Leukemia: AML, CML, ALL and CLL
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Reviewed September 2017, Expires September 2019
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Purpose
The purpose of this course is to define leukemia, describe current treatment, and describe the characteristics, symptoms, diagnosis, and treatment for the 4 primary types of leukemia: AML, CML, ALL, and CLL.

Goals
Upon completion of this course, the healthcare provider should be able to:

- Define leukemia.
- Discuss hematopoiesis of leukemia.
- Differentiate between acute and chronic forms.
- Describe at least 8 common symptoms of leukemia.
- Discuss normal and abnormal laboratory tests.
- Explain how to calculate the absolute neutrophil count.
- Discuss the implications of neutropenia.
- Discuss the normal platelet count and the implications of thrombocytopenia.
- Discuss the 3 common stages of chemotherapy.
- Explain the cell cycle and the difference between cell cycle-specific agents and cell cycle-non-specific agents.
- Discuss 10 different types of chemotherapeutic agents.
- Explain 3 types of radiation commonly used for leukemia.
- Discuss hematopoietic stem cell transplantation.
- Discuss acute myelogenous leukemia (AML), including characteristics, symptoms, diagnostic findings, and treatment considerations.
- Discuss subtypes of AML.
- Discuss chronic myelogenous leukemia (CML), including characteristics, symptoms, diagnostic findings, and treatment considerations.
- Discuss the 3 different phases of CML.
Discuss acute lymphocytic leukemia (ALL), including characteristics, symptoms, diagnostic findings, and treatment considerations.

Discuss subtypes of ALL.

Discuss chronic lymphocytic leukemia (CLL), including characteristics, symptoms, diagnostic findings, and treatment considerations.

Discuss two classification systems for CLL.

**Introduction**

Leukemia is a group of malignant disorders affecting the blood and blood-forming tissues in the bone marrow, lymphatic system, and spleen. The word *leukemia* literally means “white blood” because it is a neoplastic proliferation of one type of blood cell, typically a leukocyte or white blood cell. Leukocytosis, an increased white blood cell count, is a normal response to infection, but when leukocytosis becomes chronic or progressively elevates without obvious cause, then it may indicate malignancy.

In 2010, approximately 43,050 men and women (24,690 men and 21,840 women) in the United States were diagnosed with leukemia, and 21,840 died of the disease. Leukemia accounts for 33% of cancers in children and 1340 deaths yearly, so it is often thought of as a disease of childhood. In children, the highest incidence is between 1 to 4 and the highest death rate between 10 and 19. However, incidence is 10 times higher in adults. The median age for diagnosis is 66, and median age of death from leukemia is 74.

Despite much research into leukemia, the cause is often elusive. Leukemia appears to result from a combination of factors, which can include genetic predisposition, chromosomal changes, chemical agents (benzene), chemotherapeutic agents, radiation, immunocompromise, and viruses. Although viruses have been tied to leukemias in animals, only adult T cell leukemia is known to result from a virus, human T cell leukemia virus type 1 (HTLV-1).
Regardless of the type of leukemia, the abnormal cells in the bone marrow depress production of other cells, resulting in a number of adverse effects:

- Anemia occurs as erythrocyte (red blood cell) production falls.
- Risk of infection occurs if neutrophil count decreases.
- Clotting factors decrease, increasing risk of bleeding as thrombocytopenia (reduced platelet count) occurs.
- Risk of physiological fracture increases as periosteum weakens because of proliferation of cells in the bone marrow.
- Hypertrophy and fibrosis may occur in other organs, such as the liver, spleen, and lymph glands because of infiltration of malignant cells.
- Increased intracranial pressure, ventricular dilation, and irritation of the meninges with resultant headache, vomiting, papilledema, nuchal rigidity, coma, and death can occur from infiltration of malignant cells into the central nervous system.
- Hypermetabolic state deprives cells of nutrients and causes loss of appetite, weight loss, general fatigue, and muscle atrophy.

Classification
Hematopoiesis, the process by which blood cells are formed, involves production of specific cells from stem cell precursors according to body needs. In leukemia, a defect occurs in the myeloid or the lymphoid stem cell. The most common feature of all types of leukemia is unregulated proliferation of leukocytes in the bone marrow.

Leukemias are classified as lymphoid or myeloid, depending on the affected stem cell type. Usually leukemias classified as blast cell or stem cell refer to lymphoid defects. Additionally, leukemias are classified as acute or chronic.

The 4 primary types of leukemia are acute lymphocytic/lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML) or acute nonlymphoblastic leukemia (ANLL), chronic myelogenous leukemia (CML), and chronic lymphocytic leukemia (CLL) with a number of subtypes. Leukemias are often referred to by a number of different names, depending on the involved cell, and this can be confusing at times.

Acute and chronic forms differ in cell maturity and onset:

- **Acute forms:** Onset is often abrupt, within weeks, and death may occur within weeks to months without treatment. Proliferation of abnormal cells leaves little room for normal cell production. Cells may proliferate in the liver and spleen as well,
and they may infiltrate other organs, such as the meninges, gums, lymph nodes, and skin.

Typically, leukocyte development halts at the blast phase, so most affected leukocytes are undifferentiated or blasts. With acute leukemia, the white blood count may remain low because the cells are halted at the blast stage. Acute forms may occur in both adults and children.

- **Chronic forms:** Onset is much slower, often over months or years. Normal cell production may occur as well for a long period of time, but in late stages of chronic disease, the abnormal cells interfere with normal cell production. The majority of leukocytes are mature. Chronic forms are rare in children.

### Laboratory tests

Leukocytes are white blood cells (WBCs). Normal total values vary according to age. The white count usually increases with infection and returns to normal when infection subsides.

<table>
<thead>
<tr>
<th>Leukocyte count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
</tr>
<tr>
<td>1-3 years:</td>
</tr>
<tr>
<td>8-13 years:</td>
</tr>
<tr>
<td>Adult:</td>
</tr>
</tbody>
</table>

The differential is the percentage of each type of leukocyte out of the total. An increase in the white blood cell count is usually related to an increase in one type and often an increase in immature neutrophils, known as bands, referred to as a “shift to the left,” generally an indication of an infectious process.

