HISTIOCYTOSIS UK
No-one should die of Histiocytosis

HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

HLH – CHILDREN

Histio UK
Registered in England & Wales
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Introduction

Despite the misery it causes, Histiocytosis is too rare a disease to have generated substantial research in medical circles. Unfortunately, for every child or adult fighting for his or her life, the pain and suffering are just as severe for children and adults afflicted with other better-known disorders receiving funding.

For the children and adults battling these illnesses, there is now reason to hope. To ensure the research continues, we ask for your help, to complete the funding puzzle.

Our awareness and research programmes provide a beacon of hope for the many children and adults battling Histiocytosis, to ensure this research continues we ask you to pledge your support.

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What is Histiocytosis?

Histiocytosis is an umbrella term applied to a group of rare diseases, characterised by increased numbers of white blood cells called histiocytes in the blood and tissues. In all forms of histiocytosis, these cells, which are part of the protective immune system, begin to attack the body, targeting many organs of the body including the bone marrow, liver, spleen, lungs, skin, bone and brain.

The prognosis for patients varies greatly depending on the form of histiocytosis.

Please be advised that all the information you read in this document is not a replacement for the advice you will get from your consultant and their team.

Who we are?

Histiocytosis UK is a registered charity dedicated to promoting and funding scientific research into uncovering not only the causes of all histiocytic diseases, which include Langerhans Cell Histiocytosis and Haemophagocytic Lymphohistiocytosis, but also ensuring early diagnosis, effective treatment and a cure.

The Charity aims to support patients and their families by means of information and awareness as well as raise public and professional awareness of histiocytic disorders.

Its team of Trustees include the UK's leading paediatric LCH and HLH specialists.

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Haemophagocytic Lymphohistiocytosis (HLH)

In this disease a virus infection triggers another type of histiocyte, the macrophage, to become overactive and attack the body. Red blood cells and other white blood cells are engulfed and destroyed by the macrophages, so that the patient is unable to fight infections.

Patients therefore suffer from high fevers, may become anaemic and often have skin rashes, as well as symptoms due to the infecting virus. HLH is an acute and life-threatening disease. It frequently occurs in childhood but may occur at any age.

Diagnosis depends on detection of the infecting organism and demonstration of macrophages engulfing other cells as well as other abnormalities of white blood cells, usually in sample of bone marrow. In familial forms of HLH abnormal genes, which alter white blood cell function, are passed from the parents to children.

What is Haemophagocytic Lymphohistiocytosis (HLH)?

Haemophagocytic Lymphohistiocytosis is not a single disease but is a word that covers a number of conditions that differ in cause, treatment and outcome. The name is a combination of medical terms derived from Greek words: haem – blood; phagocyte – cell that ingests and destroys; lymphohistiocytosis – excessive number of certain types of white blood cells.

HLH can be likened to a very severe form of inflammation which the body is unable to switch off. It results from an uncontrolled increase in the numbers of lymphocytes and histiocytes (white blood cells) due to an ineffective immune (defence) response. These cells can destroy other blood cells and can cause problems for many different parts of the body.

HLH is a very rare disease with an estimated 1.2 per million children affected by HLH each year. This may be an underestimation as the diagnosis may be missed in some patients.

HLH can be difficult to diagnose as it may initially resemble a normal response to an infection. It can therefore take a while for the medical team to realise that the immune system is not working properly. HLH is treated by haematologists/ immunologists/ oncologists with steroids +/- chemotherapy +/- bone marrow transplantation.

The outcome for children with HLH has improved dramatically over the last 20 years and now more than half of the patients are cured.

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Are there different types?

There are two main types of HLH, primary (or familial) HLH which is inherited, and secondary (or acquired) HLH.

Primary HLH

Primary HLH is a genetic (inherited) disease and is most often referred to as familial HLH or FLH. In this genetic condition, defective genes are inherited from both the mother and the father (autosomal recessive inheritance). FLH is diagnosed if there is more than one affected child in the family and/or an FLH gene defect is identified. Several specific gene abnormalities (mutations) have been identified but not all patients with FLH have a recognised genetic mutation.

Approximately 1 child per 200 000 children will become unwell with FLH each year. Most children (70-80%) become unwell in the first year of life with infection-like symptoms, sometimes triggered by a viral infection. A small number (10%) develop symptoms within the first 4 weeks of life. In the same family, children with familial HLH usually develop symptoms around the same age.

Patients with FLH need treatment to get the FLH under control and will then need a bone marrow transplant to cure the disease.
If your child's Consultant feels that the HLH is due to a genetic cause, you will be referred to a Clinical Geneticist. The Clinical Geneticist will discuss with you if additional blood tests are needed from your family, will arrange to analyse the blood samples and discuss the results and other implications with you.

