# Hemophagocytic Lymphohistiocytosis: Clinical Review at the Philippine Children's Medical Center

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**BACKGROUND:** Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by extreme immune activation, resulting in pathologic inflammation that may be life-threatening. Early recognition is crucial since survival largely depends on early initiation of treatment which utilizes a combination of chemotherapy, immunotherapy and in some cases even bone marrow transplantation.

**OBJECTIVES:** This study aims to describe the clinical characteristics, treatment received and outcome of patients diagnosed with HLH at the Philippine Children's Medical Center from 2004 to 2017

**MATERIALS AND METHODS:** A retrospective analysis of records of children 0 -18 years of age diagnosed with HLH from January 2004 to December 2017 was done.

**RESULTS:** A total of 39 patients were included in the study which gave an incidence of 1.22 per 3000 patients admitted under 18 years of age. There were 29 males (74.4%) and 10 females (25.6%) with a male to female ratio of 2.9:1 Mean age was 6.12 ± 3.89 years. The average time from initial presentation to diagnosis was 6 weeks and 2 days. The most commonly seen clinical and laboratory features observed in these patients were fever (100%), splenomegaly (71.8%), anemia (87.17%), thrombocytopenia (79.48%) and hypertriglyceridemia (69.23%). Only 5 patients were confirmed to be familial HLH with 3 having XLP gene mutation, and one each having syntaxin and perforin gene mutations. Majority of patients received a combination of treatment based on the HLH 2004 regimen while almost one third only received antibiotics. Only 23% of patients survived during the study period and all but one of these patients received drug combinations based on the HLH 2004 protocol.

**CONCLUSIONS AND RECOMMENDATIONS:** HLH is a rare but important condition that must be recognized early and treated appropriately to optimize survival. The mortality rate of 39 patients seen in this institution is high. There is a need to better utilize the diagnostic criteria of the disease and to employ a more uniform treatment strategy. Increasing awareness among health care personnel can also improve case finding, characterization and treatment.

**KEYWORDS:** *Pediatric, Hemophagocytic Lymphohistiocytosis, Philippines*

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## INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by extreme immune activation, resulting in pathologic inflammation that may be life- threatening. The most common clinical signs and symptoms include fever, hepatosplenomegaly, cerebromeningeal symptoms, lymph node enlargement, jaundice, edema, and skin rash. Laboratory tests reveal cytopenias, hypertriglyceridemia, coagulopathy with hypofibrinogenemia, liver dysfunction, elevated levels of ferritin and serum transaminases, moderate spinal fluid pleocytosis with increased proteinemia[1,2].

HLH may either be inherited or acquired. Familial HLH is hereditary and diagnosed early in life, whereas acquired HLA has a later onset and is associated with infections, malignancy, rheumatologic disorders or acquired immune deficiency[3,4,5]. The worldwide incidence of HLH is not well reported and varies widely among different regions. Reported incidence is as low as 1.2 per million in Sweden[1], 1 in 100,000 in Texas[6], 0.34 in 100,000 in Japan[7], to as high 7.5 per 10,000 in Turkey[8]. The high incidence in Turkey is probably due to increased parental consanguinity and a higher frequency of perforin gene mutation.[8] Because the clinical manifestations of HLH are often nonspecific and may mimic other conditions, the Histiocyte Society as published the 2004 revised criteria for the diagnosis of HLH (Table 1).[9]

***Table 1.*** *Diagnostic Criteria of HLH from HLH-2004 Treatment Protocol*

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:

1. Molecular diagnosis of HLH consistent with HLH

2. Diagnostic criteria for HLH is fulfilled (presence of at least 5 of 8 criteria):
   a. Fever
   b. Splenomegaly
   c. Cytopenias (affecting at least 2 lineages in the peripheral blood)
      i. Hemoglobin levels <90 g/L (in infants <4 weeks old, hemoglobin <100 g/L
      ii. Platelets <100 × 109/L
      iii. Neutrophils <1.0 × 109/L
   d. Hypertriglyceridemia and/or hypofibrinogenemia (Fibrinogen ≤1.5 g/L)
   e. Documented hemophagocytosis in the bone marrow, spleen, or lymph nodes
   f. Low or absent natural killer cell activity
   g. Ferritin ≥500 ng/ml
   h. Soluble CD25 (ie, soluble interleukin-2 receptor) ≥2,400 U/mL

Information on hemophagocytic lymphohistocytosis in the Philippines to date has been limited to case reports[10,11,12,13] hence the need for more research on the demographics, family history, clinical presentation and laboratory evaluations, as well as its management and disease outcome. This study aims to describe the clinical characteristics, treatment received and outcome of patients diagnosed with Hemophagocytic Lymphohistiocytosis (HLH) at the Philippine Children's Medical Center from 2004 to 2017.

