

# LANGERHANS CELL HISTIOCYTOSIS



## Histiocyte Society

### Evaluation and Treatment Guidelines

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**Disclaimer:**

These clinical guidelines have been developed by expert members of the Histiocyte Society and are intended to provide an overview of currently recommended treatment strategies for LCH. The usage and application of these clinical guidelines will take place at the sole discretion of treating clinicians who retain professional responsibility for their actions and treatment decisions.

The following recommendations are based on current best practices in the treatment of LCH and are not necessarily based on strategies that will be used in any upcoming clinical trials. The Histiocyte Society does not sponsor, nor does it provide financial support for, the treatment detailed herein.

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## **INTRODUCTION**

There are no international studies for newly diagnosed patients with Langerhans cell histiocytosis (LCH) currently open. The guidelines detailed herein have been developed for use as recommended practices in the evaluation and treatment of patients who are not formally enrolled in clinical trials, such as the upcoming LCH IV study. These guidelines are based on the best currently known treatment approaches; and take into consideration the preliminary results of the LCH-III trial.

The Histiocyte Society protocols LCH-S-2005 (salvage therapy for patients with severe disease, Chair: J. Donadieu) and LCH-HCT-2006 (stem cell transplantation after Reduced Intensity Conditioning, Chair: K.S. Baker) are currently open for enrollment.

## **DIAGNOSTIC CRITERIA**

The diagnosis of LCH is based on histological and immunophenotypic examination of lesional tissue. The main feature is the morphologic identification of the characteristic LCH cells. Additionally, positive staining of the lesional cells with CD1a and/or Langerin (CD207) is required for definitive diagnosis (1-3). It has been demonstrated that the expression of Langerin confirms the presence of Birbeck granules (4). Because of this finding, the ultrastructural demonstration of the presence of cytoplasmic Birbeck granules (the previous diagnostic “gold standard”) is no longer necessary. Only in the case of isolated vertebra plana without a soft tissue component does the risk of biopsy outweigh the need for a tissue diagnosis. This is also true for an isolated involvement of the odontoid peg. In such a case, the patient should be closely observed to exclude a malignancy. Curettage of the center of a bone lesion is usually sufficient for pathologic diagnosis and also may trigger the initiation of a healing process. Complete excision of bone lesions is not indicated and may increase the size of the bony defect, the time to healing, and result in late skeletal morbidity.

## **PRETREATMENT CLINICAL EVALUATION**

### **1. COMPLETE HISTORY:**

A complete history should include special reference to the nature and duration of symptoms. Specific symptoms to be included in the complete history are: pain, swelling, skin rashes, otorrhea, irritability, fever, loss of appetite, diarrhea, weight loss

or poor weight gain, growth failure, polydipsia, polyuria, changes in activity level, dyspnea, smoke exposure, and behavioral and neurological changes.

## **2. COMPLETE PHYSICAL EXAMINATION:**

A complete physical examination should include measurement of temperature, height, and weight. Special attention should be paid to: pubertal status (Tanner staging), characterization of skin and scalp rashes, presence of jaundice, pallor, edema, lymphadenopathy, ear discharge, orbital abnormalities, gum and palatal lesions, dentition, soft tissue swelling, lesions on the genital and anal mucosa, tachypnea, intercostal retractions, ascites, and liver and spleen size. Specific tests should be conducted for: neurological evaluation, cranial nerve abnormalities, loss of tendon reflexes, visual deficits, and cerebellar dysfunction. This complete clinical evaluation should be performed at each follow-up visit.

