A Multidisciplinary Approach to a Complex Clinical Syndrome

Hemophagocytic Lymphohistiocytosis in Adult Patients

University of Texas Southwestern Medical Center

Internal Medicine Grand Rounds

September 8, 2017

Christian A. Wysocki M.D., Ph. D.

Division of Allergy and Immunology, Department of Internal Medicine

UT Southwestern Medical Center

Dallas, Texas

(On behalf of the Adult HLH/MAS Task Force)

Adult-hlh-mas@lists.utsouthwestern.edu

This is to acknowledge that Christian A. Wysocki, M.D., Ph.D. does not have any financial interests or other relationships with commercial interests related directly or indirectly to this program. Dr. Wysocki will not be discussing off-label uses in his presentation.

Purpose and overview:

Hemophagocytic lymphohistiocytosis (HLH) and Macrophage activation syndrome (MAS) are complex hyperinflammatory syndromes difficult to distinguish from issues such as sepsis, as the root cause (high level proinflammatory cytokine production) is very similar. This causes confusion among treating physicians, as well as diagnostic/treatment delays. Furthermore, in adult patients, HLH is often associated with hematolymphoid malignancies, and a thorough search for these should be undertaken in patients in whom HLH is suspected or diagnosed so as to best direct treatment. The treatment of HLH in children (in whom genetic defects in T cell function often underlie the disease) is standardized and protocol driven. In adults, it is currently quite variable, in part due to the variability in underlying causes. The delays in diagnosis, the frequent associations with malignancy, and the variability in treatment approaches all contribute to poorer mortality in adult HLH patients. Recognizing the need for a consensus, multidisciplinary approach to these complicated patients, and the need for research to better their care, we have created a multidisciplinary working group, which is accessible to all physicians at UT Southwestern and Parkland.

Learning objectives:

1. Understand the pathophysiology of Hemophagocytic lymphohistiocytosis (HLH) and Macrophage activation syndrome (MAS).
2. Understand the clinical presentation of HLH/MAS.
3. Understand the diagnostic criteria and lab evaluation for HLH and MAS.
4. Understand the illnesses which can predispose to HLH in adults.
5. Understand how to contact/mobilize the HLH/MAS task force to aid in the evaluation, treatment, and study of these patients.

Introduction

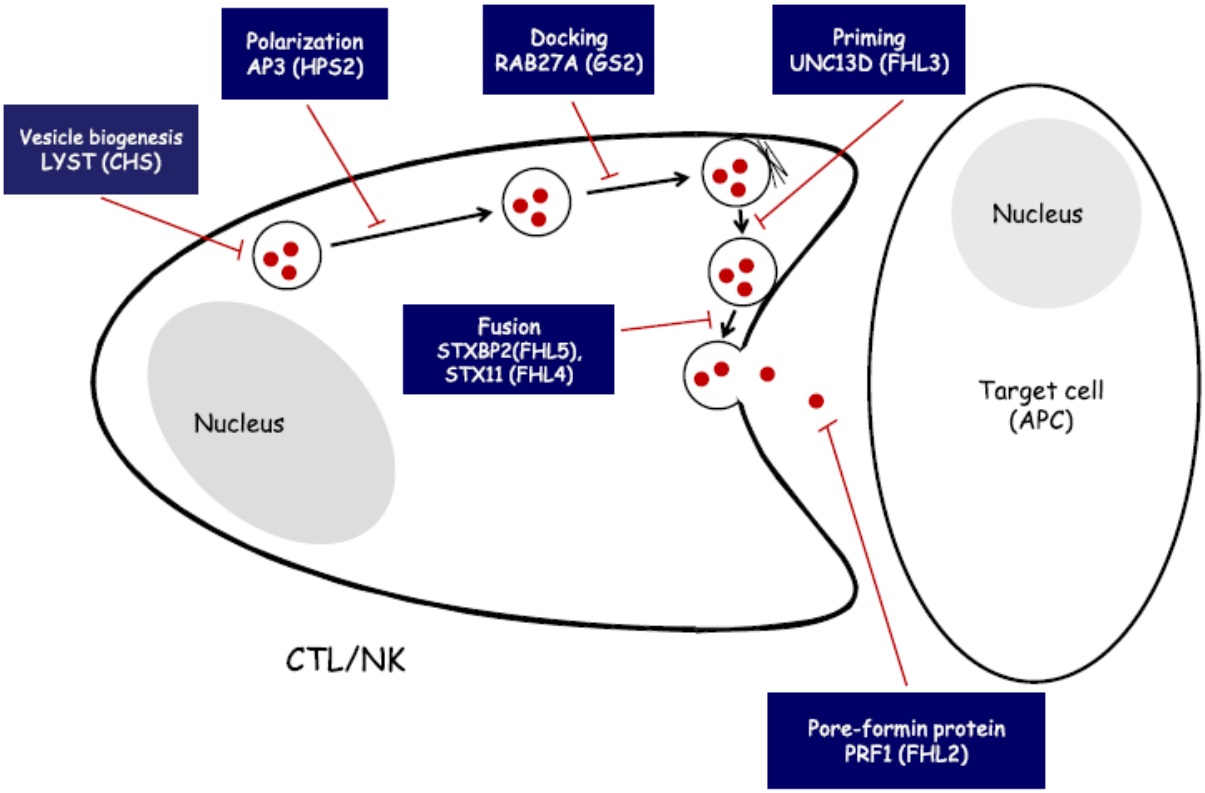
In 1939, Scott and Robb-Smith, while seeking to characterize unique clinicopathologic entities within the wastebasket previously "dismissed as atypical Hodgkin's disease", described 10 cases of "histiocytic medullary reticulosis"[1]. Their cases were all adults ranging from 26 to 69 years in age. The disease was uniformly fatal and characterized by fever, wasting, splenomegaly, lymphadenopathy, anemia, purpura and jaundice. On autopsy, they observed "systematized proliferation of erythrophagocytic histiocytes and their precursors throughout the lymphoreticular tissue." The newly described Reed-Sternberg cells were noted in some patients. Farquhar and Claireaux are credited with the first report of familial hemophagocytic lymphohistiocytosis (FHL) in infants in 1952[2]. The patients were siblings, a male and a female, born to healthy (possibly consanguineous) parents. The syndrome was similar clinically and pathologically to that described by Scott and Robb-Smith. They renamed the disease "hemophagocytic reticulosis."

