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REVIEW

Does your unwell patient have haemophagocytic lymphohistiocytosis?

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Abstract

Haemophagocytic lymphohistiocytosis is a severe systemic hyperinflammatory syndrome characterised by dysregulation of immune cells and excessive production of cytokines, also known as a cytokine storm. It has distinctive clinical features with fever, hyperferritinaemia and falling blood counts. In adults, this usually occurs secondary to an underlying driver or trigger including infection, malignancy or rheumatic diseases. Prompt treatment with immunomodulatory therapy, including corticosteroids and the recombinant IL-1 receptor antagonist anakinra, is recommended to switch off the cytokine storm. Etoposide-based regimens are sometimes needed, and newer therapies such as emapalumab and JAK inhibitors are increasingly being used.

The incidence of haemophagocytic lymphohistiocytosis has increased significantly over the last 20 years which may partly reflect increased awareness of the condition. Although relatively rare, haemophagocytic lymphohistiocytosis can be encountered by a broad range of hospital physicians, so knowing how to diagnose and treat this condition is essential. This article reviews the pathogenesis, clinical features, causes, diagnosis and treatment of haemophagocytic lymphohistiocytosis to improve physician recognition and management of this condition to improve future patient outcomes.

Key words: Cytokine storm; Fever; Haemophagocytic lymphohistiocytosis; Hyperferritaemia; Macrophage activation syndrome

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Introduction

Haemophagocytic lymphohistiocytosis is a severe systemic hyperinflammatory syndrome characterised by dysregulation of immune cells and excessive production of cytokines. This results in the distinctive clinical features of fever, rising ferritin and falling blood counts (Brisse et al, 2015). Haemophagocytic lymphohistiocytosis can be genetic or familial or occur as a secondary complication of an underlying condition, sometimes with an additional trigger. Secondary haemophagocytic lymphohistiocytosis is associated with infection, malignancy and rheumatic diseases (referred to as macrophage activation syndrome in this context). It can be triggered by some therapeutic interventions or drugs and can also be seen in pregnancy.

Haemophagocytic lymphohistiocytosis can be encompassed in the term 'cytokine storm', which also includes cytokine release syndrome and COVID-19 associated hyperinflammatory syndrome (Fajgenbaum and June, 2020). There is considerable overlap between the pathogenesis, clinical presentation and treatment of these syndromes. Although it can occur at any age, this article focuses upon haemophagocytic lymphohistiocytosis in adults.

There has been a significant increase in incidence over the last 20 years, with a two-fold increase reported in the UK between 2000 and 2016 (West et al, 2022). Whether this is related to increased recognition and diagnosis of the disease or a true increase in incidence is unknown (West et al, 2022; Abdelhay et al, 2023). Clinician awareness of haemophagocytic lymphohistiocytosis has certainly increased, especially following the COVID-19 pandemic, where a hyperinflammatory immune responses and cytokine storms, including haemophagocytic lymphohistiocytosis, were commonly encountered (Flower et al, 2021).

Without prompt treatment, haemophagocytic lymphohistiocytosis will progress to multi-organ failure and carries an all-cause mortality rate of 46% (West et al, 2022).

Haemophagocytic lymphohistiocytosis can be encountered in a range of specialties, not limited to rheumatology, haematology, infectious diseases, gastroenterology, neurology,

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emergency medicine, intensive care medicine, general medicine and obstetrics. Knowledge of this condition by all hospital physicians is essential as early recognition and treatment may prevent irreversible organ damage and reduce mortality.

Pathogenesis

Haemophagocytic lymphohistiocytosis is characterised by severe systemic inflammation caused by uncontrolled proliferation and activation of lymphocytes and macrophages, secreting a large number of pro-inflammatory cytokines, such as interferon γ, tumour necrosis factor α (TNFα), interleukins 1, 4, 6, 8, 10 and 18, resulting in a 'cytokine storm' (Ramos-Casals et al, 2014). Interleukin-1 (IL-1) appears to be central to disease pathogenesis, with IL-1 blockade being a highly effective first-line treatment for haemophagocytic lymphohistiocytosis in some patients (Henter et al, 2007; Mehta et al, 2020).

Haemophagocytosis (histiocytes actively engulfing blood cells and their precursors) is a defining feature of haemophagocytic lymphohistiocytosis (Brisse et al, 2015). Primary and secondary haemophagocytic lymphohistiocytosis are hyperinflammatory syndromes that share a common terminal pathway but have different pathogenetic roots. Therefore, the clinical and laboratory manifestations can be indistinguishable from each other (La Rosée et al, 2019). Figure 1 outlines the pathogenesis of haemophagocytic lymphohistiocytosis.