## Materials and Methods

A retrospective analysis of records of children 0-18 years of age diagnosed with HLH from January 2004 to December 2017 was done at the Philippine Children's Medical Center.

Data collected included the following age, sex, time to diagnosis, family history, clinical signs and symptoms at presentation, laboratory results, treatment received and outcome. Family history included parental consanguinity and unexplained death of either a sibling or other family member. Clinical signs and symptoms and laboratory findings include those detailed in the 2004 diagnostic criteria, as well as the presence of cerebromeningeal symptoms, lymphadenopathies, jaundice, edema, skin rash, liver enzyme elevation, hypoproteinemia, hyponatremia and elevated VLDL as well as HDL. Mutation analysis was requested but was only successfully carried out in a number of patients at diagnosis. Patients who did not fulfill 5 out of the 8 criteria but were thoroughly worked up to rule out other possible causes of prolonged fever with cytopenia and eventually treated as HLH were included in the study.

Qualitative variables were analyzed and presented using frequency distributions. The incidence rate was calculated through the number of children diagnosed during the study period divided with the total number of patients admitted at the Philippine Children's Medical Center during the study period. Confidence intervals (CI) for incidence rates were calculated using the Wilson score method.

## Results

A total of 39 patients were diagnosed with HLH with 143, 199 recorded number of admissions during the fourteen-year period at the Philippine Children's Medical Center. This gave an incidence of 1.22 cases per 3000 patients admitted under 18 years of age. The patients included 29 males (74.4%) and 10 females (25.6%) with a male to female ratio of 2.9:1. Mean age was 6.12 ± 3.89 years. Most of the children (53.84%) diagnosed with HLH were between 1 to 5 years old. The average time from initial presentation to

diagnosis was 6 weeks and 2 days. Thirteen patients (33.33%) fulfilled less than 5 while 26 (66.66%) met 5 or more diagnostic criteria as defined by HLH-2004. Only 3 patients (7.69%) presented with a history of parental consanguinity and unexplained death of a sibling or of a family member.

Table 2 shows the most seen clinical and laboratory features observed in these patients which were fever (100%), splenomegaly (71.8%), anemia (87.17%), thrombocytopenia (79.48%) and hypertriglyceridemia (69.23%). Serum ferritin levels done in 22 patients showed levels ranging between 540—>100,000 ng/ml. NK cell activity, and soluble CD25 were not done as the tests were not available in the country. Among those who underwent cerebrospinal fluid determinations, pleocytosis was seen in 10 out 14 children (71.42%) and increased spinal fluid protein was noted in 8 out of 14 children (57.14%).

***Table 2.*** *Diagnosis of HLH by clinical and laboratory criteria, (N=39)*

| Diagnostic Criteria | Frequency No (%) |
|---|---|
| **Clinical** | |
| Fever | 39 (100%) |
| Splenomegaly | 28 (71.8%) |
| **Laboratory** | |
| *Cytopenias* | |
| Low Hgb (<90g/L) | 34 (87.17%) |
| Low PLT (<100x109/L) | 31 (79.48%) |
| Low neutrophils count (<1.0x109/L) | 23 (58.97%) |
| *Triglycerides* | |
| High (>3.0mmol/L) | 27 (69.23%) |
| Normal | 9 (23.08%) |
| Test Not Done | 3 (7.69%) |
| *Fibrinogen* | |
| Low (<1.5g/L) | 3 (7.69%) |
| Normal | 0 |
| Test Not Done | 36 (92.3%) |
| *PT/PTT* | |
| Deranged | 7 (17.95%) |
| Normal | 25 (64.1%) |
| Test Not Done | 7 (17.95%) |
| *Ferritin* | |
| High (>500 ng/ml) | 22 (56.41%) |
| Normal | 0 |
| Test Not Done | 17 (43.59%) |