Much has since been learned about the genetics and pathogenesis of FHL. It has additionally become clear that a similar syndrome does occur in pediatric and adult patients who are not genetically predisposed. We continue to learn about the similarities and differences between the genetic forms of this disease, and forms which are secondary to other predisposing factors such as malignancy, autoimmunity, infection and other immunologic stimuli. We continue to debate whether the illness in adults is the same, thereby warranting the same diagnostic and treatment strategies, as in children.

Pathophysiology and clinical features of HLH

Hemophagocytic lymphohistiocytosis (HLH) represents a severe inflammatory syndrome caused by impaired regulation of the immune response. Familial HLH is caused by mutations in genes, including *UNC13D, STX11, STXBP2, RAB27A, LYST, AP3B,* which encode proteins involved in cytotoxic granule formation, trafficking or release, or encode granule contents themselves (PRF1) (reviewed in[3]) (Figure 1). Mice with deficiencies in PRF1, STX11, Rab27a, LYST or AP-3, which develop HLH in the setting of lymphocytic choriomeningitis virus (LCMV) infection, have been helpful in understanding the mechanisms of HLH. Through studies in perforin-deficient mice, CD8+ T cells and IFN-gamma were shown to be essential for disease[4]. Furthermore, dendritic cells (DC) were found to be the crucial antigen presenting cells in this disease. The cytotoxic function of CD8+ T cells is shown to regulate the number of DCs presenting viral antigen, such that in the setting of perforin-deficiency a larger number of DCs are actively presenting viral antigen[5]. Comparison of mice deficient in PRF1, LYST, Rab27a, STX11 and AP-3 showed that the severity and timing of disease correlated with the degree of impairment in cytotoxicity, and persistence of viral antigen. A similar severity gradient was demonstrated in human disease caused by these various mutations[6]. Thus, impaired cytotoxic function in CD8+ T cells leads to persistence of DCs presenting viral antigen thereby resulting in exuberant production of cytokines (including IFN-gamma, IL-6, and TNF-alpha)[7], and an infiltrative process with hyperactivated macrophages and histiocytes. Other genetic defects causing HLH include *SH2D1A, BIRC4, ITK, CD27* and *MAGT1*, which encode signaling proteins involved in optimal activation and priming of this pathway, as well as survival, differentiation and migration of T and NK cells. Abnormalities in these genes result in susceptibility to HLH and lymphoproliferative disease (reviewed in[8]).

Figure 1. Genetic mutations in familial HLH, affecting trafficking and exocytosis of cytotoxic granules. (*Parvaneh N, et al 2013 British Journal of Hematology*).



The pathophysiology of non-genetic (secondary) HLH is less clear. Multiple potential mechanisms are felt to contribute. These include abnormal immune activation, antigen persistence and cytokine production due to hematolymphoid malignancies and the response to them, hyperactive cytokine production in patients with autoimmune disease, immune derangements caused by immunosuppression or chemotherapy, and other unknown environmental factors causing overly exuberant inflammatory responses to infection and other triggers (reviewed in [9]).

Characteristic clinical features of HLH include persistent fever (caused by IL-1, IL-6 and TNF-alpha), splenomegaly, cytopenias (due to both cytokines and hemophagocytosis), hepatitis, and central nervous system dysfunction[10]. TNF-alpha inhibits lipoprotein lipase and causes triglyceride elevations, while secretion of plasminogen activator by hyperactivated macrophages causes fibrinolysis and coagulopathy[11]. Cytokine-mediated and infiltrative organ damage may be widespread. Patients frequently become critically ill and require ICU-level care[12,13]. The disease is almost universally fatal if left untreated.

Diagnosis of HLH

In 1991, the FHL study group of the Histiocyte Society, recognizing that the diagnosis of HLH was all too frequently made postmortem in infants and children, proposed a set of diagnostic criteria, geared toward earlier diagnosis[14]. They drew upon clinicopathologic data from two large studies in children[11,15]. The criteria included "Clinical and lab criteria" (persistent fever, splenomegaly,

cytopenias, hypertriglyceridemia and/or hypofibrinogenemia) and "Histopathological criteria" (hemophagocytosis in biopsy specimens). In 2004, these diagnostic guidelines were revised for use in the HLH2004 trial[16] (Figure 2). There were additional clinical and lab findings added as minor criteria. These included hyperferritinemia, elevated soluble IL-2 receptor alpha (sIL2R) levels, and depressed natural killer cell (NK cell) cytotoxic activity. They also include genetic testing, which is considered the only major diagnostic criterion.

Figure 2. HLH2004 Diagnostic Criteria.