### 3. LABORATORY AND RADIOGRAPHIC EVALUATION:

**Table 1: Recommended baseline evaluation upon diagnosis and reactivation**

**Full blood count:**

- hemoglobin, white blood cell and differential count, platelet count

**Blood chemistry:**

- total protein, albumin, bilirubin, ALT(SGPT), AST(SGOT), alkaline phosphatase,  $\gamma$ GT
- BUN, creatinine, electrolytes
- Ferritin

**Coagulation studies:**

- INR/PT, APTT/PTT, fibrinogen

**Early morning urine sample:**

- Specific gravity and osmolality

**Abdominal ultrasound:**

- Size and structure of liver and spleen

**Chest radiograph (CXR)**

**Skeletal radiograph survey\***

\* Functional imaging such as bone scan is optional and can be performed in addition to skeletal survey. PET scan has proven to be the most sensitive functional test used in the identification of LCH lesions and in evaluating patient response to therapy. However, PET scan is currently expensive and not widely available (Philips et al, 2009)

**Table 2: Laboratory investigations, imaging and specialized clinical assessments recommended for specific clinical scenarios**

<b>Indication</b>	<b>Assessment / test</b>
<b>Bicytopenia, pancytopenia, or persistent unexplained single cytopenia</b>	<ul style="list-style-type: none"> <li>• Bone marrow aspirate &amp; trephine biopsy to exclude causes other than LCH</li> </ul>
<b>Liver dysfunction</b>	<ul style="list-style-type: none"> <li>• Liver biopsy only recommended if there is clinically significant liver involvement and the result will alter treatment (i.e. to differentiate between active LCH and sclerosing cholangitis)</li> </ul>
<b>Lung involvement</b> (abnormal CXR or symptoms/signs suggestive for lung involvement)  <b>Abnormal lung CT AND findings not characteristic for LCH or suspicion for atypical infection</b>	<ul style="list-style-type: none"> <li>• Lung high resolution computed tomography (HR-CT) or preferably low dose multi-detector HR-CT if available</li> <li>• Lung function test (if age appropriate)</li> <li>• Bronchoalveolar lavage (BAL): &gt;5% CD1a-positive cells in BAL fluid is diagnostic in non-smokers</li> <li>• Lung biopsy (if BAL is not diagnostic)</li> </ul>
<b>Suspected craniofacial bone lesions including maxilla and mandible</b>	<ul style="list-style-type: none"> <li>• MRI of head*</li> </ul>
<b>Suspected vertebral lesions</b>	<ul style="list-style-type: none"> <li>• MRI of spine (to exclude spinal cord compression)</li> </ul>
<b>Visual or neurological abnormalities</b>	<ul style="list-style-type: none"> <li>• MRI of head*</li> <li>• Neurology assessment</li> <li>• Neuropsychometric assessment</li> </ul>
<b>Suspected endocrine abnormality</b> (i.e. short stature, growth failure, polyuria, polydipsia, hypothalamic syndromes, precocious or delayed puberty)	<ul style="list-style-type: none"> <li>• Endocrine assessment (including water deprivation test and dynamic tests of the anterior pituitary and thyroid)</li> <li>• MRI of head*</li> </ul>
<b>Aural discharge or suspected hearing impairment/mastoid involvement</b>	<ul style="list-style-type: none"> <li>• Formal hearing assessment</li> <li>• MRI of head*</li> <li>• HR-CT of temporal bone</li> </ul>
<b>Unexplained chronic diarrhea, failure to thrive, or evidence of malabsorption</b>	<ul style="list-style-type: none"> <li>• Endoscopy and biopsy</li> </ul>

\*MRI of head should include the brain, hypothalamus - pituitary axis and all craniofacial bones. The use of intravenous contrast (Gadolinium – DTPA) is mandatory.

