Leukaemias
**Leukaemias**: These are malignant disorders of the haematopoietic stem cell compartment, characterised by increased number of white cells in the bone marrow and/or peripheral tissue.

**Incidence**: 10/100000 per annum, of which under half are acute leukaemias. Males are more frequently affected:

- 3:2 in acute leukaemias.
- 2:1 in chronic lymphocytic leukaemias.
- 1.3:1 in chronic myeloid leukaemias.
Risk factors for leukaemia

Ionising radiation
- After atomic bombing of Japanese cities (myeloid leukaemia)
- Radiotherapy
- Diagnostic X-rays of the fetus in pregnancy

Cytotoxic drugs
- Especially alkylating agents (myeloid leukaemia, usually after a latent period of several years)
- Industrial exposure to benzene

Retroviruses
- Adult T-cell leukaemia/lymphoma (ATLL) caused by human T-cell lymphotropic virus 1 (HTLV-1), most prevalent in Japan, the Caribbean and some areas of Central and South America and Africa

Genetic
- Identical twin of patients with leukaemia
- Down’s syndrome and certain other genetic disorders

Immunological
- Immune deficiency states (e.g. hypogammaglobulinaemia)
Terminology and classification

Leukaemias are traditionally classified into four main groups:

• acute lymphoblastic leukaemia (ALL)
• acute myeloid leukaemia (AML)
• chronic lymphocytic leukaemia (CLL)
• chronic myeloid leukaemia (CML).
Acute leukaemia

Pathophysiology
There is a failure of cell maturation in acute leukaemia. Proliferation of cells that do not mature leads to an accumulation of primitive cells that take up more and more marrow space at the expense of the normal haematopoietic elements. Eventually, this proliferation spills into the blood.

Acute myeloid leukaemia (AML) is about four times more common than acute lymphoblastic leukaemia (ALL) in adults. In children, the proportions are reversed, the lymphoblastic variety being more common.
The symptoms are usually those of bone marrow failure (anaemia, bleeding or infection).

Signs (abdominal fullness*hepatosplenomegaly*, tenderness of lymph nodes *lymphadenopathy*, tenderness in bone)
Investigations

1- CBC .... Pancytopina
2- peripheral blood smear ....
Myeloblasts in AML ➔
Lymphoblast in ALL ➔
3- bone marrow biopsy (which is hypercellular and replaced by blast cells (more than 20%) .
4-immunophenotyping
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Myeloblast</th>
<th>Lymphoblast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Larger</td>
<td>Smaller</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Moderate</td>
<td>Scanty</td>
</tr>
<tr>
<td>Auer rod</td>
<td>May be present</td>
<td>Absent</td>
</tr>
<tr>
<td>Nuclear chromatin</td>
<td>Fine</td>
<td>Coarse</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>Prominent, 1–4</td>
<td>Indistinct</td>
</tr>
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Management

The first decision must be whether or not to give specific treatment to attempt to achieve remission. This is generally aggressive, has numerous side-effects, and may not be appropriate for the very elderly or patients with serious comorbidities. In these patients, supportive treatment can effect considerable improvement in well-being.
Specific therapy

The aim of treatment is to destroy the leukaemic clone of cells without destroying the residual normal stem cell compartment from which repopulation of the haematopoietic tissues will occur. There are three phases:
Remission induction. In this phase, a fraction of the tumour is destroyed by combination chemotherapy. The patient goes through a period of severe bone marrow hypoplasia lasting 3–4 weeks and requires intensive support and inpatient care from a specially trained multidisciplinary team. The aim is to achieve remission, a state in which the blood counts return to normal and the marrow blast count is less than 5%. Quality of life is highly dependent on achieving remission.

• Remission consolidation. If remission has been achieved, residual disease is attacked by therapy during the consolidation phase. This consists of a number of courses of chemotherapy, again resulting in periods of marrow hypoplasia. In poor-prognosis leukaemia, this may include allogeneic HSCT.

