MALIGNANCY ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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• HLH, also known as hemophagocytic syndrome, is an uncommon systemic inflammatory clinical syndrome

• HLH is caused by a defect in inflammatory signals that results in uncontrolled hypercytokinemia, usually in a setting of congenital or acquired defective natural killer (NK)/T-cell function in the cytotoxic pathway

• Untreated, 95% of children will die of the disease

The first reported case of hemophagocytic lymphohistiocytosis (HLH) was described in 1952 by Farquhar and Claireaux who called the disease familial hemophagocytic reticulosis

Classification of hemophagocytic lymphohistiocytosis (HLH)

Genetic HLH

Acquired HLH

### Genetic HLH

#### Familial HLH (Farquhar disease)
- First described by Farquhar and Claireaux in 1952
- Known gene defects (perforin, munc 13-4, syntaxin 11)
- Unknown gene defects

#### Immune deficiency syndromes
- Chédiak-Higashi syndrome (CHS)
- Griscelli syndrome (GS)
- Hermansky Pudlak syndrome type 2
- X-linked lymphoproliferative syndrome (XLP)

<table>
<thead>
<tr>
<th>HLH Subtype</th>
<th>Gene/Protein</th>
<th>Function</th>
<th>Location</th>
<th>% of Familial Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHL1</td>
<td>Unknown</td>
<td>Unknown</td>
<td>9q21.3-locus 6</td>
<td>~10^10</td>
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<tr>
<td>FHL2</td>
<td>PFR1/perforin 1</td>
<td>Cell lysis, membrane pore formation</td>
<td>10q21-22</td>
<td>20-50</td>
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<tr>
<td>FHL3</td>
<td>UNC13D/Munc 13-4</td>
<td>Cytolytic granule exocytosis</td>
<td>17q25</td>
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<tr>
<td>FHL4</td>
<td>STX11/syntaxin 11</td>
<td>Intracellular vesicle trafficking</td>
<td>6q24</td>
<td>~1</td>
</tr>
<tr>
<td>FHL5</td>
<td>STXB2/syntaxin binding protein 2 or UNC18B</td>
<td>Intracellular vesicle trafficking</td>
<td>19p13</td>
<td>Unknown</td>
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<tr>
<td>Griscelli syndrome type 2</td>
<td>RAB27A/Rab27a</td>
<td>Vesicle docking on microtubules</td>
<td>15q21</td>
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<tr>
<td>Chédiak-Higashi syndrome</td>
<td>LYST</td>
<td>Vesicle maturation and sorting</td>
<td>1q42.1-q42.2</td>
<td></td>
</tr>
<tr>
<td>Hermansky-Pudlak syndrome type 2</td>
<td>AP3B</td>
<td>Encoding β subunit of AP3, vesicle maturation and transport</td>
<td>5q14.1</td>
<td></td>
</tr>
<tr>
<td>XLP type 1</td>
<td>SHD2D1A/SAP protein</td>
<td>Polarization of cytolytic granules for transport to the immunological synapse</td>
<td>Xp25</td>
<td></td>
</tr>
<tr>
<td>XLP type 2</td>
<td>BIRC4/XIAP protein</td>
<td>Unclear</td>
<td>Xp25</td>
<td></td>
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</tbody>
</table>
**Acquired HLH**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exogenous agents</td>
<td>Infectious organisms, toxins (infectious organisms, toxins)</td>
</tr>
<tr>
<td>Endogenous products</td>
<td>Tissue damage, metabolic products (tissue damage, metabolic products)</td>
</tr>
<tr>
<td>Rheumatic diseases</td>
<td>Macrophage activation syndrome (MAS)</td>
</tr>
<tr>
<td>Malignant diseases</td>
<td>(M-HLH)</td>
</tr>
<tr>
<td>Others</td>
<td>Spontaneous or iatrogenic immune suppression-related HLH, and posthematopoietic or solid organ transplantation HLH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infection</th>
<th>Reported Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>Herpesviruses (EBV, CMV, HHV-8, HSV), HIV, HTLV, adenovirus, HAV, HBV, HCV, measles, mumps, rubella, dengue, hantavirus, parvovirus B19, enterovirus, influenza</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Peripheral T-cell/NK-cell lymphomas, ALCL, ALL, Hodgkin lymphoma, multiple myeloma, acute erythroid leukemia</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td>Prostate and lung cancer, hepatocellular carcinoma</td>
</tr>
<tr>
<td>MAS</td>
<td>Systemic-onset juvenile idiopathic arthritis, Kawasaki disease, systemic lupus erythematosus, seronegative spondyloarthropathies</td>
</tr>
</tbody>
</table>
**MALIGNANCY ASSOCIATED HLH**

