ABOUT HISTIO UK

Histiocytosis UK is a registered Charity in England & Wales Number: 1158789. We are a national organisation supporting research and projects into Histiocytic Disorders. We support parents and patients, individuals and families affected by all histiocytic disorders these include:

Haemophagocytic lymphohistiocytosis (HLH)

Langerhans Cell Histiocytosis (LCH)

Juvenile xanthogranuloma (JXG)

Rosai-Dorfman disease (RD)

Erdheim-Chester ECD)

Diabetes insipidus (DI)

Our website at www.histiouk.org provides useful information on this range of conditions and topics, it explains the work we do, our research and our information support programs.

If we can be of any assistance, please contact us at histio@histiouk.org

Histio UK is reliant on voluntary donations. To make a donation, please go to: www.histiouk.org and follow the donate button.

If you are a Health Professional and would like more information on or would like to join our HLH Across Speciality Collaboration, Histiocytosis Registry or our Specialist Advisory Group please email **histio@histiouk.org.**

How to contact us

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"Histio Champions" celebrating patients, families and all **Champions of Histio Awareness "Histiocytosis UK-HLH"** community support

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Supporting families affected by primary immunodeficiencies
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HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

Information for Adult and Adolescent patients and their families

PID UK
Supporting families affected by primary immunodeficiencies
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About this leaflet

This booklet has been produced by **Histio UK** in association with **HASC – the HLH Across Speciality Collaboration**, staff at the **Imperial College NHS Trust** and **Primary Immunodeficiency UK (PID UK)** and has been reviewed by the **Histio UK HLH Parent & Patient Advisory Group**. It aims to help patients and families better understand the condition called hemophagocytic lymphohistiocytosis and provides an overview of the nature of the disease, its symptoms, treatments available and prognosis. Our thanks to **Great Ormond Street Hospital for Children** and the **Great North Children's Hospital.**

HLH can also be known as macrophage activation syndrome (MAS) but here we use the term HLH.

This leaflet should not replace advice from a clinician and is designed to help answer questions adult and adolescent patients and their families may have about haemophagocytic lymphohistiocytosis (HLH).

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Haemophagocytic lymphohistiocytosis (HLH)

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What is HLH?

Haemophagocytic lymphohistiocytosis (HLH) is a rare immune disorder where the body reacts inappropriately or overreacts to a 'trigger', such as an infection, an immune disorder or a malignancy. HLH is called macrophage activation syndrome or MAS when it is caused by rheumatological disease. HLH may be a life threatening condition. Specialised white blood cells (known as T-cells and macrophages) become over-activated, causing severe inflammation and damage to tissues such as the liver, spleen and bone marrow.

HLH is a rare disease and it can be difficult to diagnose because many of the symptoms can mimic severe infection or other conditions.

What causes HLH?

HLH can be defined as either primary or secondary: primary or "familial" HLH is when the condition is inherited. This form of HLH is more common in children and young adults.

Secondary HLH is caused by an underlying condition which acts as a "trigger", such as infection, an immune/rheumatological disorder or a cancer, such as lymphoma. It can be difficult to make a diagnosis of secondary HLH and many tests are usually required.

What are the signs and symptoms of HLH?

The symptoms of HLH can vary depending on the underlying "trigger".

Common symptoms are high temperature, fatigue, weight loss, night sweating. Some patients can develop a skin rash, neurological problems such as seizures, nose bleeding or easy bruising. Patients with HLH can have enlarged spleen, liver and lymph nodes. The kidney function can become abnormal and people with HLH can also experience breathing difficulty and heart problems.

How is HLH diagnosed?

Many tests are usually needed to make the diagnosis of HLH, and to find The 'trigger'. Initially, blood samples are taken for testing in the laboratory. A wide range of tests will be carried out, including full blood count to look for low numbers of each type of blood cell and a test of inflammation called ferritin.

More specialised tests check kidney and liver function and the immune system. Some of these blood tests have to be sent to a specialist laboratory and it might take several days for the results to come through. Bone marrow examination can confirm diagnosis (but is not required in making a diagnosis). It may be needed to rule out an underlying haematological malignancy and sometimes needs to be repeated to help with the diagnosis and to see how well the HLH is being treated.