Secondary Haemophagocytic Lymphohistiocytosis

In the absence of more than one affected child in the family and/or an identified FLH gene defect, HLH is thought to be an acquired disease (secondary HLH).
Secondary HLH can occur at any age. It is not clear how common this is, but it is thought to be more common than familial HLH. Acquired HLH is usually triggered by an infection, often a viral infection. It can also occur in children with some cancers (notably specific types of lymphomas), in association with treatment for cancers with chemotherapy and in children undergoing bone marrow transplantation. HLH can also occur in association with rare inborn errors of metabolism (inherited problems with breakdown and production of sugars, proteins or fats in the body) and in association with genetic immune deficiencies such as Chediak-Higashi Syndrome 1 (CHS-1), Griscelli Syndrome 2 (GS-2) and X-linked lymphoproliferative syndrome (XLP).

Patients with secondary HLH need treatment to control the HLH and if possible, treatment for the underlying condition which caused the HLH.

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Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) is an extremely rare condition that occurs in both children and adults with autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosis (SLE). It has the same features of HLH, but some of the initial blood changes may be less severe, and problems with clotting and the function of the heart may be worse. Like the other forms of HLH, viruses have been shown to trigger MAS, but also some medications. The majority of children with MAS will recover completely, with treatment that is similar to that for HLH, but less intensive.

Diagnosis and Treatment

It is sometimes difficult to establish the diagnosis of Haemophagocytic Lymphohistiocytosis (HLH), and the combination of the physical symptoms and certain laboratory tests is required. (Note: The understanding of the pathology underlying HLH/FHL disease is evolving and recommended “diagnostic” criteria are likely to be revised in the future.)

• Low or absent NK (natural killer) cell function.
• Prolonged fever.
• Blood cell abnormalities (low white cells, low red cells, low platelets).
• Enlarged spleen.
• Increased triglycerides (fat) or decreased fibrinogen (protein necessary for clotting) in the blood
• Increased ferritin (protein that stores iron) in the blood.
• Abnormal bone marrow test with evidence of Haemophagocytosis (ingestion of red or white cells by histiocytes) but not malignancy or other cause.
• Abnormally high CD25 (also known as sIL2ra) in the blood indicating abnormally increased T-cell activation.

The test for low or absent natural killer cell (NK) function has been found useful in making a clinical diagnosis of HLH. This abnormality is found in many patients with FHL, as well as in many cases of secondary disease but rarely in the X-linked forms.

However, it is just one piece of information and should not be used to determine the diagnosis of HLH as primary or secondary. NK function cannot be determined before birth, and it may not be reliably studied until a child is at least 6 weeks of age. FHL is suspected if siblings have been diagnosed with HLH, if symptoms intensify during treatment for HLH, or if symptoms return after therapy has been stopped.

Since it is difficult to tell the difference between secondary HLH and FHL, any case of HLH should be considered for genetic testing to confirm the diagnosis. Since 1999, at least seven defective genes have been identified. Autosomal recessive: PRF1 (perforin), MUNC13-4, STX11 (Syntaxin), STXBP2, and RAB27A. X-linked: SH2D1A, BIRC4.

There are some FHL patients (approximately 30%) with no identified gene defect, so normal genetic test results do not necessarily rule out the diagnosis of FHL. Genetic testing is usually done on blood, although other kinds of tissue samples can be used. Once the genetic cause is known, the parents can quickly be tested to confirm that they are carriers for that specific genetic type of FHL. Other siblings can also be easily tested, even before

birth, once the genetic cause of the disorder in the family is known. Even in the event of death, salvaged tissue can be tested to determine if siblings are at risk.

In 1994, as a result of an international cooperative effort, the first treatment protocol for patients with HLH/FHL was designed. This included a combination of chemotherapy, immunotherapy and steroids, as well as antibiotics and antiviral drugs, followed by a stem-cell transplant in patients with persistent or recurring HLH or those with FHL. The HLH-2004 protocol was based on the HLH-94 protocol with minor changes such as cyclosporin, an immunosuppressant drug, being started at the onset of therapy rather than week #8. This protocol has been widely accepted internationally and is used in numerous countries on all continents but should still be considered experimental.
Secondary HLH may resolve spontaneously or after treatment of the underlying disease, without the use of chemotherapy. Therefore, treatment should be guided in part by the severity of the condition, as well as the cause of the disease.

FHL, however, when not treated, is usually rapidly fatal with an average historical survival of about 2 months. The treatment included in the HLH-2004 research protocol is intended to achieve stability of the disease symptoms so that a patient can then receive a stem-cell transplant, which is necessary for a cure.

In recent years, some transplant centres have adopted the use of reduced intensity conditioning (or “RIC”) to prepare for the stem cell transplant. This approach offers the possibility of better survival with stem cell transplant than the intensive chemotherapy protocols previously used.

As research continues, the outcome for patients with HLH/FHL has improved greatly in recent years. Approximately two-thirds of children with HLH who undergo transplantation can expect to be cured of their disease. However, there are a number of complications that can occur during the process of transplant, including severe inflammatory reactions, anaemia, and graft-versus-host disease.