The diagnosis of HLH† may be established:
A. Molecular diagnosis consistent with HLH: pathologic mutations of *PRF1*, *UNC13D*, *Munc18-2*, *Rab27a*, *STX11*, *SH2D1A*, or *BIRC4*
or
B. Five of the 8 criteria listed below are fulfilled:
1. Fever ≥ 38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)
Hemoglobin < 9 g/dL (in infants < 4 weeks: hemoglobin < 10 g/dL)
Platelets < 100×10^3/mL
Neutrophils < 1×10^3/mL
4. Hypertriglyceridemia (fasting, > 265 mg/dL) and/or hypofibrinogenemia (< 150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Low or absent NK-cell activity
7. Ferritin > 500 ng/mL‡
8. Elevated sCD25 (α-chain of sIL-2 receptor)§

One important difference in the performance of these diagnostic criteria between pediatric and adult patients pertains to the serum ferritin. A pediatric study[17] showed that ferritin >10,000 was 90% sensitive and 96% specific for HLH. The median maximal ferritin for HLH patients was 15,830, whereas maximal ferritins in other conditions such as chronic transfusion (1,775), liver disease (1,262) and renal disease (660) were substantially lower. This study is cited widely as indicating a high specificity of ultra-elevated ferritin for HLH. However, more recent studies addressing the specificity of ultra-elevated ferritin for HLH in adults[18-20] showed that HLH occurred in only 3-17% of these patients. More common causes of the hyperferritinemia were renal failure, acute liver injury, infection, and hematologic malignancy. Thus, while HLH is clearly on the differential diagnosis in adult patients with ultra-elevated ferritin levels, this laboratory finding is less specific for HLH in adults than in children.

HLH2004 criteria are used almost universally in both the pediatric and adult studies discussed above. As they were developed using data from pediatric studies, the validity of HLH2004 criteria in adult patients has been questioned, and there have been recent attempts to develop criteria more appropriate for adult patients. Notably, the necessity of both the sIL2R level and NK cell cytotoxicity assay in adult patients has been questioned, and note is frequently made of the limited availability of these two tests outside of major medical centers. Several new diagnostic criteria have been proposed recently for use in adult patients in order to allow for earlier detection. These include the Hscore[21], the BM score[22], and a set of clinical criteria for detection of malignancy-associated HLH which are currently being prospectively evaluated in comparison to HLH2004 criteria[23] (and reviewed in[24]). All have shown utility in early

detection of HLH (or malignancy associated HLH). However, the optimal cutoff Hscores have been quite variable between studies, the specificity of the BM score (75%) may not be optimal, and the performance of the malignancy-associated HLH criteria have as-yet only been examined retrospectively. Further validation of these criteria will be necessary to truly determine their clinical utility. In addition, there is clear utility in including the sIL2R level in the evaluation of HLH, in both children and adults, as studies in both populations have shown it to provide useful information on prognosis and response to therapy (reviewed in[25]). Others have shown the sIL2R/ferritin ratio to be a predictor of lymphoma associated HLH in adults[26,27].

NK cell cytotoxicity assays are being replaced by more reliable flow cytometry-based assays[28], which should still be included whenever possible in the evaluation of HLH as they may be the first indication of genetic defects in cytotoxic function. The role of genetic diagnosis in adult patients is still unclear and genetic testing is not routinely performed in adults. As discussed below, a surprising proportion of adults were found to have mutations in FHL genes, although many were uniallelic and of unclear relevance to the disease. More study is necessary to determine the clinical relevance of these mutations in adults, as their presence could potentially alter decisions regarding chemoimmunotherapy and transplant.

Genetic versus secondary disease

The most intuitive difference between pediatric and adult HLH, is the frequency of genetic disease. The frequency of mutations in adults with HLH is substantially lower than in infants. Adult HLH is generally presumed to be secondary to non-genetic factors which will be discussed below. A recent study of 1531 patients referred to a single institution for genetic testing due to suspected HLH demonstrated the differences in frequency and nature of FHL mutations in children and adults[29]. The highest frequency (44%) was noted in infants (0-1 years old). Somewhat surprisingly, in patient's 18 years and older (ranging from 18-74), mutations were found in 14%. Mutations in adult patients tended to be missense and splice site mutations as opposed to the nonsense mutations found in younger patients. A specific mutation (A91V) in PRF1, which is known to be a hypomorphic variant, comprised 48% of mutations in adults. More than half of mutations in adults were uniallelic, and role of these uniallelic mutations in disease causation is unclear. Interestingly, uni- and biallelic mutations in FHL genes such as PRF1, have been shown in adult lymphoma patients at a fairly high rate (pathologic PRF1 mutations in 8% of Chinese lymphoma patients[31]), arguing that these may contribute not only to adult HLH, but to the associated malignancies in presumed “secondary HLH” in adults. Similar results were noted in a study of 252 adolescent and adult patients in China[30] in which 6 HLH mutations were found in 18 (7.1%) of the patients overall with 14% of the adolescent patients and 5.1% of adult patients having mutations. Seven of the 18 patients (39%) had biallelic mutations (ranging in age from 13-54 years).

Secondary or Acquired HLH

Secondary HLH accounts for the majority of HLH in both pediatric and adult patients. This often involves underlying comorbid illnesses, often hematolymphoid malignancy, immunodeficiency, autoimmune disease, or secondary effects of immunosuppressive medications or chemotherapy. It is frequently triggered by infection. Viral infections are the most common trigger of HLH, but bacterial, mycobacterial, fungal, parasitic and protozoal infections may all play a role, as may drug hypersensitivity reactions and other hyperinflammatory states such as transplant rejection and graft-versus host disease (reviewed in[9]).