Haemophagocytic lymphohistiocytosis can be genetic or familial. Primary haemophagocytic lymphohistiocytosis is an autosomal recessive, monogenic disorder, caused by loss of function mutations in genes involved in the cytotoxic function of natural killer (NK) cells and CD8+ T cells, resulting in uncontrolled proliferation and survival of cytotoxic T cells (Brisse et al, 2015). Primary haemophagocytic lymphohistiocytosis usually presents in childhood or adolescence and has been rarely reported in adulthood (Sieni et al, 2012).

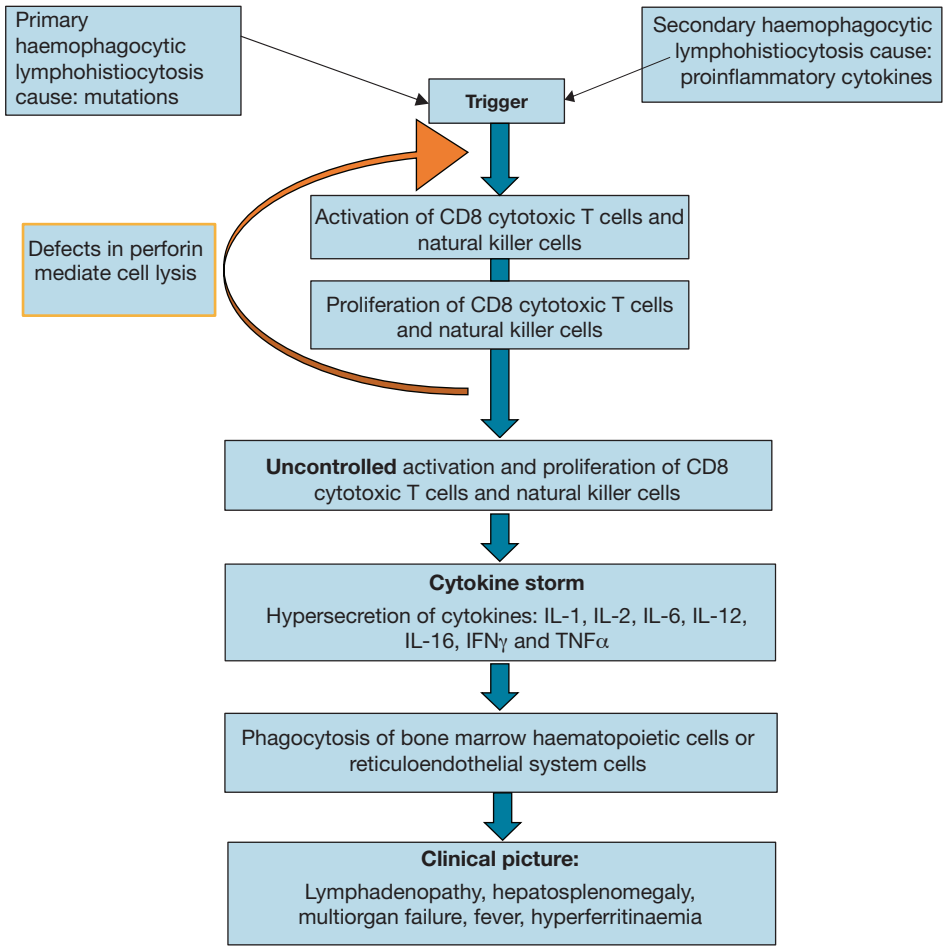

Figure 1. Pathogenesis of haemophagocytic lymphohistiocytosis.

In secondary haemophagocytic lymphohistiocytosis or macrophage activation syndrome, the immune system is unable to adequately restrict stimulatory effects of various triggers (La Rosée, 2015). The exact pathophysiological mechanisms driving secondary haemophagocytic lymphohistiocytosis are not entirely understood. There is emerging evidence that some patients have an underlying genetic susceptibility; monoallelic mutations detected in genes found in primary haemophagocytic lymphohistiocytosis result in low NK cell activity (Brisse et al, 2015; Cetica et al, 2016). However, the primary driver of secondary haemophagocytic lymphohistiocytosis is acquired immune dysfunction in response to a predisposing factor and/or acute trigger (La Rosée et al, 2019)