## DEFINITION OF ORGAN INVOLVEMENT

### Risk organs (RO)

<b>Hematopoietic involvement:</b> (with or without bone marrow involvement*)	<b>At least 2 of the following:</b> <ul style="list-style-type: none"> <li>• <b>anemia:</b> hemoglobin &lt;10 g/dl, infants &lt;9 g/dl (not due to other causes; e.g. iron deficiency)</li> <li>• <b>leukocytopenia:</b> leukocytes &lt;4,0 x 10<sup>9</sup>/l,</li> <li>• <b>thrombocytopenia:</b> platelets &lt; 100 x 10<sup>9</sup>/l</li> </ul>
<b>Spleen involvement:</b>	<ul style="list-style-type: none"> <li>• <b>enlargement</b> &gt; 2 cm below costal margin in the midclavicular line</li> </ul>
<b>Liver involvement:</b>	<ul style="list-style-type: none"> <li>• <b>enlargement</b> &gt; 3 cm below costal margin in the midclavicular line and/or</li> <li>• liver <b>dysfunction</b> (i.e. hypoproteinemia &lt;55g/l, hypoalbuminemia &lt;25g/l not due to other causes) and/or</li> <li>• <b>histopathological</b> diagnosis</li> </ul>
<b>Lung involvement:</b>	<ul style="list-style-type: none"> <li>• typical changes on <b>HR-CT</b> (low dose multi-detector CT if available) and/or</li> <li>• <b>histopathological / cytological</b> diagnosis</li> </ul>

\*Bone marrow involvement is defined as demonstration of CD1a positive cells on bone marrow smears. The clinical significance of CD1a positivity in the bone marrow remains to be proven. Hemophagocytosis may be prominent in severe progressive cases.

**“Special Sites”** – In certain situations, such as odontoid peg and vertebral lesions with intraspinal soft tissue extension, lesions are located in functionally critical anatomical sites. Lesions located in these sites may cause immediate risk to the patient because of the potential for disease progression and the hazards of attempting local therapy. These lesions are considered disease in a “Special Site.” Isolated disease in a Special Site may justify systemic therapy.

**Vertebral lesions without soft tissue extension, e.g. vertebra plana, are not regarded as “Special Site” lesions.**

**“Craniofacial bone involvement”** - lesions in the orbital, temporal, mastoid, sphenoidal, zygomatic, or ethmoidal bones; the maxilla or paranasal sinuses; or cranial fossa; with intracranial soft tissue extension

**“Eye” involvement** - proptosis, exophthalmos, or lesions in the orbits; zygomatic or sphenoidal bone

**“Ear” involvement** - external otitis, otitis media, otorrhea; or lesions in the temporal bone, mastoid, or petrous bone

**“Oral” involvement** - lesions in the oral mucosa, gums, palatal bone, maxilla, and mandible

#### **“CNS Risk Lesions”**

Recent knowledge suggests that prolonged involvement of skull bones (excluding those in the vault) predisposes patients to the development of DI (5). In this study, patients with MS-LCH and "craniofacial involvement" – particularly those with involvement of the “ear,” “eye,” and the "oral" sites at diagnosis – carried a significantly increased risk to develop DI during their course. In a bivariate model adjusted for the extent of disease (MS-LCH vs. SS-LCH), the authors found that the influence of lesions in **“ears”** (RHR 1.8, P1/40.005), **“eyes”** (RHR 1.7; P1/40.024), and **“oral cavity”** (RHR1.8; P1/4 0.007), and combined **"craniofacial lesions"** (RHR 1.6; P1/40.030) is statistically significant. This risk is augmented when the disease remains active for a longer period of time or reactivates (5).



## STRATIFICATION

Depending on the extent and localisation of the disease at the time of evaluation, the following clinical categories have been defined:

### Clinical classification of LCH:

<b>Single System LCH (SS-LCH)</b>	<b>One organ/system involved (uni- or multifocal):</b> <ul style="list-style-type: none"><li>• Bone: unifocal (single bone) or multifocal (&gt;1 bone)</li><li>• Skin</li><li>• Lymph node (not the draining lymph node of another LCH lesion)</li><li>• Lungs</li><li>• Hypothalamic-pituitary / Central nervous system</li><li>• Other (e.g. thyroid, thymus)</li></ul>
<b>Multisystem LCH (MS-LCH)</b>	<b>Two or more organs/systems involved</b> With or without involvement of "Risk Organs"

**The following localisations and disease extent categories are considered indications for systemic therapy:**

<ul style="list-style-type: none"><li>• <b>SS-LCH with "CNS-risk" lesions</b></li><li>• <b>SS-LCH with multifocal bone lesions (MFB)</b></li><li>• <b>SS-LCH with "special site" lesions</b></li><li>• <b>MS-LCH with/without involvement of "risk organs"</b></li></ul>
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## TREATMENT