Other tests are often needed to try to find the cause of the HLH. This will include testing for infections (with blood tests, bone marrow tests, swabs and imaging); testing for autoimmune conditions using blood tests; testing for lymphoma using imaging of the body, including chest x ray, CT scan or PET-CT scan and biopsies of lymph nodes if they are present.

If there are neurological (brain) symptoms, a sample of cerebrospinal fluid may be taken by lumbar puncture.

Genetic tests can also be useful, particularly in young adults, to identify the faulty genes in the primary forms of HLH.

You may see many different types of doctors which can be confusing while the HLH is being investigated, such as the infectious diseases team, haematologists, rheumatologists, immunologists, respiratory doctor (lung specialists) and the intensive care team.

This is because there are many possible triggers for secondary HLH, and it is important to make the right diagnosis.

How is HLH treated?

HLH is a very serious and life-threatening condition which requires prompt treatment usually coordinated by a specialist or team of specialists experienced in treating this condition. If there is not a local specialist in your hospital your case may be discussed with a specialist centre.

The priority of treatment is to damp down (suppress) the immune system to reduce the over-reaction and lessen the risk of tissue damage.

This will often involve courses of corticosteroids and other anti-inflammatory drugs such as ciclosporin, anakinra and intravenous immunoglobulin.

Sometimes chemotherapy drugs, such as Etoposide, can be used to treat HLH.

Some of the medicines used are listed in the table below but new treatments are being developed all the time.

Treatment will be individualised to minimise side effects, which your medical team will discuss with you. If an infectious trigger is suspected, anti-infection treatment may be given, such as antibiotics or other medication.

In the case of primary HLH, this treatment usually puts the condition into remission, but the risk of relapse remains.

Table with list of drugs

Type of Drug	**Example:** Please note over time these will be updated please refer to your Nurse or Clinician for the latest knowledge and availability.	**How is it Given**
Steroids	Dexamethasone, prednisolone	Daily by mouth or injection into a vein.
Calcineurin inhibitor	Cyclosporin	Twice daily, into a vein or by mouth
Cytotoxic chemotherapy	Etoposide	Into a vein, twice weekly at first then less often over time
	Methotrexate	By injection into the fluid around the spinal cord, up to four doses weekly if the brain is affected
Biologics	Alemtuzumab	Into a vein, daily for a few days
	Anakinra	Once or twice daily injection under the skin (subcutaneous injection) or as an infusion into the vein

Corrective treatment of HLH

Haematopoietic stem cell transplant (HSCT, including bone marrow transplant, or BMT) may offer the potential for long-term cure in patients with primary, genetic HLH or secondary HLH that does not respond to standard treatments or keeps relapsing but is not appropriate for all. HSCT aims to replace the faulty immune system with an immune system from a healthy donor.

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What happens next?

The prognosis of HLH has improved in the past few years, thanks to a better understanding of the condition and earlier treatment. New types of medicine are also being developed to treat HLH. However, prognosis remains poor in patients with an underlying malignancy and in patients in whom the trigger cannot be identified.

Treatment is intensive and has side effects but many of these can be managed. HSCT remains the only cure for primary HLH and may be offered to people with secondary HLH that does not respond to treatment or where the trigger is unknown.

In the inherited forms of HLH, genetic counselling for the family is important to understand any implications for families.

In secondary HLH potential implications for family members are currently unknown. The longer-term prognosis of HLH is dependent on the trigger and is individual to each person with HLH – your medical team will discuss this with you.

Information for Adult and Adolescent patients and their families

Is there a support group?

Histio UK offers information support to families affected by all types of histiocytosis.

