Leukemia

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Plan of lecture

- **Leukemia**: etiology and pathogenesis;
- **Leukemia**: diagnosis;
- **Leukemia**: treatment.

Leukemia

Leukemia is a malignant condition involving the excess production of immature or abnormal leukocytes, which eventually suppresses the production of normal blood cells and results in symptoms related to cytopenias.Malignant transformation usually occurs at the pluripotent stem cell level, although it sometimes involves a committed stem cell with more limited capacity for self-renewal. Abnormal proliferation, clonal expansion, aberrant differentiation, and diminished apoptosis (programmed cell death) lead to replacement of normal blood elements with malignant cells.

The American Cancer Society estimates that in the United States in 2020 there will be about 60,530 new cases of leukemia (of all types) in adults and children, and about 23,100 deaths.

(By **Ashkan Emadi** , MD, PhD, University of Maryland; **Jennie York Law** , MD, University of Maryland; Last full review/revision May 2020| Content last modified May 2020; - MSD Manual Professional Version [1] https://www.msdmanuals.com/professional/hematology-and-oncology/leukemias/overview-of-leukemia)

Leukemia [1]

Classification of Leukemia

The current approach to classifying leukemia is based on the 2016 World Health Organization (WHO) system (classification for hematopoietic neoplasms). The WHO classification is based on a combination of clinical, morphologic, immunophenotypic, and genetic features. Other less commonly used classification systems include the French-American-British (FAB) system, which is based on the morphology of the abnormal leukocytes.

Leukemias are commonly also categorized as

- Acute or chronic: Based on the percentage of blasts or leukemia cells in bone marrow or blood
- Myeloid or lymphoid: Based on the predominant lineage of the malignant cells

Leukemia [1]

For 2020, the American Cancer Society estimated the distribution of new US cases by leukemia type as follows:

- Acute myeloid leukemia (AML): 33%
- Acute lymphoblastic leukemia (ALL): 10%
- Chronic myeloid leukemia (CML): 14%
- Chronic lymphocytic leukemia (CLL): 35%
- Other leukemias: 8%

Leukemia [1]

Acute leukemias

Acute leukemias consist of predominantly immature, poorly differentiated cells (usually blast forms). Acute leukemias are divided into acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML).

Chronic leukemias have more mature cells than do acute leukemias. They usually manifest as leukocytosis with or without cytopenias in an otherwise asymptomatic person. Findings and management differ significantly between chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML).

Myelodysplastic syndromes

Myelodysplastic syndromes are a group of clonal hematopoietic stem cell disorders unified by the presence of distinct mutations of hematopoietic stem cells. They involve progressive bone marrow failure but with an insufficient proportion of blast cells (< 20%) for making a definite diagnosis of acute myeloid leukemia; 40 to 60% of cases evolve into acute myeloid leukemia.

Leukemia [1]

Leukemoid reaction

A leukemoid reaction is a neutrophil count > 50,000/mcL (> 50 × 10^9/L) not caused by malignant transformation of a hematopoietic stem cell. It can result from a variety of causes, particularly other cancers or systemic infection. Usually the cause is apparent, but apparent benign neutrophilia can be mimicked by chronic neutrophilic leukemia or chronic myeloid leukemia.

Leukemia [1]

Risk Factors for Leukemia

Risk of developing leukemia is increased in patients with

- History of exposure to ionizing radiation (eg, post–atom bomb in Nagasaki and Hiroshima) or to chemicals (eg, benzene, some pesticides, polyaromatic hydrocarbons in tobacco smoke); exposure can lead to acute leukemias
- Prior treatment with certain antineoplastic drugs, including alkylating agents, topoisomerase II inhibitors, hydroxyurea, and maintenance lenalidomide after autologous stem cell transplantation with melphalan-containing conditioning regimens for multiple myeloma; can lead to a type of acute myeloid leukemia called t-AML or therapy-related AML
- Infection with a virus (eg, human T lymphotropic virus 1 and 2, Epstein Barr virus) can rarely cause certain forms of ALL; this is seen mainly in regions where such infections are common, such as Asia and Africa

Leukemia [1]

Risk of developing leukemia is increased in patients with

- History of antecedent hematologic disorders, including myelodysplastic syndromes and myeloproliferative neoplasms , which can lead to AML
- Preexisting genetic conditions (eg, Fanconi anemia, Bloom syndrome, ataxia-telangiectasia, Down syndrome, xeroderma pigmentosum, Li-Fraumeni syndrome) predispose to acute myeloid leukemia and acute lymphoblastic leukemia.

Acute Myeloid Leukemia (AML)
(Acute Myelocytic Leukemia; Acute Myelogenous Leukemia) [2]

In acute myeloid leukemia (AML), malignant transformation and uncontrolled proliferation of an abnormally differentiated, long-lived myeloid progenitor cell results in high circulating numbers of immature blood cells and replacement of normal marrow by malignant cells. Symptoms include fatigue, pallor, easy bruising and bleeding, fever, and infection; symptoms of extramedullary leukemic infiltration are present in only about 5% of patients (often as skin manifestations). Examination of peripheral blood smear and bone marrow is diagnostic. Treatment includes induction chemotherapy to achieve remission and postremission chemotherapy (with or without stem cell transplantation) to avoid relapse.(By **Ashkan Emadi** , MD, PhD, University of Maryland; **Jennie York Law** , MD, University of Maryland; Last full review/revision May 2020| Content last modified May 2020 [2] https://www.msdmanuals.com/professional/hematology-and-oncology/leukemias/acute-myeloid-leukemia-aml). The American Cancer Society estimates that in the United States in 2020 there will be about 19,940 new cases of acute myeloid leukemia (AML) and 11,180 deaths, almost all in adults.

Acute Myeloid Leukemia [2]

AML is slightly more common among men than women, but the average lifetime risk in both sexes is about 0.5% (1 in 200 Americans).

AML comprises about 25% of childhood leukemias, often developing in infancy. However, the incidence of AML increases with age; it is the most common acute leukemia in adults, with a median age of onset of 68 years. AML also may occur as a secondary cancer after chemotherapy or radiation therapy for a different type of cancer. Secondary AML is difficult to treat with chemotherapy alone.

Pathophysiology: Similar to acute lymphoblastic leukemia, acute myeloid leukemia is caused by a series of acquired genetic aberrations. Malignant transformation usually occurs at the pluripotent stem cell level, although it sometimes involves a committed stem cell with more limited capacity for self-renewal. Abnormal proliferation, clonal expansion, aberrant differentiation, and diminished apoptosis (programmed cell death) lead to replacement of normal blood elements with malignant cells.

Acute Myeloid Leukemia [2]

Acute myeloid leukemia has a number of subtypes and precursor neoplasms that are distinguished from each other by morphology, immunophenotype, cytochemistry, and genetic abnormalities (see also The 2016 World Health Organization [WHO] Classification of myeloid neoplasms) all of which have important implications for prognosis and treatment. Seven classes are described in the WHO classification, including:

- AML with recurrent genetic abnormalities
- AML with myelodysplasia-related changes (AML-MRC)
- Therapy-related AML (t-AML)
- AML, not otherwise specified (NOS)
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm

Morphologic criteria from the previous French-American-British (FAB) classification system are used for subtypes that are not otherwise specified (NOS).

Acute Myeloid Leukemia [2]

Acute promyelocytic leukemia (APL) is a subtype of AML with recurrent genetic abnormalities. APL is a particularly important subtype, representing 10 to 15% of all cases of AML, striking a younger age group (median age 31 years) and particular ethnicity (Hispanics). Patients commonly present with a coagulation disorder (eg, disseminated intravascular coagulation [DIC]).

Therapy-related AML (t-AML) is a subtype of AML caused by prior treatment with certain antineoplastic drugs (eg, alkylating agents and topoisomerase II inhibitors). Most t-AMLs occur 3 to 10 years after initial therapy, with a longer latency for alkylating agents and hydroxyurea (mean latency 5 to 7 years) than for topoisomerase II inhibitors (mean latency 6 months to 3 years). Alkylating agents cause chromosomal deletions and unbalanced translocations. Hydroxyurea causes del(17)p and also inhibits *TP53* activation. Topoisomerase II inhibitors lead to balanced chromosomal translocations.

Myeloid sarcoma is characterized by extramedullary myeloblastic infiltration of skin (leukemia cutis), gingiva, and other mucosal surfaces.

Acute Myeloid Leukemia [2]

Symptoms and Signs

Symptoms of acute myeloid leukemia may be present for only days to weeks before diagnosis. The most common presenting symptoms are due to disrupted hematopoiesis with ensuing

- Anemia
- Thrombocytopenia
- Granulocytopenia
- **Anemia** can manifest with fatigue, weakness, pallor, malaise, dyspnea on exertion, tachycardia, and exertional chest pain.
- **Thrombocytopenia** can cause mucosal bleeding, easy bruising, petechiae/purpura, epistaxis, bleeding gums, and heavy menstrual bleeding. Hematuria and gastrointestinal bleeding are uncommon. Patients can present with spontaneous hemorrhage, including intracranial or intra-abdominal hematomas.