- Normal WBC for adults: 4,500-11,000.
- Acute infection: 11,000+, 30,000 indicates a severe infection.
- Viral infection: 4,000 and below.

Because the proportion of most leukocytes is small, only an increase in neutrophils or lymphocytes is usually significant enough to result in increased total white count with leukemia.
<table>
<thead>
<tr>
<th></th>
<th>31%</th>
<th>54%</th>
<th>59%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils (Total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils (bands)</td>
<td>3.1%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Neutrophils (segments)</td>
<td>28%</td>
<td>51%</td>
<td>58%</td>
</tr>
<tr>
<td>Absolute neutrophil count (ANC)</td>
<td>1500 to 8500</td>
<td>1800 to 8000</td>
<td>1800 to 7700</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>61%</td>
<td>38%</td>
<td>34%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>4.8%</td>
<td>4.3%</td>
<td>4%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>2.6%</td>
<td>2.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.4%</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

**Neutrophils (Total)**

31% 54% 59%

3.1% 3% 3%

28% 51% 58%

1500 to 8500 1800 to 8000 1800 to 7700

61% 38% 34%

4.8% 4.3% 4%

2.6% 2.4% 2.7%

0.4% 0.5% 0.5%

**Absolute neutrophil count (ANC)**

ANC = Total WBC X (% neutrophils + % bands/100)

Using this formula, if the white blood count is 3200 with 70% neutrophils and 3% bands, the calculation would indicate that despite the low WBC count, the patient does not have neutropenia:

ANC = 3000 X 73/100 = 2190

If the white count is 5300 with 10% neutrophils and 1% bands, neutropenia is evident despite the normal WBC:

ANC = 5300 X 11/100 = 583

**Why is neutropenia important?**

The ANC falls with increased destruction of neutrophils or decreased production. With leukemia, neutropenia is a direct result of both the leukemic disease process and chemotherapy used to treat it, so it is a primary concern during therapy.

Neutropenia increases the risk of both exogenous (environmental) and endogenous (GI tract, skin) infection, depending on the severity and duration. A short-lasting severe neutropenia may pose less actual risk than a longer mild neutropenia.

There are no specific symptoms related to neutropenia, so without
regular blood testing, it may go undiagnosed until infection occurs. In some cases, chemotherapy is withheld or reduced until the ANC rises, but this puts the patient at increased risk from the malignancy, especially if the treatment has a potential for cure. In that case, growth factors (G-CSF or CM-CSF) may be administered to stimulate production. As the bone marrow recovers, neutrophil production may increase again.

Patients who exhibit both neutropenia and fever usually have an infection and are hospitalized for broad-spectrum intravenous antibiotic therapy. Cultures of blood, urine, and sputum and chest x-ray are done to try to determine the site of infection and the pathogenic agent. When cultures and sensitivities are completed, the antibiotic regimen may be modified. Patients receiving antibiotics must be carefully monitored for superinfection, especially fungal.

**Oral moniliasis**

Maintaining adequate nutrition is necessary as decreased protein stores impair the immune system. Invasive procedures, such as IVs, increase risk of infection.

Measures to prevent infection in those with neutropenia include:
- Monitor blood count daily and temperature every 4 hours, notifying physician if temperature >38°C (101°F).
- Prohibit visitors with illness, including cold or sore throat.
- Provide private room if ANC <1000.
- Prohibit fresh flowers as stagnant water may breed bacteria.
- Change water in all containers (include humidifiers) every day.
- Plan patient care so that patient is seen before others if possible to avoid carrying contamination from one patient to another.
- Eliminate fresh salads and unpeeled fresh fruit or vegetables.
- Provide HEPA filter mask if patient is outside of room.
- Ensure total body hygiene daily and wash perineal area after each BM.
- Provide oral hygiene after meals and every 4 hours during daytime, avoiding lemon glycerine swabs, mouthwash, and hydrogen peroxide.
- Avoid plastic cannulas for peripheral IVs if ANC <500.
- Follow protocols for IV insertion and care, using antimicrobial solution to cleanse skin before insertion.

Thrombocytopenia is a common finding with leukemia. Normal values:

<table>
<thead>
<tr>
<th>Platelet count</th>
<th>Increased bleeding &lt;50,000 and increased clotting &gt;750,000.</th>
</tr>
</thead>
<tbody>
<tr>
<td>150,000 to 400,000 mmm³</td>
<td></td>
</tr>
</tbody>
</table>

**Why is thrombocytopenia important?**

Like neutropenia, thrombocytopenia can result from reduced platelet production or increased platelet destruction caused by leukemia or chemotherapy. Additionally, severe infection, which often occurs with neutropenia, can suppress platelet production.

As the platelet count drops <50,000, the ability of the blood to clot decreases. With invasive procedures, a count <50,000 increases risk of bleeding, but otherwise, risk is not usually significant until count drops to <20,000, at which point common indications include:

- Petechiae.
- Nasal bleeding.
- Gingival bleeding.
- Excessive menstrual flow.

Severe risk of bleeding occurs with a platelet count <5000:

- CNS hemorrhage.
- GI hemorrhage.

A bone marrow biopsy is often used to determine the cause of platelet deficiency.
• **Reduced platelet production** (which can occur with acute leukemias and chemotherapy): Platelet transfusions may increase platelet count.

• **Increased platelet destruction** (which can occur with CLL): The bone marrow shows increased megakaryocytes (cells from which platelets develop) and normal or increased production of platelets as the body attempts to compensate. If platelets are being destroyed, platelet transfusions provide little relief as the transfused platelets are also destroyed. In this case, treatment is usually similar to that for idiopathic thrombocytopenia purpura: Immunosuppressive agents, such as prednisone, cyclophosphamide, azathioprine, and dexamethasone.

**Standard treatment protocol**

The protocol for treatment varies depending on the type of leukemia. Generally, a combination of drugs is given as this approach is more effective than monotherapy. There are generally 3 stages to chemotherapy:

- Induction
- Consolidation
- Maintenance

**Induction**

Patients are usually hospitalized for 4 to 6 weeks during initial treatment. The purpose is to induce remission with bone marrow clear of disease and blood
counts within normal limit. During this time, chemotherapy eradicates both leukemic cells and normal myeloid cells, so the person becomes severely neutropenic, anemic, and thrombocytopenic, putting patients at risk for severe infections and bleeding. Patients may develop bacterial, fungal, and viral infections, and severe mucositis, which causes diarrhea and impairs nutritional absorption.