Contact them at www.histiouk.org

GLOSSARY OF TERMS

anaemia a condition of abnormally low haemoglobin in oxygen-carrying cells, causing pallor and tiredness. Can be caused by poor diet, autoimmunity and other medical conditions.

ataxia a type of poor coordination and unsteadiness.

autosomal recessive a type of inheritance where the presence of one copy of a faulty gene does not affect the individual him or herself. However, when two carriers of the same faulty gene have children there is a 25 per cent (or 1 in 4) chance of a child inheriting two copies of the faulty gene (one from each parent) for each pregnancy. If this happens, the child is affected by the disorder.

biopsy surgical removal of a small sample of tissue for examination under a microscope for diagnostic purposes.

bone marrow soft, spongy tissue located in the hollow centres of most bones; it contains developing blood cells and cells of the immune system.

bone marrow transplantation (BMT) transfer of bone marrow, obtained by medical procedure usually from the hip bones, from a donor – either related or unrelated – to a recipient. The donor bone marrow replaces the recipient bone marrow, giving the recipient a new immune system and curing the immunodeficiency (see also Haematopoietic stem cell transplantation).

cerebrospinal fluid a watery liquid that surrounds the brain and spinal cord.

chemotherapy is treatment which manipulates a person's immune cells to suppress abnormal immune responses, and also in preparation for stem cell (or bone marrow) transplantation.

chromosomes thread-like structures located inside the nucleus of cells. Each chromosome is made of protein and DNA.

corticosteroids (also called steroids) medicines that damp down the immune system to reduce inflammation in a range of conditions.

donor an individual who could donate bone marrow or stem cells for transplantation. Donors may be family members, or unrelated, but need to be well matched with the potential recipient by tissue-typing.

familial occurring in a family or its members gene section of DNA on a chromosome that codes for a functional RNA molecule and thus a protein. Put another way, a word, rather than a letter, in the genetic code. Genes are the fundamental units of inheritance that carry the instructions for how the body grows and develops.

genetic counselling advice from a specialist geneticist regarding the implications of carrying or being affected by a genetic disorder.

haematopoietic stem cells cells from which all blood cells and immune cells are derived.

haematopoietic stem cell transplantation (HSCT) transfer of bone marrow (obtained by a medical procedure) or stem cells (obtained from blood or stored umbilical cord blood) from a donor – either related or unrelated – to a recipient. Haematopoietic means blood-forming. The donor cells are given by intravenous infusion and make their way to the recipient bone marrow to provide a new immune system, curing the immunodeficiency.

immune system the structures and processes that protect the body against infection and disease.

inheritance the passing down of genetic information from parents to children.

intravenous inside or into a vein; for example, an immunoglobulin infusion may be given directly into a vein. A needle is inserted through the skin of the back into the space between the bones that make up the spine. This is done using local or general anaesthetic.

lymphocytes a type of white blood cell.

lymphoma blood cancer that develops in the lymphatic system.

macrophage a type of white blood cell that is important in many aspects of immune function, including the ability to destroy invading bacteria.

mutation a change in the structure of a gene or group of genes. Such changes can be passed on to the next generation. Many mutations cause no harm, but others can cause genetic disorders, such as primary immune deficiencies.

PID UK (primary immunodeficiency) a support organisation for anyone affected by a PID.

prenatal diagnosis testing during a pregnancy for specific genetic disorders. Usually performed by 'chorionic villous sampling' – taking a sample of tissue from the developing placenta and testing DNA obtained from this tissue. Amniocentesis (performed later in pregnancy) is another route to prenatal diagnosis.

refractory not responding to standard treatment

remission control of the signs and symptoms of a disease without complete cure.

rigors – involuntary shaking associated with high fevers.

spleen an organ in the upper abdomen near the stomach that plays an important role in the immune system.

splenectomy surgical removal of the spleen.

subcutaneous applied under the skin

T-cells (or T-lymphocytes) specialised lymphocytes that develop in the thymus, an organ in the chest. They are responsible, in part, for carrying out the immune response.

white blood cells (leucocytes) a group of small, colourless blood cells that play a major role in the body's immune system. There are five basic types of white blood cells: monocytes, lymphocytes, neutrophils, eosinophils and basophils.

X-linked refers to the inheritance of disorders caused by mutations in genes carried on the X (or female sex) chromosome. This is also known as sex-linked inheritance. In this situation, girls are usually carriers and boys are affected by the condition. Girls inherit one X chromosome from each parent, so have a normal X chromosome to compensate for the faulty one.

NOTES