Long-term follow-up of survivors of transplants for HLH/FHL indicates that most children return to a normal or near-normal quality of life. The results of transplantation are generally better when the procedure is performed at a major paediatric transplant centre where the doctors are familiar with this disease. Early and accurate diagnosis is essential. However, there is still a high rate of death, indicating that education of the medical community regarding prompt diagnosis and management of the diseases is required.

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FAQ

1. What causes HLH?

HLH can either be acquired (secondary HLH) or inherited (FHL). Both forms of the disease can be triggered by infections, although it is not known why this happens. Secondary HLH may be triggered by, viral infections such as Epstein-Barr, CMV (cytomegalovirus) or other herpes viruses, or other underlying diseases such as autoimmunity or cancer. In FHL, defective genes are inherited from one or both parents. Some other rare inherited immunodeficiencies may also be associated with HLH. The underlying immune defect and/or triggering events result in an abnormal immune response with activation of certain types of white blood cells (lymphocytes and macrophages) and the release of inflammatory proteins which then cause disease.

2. Is there a cure for HLH?

HLH patients with an underlying genetic defect can only be cured when the defective immune system is replaced by a healthy one which is what happens with a hematopoietic stem cell transplant. Secondary HLH cases can usually be cured by treating the underlying disease and sometimes additional immunosuppressive/immunomodulatory therapy.

3. What are the different therapies/treatments commonly used to treat HLH?

Some cases of secondary HLH can resolve spontaneously or after treatment of the underlying disease. Other cases are treated with a combination of chemotherapy (VP-16, methotrexate), immunotherapy (ATG, cyclosporin), and steroids. Any triggering infection has to be treated with appropriate antimicrobial drugs. Patients with persistent or recurring HLH or those with FHL additionally require a hematopoietic stem-cell transplant for recovery.

4. Why is routine newborn screening not available?

Although HLH may occur more frequently than some of the diseases routinely tested for, genetic testing for this disease is very complicated and very expensive.

5. How do I know if my child has primary HLH (inherited/FHL) or secondary HLH?

The clinical symptoms and laboratory findings do not differ in genetic or acquired HLH. Specific immunologic testing can raise the suspicion of genetic disease. In families with more than one affected child or in cases with disease reactivations there is a high probability of genetic disease. However, the identification of a genetic defect is necessary to prove it. Genetic testing is therefore recommended, regardless of age. Depending on the ethnic background up to 30% of patients with FHL have no identified gene defect, so negative test results do not necessarily rule out FHL.

6. How can I find out if my child's siblings have HLH?

In autosomal recessive forms of the disease, each sibling of a child with FHL has a 25% chance of being affected. In related genetic disorders, including X-linked lymphoproliferative disease, each male child has a 50% chance of being affected. If a genetic defect is known in your family, genetic testing (before or after onset of symptoms) is available to identify siblings who may also be affected.

7. How can I find out if future children are at risk for developing HLH?

If a genetic defect has been identified in your family, prenatal diagnosis is possible by performing either amniocentesis or chorionic villus sampling (CVS) to test if the foetus is affected.

8. What is MAS (macrophage activation syndrome)?

Macrophage activation syndrome is a severe, life-threatening illness caused by the excessive production of types of white blood cells called T cells and macrophages. MAS has strong similarities with familial Haemophagocytic Lymphohistiocytosis (FHL) and virus-associated Haemophagocytic Lymphohistiocytosis (HLH). The exact relationship between MAS and HLH is yet to be determined, although some researchers believe that MAS is a secondary HLH disorder. The term is typically used for the HLH-like syndrome that can occur in patients with systemic onset juvenile arthritis.

9. What is reduced-intensity conditioning (RIC)?

Reduced-intensity conditioning is a less toxic pre-transplant therapy with the goal of suppressing the patient's immune system enough so that it will accept donor stem cells while reducing the side effects of high dose chemotherapy The RIC may be used in some HLH patients, as well as some LCH patients with severe, resistant disease.

How is it diagnosed

Signs and Symptoms

The symptoms of HLH can be confused with common childhood illnesses but are more severe. They include a skin rash, raised temperature and swollen liver, spleen and lymph glands. There may be anaemia, infection or bruising and bleeding. If the brain is affected, a child may show symptoms such as seizures, ataxia (wobbliness) or drowsiness.

Diagnosis

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How is HLH treated?

Firstly the aim for treatment is to reduce the severe excessive inflammation that is responsible for the life-threatening symptoms.

Secondly, treatment aims to kill any of the immune cells that have been infected by a trigger, for example viruses and bacteria. This aims to remove the trigger for the excessive inflammation.

Unfortunately, even if the original infection that triggered the HLH is killed, that is not enough to stop the excessive inflammation, since it has spiralled out of control.

Thirdly, the ultimate aim for children with a genetic cause of HLH is stem cell transplantation. This aims to replace the defective cells in the bone marrow, with healthy cells from a donor.

