagocytic lymphohistiocytosis (sHLH). Patients with an underlying diagnosis of sJIA had a statistically significant lower rate of mortality (p=0.006) compared to those with other underlying conditions. In addition, patients who received anakinra within five days of hospitalisation had a statistically significant decreased mortality rate (p=0.046) (and a greater

drop in ferritin level (p=0.001)) compared to those who received anakinra after five days of hospitalisation. The certainty of the evidence was very low.

Limitations

The key limitation to identifying the effectiveness of anakinra compared to standard treatment for HLH is the lack of reliable comparative studies. It should be noted that HLH is a rare condition and therefore conducting prospective comparator studies may be unrealistic. Very low certainty evidence was identified from one comparator study (a retrospective subgroup analysis of patients receiving anakinra or placebo recruited to an RCT published in 1997) and five small, retrospective, single centre case series from countries outside the UK which reported outcomes for patients who were treated with anakinra. There was heterogeneity among the patients included in the studies (variation in diagnostic criteria, severity of disease and underlying diseases), along with variation in anakinra and concomitant treatments. The outcomes reported may not be wholly attributable to anakinra. The results from all these studies may not be generalisable to the current NHS practice in England.

Conclusion

The very low certainty evidence from all the studies included in this review is insufficient to draw reliable conclusions about the clinical effectiveness and safety of anakinra compared to standard treatments in patients with HLH. No evidence on the cost effectiveness of anakinra compared to current standard treatments was identified.

Implementation

Inclusion criteria

Anakinra will be prescribed to adults and children (all ages) presenting with primary or secondary HLH regardless of trigger condition, requiring treatment for HLH as part of their clinical care, and in whom first line therapy with corticosteroids has not been effective or would obscure the diagnosis of the underlying condition (see patient pathway below). Anakinra would be used in preference to IVIg. In rare situations IVIg may still be required; for example, if cardiomyopathy or central nervous system inflammation are identified, in which case it should be given according to NHS guidance.

As this policy applies to patients with a confirmed diagnosis of HLH, any relevant criteria used for the diagnosis of HLH can be applied by the clinicians.

A diagnosis of HLH can be based on either point 'a' or 'b' listed below. Since HLH is rare management decisions should be made with the support of an HLH MDT.

a. criteria of HLH-2004 protocol for pHLH which requires five of eight from:

1. fever
2. splenomegaly
3. cytopaenias affecting at least two of three lineages in the peripheral blood
4. hypertriglyceridemia and/or hypofibrinogenemia
5. haemophagocytosis in bone marrow, spleen, or lymph nodes
6. low or absent NK-cell activity
7. hyperferritinaemia
8. high levels of sIL-2r

b. (HLH) H score >169 or modified H score > 132 or ferritin level >10000/tissue diagnosis in sHLH

The clinical diagnosis of HLH can also be made in the absence of research tests including NK cell activity and sIL-2r levels.

Exclusion criteria

1. Patients with a known hypersensitivity to previous use of anakinra for another indication
2. Anakinra is licensed for some indications in children and infants aged 8 months and older with a body weight of 10 kg or above. No data is available for children below this age or weight so they are excluded within this policy.

Response criteria

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 H-score
- 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

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 HLH MDT

Dosing

Use of anakinra for sHLH is off-label as is administration by the intravenous route. Patients or next of kin should be informed of off -label use. In critical illness intravenous dosing is often used in clinical practice, 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 10mg/kg in adults and 12mg/kg in children. If there is an inadequate therapeutic response, advice from specialist centres which regularly manage HLH and are ideally members of HiHASC (found through www.hihasc.org) should be sought.

If intravenous dosing is used, the subcutaneous route is restarted as soon as possible once stable.

Dose adjustment should be considered in moderate to severe renal impairm ent (alternate daily dosing). The Electronic Medications Compendium states that in severe or life-threatening cases of HLH, the use of anakinra can be continued during pregnancy and breast feeding.