Supportive care includes administering blood products, such as packed red blood cells and platelets, providing antibiotics to treat infections, Granulocytic growth factors (G-CSF or GM-CSF) may shorten the period of neutropenia by stimulating the bone marrow to increase production of leukocytes.

**Consolidation**  After the patient has recovered from the effects of induction, consolidation treatment is provided over 4 to 8 months, often with the same chemotherapeutic agents used during induction but at lower dosages in order to kill any remaining malignant cells. Intrathecal chemotherapy may be administered concurrently as a prophylaxis to prevent CNS involvement. This treatment may be done on an outpatient basis with multiple treatment cycles.

**Maintenance**  Continued treatment may be provided for up to 3 years with some types of leukemia but with less intense chemotherapy in order to retain remission. The patient is monitored closely for both progress and side effects with weekly blood counts.

**Relapse**  Sometimes people relapse after completing the 3 stages of chemotherapy. When that occurs, re-induction may be carried out, especially with children, usually using a different protocol of drugs. Many drugs currently used to treat leukemia, especially for relapses, are those in clinical trials.

**Other treatments**  Additional treatments may be used, depending on the severity of the disease and degree of infiltration:

- Intrathecal chemotherapy is administered into the spinal fluid for treatment of infiltration of the central nervous system.
- Radiation to the brain may be indicated in addition to intrathecal chemotherapy with severe disease, especially in children when infiltration poses danger to brain development.
- Bone marrow transplant or peripheral blood stem cell transplant with donor stem cells or the patient’s stem cells.
Blood transfusions: packed red blood cells, platelets.

**The cell cycle and chemotherapy**

The purpose of chemotherapy is primarily to prevent replication of malignant cells and to treat systemic disease, such as leukemia or other metastasized cancers. Chemotherapy is used to cure, control, or provide palliation, so medications are chosen based on the realistic goal for the individual patient.

Cells that are actively proliferating are the most sensitive to chemotherapy. Cells that are not dividing but have the potential for proliferation are not destroyed by chemotherapy, so repeated cycles of therapy are required in order to kill these cells as they become activated. Cells go through predictable cell cycle patterns in which one cell divides to become two daughter cells.

**Cell phases:**
- **G1:** RNA and protein synthesis occur.
- **S:** DNA synthesis occurs.
- **G2:** DNA synthesis is complete, mitotic spindle forms.
- **M:** Mitosis occurs with cell division.
- **G0:** Resting (inactive phase).

**Classification**

Chemotherapeutic agents are classified by relationship to the cell phase and by chemical
Chemotherapeutic agents are classified by whether or not they target a particular cell phase:

- **Cell cycle-specific agents**: Some chemotherapeutic agents are classified according to which part of the cell cycle they target. These drugs are referred to as cell cycle-specific agents because they destroy cells that are actively reproducing by interfering with this process. Most target S phase or M phase.

- **Cell cycle-nonspecific agents**: Some chemotherapeutic agents act independent of the cell phase and have a longer effect, resulting in damage or death of the malignant cell.

Chemotherapeutic agents are also classified according to their chemical group, with each group providing a different mechanism of action. There are many different agents in most groups (some examples listed below).

<table>
<thead>
<tr>
<th>Alkylating agents</th>
<th>Cell cycle-specific</th>
<th>Alter DNA structure, causing breaks.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Busulfan, carboplatin, chlorambucil, cisplatin dacarbazine, melamine, ifosfamide)</td>
<td>Cell cycle-nonspecific</td>
<td>Interfere with metabolites needed for RNA and DNA synthesis.</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Cell cycle-specific (S)</td>
<td>Modify DNA function and interfere with RNA so cells die when they try to divide.</td>
</tr>
<tr>
<td>(Methotrexate AKA MTX, cytarabine AKA arabinosylcytosine or Ara-C, 5-fluoracil AKA 5-FU, gemcitabine, fludarabine, L-asparaginase)</td>
<td>Cell cycle-nonspecific</td>
<td>Disrupt cell membrane. Decrease circulating lymphocytes. Depress immune system.</td>
</tr>
<tr>
<td>Antitumor antibiotics</td>
<td>Cell cycle-nonspecific</td>
<td>Stimulate cellular differentiation.</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Cell cycle-nonspecific</td>
<td>Alter DNA structure, causing breaks.</td>
</tr>
<tr>
<td>(Cortisone, hydrocortisone, dexamethasone)</td>
<td>Cell cycle-nonspecific</td>
<td>Interfere with metabolites needed for RNA and DNA synthesis.</td>
</tr>
<tr>
<td>Hormonal agents</td>
<td>Cell cycle-nonspecific</td>
<td>Modify DNA function and interfere with RNA so cells die when they try to divide.</td>
</tr>
<tr>
<td>(Androgens, anastrozole,</td>
<td>Cell cycle-nonspecific</td>
<td>Disrupt cell membrane. Decrease circulating lymphocytes. Depress immune system.</td>
</tr>
</tbody>
</table>

Group.
### Miscellaneous agents
(L-asparaginase, tamoxifen, procarbazine, arsenic trioxide, all-trans retinoic acid AKA ATRA, hydroxyurea)
- **Varies, depending on agent**

### Mitotic spindle poisons
- **Plant alkaloids**
  - (epipodophyllotoxin, etoposide*, teniposide, vinblastine, vincristine)
- **Taxanes** (paclitaxel, docetaxel)

### Nitrosoureas
(Carmustine, lomustine, semustine, streptozocin)
- **Cell cycle-nonspecific**

### Topoisomerase inhibitors
- **Type I** (Irinotecan, topotecan)
- **Type II** (Amsacrine, etoposide, etoposide phosphate, teniposide)

*Also classified as a Topoisomerase inhibitor*

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**Targeted therapy**

Targeted therapy is a new approach to chemotherapy in which characteristics that differentiate cancer cells from normal cells are targeted. There are 3 categories of targeted therapy:

- **Varied targeted therapy**: Small molecules enter cells and disrupt cell function, causing the cells to die:
  - Signal transduction inhibitors: Imatinib mesylate, gefitinib, cetuximab, lapatinib.
  - Biologic response modifier agent: Denileukin, Diftitox.
  - Proteasome inhibitor: Bortezomib.
- **Monoclonal antibodies**: Target specific antigens (proteins) on B or T-lymphocyte cancer cells so immune system can destroy
them. Agents used for leukemia include rituximab, alemtuzumab and ofatumumab.