**HLH as the initial manifestation of malignant disease**

"Malignancy-Triggered HLH"

In vitro data suggest that secretion of **cytokines** (including IFN-γ and IL-6) by the malignant cells contributes to the development of hyperinflammation

**HLH in the setting of iatrogenic immunosuppression from chemotherapy**

"Chemotherapy Triggered HLH"

- Patients frequently are in remission from malignancy
- In the majority of cases, in association with triggering infections that occur as the result of CMT-induced immunosuppression
In a normal subject, viral infection leads to the stimulation of antigen-specific CD8+ T cells, which transiently undergo clonal expansion, produce IFN-γ, and carry out cell-mediated cytolysis to eliminate the infected cells.

Following pathogen clearance, most of the effector cells die, leaving a small number of memory CD8+ T cells.
Patients with HLH display uncontrolled strong expansion of antigen-specific effector T cells, which secrete high levels of IFN-γ, further activating Macrophages.

High levels of secretion of inflammatory cytokines lead to an uncontrolled systemic inflammatory response.

Activated macrophages take up hematopoietic cells by phagocytosis (hemophagocytosis).

Activated lymphocytes and macrophages infiltrate various organs, massive tissue necrosis and organ failure.
HYPOTHESIS of Primary HLH that it involves:

- **Defective termination of the immune response** that results in persistent activation of macrophages and cytotoxic T cells.

- **Failure to remove Ag**, which results in ongoing stimulation of the immune effector cells.

- It is possible that **both failure to clear the pathogen, resulting in continued Ag stimulation, and failure to terminate the immune response** play important roles.
PATHOGENESIS OF HLH

Pathogenesis of secondary (acquired) HLH is even less clear, although patients with secondary forms of HLH are increasingly being found to have heterozygous changes or polymorphisms in the familial HLH genes.
Evolving views about the diversity of hemophagocytic lymphohistiocytosis (HLH)

(a) Historical view of HLH: primary vs. secondary

**Primary HLH:**
- FHL, XLP, other
- Infants
- Unknown triggers
- Recurrent (if untreated)
- Fixed NK cell defect

**Secondary HLH:**
- IAHS, MAHS, MAS
- Older children and adults
- Clearly identified triggers
- Low recurrence risk
- No fixed NK cell defect

(b) Emerging view of HLH: a continuum of risk

Threshold for development of HLH

- Null
- Hypomorphic
- Polygenic(?)
- None

Genetic mutations

Risma and Jordan Curr Opin Pediatr 2012
Clinical features HLH

- Fever [prolonged]
- Hepatosplenomegaly
- Bleeding
- Skin rash
- CNS abnormalities
- Jaundice

**The laboratory findings of**

- Bicytopenia or pancytopenia
- Coagulopathy
- Hyperlipidemia
- Hypofibrinogenemia
- Hyperferritinemia
- Transaminitis, hyperbilirubinemia
- Hypoalbuminemia
- Hyponatremia

HLH should be suspected in cases of an unexplained systemic inflammatory response syndrome (SIRS)

Very high serum levels of numerous cytokines including IFN-γ, tumor necrosis factor-α, IL-6, IL-10, and macrophage-colony-stimulating factor