Treatment is tailored for individual patients, and is guided by the type of HLH your child has, the severity of the severity of the symptoms, the age of the patient, and any other underlying conditions As HLH is uncommon and serious, treatment is usually coordinated by a specialist centre experienced in treating rare immune disorders.
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 chemotherapy medicines, usually given into a vein (intravenously) in hospital. Some of the medicines used are listed in the table below but new treatments are being developed all the time. Treatment will be individualized 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.

Type of drug: Example: How it is given
Steroid: Dexamethasone, prednisolone: Daily injection into a vein or by mouth
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

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

Corrective treatment of HLH

In many cases, haematopoietic stem cell transplant (HSCT, including bone marrow transplant, or BMT) offers the potential for long-term cure of primary HLH. HSCT aims to replace the faulty immune system with an immune system from a healthy donor. Stem cells, from which all the cells of the immune system develop, can be obtained from healthy bone marrow, or in some cases from umbilical cord blood or donor blood. The healthy stem cells can be given by transfusion into a vein to a child with HLH.
The symptoms, the age of the patient, and any other underlying conditions.

HLH Treatment Protocol

The vast majority of children with HLH will be treated with chemotherapy and immunotherapy guided by an international protocol (see example below), which maps out the dates for the different medications. The protocol will be tailored to your child.

If your child needs chemotherapy, he or she will probably need a central line. This is a tube that is inserted into a large blood vessel and tunnelled under the skin to where it can be easily accessed. It allows blood samples to be taken and treatment, including chemotherapy, to be given easily and painlessly. The central line is put in under general anaesthesia and will stay in place until the end of your child’s treatment. Your hospital will provide more information about the types of central lines they offer.

If your child is unwell or requires more intensive treatment he or she will need to be in hospital. Some children however receive some of their intravenous treatment by visiting their hospital out-patient or day-care facility. This may only be available at your treating oncologist/haematologist’s hospital or at your local hospital under a shared care arrangement with a local doctor. Some treatment, like that taken by mouth, can be given at home.

While on chemotherapy, for up to 6 months afterwards, and up to a year after a bone marrow transplant, your child will be susceptible to infections.

This is known as being immunocompromised. If he or she develops a fever or becomes unwell you need to contact your treating team immediately for advice. Your child may need immediate hospital admission and treatment with antibiotics.

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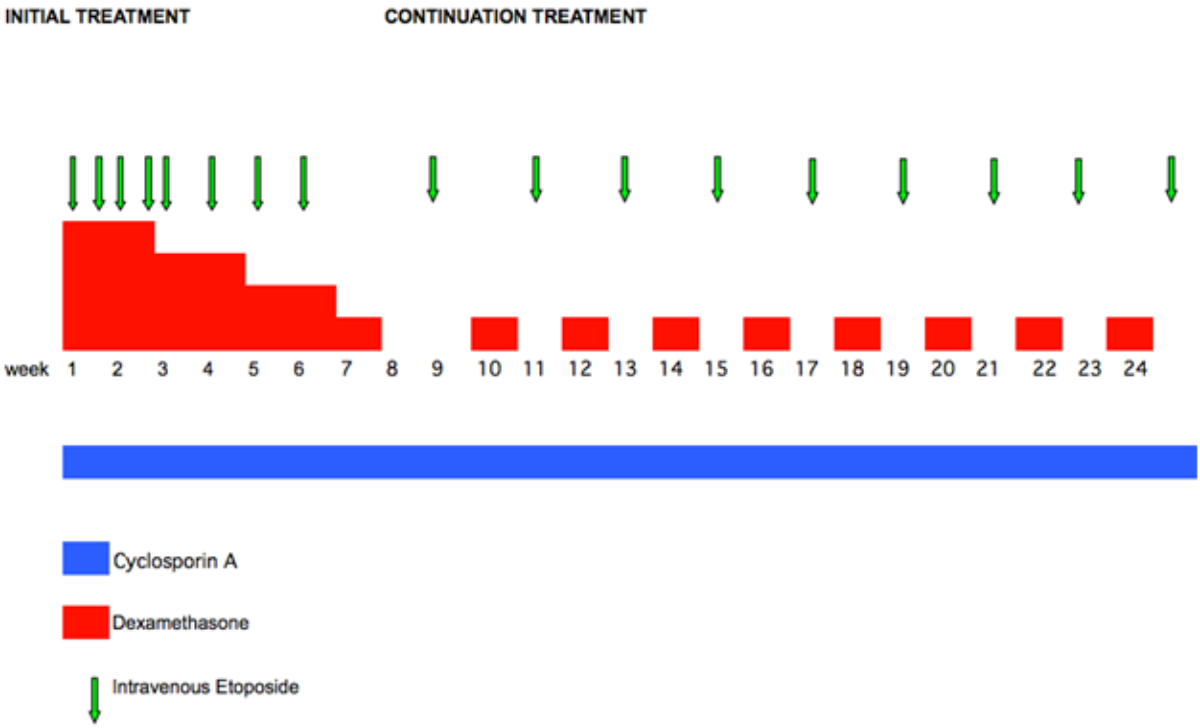
EXAMPLE OF PROTOCOL FLOW SHEET



Main treatment options:

• Steroids – corticosteroids are a medicine used to reduce inflammation and stop the body's immune system acting the wrong way. Your child may be given dexamethasone (a type of steroid) that is usually taken by mouth.

