6th Annual HLH Conference Notes 2015

By Kelly Marsh / September 2015

This is an annual conference, put on by the HLH Center of Excellence at Cincinnati Children's Hospital geared toward educating physicians about Hemophagocytic Lymphohistiocytosis.

If your hospital is interested in scheduling HLH grand rounds, please contact the HLH Center of Excellence at 855-346-6627. Also, for any and all information related to HLH, please visit the website, where you will find various diagnostic algorithms, genetic testing information and lab requisition forms. Julie Daisey is the coordinator and a valuable resource at CCH to get information to physicians and families.
www.cincinnatichildrens.org/**HLH**

What is HLH?

HLH is considered to be a life threatening uncontrolled genetic hyper-inflammatory disease which results from a failure in normal homeostasis. Basically, the immune system fires up, but unable to do targeted killing to the infection, and there is no command to stop firing. So with the immune system in overdrive, it tends to cause lots of collateral damage, with multi-organ failure and generally life threatening results. It is due primarily to genetic defects that affect lymphocyte function. It leads to low counts and multi-organ failure. HLH can be rapidly fatal, and without effective treatment most patients will die. Few physicians are knowledgeable, and a cure requires accurate diagnosis and timely therapy. What was once thought as a childhood disease, now affects people of all ages. The initial belief was that it affected 1 in 1.2 million children, is now more like 1 in 50,000.

Cincinnati Children's Hospital Medical Center (CCHMC) is the most experienced center in the United States in treating HLH. It's the only center offering genetic testing, and CCHMC performs the largest number of transplants for HLH annually in the United States. It also has the best success rates for Hematopoietic cell transplantation (HCT). There are 6 doctors there focused on HLH and research, and there is ongoing research regarding the development of an HLH Gene Chip, novel treatment protocol (HIT-HLH), and preclinical studies of gene therapy in PRF1 deficiency. CCH has the best success rates for HCT in the country.

Vision of CCH:

- Internationalize reach
- Increase capacity to treat HLH at CCHMC
- Increase awareness
- Train the Next Generation
- Extend scientific collaboration
- Increase research funding.
- Educate doctors
- HLH Conferences
- Work with other doctors who treat adult patients with HLH

Diagnositic Criteria:

Diagnosis of HLH is still a big challenge, because HLH doesn't go 'by the book', and there are various salvage therapies. CCH carries a vision to internationalize their reach, and increase capacity to treat HLH at CCHMC. The goal is to increase awareness through educating doctors, HLH conferences, and working with doctors who treat adults, then train the next generation, extend scientific collaborations, and increase research funding. Acquired cases of HLH do occur, however, it is believed that there is a genetic predisposition to getting HLH, and this area still needs research. Once believed to be only linked to children, it now seems to affect people of all ages. Tissues affected include bone marrow, lymphocytes, spleen, liver and brain.

The progression of HLH results in abnormal NK function, abnormal T Cell function, and abnormal macrophage function. Often there is a trigger, but not always. Triggers are often infection, and sometimes vaccines. There are a couple of categories with the initial onset of HLH. The first being what they call 'silent immune deficiency' resulting in low NK function. The second category shows significant immune activation, followed by fever, splenomegaly, elevated ferritin levels and elevated CD25. The 3rd category shows severe cytopenia and Hepatitis. There is a great article published by Dr. Jordan in Blood Journal "How I treat HLH" that explains the pathophysiologic view of HLH patterns, along with an article written by Dr. "Hemophagocytic Lymphohistiocytosis: Advances in Pathophysiology, Diagnosis, and Treatment" **Both of these articles can be found on the HLH Support website: http://www.hlhsupport.org/what-you-need-to-know.html**

There are several clinical signs of HLH, the main ones are fever, hepatitis (inflamation of the liver), splenomeglay (inflammation of the spleen), cytopenia (low blood counts), and neurologic dysfunction, low fibrinogen levels, elevated Ferritin and SIL2 levels, decreased NK cell function, as well as hemophagocytosis evident in biopsies of liver, spleen, and the bone marrow. Hemophagocytosis may not appear until later. **If Ferritin or SIL2R is not elevated, then HLH is unlikely.**

Some of the diagnostic obstacles the medical industry is facing is the fact that because of its rarity, HLH is still widely misdiagnosed. Some HLH patients do not meet the criteria until it's too late. Do not wait for diagnostic testing and genetic testing results, begin treatment right away.