- **Angiogenesis inhibitors**: Blood vessels that supply nutrients to the cell are targeted in order to starve the cells.

**Protocol** In designing a treatment protocol, often combinations of drugs are used. For example, a protocol may call for the following:

- **Antimetabolite**: Cytarabine (cell cycle-specific targeting S phase).
- **Antitumor antibiotic**: Daunorubicin (cell cycle-non-specific).
- **Mitotic spindle poison**: Etoposide (cell cycle-specific targeting M phase).

Most chemotherapeutic agents have adverse effects, often severe, depending upon the particular agent. Common adverse effects include:

- Bone marrow suppression.
- Nausea and vomiting.
- Thrombocytopenia.
- Neutropenia.
- Neuropathies.
- Anorexia.
- Hepatic, renal, and/or cardiac toxicity.
- Hair loss.
- Stomatitis.
- Renal toxicity.
- Diarrhea.

**ALERT** Healthcare providers should always be aware of specific guidelines for the administration of chemotherapeutic agents as they are often highly toxic and may be absorbed through inhalation or contact with skin. OSHA provides guidelines for proper handling of chemotherapeutic agents.

**Extravasation** Chemotherapy for leukemia is usually administered intravenously although some types may be given orally. Patients receiving intravenous chemotherapy must be monitored carefully as the agents may irritate vessel walls, and extravasation (infiltration) may result in severe pain.
and local tissue damage, as many agents are vesicants that can cause necrosis.

Early signs of extravasation include swelling, redness, itching, and vesicles on the skin. Most patients experience pain initially, but some do not. If the agent is a vesicant, the tissue begins to ulcerate within a few days and may create a large open ulcer that requires skin grafting, so monitoring the IV and instructing patients about the signs of extravasation are critical.

If extravasation does occur, the medication should be stopped immediately. The site should be assessed and measured. Photographing the site is also helpful for reference if the tissue deteriorates. Local cooling is used for DNA-binding agents (anthracyclines such as doxorubicin, daunorubicin, epirubicin, idarubicin) to constrict blood vessels while local heat is used for non-DNA binding agents (vinca alkaloids such as vincristine, vinblastine) to increase blood flow. Specific antidotes may be available for some chemotherapeutic agents.

A vascular access device may be used for administration of chemotherapeutic agents, especially with combination therapies, but these pose an increased risk of systemic infection, especially if neutropenia occurs. Commonly used types of vascular access devices are the silastic right atrial catheter, peripherally inserted central venous catheter (PICC), midline catheter (MLC), implanted infusion ports, and infusion pumps (external or implanted).

**Radiotherapy and HCST**
**Radiotherapy**  
Radiation is used for all types of leukemia. Radiotherapy is usually used in conjunction with chemotherapy, but it may also be used as CNS prophylaxis to prevent spread of acute leukemias to the brain and spinal cord. Cranial irradiation lowers the risk of relapse in acute leukemias. Radiotherapy may be used to relieve pain from hepatomegaly and splenomegaly.

Three types of radiation are commonly used with leukemia patients:
- **External beam radiation:** EBRT is commonly used with CML and helps decrease swelling of liver, spleen, and lymph nodes.
- **Total body irradiation:** A linear accelerator irradiates the entire body in preparation for chemotherapy and stem cell transplant.
- **Total marrow irradiation:** This form of radiation targets major marrow sites and reduces radiation exposure to internal organs. TMI is used as preparation for stem cell transplant.

### Stem cell transplantation
Hematopoietic stem cell transplantation (HSCT) comprises bone marrow transplant (BMT), peripheral blood stem cell transplant (PBSTC, and umbilical cord blood stem cell transplant (UCBSTC).

Sources of stem cells include:
- **Syngenic:** From identical twin.
- **Autologous:** From the patient. Autologous purged transplant requires treatment *ex vivo* to remove malignant cells prior to transplantation.
- **Allogenic:** From a family member, usually a sibling. In some cases, partially-matched related donor may be used. Allogenic donors are usually the first choice.
- **Matched unrelated donor** (MUD): Donors are usually matched through a donor registry. In some cases, partially matched cord blood stem cells may be used.

HCST allows for higher doses of chemotherapeutic agents because there is less concern about marrow toxicity. Transplantation is usually done after chemotherapy and radiation has ablated the patient’s bone marrow. The transplanted cells then begin to produce normal blood cells.
- **BMT** is an invasive procedure that requires bone marrow to be extracted from the donor, usually from the pelvic bones. The extraction is done as an out-patient procedure under general or
regional anesthesia.

- **PBSCT** is less invasive for the donor, but stem cells are sparse in the peripheral blood so it may be difficult to extract enough from the bloodstream; therefore, the donor must take medication (granulocyte colony-stimulating factor—G-CSF) for a few days prior to donation to increase the number of stems cells released from the bone marrow into the bloodstream.

- **UCBSCT** is not as readily available, but this type of transplant is less prone to rejection and has lower incidence of graft vs host disease. Only about 50 mL of cord blood is obtained with each donation, so this amount is usually suitable only for transplantation in small children. However, *ex vivo* expansion techniques and combining cord donations from two donors are being explored to allow UCBSCT for adults.

While HSCT may be lifesaving, it is not a benign procedure. Complications of HSCT include:

- Toxicity from radiation and chemotherapy.
- Complications related to pancytopenia (bleeding, infection, anemia).
- Immunological disorders (graft vs host disease, graft rejection, immunodeficiency).
- Endocrine and growth abnormalities.
- Decreased fertility.
- Cataracts.
- Learning disabilities.
- Secondary malignancy.