Treating physicians participating in clinical trials of the Histiocyte Society are encouraged to formally enroll their patients on these protocols after obtaining the approval of their institution's ethical board. By enrolling their patients on these protocols, physicians will help to advance knowledge about the biology and treatment of LCH. The Histiocyte Society intends for the recommendations provided below to serve as physician guidelines in the management of patients who are unwilling or unable to be treated on, or enrolled in, such a protocol. In order for patients to be treated on a research protocol, they must first indicate their agreement to participate in the study by providing their informed consent. It is ethically unsound, and strongly discouraged, for physicians to treat patients who have not provided their informed consent on a research protocol.

## **1. GENERAL CONSIDERATIONS:**

- Recent evidence (unpublished preliminary data of the LCH-III Trial of the Histiocyte Society) suggests that treatment duration of 12 months reduces the rate of reactivation as compared to 6 months of total treatment. Patients with MS-LCH at diagnosis can have a variable clinical course. Those without involvement of risk organs, as well as those with involvement of risk organs who respond to standard initial therapy, have an excellent chance of long-term survival. A combination of prednisone (PRED) and vinblastine (VBL) has been proven to be effective treatment with minimal toxicity (6-8) and is therefore the standard initial therapy for all patients in whom systemic therapy is indicated. Patients with risk organ involvement who do not respond within the first 6 weeks of therapy – especially those with evident clinical progression – have an unfavourable prognosis (7, 9,10). For such patients, early therapy intensification is justified.
- Patients with MFB are known to have an excellent prognosis (survival of 100%), but have a high tendency for disease reactivation (30-50%) and permanent consequences. The same is true for patients with “special site” and “CNS-risk” lesions. There is a 40% likelihood that these patients will develop diabetes insipidus and other endocrinopathies; as well as parenchymal brain disease. There is greatest risk of parenchymal brain disease developing in the basal ganglia and cerebellum. Therapy is to be used in these groups for the purpose of preventing reactivations, permanent consequences and disabilities. However, evidence to support different regimens is limited and is mainly based on retrospective analyses (11) and expert opinion.

## **2. FIRST LINE TREATMENT**

### **2.1. Multisystem Disease**

An initial 6-week course of therapy with vinblastine and prednisone (**Figure 1**) is suggested for all patients with MS-LCH; regardless of risk organ involvement. Further therapy depends on patient response to initial therapy. In order to determine response to initial therapy, assessment at the end of the initial 6 week course of therapy is necessary.

Patients found to have RO involvement at diagnosis and who have not demonstrated improvement in risk organs are candidates for salvage therapy options (see below).

The same is recommended for patients who were not found to have RO involvement at diagnosis, but developed RO disease while on therapy.

For patients without RO involvement who have not shown improvement (e.g. AD intermediate), and for patients with RO involvement at diagnosis who have responded to the initial course (e.g. AD better), a second course of treatment with vinblastine and prednisone (Figure 2) is recommended.

It is also recommended that all patients who have complete disease resolution (NAD) after 6-12 weeks of initial therapy continue with maintenance therapy. Maintenance therapy consists of pulses of vinblastine and prednisone every 3 weeks and daily continuous 6-mercaptopurine (6MP) for a total treatment duration of 12 months (Figure 3).

It is recommended that patients who continue to experience involvement of risk organs after initial course 2 (12 weeks of therapy) are switched to salvage therapy. It is also recommended that patients without risk organ involvement who do not demonstrate improvement after course 2 be administered another course of therapy with alternative drugs (see “Second-line therapy for non-risk LCH” below)

## **2.2. Multifocal bone (MFB), “special site” and “CNS-risk” lesions**

At the present time, there is no conclusive evidence to support an optimal course of treatment for use with these patient subgroups. The rationale for systemic treatment is the considerable risk of permanent consequences and disabilities that may adversely affect individuals’ quality of life. Data from the DAL-HX 83 and DAL-HX 90 non-randomized prospective trials indicates that 1 year of systemic treatment with vinblastine, prednisone, and 6-mercaptopurine has the potential to reduce both the reactivation rate and the frequency of permanent consequences when compared to historical controls (11). Based upon this data, the Histiocyte Society recommends systemic therapy, consisting of course 1 (**Figure 1**) ± course 2 (**Figure 2**); and a continuation therapy with PRED/VBL pulses every 3 weeks. The total recommended duration of treatment is 12 months (as in Figure 3 but without 6MP).