Weitzman S, ASH 2011
SKIN RASH IN HLH
The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:
1. A molecular diagnosis consistent with HLH is made.
2. Diagnostic criteria for HLH are fulfilled (5 of the 8 criteria below):*
   Febrile
   Splenomegaly
   Cytopenias (affecting ≥ 2-3 lineages in the peripheral blood):
     - hemoglobin < 90 g/L (in infants < 4 weeks of age,
     - hemoglobin < 100 g/L), platelets < 100 × 10⁹/L,
     - neutrophils < 1.0 × 10⁹/L
   Hypertriglyceridemia and/or hypofibrinogenemia: fasting
     - triglycerides ≥ 3.0 mmol/L (ie, ≥ 265 mg/dL), fibrinogen ≤ 1.5 g/L
   Hemophagocytosis in BM, spleen, or lymph nodes
   Low or absent NK-cell activity (according to local laboratory reference)
   Ferritin ≥ 500 μg/L
   Soluble CD25 (ie, sIL2r) ≥ 2400 U/mL†

Weitzman S, ASH 2011
Supportive criteria include neurologic symptoms, cerebrospinal fluid pleocytosis, conjugated hyperbilirubinemia and transaminitis, hypoalbuminemia, hyponatremia, elevated D-dimers, and lactate dehydrogenase.

The absence of hemophagocytosis in the BM does not exclude a diagnosis of HLH.

Weitzman S, ASH 2011
The utility of HLH criteria are questioned because of the lack of specificity of the various criteria.

Individual criteria may lack specificity, but it is the presence of multiple criteria, reflecting the severity of the condition, that is important, along with the magnitude and progression of the abnormalities.

Weitzman S, ASH 2011
POINTS TO CONSIDER IN DIAGNOSIS

SERUM FERRITIN

- Ferritin levels > 10,000 μg/mL were 93% specific for the HLH.
- Suggested that levels > 30,000 are not uncommon in HLH and are 100% specific in the absence of an inborn error of iron metabolism.
- However, patients with proven HLH may have ferritin levels only slightly above normal.

sIL2r (sCD25)

- Measurement of sIL2r, reflecting the degree of activation of T cells, is useful in diagnosis and follow-up because very high levels are almost never seen outside of HLH

- Recent work has shown age-related variations in normal levels of sIL2r, which are not reflected in the published criteria and need be taken into account in future studies.
Hemophagocytosis

- Hemophagocytosis, a hallmark of activated macrophages, is neither specific nor sensitive for HLH and its presence should only be considered supportive.

Histiocyte with phagocytosis of erythrocytes and platelets
Helpful findings that are not part of published criteria

- The **presence of conjugated hyperbilirubinemia** (due to the tropism of histiocytes to the biliary tree), transaminitis, hypoalbuminemia, hyponatremia
- **High D-dimers** even when INR and PTT are normal
- **CNS pleocytosis**

Other evidence of ongoing consumption, such as a poor **response to transfusions**, may help to distinguish HLH-induced cytopenia from cytopenia due to other causes in the absence of HLH
DIAGNOSTIC DIFFICULTIES IN MALIGNANCY ASSOCIATED HLH
HLH as the initial manifestation of malignant disease “Malignancy-Triggered HLH”

In vitro data suggest that secretion of cytokines (including interferon-γ and interleukin-6) by the malignant cells contributes to the development of hyperinflammation.

• HLH in the setting of iatrogenic immunosuppression from chemotherapy “HLH During Chemotherapy”
  • Patients frequently are in remission from malignancy
  • In the majority of cases, in association with triggering infections that occur as the result of CMT-induced immunosuppression
Several possible mechanisms of pathogenesis

- First, it is postulated that the hyperinflammation is triggered by the neoplasm because of an excessive secretion of proinflammatory cytokines and persistent antigen stimulation by the tumor cells.

- Second, inherited immune disorders that predispose to both HLH and malignancy (e.g., X-linked lymphoproliferative diseases) may further predispose patients to the development of M-HLH.

- Third, M-HLH related to the combined immunodeficiency generated by the underlying malignancy and the loss of immune homeostasis because of chemotherapy (or hematopoietic stem cell transplantation or infection) further aggravates T-cell dysfunction that lowers the threshold for triggering HLH in these patients.

