



# **Hemophagocytic** Lymphohistiocytosis

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# HEMOPHAGOCYTC LYMPHOHISTIOCYTOSIS

## A HANDBOOK FOR FAMILIES

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## ■ WHAT IS HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)?

Hemophagocytic lymphohistiocytosis (HLH) is a very rare disorder of the body's defense system during which the body's normal infection-fighting process becomes out of control. Instead of fighting invading cells from infection, the disorderly immune system begins to attack the body's normal cells. When the body's infection-fighting process does not work correctly, the patient usually becomes very sick.

## ■ WHAT CAUSES HLH?

HLH occurs as a result of overreaction of the immune system. It is usually triggered by an infection. Normally, when an infection occurs, the body's defense system (immune system) goes into action, releasing infection-fighting cells to control the infection. To help the infection-fighting cells do their job, a lot of special chemicals are also released in a process called *inflammation*. This process occurs in a very orderly fashion, and when the infection is finally under control, the cells and chemicals of the immune system go back to their usual quiet, inactive state.

However, because there is a defect in the immune system with HLH, it cannot turn off. Therefore, the cells and chemicals that were activated to attack the "invaders" begin to affect normal cells instead. As a result, many normal cells are destroyed in a process called *hemophagocytosis*, which can cause a decrease in the amount of red blood cells, white blood cells, and platelets. Another effect of this out-of-control immune system is an abnormal production of the chemicals that cause inflammation, which can result in fevers, rashes, and problems with bleeding.

One important part of the defect in the immune system that results in HLH involves a special infection-fighting cell called a natural killer cell.

## ■ WHAT IS A NATURAL KILLER CELL?

Natural killer (NK) cells are an important part of the immune system. Every cell in the human body carries a marker showing that it is a cell that belongs to that specific person. NK cells are like watch dogs. They reside in tissues all over the body, and their job is to constantly check the identification of every cell they meet to be sure that it carries the correct marker and is not a foreign invader. When an NK cell meets a cell without proper identification, it sounds the alarm to other cells of the body's defense system. Then it latches on to the foreign cell and releases little particles that puncture the foreign cell's outer cover and make it easier for other immune system cells to destroy the invader. Patients who develop HLH have either a decreased amount of NK cells or NK cells that do not work correctly. In either case, when an infection occurs, the cells that are supposed to be serving as watch dogs are not able to sound the alarm, which can allow a serious infection to develop. This then stimulates the body to respond with a second wave of defense—the inflammatory process. In patients with HLH, however, there is an overresponse of inflammation, which results in symptoms such as fevers, rashes, and enlargement of the liver or spleen.

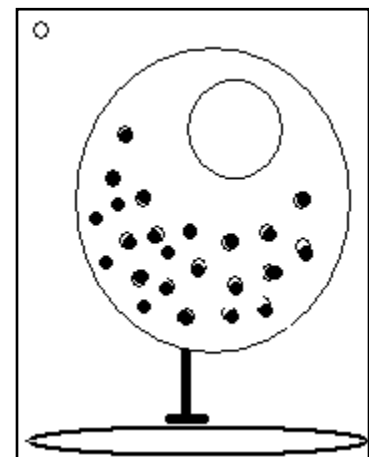


Figure 1. Natural killer cell attaching to an unidentified cell

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## ■ WHO GETS HLH?

HLH can occur at any age from birth to adulthood, but most patients are younger than 15 years of age. About 1 out of every 100,000 children younger than the age of 15 years will be diagnosed with HLH. Boys and girls are diagnosed with HLH in equal numbers. The inherited form of the disease usually occurs in children younger than the age of 2 years.

## ■ IS HLH INHERITED?

Yes, there is an inherited form of HLH. Researchers have discovered five different abnormal genes that can result in HLH. When blood tests show the presence of one of these gene mutations in a child with HLH, the brothers and sisters also may be at risk for developing HLH. However, not all forms of the disease are inherited (see below).