Often the diagnosis depends on which doors the patient goes through (liver docs, infectious disease doctors) as it mimics other diseases. Then they wait for at least 5 of the 8 criteria to make itself present. Often intensive care measures are tried, but these will not reverse HLH, it may just cover it up making the diagnosis difficult. They stressed the importance of not waiting on genetic testing results to begin the HLH protocol, it could mean the difference between life and death. Without specific treatment, the median survival for patients with HLH has been estimated to be approximately 2 months. One of the reasons for early mortality after diagnosis can be attributed to organ damage, resistant disease, and secondary infections. Relapse can be very subtle and often the signs are missed. There is an HLH panel that can be useful as a checklist of test needed as part of the diagnostic testing that include SIL2, NK function, PRF/GRB genetic screening, and checking the Ferritin levels. Because HLH is often referred to as the silent killer, doctors are urged to maintain a high degree of suspicion for central nervous system involvement and should do MRIs and lumbar punctures as early as possible and then consider treating CNS disease without delay. Case in point, many patients with initial CNS involvement commonly come through the neurology door before HLH is diagnosed.

Treating HLH:

Treating HLH comes with many pitfalls as we all well know. Diagnosing it in a timely fashion is crucial and sometimes doctors are anxious about starting immune suppressive therapy in the face of cytopenia and infections. There could also be a undiagnosed underlying infection and then dealing with low blood counts.

There could also be damaging CNS involvement and the relapse of HLH could be subtle, that's why its so important to keep checking Ferritin and SIL2 levels because if there is a return of HLH, it could attack with a vengeance. Diagnosis/definitive treatment for HLH is often delayed because doctors are waiting for genetic testing to result, and that is one of the pitfalls in early death. Physicians are urged not to wait for the patient to meet each criteria, and should start the protocol immediately. Often times, there is acute liver failure, and there are 8 known cases of HLH where the patients went on to have liver transplants prior to the HLH diagnosis, and it's still being missed.

50% of HLH has a primary underlying genetic etiology (Genetic/Sporadic). It can depend on affected siblings, if mutations are identified, and the early age of the patient at the onset of the disease. Currently 70% of all HLH cases have identified genetic mutations. The top three include the Perforin, Munc and Syntax11 mutations, however, there are others such as the RAB27A, and STXBP2, SAH2 D1A, BIRC4, SAP and XIAP (Note: NK Cytotoxicty is normal in XIAP deficiency). Then there are HLH cases shown in males only where they are x-linked (XLP1 and XLP2 are some of the most common), but there is a newly discovered x-linked component (XLP3) that is being looked at. Also, almost all African and Hispanic ethnicities fall into the PRF1 genetic category. Apparently the rest of the 30% of Familial HLH, these mutations are not yet identified, but interestingly to know, they are almost all Caucasians. Note: Genetic testing can take approximately 8 weeks.

Future of Genetic Testing:

Cost of effective testing is very high, but they hope to identify additional FHL causing genes, and identify other genetic factors that may act as triggers of FHL. CCHMC is trying to identify additional FHL causing genes via whole exome sequencing by sequencing DNA. The challenge is how to manage and collect the data and how to tell us in a user friendly way of what it all means. They are also trying to identify genetic modifiers of HLH. Genetic testing is important to identify various gene panels. There are definitive known mutations, but approximately 20% of HLH cases have an unknown genetic mutation. Cincinnati Children's is the ONLY lab in the country that tests for HLH genetic mutations. There is single gene test, a multi gene panel, whole exome sequencing, and whole genome sequencing available. The advantages of testing can determine the cause of the HLH which then directs the right treatment. It also provides information for the family and helps to determine recurrence risk. The disadvantages of testing is the psychological distress that a diagnosis can bring, the variants of uncertain significance, incidental genetic finding, and concerns about insurance. One of the ways to progress HLH mutation efforts is RESEARCH and we need more of it, so we all can do our parts by helping to raise funds for this research, and supporting foundations and organizations that contribute directly to research, because as you are likely aware, HLH gets no government funding, because it's considered an orphan disease and affects too few people. We have seen over the years, that the numbers are not as rare as first thought, it's just rarely diagnosed, because it's mis-diagnosed!!