- Fourth, malignancy-induced immunodeficiency combined with tumor-directed therapy predisposes to infections, which may act as independent triggers of M-HLH in these patients.

Daver N et al, Cancer, June 2017
Several possible mechanisms of pathogenesis

More recently, HLH have been described in patients who were receiving immunotherapies.

These symptoms are caused by proinflammatory cytokine overproduction by T-cell–activating immunotherapies used in the treatment of leukemia/lymphoma and solid tumors (eg, bispecific monoclonal antibody blinatumomab, chimeric antigen receptor T-cell therapies, dendritic vaccines, combinations with checkpoint inhibitors, and immunomodulatory drugs, such as lenalidomide and thalidomide).

The cytokine release syndrome with these agents bears a clinical and immunologic signature similar to that of HLH and often responds to the therapies used in HLH.

Daver N et al, Cancer, June 2017
### PROGNOSIS IN MALIGNANCY ASSOCIATED HLH IN ADULTS

#### Summary of Malignancy-Associated Hemophagocytic Lymphohistiocytosis Clinical Outcomes Across Different Institutions

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Most Frequent Associated Malignancy</th>
<th>Six-Month Survival Rate, %</th>
<th>Median Survival, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamamyan 2016&lt;sup&gt;33&lt;/sup&gt;</td>
<td>35</td>
<td>AML/MDS (n = 13), T-cell lymphoma (n = 10), DLBCL (n = 6), HL (n = 6), CLL (n = 4), CML (n = 2), follicular lymphoma (n = 2)</td>
<td>30</td>
<td>2.0</td>
</tr>
<tr>
<td>Parikh 2014&lt;sup&gt;23&lt;/sup&gt;</td>
<td>32</td>
<td>T-cell lymphoma (n = 19), DLBCL (n = 6), EBV-associated PTLD (n = 3), HL (n = 1), CMML (n = 1), hemangioendothelioma (n = 1), systemic histiocytosis (n = 1)</td>
<td>Not reported</td>
<td>1.4</td>
</tr>
<tr>
<td>Otrock &amp; Eby 2015&lt;sup&gt;32&lt;/sup&gt;</td>
<td>21</td>
<td>B-cell neoplasms (n = 10), T-cell neoplasms (n = 6), HL (n = 3), AML (n = 1), MDS (n = 1)</td>
<td>20</td>
<td>1.1</td>
</tr>
<tr>
<td>Lehmberg 2015&lt;sup&gt;25&lt;/sup&gt;</td>
<td>21</td>
<td>T-cell neoplasms (n = 12), B-cell neoplasms (n = 7)</td>
<td>67</td>
<td>1.2</td>
</tr>
<tr>
<td>Machaczka 2011&lt;sup&gt;10&lt;/sup&gt;</td>
<td>8</td>
<td>HL (n = 2), MM (n = 2), 1 each of B-CLL, PTCL, AILD, WM, ATL</td>
<td>38</td>
<td>2.4</td>
</tr>
<tr>
<td>Shabbir 2011&lt;sup&gt;24&lt;/sup&gt;</td>
<td>6</td>
<td>AML (n = 2), T-cell lymphoma (n = 2), postauto-SCT for MM (n = 2)</td>
<td>Not reported</td>
<td>1.2 (Entire adult HLH cohort; n = 18)</td>
</tr>
</tbody>
</table>

Daver N et al, Cancer, June 2017
Malignancy-Triggered HLH occurs most frequently but not exclusively with:
- T-cell and NK-cell lymphomas or leukemias
- diffuse large B-cell lymphoma (DLBCL)
- Hodgkin lymphoma.

Solid tumors are not commonly associated with HLH with only a 3% prevalence in adults.
HLH during chemotherapy

• Most frequently found during leukemia and lymphoma treatment
• During any phase of the therapy
• The prevalence of an infectious trigger ranges from 75% to 100%
• Infectious trigger could be viruses, bacteria, and fungi
DIAGNOSTIC DIFFICULTIES IN MALIGNANCY ASSOCIATED HLH

• In patients with Malignancy-Triggered HLH, viral infections may act as co-triggers.
• This is exemplified by EBV-associated lymphomas where both the virus and the lymphoma can drive HLH.