Nearly a third of reported cases of haemophagocytic lymphohistiocytosis in one review were identified to having more than one underlying cause (Ramos-Casals et al, 2014). A threshold model for hyperinflammatory and cytokine storm syndromes has been hypothesised in haemophagocytic lymphohistiocytosis, where a patient may have an underlying predisposing factor for the development of haemophagocytic lymphohistiocytosis, such as an underlying autoimmune condition, malignancy or underlying genetic predisposition. An acute trigger such as an infection causes uncontrolled release of pro-inflammatory cytokines and hyperinflammation, culminating in the clinical presentation of haemophagocytic lymphohistiocytosis (Ramos-Casals et al, 2014).

Causes of secondary haemophagocytic lymphohistiocytosis

There are extensive potential triggers for haemophagocytic lymphohistiocytosis (Table 1). The American College of Rheumatology/European League Against Rheumatism guidelines for the early management of haemophagocytic lymphohistiocytosis recommend investigating and treating modifiable contributors to systemic hyperinflammation in the management of

Table 1. Triggers and predisposing factors of secondary haemophagocytic lymphohistiocytosis in adults

Cause (incidence %)	Examples	
Genetic causes (2.5%)		
Autoimmune conditions (20.8%)	Connective tissue diseases (18.6%)	■ Systemic juvenile idiopathic arthritis ■ Adult-onset Still's disease ■ Systemic lupus erythematosus ■ Rheumatoid arthritis ■ Vasculitis ■ Myositis
	Inflammatory bowel disease (2.5%)	
Malignancy (30.7%)	Haematological (28.6%)	■ Hodgkin's lymphoma ■ T cell lymphoma ■ B cell lymphoma ■ Leukaemia ■ Castleman's disease
	Solid organ malignancy (2.7%)	
Infection (24.3%)	Viral infections (21.6%)	Epstein–Barr virus, human immunodeficiency virus, cytomegalovirus, COVID-19
	Bacterial infections (1.7%)	Tuberculosis
	Parasitic (0.4%)	*Leishmania* spp, *Plasmodium* spp, *Toxoplasma* spp
	Fungi (2.2%)	*Histoplasma* spp
Idiopathic (35.8%)		

Incidence data included from USA registry data published by Abdelhay et al (2023)

every patient. While haemophagocytic lymphohistiocytosis can occur in any inflammatory state, certain predisposing conditions and/or inflammatory triggers would warrant a high level of clinical suspicion for haemophagocytic lymphohistiocytosis (Shakoory et al, 2023).

Predisposing conditions

Malignancy

Malignancy is a major contributory factor and is an associated condition in up to 30% of adults diagnosed with secondary haemophagocytic lymphohistiocytosis (Abdelhay et al, 2023). Haematological malignancies most commonly cause haemophagocytic lymphohistiocytosis, and it affects an estimated 1% of adults with haematological malignancy, but the prevalence can rise to 20% in patients with some types of B-cell and T-cell lymphoma (Machaczka et al, 2011). Solid organ malignancies are much less commonly associated with haemophagocytic lymphohistiocytosis.

Haemophagocytic lymphohistiocytosis can occur as a result of the disease process and present as the index presentation or relapse. It can also be triggered by treatment of the malignancy, eg chemotherapy or after bone marrow transplantation where acute graft vs host disease can mimic haemophagocytic lymphohistiocytosis, or with a secondary viral trigger such as severe acute respiratory syndrome coronavirus 2 (SARS Co-V-2) (Flower et al, 2021). Epstein–Barr virus is an important trigger to consider as this, along with malignancy, can co-trigger haemophagocytic lymphohistiocytosis in the context of an Epstein–Barr virus-associated lymphoma (Carter et al, 2019).

Macrophage activation syndrome

Macrophage activation syndrome refers to haemophagocytic lymphohistiocytosis on a background of autoimmune rheumatic disease. Macrophage activation syndrome is most associated with adult onset Still's disease and systemic lupus erythematosus. More cases of systemic lupus erythematosus-associated macrophage activation syndrome have been reported than adult onset Still's disease, but the prevalence of macrophage activation syndrome is higher in adult onset Still's disease patients (12% vs 4%). The acute trigger of macrophage activation syndrome is mainly infection and, less frequently, immunosuppression (Ramos-Casals et al, 2014).

