Leukaemia
Leukaemias and lymphomas are the commonest forms of haematological malignancy.
Many forms of leukaemia exist, but they are all characterised by the production of excessive numbers of abnormal white blood cells.

The leukaemias can be broadly divided into four groups:

- acute myeloblastic leukaemia (AML)
- acute lymphoblastic leukaemia (ALL)
- chronic myelocytic leukaemia (CML)
- chronic lymphocytic leukaemia (CLL)
Blood stem cell

Myeloid stem cell

Myeloblast

Granulocytes

Red blood cells

Platelets

Lymphoid stem cell

Lymphoblast

B lymphocyte

T lymphocyte

Natural killer cell

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Epidemiology

Chronic leukaemia

- Chronic lymphocytic leukaemia (CLL)
  - CLL is the most common form of leukaemia.
  - CLL mainly affects an older age group.
  - It rarely occurs in young people and is twice as common in men as in women.

- Chronic myelocytic leukaemia (CML)
  - CML is primarily a disease of middle age with the median onset in the 40–50 year old age group.
  - It can occur in younger people.
Acute leukaemia

- Acute myeloblastic leukaemia (AML)
  - AML is the most common form of the disease.
  - The incidence of AML rises steadily with age, occurring rarely in young children.

- Acute lymphoblastic leukaemia (ALL)
  - ALL is predominantly a childhood disease, with the peak incidence in the 3–5 year age group.
  - It is the most common childhood cancer.
Etiology

• Leukaemia is thought to result from a combination of factors that induce genetic mutations which allow mutated cells to proliferate faster than normal cells.
• and/or to fail to die in response to normal apoptotic signals.

**Risk factors for leukaemia**

✓ Radiation
✓ Exposure to chemicals and cytotoxic drugs
✓ Viruses
✓ Genetic factors
✓ Haematological disorders
Pathophysiology

Chronic leukaemias

• In chronic leukaemia, the normal bone marrow is replaced by a malignant clone of maturing haemopoietic cells.

Chronic lymphocytic leukaemia

• CLL is characterized by small, relatively incompetent B lymphocytes that accumulate in peripheral blood and bone marrow.
Chronic Myeloid Leukemia

- The characteristic feature of CML is the predominance of maturing myeloid cells in blood, bone marrow, liver, spleen and other organs.
- CML was the first cancer to be associated with chromosomal abnormality, mainly the Philadelphia chromosome (Ph), named for the city in which it was identified. This abnormality results in the over-activation of the enzyme Tyrosine kinase.
Acute leukaemias

• In acute leukaemia, the normal bone marrow is replaced by a malignant clone of immature blast cells derived from the myeloid (in AML) or lymphoid (in ALL) series.

• In **ALL**, the blasts may infiltrate lymph nodes and other tissues such as liver, spleen, testis and the meninges.

• In **AML**, blasts tend to infiltrate skin, gums, liver and spleen.
Clinical manifestation

Chronic leukaemias
Chronic lymphocytic leukaemia

• The majority of patients are asymptomatic when diagnosed.
• CLL is often diagnosed by chance.
• Symptoms presented may include:
  ✓ Fatigue, chills, bleeding, and lymphadenopathy.
  ✓ Chronic infections.
  ✓ Organomegaly consist of splenomegaly & Hepatomegaly
  ✓ haemolytic anaemia, are common.
Chronic Myeloid Leukemia

✓ Patient with CML commonly presented with non-specific symptoms such as malaise, weight loss and night sweat.

✓ The main physical sign is enlarged spleen that may give rise abdominal discomfort.

✓ Hepatomegaly is present in about 40% of patients.