Differences in the comorbid illnesses and triggers in pediatric and adult patients are notable when reviewing large cohort studies. The largest and perhaps most comprehensive, was a nationwide survey of HLH in all ages in Japan, allowing direct comparisons[32]. Pediatric patients made up 60% of the 567 evaluable HLH cases, adults 40%. FHL was diagnosed in 20 patients, almost exclusively infants. Notably, lymphoma-associated HLH, which occurred in 108 patients, occurred exclusively in adult patients. HLH associated with autoimmune disease occurred in a similar proportion of pediatric and adult patients (10% of pediatric patients, 8.5% of adult patients). Infection associated HLH (particularly EBV-driven), occurred with a substantially higher frequency in pediatric patients. Specifically, 68% of patients less than 15 years old had infection associated HLH versus 33% of adults. Overall survival was similar for patients with EBV-driven HLH (82%), other infection triggered cases (89%) and autoimmune disease associated HLH (89%). Overall survival for B cell lymphoma associated HLH was 42% and T/NK lymphoma was 12%.

Reviewing additional adult and pediatric HLH studies, it is apparent that malignancy-associated HLH is more frequently reported in adult patients, ranging from 29% to 57% of all cases with the majority of malignancies being lymphomas[12,13,33-36]. This is substantially lower in pediatric studies, in which the rate of malignancy in children with HLH ranges from 0 to 21%, although in some studies it is either not reported or patients are specifically excluded for associated malignancy[37-41]. The increased frequency of lymphoma-associated HLH in adults likely reflects the increased prevalence of lymphoma in adults versus children in general[42]. One recent study on malignancy in pediatric and adolescent HLH found 8.4% to have associated malignancies[43]. Like adults, most had T or B cell lymphomas. Another similar study differed somewhat, finding the majority of malignancies in pediatric HLH to be ALL or AML, with only 4 out of 29 patients in the study having lymphoma[44]. In both studies, a substantial proportion of malignancy-associated HLH occurred during treatment of the malignancy and was felt to reflect the increased infectious susceptibility imparted by chemotherapy. Mortality in malignancy-associated HLH is universally higher than non-malignant HLH, both in adult patients[12,13,32,34-36] and in children[39].

Regarding autoimmune-associated HLH and MAS, the specific autoimmune diseases differ somewhat between pediatric and adult patients. This is related to the prevalence of specific autoimmune diseases in these populations, with systemic onset juvenile idiopathic arthritis and Kawasaki disease being the most prevalent in pediatric HLH patients and systemic lupus erythematosus, adult onset Still's disease, and rheumatoid arthritis being most prevalent in adults. As discussed above, the nationwide survey by Ishii et al indicated substantially better overall survival in this group. Furthermore, patients with MAS often require less intensive treatment[39].

Treatment and outcome

Management of pediatric HLH is quite protocol driven at this point. Most centers primarily use the HLH94 protocol[38], which is an 8-week treatment cycle consisting of tapering doses of Dexamethasone and Etoposide, with intrathecal Methotrexate included for patients with CNS involvement. In FHL patients, this treatment regimen is generally used as a bridge to allogeneic bone marrow transplantation, which is curative and generally required to prevent lethal recurrences in these patients. Five-year overall survival with HLH94 was 54%. Notably, 124 patients went on to transplant, which improved 5-year survival to 66%[38]. A discussion of other treatment and salvage protocols for pediatric HLH is outside the scope of this protocol (reviewed in[45]).

Treatment of adult patients is much more variable. This is highlighted in a recent study from Mayo Clinic in which 14 different treatment approaches were documented in 62 adult HLH patients[35]. Malignancy-associated HLH tended to be treated with a chemotherapy regimen specific to the malignancy, with or without the addition of etoposide. HLH94 alone was used in only two of the 30 malignancy-associated HLH patients in that study. Three cases of HLH associated with EBV driven

posttransplant lymphoproliferative disorder were treated with rituximab alone. Treatment of non-malignancy-associated HLH was highly variable and ranged from supportive care-only in two patients, steroid plus or minus IVIG or cyclosporine (without etoposide) in 14 patients, antimicrobial therapy with or without steroid in 7 patients, and HLH 94 (with or without antimicrobial therapy) in 14 patients. Other adult cohort studies document between 6 and 14 different treatment protocols per study[13,33-35].

The frequency with which allogeneic bone marrow transplant is performed in adult HLH patients is substantially lower than in pediatric patients. In the 3 adult studies in which patients underwent bone marrow transplantation, the frequency of transplantation was 1-6% of all patients. The number of patients transplanted was reported in 5 of the 6 pediatric studies, ranging from 3-50% of patients. As discussed above, transplant was shown to improve overall survival in pediatric HLH patients in the HLH94 study[38]. Survival with transplant ranges from 64-76% in the pediatric studies above [32,37-40]. However, numbers of successful transplants are too low to reliably determine the impact of transplant on survival in adult HLH.