Acute Myeloid Leukemia [2]

Granulocytopenia (neutropenia) can lead to a high risk of infections, including those of bacterial, fungal, and viral etiologies. Patients may present with fevers and a severe and/or recurrent infection. The cause of fever often is not found, although granulocytopenia may lead to a rapidly progressing and potentially life-threatening bacterial infection.

Leukemia cutis can have various appearances, including papules or nodules, and plaques, and may be erythematous, brown, hemorrhagic, or violaceous/gray-blue.

Acute Myeloid Leukemia [2]

Leukemic cell infiltration of other organ systems tends to be less common and severe in AML than in ALL, however:

- Infiltration can enlarge the liver, spleen, and lymph nodes.
- Bone marrow and periosteal infiltration may cause bone and joint pain.
- Meningeal infiltration can result in cranial nerve palsies, headache, visual or auditory symptoms, altered mental status, and transient ischemic attack/stroke.

Diagnosis

- Complete blood count (CBC) and peripheral blood smear
- Bone marrow examination
- Histochemical studies, cytogenetics, immunophenotyping, and molecular biology studies

Acute Myeloid Leukemia [2]

A diagnosis of acute myeloid leukemia is made when myeloid blast cells are ≥ 20% of marrow nucleated cells or ≥ 20% of nonerythroid cells when the erythroid component is > 50%, or at any blast percentage in the presence of recurrent cytogenetic abnormalities [t(8;21), t(15;17), inv(16) or t(16;16)]. Diagnosis can be made by the same criteria using peripheral blood.

CBC and peripheral smear are the first tests done; pancytopenia and peripheral blasts suggest acute leukemia. Blast cells in the peripheral smear may approach 90% of white blood cell (WBC) count.

Aplastic anemia, viral infections such as infectious mononucleosis, vitamin B12 deficiency, and folate deficiency should be considered in the differential diagnosis of severe pancytopenia.

Acute Myeloid Leukemia [2]

Leukemoid reactions (marked granulocytic leukocytosis [ie, WBC > 50,000/mcL, > 50 × 10^9/L] produced by normal bone marrow) to infectious disease never manifest with high blast counts.

Bone marrow examination (aspiration and needle biopsy) is routinely done. Blast cells in the bone marrow are classically between 25 and 95%.

Histochemical studies, cytogenetics, immunophenotyping, and molecular biology studies help distinguish the blasts of ALL from those of AML or other diseases. Histochemical studies include staining for myeloperoxidase, which is positive in cells of myeloid origin. Crystallization of myeloperoxidase-rich granules leads to formation of Auer rods (linear azurophilic inclusions in the cytoplasm of blast cells), which are pathognomic for AML. Detection of specific immunophenotypical markers (eg, CD13, CD33, CD34, CD117) is essential in classifying the acute leukemias.

Commonly observed cytogenetic abnormalities in AML include t(15;17), trisomy 8, t(8;21), inv(16) or t(16;16) and 11q23.3 rearrangements

Acute Myeloid Leukemia [2]

Less common cytogenetic abnormalities include

- t(9;11)(p22.3;q23.3) *MLLT3-KMT2A*
- t(1;22)(p13.3;q13.1) *RBM15-MKL1*
- t(6;9)(p23;q34.1) *DEK-NUP214*
- inv(3)(q21.3q26.2)

Other laboratory findings may include hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and elevated lactic dehydrogenase. These findings indicate a tumor lysis syndrome. Elevated serum hepatic transaminases and/or creatinine and hypoglycemia may also be present.

CT of the head is done in patients with CNS symptoms. Echocardiography or multi-gated acquisition (MUGA) scan is typically done to assess baseline cardiac function prior to giving anthracyclines, which are cardiotoxic.

Acute Myeloid Leukemia [2]

Prognosis

Remission induction rate ranges from 50 to 85%. Long-term disease-free survival is about 20 to 40% overall but is 40 to 50% in younger patients treated with intensive chemotherapy or stem cell transplantation.

Prognostic factors help determine treatment protocol and intensity; patients with strongly negative prognostic features are usually given intense forms of therapy followed by allogeneic stem cell transplantation. In these patients, the potential benefits of intense therapy are thought to justify the increased treatment toxicity.

The **leukemia cell karyotype** is the strongest predictor of clinical outcome. Based on the specific chromosomal rearrangements, three clinical groups have been identified: favorable, intermediate, and poor

Molecular genetic abnormalities are also important in refining prognosis and therapy in AML. Many different mutations exist; these are categorized into groups based on their effect on prognosis and treatment. Patients with AML average 5 recurrent gene mutations.

Acute Myeloid Leukemia [2]

Patients with mutations in *NPM1*, which codes for the protein nucleophosmin, or in *CEBPA* have a more favorable prognosis. Mutations in *FLT3*, on the other hand, have a poorer prognosis (including in patients who also have an otherwise favorable *NPM1* mutation).

Other factors that suggest a poorer prognosis include a preceding myelodysplastic phase, therapy-related AML, and a high WBC count. Patient-specific adverse prognostic factors include age ≥ 65, poor performance status, and comorbidities. Older patients are more likely to have high-risk cytogenetic abnormalities, secondary AML, and AML that is resistant to multiple drugs.

Minimal residual disease is defined as having < 0.1 to 0.01% (based on the assay used) leukemic cells in bone marrow. In AML, minimal residual disease can be assessed by multiparameter flow cytometry detection of leukemia-associated immunophenotype or by mutation-specific polymerase chain reaction (PCR). These tools are prognostically accurate but are not quite ready for use in clinical practice.

Acute Myeloid Leukemia [2]

Treatment

- For medically fit patients: Chemotherapy (induction and consolidation) with or without allogeneic hematopoietic stem cell transplantation
- For medically frail patients: Less intensive therapies
- For all: Supportive care

Treatment of acute myeloid leukemia depends on the patient's overall medical condition. Medically fit patients tend to be younger and have lower-risk cytogenetic abnormalities, better functional status, and fewer comorbidities than medically frail patients.

Because treatment of AML is complex and evolving, it is best done at the most specialized center available, particularly during critical phases (eg, remission induction); clinical trials are the first choice when available.

Medically fit patients with AML

- In medically fit patients, initial treatment is induction chemotherapy to try to induce complete remission.

Acute Myeloid Leukemia [2]

Patients in remission then undergo consolidation therapy that may include allogeneic hematopoietic stem cell transplantation.

Complete remission is defined as < 5% blast cells in the bone marrow, absolute neutrophil count > 1000/mcL (> 1×10^9/L), platelet count > 100,000/mcL (> 100×10^9/L), and independence from blood transfusion.

The **basic induction regimen** (known as 7+3) includes cytarabine by continuous IV infusion for 7 days and daunorubicin or idarubicin given IV for 3 days during this time. Treatment usually results in significant myelosuppression, with infection or bleeding. There is significant latency before marrow recovery. During this time, meticulous preventive and supportive care are vital.

Acute Myeloid Leukemia [2]

Complete remission rates with 7+3 are about 70 to 85% (favorable genetics), 60 to 75% (intermediate genetics), and 25 to 40% (adverse genetics); complete remission rates also depend on patient-specific and other disease risk factors (eg, secondary vs *de novo* AML). However, most patients who achieve a CR with 7+3 (or another conventional induction regimen) ultimately relapse.

Re-induction is usually recommended for patients with residual leukemia on day 14, although there is no high-quality evidence that it improves outcome. Residual leukemia is defined variably as bone marrow blasts > 10% with bone marrow cellularity > 20%. The various recommended re-induction regimens include different dosages of cytarabine. Some include anthracyclines with or without a third agent.

Several drugs can be used with or instead of traditional 7+3 chemotherapy. Addition of midostaurin, a kinase inhibitor, to chemotherapy appears to prolong survival in certain patients (eg, adults < 60 with newly diagnosed *FLT3* mutated AML—1). Gemtuzumab ozogamicin (a CD33 directed antibody-drug conjugate) can be combined with chemotherapy in patients with newly diagnosed CD33-positive AML.

Acute Myeloid Leukemia [2]

Gemtuzumab ozogamicin is also sometimes used as monotherapy for induction and consolidation.

A **consolidation phase** follows remission in many regimens. This can be done with the same drugs used for induction or other drugs. High-dose cytarabine regimens may lengthen remission duration, particularly when given for consolidation in patients < 60 years old. For patients with favorable cytogenetic non-APL AML in first complete remission, consolidation with high-dose cytarabine is considered standard post-induction therapy.

A liposomal combination of daunorubicin and cytarabine is available for the treatment of adults with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

Acute Myeloid Leukemia [2]

This combination showed superiority in overall survival compared with the standard-of-care cytarabine plus daunorubicin (7+3 regimen) in patients 60 to 75 years of age with newly diagnosed t-AML or AML-MRC (2).

Allogeneic stem cell transplantation done during the first complete remission can generally improve outcome in patients with intermediate or adverse-risk cytogenetics. Generally, it takes 6 to 12 weeks to prepare for stem cell transplant. Recommendations are to proceed with standard high-dose cytarabine consolidation chemotherapy while awaiting definitive stem cell transplantation. Conditions that may render patients ineligible for allogenic stem cell transplantation include poor overall performance status and moderate to severe impairment of pulmonary, liver, kidney, or cardiac function.