### **3. SECOND LINE TREATMENT**

#### **3.1. Salvage therapy options for Risk patients:**

Currently, there is insufficient evidence to support an optimal course of treatment for use with patients suffering from severe progressive MS-LCH who do not respond to standard therapy. Recently, promising results have been reported for patients treated with a combined regimen of 2-chlorodeoxyadenosine (2-CdA, Cladribin, Leustatin) and cytarabine (Ara-C) (12); as well as stem cell transplantation after reduced intensity conditioning regimen (RIC-SCT) (13).

However, the results generated by both reports are based on limited observations and must be validated by the prospective clinical trials. The Histiocyte Society currently has open trials for both treatment options. For the rare cases in which salvage therapy is planned, it is recommended that you contact an LCH expert or the principal investigators of one of the aforementioned open studies.

#### **3.2. Second-line therapy for Non-Risk patients:**

Presently, optimal second-line options for patients diagnosed with persisting or relapsing LCH in non-risk organs have not yet been identified.

In the future, the Histiocyte Society will conduct a clinical trial for the purpose of identifying optimal second-line options for these patients.

Previously used treatments that have demonstrated success include the intralesional injection of steroids (14); the combination of vincristine, prednisone, and cytarabine (15); and 2-chlorodeoxyadenosine as a single agent (16-18).

### **4. CNS DISEASE**

Treatment for patients diagnosed with CNS disease depends on the type and extent of disease and prior treatment received and thus must be determined on an individual basis.

## **SUPPORTIVE CARE**

### **1. PNEUMOCYSTIS CARINII (PCP) PROPHYLAXIS**

Patients receiving systemic therapy for LCH are at risk for PCP infection. Prophylaxis against PCP should be given in accordance with local standards.

## **2. TRANSFUSIONS OF RED CELLS AND PLATELETS**

Patients receiving “salvage” therapy for LCH are at risk for transfusion-related complications, including cytomegalovirus infection and graft-vs.-host disease (GvHD). Blood cell components should be filtered and irradiated (> 2500 rad or 25 Gy) for prevention of GvHD.

## **3. G-CSF**

In case of prolonged neutropenia, G-CSF may be given subcutaneously or intravenously. The use of GM-CSF is not recommended.

## **4. THERAPY MODIFICATIONS**

### **Infants with body weight under 10 kg**

Drug doses are calculated on body surface area (BSA) and adjusted for age as follows:

< 6 months	50% of dose calculated from BSA
> 6 months < 12 months	75% of dose calculated from BSA
> 12 months	100% of dose calculated from BSA

### **Bone marrow toxicity**

It is recommended that an absolute neutrophil count greater than  $1.0 \times 10^9/l$  and a platelet count greater than  $100 \times 10^9/l$  be observed before each course of therapy is initiated, unless cytopenias are disease related. In the case of persistent disease activity, it is recommended that physicians consider continuing treatment regardless of the patient’s hematological values.

### **Continuation Therapy with Oral 6-Mercaptopurine**

If neutrophils fall below  $1.0 \times 10^9/l$  or platelets below  $100 \times 10^9/l$ , treatment should be stopped until recovery occurs above these levels, and then resumed as tolerated. If neutrophils fall below  $0.5 \times 10^9/l$  or platelets below  $50 \times 10^9/l$  on >2 occasions, consider discontinuation of co-trimoxazole. Pentamidine or dapsone can be used as alternative prophylaxis for PCP.

### **Neurotoxicity**

In the event of significant toxicity (extensive weakness, severe paresthesia, severe ileus), vinblastine may be temporarily discontinued and resumed at 50% dose when toxicity resolves, with progressive increase to full dose as tolerated.

