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## Childhood Leukemia

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# Childhood Leukemia

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Dr Hutter has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

**Objectives** After completing this article, readers should be able to:

1. Discuss the potential roles of genetic and environmental influences in causing leukemia, including congenital disorders that carry an increased risk for developing leukemia.
2. Explain why proliferation of leukemic cells and the subsequent reduction in production of normal blood cells contribute to clinical manifestations of leukemia.
3. Recognize the importance of a bone marrow aspiration or biopsy procedure in establishing the diagnosis of leukemia.
4. Delineate current initial remission rates and 5-year survival rates achievable for children who have acute lymphoblastic leukemia and who reside in developed countries.
5. Describe potential problems that may occur in some children who have leukemia after completion of therapy, including recurrence of leukemia in extramedullary sites and long-term treatment complications.

## Case Study

A 6-year-old boy who has Down syndrome presents with a 2-day history of fever (temperature to 39.0°C) and a painful limp and favoring of his right leg. During the past 2 weeks, he has had decreased appetite, increased pallor, and increased bruises on his upper and lower extremities. Physical examination reveals pallor and multiple ecchymoses on his arms, legs, and trunk. Bilateral cervical and supraclavicular lymph nodes are palpable; the nodes are firm, nontender, and 1 to 2 cm in size. The liver is palpable 3 cm below the right costal margin, and the spleen is palpable 2 cm below the left costal margin. Tenderness is elicited over the right distal femur. Radiographs of the right distal femur reveal osteopenia plus a small lytic lesion. A chest radiograph shows normal results with no mediastinal mass or pulmonary infiltrate. His white blood cell count is  $2.8 \times 10^3/\text{mcL}$  ( $2.8 \times 10^9/\text{L}$ ) with 10% neutrophils, 5% monocytes, 85% lymphocytes, and no blasts. His hemoglobin measures 8.2 g/dL (82 g/L) and platelet count is  $38 \times 10^3/\text{mcL}$  ( $38 \times 10^9/\text{L}$ ). Due to the presence of severe neutropenia with fever, intravenous broad-spectrum antibiotics are administered after blood cultures are obtained. The child is referred to a pediatric hematologist/oncologist, and a bone marrow aspirate and biopsy demonstrate more than 90% lymphoblasts. The patient is enrolled in a Children's Oncology Group clinical trial for treatment of acute lymphoblastic leukemia (ALL). Chemotherapy is initiated and a complete remission is achieved.

## Incidence and Epidemiology

Childhood cancer is rare, with a reported incidence in the United States of approximately 1 case per 7,000 children age 15 years and younger. In contrast to the adult population, in whom solid tumor malignancies predominate, almost 40% of childhood cancers are hematologic malignancies (leukemia and lymphoma). Leukemia is the most frequent malignancy that occurs during childhood and comprises approximately 30% of all childhood cancers. Historically, leukemia was classified initially in four groups based on clinical presentation and morphologic appearance of the malignant cells: ALL, acute nonlymphocytic leukemia (ANLL), chronic myelogenous leukemia (CML), and chronic lymphocytic leukemia (CLL).

### Abbreviations:

**ALL:** acute lymphoblastic leukemia  
**ANLL:** acute nonlymphocytic leukemia  
**CLL:** chronic lymphocytic leukemia  
**CML:** chronic myelogenous leukemia  
**CNS:** central nervous system

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**Table 1. Frequency of Types of Childhood Leukemia in Historic Classification\***

Leukemia Classification	% of Childhood Leukemia
Acute lymphocytic (ALL)	80
Acute nonlymphocytic (ANLL)	17
Chronic myelogenous (CML)	3
Chronic lymphocytic (CLL)	Virtually none

\*Based on cellular morphology and clinical features.

(CML), and chronic lymphocytic leukemia (CLL). Subsequent research investigations, which evaluated the morphologic, immunologic, growth regulation, cytogenetic, and molecular abnormalities in leukemia cells, further established that the leukemias represent a much more heterogeneous group of malignancies than initially suggested by the four-group classification. However, the designations of the initial classification still are used clinically, and it remains useful to consider how the classification pertains to childhood leukemia (Table 1).

In the United States, the incidence of childhood ALL is highest in children 2 to 5 years of age. Sex differences have been reported, with the incidence being greater in boys. Race differences in incidence also have been observed. Compared with white children, African American children have a much lower incidence of childhood ALL, particularly during the peak 2- to 5-year age range. Leukemia occurs slightly more frequently among Hispanic children than among whites, but the extent of this difference is not as pronounced as the difference observed between whites and African Americans.

### Pathogenesis and Causes

Leukemia results from an expansion of malignant hematopoietic or lymphoid cells, and the leukemic cellular proliferation is usually monoclonal. Both genetic and environmental factors may contribute to the development of leukemia, but in most children, the causal factors remain unknown. Children who have certain conditions have an increased risk for developing leukemia. The most common congenital disorder associated with an increased risk of leukemia is Down syndrome, in which the overall relative risk of leukemia is greater than 15 times that of the general population. Children born with Down syndrome have an increased occurrence of both ALL and ANLL, and it has been estimated that 1% of children who have Down syndrome develop leukemia by

5 years of age. Newborns who have Down syndrome and manifest transient myeloproliferative disease have at least a 25% chance of developing a particular subtype of ANLL called acute megakaryoblastic leukemia, which may evolve during early childhood in children who have Down syndrome and neonatal myeloproliferative disorder after apparently complete resolution of the neonatal myeloproliferative disorder. Additional disorders associated with an increased risk of leukemia include ataxia telangiectasia and other immunodeficiency syndromes, Fanconi anemia, Bloom syndrome, Klinefelter syndrome, and neurofibromatosis.