**Acute myelogenous leukemia (AML)**

Acute myelogenous leukemia is also referred to a granulocytic, myelocytic, myeloid, monocytic, myeloid, monoblastic, monomyeloblastic, and acute nonlymphoblastic leukemia (ANLL). AML is characterized by uncontrolled proliferation of myeloblasts, which are precursors of granulocytes. AML is the second most common leukemia in children, causing 17%, usually those <2 years and adolescents. AML occurs more frequently in males than females.

Some genetic risk occurs as there is high concordance in identical twins, and fraternal twins carry 2 to 4 times the risk of developing AML up to age 6, after which risk decreases. Myelogenous malignancies are also associated with a number of inherited and acquired genetic syndromes, such as Down syndrome, Fanconi anemia, familial platelet
disorder, familial and acquired monosomy 7, and severe aplastic anemia.

AML is the most common adult leukemia, causing 85% of leukemias. In adults, onset is usually after age 60, especially in males, and may be associated with a history of smoking, previous radiation, and/or chemotherapy. AML may result from childhood treatment of ALL or other cancers. Most people who develop secondary cancers related to treatment develop AML rather than other forms of leukemia.

Prognosis varies depending on the subtype, but 5-year survival rates for children <15 have increased to 58% and for those 15 to 19 to 40%. About 60 to 70% of adults achieve remission after induction therapy with about 25% surviving for 3 years or more. Remission tends to be shorter in duration in adults >60.

**Symptoms**

Onset of symptoms is usually quite abrupt and may include severe infection and abnormal bleeding. Symptoms most often result from decreased production of other blood cells because of the large number of leukemic myeloblasts in the bone marrow although other organs may become infiltrated. Neutropenia and thrombocytopenia are common. Typical signs and symptoms include:

- Weakness, lethargy.
- Increased bruising, petechiae.
- Abnormal bleeding, nosebleeds.
- Fever.
- Anorexia, weight loss.
- Anemia.
- Increased infection.
- Mouth sores.

With infiltration of the central nervous system through the blood or lymphoid system, symptoms may include headache, vomiting, and papilledema. Sixth cranial nerve palsy results from masses of leukemic cells putting pressure on the nerves, preventing the eye from moving laterally. Other common sites for infiltration include the spinal cord and testicles, which painlessly enlarge. The liver may become enlarged and painful. Hyperplasia of the gums may occur. Proliferation in the bone may cause bone pain as the bone marrow expands.

Complications can include bleeding and infection. Major hemorrhage occurs when platelet count drops to <10,000, with common sites GI, pulmonary, and intracranial. Decreasing neutrophil counts increase the risk of systemic infection and sepsis. Patients may develop severe fungal infections.

**Diagnostic findings**

The first test to show abnormalities is typically the complete blood count and differential.

- Erythrocytes decrease.
- Thrombocytes (platelets) decrease, affecting blood clotting.
- Total white count may be low, high, or normal, but the percentages of normal cells decrease.

Bone marrow analysis typically shows excess immature blast cells at >30%.

**Treatment considerations**

Usually a two-phase approach to chemotherapy is used with induction and consolidation but not maintenance. Treatment usually involves combination chemotherapy. A common approach to adult induction is referred to as “3 and 7.”

- 3 days of 15 to 30 minutes of infusions with idarubicin or daunorubicin or mitoxantrone followed by arabinosylcytosine (ara-C) in 24-hour infusions daily for 7 days.

This is usually followed by consolidation treatment with high-dose ara-C.

However, this treatment protocol may vary according to the patient’s age and condition. In many cases, patients are enrolled in clinical trials, especially with recurrent disease. Some may receive bone marrow transplant (BMT) or peripheral blood stem cell transplants (PBSCT).
Treatment approaches are similar for all subtypes except acute promyelocytic leukemia (M3), which is usually treated with arsenic trioxide and all-trans retinoic acid (ATRA).

**Subtypes** Subtypes are classified with two different systems: French, American, British (FAB) and World Health Organization (WHO).

**French, American, British** (FAB): This is commonly used and is based on the type of blood cell the leukemia originates from and the maturity of leukemic cells. Using the FAB classification system, there are 8 primary subtypes:

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Name</th>
<th>Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0 5%</td>
<td>Undifferentiated acute myeloblastic leukemia.</td>
<td>Minimally-differentiated AML. Prognosis is poor.</td>
</tr>
<tr>
<td>M1 15%</td>
<td>Acute myeloblastic leukemia with minimal maturation</td>
<td>Dominant leukemic cells in the marrow at diagnosis are myeloblasts. Prognosis is average.</td>
</tr>
<tr>
<td>M2 25%</td>
<td>Acute myeloblastic leukemia with maturation</td>
<td>Many myeloblasts evident but some are maturing into normal cells. Prognosis is better than average.</td>
</tr>
<tr>
<td>M3 10%</td>
<td>Acute promyelocytic leukemia</td>
<td>Leukemic cells show translocation between chromosomes 15 and 17. Most common in middle-aged adults and may cause bleeding and blood clotting, so identifying APL and using correct treatment is critical. Prognosis is best of AML subtypes.</td>
</tr>
<tr>
<td>M4 20%</td>
<td>Acute myelomonocytic leukemia</td>
<td>Leukemic cells often have inversion of chromosome 16. Prognosis is average.</td>
</tr>
<tr>
<td>M4 eos 5%</td>
<td>Acute myelomonocytic leukemia with eosinophilia</td>
<td>Prognosis is better than average.</td>
</tr>
<tr>
<td>M5 10%</td>
<td>Acute monocytic leukemia</td>
<td>Leukemic cells have features of developing monocytes. Prognosis is average.</td>
</tr>
<tr>
<td>M6</td>
<td>Acute erythroid</td>
<td>Leukemic cells have features of</td>
</tr>
<tr>
<td>5%</td>
<td>leukemia</td>
<td>developing red blood cells. Acute erythroid leukemia. Prognosis is poor.</td>
</tr>
<tr>
<td>-----</td>
<td>----------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td>M7 5%</td>
<td>Acute megakaryocytic leukemia</td>
<td>Leukemic cells have features of developing platelets. Prognosis is poor.</td>
</tr>
</tbody>
</table>

**World Health Organization (WHO):** This newer classification divides subtypes into broad groups based on expected outcomes.