History of HLH

Apparently in 1939, there was possibly the first form of familial HLH. In 1952, there were some documents noted that recognized FHL as a rare and invariably fatal condition, diagnosed post mortem. In the 1970s, treatment attempts begin. The first successful treatment of HLH was with VP-16 (Chemo: Etoposide) in 1980. Then in 1986, they had the 1st successful BMT. Then in the early 90s, the HLH-94 protocol was introduced with included Etoposide and Dexamethasone). In 1993, ATG was introduced and reported by some of the European nations to be an effective treatment, and then with the newest protocol (HLH-2004), Cyclosporine was added. They went on to discuss studies coming out of France, that is showing use of ATG in their protocol having better success, but having a higher chance of relapse. Patients tended to go to transplant very early, and there was a higher death from toxity from the drugs with a 50% survival rate. In addition to early death, reactivation is a significant issue that could contribute to post transplant fatality. Since 1999 additional genetic mutations

are found, and 70% of HLH have an identified genetic mutation. Excessive activation of CD8+ T cells drives HLH.

HLH Protocol:

Currently, the HLH94 Protocol (Etoposide/VP-16 and Dexamethasone) is considered the standard of care. It has a 20 year track record and has the strongest data to support it, and although the 2004 protocol includes Cyclosporine to bring the disease into remission, Cincinnati has not been using this as a standard because it is not clearly justified. There is much toxicity concerning PRESS and ARF (Acute Renal Failure). Cylosporine is usually introduced a few days after the transplant itself. ATG/Prednisone may be considered though not considered the standard of care (not enough data).

If there is significant renal failure, then that may justify Etoposide dose reduction because it is secreted through the kidneys and in turn could cause more damage. They indicated the importance of monitoring a response to the protocol by checking things weekly, such as the Soluble IL2 and ferritin. The testing time for SolubleIL2 is approximately one week turn-around time. These are considered good markers to check for active disease. Often low counts could also mean creeping relapse. Also, treatment of underlying infections is definitely warranted as the initial trigger of HLH could include various infections such as EBV, CMV, etc.) Supportive care is also important (IVIG, antivirals, antifungals). Serial disease monitoring is equally important by tracking SIL2, SCD25, ferritin levels is a valuable guide to see if therapy is working). Requisition forms are on the HLH Center of Excellence website on the Physician's link. Repeat labs can be drawn, and there is a phone number on the lab requisition forms available for physicians to call the lab directly for results.

Resistant disease warrants salvage therapy (Campath, aka Alemtuzemab). There is a need for salvage therapy in 30% of patients when they do not respond to the HLH protocol. Usually they would see a response with 2 weeks of being given Campath. It appears to be reasonably safe for refractory HLH, and often used as RIC-HCT. Ideally the patient needs to be depleted of T-cells before heading to transplant.

Current Trial Open for Anti– interferon Gamma therapy

Hybrid Immunotherapy Trial (HIT)-HLH Studies

It has been discovered that elevated levels of Interferon Gamma has been found in HLH patients. **There is a open trial through NovImmune that targets Interferon Gamma and suppresses it showing very good results in HLH treatment**. They have trials now open in Europe and various locations in the US.

Balancing toxicity with efficacy

- Etoposide, myelosuppression, secondary AM
- ATG/Campath, global, prolonged suppression
- Dexamethasome – Long term adverse effects

NovImmune Commitment:

- Who is NovImmune? They create antibodies for immune diseases
- Since 2008, NovImmune has been dedicating resources to the development of a targeted therapy for HLH: NI-0501
- In January 2013, the first investigational site of the pilot study in HLH patients was open for recruitment.

- Requirements for a successful development of a new targeted therapy for HLH
    - Generate robust data on the safety and efficacy of NI-0501
    - Validation of the data by the scientific community
    - Obtain the active support from the treating physicians and the parent/patient associations

What is the NI-O501 study?

The purpose of this study is to assess the safety, tolerability and preliminary efficacy of a new drug aimed at controlling disease reactivation in patients diagnosed with primary **haemophagocytic lymphohistiocytosis** and having previously shown partial response to current recommended treatment. The new drug will be administered on top of a glucocorticosteroid, which is usually part of the current recommended treatment. Phase III of the trial is ahead and has shown great recourse. ***If you qualify for the study, and are interested in participating, and are willing to go to one of the approved treatment facilities, please go to HLH Support for the link. See below.***

http://www.hlhsupport.org/what-you-need-to-know.html

When to Go to Transplant:

When HLH genetic testing comes back as positive, especially with FHLH markers, the disease WILL come back. Other factors include a family history of HLH, persistent low (decreased) NK function, an incomplete response to therapy, if the disease recurs and especially if the patient is under 2 years of age.

