Objectives:
1. Explain why proliferation of leukemic cells and the subsequent reduction in production of normal blood cells contribute to clinical manifestations of leukemia.
2. Recognize the importance of a bone marrow aspiration or biopsy procedure in establishing the diagnosis of leukemia.
3. The approaches to establishing a diagnosis and initial management aimed at preserving life with respect to transfusion of blood and platelets and the risk of metabolic and clotting abnormalities.
4. Lymphoma- describe the organ / system of origin, the typical signs and symptoms and common clinical associations, outline the main features and differences of Non-Hodgkin’s (NHL T and B Cell) and Hodgkin’s Lymphoma, be aware of the long term complications of tumor treatment as a consequence of chemotherapy, radiotherapy and surgery.

Childhood Leukemia

Incidence and Epidemiology
Childhood cancer is rare. In contrast to the adult population, in whom solid tumormalignancies predominate, almost 40% of childhood cancers are hematologic malignancies (leukemia and lymphoma).
Leukemia is the most frequent malignancy that occurs during childhood and comprises approximately 30% of all childhood cancers. Historically, leukemia was classified initially in four groups based on clinical presentation and morphologic appearance of the malignant cells: acute lymphocytic leukemia (ALL), acute nonlymphocytic leukemia (ANLL), chronic myelogenous leukemia (CML), and chronic lymphocytic leukemia (CLL).

Frequency of Types of Childhood Leukemia in Historic Classification*

<table>
<thead>
<tr>
<th>Leukemia Classification</th>
<th>% of Childhood Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphocytic (ALL)</td>
<td>80</td>
</tr>
<tr>
<td>Acute nonlymphocytic (ANLL)</td>
<td>17</td>
</tr>
<tr>
<td>Chronic myelogenous (CML)</td>
<td>3</td>
</tr>
<tr>
<td>Chronic lymphocytic (CLL)</td>
<td>Virtually none</td>
</tr>
</tbody>
</table>

*Based on cellular morphology and clinical features

Definitions
I. Acute leukemia: Accumulation of over 30% of malignant white cells in the bone marrow and blood
II. Chronic myelogenous leukemia: Myeloproliferative disease characterized by the predominance of relatively mature myeloid cells.
Clinical Presentation and Diagnosis

The clinical manifestations of leukemia result from the effects of proliferation of malignant cells within the bone marrow and other organs.

- The extramedullary organs most frequently experiencing leukemia infiltration are the liver, spleen, and lymph nodes. Other important sites of potential leukemia infiltration are the central nervous system (CNS) and the testes. Leukemia has the potential to involve any body organ, including skin, kidney, lung, pleura, pericardium, eye, breast, ovaries, and gastrointestinal tract.

- Leukemia expansion within the bone marrow may produce signs and symptoms of bone involvement. Approximately 25% of children who have newly diagnosed leukemia present with a complaint of severe bone pain. When bones of the lower extremity are involved, the child may exhibit a limp or refusal to walk. Leukemia proliferation within the bone marrow results in decreased production of normal white blood cells, red blood cells, and platelets.

- Malignant leukemic blast cells are frequently, but not always, observed circulating in the blood. Because conditions such as infectious mononucleosis occasionally can result in large numbers of atypical white cells in the blood, a bone marrow examination is essential for a conclusive diagnosis of leukemia.

- Bone marrow studies in children who have leukemia are important to assist in identifying specific subtypes of leukemia. Also, because children who have leukemia do not always present with lymphadenopathy or hepatosplenomegaly and may not have detectable leukemia cells in the blood, a bone marrow examination serves to distinguish leukemia from other conditions involving severe bone marrow failure such as aplastic anemia or myelofibrosis. Children who have aplastic anemia and children who have acute leukemia may present with similar degrees of severe anemia, neutropenia, or thrombocytopenia and similar clinical signs and symptoms produced by the cytopenias.

- Many initial signs and symptoms of leukemia are related to decreased production of normal blood cells.

- The major life-threatening complication in a child who has acute leukemia:
  - Overwhelming infection, often sepsis or severe pneumonia. The risk of sepsis can be correlated directly with the severity of neutropenia.
  - Bleeding manifestations in a child who has leukemia most frequently are due to: severe thrombocytopenia. On occasion, Severe coagulation factor deficiencies in a rare subtype of ANLL known as acute promyelocytic leukemia.
Severe airway obstruction with respiratory distress may result from massive mediastinallymphadenopathy.

Hyperleukocytosis, defined as a white blood cell leukemia blast count more than $100\times10^9/L$, can result in damage to vital organs in children who have ANLL. The elevated numbers of leukemia blast cells may sludge in the vascular supply of the brain, lungs, and liver, producing infarction within these organs.