Acute triggers

Infection

Worldwide, infection is the leading cause of haemophagocytic lymphohistiocytosis. This is specifically viral infection which can occur as a primary trigger in the healthy population or after reactivation in immunosuppressed patients. Viruses account for 34% of cases of haemophagocytic lymphohistiocytosis, with 42% of viral cases caused by Epstein–Barr virus and 9% by cytomegalovirus (Ramos-Casals et al, 2014).

A cause will not be identified in a significant number of cases. Rarely reported acute triggers include pregnancy and medications such as lamotrigine (Kim et al, 2019).

Clinical features

Fever is reported in 96% of cases (Ramos-Casals et al, 2014) and haemophagocytic lymphohistiocytosis should be considered as a differential diagnosis in any patient presenting with pyrexia of unknown origin, particularly those with known underlying predisposing conditions. It is important to also consider haemophagocytic lymphohistiocytosis in patients with a significant inflammatory response but whose fever is suppressed by interventions such as haemofiltration.

Initial symptoms are non-specific and can be similar to those of sepsis, malignancy or rheumatic diseases. Early clinical features may include bleeding diathesis, dyspnoea, diarrhoea, lymphadenopathy, rash and arthralgias (Ramos-Casals et al, 2014).

Symptoms may progress unexpectedly and dramatically, and patients can rapidly progress to multi-organ failure. CNS and respiratory involvement (such as acute respiratory distress syndrome requiring mechanical ventilation) are both poor prognostic markers (Kim et al,

2012; Seguin et al, 2016). Acute kidney injury occurred in up to 62% of patients with 59% of those requiring renal replacement therapy (Aulagnon et al, 2015).

A systematic and thorough history and examination should be undertaken in every patient. Features to consider include any features of underlying malignancy (eg B symptoms), infection (including recent travel history), rheumatic diseases (features suggesting an underlying connective tissue disorder) and drug (medication history) and family history (including history of consanguinity).

Clinical features that could suggest a genetic cause include young age at presentation, positive family history, consanguinity and CNS disease (Shakoory et al, 2023).

Diagnostic tools

No single diagnostic test is pathognomonic for the diagnosis of haemophagocytic lymphohistiocytosis, so a diagnostic tool can be useful to estimate the probability of a patient having this condition. Fardet et al (2014) developed the H-score based on nine variables (Table 2) that has been validated for haemophagocytic lymphohistiocytosis in adults. The authors recommend using this as a screening tool to predict the probability of a patient having haemophagocytic lymphohistiocytosis. A score of ≥169 is 93% sensitive and 86% specific for a diagnosis of haemophagocytic lymphohistiocytosis, with 90% of patients being accurately classified. The score should be repeated in patients who remain unwell but have a low score initially, as the syndrome can rapidly evolve.

Diagnosing haemophagocytic lymphohistiocytosis

Table 3 summarises suggested laboratory and radiological investigations that should be performed to establish a diagnosis of haemophagocytic lymphohistiocytosis. Hyperferritaemia is a key laboratory feature, part of all diagnostic criteria and should be checked in all patients with suspected haemophagocytic lymphohistiocytosis. A serum ferritin level of >10 000 mcg/litre has a 96% specificity and 90% sensitivity for diagnosis of haemophagocytic lymphohistiocytosis in children (Allen et al, 2008). However, other causes of a raised ferritin level, such as haematological malignancy, blood transfusions, liver infarctions or sepsis, form part of the differential diagnosis (Sandnes et al, 2021). Serial ferritin measurements should be used to assess response to therapy.

Other widely available clinical and laboratory indicators of inflammation, hepatic injury and coagulopathy also raise the suspicion of haemophagocytic lymphohistiocytosis (Table 2) and should be regularly monitored for further deterioration or resolution of the condition. Imaging should be performed to look for evidence of hepatosplenomegaly. Bone marrow aspiration is routinely performed to look for histological evidence of

Table 2. H-score

Parameter	No. of points (criteria for scoring)
Known underlying immunosuppression	0 (no) or 18 (yes)
Temperature (°C)	0 (<38.4), 33 (38.4–39.4) or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly) or 38 (hepatomegaly and splenomegaly)
Number of cytopenias	0 (1 lineage), 24 (2 lineages) or 34 (3 lineages)
Ferritin (mcg/litre)	0 (<2000), 35 (2000–6000) or 50 (>6000)
Triglyceride (mmol/litre)	0 (<1.5), 44 (1.5–4) or 64 (>4)
Fibrinogen (g/litre)	0 (>2.5) or 30 (≤2.5)
Aspartate aminotransferase (U/litre)	0 (<30) or 19 (≥30)
Haemophagocytosis on bone marrow aspirate	0 (no) or 35 (yes)

From Fardet et al (2014)

haemophagocytic lymphohistiocytosis, with haemophagocytosis the defining feature with a specificity of 93%. However, haemophagocytosis has a low sensitivity and is often a late feature, so its absence does not exclude haemophagocytic lymphohistiocytosis (Knaak et al, 2020).