## ■ IS HLH A FORM OF CANCER?

No, HLH is a disorder of the immune system. It is not cancer, but chemotherapy is often used to treat HLH because one of the main side effects of chemotherapy is its ability to decrease the body's infection-fighting response.

## ■ WHAT ARE SOME OF THE SIGNS AND SYMPTOMS OF HLH?

Children with HLH are usually very sick at first. The symptoms of HLH are the same for both the inherited and the acquired form. They include

- fevers that last for a long time
- enlarged liver and/or spleen
- rash
- increased bleeding and bruising
- abnormal blood tests
  - low blood counts (white blood cells, hemoglobin, and/or platelets)
  - low fibrinogen and/or high triglycerides
  - high ferritin
- abnormal brain function causing increased irritability.

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## ■ WHICH TESTS AND PROCEDURES WILL MY CHILD NEED?

To make the diagnosis of HLH, the following tests will need to be done:

- physical exam to check for fever and a big spleen or liver
- bloodwork
  - complete blood count
  - ferritin
  - triglycerides
  - fibrinogen
  - liver enzymes
  - clotting studies
  - NK cell function
  - other special tests to evaluate immune system function
- biopsy, usually of bone marrow, but can also biopsy other tissue.



## ■ HOW ARE PATIENTS WITH HLH CLASSIFIED OR STAGED?

There are two forms of the disease:

- *inherited form* (called familial HLH [FHLH] or primary HLH)—usually diagnosed in children younger than 2 years of age, and there is often a family history of unexplained deaths
- *acquired form*—usually associated with infection, malignancy, or preexisting autoimmune disease (such as juvenile rheumatoid arthritis).

It is not possible to tell the difference between the two forms of the disease at the time of diagnosis. The initial treatment is the same for either form of the disease. The only way to be sure that a child has the inherited form of HLH is to do blood tests that look for one of the five known genetic defects that have been linked to HLH: PRF-1, Munc 13-4, STX-11, RAB27A, and STXBP2. There also may be other gene defects associated with HLH that have not been identified yet.

Certain rare syndromes have also been linked to HLH, such as Chediak-Higashi syndrome, Griscelli syndrome, and X-linked lymphoproliferative syndrome.

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## ■ HOW IS HLH TREATED?

- The treatment for HLH involves turning down the body's infection-fighting response, a process is called *immunosuppression*. The most commonly used medications are dexamethasone, etoposide, and cyclosporine. Sometimes parents are confused when chemotherapy is used to fight HLH. However, in this situation, chemotherapy is being used for its well-known side effect of suppressing the immune system, which is what patients with HLH need—a way to turn down or regulate their immune system.
- The only curative treatment for patients with the inherited form of HLH is to replace their defective immune system with a healthy one through the process of stem cell transplant. Patients with the acquired form of HLH may also need a stem cell transplant if they do not get better after several weeks of chemotherapy.



## ■ HOW LONG WILL MY CHILD'S THERAPY LAST?

The initial treatment phase lasts for 8 weeks. At that time, if your child has the inherited form of the disease, or if blood tests show that NK cells still are not working correctly, then your child will continue chemotherapy while your doctors make plans for stem cell transplant as soon as a suitable donor can be found.

After the initial 8 weeks of chemotherapy, if your child has the acquired form of HLH, and the special blood tests show that NK cells are working normally again, your doctors may stop chemotherapy and continue to watch for improvement by checking blood tests.

## ■ HOW SUCCESSFUL IS THE TREATMENT?

Successful treatment of HLH depends on making the diagnosis quickly so that therapy can be started as soon as possible and the disease can be brought under control. After 8 weeks of treatment with dexamethasone and etoposide, about 75% of children diagnosed with HLH will be in remission, based on the results of the first international clinical trial for treatment of HLH (Filipovich, 2008). Overall survival rates for HLH are 55%. The survival rates for the inherited form of HLH have increased to 60% with early treatment and use of stem cell transplant (Gupta & Weitzman, 2010). Clinical trials are currently evaluating ways to improve early response without causing intolerable side effects.