**Diagnosis:**

Although the diagnosis of leukemia may be evident from the peripheral blood smear, bone marrowsamples for morphology, flow cytometry, and cytogenetics are obtained to outline the type of leukemia and the appropriate therapy.

- **Morphologic examination of marrow smears** is the traditional diagnostic study; According to the French-American-British (FAB) classification system, acute lymphoblastic leukemia (ALL) is classified into 3 groups based on morphology (L1, L2 and L3) and acute non lymphoblastic leukemia (ANLL) is classified into 3 groups based on morphology (M0-M7).
- **Immunophenotyping using flow cytometry** which permits more accurate diagnosis. This technique uses monoclonal antibodies directed against specific cell antigens (called cluster designation [CD] markers) to determine the type of leukemia immunologically.
- **Cerebrospinal fluid (CSF)** is examined to verify that central nervous system (CNS) leukemia is not present.
**Childhood Lymphomas**

- Lymphoma is the third most common cancer among children.
- The two broad categories of lymphoma, Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL), have different clinical manifestations and treatments.

**HL Histology**

The pathologic hallmark of HD is the identification of Reed – Sternberg cells in tumor tissue.

Reed-Sternberg cells are giant binucleated cells with prominent nucleoli, classically a single giant nucleolus in each nucleus.

The four histologic subtypes of:

1. Lymphocyte predominance
2. Mixed cellularity
3. Nodular sclerosis
4. Lymphocyte depletion

**NHL Histology**

Pediatric NHLs show diffuse destruction of the lymph node architecture, they are all high-grade malignancies.

NHLs are distributed primarily into three major categories:

1. Small, non-cleaved cell lymphoma (Burkitt and non-Burkitt subtypes) found in about 50% of cases
2. Lymphoblastic lymphoma in about 35% of cases
3. Large cell NHL in about 15% of cases.

**Clinical Presentation of Hodgkin Disease and Non-Hodgkin Lymphoma**

The most common first clinical manifestation of HL or NHL is painless lymph node enlargement, most often in the cervical on supraclavicular chains. The onset is typically subacute and prolonged for HL and rapid through the course of a few days or weeks.
HL

- Patients commonly present with painless, non-tender, firm, rubbery, cervical or supraclavicular lymphadenopathy.
- Patients may present signs of airway obstruction (dyspnea, hypoxia, cough), pleural or pericardial effusion, hepatocellular dysfunction, or bone marrow infiltration.
- Asymptomatic discovered by CXR
- Systemic symptoms, classified as B symptoms, are unexplained fever >39°C, weight loss >10% total body weight over 3 mo, or drenching night sweats

NHL

- Depend primarily on pathological subtype and sites of involvement.
- 70% present with advanced stages III or IV including extranodal disease as GIT, bone marrow, and central nervous system (CNS) involvement.
- BL commonly presents with abdominal or head and neck disease with involvement of the bone marrow or CNS.
- LL commonly presents with an intrathoracic or mediastinal supradiaphragmatic mass, and may spread to the bone marrow and CNS.

Diagnosis:

- Any patient with persistent, unexplained lymphadenopathy unassociated with an obvious underlying inflammatory or infectious process should have a chest radiograph to identify the presence of a mediastinal mass before node biopsy
- Lymph node or tissue biopsy is mandatory for histologic diagnosis; excisional biopsy is preferred over needle biopsy to ensure that adequate tissue is obtained, for appropriate immunocytochemical and molecular studies, culture, and cytogenetic analysis

Recommended Diagnostic Evaluation for Children Who Have Lymphoma

1. Complete history and physical examination
2. Complete blood count with differential count, erythrocyte sedimentation rate
3. Chemistries: renal and hepatic function tests, serum electrolytes, and mineral panel
4. Serum lactate dehydrogenase and uric acid; alkaline phosphatase
5. Imaging studies: Chest radiograph, computed tomography (CT) of neck and chest, CT or magnetic resonance imaging of abdomen and pelvis, gallium scan, bone scan
6. Bone marrow examination
7. Cerebrospinal fluid examination (cytology)

1&3 Recommended primarily for Hodgkin lymphoma
2&5 Recommended primarily for non-Hodgkin lymphoma
4 If gallium scan suggests bone involvement or for children who have bone pain and elevated alkaline phosphatase level
Treatment Options of lymphomas:

● Supportive
  – Tumour lysis
  – Neutropenic sepsis
  – Nutrition
  – Organ dysfunction

● Chemotherapy
  – multi-agent
  – intensive

● Radiotherapy in special cases