Specialised biomarkers and cytokine panels are increasingly available in academic centres, but as they are not widely available and often have a long turnaround time, they do not form part of a routine investigation panel. An important retrospective study demonstrated the superiority of serum soluble IL-2 receptor compared to ferritin in the diagnosis of adult haemophagocytic lymphohistiocytosis, although cut-off levels vary between techniques and laboratories. However, this study involved patients with a high pre-test probability of haemophagocytic lymphohistiocytosis, so may have overestimated its sensitivity and underestimated specificity relative to lower risk populations (Hayden et al, 2017).

In addition to performing investigations to establish a diagnosis of haemophagocytic lymphohistiocytosis, meticulous searching is needed for possible underlying causes, tailored to individual patient factors. Table 4 summarises investigations to consider.

Table 3. Recommended minimum baseline laboratory testing and imaging in haemophagocytic lymphohistiocytosis

Test		Trend in haemophagocytic lymphohistiocytosis	Biology
Full blood count	Neutrophil count	↓	Affected by marrow production, tissue sequestration, consumption
	Lymphocyte count	↓	
	Haemoglobin	↓	
	Platelet count	↓	
Inflammatory biomarkers	C-reactive protein	↑	Hepatic release in response to IL-6
	Ferritin	↑	Macrophage or hepatocyte activation
	Erythrocyte sedimentation rate	↑↓	Falls with fibrinogen consumption
	Lactate dehydrogenase	↑	Cellular death or injury
Liver function tests	Alanine transaminase, aspartate aminotransferase, bilirubin	↑	Hepatocyte injury
	Triglycerides	↑	Cytokine inhibition of lipoprotein lipase
	Albumin	↓	Vascular leak-third spacing
Renal profile	Creatinine	↑	Acute kidney injury
Coagulopathy tests	Fibrinogen	↓	Fibrinogen consumption or fibrin degradation
	D-dimer	↑	
	Prothrombin time, international normalised ratio and activated partial thromboplastin clotting time	↑	Factor consumption
Imaging	Cross-sectional imaging plus ultrasound	↑	Hepatosplenomegaly
	Bone marrow aspirate*		Looking for haemophagocytosis as histological evidence of haemophagocytic lymphohistiocytosis
Cardiac investigations	Echocardiogram		Looking for evidence of myocardial dysfunction
	Electrocardiogram		Looking for evidence of tachycardia and arrhythmia

*Adapted from Shakoory et al (2023). *May also be performed to look for evidence of haematological malignancy or infection*

Investigating for a trigger can be challenging and needs to be carefully balanced with prompt treatment for haemophagocytic lymphohistiocytosis, as corticosteroids may mask a diagnosis of lymphoma or leukaemia (Borenstein et al, 2000). Where possible, definitive testing (usually a tissue diagnosis) for a suspected malignancy should be performed before glucocorticoid administration.

Multidisciplinary team approach

Specialists who may need to be involved in the care of a patient with haemophagocytic lymphohistiocytosis include rheumatologists, haematologists, infectious disease or microbiology specialists, intensive care doctors, neurologists, emergency medics, general medics and others as indicated. Early subspecialty review may improve early recognition of haemophagocytic lymphohistiocytosis and reduce mortality (Patel et al, 2022). American College of Rheumatology/European League Against Rheumatism guidelines for the management of early haemophagocytic lymphohistiocytosis recommend a multidisciplinary team approach to optimise diagnosis and management (Shakoory et al, 2023). Multidisciplinary team discussions can aid review of clinical and diagnostic findings and help to decide what additional investigations may be required, as this will need to be prioritised and tailored on an individual patient basis.

