# Histiocytic Disorders

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Histiocytic disorders are a group of diseases that occur when there's an over-production of white blood cells known as histiocytes, which leads to organ damage. There are different types of histiocytes throughout our body, namely dendritic cells and macrophages/monocytes.

Histiocytic diseases can be divided into three major classes of disorders, based on the type of histiocyte involved:
- Langerhans cell histiocytosis (LCH) – a dendritic cell disorder
- Juvenile xanthogranuloma (diagnosed in children and adults) – a macrophage disorder
- Hemophagocytic lymphohistiocytosis (HLH) – a disorder of macrophages/monocytes

We reviewed the diagnosis, treatment and outcomes of patients with LCH and HLH at Akron Children's Hospital from 2006-2013 and compared our experience to the published results of large cooperative group studies. We saw one patient with both juvenile xanthogranuloma and LCH during this time period, but no review was done due to the rarity.

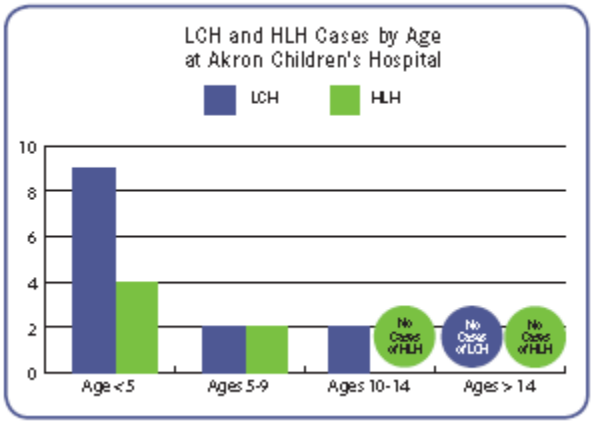
## Clinical features

The clinical presentation of LCH is broad and variable. Clinical involvement can be highly variable, but most often involves bony lesions (present in about 80% of cases), which may be painful or painless. Skin involvement, typically papulosquamous lesions, often affects the scalp and is frequently mistaken for cradle cap (seborrhea). The disorder can be localized to a single site, found in multiple sites within a single system (usually bone), or disseminated and involving multiple organ systems. Other systemic involvement includes fever, hepatosplenomegaly, liver dysfunction, hematopoietic failure and intestinal involvement. In the most typical form of HLH, the clinical course is characterized by prolonged fever and hepatosplenomegaly. Standard blood testing typically reveals cytopenias – especially anemia and thrombocytopenia, liver dysfunction, hypofibrinogenemia, hypertriglyceridemia, hypoalbuminemia, elevated ferritin and elevated soluble IL2Ra (sCD25). FHL is a fatal disease with a median survival of less than 2 months after diagnosis, if untreated. It typically occurs during infancy or early childhood.

## How can we improve patient outcomes?

### Incidence

Annual estimates for LCH range from 2.6 to 8.9 cases per 1 million children younger than 15 years. The male to female ratio is close to one and the median age of presentation is 30 months. HLH is comprised of two different forms that may be difficult to distinguish from one another: a primary and a secondary form. The primary autosomal recessive form, familial hemophagocytic lymphohistiocytosis (FHL), has an estimated incidence of 1:50,000 live-born children. There are no good estimates for incidence of non-familial HLH, but it's very rare. HLH has an equal distribution among males and females. The age of onset is usually younger than 1 year for the familial form but can be later for the secondary sporadic form, usually after age 6.



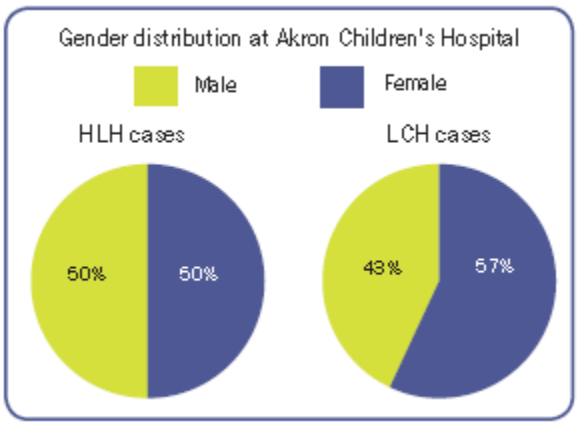
## Treatment

LCH that is localized to skin, bone and lymph nodes generally has a good prognosis and requires minimal treatment. LCH in only one bone is generally benign, and the disease responds well to several treatment modalities including observation, surgical excision or steroid injection. Children with lung, liver, spleen and bone marrow involvement usually have a worse prognosis and are considered higher risk. Combination chemotherapy is the mainstay of treatment for children with higher risk LCH. The three most commonly used drugs are vinblastine, prednisone and mercaptopurine.

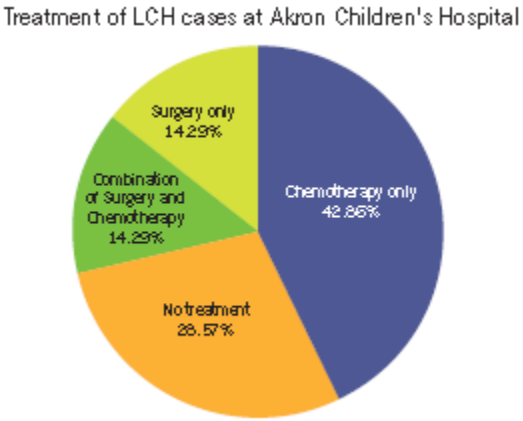
Effective initial therapy for HLH consists of a combination of chemotherapy and immunosuppressive drugs targeting the hyperactivated T cells and histiocytes. Commonly used and effective agents include etoposide, steroids and anti-thymocyte globulin. Definitive treatment for familial HLH is hematopoietic stem cell transplantation.

## Experience at Akron Children's Hospital

We reviewed our experience in treating children with LCH over a 7-year period spanning from 2006 to 2013. During this time, 14 new cases of LCH were diagnosed at Akron Children's Hospital. Almost 70% (9/14) were under the age of 5 years and 57% were females. Three out of the 14 had multifocal disease. Six of the patients were treated with combination chemotherapy only. Two of the 14 required surgery only and another two were treated with both chemotherapy and surgery. Four of the 14 didn't require any treatment and were followed by close observation only. All 14 of the patients seen during this period are still alive. Data from the large European cooperative group study, HISTSOC-LCH III, showed an 84% overall survival rate for patients treated with systemic chemotherapy for 12 months.




During the same 7-year time period, we saw 6 cases of HLH at Akron Children's Hospital. Two-thirds were under the age of 5 years at diagnosis. Of the 5 who received treatment, 3 were treated with chemotherapy and hematopoietic stem cell transplantation and 2 received chemotherapy only. One patient was diagnosed right after birth and died within a few weeks. The 5 patients treated during this period are still alive. Reported mortalities in secondary HLH vary from 18%-24%.

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