• Chemotherapy – this is used to destroy HLH cells and is usually given intravenously. This means that the chemotherapy medicine is diluted in fluid and given straight into a vein, via a drip. Occasionally some medicines may be taken by mouth.

• Immunosuppressant medications – these are drugs which suppress the abnormal immune response, for example cyclosporin.

• Stem Cell Transplant (also called a bone marrow transplant) – this involves replacing the diseased cells in the bone marrow with healthy cells from a donor. Bone marrow is a spongy material found in the hollow centre of some bones.

It is important as it contains special cells known as stem cells, which repeatedly generate specialized cells that carry oxygen, fight infection and stop bleeding.

Those children without disease in the central nervous system (CNS – brain and spinal cord) and mild symptoms may receive milder treatment. These children need

to be followed carefully for signs of disease progression, and more intensive treatment started if present.

Children with disease of the central nervous system (CNS – brain and spinal cord) receive additional intra-thecal (into the fluid surrounding the brain and spinal cord), chemotherapy or steroid.

Your child will have had blood tests to monitor disease progression already, but after 6-8 weeks of treatment, your child will have further blood tests, and bone marrow examination to see if the HLH has resolved. If your child has acquired HLH that has resolved, they will then be followed up to check for possible relapse. Reactivation of HLH is a frequent problem and may occur in the brain and spinal cord and usually requires more intensive treatment.

If the acquired HLH persists or your child has familial HLH, they will need to continue this treatment until they can have a stem cell transplant. All cells in the body have specific markers on them, and to be a match for transplantation, the donor cells must match these markers. While finding a suitable donor, your child will continue the medication to keep the inflammation at bay.

About a quarter of children who need stem cell transplantation do not reach it because their disease has progressed quickly and severely. For those children, in whom the HLH has not responded after the first 4 weeks of treatment, there are other treatment options with immunological drugs and further options that will be advised by your consultant.

Stem Cell Transplantation

Stem cells are mainly present in the bone marrow (the cavity inside large bones) and are the origins of all the blood cells in the body. If these stem cells are defective, then all the blood cells that they produce will be the same. The white blood cells interact to form part of the immune system that protects against infection.

Stem cell transplantation involves killing the child's (host) defective stem cells using a specialised programme of chemotherapy so that the child can be given an injection of new donor stem cells. These donor stem cells will establish in the bone marrow so that they can produce new healthy blood cells.

All cells in the body have a number of markers on them that vary between person to person. Before transplantation, the markers on the host's cells must be matched to those on the donor cells. Matched donor stem cells from a sibling are more favourable with a greater probability of survival, than from a mismatched unrelated donor, or a non-sibling donor. However, as HLH can be a familial disease, siblings may not be suitable to be used as donors.

Both HLH and some of the therapies used to treat it, affect the blood cells so that the numbers and function of platelets, and red and white blood cells are reduced. This means that your child may require supportive care with transfusions of blood products, including red blood cells and platelets while their counts are low and antibiotics to fight infection.

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What are the side-effects of the Treatments?

The main drugs used to treat HLH and their common side effects are described below.

Steroids:

Dexamethasone/prednisolone - these are corticosteroids (steroids) that can reduce inflammation and suppress the immune system. They are usually given by mouth, in the form of pills, pills that dissolve in water, or as a liquid medicine.

There are a number of known possible side effects. You will not necessarily experience all of these.

Possible side-effects include: irritation of the stomach lining Indigestion /discomfort/pain), increased appetite, weight gain, changes in behaviour (mood swings/difficulty in sleeping/anxiety/irritability), temporary increase in blood-sugar level (like someone with diabetes), high blood pressure, increased risk of infection due to suppression of the immune system, impaired wound healing, irregular or absent periods, and inflammation of the pancreas. Long-term steroid use may also cause muscle weakness, a reduction in bone density (bones become more fragile), cataracts and growth failure.

Chemotherapy:

Chemotherapy is a drug usually used to treat cancer but some chemotherapy drugs are also very effective against HLH. These drugs work by killing cells that are dividing and reproducing themselves.
Different chemotherapy drugs cause different side effects. Everyone is different and will react to chemotherapy treatment in a different way. Some patients may have very few side effects while others will have a lot. Almost all side effects are only short-term and will gradually disappear once the treatment has stopped.
The main areas of your body that may be affected by chemotherapy are those where normal cells rapidly divide and grow. Examples include the lining of the mouth causing a sore mouth, the digestive system causing diarrhoea, skin and hair, causing hair loss, and the bone marrow (spongy material that fills the bones and produces new blood cells), causing low blood counts.