Table 4. Further investigations to determine the trigger for haemophagocytic lymphohistiocytosis

Underlying trigger	Investigation
Infection	Blood, urine, CSF, stool, other bodily fluid cultures
	Procalcitonin
	Viral polymerase chain reaction tests (Epstein–Barr virus, cytomegalovirus, adenovirus, human immunodeficiency virus)
	Respiratory viral screen
	Parvovirus serology
	Fungal screen cultures (beta D glucan, galactomannan, Pneumocystis pneumonia from bronchoscopy)
	Consider tuberculosis (eg cultures, histopathology)
	Parasitology (blood film for malaria, serology for toxoplasma and leishmaniasis)
	Tissue biopsy
	Infectious diseases review
Malignancy	Bone marrow aspirate or trephine (note steroids may mask lymphoma diagnosis and may be useful to consider serial bone marrow aspirations)
	Deep skin tissue biopsy (T-cell lymphoma)
	Cross-sectional imaging (eg computed tomography neck, chest, abdomen and pelvis, positron emission tomography and computed tomography)
	Focused biopsies as indicated
	Haematology review
Rheumatic	Autoimmune screen (antinuclear antibody, extractable nuclear antigen, rheumatoid factor, anti-cyclic citrullinated peptide, anti-neutrophil cytoplasm antibodies, complements, immunoglobulins)
	Rheumatology review
Genetic	Genetic testing, perforin expression*
	Liaison with geneticist
Other	Magnetic resonance imaging of the brain
	CSF fluid analysis

**Genetic testing should only be undertaken following consultation with a genetic specialist and appropriate genetic counselling*

In the UK, the Haemophagocytic Lymphohistiocytosis Across Specialty Collaboration was set up in 2018 as a professional network for haemophagocytic lymphohistiocytosis and hyperinflammatory medicine. Local haemophagocytic lymphohistiocytosis multidisciplinary teams are being increasingly established. Patients can also be referred to the University College London Hospitals tertiary haemophagocytic lymphohistiocytosis multidisciplinary team which clinicians from all specialties and from any NHS hospital are able to join (Ludwig et al, 2021).

Management of haemophagocytic lymphohistiocytosis

Treatment should be guided by the degree of inflammation and extent of organ dysfunction. Management should focus on three key areas:

1. Switch off the cytokine storm
2. Treat the underlying cause
3. Manage any potential complications (Mehta et al, 2020).

Supportive care with antipyretics, fluids, adequate nutrition, blood products and organ support as required needs to be considered alongside immunomodulation therapy. Patients with haemophagocytic lymphohistiocytosis must be monitored very closely and admitted early to an intensive care unit or high dependency unit, where appropriate, if they are not already in one of these settings. As with establishing a diagnosis of haemophagocytic lymphohistiocytosis, treatment decisions should be guided by multidisciplinary team input with regular re-evaluation of clinical progress and response to therapy.

Switch off the cytokine storm

First-line treatments

The American College of Rheumatology/European League Against Rheumatism guidelines recommend starting empirical therapy with glucocorticoids, the recombinant IL-1 receptor antagonist (IL-1RA) anakinra and/or intravenous immunoglobulin. Multiple treatments can be started concurrently (Shakoory et al, 2023). Steroids are typically started at high dose and intravenously, and then weaned as appropriate. Intravenous immunoglobulin is given at 1 g/kg on two consecutive days which can be repeated 2 weeks later.

Anakinra is a short-acting medicine that can be given subcutaneously or intravenously (the latter is often preferred in critically unwell patients). A review of 44 children with haemophagocytic lymphohistiocytosis showed an improvement in mortality when anakinra was given within 5 days of being hospitalised (P=0.046) (Eloseily et al, 2020). Secondary haemophagocytic lymphohistiocytosis is often caused by infectious triggers and anakinra may be preferred over other therapies because it is relatively less myelosuppressive, has a shorter half life, reduced hepatotoxicity and lack of blunting of the inflammatory response (Mehta et al, 2020). Anakinra forms a major part of treatment pathways for haemophagocytic lymphohistiocytosis and, even though it is not licenced in the UK, is recommended through the NHS clinical commissioning policy for children and adults (NHS, 2021).

Second-line treatments

Refractory haemophagocytic lymphohistiocytosis that does not respond to initial therapy should prompt a careful review of the underlying diagnosis and therapeutic management, with ongoing multidisciplinary team review and discussion (Shakoory et al, 2023). There are multiple treatment options for those with refractory haemophagocytic lymphohistiocytosis or with initial treatment intolerances.

