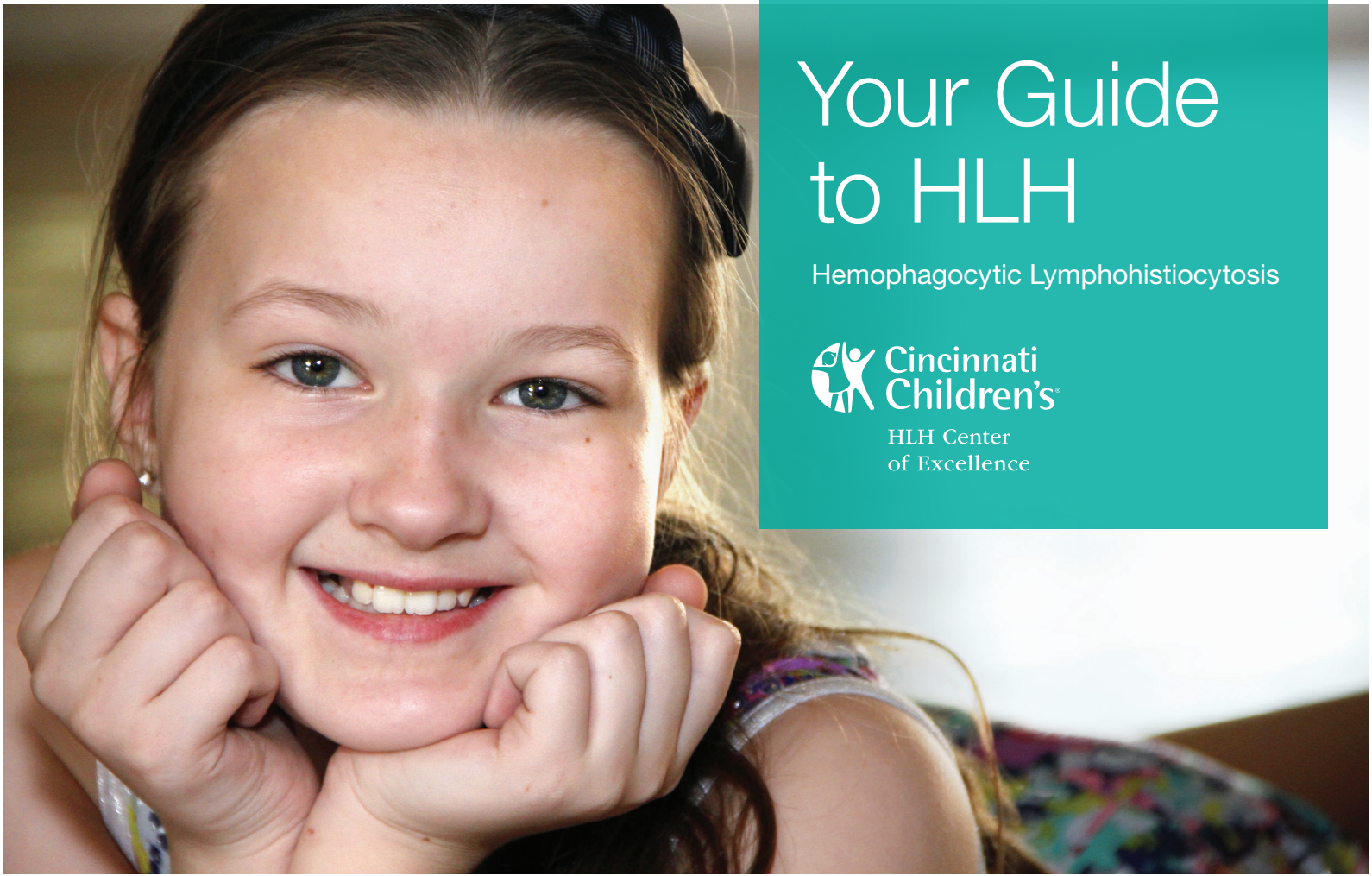

Your Guide to HLH

Hemophagocytic Lymphohistiocytosis

Cincinnati Children's®

HLH Center of Excellence

What is HLH?

Pronounced: HEE-moh-FA-goh-SIH-tik LIM-foh-HIS-tee-oh-sy-TOH-sis

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening immune disorder, involving severe uncontrolled inflammation in the body. In patients with HLH, the immune system does not work as it should. This is due to rapid and uncontrolled growth of the body's defense cells, called lymphocytes and macrophages. Normally, these cells keep our bodies well by destroying infected or damaged cells. However, in patients with HLH, these cells not only destroy the damaged cells, but they do not "shut off" as they should and go on to destroy other cells such as red blood cells, platelets and neutrophils within the body. Macrophages and lymphocytes can also build up in organs including the skin, spleen and liver. This causes fevers and can damage the liver and spleen. HLH is considered a rare disease, and many healthcare providers are unfamiliar with its symptoms.