- **AML with certain genetic abnormalities:**
  - AML with a translocation between chromosomes 8 and 21
  - AML with a translocation or inversion in chromosome 16
  - AML with changes in chromosome 11
  - APL (M3), which usually has translocation between chromosomes 15 and 17
- **AML with multi-lineage dysplasia** (more than one abnormal cell).
- **Therapy-related AML.**
- **AML not otherwise specified:**
  - undifferentiated AML (M0)
  - AML with minimal maturation (M1)
  - AML with maturation (M2)
  - acute myelomonocytic leukemia (M4)
  - acute monocytic leukemia (M5)
  - acute erythroid leukemia (M6)
  - acute megakaryoblastic leukemia (M7)
  - acute basophilic leukemia
  - acute panmyelosis with fibrosis
  - myeloid sarcoma (also known as granulocytic sarcoma or chloroma)
- **Undifferentiated or biphenotypic acute leukemias** (having both lymphocytic and myeloid features).

**Chronic myelogenous leukemia (CML)**

Chronic myelogenous leukemia is also referred to as chronic myeloid leukemia, chronic myelocytic, and chronic granulocytic leukemia. CML results from mutation of the myeloid stem cells and resultant proliferation of mature neoplastic granulocytes and blast forms in the bone marrow although some normal cells are still produced, so a wide range of cell forms exists.
Huge numbers of abnormal cells expand the bone marrow and spread into the peripheral circulation and eventually infiltrate the liver and spleen, where more cells are formed in a process referred to as extramedullary hematopoiesis, causing the organs to enlarge.

In up to 95% of those with CML, these abnormal cells contain a genetic marker that makes them distinct, the Philadelphia chromosome (Ph1), a translocation between chromosomes 9 and 22. The location of these changes is on the BCR gene of chromosome 22 and the ABL gene on chromosome 9. The two genes fuse and produce an abnormal protein that increases the rate that leukocytes divide. This BCR-ABL gene is present is almost everyone with CML.

Currently about 20,000 people in the United States have CML with 4870 people diagnosed in 2010 and 440 deaths in 2010. CML is rare in people <20 and occurs primarily in older adults, with a median age of 67 at diagnosis if Ph1-positive CML. CML accounts for 20% of adult cases of leukemia. When CML occurs in younger adults (20-29), it is often more aggressive.

Many people are asymptomatic for long periods, and CML may be discovered with a routine CBC. Sometimes patients develop dyspnea or mild confusion because the increased number of malignant cells in the blood inhibits blood flow. Some exhibit non-specific symptoms:

- General malaise.
- Anorexia.
- Weight loss.

Over time, the disease becomes more severe and people begin to develop other symptoms. The disease goes through different phases:

- **Chronic:** This phase is fairly stable and may persist for 2 to 5 years without treatment. During this phase, the white blood count rises but most cells are mature and function normally. Typical symptoms include fatigue, headache, and pain or fullness in the left abdomen from splenomegaly. With treatment, the chronic phase may be prolonged.

- **Accelerated:** The number of immature blasts in the marrow, blood, liver, and spleen increase, and fewer normal mature cells are produced, so the immune system is impaired. This stage usually lasts 1 to 6 months if the leukemia is untreated but may last >1 year with treatment. In addition to the symptoms experienced during the chronic phase, the patient may
experience fever, night sweats, weight loss, anemia, and dyspnea.

- **Blast crisis:** Blast cells begin to proliferate in large number and production of other blood cells, including erythrocytes and platelets, so the patient can experience bruising, bleeding, and infection. During this phase the disease resembles AML in most patients and ALL in a few.

**Diagnostic findings**  
**CML** is usually diagnosed with blood studies that show a white count of 20,000 to 60,000 with increase in mature granulocytes. Basophils and eosinophils show a mild increase. The mature granulocytes exhibit a delay in normal apoptosis (programmed cell death), so they live longer and begin to accumulate. These cells have no or low levels of alkaline phosphatase, so stains show a low score. Mild to moderate normochromic, normocytic anemia is usually present. Platelet counts may vary from low to high. Bone marrow biopsy with cytogenic studies provides definitive diagnosis, especially with a finding of the Philadelphia (Ph1) chromosome.

**Treatment considerations**  
Treatment introduced during the chronic phase of CML is more effective than treatment started in more advanced phases. The current drugs of choice include imatinib mesylate (Gleevec), which promotes apoptosis and inhibits tyrosine kinase activity in cells positive for BCR-ABL (Philadelphia). Remission rates are 70% and survival of 94% at 3 years for those treated in the chronic phase. Complete remission rates drop to 28% if treatment is given during acceleration phase and 4% if during blast crisis.

Two newer generation drugs, nilotinib and dasatinib, shower higher rates of remission but are associated with more side effects and are more expensive. In up to 30% of patients, imatinib is not effective in bringing about complete remission. In these cases, further treatment with nilotinib or dasatinib may be used. Myelosuppressive therapy, which was used before FDA approval of imatinib, is rarely used currently. HCST may be considered in patients <55 with a matched sibling donor.

**Acute lymphocytic leukemia (ALL)**

ALL is also referred to as lymphatic, lymphocytic, lymphoblastic, or lymphoblastoid leukemia and is caused by a defect in the stem cells
that differentiate into lymphocytes, preventing development of other
types of cell. The cell of origin is the precursor to B lymphocytes in
75% and to T lymphocytes in 25%.

This is the most common type of childhood leukemia (85%), peaking
between ages 2 to 5 and rare after age 15 with incidence in males
higher than females. Down syndrome increases risk. ALL accounts for
only 15% of adult leukemias, often after age 70, especially in those
with history of chemotherapy or radiation exposure.

Five-year survival rates are 90.8% for children <5, 89% for children
<15 and 40% for adults. In 2010, approximately 1420 people died of
ALL. Despite positive survival rates, long-term morbidity and mortality
related to treatment are high, including cardiac disease, pulmonary
disease, and secondary cancers. Increasing cases of ALL have been
recorded in people previously treated with topoisomerase II inhibitors
for other malignancies.