✓ Neutropenia and thrombocytopenia are uncommon at presentation. Thus unlike acute leukemia, patients with CML rarely present with symptoms of infection or hemorrhage.
Acute leukemia

✓ Most of the clinical manifestations of acute leukaemia are related to bone marrow failure.
✓ Symptoms of infection, anaemia and bleeding are common and life-threatening presenting problems.
✓ The involvement of other tissues such as spleen, liver, lymph nodes and meninges is more common in ALL than AML.
✓ Involvement of the central nervous system (CNS) may give rise to headaches, vomiting and irritable behaviour.
✓ Less commonly, patients present with features of hypermetabolism, hyperuricaemia or generalised aches and pain.
# Investigations

<table>
<thead>
<tr>
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<th>AML</th>
<th>ALL</th>
<th>CML</th>
<th>CLL</th>
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<tr>
<td><strong>WBC</strong></td>
<td>↑, may be N or ↓</td>
<td>↑, may be N or ↓↓</td>
<td>↑↑ commonly</td>
<td>commonly ↑</td>
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<td><strong>Differential WBC</strong></td>
<td>Mainly myeloblasts</td>
<td>Mainly lymphoblasts</td>
<td>Granulocytes ↑↑, especially neutrophils, myelocytes, basophils and eosinophils &lt;10% blasts present</td>
<td>monoclonal lymphocytes</td>
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<td><strong>RBC</strong></td>
<td>Severe anaemia</td>
<td>Severe anaemia</td>
<td>Anaemia common</td>
<td>Anaemia in 50% of patients, generally mild</td>
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<td><strong>Platelets</strong></td>
<td>↓↓</td>
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<td>Usually ↑↑, may be N or ↓</td>
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<td></td>
<td>AML</td>
<td>ALL</td>
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<td>Bone marrow</td>
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<td>Predominantly blasts</td>
<td>Hypercellular blasts &lt; 10%</td>
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<td>splenomegaly</td>
<td>50%</td>
<td>60%</td>
<td>Usual and severe</td>
<td>Usual and moderate</td>
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<td>Other features</td>
<td>DIC, high urate</td>
<td>High urate, CNS involvement</td>
<td>↑Serum uric acid</td>
<td>Immune paresis</td>
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Treatment

Acute leukemia

• The short term goal of treatment for acute leukemia is to rapidly achieve a complete clinical and hematological remission.

• Complete remission (CR) is defined as the disappearance of all clinical and bone marrow evidence (normal cellularity > 20% with < 5% blasts) of leukemia, with restoration of normal hematopoiesis (neutrophils ≥ 1,500/mm3 and platelets > 100,000/mm3).
Acute lymphoblastic leukemia

Therapy for ALL has been divided into three phases:
1- Remission induction
2- Consolidation therapy
3- Maintenance therapy
Central nervous system prophylaxis

- Patients with ALL are at high risk of developing CNS infiltration.
- Cytotoxic drugs penetrate poorly into the CNS which thus acts as a sanctuary site for leukaemic cells. For this reason, all patients with ALL receive CNS prophylaxis. Cranial irradiation plus Intrathecal methotrexate or high dose intravenous methotrexate can be used.
1- Remission induction

• The goal of remission induction is to rapidly induce a complete clinical and hematologic remission.
• This process can involve prephase, induction I, and induction II.

• During prephase, all relevant diagnostic and prognostic information are collected, and corticosteroids used to identify prednisone good responders.

• Induction I consists of vincristine, prednisone, and anthracycline combination, with or without asparaginase and cyclophosphamide.
• Prednisone is sometimes substituted by dexamethasone, which is more powerful and penetrates the blood brain barrier.
• Induction II consists of cyclophosphamide, mercaptopurine, and cytarabine, regardless of CR status, but a more intensive regimen can be used in patients refractory to induction I.
2- Consolidation

• Consolidation (or intensification) therapy in ALL is started after a CR has been achieved, and refers to continued intensive chemotherapy in an attempt to eradicate clinical undetectable disease.