In APL and some other cases of AML, disseminated intravascular coagulation (DIC) may be present when leukemia is diagnosed and may worsen as leukemic cell lysis releases procoagulant chemicals. In APL [with the translocation t(15;17)], all-*trans* retinoic acid (tretinoin) corrects the DIC in 2 to 5 days; combined with daunorubicin or idarubicin, this regimen can induce remission in 80% to 90% of patients and bring about long-term survival in 65% to 70%.

Acute Myeloid Leukemia [2]

Arsenic trioxide is also very active in APL. Targeted therapy with tretinoin and arsenic trioxide without conventional cytotoxic chemotherapy is very well tolerated and has been extremely successful in APL with a 100% complete remission rate and > 90% cure rate (3).

Medically frail patients with AML

In older and medically frail patients, initial therapy is typically less intensive.

Because the median age for diagnosis of AML is 68, most newly diagnosed patients are considered older. Older patients are more likely to have comorbidities that limit their therapeutic options. Older patients also are much more likely to have high-risk cytogenetic abnormalities (eg, complex karyotype, monosomy 7), secondary AML arising from myelodysplastic syndrome or myeloproliferative neoplasms, or AML with multidrug resistance.

Although intensive chemotherapy is typically denied to older patients solely based on their age, it nevertheless improves rate of complete remission and overall survival in patients < 80, particularly those with favorable-risk karyotypes. Achieving complete remission also improves quality of life by reducing hospitalizations, infections, and transfusion requirements.

The DNA methyltransferase inhibitors decitabine and azacitidine are pyrimidine nucleoside analogs that modulate DNA by reducing methylation of the promoter region of tumor suppressor genes.

Acute Myeloid Leukemia [2]

They have improved clinical outcomes in elderly patients with *de novo* AML as well as those with s-AML (AML preceded by myelodysplastic syndrome), t-AML (therapy-related AML) and AML harboring *TP53* mutations. One of these drugs can be given alone as first-line treatment for many older patients, particularly those with compromised functional/performance status, organ dysfunction, and tumor biology (eg, karyotype, molecular aberrations) that predict poor response to intensive chemotherapy.

Venetoclax is an inhibitor of anti-apoptotic protein BCL-2 and is used in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly diagnosed AML in adults who are ≥ 75 years, or who have comorbidities that preclude use of intensive induction chemotherapy. Further study is needed to confirm these response rates, and continued recommendation for this indication. Glasdegib is a hedgehog pathway inhibitor used, in combination with low-dose cytarabine, for treatment of newly diagnosed AML in patients ≥ 75 years or who have comorbidities that preclude use of intensive induction chemotherapy.

Acute Myeloid Leukemia [2]

Following induction therapy and provided their performance status is appropriate, older patients may undergo allogeneic hematopoietic stem cell transplantation. Allogeneic hematopoietic stem cell transplantation prolongs survival in elderly patients. If patients are not candidates for full intensity regimens, reduced intensity (non-myeloablative) regimens can be used. Older and frail patients who do not undergo transplantation usually proceed to consolidation chemotherapy (eg, cytarabine or combined cytarabine and anthracycline at lower doses than used for induction).

Relapsed or resistant AML

Patients who have not responded (are resistant) to treatment and patients who have relapsed generally have a poor prognosis. A second remission can be achieved in 30% to 70% of patients who relapsed following a first remission. These second remissions are achieved more readily in patients with initial remissions > 1 year and/or with favorable cytogenetics and are generally shorter in duration than first remissions.Patients with relapsed or resistant AML may be candidates for allogeneic stem cell transplantation preceded by re-induction salvage chemotherapy. Many salvage chemotherapeutic regimens include various dosages of cytarabine combined with drugs such as idarubicin, daunorubicin, mitoxantrone, etoposide, antimetabolites (eg, cladribine, clofarabine, fludarabine), and asparaginase. Regimens containing decitabine and azacitidine are sometimes used.

Acute Myeloid Leukemia [2]

Donor lymphocyte infusion is another option in relapsed or resistant AML if initial allogeneic stem cell transplant is unsuccessful. Other novel treatment strategies include enasidenib, an isocitrate dehydrogenase-2 (*IDH2*) inhibitor, or ivosidenib, an isocitrate dehydrogenase-1 (*IDH1*) inhibitor, that may be useful for adult patients with relapsed or refractory AML who have an *IDH2* or an *IDH1* mutation, and gemtuzumab ozogamicin as monotherapy for relapsed or refractory AML.

Gilteritinib is a kinase inhibitor used for the treatment of adult patients who have relapsed or refractory AML with a *FLT3* mutation. In the phase 3 study, patients randomized to receive gilteritinib had significantly longer survival than patients treated with chemotherapy (Hazard ratio 0.64; 95% CI: 0.49 - 0.83) (4).

Chimeric antigen receptor T (CAR-T) cells targeting CD123 or CD33 and antibody-drug conjugates targeting CD33 have also been used in clinical trials.

- **Supportive care**
- Supportive care is similar in the acute leukemias and may include
- Transfusions
- Antimicrobials
- Hydration and urine alkalinization
- Psychologic support

Acute Myeloid Leukemia [2]

Transfusions of red blood cells and platelets are administered as needed to patients with anemia or bleeding. Prophylactic platelet transfusion is done when platelets fall to < 10,000/mcL (< 10 × 10^9/L). Anemia (hemoglobin < 7 or 8 g/dL [< 70 or 80 g/L]) is treated with transfusions of packed red blood cells. Granulocyte transfusions are not routinely used.

Antimicrobials are often needed for prophylaxis and treatment because patients are immunosuppressed; in such patients, infections can progress quickly with little clinical prodrome. After appropriate studies and cultures have been done, febrile patients with neutrophil counts < 500/mcL (< 0.5 × 10^9/L) should begin treatment with a broad-spectrum bactericidal antibiotic that is effective against gram-positive and gram-negative organisms (eg, ceftazidime, piperacillin and tazobactam, meropenem). Fungal infections, especially pneumonias, are becoming more common; these are difficult to diagnose, so chest CT to detect fungal pneumonia should be done early (ie, within 72 hours of presentation with neutropenic fever depending on the degree of suspicion).

Acute Myeloid Leukemia [2]

Antibiotic therapy is the mainstay of treatment for community-acquired pneumonia. Appropriate treatment involves starting empiric antibiotics as soon as possible, preferably ≤4 hours after presentation. Because pathogen identification is difficult and takes time, the empiric antibiotic regimen is selected based on likely pathogens and severity of illness. Consensus guidelines have been developed by many professional organizations;

With empiric treatment, 90% of patients with bacterial pneumonia improve. Improvement is manifested by decreased cough and dyspnea, defervescence, relief of chest pain, and decline in white blood cell count. Failure to improve should trigger suspicion of

- An unusual organism
- Resistance to the antimicrobial used for treatment
- Empyema
- Coinfection or superinfection with a 2nd infectious agent
- An obstructive endobronchial lesion
- Immunosuppression
- Metastatic focus of infection with reseeding (in the case of pneumococcal infection)
- Nonadherence to treatment (in the case of outpatients)
- Wrong diagnosis (ie, a noninfectious cause of the illness such as acute hypersensitivity pneumonitis)

Acute Myeloid Leukemia [2]

Empiric antifungal therapy should be given if antibacterial therapy is not effective within 72 hours. In patients with refractory pneumonitis, Pneumocystis jirovecii infection or a viral infection should be suspected and confirmed by bronchoscopy and bronchoalveolar lavage and treated appropriately. Posaconazole, a 2nd-generation triazole antifungal agent, is indicated for primary prophylaxis in patients age > 13 years who are at high risk of developing invasive *Aspergillus* or *Candida* infections because of immunosuppression. Acyclovir or valacyclovir prophylaxis is generally recommended for all patients.

Hydration and allopurinol or rasburicase are used for treatment of hyperuricemia, hyperphosphatemia, hypocalcemia, and hyperkalemia (ie, a tumor lysis syndrome) caused by the rapid lysis of leukemic cells during initial therapy in AML.

Psychologic support may help patients and their families with the shock of illness and the rigors of treatment for a potentially life-threatening condition.