## ■ ARE THERE ANY NEW TREATMENTS?

According to the well-established treatment regimen of the Histiocyte Society, the best known treatment for HLH involves suppression of the immune system with etoposide, dexamethasone, and cyclosporine. Stem cell or bone marrow transplants are used for patients with the inherited form of the disease. Other treatment regimens have been reported using different combinations of immunosuppressive medications. Alemtuzumab (Campath®) is being investigated as a possible treatment for patients who do not respond to established therapies.

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## ■ HOW CAN I WORK WITH MY CHILD'S HEALTHCARE TEAM?

Your child's care requires a team approach. As a parent, you are a very important part of the team. Other members of the team may include doctors, nurses, social workers, child life specialists, therapists, and others. Because you know your child better than anyone else, your healthcare team will need your help to give your child the very best comprehensive treatment for his or her disease.



It is important to have two-way communication with your child's healthcare team. Be sure to ask your child's doctor or nurse questions whenever there is anything that you are not sure about. It helps to write down questions when you think of them.

The following are some examples of questions to ask:

- What is HLH?
- What parts of my child's body are involved?
- What type of HLH does my child have?
- What treatment choices are available?
- What treatment do you recommend and why?
- What risks or side effects does the recommended treatment have?
- What should we do to prepare for the treatment?
- What is my child's chance for survival?
- What are the chances that the disease will come back?
- What long-term effects might occur as a result of treatment?

Use this space to write down some other questions that you might have.

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## ■ ARE MY FEELINGS NORMAL AND WHAT CAN I DO ABOUT THEM?

Learning that your child has a life-threatening illness can produce a variety of emotions. At first you may not believe it, or you may hope that the diagnosis is wrong. These are normal feelings to have after the diagnosis is made.

Sometimes family members feel that they are somehow responsible for their child's disease, or they feel guilty that they were not able to detect it sooner. Remember that there is no way that you could have predicted that your child would get this disease and no way that you could have prevented it from happening. This disease was not caused by anything your child did or anything that he or she ate. It is the result of a faulty immune system.

In addition to shock and guilt, you and your family will probably feel anger and sadness. Even the youngest members of your family will probably be affected by this illness. These feelings of anger, sadness, guilt, and shock are all normal. Each member of your family will express these feelings in different ways and at different times. It can be very difficult to feel so many strong emotions at once. Talking honestly with each other about feelings, reactions, and questions will help everyone in the family.

It may seem difficult to talk to friends, family, or even medical staff, but sharing your feelings can help you cope with the situation. Remember that your child will benefit if family members continue to show that they care by being supportive and keeping open communication. If your friends and family give you information that seems to conflict with what your doctors have told you, be sure to talk to your doctors to clear up any confusion.

## ■ HOW CAN I HELP MY CHILD?

As a parent, you will often notice changes in your child during treatment. These changes or symptoms can make you feel even more helpless. It is important to always remember that, in spite of changes on the outside, your child is still the same person on the inside. Hair loss, weight gain, and other changes in body appearance are temporary. All of your feelings about what your child is going through during treatment must be balanced by remembering that the treatment provides an opportunity to cure the disease and to have your child go on to live a normal, full, and meaningful life.

It is important to reinforce to your child that nothing he or she did caused this disease. Tell your child that your angry or sad feelings are directed at the disease and not at him or her. This will help maintain honesty and closeness in your relationship. Like you, your child will need someone with whom he or she can share feelings. Don't hesitate to ask your child to express his or her feelings. Don't be afraid to explain, in age-appropriate terms, what is happening and why. Do not avoid using direct terms and explanations with your child. Children tolerate treatment better if they understand it and are allowed to be active decision makers whenever possible. The same is true for parents.

