Lysosomal Storage Diseases
A group of inherited, autosomal recessive diseases resulting from deficiency of various lysosome enzymes responsible for degradation of macromolecules or transportation of degraded product out of lysosome. These molecules accumulate “store” in lysosomes in histiocytes
- Sphingolipidosis: Gaucher disease, Neimann-Pick disease, Tay-Sachs disease
- Mucopolysaccharidosis (MPS I and MPS II): Hunter disease, Hurler disease
- Glycogenosis: Mannosidosis
- Glycogenosis (type II): Pompe glycogenosis
- Mucolipidosis: Mucolipidosis I-VI
- Lysosomal transport defect

**Blood morphology:** Non-specific

**Bone marrow morphology:** Gaucher: Accumulation of “tissue paper” type histiocytes
   - Neimann-Pick: Accumulation of foamy, vacuolated histiocytes, some cases have “sea-blue” histiocytes

**Blood work:** Diagnosis established by testing specific enzyme activity in blood mononuclear cells or fibroblasts

**Differential diagnosis:** Conditions associated with increased cell turnover, hyperlipidemia, plasma expander therapy, total parenteral nutrition
   - Granulomatous inflammation, Macrophage activation syndrome and HLH

**Macro巨phage Activation Syndrome (MAS) and Hemophagocytic Lymphohistiocytosis (HLH)**

**Macrophage activation syndrome (MAS)**
Increased macrophage phagocytic activity of hematopoietic cells in bone marrow and reticuloendothelial system resulting in peripheral cytopenia.
- Common causes include viral infection, malignant neoplasm, rheumatologic disorders, multi-organ failure
- These conditions increase production of cytokines (interleukins) and other pro-inflammatory mediators (TNF etc), which drive macrophage phagocytic activity

**Blood morphology:** Pancytopenia

**Bone marrow morphology:** Increased phagocytic macrophages in variable degrees

**Blood work:** Markedly increased acute phase reactants: ferritin, C reactive protein

**Differential diagnosis:** HLH

**Treatment and Prognosis:** Treat underlying disease, control cytokine storm. Most patients recover

**Hemophagocytic lymphohistiocytosis (HLH)**
Inherited syndrome resulting in uncontrolled phagocytic activity by macrophages due to mutations of apoptotic genes
- Primarily affect children, 90% younger than 2 years
Clinical presentation: prolonged fever, cytopenia, high ferritin (marked), high triglyceride, low fibrinogen, hepatosplenomegaly, lymphadenopathy

**Blood morphology:** Pancytopenia

**Bone marrow morphology:** Increased phagocytic macrophages in variable degrees

**Blood work:**
- Mutations in *perforin* gene (pore-forming cytolytic protein, causes release of granzyme, 30-50% cases): diagnostic
- Diagnosis by clinical features (when absence of genetic information): requires 5 of the 8 clinical criteria (see table below)

**Diagnostic diagnosis:** MAS, other conditions with increased bone marrow macrophages

**Prognosis and Treatment:** Fatal if untreated. 50% survival when treated by immunosuppressant and chemotherapy followed by stem cell transplant

### Diagnostic criteria of HLH proposed by Histiocytic Society 1997

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<thead>
<tr>
<th>Requires 5 of the following 8 features</th>
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<tbody>
<tr>
<td>1. Fluctuating fever</td>
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<td>2. At least bicytopenia (must have thrombocytopenia)</td>
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<td>3. Marked increase of ferritin</td>
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<td>4. Hypertriglyceridemia or hypofibrinogenemia</td>
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<td>5. Hepatosplenomegaly</td>
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<td>6. Evidence of hemophagocytosis (bone marrow, spleen, liver, or CSF)</td>
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<td>7. Low/absent NK cell function</td>
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<td>8. Increased soluble CD25</td>
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#### Autoimmune Myelofibrosis

Cytopenia due to bone marrow fibrosis associated with any autoimmune conditions, some patients may only have increased autoimmune antibodies without clinical disease

Anemia is present in all patients, thrombocytopenia neutropenia in some patients

**Blood morphology:** Anemia with or without thrombocytopenia or neutropenia. No specific morphologic abnormalities. Minimal tear drop cells or leukoerythroblastosis

**Bone marrow morphology:** Normal hematopoiesis, erythroid hyperplasia common, bone marrow reticulin fibrosis at least 2+, frequent reactive lymphoid aggregates

**Blood work:** Serum autoimmune antibodies detectable, most common DAT and antinuclear antibodies

**Differential diagnosis:** Primary myelofibrosis, other marrow fibrotic conditions

**Treatment and Prognosis:** Excellent prognosis, response to steroids