There are three main types of blood cells that might be affected:
• Red blood cells which carry oxygen around the body
• White blood cells which fight infections
• Platelets which help to clot the blood to prevent bleeding and bruising

Chemotherapy reduces the production and therefore, the number of blood cells in the body. Too few red blood cells cause anemia, and the person becomes tired and pale. If there are too few white blood cells, particularly those called neutrophils (neutropenia), the person is at increased risk of infection. Too few platelets mean the person is at increased risk of excessive bleeding when injured, having nose-bleeds or bruising easily. If the counts get really low, you may need a red cell transfusion or

platelet transfusion. Transfusions are also needed to support those patients who undergo intensive chemotherapy.

As the chemotherapy affects your immune system, you may need antibiotics to help fight any infection. This means if you have a temperature of 38°C or more, or becomes unwell (even with a normal temperature) you must go to hospital where you may have to stay for a couple of days whilst being given antibiotics. You may also have to avoid giving paracetamol or ibuprofen until you are reviewed in hospital, as these drugs lower high temperatures and can potentially mask an infection. In addition, if you are in contact with someone who has chickenpox, shingles or measles, then you should let your hospital know as these are dangerous infections for a patient with a low (suppressed) immune system. Both you and the rest of your family should have the annual flu jab during the autumn/winter.

Chemotherapy can also cause nausea and vomiting, but anti-sickness medicines known as anti-emetic drugs can control this side effect.

Hair loss can occur, but this does not always happen with the chemotherapy used to treat HLH. Young patient often get used to hair loss fairly quickly but for others it is far more traumatic, fortunately, all hair loss from chemotherapy is temporary and hair growth returns once treatment has stopped.

Fertility may be affected, depending on which chemotherapy drugs you receive. You should discuss your particular treatment with your oncologist/haematologist for more information.
Other side effects are an increased sensitivity to the sun, so you should keep out of intense sunlight and use sun block.

Treatment Centres

Haemophagocytic Lymphohistiocytosis is a rare disease. Treatment and full investigation are performed at specialist treatment centres that have experience with dealing with patients with HLH and the specialist medications. There are specialist centres in the UK which treat cancer and rare diseases and you care will be coordinated from there. To make things a bit easier for your family, you may receive some treatment in a hospital local to your home (shared care), but the overall management plan for your treatment will ultimately be undertaken from your closest treatment centre.

Complementary (Alternative) Therapies

In the past, many doctors dismissed alternative or complementary medicine, but it is now recognised that families often benefit from the positive effects of treatments such as acupuncture, massage, counselling or nutritional therapy.

Several effective chemotherapy drugs are derived from natural sources, especially fungi and plants. The main ‘problem’ with complementary therapy is that individual treatments are hardly ever subjected to the same intense scrutiny and ‘clinical trials’ as official drugs, and that is a matter of considerable concern. It is therefore, important that you discuss with your consultant any of the alternative therapies you plan to use, to ensure that they do not interact in any harmful way with your medication. Herbal ‘remedies’ are a case in point, since some of them are known to

interfere with medically prescribed drugs proven to help. The following are just some of the over-the counter treatments that interfere with the action of chemotherapy drugs, or other medicines such as antibiotics: bilberry; Echinacea; fish oils; garlic; glucosamines; meadowsweet; selenium and St John's wort.

What Are Clinical Trials?

HLH is very rare, with only a very small number of patients diagnosed each year. HLH covers conditions with many causes, so each case is different, with less predictable response to treatment. Clinical trials which randomly split the patients into different groups to look at treatment effects and side-effects are thought to be the best. However, because of the small and wide ranging cases, no randomised trials have yet been able to be performed in HLH but are planned for the future.

Clinical trials are an essential step in the development of treatment for various diseases and are necessary for improving the outcome of patients. Clinical trials are the only way to find out if a new treatment approach to a disease is better than the standard treatments currently used. Patients volunteering to take part in a trial are randomly assigned to either receiving the standard treatment or a different or experimental treatment. This is known as a randomised trial and is the most common way in which treatments are tested. The choice of which treatment is offered to a particular patient is usually done with the help of a computer and the process ensures that the groups are similar in every way other than the fact that they receive different treatments. Any difference in outcome between the groups is then likely to be caused by the difference in the treatment and not by other differences between the groups. If an experimental treatment proves to be better than the standard treatment and does not cause unacceptable side-effects, it is recommended as the new standard treatment for future patients. This is how new treatments or approaches to treatment are introduced to patients.

The conduct of clinical trials is carefully regulated to ensure patients' well-being is protected. Patients will only be able to participate in a trial if there is an open trial at that time, if they meet the eligibility criteria, and if their treating hospital is taking part. Parents and when appropriate, children must understand the implications of taking part in a clinical trial and give written consent (agreement) to allow them to be enrolled on a trial. If a trial is available to your child, your doctor will explain it in more detail and you will be given the necessary information to allow you to decide whether to take part or not. While on a clinical trial your child will be very closely monitored.

How do I cope with the diagnosis?