Acute Myeloid Leukemia [2]

Treatment references

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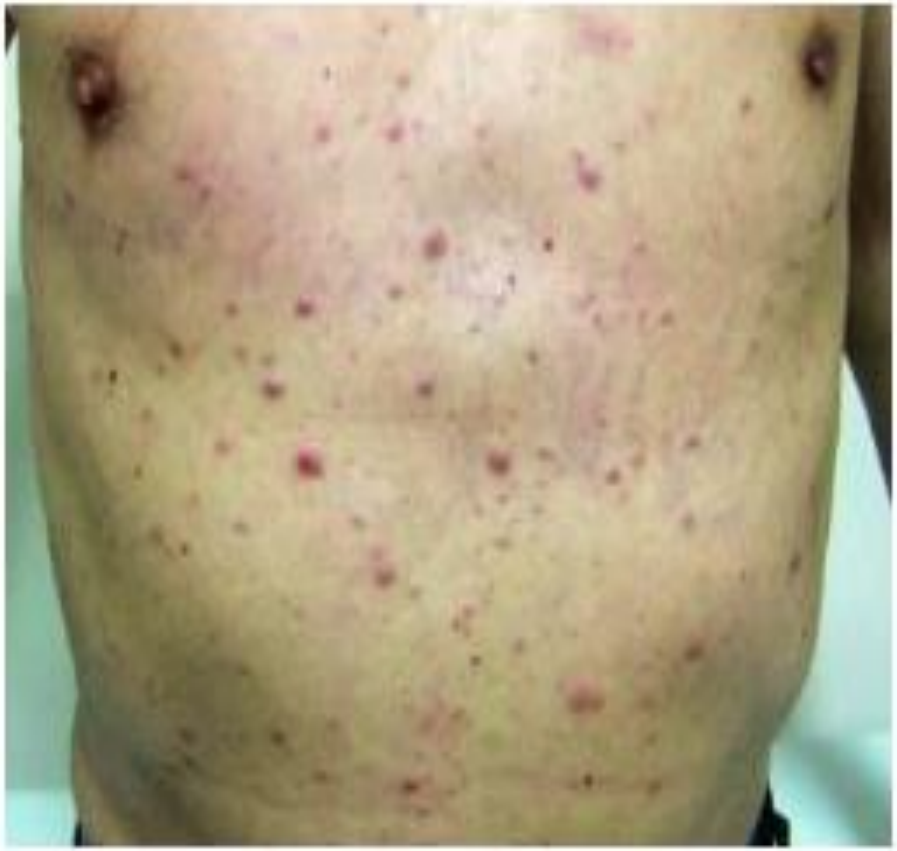
Acute Myeloid Leukemia [2]

Supportive care includes fluids, antipyretics, analgesics, and, for patients with hypoxemia, oxygen. Prophylaxis against thromboembolic disease and early mobilization improve outcomes for patients hospitalized with pneumonia.

Key Points

- Acute myeloid leukemia (AML) is the most common acute leukemia in adults.
- There are a number of subtypes, typically involving very immature myeloid cells.
- Chromosomal and molecular genetic abnormalities are common and have implications for prognosis and treatment.
- In medically fit patients, treat with induction and consolidation chemotherapy followed by allogeneic hematopoietic stem cell transplantation (in patients with intermediate and unfavorable genetic features).
- In medically frail patients, treat with less intensive regimens such as DNA methyltransferase inhibitors and consider allogeneic hematopoietic stem cell transplantation.
- In relapsed and/or resistant patients, treat with salvage chemotherapy followed by allogeneic hematopoietic stem cell transplantation when feasible, or use targeted therapies.

Leukemia Cutis (Disseminated)



Acute Lymphoblastic Leukemia (ALL) [3]

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer; it also strikes adults of all ages. Malignant transformation and uncontrolled proliferation of an abnormally differentiated, long-lived hematopoietic progenitor cell results in a high circulating number of blasts, replacement of normal marrow by malignant cells, and the potential for leukemic infiltration of the central nervous system (CNS) and testes. Symptoms include fatigue, pallor, infection, bone pain, CNS symptoms (eg, headache), easy bruising, and bleeding. Examination of peripheral blood smear and bone marrow is usually diagnostic. Treatment typically includes combination chemotherapy to achieve remission, intrathecal and systemic chemotherapy and/or corticosteroids for CNS prophylaxis, and sometimes cerebral irradiation for intracerebral leukemic infiltration, consolidation chemotherapy with or without stem cell transplantation, and maintenance chemotherapy for up to 3 years to avoid relapse (By **Ashkan Emadi** , MD, PhD, University of Maryland; **Jennie York Law** , MD, University of Maryland Last full review/revision May 2020| Content last modified May 2020 - MSD Manual Professional Version [3] https://www.msdmanuals.com/professional/hematology-and-oncology/leukemias/acute-lymphoblastic-leukemia-all?query=acute%20lymphoblastic%20leukemia%20acute)

Acute Lymphoblastic Leukemia[3]

The American Cancer Society estimates that in the United States in 2020 there will be about 6,150 new cases of acute lymphoblastic leukemia (ALL) and about 1,520 deaths. Sixty percent of all ALL cases occur in children, with a peak incidence at age 2 to 5 years; a second peak occurs after age 50. ALL is the most common cancer in children, and represents about 75% of leukemias among children < 15 years of age, and is the 2nd most common cause of death in children < 15 years. The risk declines slowly until the mid-20s and then begins to rise again slowly after age 50. ALL accounts for about 20% of adult acute leukemias. The average lifetime risk of ALL in both sexes is about 0.1% (1 in 1000 Americans). Hispanic populations have a higher incidence of ALL than other racial/ethnic populations due in part to polymorphisms in the *ARID5B* gene.

Acute Lymphoblastic Leukemia[3]

Pathophysiology

Similar to acute myeloid leukemia (AML), acute lymphoblastic leukemia is caused by a series of acquired genetic aberrations. Malignant transformation usually occurs at the pluripotent stem cell level, although it sometimes involves a committed stem cell with more limited capacity for self-renewal. Abnormal proliferation, clonal expansion, aberrant differentiation, and diminished apoptosis (programmed cell death) lead to replacement of normal blood elements with malignant cells.

Classification

In acute lymphoblastic leukemia, the precursor lymphoid neoplasms are broadly categorized based on their lineage into

- B-lymphoblastic leukemia/lymphoma (B-ALL/LBL)
- T-lymphoblastic leukemia/lymphoma (T-ALL/LBL)

Disease can manifest as leukemia when neoplastic cells (lymphoblasts) involve blood and bone marrow (defined as > 20% bone marrow blasts) or as lymphoma when blasts infiltrate mainly extramedullary tissue.

Acute Lymphoblastic Leukemia[3]

The 2016 World Health Organization (WHO) classification of lymphoid neoplasms incorporates genetic data, clinical features, cell morphology, and immunophenotype, all of which have important implications for disease prognosis and management.

Symptoms and Signs

Symptoms and signs of acute lymphoblastic leukemia may be present for only days to weeks before diagnosis.

The most common presenting symptoms are due to disrupted hematopoiesis with ensuing

- Anemia
- Thrombocytopenia
- Granulocytopenia

Anemia can manifest with fatigue, weakness, pallor, malaise, dyspnea on exertion, tachycardia, and exertional chest pain.

Thrombocytopenia can cause mucosal bleeding, easy bruising, petechiae/purpura, epistaxis, bleeding gums, and heavy menstrual bleeding.

Acute Lymphoblastic Leukemia [3]

Hematuria and gastrointestinal bleeding are uncommon. Patients can present with spontaneous hemorrhage, including intracranial or intra-abdominal hematomas.

Granulocytopenia or neutropenia can lead to a high risk of infections, including those of bacterial, fungal, and viral etiologies. Patients may present with fevers and a severe and/or recurrent infection.

Organ infiltration by leukemic cells results in enlargement of the liver, spleen, and lymph nodes. Bone marrow and periosteal infiltration may cause bone and joint pain, especially in children wth ALL. CNS penetration and meningeal infiltration are common and can result in cranial nerve palsies, headache, visual or auditory symptoms, altered mental status, and transient ischemic attack/stroke.

Acute Lymphoblastic Leukemia [3]

Diagnosis

- Complete blood count (CBC) and peripheral blood smear
- Bone marrow examination
- Histochemical studies, cytogenetics and immunophenotyping

A diagnosis of acute lymphoblastic leukemia is made when blast cells of lymphoid origin are ≥ 20% of marrow nucleated cells or ≥ 20% of non-erythroid cells when the erythroid component is > 50%. If marrow cells are insufficient or unavailable, diagnosis can be made by the same criteria using a peripheral blood sample.

CBC and peripheral smear are the first tests done; pancytopenia and peripheral blasts suggest acute leukemia. Blast cells in the peripheral smear may approach 90% of the white blood cell (WBC) count. Aplastic anemia, viral infections such as infectious mononucleosis, and vitamin B12 deficiency, and folate deficiency should be considered in the differential diagnosis of severe pancytopenia. Leukemoid reactions (marked granulocytic leukocytosis [ie, WBC > 50,000/mcL, > 50 × 10^9/L] produced by normal bone marrow) to infectious disease never manifest with high blast counts. Unlike in AML, Auer rods (linear azurophilic inclusions in the cytoplasm of blast cells) are never present in acute lymphoblastic leukemia.

Acute Lymphoblastic Leukemia [3]

Bone marrow examination (aspiration and needle biopsy) is routinely done. Blast cells in the bone marrow are classically between 25 and 95%.

Histochemical studies, cytogenetics, and immunophenotyping studies help distinguish the blasts of ALL from those of AML or other disease processes. Histochemical studies include staining for terminal deoxynucleotidyl transferase (TdT), which is positive in cells of lymphoid origin. Detection of specific immunophenotypical markers such as CD3 (for lymphoid cells of T cell origin) and CD19, CD20, and CD22 (for lymphoid cells of B cell origin) is essential in classifying the acute leukemias. Common cytogenetic abnormalities in ALL include t(9;22) in adults and t(12;21).