## ASSESSMENT OF TREATMENT RESPONSE

In accordance with the nature of LCH, the following definitions should be applied to judge the effect of treatment:

### Definition of disease state

NON ACTIVE DISEASE (NAD)	no evidence of disease	Resolution of all signs or symptoms
ACTIVE DISEASE (AD)	regressive disease	Regression of signs or symptoms, no new lesions
	stable disease	persistence of signs or symptoms, no new lesions
	progressive disease*	progression of signs or symptoms and/or appearance of new lesions

### Definition of response criteria

There are three categories of response

BETTER	complete resolution	NAD
	regression	AD better
INTERMEDIATE	mixed	new lesions in one site, regression in another site
	stable	Unchanged
WORSE	progression*	

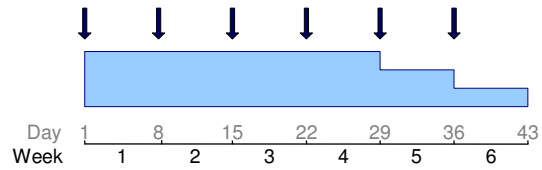
\*In isolated bone disease progression is defined as appearance of new bone lesions or lesions in other organs

## FOLLOW UP INVESTIGATIONS AFTER END OF THERAPY

	<b>YEAR 1*</b>	<b>YEARS 2 – 5*</b>
Clinical examination	Every 6 weeks	Every 6 months
Height, weight, pubertal status	Every 6 months	Every 6 months
Lab-examinations in patients who have had respective organ involvement: Blood count, ESR, liver and renal function tests, urine osmolality	Every 3 months	Yearly
Radiographs of bone lesions	Only if new lesions or reactivation suspected	Only if new lesions or reactivation suspected
Audiology in patients with history of ear/mastoid involvement	At 1 year	At 5 years
HR-CT, pulmonary function tests in patients with pulmonary involvement	Every 6 months	Only if progression suspected
Ultrasound in patients with liver involvement	Every 6 months	Yearly
Brain MRI in patients with DI or other endocrinopathies or patients with CNS risk lesions	At 1 year	Every 2 years
Neuropsychometric assessment in patients with CNS involvement	At 1 year	Every 2 years

\*Adapt for individual patients on the basis of systems involved and clinical indications

### Initial Treatment: Course 1



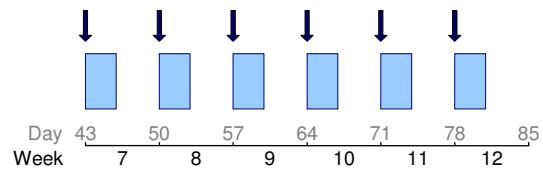
LEGEND:

PRED 40 mg/m<sup>2</sup>/day orally, weekly reduction after week 4

VBL 6 mg/m<sup>2</sup> i.v. bolus

**Figure 1**

### Initial Treatment: Course 2



LEGEND:

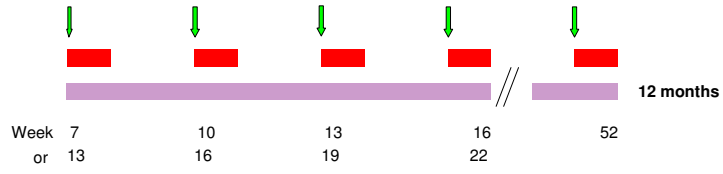
PRED 40 mg/m<sup>2</sup>/day orally, weekly for 3 days i.v. bolus

VBL 6 mg/m<sup>2</sup> i.v. bolus




**Figure 2**



## Continuation Treatment



### LEGEND:

-  PRED 40 mg/m<sup>2</sup>/d orally day 1-5 of week (7, 10), 13, 16, 19, ...52
-  VBL 6 mg/m<sup>2</sup>/d i.v. bolus q3 weeks
-  6-MP 50 mg/m<sup>2</sup>/d orally for 12 months

**Figure 3**

**For more information please contact the principal investigators or national LCH experts:**

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