**Symptoms**

ALL results in impaired immune system, anemia, and
increased bleeding tendencies. About 10% of patients
initially present with disseminated intravascular coagulation (DIC)
because of thrombocytopenia. Typical symptoms include:

- Fever (common).
- Weakness, lethargy.
- Increased bruising, petechiae.
- Abnormal bleeding, nosebleeds.
- Anorexia, weight loss.
- Palpitations.
- Anemia.
- Increased infection.
- Dyspnea.
- Pallor.

Infiltration of leukemic cells to other organs if more common with ALL
than with other forms of leukemia:

- Bone infiltration with bone pain.
- Mediastinal mass (associated with T lymphocyte ALL).
- Painless lesions (lymphadenopathy) in neck, axillae, abdomen,
  and groin.
- Hepatomegaly (10-20%) with pain and fullness inferior to ribs.
- Splenomegaly (30-54%) with left upper abdominal fullness.
- CNS infiltration with headaches, nausea, and vomiting.
- Rash from infiltration into skin.
- Hyperuricemia with renal failure.
Because production of normal blood cells is inhibited, laboratory testing usually shows decreased numbers of leukocytes, erythrocytes, and platelets. In some cases the leukocyte count is low but with a high proportion of immature cells.

LDH and uric acid levels are usually elevated. If DIC is present, laboratory studies show an elevated prothrombin time, decreased fibrinogen levels, and the presence of fibrin split products.

Chest x-ray may show pneumonia and mediastinal mass in those with T lymphocyte ALL, and CT scan shows the extent of lymphadenopathy. A bone marrow biopsy provides the definitive diagnosis.

Because only about 20% of adults are cured with standard chemotherapy, many are entered into clinical trials.

The standard adult treatment protocol comprises 4 phases:

- **Induction:** A 4-drug regimen of vincristine, prednisone, anthracycline, and cyclophosphamide or L-asparaginase or a 5-drug regimen of vincristine, prednisone, anthracycline, cyclophosphamide, and L-asparaginase is given over the course of 4-6 weeks.
- **Consolidation:** Studies show varying results from consolidation treatment, but most studies show benefit. Regimens using a standard 4- to 5-drug induction usually include Ara-C in combination with an anthracycline or epipodophyllotoxin.
- **Maintenance:** While studies show that adults on maintenance have longer periods of remission, the definitive protocol has not been developed, so various treatment protocols are used, including a 4-drug regimen for 12 months.
- **CNS prophylaxis:** Meningeal infiltration is common with relapse, so intrathecral chemotherapy is necessary.

The pediatric treatment protocol comprises 5 phases:

- **Induction:** 3-4 drugs, which may include a glucocorticoid, vincristine, asparaginase, and possibly an anthracycline.
- **Consolidation:** drugs are given at doses higher than those used during induction or the patient is given different drugs (ie, high-dose MTX and 6-mercaptopurine [6-MP]), epipodophyllotoxins with Cytarabine (Ara-C), or multiagent combination therapy
• Interim maintenance: oral medications are administered to maintain remission and allow the bone marrow to recover for 4 weeks.
• Delayed intensification: Intensified treatment for any remaining leukemic cells that were resistant to previous phases.
• Maintenance: Intrathecal MTX every 3 months, monthly vincristine, daily 6-MP and weekly MTX.

The duration of pediatric treatment varies depending on the type of ALL. B-cell acute lymphoblastic leukemia is usually treated with two months to 8 months of intensive therapy. However, those with B-precursor and T-cell acute lymphoblastic leukemia require approximately 2 to 2.5 years of continuation therapy to prevent high relapse rates. In current acute lymphoblastic leukemia clinical trials, the total duration of therapy for girls is 2 years from the start of interim maintenance and for boys is 3 years from the start of interim maintenance.

Subtypes

The **FAB classification** identifies 3 subtypes of ALL, based on the way the cells look:

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percentage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>30% of adult cases</td>
<td>Small cells with homogeneous chromatin, regular nuclear shape, small or absent nucleolus, and scanty cytoplasm. Corresponds to T-cell or pre-B cell.</td>
</tr>
<tr>
<td></td>
<td>85% of pediatric</td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>65% of adult cases</td>
<td>Large and heterogeneous cells, heterogeneous chromatin, irregular nuclear shape, and nucleolus often large. Corresponds to T-cell or pre-B cell.</td>
</tr>
<tr>
<td></td>
<td>14% of pediatric</td>
<td></td>
</tr>
<tr>
<td>L3</td>
<td>5% of adult cases</td>
<td>Large and homogeneous cells with multiple nucleoli, moderate deep blue cytoplasm, and cytoplasmic vacuolization that often overlies the nucleus. Corresponds to B cell. Prognosis is poor.</td>
</tr>
<tr>
<td></td>
<td>1% of pediatric</td>
<td></td>
</tr>
</tbody>
</table>

The **WHO classification** bases subtypes on certain cell features and maturity (adult percentages):

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-cell</strong></td>
<td>- Early precursor-B ALL (also called pro-B ALL) -- about</td>
</tr>
</tbody>
</table>
10% of cases.

- Common ALL - about 50% of cases
- Precursor-B ALL - about 10% of cases
- Mature B-cell ALL (Burkitt leukemia) -- about 4% of cases

| T-cell |  
|---|---|
|  
| • Precursor-T ALL - about 5% to 10% of cases  
| • Mature T-cell ALL - about 15% to 20% of cases  |

Prognosis is usually better for T-cell ALL than B-cell. Mature B cell has the worst prognosis. Other B-cell subtypes fall in the middle. Younger patients have a better prognosis than older. People with a lower white blood count (< 30,000 for B-cell ALL and <100,000 for T-cell ALL) at the time of diagnosis tend to have a better prognosis.

About 25 to 30% of those with ALL have a translocation between chromosomes 9 and 22, which predicts a poor prognosis. About 5% have a translocation between chromosomes 4 and 11, also predicting a poor prognosis. Those who go into remission within 4 to 5 weeks have a better prognosis than those who take longer.

**Chronic lymphocytic leukemia (CLL)**

Chronic lymphocytic leukemia, also called chronic lymphoid leukemia and chronic lymphoblastic leukemia is the most common leukemia in adults, with two-thirds >55. CLL is rare <30 and occurs more frequently in males than females. However, rates in those ≤35 have been increasing in recent years.