Acute Lymphoblastic Leukemia[3]

Less common cytogenetic abnormalities include the following:

- t(v;11q23) /*MLL* or *KMT2A* rearranged, including t(4;11)/*KMT2A-AF4*
- t(1;19)/*E2A-PBX1* (*TCF3-PBX1*)
- t(5;14)/*IL3-IGH*
- t(8;14), t(8;22), t(2;8)/*C-MYC* rearranged
- *BCR-ABL*-like acute lymphoblastic leukemia overlaps genetically with ALL in which the Philadelphia chromosome [a reciprocal balanced translocation between chromosomes 9 and 22, t(9;22)] is present (Ph+ ALL).

Other laboratory findings may include hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and elevated lactate dehydrogenase (LDH), which indicate a tumor lysis syndrome. Elevated serum hepatic transaminases or creatinine, and hypoglycemia may also be present. Patients with Ph+ ALL and patients with t(*v*;11q23) involving *MLL* rearrangements often present with hyperleukocytosis.

Acute Lymphoblastic Leukemia [3]

Symptoms and signs of hospital-acquired pneumonia in nonintubated patients are generally the same as those for community-acquired pneumonia and include malaise, fever, chills, rigor, cough, dyspnea, and chest pain.

CT of the head is done in patients with CNS symptoms. CT of the chest and abdomen should be done to detect mediastinal masses and lymphadenopathy and may also detect hepatosplenomegaly. Echocardiography or multi-gated acquisition (MUGA) scanning is typically done to assess baseline cardiac function (prior to administration of anthracyclines, which are cardiotoxic).

Acute Lymphoblastic Leukemia [3]

Prognosis

Prognostic factors help determine treatment protocol and intensity.

Favorable prognostic factors are

- Age 3 to 9 years
- WBC count < 25,000/mcL (< 25 × 10^9/L) or < 50,000/mcL (< 50 × 10^9/L) in children
- Leukemic cell karyotype with high hyperdiploidy (51 to 65 chromosomes), t(1;19), and t(12;21)
- No CNS disease at diagnosis

Acute Lymphoblastic Leukemia [3]

Unfavorable factors include

- Leukemic cell karyotype with 23 chromosomes (haploidy), with < 46 chromosomes (hypodiploidy), or with 66 to 68 chromosomes (near triploidy)
- Leukemic cell karyotype with t(*v*;11q23) *MLL* (*KMT2A*) rearranged, including t(4;11)/*KMT2A-AF4*
- Leukemic cell karyotype t(5;14)/*IL3-IG*
- Leukemic cell karyotype t(8;14), t(8;22), t(2;8) *C-MYC* rearranged
- Presence of the Philadelphia (Ph) chromosome t(9;22) *BCR-ABL1*
- Increased age in adults
- *BCR/ABL*-like molecular signature

Acute Lymphoblastic Leukemia [3]

Regardless of prognostic factors, the likelihood of initial remission is ≥ 95% in children and 70 to 90% in adults. Of children, > 80% have continuous disease-free survival for 5 years and appear to be cured. Of adults, < 50% have long-term survival. Factors contributing to poorer clinical outcomes in adults compared with children include the following:

- Less ability to tolerate intensive chemotherapy
- More frequent and severe comorbidities
- Higher risk ALL genetics that confer chemotherapy resistance
- Poorer adherence to ALL treatment regimens, which include frequent (often daily or weekly) out-patient chemotherapy and doctor visits
- Less frequent use of pediatric-inspired treatment regimens
- Most investigatory protocols select patients with poor prognostic factors for more intense therapy because the increased risk of and toxicity from treatment are outweighed by the greater risk of treatment failure leading to death.

Acute Lymphoblastic Leukemia [3]

Treatment

- Systemic chemotherapy
- Prophylactic CNS chemotherapy and sometimes CNS radiation
- For Ph+ ALL, also a tyrosine kinase inhibitor
- Supportive care
- Sometimes immunotherapy, targeted therapy, stem cell transplantation, and/or radiation therapy

Treatment for newly diagnosed acute lymphoblastic leukemia generally consists of 3 to 4 cycles of chemotherapy blocks of non–cross-resistant chemotherapy for the first 9 to 12 months, followed by 2.5 to 3 years of maintenance chemotherapy.

Acute Lymphoblastic Leukemia [3]

Chemotherapy

- The **4 general phases of chemotherapy** for acute lymphoblastic leukemia include
- Remission induction
- Postremission consolidation
- Interim maintenance and intensification
- Maintenance

The goal of induction treatment is complete remission, defined as < 5% blast cells in the bone marrow, an absolute neutrophil count > 1000/mcL (> 1×10^9/L), a platelet count > 100,000/mcL (> 100×10^9/L), and no need for blood transfusion. In patients with complete remission, a low measurable residual disease (also known as minimal residual disease or MRD) is the most important prognostic factor (1). Measurable or minimal residual disease is microscopic disease that is not detected by standard assays but can be measured by more sensitive assays. A low measurable residual disease (MRD negativity) is defined variably (based on the assay used) as < 0.01 to 0.1% leukemic cells in bone marrow

Acute Lymphoblastic Leukemia [3]

Components of **induction therapy** include

- A high-dose corticosteroid (eg, dexamethasone, prednisone)
- An anthracycline (eg, daunorubicin, doxorubicin, idarubicin)
- Vincristine

Some regimens use a corticosteroid to reduce disease burden prior to intensive induction. In younger adults, a regimen that includes asparaginase and/or cyclophosphamide for induction, similar to treatment protocols used in children, may increase rates of response and achievement of undetectable minimal residual disease. If complete remission is not achieved after induction, some regimens recommend a second induction course to try to get more patients to complete remission before consolidation.

For patients with Philadelphia chromosome–positive (Ph+) ALL, a tyrosine kinase inhibitor (eg, imatinib, dasatinib) can be added to the drug regimen. For patients with CD20 positive B-lymphoblastic leukemia, rituximab can be added.

Acute Lymphoblastic Leukemia [3]

The goal of **consolidation** is to prevent leukemic regrowth. Consolidation therapy usually lasts a few months and combines regimen-specific courses of non–cross-resistant drugs that have different mechanisms of action. For adults with Ph+ ALL, allogeneic stem cell transplantation is recommended as consolidation therapy.

Interim maintenance and late/delayed intensification therapy are used after consolidation therapy. These phases of therapy incorporate a variety of chemotherapeutic agents with different doses and schedules that are less intense than induction and consolidation.

Most regimens include **maintenance therapy** with monthly vincristine, weekly methotrexate, daily mercaptopurine, and 5 days/month corticosteroid. Therapy duration is usually 2½ to 3 years.

Acute Lymphoblastic Leukemia [3]

CNS prophylaxis starts during induction and continues throughout all phases of treatment. Because lymphoblasts often infiltrate the spinal fluid and meninges, all regimens include CNS prophylaxis and treatment with intrathecal methotrexate, cytarabine, and hydrocortisone in combination or as monotherapy. High doses of systemic methotrexate and/or cytarabine penetrate the CNS, providing extra CNS prophylaxis if regimens include these drugs. Cranial nerve or whole-brain irradiation was previously often done for patients at high risk of CNS disease (eg, high WBC count, high serum lactate dehydrogenase, B-cell phenotype), but its use has been decreasing in recent years.

Acute Lymphoblastic Leukemia [3]

Medically frail patients with ALL

- About one third of patients with acute lymphoblastic leukemia are older adults (> 65). Older ALL patients are more likely to have precursor B-cell ALL and have higher risk and more complex cytogenetics, including Philadelphia chromosome positive (Ph+) or t(*v*;11q23) *MLL* (*KMT2A*) rearranged disease.
- Some, but not all, older patients can tolerate standard induction therapy. Subsequent treatment regimens (CNS prophylaxis, postremission consolidation or intensification, and maintenance) depend on the individual patient's comorbidities and performance status. For example, older patients with several comorbidities and poor performance status may undergo gentler induction therapy without consolidation or maintenance. In older patients with Ph+ ALL, tyrosine kinase inhibitors (eg, imatinib, dasatinib) plus corticosteroids given with either low-intensity or no chemotherapy have resulted in 95 to 100% complete remission rate, with 45 to 50% 2-year relapse free survival and about 70% 2-year overall survival.

Acute Lymphoblastic Leukemia [3]

For older patients with ALL who are in their first complete remission, nonmyeloablative or reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation is an option.

Targeted immunotherapy drugs that are available for treatment of relapsed or refractory ALL are increasingly used for treatment of older patients with ALL in clinical trials or clinical practice.

Older patients with ALL probably tolerate asparaginase more poorly than younger patients do.

Relapsed or refractory ALL

Leukemic cells may reappear in the bone marrow, CNS, testes, or other sites. Bone marrow relapse is particularly ominous. Although a new round of chemotherapy may induce a second remission in the majority of children and about one third of adults, subsequent remissions tend to be brief. Chemotherapy causes only a few patients with early bone marrow relapse to achieve long disease-free second remissions or cure.