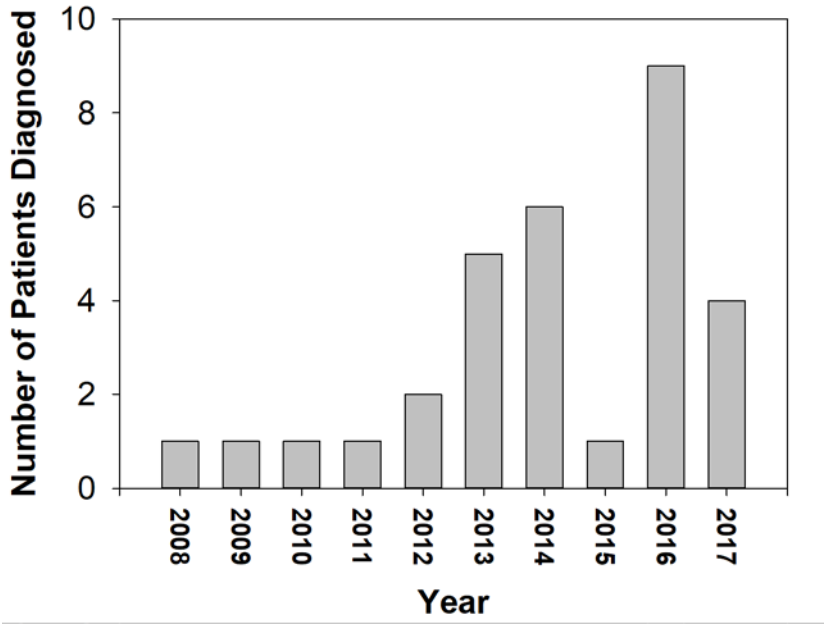
Although direct comparisons are difficult, overall mortality seems to be higher in adult patients in general. Mortality in the adult studies ranged from 42-75% (30-day mortality ranging 20-27%). Median follow up time was highly variable ranging 4.3 to 42 months. Mortality in the pediatric studies ranged 29-46%, with median follow up times ranging 3 months to 6 years. The best direct comparison is found in the Ischii study[32] in which survival was significantly longer in EBV-driven HLH (which made up the largest subgroup) in patients ages 0-14 years (87.3% 3-year OS) as compared to those 15-29 years (68.8%), 30-59 years (66.7%), and 60 years or older (50%) (p=0.0298). Three-year OS was worst in lymphoma-associated HLH (ranging 15-25%), which was exclusively seen in adult age groups. Thus, while other age-associated factors and comorbidities likely contribute as well, the higher frequency of malignancy-associated HLH accounts, in part, for the poorer overall survival in adults with HLH.

The UT Southwestern/Parkland Experience

We have performed a 10-year retrospective chart review of all patients at St. Paul Hospital, Zale-Lipshy, Clements University Hospital and Parkland, who received diagnosis codes for HLH/MAS (ICD9 288.4, ICD10 D76.1 and D76.2) between 6/30/2007 and 6/30/2017. 41 patients were identified. Upon chart review, 10 patients were excluded – 2 due to insufficient records (having been treated in 2007 before notes were available in EPIC), 5 due to their having been diagnosed and treated at outside facilities and having had only outpatient follow up at UT Southwestern or Parkland, 1 patient due to HLH having been ruled out and the diagnosis never formally given, and 2 because although they were given the diagnosis of HLH, they did not meet HLH2004 diagnostic criteria. This left 31 patients who were given the diagnosis by the treating team and met HLH2004 criteria. Of these, 10 patients were from UT Southwestern Hospitals and 21 patients were from Parkland.

The diagnoses were substantially more frequent after 2011, and rose persistently through 2016 (with the exception of 2015, in which only one patient was diagnosed). In 2016, there were 9 patients diagnosed, and we are on pace to match this is 2017. Estimating 50,000 admissions per year between UT Southwestern and Parkland, this equates to a frequency of 1: 5,555 inpatient admissions (comparable to that seen at Mayo clinic, which was 1: 2,000)[35] (Figure 3.).

Figure 3. Year of diagnosis of HLH patients at UT Southwestern and Parkland.



The distribution of causes of HLH is shown in Table 1. Like other studies in the literature, malignancy-associated HLH was seen in 47% of our patients, with T cell lymphoma being the most common associated malignancy. Infectious triggers (without associated malignancies or autoimmune disease) were seen in 35% of patients and autoimmune disease was felt to be the cause of HLH in 9.6%. Notably, infectious triggers were seen in malignancy-associated HLH and autoimmune associated HLH as well.

Malignancy-associated (n=15, 47%)	
T cell lymphoma	6 (40%)
Hodgkins lymphoma	3 (20%)
B cell lymphoma	2 (13%)
AML	2 (13%)
Multicentric castleman's	1 (6.7%)
Neuroendocrine tumor	1 (6.7%)
Infection-only (n=11, 35%)	
EBV	3 (27%)
Histoplasmosis	2 (18%)
Mycobacterium kansasii	2 (18%)
HHV6	1 (9%)
Parainfluenza	1 (9%)
MSSA pneumonia	1 (9%)
HIV+HBV	1 (9%)
Autoimmune (n=3, 9.6%)	
SLE	2 (67%)
Adult onset Still's	1 (33%)
Idiopathic (n=2, 6.4%)	

Table 1. Causes of HLH at UT Southwestern and Parkland

The median overall survival in our cohort was 8 months (Figure 4.). As has been shown previously, malignancy-associated HLH carried a significantly worse prognosis with median survival 0.56 months versus 36.5 months in non-malignant HLH (p = 0.002) (Figure 5.).

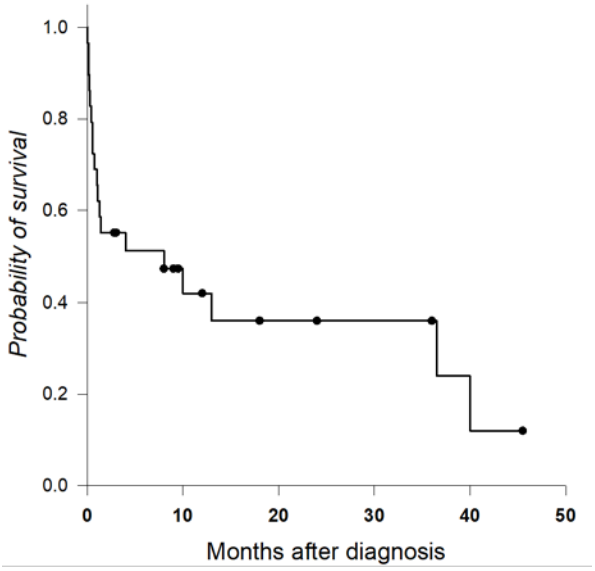


Figure 4. Kaplan-Meier survival curve (all patients). Median survival 8 months.