Monitoring

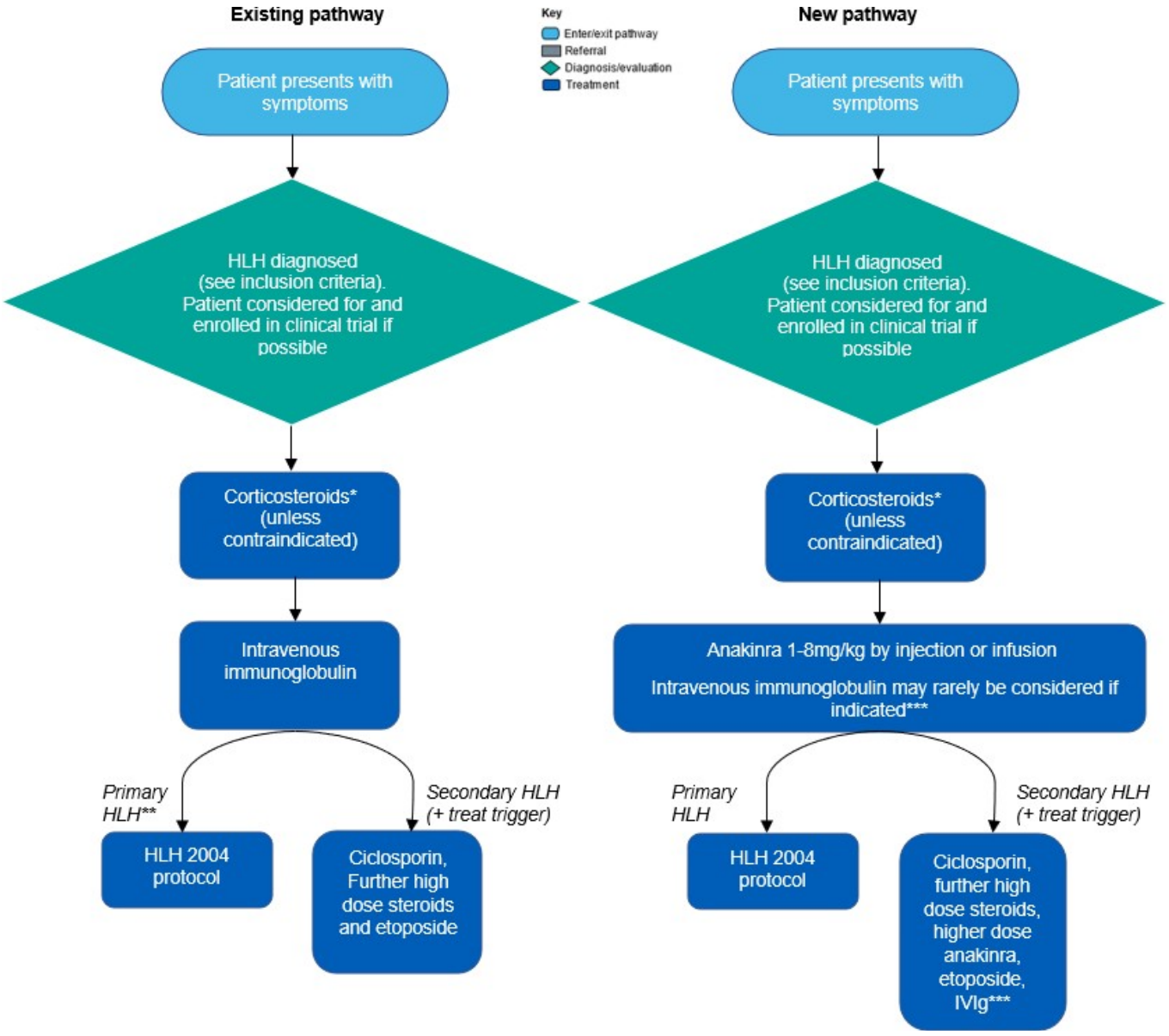
Patients treated with anakinra treatment should be monitored for active infections and allergic reactions. Monitoring should include monitoring of hepatic enzymes and neutrophil counts.

Patient pathway

Once HLH is recognised, corticosteroid treatment is a first line therapy unless contraindicated. Patients are considered for and enrolled in clinical trials if available.

If the patient shows incomplete response to early use of corticosteroids, or where corticosteroids are contraindicated, anakinra is prescribed second line either alone (or rarely in combination with IVIG if additional indications such as cardiomyopathy or CNS inflammation are present).

Dosage of anakinra: Up to 12 mg/kg, by subcutaneous injection or intravenous infusion titrated to clinical response. In pHLH, the HLH 2004 protocol is used involving IVIg, methotrexate, ciclosporin and etoposide. In sHLH which is refractory to first line treatment with corticosteroids and anakinra, additional treatments given on a case-by-case basis for refractory sHLH include ciclosporin, further high-dose steroids, further higher-dose anakinra, IVIg and etoposide are considered.



* Corticosteroids can be withheld if haematological malignancy suspected until diagnostic imaging and biopsy are performed.
****** Anakinra may be used in primary HLH while awaiting BMT, or in cases where cardiomyopathy or CNS disturbance is present.
******* Intravenous immunoglobulin used as per NHS guidance.

Governance arrangements

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Each provider organisation treating children with a medicine approved under this policy will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics Committee (or similar) and NHS England can ask for documented evidence that these processes are in place.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

Anakinra for the treatment of HLHs within the criteria in this document will be commissioned and funded by NHS England and NHS Improvement Specialised Commissioning under existing arrangements for the provision of specialised services. Associated activity should be recorded to the following lines:

- NCBPS26Z Rheumatology (Adults)
- NCBPS23W Children's Services – Rheumatology

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Haemophagocytic Lymphohistiocytosis (HLH)	A rare condition and comprises a syndrome of severe, uncontrolled, self-perpetuating inflammation or hyperinflammation causing multi-organ failure with a very high mortality rate.
Primary (pHLH)	A genetic immune system defect usually identified in infants or childhood leading to a failure of immune regulation and hyperinflammation
Secondary HLH (sHLH)	Results from a trigger from another disease process leading to uncontrolled, pathological inflammation (hyperinflammation). Most commonly this is cancer (malignancy), infection (sepsis) or rheumatological disease
Macrophage Activation Syndrome (MAS)	sHLH triggered by rheumatic disease
Macrophage Activation Like Syndrome in Sepsis (MALS)	sHLH triggered by sepsis
Cytokine storm syndrome (CSS)	This term includes, but is not limited to, HLH (e.g., may also refer to MALS, CRS, MAS)
Cytokine release syndrome (CRS)	sHLH triggered by CART cell therapy
Hyperferritinaemic syndrome	Synonym for any cause of HLH

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