HLH survivor Isaac, age 16 from South Carolina. Photo taken eight years following a bone marrow transplant for HLH.

What triggers HLH?

Sometimes HLH can be triggered by a virus like EBV, the virus that causes mono, but sometimes doctors aren't sure what triggers it. The defense system continues to be stimulated and is over activated because the body's immune system is unable to "switch off". If HLH is not treated, the continuing inflammation can damage the patient's own body, including its organs.

What symptoms are associated with HLH?

HLH can be very hard to diagnose because it can initially appear like other, more common diseases, such as infections.

Symptoms of HLH that you may notice in your child may include:

- Persistent fevers
- Rash
- Enlarged lymph nodes
- Yellowish-looking skin and eyes (jaundice)
- Coughing, trouble breathing
- Seizures
- Altered mental functioning

Other issues that your child's doctor may find include:

- Hepatitis
- Liver failure
- Low blood counts
- Enlarged liver
- Enlarged spleen

What tests are used?

HLH can only be diagnosed with proper blood tests. These tests may include looking at blood cell counts and for evidence of liver inflammation, as well as monitoring immune system activation through tests such as ferritin and soluble IL-2 receptor levels. A sample of bone marrow (where all blood cells are produced) may also be obtained to look for hemophagocytosis. Hemophagocytosis is when immune system cells "eat up" other cells.

A sample of spinal fluid may be collected if there is a concern about inflammation in the brain. Imaging tests, including X rays, CT scans, or MRI, may be done, as well as blood tests looking for infection or abnormal cells in the body. These can help in determining the causes associated with an episode of HLH. Additionally, testing for genetic causes of HLH may be ordered. Your physician can tell you more about these tests and what they mean for you.

How do we diagnose HLH?

Traditionally, HLH is diagnosed if at least five of these eight criteria are fulfilled:

- Fever (over 38.5 C)
- Cytopenias (low blood counts)
- Hemophagocytosis
- Elevated ferritin
- Enlarged spleen
- Elevated triglycerides, and/or low levels of fibrinogen
- Low or absent NK cell activity
- Elevated soluble IL-2 receptor

What are the types of HLH?

HLH is an immune disorder with two forms. Most commonly, HLH is due to an inherited (genetic) problem in the body's defense mechanism, known as the immune system. **This is called primary, or familial, HLH.** Most cases appear in early infancy or childhood, though some have been reported in adulthood. It is important to screen for these inherited genetic problems in all patients with HLH, as these mutations greatly increase the likelihood that HLH episodes will recur.

HLH can also occur when the immune system is disturbed (e.g., infections), but not necessarily because of an inherited condition. In these cases, the HLH can occur for a variety of different reasons and can be related to other underlying conditions including infections, cancer and autoimmune diseases, but not necessarily because of a genetic defect. **This is called secondary HLH.**

Both types of HLH are life-threatening. HLH can lead to liver failure, breathing problems, inflammation in the brain, and the inability to fight infection. Primary HLH happens more often in infants and children. But it can occur at any age, including in the teenage years and adulthood.

HLH survivor Jenna, age 4 from Georgia. Photo taken three years following a bone marrow transplant for HLH.

What genetic conditions cause HLH?

Primary, or familial, HLH is caused by inherited problems in genes that control how some of the body's defense system cells work. Scientists have identified mutations in certain genes that can cause HLH. These include PRF1, MUNC 13-4, STX11, and STXBP2.

There are several other very closely related conditions, which also predispose patients to recurrent episodes of HLH. These include X-linked lymphoproliferative disease, or XLP, which is due to mutations in the SH2D1A or XIAP/BIRC4 genes, Griscelli syndrome type II, which is due to mutations in the Rab27a gene, and Chediak-Higashi syndrome, which is due to mutations in the LYST gene.

Genetic testing for HLH can be performed in the Cincinnati Children's Hospital Molecular Genetics Laboratory. Results can take several weeks.

Why do these genetic mutations lead to HLH?