In contrast to infection-associated HLH in non-immunocompromised patients, where viruses are the major inciting pathogens, invasive fungi and bacterial infections may also play a substantial role in HLH during chemotherapy.
It is often difficult to differentiate between Malignancy-Triggered HLH and HLH During Chemotherapy.

These conditions may co-exist, such as in a patient with reactivation of a malignancy that also has an infection. In such situations, both the malignancy and the infection may contribute to the HLH.
In HLH, the likelihood of an underlying malignant disease increases with age.

- In adults, **nearly 50%** of the published cases were triggered by a neoplasm mainly lymphoma, and
- approximately **1% of adult patients with a hematologic malignancy** develop HLH.

In **children and adolescents**, a malignant context in HLH has a reported prevalence of **8%**.
Currently, there are no generally accepted criteria for the definition of Malignancy-Triggered HLH or HLH During Chemotherapy.

The HLH-2004 criteria may serve as a substitute definition, but they have substantial weaknesses.
The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:
1. A molecular diagnosis consistent with HLH is made.
2. Diagnostic criteria for HLH are fulfilled (5 of the 8 criteria below):*
   - Fever
   - Splenomegaly
   - Cytopenias (affecting ≥ 2-3 lineages in the peripheral blood):
     - hemoglobin < 90 g/L (in infants < 4 weeks of age, hemoglobin < 100 g/L), platelets < 100 × 10⁹/L,
     - neutrophils < 1.0 × 10⁹/L
   - Hypertriglyceridemia and/or hypofibrinogenenemia: fasting
     - triglycerides ≥ 3.0 mmol/L (ie, ≥ 265 mg/dL), fibrinogen ≤ 1.5 g/L
   - Hemophagocytosis in BM, spleen, or lymph nodes
   - Low or absent NK-cell activity (according to local laboratory reference)
   - Ferritin ≥ 500 µg/L
   - Soluble CD25 (ie, sIL2r) ≥ 2400 U/mL†

Weitzman S, ASH 2011
In the context of malignancy, several of these characteristics may be present and caused by the HLH and/or by the neoplasm (e.g. fever, organomegaly, cytopenias, elevated LDH, and coagulation disturbances).

Elevation of ferritin must be differentiated from transfusion-related iron overload.

Hemophagocytosis in the bone marrow, lymph nodes, or liver is neither a sensitive nor a specific finding in HLH, and it may be present in several conditions related with malignancies, such as septicemia.

Lehmberg K, et al; Haematologica 2015
Daver N et al, Cancer, June 2017
Elevated soluble CD25 is considered a marker of T-cell activity in HLH, as well as a marker that correlates with tumor burden in non-Hodgkin lymphoma.

Fujiwara S et al, Blood 2013
For clinical purposes, it is thus crucial to judge whether:

- the combination
- the extent, and
- the progression of the mentioned clinical and laboratory abnormalities are unusual, unexpected, and otherwise unexplained
Follow up of malignancy associated HLH

- Temperature, spleen size, blood count, ferritin, fibrinogen, soluble CD25, and LDH can be used as markers of disease activity and treatment response.

- Platelets tend to rapidly reflect the level of HLH activity, with a drop in the platelet count indicating flares of disease.
Ferritin rapidly increases in active HLH; however, levels normalize rather slowly following resolution of inflammation.

Here again, differentiation between the effects of the underlying neoplasm and HLH can be difficult.

A repeat bone marrow aspirate may be indicated if cytopenias persist to determine whether they are related to treatment toxicity or active HLH.
Malignancy-Triggered HLH has been described in patients with hereditary HLH and other primary immunodeficiencies.

The decision as to whether a hereditary defect predisposing to HLH should be excluded in a patient with HLH in the context of malignancy should be taken on a case-by-case basis.
TREATMENT OF HLH
Traditional Treatment of HLH

- Effective early therapy reduced the mortality from HLH from 95% to \( \sim 30\%-35\% \) in the HLH-94 trial.