Etoposide-based regimens substantially improved the survival for children with newly diagnosed primary haemophagocytic lymphohistiocytosis, aiming to achieve remission in order to proceed to bone marrow transplantation (Henter et al, 2007; Arca et al, 2015). Etoposide is indicated in some adults with refractory primary or secondary disease, with dose titration for liver dysfunction. In secondary haemophagocytic lymphohistiocytosis, often only a few doses are required as a bridge to definitive treatment of the underlying disease, eg chemotherapy. Bone marrow transplant is used in adults with primary haemophagocytic lymphohistiocytosis, and in some adults with relapsing cases (Masood et al, 2022).

Ciclosporin, either oral or intravenous, is also used as part of second-line therapies, with doses kept as low as possible to limit toxicity.

Newer cytokine-targeted drugs are being developed or repurposed to treat haemophagocytic lymphohistiocytosis. Emapalumab, an anti-interferon-gamma antibody, is currently not approved for use in the UK, although evidence from a phase 2–3 trial in patients with primary haemophagocytic lymphohistiocytosis has led to its approval elsewhere (Locatelli et al, 2020), and an adult trial is now underway. Ruxolitinib is a Janus kinase (JAK) 1/2 inhibitor that reduces CD8 T cell accumulation and cytokine production. Keenan et al (2021) reviewed 18 studies of the use of ruxolitinib in haemophagocytic lymphohistiocytosis, and reported good outcomes, but noted that data are retrospective and the majority are case studies. Figure 2 outlines treatment targets.

Further novel treatments being studied include interleukin-6 inhibition with tocilizumab (Dufranc et al, 2020; Ohmura et al, 2020) and the CD52 targeting monoclonal antibody slemtuzumab (Strout et al, 2010; Marsh et al, 2013).

Treat the underlying cause

Failure to treat the underlying cause could lead to a recrudescence of hyperinflammation.

Manage any potential complications

Secondary infection is a common complication so needs to be closely monitored for. It can be clinically challenging to distinguish from relapse of haemophagocytic lymphohistiocytosis and no single test can differentiate between them.