• Consolidation phase consists vincristine, daunorubicin, prednisolone, etoposide, cytarabine and thioguanine or a combination of these chemotherapy and bone marrow transplantation.
3- Maintenance

- Maintenance treatment is important to sustain a CR.
- Treatment usually consists of methotrexate and 6-mercaptopurine with intermittent vincristine and prednisolone.
- The treatment of relapsed disease varies with the site of relapse. Isolated CNS or testicular relapse may be successfully treated with radiation and reinduction therapy.
- Bone marrow relapse is much more difficult to cure, especially if it occurs early.
• A small proportion of paediatric patients and a larger proportion of adult patients have the Philadelphia chromosome translocation within their ALL blasts. Such patients have a relatively poor prognosis and therefore require more intensive therapy. There is some evidence that drug combinations including imatinib may enhance the response of these leukaemias to therapy.
Acute myeloblastic leukaemia

the treatment of AML involves induction and consolidation chemotherapy.

1- Remission induction

• Induction phase consists of cytarabine, daunorubicin and Etoposide.
2- Consolidation

• Intensive consolidation chemotherapy consists of high-dose cytarabine and daunorubicin or amsacrine.

• An alternative approach to post-remission therapy is stem cell transplantation.
Treatment of relapsed or refractory acute myeloid leukemia

• Treatment of AML in relapse is difficult and the prognosis is generally poor.

• For treatment of relapsed or refractory AML Cytarabine has been administered alone or in combination with various agents, including etoposide, fludarabine, topotecan, and an anthracycline.

• Another treatment approach for it consists of combination of anti-CD33 antibody, which targets myeloid blasts, with calicheamicin, an anthracycline antibiotic.
Other agents used for relapsed or refractory AML includes clofarabine and 5-Azacytidine.

Clofarabine
It is effectiveness particularly in the treatment of older patients and toxic effects may be less severe than those associated with other chemotherapy regimens.

5-Azacytidine
It is also used, especially in older patients and those whose disease has evolved from myelodysplastic syndrome MDS.
Acute Promyelocytic Leukaemia (APL)

- The disease is clinically characterized by the presence of disseminated intravascular coagulopathy (DIC) at presentation. Since these patients are so prone to life-threatening haemorrhage at diagnosis, the management of a new case of APL is considered a medical emergency.

- The leukaemic cells are sensitive to all-trans retinoic acid (ATRA) (Tretinoin), which induces blast maturation and can induce remission when used as a single agent.
• Using a combination of ATRA and anthracycline chemotherapy, it is now possible to achieve long-term cure in >80% patients.

• ATRA is used in consolidation and maintenance treatment to improve outcome further.

• Arsenic trioxide (ATO) is used in treating relapsed or refractory APL.
Chronic leukaemia

Chronic myelocytic leukaemia

• Hydroxyurea was the most widely used drug in the management of CML in chronic phase.
• Interferon can control symptoms of CML but was also the first agent shown to modify the disease process. Its effects seem to be enhanced by the addition of low-dose cytarabine.
• The treatment of CML has experienced a dramatic change since the introduction of imatinib.
• Many patients were intolerant of the interferon and cytarabine combination and crossed over to receive imatinib.
• Dasatinib and nilotinib are second-generation tyrosine kinase inhibitors (TKIs) designed to overcome resistance to Imatinib.
Chronic lymphocytic leukaemia

- The alkylating agent chlorambucil was the most common agent used in the treatment of CLL.
- Corticosteroids can reduce the lymphocyte count without contributing to myelosuppression and are used to treat autoimmune phenomena such as haemolytic anaemia and immune thrombocytopenia.
• Fludarabine-based chemotherapy today is used as first-line therapy for younger patients with CLL. Although good responses were seen even in patients whose leukaemia was resistant to alkylating agents.
• Splenic complications may necessitate splenectomy or splenic irradiation.
• Radiotherapy can also be used to control localized painful lymphadenopathy.
• Combination chemotherapy, such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone and rituximab) used in lymphoma, may be beneficial in advanced disease.
• Alemtuzumab (Campath-1H) is a humanised monoclonal anti-CD52 antibody. CD52 is present on most lymphocytes including malignant lymphocytes in CLL. Binding of this antibody induces both antibody-mediated and complement-mediated T-cell cytotoxicity against malignant B cells.

• In relapsed patients, the duration of response to Campath-1H is relatively short.