HLH can be difficult to diagnose and can be mistaken for other things. You may have been afraid that your child has a form of cancer and feel relieved that it is not. You may feel angry that it wasn't picked up earlier. You will probably feel confused as you won't have heard of HLH before and worried and scared about what it means for your child. The consultant and medical and nursing teams are there to help you through this very difficult time and to plan with you the treatment your child will need.

It is very likely at this stage you will not take in much of the information you are given. You may be in shock and find it hard to function as normal. Don't worry if you have not asked all of the questions you meant to. You will have plenty of opportunities to do so later. Quite often, parents feel overwhelmed by the enormity of what has happened and cannot deal with anything else at this time.

As parents, being able to have even a few hours alone together to get used to the news and to talk about what has happened before starting to tell everyone else can be very helpful. If you are a single parent dealing with this news, it is important to have a close friend or family member with whom you can share your worries and fears.

Telling friends and family can be emotionally difficult, and also takes a huge amount of time. It can help to tell one family member or friend and ask them to ring round others. Many parents also set up a webpage on one of the specialised websites such as Caringbridge or Carepages (see other links' section at the end). This means that the latest information can be quickly passed on to friends and family who desperately want to know what's happening, while not taking up all your time and energy having to repeat everything. It also gives people an easy way to let you know they care, through leaving messages in the guestbooks. Despite your best efforts, you will probably still find the telephone rings constantly. Don't feel bad about using the answer phone. Let people leave messages and call them back if and when you want to.

It is probable that your child's treatment will begin quite quickly after diagnosis. Although you will be worried about the treatment and its side-effects, it is important to start treatment promptly. Once the initial shock has faded, you may well be impatient for the doctors to start to deal with your child's HLH, however worried you may feel about the effects of the treatment on him or her.

People deal with bad news in different ways. Over the first few days, it is important that you give your spouse, partner, close friend or family member space to get used to the news in his or her own way.

How do I get the information I want?

When you are worried about your child and meeting a doctor that you may not know very well, it is easy to forget what you meant to ask, and what you have been told. If you can, try to take notes when you attend the main meetings with the consultant. It might be better to take a friend or relative along with you, as they might be able to pay more attention to some of the discussion and take notes for you. It is often the case that you will remember different pieces of information and you may have

different questions or concerns. Write down any questions beforehand, so that you don't forget them, and make sure you know whom to contact if you have any more questions, or urgent queries.

How do I listen to and talk to my child/their siblings about this?

A child of any age will notice a tense atmosphere and hushed conversations. It is very important that you talk to your children about what is happening. What you actually say to your child and their siblings will depend on their age. For younger children, it may be enough to say that they have some bad cells and the doctors are giving them some medicine to make the bad cells go away.

Older children and teenagers may want to know all that you know about their illness and may well have been with you when you were told the diagnosis. Being open and honest with them and talking together with the consultant about their questions will help you all to deal with the diagnosis. It may also be helpful for them to talk privately about their worries with members of the medical team, such as the doctor, social worker or psychologist. Some children may consider themselves mature enough to make their own decisions regarding their treatment and should therefore be involved.

Siblings may feel ignored and side-lined due to your child's illness. Their lives have changed a lot due to their sibling's illness and they may start to feel resentful about all the attention their sibling is receiving.

They may also be extremely worried and upset to see what their sibling is going through, and it can raise difficult questions in their minds. You will need to give them opportunities to ask these questions and bear in mind that they might find it easier to talk to another adult (close friend or family) as they may not want to upset you.

There are many things you can do to help your family get through any difficult times during treatment. Some suggestions that have helped other families are:

• You and your partner spend time individually with your other children.
• Make sure that when your ill child receives presents from visitors, you even things up by giving something to your other children.
• Try and keep discipline consistent, even if it means relaxing things a little for everyone.

How do we deal with the treatment?

Parenting a sick child can be a very difficult experience. While it is good to keep things as normal as possible, worries about infections and the physical effects of the chemotherapy can make that impossible. How you change what you do depends on you and your family, on how your child is reacting and on advice from your doctors. For example, if your child loses their appetite, you may find that you are not so strict on table manners. Likewise, it may be fine for your child to attend nursery, while another family will prefer to keep them away from large groups of children.

If your child is at school or nursery, you should talk to the staff as soon as you can. You could also write to them with the facts about your child's illness and ask that they pass on the information to other members of staff and parents of your child's classmates. This is particularly important if your child is immunosuppressed, as you will need to be told if anyone who is in contact with your child develops chicken pox, shingles or measles. Your child may be assigned an outreach / community nurse from the hospital who can meet with staff at your child's school or nursery to explain

more about the disease and what they need to be aware of. This is important, as you will need to rely on the school or nursery to recognise when your child is very tired or ill.

Having a child with LCH can at times feel like a full-time job all by itself - just keeping track of medications, arranging and attending hospital appointments, getting test results, and generally making sure your child is getting the best treatment.