Acute Lymphoblastic Leukemia [3]

New immunotherapy approaches show impressive results in relapsed/refractory ALL. Antibodies, such as blinatumomab, that bring T cells into close proximity to leukemic blasts demonstrate activity in relapsed ALL. Chimeric antigen receptor T (CAR-T) cells, engineered and generated from the patient's T cells, induce remission in patients with relapsed ALL with remarkable efficacy, albeit with significant toxicity (2).

Available immunotherapies for relapsed or refractory ALL include

- Blinatumomab
- Inotuzumab ozogamicin
- Tisagenlecleucel

Blinatumomab, a biospecific CD19-directed CD3 T-cell engager, prolongs overall survival for children and adults with relapsed or refractory B-cell precursor ALL, whether Ph+ or Ph-. Life-threatening toxicities may include cytokine release syndrome and neurologic toxicities (eg, seizures, encephalopathy with altered consciousness, and disordered speech, coordination, and/or balance). Interruption or stopping blinatumomab with or without use of high-dose dexamethasone may be necessary. The most common neurologic symptoms after blinatumomab use are headache and tremor (3).

Acute Lymphoblastic Leukemia [3]

- **Inotuzumab ozogamicin,** a CD22-directed antibody-drug conjugate with calicheamicin, is also available for adults with relapsed or refractory B-cell precursor ALL. One study found significantly higher remission rates after 1 to 2 cycles of therapy with inotuzumab ozogamicin than with standard chemotherapy (4). Inotuzumab may cause hepatotoxicity, including fatal and life-threatening veno-occlusive disease and is associated with higher post-transplant non-relapse mortality.
- **Tisagenlecleucel,** a CD19-directed genetically modified autologous T-cell immunotherapy, is available for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in a 2nd or later relapse. Cytokine release syndrome and life-threatening or fatal neurologic toxicities may occur (5).

Acute Lymphoblastic Leukemia [3]

Other agents that are available, but for which clinically meaningful outcomes have not been convincingly demonstrated, include Liposomal vincristine (a vinca alkaloid): For adults with Ph- ALL in at least 2nd relapse or that has progressed despite ≥ 2 antileukemia therapies

- Clofarabine (a purine nucleoside analog): For patients age 1 to 21 years with relapsed or refractory ALL after ≥ 2 prior regimens
- Nelarabine (a purine nucleoside) analog prodrug of guanosine arabinoside: For T-cell ALL that has not responded to or has relapsed after ≥ 2 prior regimens

Stem cell transplantation following reinduction chemotherapy or immunotherapy offers the greatest hope of long-term remission or cure if an HLA-matched sibling is available. Cells from other relatives or from matched, unrelated donors are sometimes used. Transplantation is rarely used for patients > 65 years because it is much less likely to be successful and because adverse effects are much more likely to be fatal.

Acute Lymphoblastic Leukemia [3]

CNS relapse treatment includes intrathecal methotrexate (with or without cytarabine or corticosteroids) twice weekly until all signs disappear. The role of continued intrathecal drug use or CNS irradiation is unclear.

Testicular relapse may be evidenced clinically by painless firm swelling of a testis or may be identified on biopsy. If unilateral testicular involvement is clinically evident, the apparently uninvolved testis should undergo biopsy. Treatment is radiation therapy of the involved testis and administration of systemic reinduction therapy.

Supportive care

- Supportive care is similar in the acute leukemias and may include
- Transfusions
- Antimicrobials
- Hydration and urine alkalinization
- Psychologic support

Acute Lymphoblastic Leukemia [3]

Transfusions of red blood cells and sometimes platelets are administered as needed to patients with bleeding or anemia. Prophylactic platelet transfusion is done when platelets fall to < 10,000/mcL (< 10 × 10^9/L). Anemia (hemoglobin <7 or 8 g/dL [< 70 to 80 g/L]) is treated with transfusions of packed red blood cells. Granulocyte transfusions are not routinely used.

Antimicrobials are often needed for prophylaxis and treatment because patients are immunosuppressed; in such patients, infections can progress quickly with little clinical prodrome. After appropriate studies and cultures have been done, febrile patients with neutrophil counts < 500/mcL (< 0.5 × 10^9/L) should begin treatment with a broad-spectrum bactericidal antibiotic that is effective against gram-positive and gram-negative organisms (eg, ceftazidime, piperacillin and tazobactam, meropenem). Fungal infections, especially pneumonias, are becoming more common; these infections are difficult to diagnose, so chest CT to detect fungal pneumonia should be done early (ie, within 72 hours of presentation with neutropenic fever, depending on the degree of suspicion).

Acute Lymphoblastic Leukemia [3]

Empiric antifungal therapy should be given if antibacterial therapy is not effective within 72 hours. There is a significant drug-drug interaction between vincristine, which is commonly used in all ALL treatment regimens, and azole antifungals. In patients with refractory pneumonitis, Pneumocystis jirovecii infection or a viral infection should be suspected and confirmed by bronchoscopy and bronchoalveolar lavage and treated appropriately. Posaconazole, a 2nd-generation triazole antifungal drug, is indicated for primary prophylaxis in patients age > 13 years who are at high risk of developing invasive *Aspergillus* and *Candida* infections because of immunosuppression (eg, hematopoietic stem cell transplant recipients with graft-versus-host disease). In patients with drug-induced immunosuppression (eg, prolonged use of corticosteroids for **Acute Lymphoblastic Leukemia treatment,** trimethoprim/sulfamethoxazole (TMP/SMX), dapsone, atovaquone, or pentamidine is indicated to prevent *P.jirovecii* pneumonia.

Acyclovir or valacyclovir prophylaxis is generally recommended for all patients.

Acute Lymphoblastic Leukemia [3]

- **Hydration,** urine alkalinization with IV sodium bicarbonate, and allopurinol or rasburicase can prevent and treat the hyperuricemia, hyperphosphatemia, hypocalcemia, and hyperkalemia (ie, tumor lysis syndrome) caused by the rapid lysis of leukemic cells during initial therapy in ALL. Hyperuricemia is minimized by reducing the conversion of xanthine to uric acid by giving allopurinol (a xanthine oxidase inhibitor) or rasburicase (a recombinant urate-oxidase enzyme) before starting chemotherapy.
- **Psychologic support** may help patients and their families with the shock of illness and the rigors of treatment for a potentially life-threatening condition.

Acute Lymphoblastic Leukemia [3]

Treatment references

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Acute Lymphoblastic Leukemia [3]

Key Points

- Acute lymphoblastic leukemia (ALL) is the most common cancer in children but also occurs in adults.
- Central nervous system (CNS) involvement is common; most patients receive intrathecal chemotherapy and corticosteroids and sometimes CNS radiation therapy.
- Response to treatment is good in children, with cure possible in > 80% of children but in < 50% of adults.
- Repeat induction chemotherapy, immunotherapy, and stem cell transplantation may be helpful for relapse.

Chronic Lymphocytic Leukemia (CLL) [4]

Chronic lymphocytic leukemia (CLL) is characterized by progressive accumulation of phenotypically mature malignant B lymphocytes. Primary sites of disease include peripheral blood, bone marrow, spleen, and lymph nodes. Symptoms and signs may be absent or may include lymphadenopathy, splenomegaly, hepatomegaly, fatigue, fevers, night sweats, unintentional weight loss, and early satiety. Diagnosis is by flow cytometry and immunophenotyping of peripheral blood. (By **Ashkan Emadi** , MD, PhD, University of Maryland; **Jennie York Law** , MD, University of Maryland Last full review/revision May 2020| Content last modified May 2020 - MSD Manual Professional Version [4] - https://www.msdmanuals.com/professional/hematology-and-oncology/leukemias/chronic-lymphocytic-leukemia-cll)

Chronic Lymphocytic Leukemia (CLL) [4]

Treatment is delayed until symptoms develop and generally involves chemotherapy and immunotherapy. However, treatments are evolving, and first-line regimens may include targeted agents such as inhibitors of Bruton tyrosine kinase (Btk) and Bcl-2, with or without chemotherapy.

Chronic lymphocytic leukemia is the most common type of leukemia in the Western world. The American Cancer Society estimates that in the United States in 2020 there will be about 21,040 new cases of CLL and about 4060 deaths; most cases and almost all deaths will be in adults. The average age of a patient with CLL is 70 years; CLL is extremely rare in children. The average lifetime risk of CLL in both sexes is about 0.57% (1 in 175 Americans).

Although the cause of CLL is unknown, some cases appear to have a hereditary component. CLL is rare in Japan and China, and the incidence does not seem to be increased among Japanese expatriates in the United States, suggesting the importance of genetic factors. CLL is more common among Jews of Eastern European descent.

Chronic Lymphocytic Leukemia (CLL) [4]

Pathophysiology

In chronic lymphocytic leukemia, CD5+ B cells undergo malignant transformation. The B cells become continuously activated by acquisition of mutations that lead to monoclonal B-cell lymphocytosis (MBL). Further accumulation of genetic abnormalities and subsequent oncogenic transformation of monoclonal B cells leads to CLL. Lymphocytes initially accumulate in the bone marrow and then spread to lymph nodes and other lymphoid tissues, eventually inducing splenomegaly, hepatomegaly, and systemic symptoms such as fatigue, fever, night sweats, early satiety, and unintentional weight loss.