| | |
|---|---|
| *Spinal fluid pleocytosis* | |
| Positive result | 10 (25.64%) |
| Negative result | 4 (10.26%) |
| Test Not Done | 25 (64.1%) |
| *Spinal fluid protein* | |
| Positive result | 8 (20.5%) |
| Negative result | 6 (15.38%) |
| Test Not Done | 25 (64.1%) |
| *Liver Enzymes* | |
| Positive result | 1 (2.56%) |
| Negative result | 3 (7.69%) |
| Test Not Done | 35(89.74%) |
| *NK Cell Activity* | Test Not Done |
| *Soluble CD25* | Test Not Done |

The presence of hemophagocytosis in tissues was not documented in all patients. Among those who underwent bone marrow aspiration, 27 out of 35 (77.14%) revealed significant presence of hemophagocytic cells. Biopsy and histopathology of the spleen and lymph nodes were done on one patient each.

Mutational analysis was only available for 6 out of 39 patients. Among those who underwent gene testing, mutations were identified in 5 patients with 3 having XLP gene mutations, and one each having syntaxin and perforin gene mutations. Thus, out of the 39 patients included in the study only 5 (13%) patients were confirmed to have primary or familial HLH.

Four patients (10.25%) were noted to develop other disease conditions after the diagnosis of HLH. These include acute myelogenous leukemia in 2 patients, inflammatory bowel disease and systemic lupus erythematosus. Infection associated with HLH was observed in 2 patients, due to Salmonella typhi and Epstein Barr Virus.

Other clinical and laboratory findings were summarized in Table 3. Clinical signs and symptoms such as cerebral meningeal symptoms (28.2%), lymph node enlargement (41%), jaundice (48.71%), edema (46.15%), and skin rash (33.33%) were also noted. A large proportion of children developed liver enzyme elevation (66.66%), hypoproteinemia (51.28%), and hyponatremia (56.41%). Tests on VLDL and HDL were done but only in a small number of patients.

***Table 3.*** *Additional Clinical and Laboratory Findings in Children with HLH, (N=39)*

| Clinical Findings | Frequency No (%) |
|---|---|
| Cerebromeningeal symptoms | 11 (28.2%) |
| Lymph Node Enlargement | 16 (41%) |
| Jaundice | 19 (48.71%) |
| Edema | 18 (46.15%) |
| Skin Rash | 13 (33.33%) |
| **Laboratory** | |
| Liver Enzyme Elevation | 26 (66.66%) |
| Hypoproteinemia | 20 (51.28%) |
| Hyponatremia | 22 (56.41%) |
| VLDL | |
| Decreased | 5 (12.82%) |
| Normal | 11 (28.2%) |
| Not Done | 23 (58.0%) |
| HDL | |
| Increased HDL | 2 (5.13%) |
| Normal | 13 (33.33%) |
| Not Done | 24 (61.54%) |

## Treatment and Outcome

Patients received different drug combinations based on the HLH 2004 regimen while almost one-third of patients did not. Dexamethasone and etoposide were utilized either as sole agent or part of a combination regimen, while 11 (28.2%) received a combination of etoposide, dexamethasone, cyclosporine A, intrathecal injections, and IVIg. Three patients (7.69%) received a combination of etoposide, dexamethasone, cyclosporine and immunoglobulins, and 3 (7.69%) received almost the same regimen but the immunoglobulin was replaced with intrathecal injections. Table 4 summarizes the treatment combinations given to patients.

***Table 4.*** *Combination of therapeutic agents for the management of HLH, (N=39)*

| Therapeutic Agents | Frequency No (%) |
|---|---|
| Antibiotics only | 12 (30.77%) |
| Etoposide + Dexamethasone + Cyclosporine A + Intrathecal injections + IV Immunoglobulin only | 11 (28.2%) |
| Etoposide + Dexamethasone + Cyclosporine A + IV Immunoglobulin only | 3 (7.69%) |
| Etoposide + Dexamethasone + Cyclosporine A + Intrathecal Injections only | 3 (7.69%) |
| Etoposide only | 2 (5.13%) |
| Dexamethasone + Cyclosporine A + IV Ig only | 1 (2.56%) |
| Etoposide + Dexamethasone + IV Ig only | 1 (2.56%) |
| Etoposide + Dexamethasone + Cyclosporine A only | 1 (2.56%) |
| Dexamethasone + IV Ig only | 1 (2.56%) |
| Etoposide + IV Ig only | 1 (2.56%) |
| Etoposide + Dexamethasone only | 1 (2.56%) |
| IV Ig only | 1 (2.56%) |
| Dexamethasone only | 1 (2.56%) |