As well as the time spent dealing with hospital appointments and related tasks, the emotional trauma can make it hard to keep up with all the usual everyday jobs and work. Don't be shy to ask for help – friends and family are often grateful to be able to do something concrete, so ask them to make a meal, do the ironing, mow the lawn, pick up the prescriptions. There may also be organisations that can help, such as local charities that will offer support or services such as doing your shopping. CLIC Sargent provides social workers and community young adult workers to support patients and their families, so ask for a referral in your hospital or contact them yourselves.

There are variations in what your local health service may offer. Some areas offer children's community nurses (or paediatric home nursing teams) who will come to your house to take blood tests, change dressings which will save you a hospital trip. Your local pharmacist may be able to supply some of the less specialised medications, on prescription from your GP, which can be more convenient than using the hospital pharmacy. There may also be a 'shared care' arrangement with a doctor in your local hospital so that you can go to a closer hospital for blood tests, chemotherapy or if your child gets an infection.

Your child's appetite may be affected by the chemotherapy and steroids and can change a lot depending on where they are in the treatment schedule. If you are worried about your child's nutrition, talk to your medical team who will be able to advise you, or refer you to a dietician.

During the period of treatment, you will have ups and downs. Although the first shock of diagnosis will fade and you will feel that at least action is being taken to deal with the illness, worries about your child's progress and prognosis will come back from time to time, particularly if things do not go according to plan. It can be difficult to maintain the stability of your child's home environment and minimise the impact on your family. Help and support from close family and friends, online support networks or your community group can all help to keep your spirits up. Doing fun activities as a family can help distract you and give you all a break from the worry and stress.

The duration of the treatment will depend on what type of HLH your child has and how they respond to treatment. It is helpful when you are given some idea of what treatment is panned and how long it might carry on for so that you can try and organise your lives to cope with the situation. Where possible, talk to your Consultant about the possible duration of treatment, though this might not always be easy to predict and depends on how your child responds to initial management

What happens at the end of treatment?

Even though the treatment is stressful, many parents find the end of treatment difficult. Some parents have said they felt the disease had only been kept at bay while the drugs were being given. When treatment ends, it can feel as if the 'safety net' has been taken away, so you feel more worried about the return of symptoms.

This uncertainty can be eased a little by the regular follow-ups that your child will receive and by talking to your medical team about any concerns you have.

If the disease does occur again, known as a reactivation, your consultant will discuss what treatment will be used. It may be that either the drugs or the time period will change, and they will discuss this with you.

What resources are there for sibling or family support?

Families should be able to gain support from the group of professionals who work with their child's consultant. They are known as a multi-disciplinary team (or MDT) and usually include nurses, social workers, play therapists and psychologists. Many centres also run patient, sibling and parent support groups.

Your GP will be kept informed by the hospital, but it is also useful to keep him or her up to date yourself. They can be a useful source of support for the whole family as he or she may be able to refer you for specialised support locally if needed.

Counselling can be useful for you and/or your children. Your GP may be able to refer you to a counsellor, or a child psychologist if required. 'Relate' provides counselling for couples, which can help to mitigate the strain that can be placed on your relationship with your partner.

There are a number of different charities, such as CLIC Sargent and Barretstown that offer holidays for families with children with serious diseases.

It is not always easy to find the help you need and you may need to ask a few people before you find the right support for you. As well as talking to your GP, try talking to the medical team at your hospital or shared care hospital, your community nurse, paediatric oncology outreach nurse specialist or CLIC Sargent social worker.

How do I find other parents?

One of the real difficulties for parents of children with a rare disease, such as HLH, is being able to talk to other parents, who have been through, or are going through the same experience as you.

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Histiocytosis UK has a number of multimedia ways that you can contact other patients and families many of which hold family events.

You may find helpful national or regional support and advice on our Useful Links page or you may also like to join one of our facebook groups.

- **Facebook: "Histio Champions"**' celebrating patients, families and champions of all Histio Awareness,
- **Facebook: "Histio Champions LCH"** community
- **Facebook: "Histio Champions HLH"** community or **Twitter**: @histiouk.

Where can I get financial support?

In the UK the NHS covers all medical treatment and tests free of charge. Prescriptions for medications are free for children. Having a sick child, however, inevitably puts additional financial pressure on families (travel, parking, loss of income etc.).

Children who receive chemotherapy can apply for Disability Living Allowance. CLIC Sargent has produced two excellent leaflets entitled Claiming Disability Living Allowance and Parental Leave and Flexible Working which can be obtained from their website. There is also a helpline. You could also contact the Disability Benefits Centre or the Citizens Advice Bureau for further information. Contact details can be found in Other Links.

It is vital that you talk to your employer to explain what is going on and find out what they can provide in terms of flexibility. A carers allowance may also be available. This is means-tested, so depends on your income. For further information, talk to your outreach nurse or social worker. CLIC Sargent offer grants to help with the additional financial costs, such as unpaid leave from work, after school care for siblings and travel. More information on these grants can be found on their website, or through your social worker.