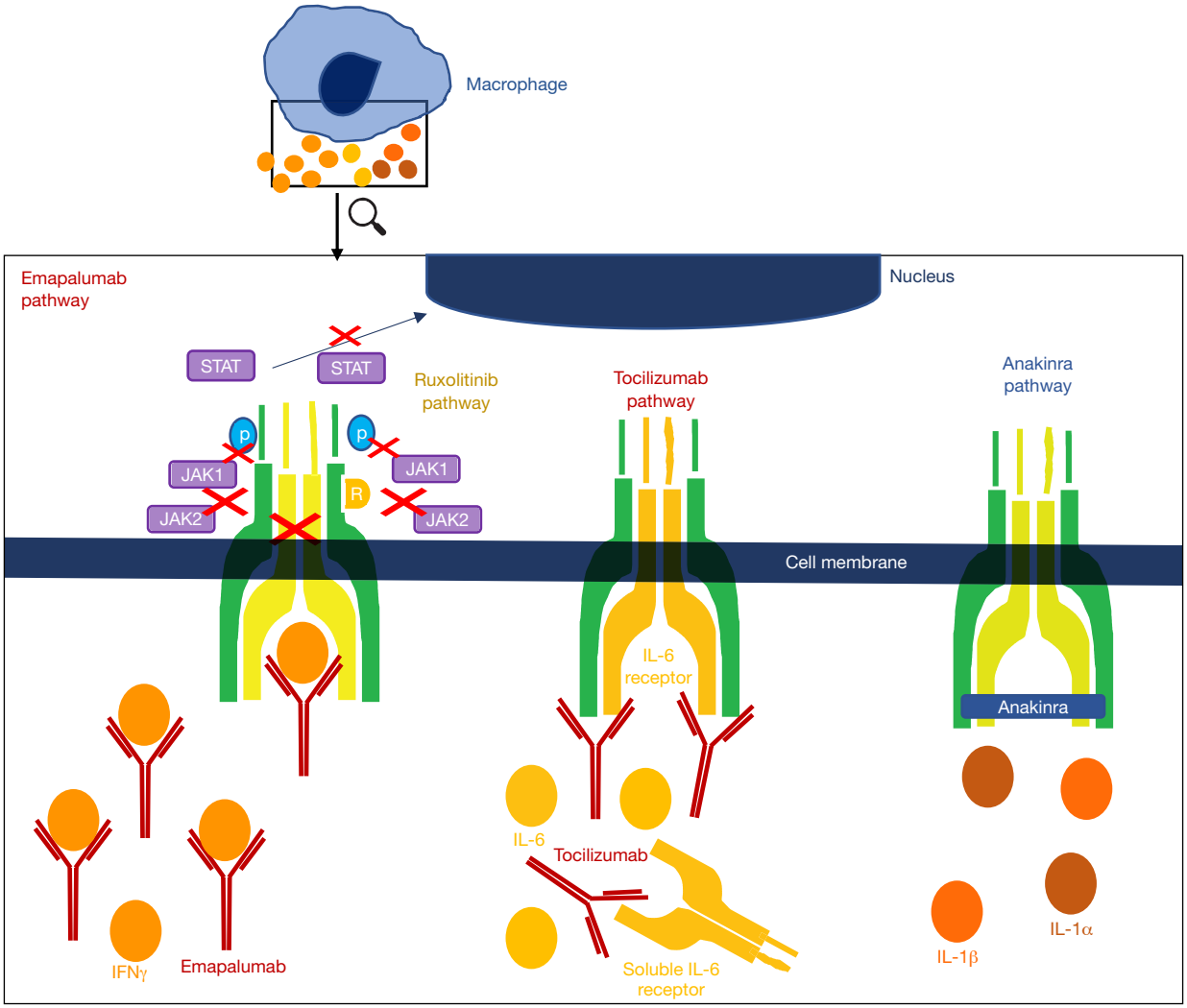

Figure 2. Novel treatment targets in haemophagocytic lymphohistiocytosis. IFN = interferon; IL = interleukin; JAK = Janus kinase; P = phosphate; R = receptor; STAT = signal transducer and activator of transcription.

Patients with haemophagocytic lymphohistiocytosis are at high risk of severe and complex infection, partly as a result of abnormal immune function, cytopaenias and treatment with potent immunosuppressive therapy (Zhang et al, 2023).

Prophylactic administration of antimicrobial therapy should be considered, as should prophylaxis against *Pneumocystis jirovecii*, other fungi and viruses in patients in certain at-risk groups and on treatments (La Rosée et al, 2019).

Ongoing monitoring and treatment withdrawal

Once disease control has been achieved, treatment should be tapered. There are no guidelines on how to do this safely, and the order of drug withdrawal varies case by case, but trying to use the lowest possible dose of the least toxic drug should guide decision making.

Monitoring for disease progression, new organ involvement and potential complications of treatment is essential and should be performed regularly (tailored to the severity or organ involvement of patient disease). The underlying trigger should also be closely monitored.

Prognosis

Mortality remains high, with UK registry data showing a 1-year survival of 56% for all patients. Survival varied significantly with underlying disease, with 1-year survival of 74% in patients with rheumatological drivers compared to 21% in those with haematological malignancy. Age over 75 years was also associated with particularly poor outcome (West et al, 2022).

Future research considerations

Haemophagocytic lymphohistiocytosis is relatively rare with significant heterogeneity, so good quality clinical evidence is lacking. While there is some emerging retrospective registry data, this remains limited and there is a clear need to collect data through national registries with matched biobanks. These should guide the design of prospective interventional trials.

Conclusions

Haemophagocytic lymphohistiocytosis is a complex disorder characterised by a dysregulated immune response resulting in hyperinflammation and a life-threatening clinical syndrome. It should be considered in the differential diagnosis of patients with pyrexia of unknown origin, or in any febrile patient not responding to treatment in the expected way.

An increasing number of immunomodulatory treatments is available but high-quality trials are often lacking. A multidisciplinary team approach is paramount to managing this condition and services must be accessible in an equitable way. Despite recent advances, prognosis remains poor and good quality prospective studies are required to help improve patient care.

Key points

- Haemophagocytic lymphohistiocytosis is under-recognised and misdiagnosed as it can closely mimic other conditions. It should be strongly suspected in any patient with fever, falling counts (cytopaenias) and hyperferritaemia (the 3 Fs).
- Without prompt recognition and treatment, haemophagocytic lymphohistiocytosis can rapidly progress to multi-organ failure, with a high mortality rate.
- Most adults will have haemophagocytic lymphohistiocytosis secondary to an underlying trigger, such as infection, malignancy or autoimmune rheumatic diseases.
- Secondary haemophagocytic lymphohistiocytosis requires treatment of the hyperinflammation, with corticosteroids and interleukin-1 blockage, with identification and treatment of the underlying trigger.
- A multidisciplinary approach is vital for providing quality care and improving patient outcomes.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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