As of last follow up only 9 out of 39 patients (23.07%) are alive and off treatment with no disease recurrence. Table 5 shows the characteristics of the surviving 9 patients. All but one were treated with chemotherapy based on HLH regimen and 6 out of 9 were given IVIG as an adjunct treatment.

***Table 5.*** *Characteristics of Surviving Patients, (N=9)*

| Patient | Age | Sex | Type of HLH | Treatment/Supportive Care Given |
|---|---|---|---|---|
| 1 | 1 y/o | Female | Not Determined | Etoposide, Dexamethasone, Cyclospor-ine, IVIG |
| 2 | 4 4/12 | Female | Not Determined | Antibiotics only |
| 3 | 3 5/12 | Female | Not Determined | Etoposide, Dexamethasone, Cyclospor-ine, IVIG |
| 4 | 5 11/12 | Male | Familial | Etoposide, Dexamethasone, Cyclospor-ine |
| 5* | 4 | Male | Familial | Etoposide, Dexamethasone, Cyclospor-ine, IVIG |
| 6 | 9 | Male | Familial | Etoposide, Dexamethasone, Cyclospor-ine, IVIG |
| 7 | 4 | Male | Not Determined | Etoposide, Dexamethasone, Cyclospor-ine, IVIG |
| 8 | 4 5/12 | Male | Not Determined | Etoposide, Dexamethasone, Cyclospor-ine, IVIG |
| 9 | 4 3/12 | Female | Not Determined | Etoposide, Dexamethasone, Cyclospor-ine, IVIG |

**Died of Cerebrovascular Aneurysm after 6 years*

## RESULTS

This study described the clinical and laboratory characteristics, treatment and outcome of children diagnosed with HLH at the Philippine Children's Medical Center, a national tertiary referral center for children and adolescents. To date this is the largest number of cases reported in the country.

The estimated incidence of HLH is among patients admitted at the Philippine Children's Medical Center from 2004 to 2017 in this series was 1.22 per 3000 children under the age of 18. This is likeincidence for tertiary referral centers which is 1 in 3000.[15] The patients in this report tend to be older with and average age at diagnosis of 6.12 $\pm$ 3.89 years, with more males than females affected, compared to other reports.[5,6,7,8] A family history of parental consanguinity was reported to be at 7.69% (3 out of 39) for this population, and these patients also had a history of a sibling or a family member who had an unexplained death. This is lower than

that reported by Henter in Sweden (18.75%) and Gurgey in Turkey (68.74%).[1,8]

The average time from initial presentation to diagnosis of the disease is 6 weeks and 2 days. This was affected by the turn-round rate of tests, which were performed in reference laboratories. It should also be considered that HLH presents with protean manifestations which could also be observed in many inflammatory, malignant and infectious conditions, making it an uncommon initial consideration. Furthermore, clinicians did not frequently encounter HLH being a rare disorder hence general awareness was limited.

The HLH 2004 diagnostic criteria requires that 5/8 clinical and laboratory parameters for confirming the diagnosis of HLH are fulfilled. In this report, 13 (33%) satisfied less than 5 conditions in the clinical criteria for diagnosis, while 26 (67%) have met at least 5 conditions in the said criteria. Fever and cytopenia were the most observed clinical manifestation among those who did not fulfill the required number of criteria followed by cytopenia. These patients were all referred to the hematology service for assessment because of fever of unknown origin. Since these patients had prolonged fever with or without cytopenia, bone marrow examination and culture were recommended. Bone marrow aspiration was done in 11 of the 13 patients, with 4 of these positive for hemophagocytosis. Commitment to a diagnosis is necessary to start treatment and it has been reported that HLH can be a disease in evolution and treatment should be started once HLH is strongly considered. Only 4 of the patients survived and 3 of them were started on HLH treatment despite nonfulfillment of the required 5 out of 8 criteria. Unfortunately, all the other 9 patients were referred late in the course of the illness and HLH treatment was not initiated immediately.