Myeloablative Conditioning Prep is rarely used, unless there is no other option, because of high rate of fatality. Outcomes are better with Reduced Intensity Conditioning (RIC):

History of RIC:

The Reduced Intensity Conditioning (RIC) was introduced at CCHMC for HLH in April of 2006. They said that mixed chimerism (mixed engraftment) is more common in patients receiving the proximal Campath with RIC, whereas Acute GVH tends to be less common in patients receiving the proximal Campath. When using cord blood, the RIC is avoided at all costs and the Myeloblative prep is the regimen they use. It was also noted that cord blood is the last optimum type of transplant method for HLH.

Complications of RIC

- Increased viremias (CMV, EBV, Adenovirus) – close monitoring is needed, weekly PCRs.
- Mixed Chimerisms: 100% donor chimerism is not needed. Many of you have asked about mixed chimerisms (a mixture of donor/recipient cells) and this is the latest information to come out of Cincy. 10-20% is okay, it all depends on the T cell count. The risk of return of HLH is substantial in you fall below this number. One patient had 25 – 28% mixed chimerism and developed recurrent HLH. The important thing to note is that aggressive monitoring of chimerisms should be done once/twice a week, for at least 6 months. We have been horrified to learn of other hospitals waiting upwards of 3 to 6 months before checking engraftment again and this is early on after transplant. This makes me sick to my stomach knowing that many of these families will be going through the BMT process AGAIN due to lack of care. The loss of time in between these engraftment checks interfere with treatment, and may

go on to have a 2nd or 3rd transplant and needlessly. If engraftment is checked frequently, DLIs (boost of cells) can be given to jump start their system. The minimum level of chimerisms needed to control HLH and the answer is considered to be around 20%. DLIs should not be given just because engraftment is dropping. This is why it needs to be closely monitored. Holding engraftment numbers in the 90s is absolutely incredible, so are the 70s and 80s. When engraftment numbers start trending downwards steadily and reach the 20s or 30s, that's when a boost of a Donor Leukocyte Infusion (DLI) is considered.

We've seen it time and time again from patients that are holding in the 20s with no return of HLH. Also, DLIs should be given and then wait a period of a month at minimum to wait for engraftment changes. It can take a while for cells to make their way and mature enough to be seen on test results. If there are HLH symptoms that come hand in hand with low engraftment numbers, it can be verified and checked doing Soluble IL2 testing, as this is one of the true markers for HLH, and not necessarily based on Ferritin numbers. Ferritin numbers can be skewed by medications given after transplant like anti-fungal medications. **Be vigilant and get educated.**

As you can see, there is so much knowledge shared about HLH, not only to physicians but also to other HLH families. This is my 6th year in attendance and each time I go, I learn something new and obviously meet many more affected families. It's wonderful to meet other survivors, and also to give hope to those about to embark on the same journey. Knowledge really is power, and for HLH, which was once thought to be universally fatal, now has a fighting chance.

Last, but certainly not least, is the development of the HLH Center of Excellence. "As the most experienced facility in the nation in treating HLH, Cincinnati Children's Hospital has assembled a team of researchers, physicians, families who have faced an HLH diagnosis, and philanthropists to create the HLH Center of Excellence at Cincinnati Children's Hospital Medical Center. The center focuses on four core priorities: Research, Clinical Care, Education, Family Support. The discovery, innovation, and improved care that will develop from the HLH Center of Excellence will save lives, and change the outcome for children and families faced with this devastating disease." We are so excited to see the development of this center and thrilled to being a part of it. When I created the HLH Family group on Facebook years ago, I never would have imagined that we would grow from just a handful of members, to now over 1,400. People are hearing about the group, they are reaching out, and they are getting the help they need. It is so fulfilling knowing that we can reach out to other families and let them know they are not alone. Please, do us a favor, if you hear about other HLH families, let them know there is help out there, tell them about the HLH family support group, and share all the success stories. . . . Often, that's all they need to know . . . that there is HOPE!