• Remission maintenance. If the patient is still in remission after the consolidation phase for ALL, a period of maintenance therapy is given, with the individual as an outpatient and treatment consisting of a repeating cycle of drug administration. This may extend for up to 3 years if relapse does not occur.
In patients with ALL, it is necessary to give prophylactic treatment to the central nervous system, as this is a sanctuary site where standard therapy does not penetrate. This usually consists of a combination of cranial irradiation, intrathecal chemotherapy and high-dose methotrexate, which crosses the blood–brain barrier if a patient fails to go into remission with induction treatment, alternative drug combinations may be tried, but the outlook is poor unless remission can be achieved. Disease that relapses during treatment or soon after the end of treatment carries a poor prognosis and is difficult to treat. The longer after the end of treatment that relapse occurs, the more likely it is that further treatment will be effective.
Supportive therapy

**Anaemia** Anaemia is treated with red cell concentrate transfusions.

**Bleeding** Thrombocytopenic bleeding requires platelet transfusions

**Infection** Fever (> 38°C) lasting over 1 hour in a neutropenic patient indicates possible sepsis. Parenteral broad-spectrum antibiotic therapy is essential. Empirical therapy is given according to local bacteriological resistance patterns

**Metabolic problems** Frequent monitoring of fluid balance and renal, hepatic and haemostatic function is necessary. Patients are often severely anorexic and diarrhoea is common as a consequence of the side-effects of therapy; they may find drinking difficult and hence require intravenous fluids and electrolytes.

Cellular breakdown during induction therapy (tumour lysis syndrome) releases intracellular ions and nucleic acid breakdown products, causing hyperkalaemia, hyperuricaemia, hyperphosphataemia and hypocalcaemia. This may lead to renal failure. Allopurinol and intravenous hydration are given to try to prevent this.

**Psychological problems**
Chronic leukaemia

*CL VS AL
Chronic myeloid leukaemia

Pathophysiology

Chronic myeloid leukaemia (CML) is a myeloproliferative stem cell disorder resulting in proliferation of all haematopoietic lineages but manifesting predominantly in the granulocytic series. Maturation of cells proceeds fairly normally.

The defining characteristic of CML is the chromosome abnormality known as the Philadelphia (Ph) chromosome. This is a shortened chromosome 22 resulting from a reciprocal translocation of material with chromosome 9. The break on chromosome 22 occurs in the breakpoint cluster region (BCR). The fragment from chromosome 9 that joins the BCR carries the abl oncogene, which forms a fusion gene with the remains of the BCR. This BCR ABL fusion gene codes for a 210 kDa protein with tyrosine kinase activity, which plays a causative role in the disease as an oncogene, influencing cellular proliferation, differentiation and survival. In some patients in whom conventional chromosomal analysis does not detect a Ph chromosome, the BCR ABL gene product is detectable by molecular techniques.
The disease has three phases:

- **A chronic phase**: in which the disease is responsive to treatment and is easily controlled, which used to last 3–5 years. With the introduction of imatinib therapy, this phase has been prolonged to encompass a normal life expectancy in many patients.

- **An accelerated phase**: (not always seen), in which disease control becomes more difficult.

- **Blast crisis**: in which the disease transforms into an acute leukaemia, either myeloblastic (70%) or lymphoblastic (30%), which is relatively refractory to treatment. This is the cause of death in the majority of patients.
Investigations

1- CBC results are variable between patients. There is usually a normocytic, normochromic anaemia. The leucocyte count can vary from 10 to $600 \times 10^9 /L$. In about one-third of patients, there is a very high platelet count, sometimes as high as $2000 \times 10^9 /L$.

2- Blood film, the full range of granulocyte precursors, from myeloblasts to mature neutrophils, is seen but the predominant cells are neutrophils and myelocytes. There is often an absolute increase in eosinophils and basophils, and nucleated red cells are common.

3- Bone marrow should be obtained to confirm the diagnosis and phase of disease by morphology,

4- Chromosome analysis to demonstrate the presence of the Ph chromosome, and RNA analysis to demonstrate the presence of the BCR ABL gene product.

5- Blood LDH levels are elevated and the uric acid level may be high due to increased cell breakdown.
Management

Chronic phase

There are now five available tyrosine kinase inhibitors (TKIs) for the treatment of CML, these specifically inhibit BCR ABL tyrosine kinase activity. Imatinib, nilotinib and dasatinib are recommended as first-line therapy in chronic phase CML; they usually normalise the blood count within a month and within 3–6 months produce complete cytogenetic response (disappearance of the Ph chromosome) in some 90% of patients. A sample of bone marrow is taken at 6 months to confirm complete cytogenetic response, and patients are subsequently monitored by 3-monthly real-time quantitative polymerase chain reaction (PCR) for BCR ABL mRNA transcripts in blood.