One widely available test of significant importance in the diagnosis of HLH is serum ferritin levels. A serum ferritin level > 500 ng/ml is part of the diagnostic criteria for HLH. In our patients, all the 22 patients who had serum ferritin determination had elevated levels ranging from 540 to more than 100,000 ng/ml. Majority (82%) also fulfilled the 5 out of 8 clinical criteria for HLH and treated with at least one or two chemotherapeutic drugs included in the HLH regimen. Although a higher cut-off value is suggested to reliably rule out other conditions which can give rise to hyperferritinemia, it is usually one of the first laboratory parameters requested if HLH is suspected because it is an easily attainable criterion and can be performed quickly and reliably in any modern laboratory facility.[14] A serum ferritin level of 3120 ng/ml as the cut-off was reported to have a sensitivity of 70% and specificity of 88.9% for HLH diagnosis, exceeding the currently prescribed cut-off of 500 ng/ml.[15] Furthermore, hyperferritinemia below 3120 ng/ml has higher negative

predictive value to rule out secondary HLH. Allen, et.al. reported that a ferritin level of ≥ 10,000 ng/ml had a 90% sensitivity and 98% specificity for HLH [14] but this very high value may miss true HLH cases if used as the cut off screening level. The usefulness of serum ferritin levels extends beyond screening, it has also been reported to be of value in monitoring response to treatment with decreasing levels associated with favorable outcome.[15]

The diagnosis of primary or familial HLH was confirmed in only 5 out of 39 patients due to lack of available genetic testing in the country. Specimens had to be processed for DNA extraction then were sent abroad for mutation analysis. Identifiable secondary causes of HLH such as infection, inflammatory disease and malignancy was seen in 4 patients. Familial or primary HLH can only be confirmed in the presence of an identifiable mutation and since this was not tested among all the patients, classifying the type of HLH will be challenging. Some of the patients were also too critically ill and financially drained for further work up.

Patients diagnosed with HLH deteriorate rapidly and often need pediatric intensive care to maximize chances of survival. Moreover, differentiating HLH from sepsis is also very difficult. Others were considered infection associated with HLH for which IVIG was given as an initial treatment especially if sepsis as an associated condition could not be ruled out.[16] In this study, 19 out of 39 patients were given IVIG either as the only treatment or as an adjunct to the HLH regimen.

Although HLH-2004 outlines the treatment recommended by the Histiocyte Society, the patients in this study received various drug combinations, with about 60% receiving dexamethasone and/or etoposide containing regimens. Dexamethasone and etoposide are part of the backbone of both HLH 1994 and 2004 regimens. The variation in choice of treatment was due to differences in the management principles adhered to by the clinical service in charge of the patients. Moreover, 30 % of children only received antibiotics, since they presented at a very advanced state and died shortly after diagnosis.

The outcome of patients in this study is dismal, with a high mortality rate of 76.9%. This rate is much higher compared to 3.3% as reported by Allen, et al., as well 8-22% for primary HLH and 50% for secondary HLH as reported in various collaborative studies.[10,17,18] Deaths were seen in both patients who did and did not receive treatment. Of the nine surviving patients, majority received a combination of chemotherapy based on the HLH 2004 regimen despite 4 of them not having fulfilled the required clinical criteria for HLH.

Early recognition of HLH and prompt institution of treatment are the keys to successful management of HLH. However, because of its rarity, non-specific and variable clinical manifestations as well as lack of diagnostic modalities to confirm the diagnosis, delays in both diagnosis and treatment occur. Delayed treatment is associated with poor outcome due to severe inflammation and irreversible organ damage. In a country with limited resources, test availability, affordability of diagnostics and treatment modalities lead to less than optimal care for these patients.

This study has several limitations. These include a lack of complete information as obtained from historical data as well as variations in the diagnostic evaluation and treatment of patients. There is a need to improve case finding, documentation of data and for the health care personnel to collaborate better in the diagnosis and management of these patients.

In summary, HLH is a rare but important condition that must be recognized early and treated appropriately to optimize survival. The mortality rate in 39 patients seen in this institution is high. There is a need to better utilize the diagnostic criteria of the disease and to employ a more uniform treatment strategy. Increasing awareness among health care personnel can also improve case finding, characterization and treatment.

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