As CLL progresses, abnormal hematopoiesis results in anemia, neutropenia, thrombocytopenia, and decreased immunoglobulin production. Hypogammaglobulinemia can develop in up to two thirds of patients, increasing risk for infectious complications. Patients have increased susceptibility to autoimmune hemolytic anemias (with a positive direct antiglobulin test) and autoimmune thrombocytopenia.

Chronic Lymphocytic Leukemia (CLL) [4]

CLL can evolve into B-cell prolymphocytic leukemia and can transform to a higher grade non-Hodgkin lymphoma. About 2 to 10% of CLL cases develop into diffuse large B-cell lymphoma (called Richter's transformation).

Symptoms and Signs

Patients are often asymptomatic early on, with insidious onset of nonspecific symptoms (eg, fatigue, weakness, anorexia, weight loss, fever, and/or night sweats) that may prompt evaluation. More than 50% of patients have lymphadenopathy.

Chronic Lymphocytic Leukemia (CLL) [4]

Lymphadenopathy can be localized (with cervical and supraclavicular nodes being the most commonly involved) or generalized. Splenomegaly and hepatomegaly are less common than lymphadenopathy. Skin involvement (leukemia cutis) is rare.

Diagnosis

- Complete blood count (CBC) and peripheral smear
- Flow cytometry of peripheral blood
- Immunophenotyping

The diagnosis of chronic lymphocytic leukemia is first suspected when an absolute peripheral lymphocytosis of > 5000/mcL (> 5×10^9/L)) is found. Peripheral blood flow cytometry can confirm clonality in circulating B cells. The circulating lymphocytes should express CD5, CD19, CD20, CD23, and kappa or lambda light chains. Patients with an absolute lymphocyte count < 5000/mcL (< 5×10^9/L) but evidence of clonality are diagnosed with monoclonal B cell lymphocytosis (MBL).

Chronic Lymphocytic Leukemia (CLL) [4]

About 1 to 2% of monoclonal B-cell lymphocytosis cases progress to CLL per year (1). Bone marrow aspirate and biopsy are not required for the diagnosis of CLL. However, if done, the marrow often demonstrates > 30% lymphocytes.

Other findings at diagnosis can include hypogammaglobulinemia (< 15% of cases), elevated lactate dehydrogenase (LDH), elevated uric acid, elevated hepatic enzymes, and rarely, hypercalcemia. Cytogenetic and molecular studies done from peripheral blood at the time of diagnosis help in determining prognosis.

Classification uses the Rai or Binet staging systems. Neither system effectively predicts early disease progression. Routine imaging is not recommended for initial staging.

Diagnosis reference

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Chronic Lymphocytic Leukemia (CLL) [4]

Prognosis

The natural history of chronic lymphocytic leukemia is highly variable. Survival ranges from about 2 to > 20 years, with a median of about 10 years. Patients presenting as Rai stage 0 to II may survive for 5 to 20 years without treatment.

Other prognostic features of CLL include:

- Lymphocyte doubling time
- Specific genetic abnormalities

Lymphocyte doubling time is the number of months it takes the absolute lymphocyte count to double. Untreated patients with a lymphocyte doubling time < 12 months have a more aggressive clinical course.

Specific high-risk cytogenetic abnormalities include del(17p) and del(11q). Other adverse prognostic features include an unmutated immunoglobulin heavy chain variable gene, presence of CD38 on flow cytometry, and expression of ZAP-70.

Chronic Lymphocytic Leukemia (CLL) [4]

Treatment

- Chemoimmunotherapy, targeted therapy, and sometimes radiation therapy
- Supportive care

Chronic lymphocytic leukemia is considered incurable with the current standard of care; treatment is aimed at symptom amelioration. Thus, treatment is withheld until patients have one of the following:

- Symptoms attributed to CLL
- Progressive lymphocytosis with an increase of ≥ 50% over a 2-month period
- Lymphocyte doubling time of less than 6 months
- Symptoms that prompt treatment in patients with CLL include
- Constitutional symptoms (fever, night sweats, extreme fatigue, weight loss)
- Significant hepatomegaly, splenomegaly, or lymphadenopathy
- Recurrent infections
- Symptomatic anemia and/or thrombocytopenia

Chronic Lymphocytic Leukemia (CLL) [4]

Disease-directed treatment options include

- Chemoimmunotherapy
- Targeted therapy
- Radiation therapy

Supportive care includes

- Transfusion of packed red blood cells for anemia
- Platelet transfusions for bleeding associated with thrombocytopenia
- Antimicrobials for bacterial, fungal, or viral infections

Because neutropenia and hypogammaglobulinemia limit bacterial killing, antibiotic therapy should be bactericidal. Gamma-globulin infusions should be considered for treatment in patients with hypogammaglobulinemia and refractory infections or for prophylaxis when ≥ 2 severe infections occur within 6 months.

Chronic Lymphocytic Leukemia (CLL) [4]

Initial therapy

- Chemoimmunotherapy aims to Relieve symptoms
- Induce durable remissions
- Prolong survival

There is no standard chemoimmunotherapy regimen. Selection of initial therapy depends on patient characteristics, disease-specific features such as presence of del(17p), and the overarching goals of therapy.

Purine analogs (eg, fludarabine) as well as alkylating agents (eg, bendamustine, chlorambucil, cyclophosphamide) have been used in combination with the anti-CD20 monoclonal antibody, rituximab. Untreated patients who can tolerate chemotherapy are often offered the combination of fludarabine, cyclophosphamide, and rituximab. Alternatively, elderly untreated patients are often offered bendamustine and rituximab because this regimen is easier to tolerate (1).

Chronic Lymphocytic Leukemia (CLL) [4]

CLL with del(17p) is often refractory to chemoimmunotherapy, but ibrutinib has been shown to improve outcome. Ibrutinib is a novel, oral inhibitor of Bruton tyrosine kinase (Btk), an enzyme essential for activation of several pathways that enhance CLL cell survival. Studies comparing ibrutinib monotherapy with ibrutinib plus chemoimmunotherapy are ongoing.

In older patients with comorbid conditions, the anti-CD20 monoclonal antibody obinutuzumab is added to chlorambucil. Obinutuzumab targets the same CLL cell surface protein as rituxumab. Obinutuzumab plus chlorambucil was recently found to be superior to rituximab plus chlorambucil in prolonging progression-free survival and achieving a complete response (2).

Relapsed or refractory CLL

- Relapsed or refractory CLL should be confirmed histologically before restarting treatment. Transformation to large cell lymphoma (Richter's transformation) should be excluded specifically. Asymptomatic patients with recurrent CLL are monitored closely for symptoms that warrant treatment.

Chronic Lymphocytic Leukemia (CLL) [4]

Factors that influence choice of treatment at relapse include

- Initial therapy used
- Initial duration of response

Ibrutinib (a Btk inhibitor) can improve response rate and progression-free survival in relapsed or refractory CLL. Ibrutinib is continued until toxicity develops or disease progresses. Other effective targeted therapies for relapsed CLL included idelalisib (an oral inhibitor of phosphoinositide 3'-kinase [PI3K] delta) and venetoclax (an oral inhibitor of Bcl-2). Venetoclax can be used for patients with del(17p) who have received at least one prior therapy.

Monotherapy with an anti-CD20 monoclonal antibody (rituximab, ofatumumab, obinutuzumab) may transiently palliate symptoms.

Chronic Lymphocytic Leukemia (CLL) [4]

Radiation therapy

Palliative irradiation may be given to areas of lymphadenopathy or for liver and spleen involvement that does not respond to chemotherapy. Total body irradiation in small doses is occasionally successful in temporarily relieving symptoms.

Treatment references

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Chronic Lymphocytic Leukemia (CLL) [4]

Key Points

- Chronic lymphocytic leukemia (CLL) is an indolent lymphoproliferative malignancy involving mature lymphocytes which predominantly affects older individuals.
- CLL is the most common type of leukemia in the Western world.
- Natural history is highly variable.
- Treatment is generally not curative and is not initiated until symptoms develop.
- Chemoimmunotherapy decreases symptoms and prolongs survival.

Chronic Myeloid Leukemia (CML) [5]

Chronic myeloid leukemia (CML) occurs when a pluripotent stem cell undergoes malignant transformation and clonal myeloproliferation, leading to a striking overproduction of mature and immature granulocytes. Initially asymptomatic, CML progression is insidious, with a nonspecific “benign” stage (malaise, anorexia, weight loss) eventually giving way to accelerated or blast phases with more ominous signs, such as splenomegaly, pallor, easy bruising and bleeding, fever, lymphadenopathy, and skin changes. Peripheral blood smear, bone marrow aspirate, and demonstration of the Philadelphia chromosome are diagnostic. Treatment is with tyrosine kinase inhibitors (TKI) such as imatinib, dasatinib, nilotinib, bosutinib, and ponatinib, which significantly improve response and prolong survival. Myelosuppressive drugs (eg, hydroxyurea), stem cell transplantation, and interferon alfa are also sometimes used. By **Ashkan Emadi** , MD, PhD, University of Maryland; **Jennie York Law** , MD, University of Maryland

Last full review/revision May 2020| Content last modified May 2020 - MSD Manual Professional Version [5]
https://www.msdmanuals.com/professional/hematology-and-oncology/leukemias/chronic-myeloid-leukemia-cml?query=chronic%20myeloid%20leukemia%20(CML)

Chronic Myeloid Leukemia (CML) [5]

The American Cancer Society estimates that in the United States in 2020 there will be about 8,450 new cases of CML and about 1,130 deaths. The average age of a patient with CML is 64 years. The average lifetime risk of CML in the United States among both sexes is about 0.19% (1 in 526).