For those failing to respond or who lose their response and progress on first-line therapy, options include switching to a different TKI. The third-generation TKI ponatinib is effective, however. Allogeneic HSCT is now reserved for patients who fail TKI therapy.

Hydroxycarbamide and interferon were previously used for control of disease. Hydroxycarbamide is still useful in palliative situations and interferon is used in women planning pregnancy.
Accelerated phase and blast crisis

Management is more difficult. For patients in accelerated phase, TKI therapy is indicated, most commonly with nilotinib or dasatinib. When blast transformation occurs, the type of blast cell should be determined. Response to appropriate acute leukaemia treatment is better if disease is lymphoblastic than if myeloblastic. Second- or third-generation TKIs such as dasatinib are used in combination with chemotherapy to try and achieve remission. In younger and fitter patients an allogeneic HSCT is appropriate therapy if a return to chronic phase is achieved. Hydroxycarbamide can be an effective single agent and low-dose cytarabine can also be used palliatively in older patients
Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is the most common variety of leukaemia, accounting for 30% of cases. The male-to-female ratio is 2 : 1 and the median age at presentation is 65–70 years. In this disease, B lymphocytes, which would normally respond to antigens by transformation and antibody formation, fail to do so. An ever-increasing mass of immuno-incompetent cells accumulates, to the detriment of immune function and normal bone marrow haematopoiesis.
Investigations

1- peripheral blood findings of a mature lymphocytosis (> $5 \times 10^9$ /L) with characteristic morphology and cell surface markers.

2- Immunophenotyping reveals the lymphocytes to be monoclonal B cells expressing the B-cell antigens CD19 and CD23, with either kappa or lambda immunoglobulin light chains and, characteristically, an aberrant T-cell antigen CD5. On flow cytometry, some people are shown to have circulating CLL cells at a level less than $5 \times 10^9$ /L. This is known as monoclonal B lymphocytosis of uncertain significance.

3- reticulocyte count

4- direct Coombs test, as autoimmune haemolytic anaemia may occur Serum immunoglobulin levels should be estimated to establish the degree of hypogammaglobulinaemia, which is common and progressive.

5- Bone marrow examination by aspirate and trephine is not essential for the diagnosis of CLL, but may be helpful in difficult cases, for prognosis (patients with diffuse marrow involvement have a poorer prognosis) and to monitor response to therapy.
Staging of chronic lymphocytic leukaemia

Clinical stage A (60% patients)
• No anaemia or thrombocytopenia and fewer than three areas of lymphoid enlargement

Clinical stage B (30% patients)
• No anaemia or thrombocytopenia, with three or more involved areas of lymphoid enlargement

Clinical stage C (10% patients)
• Anaemia and/or thrombocytopenia, regardless of the number of areas of lymphoid enlargement
Management

No treatment is required in clinical stage A and life expectancy in old age is normal. Treatment is required only if there is bone marrow failure, massive or progressive lymphadenopathy, splenomegaly, systemic symptoms such as weight loss or night sweats, or rapidly increasing lymphocyte count, autoimmune haemolytic anaemia or thrombocytopenia.

Treatment is based on the age and fitness of the patient and mutations.

Fludarabine plus alkylating agent cyclophosphamide, rituximab, bendamustine and oral chlorambucil. CLL cells are dependent on abnormal or persistent signaling through B-cell receptor BCR pathway. Drugs that inhibit this pathway are now available and show great promise. Ibrutinib, inhibits Bruton’s tyrosine kinase and idelalisib inhibits P13 kinase, both are components of the BCR.

Bone marrow failure or autoimmune cytopaenia may respond to glucocorticoid treatment. Supportive care is increasingly required in progressive disease, such as transfusion for symptomatic anaemia or thrombocytopenia, prompt treatment for infection, and for patient with hypogammaglobulinaemia, immunoglobulin replacement. Radiotherapy may be used for large lymph nodes causing discomfort or local obstruction or for symptomatic splenomegaly. Splenectomy may be required for low blood count due to autoimmune destruction or to hypersplenism, and can relieve massive splenomegaly.