- The HLH-94 and HLH-2004 trials used high-dose dexamethasone, etoposide, and cyclosporine A (CSA), together with intrathecal methotrexate (IT MTX) for patients in whom CNS-HLH did not remit after 2 weeks of dexamethasone.

Traditionally, the initial goal of therapy in HLH has been to suppress the overactive immune system, thus preventing immune-mediated organ damage.

Carren and Behrens, Curr Opin Rheumatol 2012, Weitzman S, ASH 2011
Figure 1: Flow-sheet for Children with Hemophagocytic Lymphohistiocytosis (HLH) in HLH-2004

Patients with HLH * → Register and start #: Initial 8 weeks chemotherapy

<table>
<thead>
<tr>
<th>Genetically verified or Familial disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuation therapy until SCT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Persistent non-familial, non-genetically verified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuation therapy until SCT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resolved non-familial, non-genetically verified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuation therapy until SCT</td>
</tr>
</tbody>
</table>

* If there is a treatable infection it should be treated but be aware that this may not be sufficient and the patient may need HLH-treatment in addition. All severe forms should start HLH-treatment. If HLH is persistent or recurring consider that the patient may have an undiagnosed inherited disease. HLH may also develop secondary to a number of other diseases as malignancies, rheumatic diseases and metabolic disorders, requiring a different treatment.

# Start therapy if the patient has a genetically verified disease, a familial form of HLH, or if the disease is severe, persistent, or recurrent.
All primary HLH patients need HST for cure, survival after myeloablative-conditioning HST ranging from 50% for haploidentical donor HST to 70% for HLA matched family donor

Carren and Behrens, Curr Opin Rheumatol 2012, Weitzman S , ASH 2011
Treatment of Acquired HLH

- Except for rheumatologic-HLH (MAS), all forms of HLH can be initially treated on same protocol, and there is no need to distinguish 1ry from 2ry HLH at the time of diagnosis.

- There should be no delay in starting therapy for this purpose.

Carren and Behrens, Curr Opin Rheumatol 2012
Management in Malignancy-Triggered HLH

• It is uncertain whether primarily a malignancy-directed or an HLH-directed regimen should be used
• This must be decided case by case

- Infectious triggers require rigorous treatment

- Anti-infectious prophylaxis (anti-fungal, *pneumocystis jiroveci*) and regular surveillance for secondary infections or reactivations (fungi, EBV, CMV) should be strongly considered in active HLH

- Anti-B-cell therapy (e.g. rituximab) may be considered in cases marked by highly replicative EBV infection.
Management In HLH During Chemotherapy

Postponing subsequent chemotherapeutic blocks or interruption of maintenance therapy should be strongly considered, except for the event of relapse of the neoplasm.

The necessity and extent of HLH-directed treatment depends on the clinical severity.
<table>
<thead>
<tr>
<th>Research group</th>
<th>Clinical trial identifier</th>
<th>Drug or treatment</th>
<th>Region</th>
<th>Years</th>
<th>Overall survival, %</th>
<th>Target</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beijing Friendship Hospital</td>
<td>NCT02631109</td>
<td>Pegaspargase, doxorubicin, etoposide, methylprednisolone</td>
<td>Beijing, China</td>
<td>2015-present</td>
<td>46</td>
<td>EBV-HLH</td>
<td>Recruiting</td>
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<tr>
<td>Children's Hospital of Philadelphia</td>
<td>NCT02007239</td>
<td>Tocilizumab</td>
<td>Philadelphia, PA</td>
<td>2013-present</td>
<td>NA</td>
<td>IL-6 receptor</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Children's Hospital Medical Center, Cincinnati</td>
<td>NCT01104025</td>
<td>ATG, etoposide, dexamethasone/hydrocortisone</td>
<td>Cincinnati, OH</td>
<td>2010-2016</td>
<td>NA</td>
<td>T cells, proliferation</td>
<td>Complete, data pending</td>
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<tr>
<td>Karolinska University Hospital</td>
<td>NCT00426101</td>
<td>Dexamethasone, etoposide, cyclosporine A</td>
<td>Multiple</td>
<td>2007-present</td>
<td>55</td>
<td>Proliferation</td>
<td>Ongoing</td>
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<tr>
<td>Assistance Publique - Hôpitaux de Paris</td>
<td>NCT02472054</td>
<td>Alemtuzumab, prednisone/metylprednisolone, cyclosporine A</td>
<td>Paris, France</td>
<td>2015-present</td>
<td>NA</td>
<td>CD-52, proliferation</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