Pathophysiology

The Philadelphia (Ph) chromosome is present in 90 to 95% of cases of chronic myeloid leukemia. The Ph chromosome is the product of a reciprocal translocation between chromosomes 9 and chromosome 22, t(9;22). During this translocation, a piece of chromosome 9 containing the oncogene ABL is translocated to chromosome 22 and fused to the *BCR* gene. The chimeric fusion gene *BCR-ABL* is responsible for production of the oncoprotein bcr-abl tyrosine kinase.

The bcr-abl oncoprotein has uncontrolled tyrosine kinase activity, which deregulates cellular proliferation, decreases adherence of leukemia cells to the bone marrow stroma, and protects leukemic cells from normal programmed cell death (apoptosis).

Chronic Myeloid Leukemia (CML) [5]

CML ensues when an abnormal pluripotent hematopoietic progenitor cell initiates excessive production of all myeloid lineage cells, primarily in the bone marrow but also in extramedullary sites (eg, spleen, liver). Although granulocyte production predominates, the neoplastic clone includes red blood cells, megakaryocytes, monocytes, and even some T cells and B cells. Normal stem cells are retained and can emerge after drug suppression of the CML clone.

Untreated, CML undergoes 3 phases:

- **Chronic phase:** An initial indolent period that may last 5 to 6 years
- **Accelerated phase:** Treatment failure, worsening anemia, progressive thrombocytopenia or thrombocytosis, persistent or worsening splenomegaly, clonal evolution, increasing blood basophils, and increasing marrow or blood blasts (up to 19%)
- **Blast phase:** Accumulation of blasts in extramedullary sites (eg, bone, central nervous system, lymph nodes, skin); blasts in blood or marrow increase to ≥ 20%

Chronic Myeloid Leukemia (CML) [5]

The blast phase leads to fulminant complications resembling those of acute leukemia, including sepsis and bleeding. Some patients progress directly from the chronic to the blast phase.

Symptoms and Signs

About 85% of patients with CML present in the chronic phase. Patients are often asymptomatic early on, with insidious onset of nonspecific symptoms (eg, fatigue, weakness, anorexia, weight loss, night sweats, a sense of abdominal fullness particularly in left upper quadrant, gouty arthritis, symptoms of leukostasis such as tinnitus, stupor, and urticaria), which may prompt evaluation.

Initially, pallor, bleeding, easy bruising, and lymphadenopathy are unusual, but moderate or occasionally extreme splenomegaly is common (60 to 70% of cases). With disease progression, splenomegaly may increase, and pallor and bleeding occur. Fever, marked lymphadenopathy, and maculopapular skin involvement are ominous developments.

Chronic Myeloid Leukemia (CML) [5]

Diagnosis

- Complete blood count (CBC)
- Bone marrow examination
- Cytogenetic studies (Ph chromosome)

Chronic myeloid leukemia is most frequently suspected based on an abnormal CBC obtained incidentally or during evaluation of splenomegaly. The granulocyte count is elevated, usually < 50,000/mcL (≤ 50 × 10^9/L) in asymptomatic patients and 200,000/mcL (200 × 10^9/L) to 1,000,000/mcL (1,000 × 10^9/L) in symptomatic patients. Neutrophilia (a left-shifted white blood cell differential), basophilia, and eosinophilia are common. The platelet count is normal or moderately increased, and in some patients, thrombocytosis is the presenting manifestation. The hemoglobin level is usually > 10 g/dL (> 100 g/L).

Peripheral smear review may help differentiate CML from leukocytosis of other etiology. In CML, the peripheral smear frequently shows immature granulocytes as well as absolute eosinophilia and basophilia. However, in patients with white blood cell counts ≤ 50,000/mcL (≤ 50 × 10^9/L) and even in some with higher white blood cell counts, immature granulocytes may not be seen.

Chronic Myeloid Leukemia (CML) [5]

Bone marrow examination should be done to evaluate the karyotype as well as cellularity and extent of myelofibrosis.

Diagnosis is confirmed by finding the Ph chromosome in samples examined with cytogenetic or molecular studies. The classic Ph cytogenetic abnormality is absent in 5% of patients, but the use of fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR) can confirm the diagnosis.

During the **accelerated phase** of CML, anemia and thrombocytopenia usually develop. Basophils may increase, and granulocyte maturation may be defective. The proportion of immature cells may increase. In the bone marrow, myelofibrosis may develop and sideroblasts may be present. Evolution of the neoplastic clone may be associated with development of new abnormal karyotypes, often an extra chromosome 8 or isochromosome 17q [i(17q)].

Further evolution may lead to a **blast phase** with myeloblasts (60% of patients), lymphoblasts (30%), megakaryoblasts (10%) and, rarely, erythroblasts. In 80% of these patients, additional chromosomal abnormalities occur.

Chronic Myeloid Leukemia (CML) [5]

Prognosis

With use of tyrosine kinase inhibitors , survival is now > 90% at 5 years after diagnosis for chronic phase CML. Before tyrosine kinase inhibitors were used, even with treatment, 5 to 10% of patients died within 2 years of diagnosis; 10 to 15% died each year thereafter. Median survival was 4 to 7 years. Most (90%) deaths followed a blast phase or an accelerated phase of the disease. Median survival after blast crisis was about 3 to 6 months or longer if remission was achieved.

Treatment

- Tyrosine kinase inhibitors
- Sometimes, allogeneic stem cell transplantation

Treatment of chronic myeloid leukemia depends on the stage of disease. Tyrosine kinase inhibitors (eg, imatinib, nilotinib, dasatinib, bosutinib, ponatinib) are not curative but are extremely effective in the asymptomatic chronic phase and are the initial treatment choice for patients in this phase. Tyrosine kinase inhibitors are also sometimes used in the accelerated or blast phase. Allogeneic hematopoietic stem cell transplant is reserved for patients with accelerated or blast phase CML or those with disease resistant to the available tyrosine kinase inhibitors.

Chronic Myeloid Leukemia (CML) [5]

Except when stem cell transplantation is successful, treatment is not proven to be curative. However, tyrosine kinase inhibitors prolong survival. Some patients may be able to discontinue tryrosine kinase inhibitors and remain in remission. The durability of these remissions is not yet known.

Tyrosine kinase inhibitors inhibit the *BCR-ABL* oncogene, which is responsible for induction of CML. These drugs are dramatically effective in achieving complete hematologic and cytogenetic remissions of Ph chromosome–positive CML (Ph+ CML) and are clearly superior to other drug regimens (eg, interferon with or without cytarabine).

The response to TKI therapy is the most important prognostic factor for patients with CML. Patient's response is measured at baseline and then at 3 months, 6 months, and 1 year. The response can be assessed with either a molecular test (measurement of BCR-ABL protein) or a cytogenetic test (measurement of Ph+ chromosome cells), but both are recommended whenever possible. A major molecular response is defined as blood BCR-ABL < 1/1000th (or less) of the expected value for untreated CML. If, after 12 months, a major molecular response is achieved, the response can be monitored every 3 to 6 months by real time quantitative polymerase chain reaction of BCR-ABL protein; cytogenetic testing is required only in case of failure or if standardized molecular testing is not available.

Chronic Myeloid Leukemia (CML) [5]

Rarely, other drugs are used as palliation in CML. These drugs include hydroxyurea, busulfan, and recombinant interferon or pegylated interferon. The main benefit of hydroxyurea is reduction in distressing splenomegaly and adenopathy and control of the tumor burden to reduce the incidence of tumor lysis syndrome and gout. None of these drugs seems to prolong survival, although interferon can produce a clinical remission in about 19 % of patients.

Allogeneic stem cell transplantation, because of its toxicity and because of the efficacy of tyrosine kinase inhibitors, is used selectively. Transplantation is reserved for patients with accelerated- or blast-phase CML resistant to BCR-ABL inhibitors. Transplant can be curative.

Chronic Myeloid Leukemia (CML) [5]

Key Points

- Chronic myeloid leukemia (CML) involves a chromosomal translocation that creates the Philadelphia chromosome, t(9;22) .
- The peripheral smear (typically showing immature granulocytes, basophilia, and eosinophilia) helps distinguish CML from leukocytosis of other etiologies (eg, leukocytosis due to infection).
- Tyrosine kinase inhibitors are extremely effective, prolong survival, and may even be curative.
- Stem cell transplantation can be curative and may help patients who do not respond to tyrosine kinase inhibitors or who progress to accelerated or blast phase.