Genes provide instructions to cells in our bodies on how to function. When there are mutations in the genes mentioned above, they can cause problems in the way that the body's immune system cells work. T cells and Natural Killer (NK) cells are types of lymphocytes or white blood cells that help clear infected or damaged cells in the body. The T cells and NK cells in patients with primary/familial HLH can't kill virus-infected or other abnormal cells in the patient's body like they normally would. T cells and NK cells normally do this by secreting death signals into targeted abnormal cells. A defect in any part of this complex process can lead to an inability to destroy inflammatory cells. Because of this, the immune system can become overstimulated and over activated. The immune system then begins to damage the patient's own tissues and organs, including the bone marrow, the liver and the brain.

What are the differences in genetic mutations?

The proteins made by the MUNC 13-4, STXBP2, STX11, Rab27a and LYST genes work like the machinery of a conveyor belt, and are responsible for the secretion of the death signals out of T cells and NK cells. The PRF1 gene makes a protein called perforin. It works like a key, and allows the secreted death signals to enter inside a targeted abnormal cell, where the death signals can work. SH2D1A is responsible for a more specialized mechanism of killing, and also controls how the T cells themselves die. It is not yet entirely clear why XIAP/BIRC4 mutations cause HLH.

What about my other children?

If your child is diagnosed with primary HLH, then all your children should be tested, as the genetic defects are inherited and can be passed to siblings as well. Subsequent children should also be tested at birth. Technology exists that could help with diagnosis prior to birth. Discussion with a genetic counselor can help identify which is the right testing for you and your family.

How is HLH treated?

HLH is life-threatening and requires treatment. It is very unlikely to get better on its own. The goal of treatment is to decrease the body's overwhelming inflammatory response, and then to reset the immune system by suppressing it. Typically patients are treated with steroids, possibly with the addition of a second medication called etoposide. Other medications may be used as well if the inflammation is unable to be calmed down with this regimen.

Additionally, medications to specifically target an infection that may have initiated the HLH event may also be required. All of these drugs will depress the immune system and so, it is likely that medications to prevent infections will also be given.

With treatment, HLH may come under control after a few weeks. However, it may flare again later, especially as treatment is decreased and a patient may need further treatment.

Most patients with secondary HLH will respond to the immune suppressive medications, and will not have a repeat episode of HLH.

However, we know patients with primary HLH have a very high risk of recurrence even if we are able to fully control the inflammation of the initial episode, because they have an abnormal gene in their cells. Often, patients with primary HLH may need a bone marrow transplant (BMT) to replace their immune systems. Your doctor can tell you if this is the case for your child.

How is bone marrow transplant helpful for patients with HLH?

A bone marrow transplant (BMT) is a procedure to replace damaged bone marrow with healthy bone marrow cells. Bone marrow is the soft, fatty tissue inside your bones. Stem cells are immature cells in the bone marrow that produce all of your blood cells, including your white blood cells.

A BMT can provide patients with normally functioning macrophages and T lymphocytes, which will then be able to switch off at the right time and prevent further HLH episodes from occurring.

Sometimes, bone marrow transplantation may be recommended, even if no evidence of familial HLH is found. This is usually discussed if the inflammation is so severe that it cannot be controlled with the standard treatment, or if an episode is cleared but then recurs. Your doctor can tell you if this is the case for you or your child. Often patients who have a successful BMT go on to lead full, productive lives.

What about insurance issues?

The majority of insurance companies will cover treatment for HLH and genetic testing. It is important to contact your insurance company as early as possible once the diagnosis is suspected to discuss what coverages you have. Every insurance policy is different and may have specific rules. Your doctors and the team at Cincinnati Children's Hospital can help you understand insurance issues.

How can Cincinnati Children's help?

Treatment for HLH can take a long time. At Cincinnati Children's, there are many services designed to help make your stay with us easier during this difficult time.

Visit our website for more information on preparing for your visit.

For More Information

For more information about HLH and our current clinical research studies:

www.cincinnatichildrens.org/hlh

To connect with other organizations involved with HLH awareness and support:

Histiocytosis Association
www.histio.org

The Matthew and Andrew Akin Foundation
www.matthewandandrew.org

Liam's Lighthouse Foundation
www.liamslighthousefoundation.org

HLH Support for Families
www.HLHSupport.org
HLH Family (Survivors & Angels) Facebook group

National Bone Marrow Registry
bethematch.org

How can Cincinnati Children's help?

To inquire about treatment at Cincinnati Children's, contact:

HLH Center of Excellence
hlh@cchmc.org
513-803-3872 or 877-920-3590
www.cincinnatichildrens.org/hlh

On the Cover:

HLH survivor Hannah, age 10 from Florida. Photo taken four years following a bone marrow transplant for HLH.

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