As you begin to learn the new, special needs of your child, it is important to remember that he or she is still a normal child and is still growing and developing. All children—both sick and well—need love, attention, discipline, limits, and the opportunity to learn new skills and try new activities that are appropriate for their age.



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## ■ IS MY CHILD'S DIET IMPORTANT DURING THE TREATMENT?

Yes. We know from research that well-nourished children tolerate therapy better and have fewer treatment delays due to illness. It may be difficult for your child to keep normal eating habits during therapy so you will need to be flexible and creative. The steroids (dexamethasone) that your child will take as part of the treatment for HLH will cause an increased desire to eat. You will notice that



your child wants to eat very often and wants to eat larger amounts of food than usual. Your child's food preferences will also change; children on steroids often want to eat foods that have a lot of salt or carbohydrates and fat. As the parent, you will want to set some limits on when and what your child eats while taking steroids. Be sure to keep fruits and vegetables handy for snacking. Try to limit snacking on chips and sweets. Make sure that foods high in protein are included in your child's daily diet. Often several small meals during the day are tolerated better than three large meals. It is also important to include your child in the social activity of family meals.

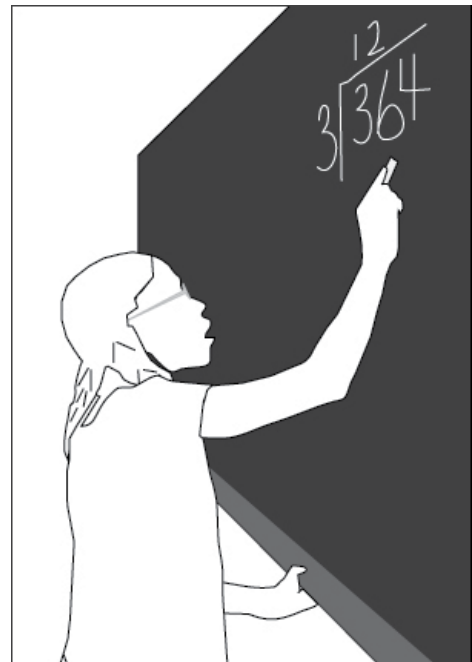
Multivitamins, other medicines (over the counter or prescribed by other doctors), and herbs should be discussed with your healthcare team before you give them to your child. Sometimes other medicines can interact with chemotherapy and cause additional side effects or change the effectiveness of the treatment so it is important for your doctors to know about any other medicines, vitamins, or herbs that you plan to give your child.

A dietician trained in children's calorie and energy needs can offer you guidance and food suggestions. The medical staff can also intervene if your child develops a nutritional problem.

## ■ CAN MY CHILD ATTEND SCHOOL DURING TREATMENT?

Your child's ability to attend school will depend on the intensity of the therapy and his or her response to treatment. Some children tolerate chemotherapy better than others. Your child may not be able to attend school for several weeks or months because of a weakened immune system, the treatment schedule, and/or hospitalizations. However, it is important for your child to keep up with his or her schoolwork. Talk to the staff at his or her school about arranging for a tutor or homebound teacher until your child is able to return to school. You should also discuss school attendance with your child's doctor. Many pediatric hospitals have programs that help children attend school while they are hospitalized.

School is important because it helps children maintain social contact with other children of the same age. Maintaining time with friends will be an important part of your child's recovery and will ease the adjustment when he or she returns to school. It is important for your child to return to school as soon as he or she is medically able to do so.



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■ **INTERNET RESOURCES**

- Histiocytosis Association of America  
[www.histio.org](http://www.histio.org)  
(This website includes disease information, family support information, and a searchable list of physicians who treat HLH.)
- Gene and Rare Diseases Center—National Institutes of Health  
[http://rarediseases.info.nih.gov/GARD/Condition/6589/Hemophagocytic\\_lymphohistiocytosis](http://rarediseases.info.nih.gov/GARD/Condition/6589/Hemophagocytic_lymphohistiocytosis)



■ **IMPORTANT PHONE NUMBERS**

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■ **NOTES**

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