CLL is the most common adult leukemia in the United States and Europe but is rare in Asia. Approximately 17,000 new cases are reported yearly in the United States, but researchers believe the actual figure may be up to 38% higher as many cases are not reported to the tumor registry.

CLL develops primarily from a malignant clone of B-lymphocytes. T-lymphocyte CLL is rare. About 1% of CLL cases express T-cell markers (CD4 and CD7) and have clonal rearrangements of their T-cell receptor genes. These patients have median survival of 13 months with minimal responses to chemotherapy. A number of different chromosomal abnormalities have been noted in CLL, including 13q deletion (in 50%) and trisomy 12 (in 15%).

One difference between ALL and CLL is that most leukemic cells appear mature; however, they are functionally inactive and have abnormal
apo•ptosis so that they don’t die but accumulate in the marrow and blood.

CLL is more aggressive in some patients, and these may live only 2 to 3 years after diagnosis, but most people live 5 to 10 years. Thrombocytopenia and anemia are important negative variables, suggesting a more aggressive course of the disease.

CLL is classified in 2 different ways, and treatment and prognosis depends on the classification:

<table>
<thead>
<tr>
<th>Rai Classification</th>
<th>Binet Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absolute lymphocytosis (&gt;15,000/mm³) without adenopathy, hepatosplenomegaly, anemia, or thrombocytopenia.</td>
</tr>
<tr>
<td></td>
<td>A No anemia or thrombocytopenia and fewer than three areas of lymphoid involvement (Rai stages 0, I, and II).</td>
</tr>
<tr>
<td>I</td>
<td>Absolute lymphocytosis with lymphadenopathy without hepatosplenomegaly, anemia, or thrombocytopenia.</td>
</tr>
<tr>
<td></td>
<td>B No anemia or thrombocytopenia with three or more areas of lymphoid involvement (Rai stages I and II).</td>
</tr>
<tr>
<td>II</td>
<td>Absolute lymphocytosis with either hepatomegaly or splenomegaly with or without lymphadenopathy.</td>
</tr>
<tr>
<td></td>
<td>C Anemia and/or thrombocytopenia regardless of the number of areas of lymphoid enlargement (Rai stages III and IV).</td>
</tr>
<tr>
<td>III</td>
<td>Absolute lymphocytosis and anemia (hemoglobin &lt;11 g/dL) with or without lymphadenopathy, hepatomegaly, or splenomegaly.</td>
</tr>
<tr>
<td>IV</td>
<td>Absolute lymphocytosis and thrombocytopenia (&lt;100,000/mm³) with or without lymphadenopathy, hepatomegaly, splenomegaly, or anemia.</td>
</tr>
</tbody>
</table>

**Symptoms** Patients are often asymptomatic at the time of diagnosis, especially in the early stages of the disease, but they are progressively more at risk for infection because of defects
in humor and cell-mediated immune systems. Infections, such as herpes zoster, may become widespread. Patients may develop a group of symptoms referred to as “B symptoms”:
- Fever.
- Diaphoresis, especially night sweats.
- Weight loss.

Lymph nodes typically are enlarged and painful as lymphocytes become trapped in the nodes. Hepatomegaly and splenomegaly also develop. Patients may complain of abdominal fullness and discomfort and early satiety because of splenomegaly. Skin lesions may occur with T-cell CLL.

Autoimmune complications are common and can occur at any stage of the disease. About 10% of those with CLL present with autoimmune hemolytic anemia. Some develop idiopathic thrombocytopenia purpura (ITP). In these autoimmune disorders, the reticuloendothelial system (RES) destroys the body’s erythrocytes or platelets.

Frequent infections occur, including herpes zoster, *Pneumocystis jiroveci*, and *Candid albicans*. In some cases, CLL may transform to diffuse large cell lymphoma (Richter syndrome), which carries a poor prognosis.

**Diagnostic findings**

The total WBC count increases and the lymphocyte count may exceed 100,000. Despite these numbers, because lymphocytes are small, they are able travel through the capillaries so pulmonary and cerebral complications that occur with myelogenous leukemias do not usually occur with CLL. In later disease stages, reduced erythrocyte count and thrombocytopenia occur. An antigen, CD52, which is usually present on T-cells, is present on the surface of many leukemic B cells.

Zeta-chain-associated protein kinase 70 (ZAP-70) is often used to determine the need for treatment. A positive ZAP-70 finding in asymptomatic patients (>30%) is associated with median survival of 6 to 10 years while a negative ZAP-70 is associated with median survival of >15 years.

The immunoglobulin variable region heavy chain gene (IgVH) mutation in significant numbers is associated with a median survival in excess of 20 to 25 years. The absence of mutations is associated with a median survival of 8 to 10 years.
Because some types of CLL have a long period with slow progression, some older adults may fare better with monitoring than with aggressive treatment. CLL is usually not curable, so patients may be treated symptomatically for complications, such as hemolytic anemia, infections, or ITP.

Typically, patients with low risk or Binet A classification are simply monitored because early chemotherapy has not been associated with increased survival. Corticosteroids are commonly used to treat autoimmune hemolytic anemia and thrombocytopenia.

Many chemotherapeutic agents, such as chlorambucil, have been used to treat CLL and some clinical trials are in place for more aggressive forms of CLL. The first line agent is fludarabine, which is either given alone or in combination with cyclophosphamide and/or rituximab (a monoclonal antibody). Alemtuzumab (a monoclonal antibody directed at CD52) is approved for use in CLL as both a first-line agent and for salvage in patients with fludarabine-refractory disease. Allogenic stem cell transplant is the only known curative treatment.

Summary
Leukemia is a group of malignant disorders affecting the blood and blood-forming tissues in the bone marrow, lymphatic system, and spleen. Leukemias are classified as lymphoid or myeloid, depending on the affected stem cell type, and may be acute or chronic. The 4 primary types of leukemia are acute lymphocytic/lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML) or acute nonlymphoblastic leukemia (ANLL), chronic myelogenous leukemia (CML), and chronic lymphocytic leukemia (CLL) with a number of subtypes. Two primary concerns with leukemia are neutropenia, which increases risk of infection, and thrombocytopenia, which increases risk of bleeding. Treatment options include chemotherapy, radiotherapy, and HSCT.

References