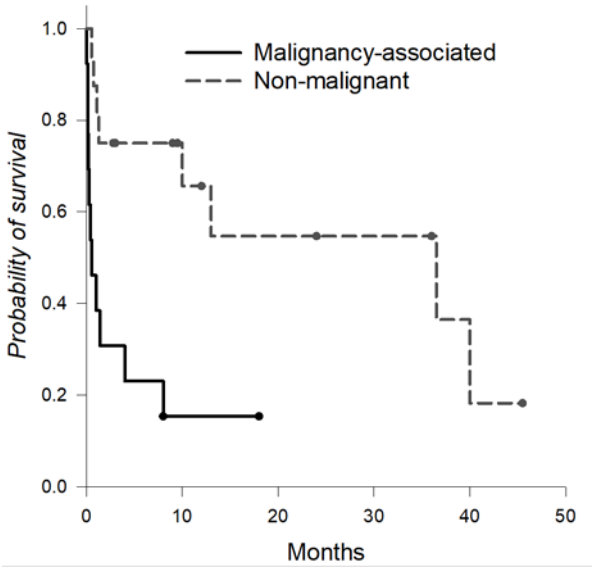


Figure 5. Survival of patients with malignancy-associated HLH versus non-malignant HLH. Malignancy associated HLH patients had median survival 0.56 months, versus 36.5 months in non-malignant HLH (*P*=0.002).

Time to diagnosis was slow, with the mean time to diagnosis being 10.5 days after admission. Time to treatment was similarly delayed (10 days after admission). Interestingly, the time to meet HLH2004 diagnostic criteria, while delayed (8.4 days after admission) was shorter than both time to formal diagnosis and time to treatment, arguing that there were either or both delays in lab or pathology result

reporting, or delays in recognition by the treating medical team that criteria were met. Univariate and multivariate analyses for other clinical parameters contributing to prognosis are under way but the data are not yet available.

Treatment was highly variable, with 13 different medications used in various combinations. Notably, only 7 out of 31 patients received etoposide, which forms the backbone of the HLH94 protocol received by nearly all pediatric patients.

The HLH/MAS task force

In February 2017, recognizing the need for better and more efficient multidisciplinary care of these very complex patients, we created a working group or "task force," which includes clinicians from the divisions of Allergy and Immunology, Hematology and Oncology, Infectious Diseases, Rheumatology, Pulmonary and Critical Care, Bone Marrow Transplant, Digestive and Liver diseases, as well as members of the Dermatology and Pathology departments.

Our objectives center around the study of adult HLH and MAS patients and the optimization of their diagnosis and treatment, with the goal of improving outcomes. Our first objective was to complete the retrospective analysis of HLH/MAS patients at UT Southwestern Hospitals and Parkland, described above. This should allow an accurate assessment of the patient populations, the historical outcomes, and the deficiencies which we may improve upon to optimize care. Furthermore, we hope that this retrospective analysis will illuminate areas of future research, both clinical and translational.

We are also synergizing with an analogous multidisciplinary task force, created in Pediatrics, at Children's Medical Center Dallas, to compare clinical experiences and combine research efforts. We are meeting quarterly with this group (which was established approximately 1 and a half years ago), and two of our members are also members of the pediatric task force. The pediatric task force is in the process of optimizing a best practice alert in EPIC, for patients with persistent fevers an cytopenias, which may facilitate early diagnosis. We hope that our two task forces cross-pollinate and that both sides see improved outcomes as a result.

Our retrospective analysis showed significant diagnostic delays (mean 8 days to achieve HLH2004 criteria and 10.4 days for the treating team to consider the diagnosis confirmed). This resulted in delayed treatment (mean 10 days after admission to start of HLH-directed therapy). To address these delays, we are taking several approaches. First, we are attempting to increase physician education about HLH/MAS, through events such as this one, and lectures/case conferences given to residents, fellows and faculty in various settings. Second, we have created an email listserv (adult-hlh-mas@lists.utsouthwestern.edu), which can be accessed by any physician at UT Southwestern or Parkland. All members of the task force are listserv members. Our vision is that any patient in whom there is concern for HLH/MMAS would prompt an email to the listserv, which would in turn facilitate multidisciplinary discussion, and a consensus approach to diagnosis and treatment. This will also alert the pathology team to possible HLH cases, which may help expedite pathologic assessment if needed. Notably, emailing the listserv should not substitute for consultation of appropriate specialty services, who will then be in communication with task force team members.

To further address diagnostic and treatment delays, we have been working with the pathology department and lab directors, to streamline send out labs such as the soluble IL2 receptor assay, to improve turnaround times.

Lastly, we are working to standardize our treatment approach. As we analyze the data from the retrospective analysis, it seems clear that an algorithmic approach, in which conservative immunomodulatory therapies such as IVIG and or steroids, are reasonable initial therapies to help stabilize the patient while allowing further diagnostic workup (which may include biopsies of lymph nodes or other tissues to most accurately diagnose lymphomas or other malignancies) to continue without

hindering them by addition of cytotoxic agents. Once the underlying illness is accurately diagnosed, cytotoxic therapies to most aggressively address HLH, and/or therapies targeted at the underlying illness, may be added. Once we have established a treatment algorithm, we will track outcome data prospectively.

Conclusions

Hemophagocytic lymphohistiocytosis and macrophage activation syndrome are hyperinflammatory syndromes, usually triggered by infection in a host predisposed either by a genetic mutation hindering cytotoxic function in CTL or NK cells, or through immune dysfunction, hyperactivation and antigen persistence caused by an underlying hematolymphoid malignancy or autoimmune disease. Outcomes in adult patients are poorer than in children, and this is in part related to the higher incidence of malignancy-associated HLH in adults as well as possible other factors related to age and comorbid illnesses. Furthermore, diagnostic delays and extreme variability in treatment approaches in adults undoubtedly contribute to poor outcomes.