Vick E et al. Blood Advances 2017
# Ongoing clinical trials in HLH

<table>
<thead>
<tr>
<th>Research group</th>
<th>Clinical trial identifier</th>
<th>Drug or treatment</th>
<th>Region</th>
<th>Years</th>
<th>Overall survival, %</th>
<th>Target</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Michigan Cancer Center</td>
<td>NCT02400463</td>
<td>Ruxolitinib</td>
<td>Ann Arbor, MI</td>
<td>2015-present</td>
<td>NA</td>
<td>Jak1/2</td>
<td>Ongoing</td>
</tr>
<tr>
<td>NovImmune SA</td>
<td>NCT01818492</td>
<td>NI-0501 (anti-IFN-γ)</td>
<td>Multiple</td>
<td>2013-present</td>
<td>NA</td>
<td>IFN-γ</td>
<td>Ongoing</td>
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<tr>
<td>Peking University People's Hospital</td>
<td>NCT02569463</td>
<td>IL-2</td>
<td>Beijing, China</td>
<td>2014-present</td>
<td>NA</td>
<td>BM suppression</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Baylor College of Medicine</td>
<td>NCT01494103</td>
<td>T cells with iCaspase-9</td>
<td>Houston, TX</td>
<td>2011-present</td>
<td>NA</td>
<td>BM suppression</td>
<td>Ongoing</td>
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Vick E et al. Blood Advances 2017
A.M.H

- Two years old diagnosed preB ALL in 9/2013
- Started CMT on CCG standard risk
- During interim maintenance II he developed persistent pancytopenia, fever, progressive firm liver enlargement
- DD: relapse # HLH # viral infection
- BM was hypocellular, blasts 1.5%, no hemophagocytosis
- HLH markers: serum ferritin 4500ng/ml, TG 231mg/dl, fibrinogen 227mg/dl
- CMV Ig M was very high and CMV PCR positive
- EBV serology was negative
- HLH 2004 protocol was started with gancyclovir
- Genotyping for familial HLH was negative
- The patient improved and survived ALL and HLH
43 patients with HLH diagnosed in the last 5 years

21 patients with potentially secondary HLH, including 5 patients on top of malignancy: 4 had ALL and one had HD, in addition to one patient who had myelodysplasia and one patient on top of Langerhans cell histiocytosis

Viral trigger was evident in 67% mainly CMV

Genetic mutations were positive in 30%, negative in 25% and not done in 45%
Summary and Conclusions

• **Malignancies and infections during chemotherapeutic immunosuppression are major triggering events of HLH**

• **The tools** currently being used to diagnose HLH when it occurs in the context of a malignancy **are far from perfect**

• Heightened **clinical awareness** and use of the criteria available can facilitate HLH diagnosis and thus direct subsequent therapy

• Given the **lack of robust evidence on the optimal choice of therapeutic interventions**, treatment decisions must currently be made on a case-by-case basis.
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Summary and Conclusions

• Malignancies and infections during chemotherapeutic immunosuppression are major triggering events of HLH.

Furthermore, although new agents and protocols will no doubt improve morbidity and mortality, early diagnosis remains the key in prevention of catastrophic effects.

➢ Awareness
➢ Early Available Diagnostic tools
➢ Prevention of infectious triggers

In the absence of robust evidence on the optimal choice of therapeutic interventions, treatment decisions must currently be made on a case-by-case basis.
THANK YOU