We have created a multidisciplinary task force to address these deficiencies. We have thus far obtained preliminary data from a retrospective analysis of HLH and MAS at UT Southwestern Hospitals and Parkland over the past 10 years which highlights the diagnostic delays and treatment variability discussed above, and helps to delineate ways to optimization of the care of these patients.

Please contact our task force if you suspect HLH or MAS in your patient!

adult-hlh-mas@lists.utsouthwestern.edu

Adult HLH/MAS Task Force members:

Chris Wysocki	Immunology
Maite De La Morena	Immunology
Sri Nagalla	Heme/Onc
Bonnie Prokesch	Infectious Diseases
Corey Kershaw	Pulmonary Critical Care
Fatemeh Ezzati	Rheumatology
Shannan Tujios	Digestive and Liver Disease
Prapti Patel	Bone Marrow Transplant
Arturo Dominguez	Dermatology
Weina Chen	Pathology

References

1. Scott RB, Robb-Smith AHT: **Histiocytic Medullary Reticulosis.** . *The Lancet* 1939, **234**:194-198.
2. Farquhar JW, Claireaux AE: **Familial haemophagocytic reticulosis.** . *Archives of Disease in Childhood* 1952, **27**:519-525.
3. Chandrakasan S, Filipovich AH: **Hemophagocytic lymphohistiocytosis: advances in pathophysiology, diagnosis, and treatment**. *J Pediatr* 2013, **163**:1253-1259.
4. Jordan MB, Hildeman D, Kappler J, Marrack P: **An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder**. *Blood* 2004, **104**:735-743.
5. Terrell CE, Jordan MB: **Perforin deficiency impairs a critical immunoregulatory loop involving murine CD8(+) T cells and dendritic cells**. *Blood* 2013, **121**:5184-5191.
6. Jessen B, Kogl T, Sepulveda FE, de Saint Basile G, Aichele P, Ehl S: **Graded defects in cytotoxicity determine severity of hemophagocytic lymphohistiocytosis in humans and mice**. *Front Immunol* 2013, **4**:448.
7. Henter JI, Elinder G, Soder O, Hansson M, Andersson B, Andersson U: **Hypercytokinemia in familial hemophagocytic lymphohistiocytosis**. *Blood* 1991, **78**:2918-2922.
8. Parvaneh N, Filipovich AH, Borkhardt A: **Primary immunodeficiencies predisposed to Epstein-Barr virus-driven haematological diseases**. *Br J Haematol* 2013, **162**:573-586.
9. Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X: **Adult haemophagocytic syndrome**. *Lancet* 2014, **383**:1503-1516.
10. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL: **How I treat hemophagocytic lymphohistiocytosis**. *Blood* 2011, **118**:4041-4052.
11. Janka GE: **Familial hemophagocytic lymphohistiocytosis**. *Eur J Pediatr* 1983, **140**:221-230.
12. Riviere S, Galicier L, Coppo P, Marzac C, Aumont C, Lambotte O, Fardet L: **Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients**. *Am J Med* 2014, **127**:1118-1125.
13. Schram AM, Comstock P, Campo M, Gorovets D, Mullally A, Bodio K, Arnason J, Berliner N: **Haemophagocytic lymphohistiocytosis in adults: a multicentre case series over 7 years**. *Br J Haematol* 2016, **172**:412-419.
14. Henter JI, Elinder G, Ost A: **Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society**. *Semin Oncol* 1991, **18**:29-33.
15. Henter JI, Elinder G, Soder O, Ost A: **Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis**. *Acta Paediatr Scand* 1991, **80**:428-435.
16. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, et al.: **HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis**. *Pediatr Blood Cancer* 2007, **48**:124-131.
17. Allen CE, Yu X, Kozinetz CA, McClain KL: **Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis**. *Pediatr Blood Cancer* 2008, **50**:1227-1235.
18. Beer T, Vadakara J: **Etiologies and Short-Term Mortality in Patients with Ultraelevated Serum Ferritin**. *South Med J* 2015, **108**:574-578.
19. Schram AM, Campigotto F, Mullally A, Fogerty A, Massarotti E, Neuberg D, Berliner N: **Marked hyperferritinemia does not predict for HLH in the adult population**. *Blood* 2015, **125**:1548-1552.
20. Sackett K, Cunderlik M, Sahni N, Killeen AA, Olson AP: **Extreme Hyperferritinemia: Causes and Impact on Diagnostic Reasoning**. *Am J Clin Pathol* 2016, **145**:646-650.

21. Hejblum G, Lambotte O, Galicier L, Coppo P, Marzac C, Aumont C, Fardet L: **A web-based delphi study for eliciting helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients**. *PLoS One* 2014, **9**:e94024.
22. Wang HY, Yang CF, Chiou TJ, Yang SH, Gau JP, Yu YB, Chen PM, Hsu HC, Fung CP, Lin HY, et al.: **Risk of hemophagocytic lymphohistiocytosis in adults with fevers of unknown origin: the clinical utility of a new scoring system on early detection**. *Hematol Oncol* 2016.
23. Tamamyan GN, Kantarjian HM, Ning J, Jain P, Sasaki K, McClain KL, Allen CE, Pierce SA, Cortes JE, Ravandi F, et al.: **Malignancy-associated hemophagocytic lymphohistiocytosis in adults: Relation to hemophagocytosis, characteristics, and outcomes**. *Cancer* 2016, **122**:2857-2866.
24. Daver N, McClain K, Allen CE, Parikh SA, Otrock Z, Rojas-Hernandez C, Blechacz B, Wang S, Minkov M, Jordan MB, et al.: **A consensus review on malignancy-associated hemophagocytic lymphohistiocytosis in adults**. *Cancer* 2017, **123**:3229-3240.
25. Lin M, Park S, Hayden A, Giustini D, Trinkaus M, Pudek M, Mattman A, Schneider M, Chen LYC: **Clinical utility of soluble interleukin-2 receptor in hemophagocytic syndromes: a systematic scoping review**. *Ann Hematol* 2017, **96**:1241-1251.
26. Tabata C, Tabata R: **Possible prediction of underlying lymphoma by high sIL-2R/ferritin ratio in hemophagocytic syndrome**. *Ann Hematol* 2012, **91**:63-71.
27. Tsuji T, Hirano T, Yamasaki H, Tsuji M, Tsuda H: **A high sIL-2R/ferritin ratio is a useful marker for the diagnosis of lymphoma-associated hemophagocytic syndrome**. *Ann Hematol* 2014, **93**:821-826.
28. Rubin TS, Zhang K, Gifford C, Lane A, Choo S, Bleesing JJ, Marsh RA: **Perforin and CD107a testing is superior to NK cell function testing for screening patients for genetic HLH**. *Blood* 2017, **129**:2993-2999.
29. Zhang K, Jordan MB, Marsh RA, Johnson JA, Kissell D, Meller J, Villanueva J, Risma KA, Wei Q, Klein PS, et al.: **Hypomorphic mutations in PRF1, MUNC13-4, and STXBP2 are associated with adult-onset familial HLH**. *Blood* 2011, **118**:5794-5798.
30. Wang Y, Wang Z, Zhang J, Wei Q, Tang R, Qi J, Li L, Ye L, Wang J, Ye L: **Genetic features of late onset primary hemophagocytic lymphohistiocytosis in adolescence or adulthood**. *PLoS One* 2014, **9**:e107386.
31. Ding Q, Yang LY: **Perforin gene mutations in 77 Chinese patients with lymphomas**. *World J Emerg Med* 2013, **4**:128-132.
32. Ishii E, Ohga S, Imashuku S, Yasukawa M, Tsuda H, Miura I, Yamamoto K, Horiuchi H, Takada K, Ohshima K, et al.: **Nationwide survey of hemophagocytic lymphohistiocytosis in Japan**. *Int J Hematol* 2007, **86**:58-65.
33. Shabbir M, Lucas J, Lazarchick J, Shirai K: **Secondary hemophagocytic syndrome in adults: a case series of 18 patients in a single institution and a review of literature**. *Hematol Oncol* 2011, **29**:100-106.
34. Li J, Wang Q, Zheng W, Ma J, Zhang W, Wang W, Tian X: **Hemophagocytic lymphohistiocytosis: clinical analysis of 103 adult patients**. *Medicine (Baltimore)* 2014, **93**:100-105.
35. Parikh SA, Kapoor P, Letendre L, Kumar S, Wolanskyj AP: **Prognostic factors and outcomes of adults with hemophagocytic lymphohistiocytosis**. *Mayo Clin Proc* 2014, **89**:484-492.
36. Otrock ZK, Eby CS: **Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis**. *Am J Hematol* 2015, **90**:220-224.
37. Niece JA, Rogers ZR, Ahmad N, Langevin AM, McClain KL: **Hemophagocytic lymphohistiocytosis in Texas: observations on ethnicity and race**. *Pediatr Blood Cancer* 2010, **54**:424-428.
38. Trottestam H, Horne A, Arico M, Egeler RM, Filipovich AH, Gadner H, Imashuku S, Ladisch S, Webb D, Janka G, et al.: **Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol**. *Blood* 2011, **118**:4577-4584.

39. Gupta AA, Tyrrell P, Valani R, Benseler S, Abdelhaleem M, Weitzman S: **Experience with hemophagocytic lymphohistiocytosis/macrophage activation syndrome at a single institution**. *J Pediatr Hematol Oncol* 2009, **31**:81-84.
40. Koh KN, Im HJ, Chung NG, Cho B, Kang HJ, Shin HY, Lyu CJ, Yoo KH, Koo HH, Kim HJ, et al.: **Clinical features, genetics, and outcome of pediatric patients with hemophagocytic lymphohistiocytosis in Korea: report of a nationwide survey from Korea Histiocytosis Working Party**. *Eur J Haematol* 2015, **94**:51-59.
41. Xu XJ, Wang HS, Ju XL, Xiao PF, Xiao Y, Xue HM, Shi HY, Gao YJ, Jia GC, Li XR, et al.: **Clinical presentation and outcome of pediatric patients with hemophagocytic lymphohistiocytosis in China: A retrospective multicenter study**. *Pediatr Blood Cancer* 2017, **64**.
42. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, et al.: **SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD,** https://seer.cancer.gov/csr/1975_2014/**, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.** 2017.
43. Lehmberg K, Sprekels B, Nichols KE, Woessmann W, Muller I, Suttorp M, Bernig T, Beutel K, Bode SF, Kentouche K, et al.: **Malignancy-associated haemophagocytic lymphohistiocytosis in children and adolescents**. *Br J Haematol* 2015, **170**:539-549.
44. Celkan T, Berrak S, Kazanci E, Ozyurek E, Unal S, Ucar C, Yilmaz S, Gurgey A: **Malignancy-associated hemophagocytic lymphohistiocytosis in pediatric cases: a multicenter study from Turkey**. *Turk J Pediatr* 2009, **51**:207-213.
45. Marsh RA, Jordan MB, Talano JA, Nichols KE, Kumar A, Naqvi A, Vaiselbuh SR, Histiocyte Society Salvage Therapy Working G: **Salvage therapy for refractory hemophagocytic lymphohistiocytosis: A review of the published experience**. *Pediatr Blood Cancer* 2017, **64**.