Certain environmental factors have an established role in human leukemogenesis. Japanese survivors of the atomic bomb explosions had an increased leukemia occurrence rate, demonstrating that exposure to large doses of ionizing radiation contributes to an increased risk of leukemia. The incidence of leukemia was higher in survivors who were closer to the atomic epicenter, suggesting a dose-dependent relationship between ionizing radiation exposure and leukemia. Of note, the time interval from radiation exposure to the peak incidence of leukemia in the atomic bomb survivors was several years. Studies that analyzed the risk of childhood leukemia following exposure to doses of radiation administered during conventional prenatal or postnatal radiographic procedures or from exposures to nonionizing electromagnetic field irradiation have produced conflicting results. (1)(2)

The role of chemical agents in the pathogenesis of leukemia is established best for the occurrence of ANLL after benzene exposure in susceptible individuals. The extent to which chemical exposures may contribute to the development of childhood ALL is less well established. Exposures to tobacco smoke, organic solvents, and pesticides, among other agents, have been associated with an increased relative risk of developing childhood leukemia, but determination of exact causal relationships requires additional studies.

Establishing specific timing and quantifying possible dose relationships of environmental exposures remain problematic. The potentially long interval of years between exposure to a possible carcinogen and the clinical manifestations of leukemia contributes to this difficulty. Theoretically, exposures contributing to childhood leukemia also might vary by timing and type of exposure: 1) parental exposure, including parental occupational exposure; 2) prenatal exposure; and 3) exposures during childhood.

A recent study conducted by the Children's Oncology Group observed that higher mutation rates of the *ras*

proto-oncogene in children who have ALL may be associated with parental exposure to hydrocarbons and specific medications. (3) Maternal exposure to pesticides and chemical agents has been associated with an increased risk of ALL in children who have Down syndrome. (4) Viral infections have been implicated in the pathogenesis of certain rare human leukemias, but no viral agent has been demonstrated to have a definitive role in causing the more frequent subtypes of childhood ALL.

The increased incidence of ALL in children who reside in developed countries has prompted studies on the possible relationship of ALL to frequency of infections during infancy and early childhood. Data from these reports have been divergent regarding the association of the risk of leukemia and early childhood infection, resulting in differing speculative hypotheses. The observations of an increased risk of leukemia in children who have greater social isolation with fewer exposures to infectious agents during early childhood (5)(6) has suggested the possibility of a predisposition to developing leukemia resulting from lack of stimulation of a child's immune system by common infectious agents. Another study that observed an increased occurrence of leukemia in children who had documentation of infection in the neonatal period or early infancy hypothesized that these early infections were an indication of possible abnormal immune responses, which later increased the risk of leukemia. (7)

### Clinical Presentation and Diagnosis

The clinical manifestations of leukemia result from the effects of proliferation of malignant cells within the bone marrow and other organs. The extramedullary organs most frequently experiencing leukemia infiltration are the liver, spleen, and lymph nodes; many, but not all, affected children initially present with enlargement of these organs detectable on physical examination. Although hepatomegaly may be massive in some children who have leukemia, it is unusual to have corresponding marked abnormalities in liver function. Other important sites of potential leukemia infiltration are the central nervous system (CNS) and the testes. Leukemia has the potential to involve any body organ, including skin, kidney, lung, pleura, pericardium, eye, breast, ovaries, and gastrointestinal tract.

Leukemia expansion within the bone marrow may produce signs and symptoms of bone involvement. Approximately 25% of children who have newly diagnosed leukemia present with a complaint of severe bone pain. When bones of the lower extremity are involved, the

child may exhibit a limp or refusal to walk. Bone radiographs may demonstrate osteopenia and, in some instances, lytic lesions. Children also may have abnormalities detected on radionuclide bone scan. Because some children can present without malignant leukemia cells detected on a routine blood count, mistaken diagnoses of juvenile idiopathic arthritis or osteomyelitis occasionally have been considered in children who have leukemia with bone pain. Pathologic fractures through leukemic bone are uncommon presentations of leukemia, but they should be considered if the pattern is atypical or if there are other signs or symptoms suggestive of leukemia.

Leukemia proliferation within the bone marrow results in decreased production of normal white blood cells, red blood cells, and platelets. Malignant leukemia blast cells are frequently, but not always, observed circulating in the blood. Because conditions such as infectious mononucleosis occasionally can result in large numbers of atypical white cells in the blood, a bone marrow examination is essential for a conclusive diagnosis of leukemia. Bone marrow studies in children who have leukemia are important to assist in identifying specific subtypes of leukemia. Also, because children who have leukemia do not always present with lymphadenopathy or hepatosplenomegaly and may not have detectable leukemia cells in the blood, a bone marrow examination serves to distinguish leukemia from other conditions involving severe bone marrow failure such as aplastic anemia or myelofibrosis. Children who have aplastic anemia and children who have acute leukemia may present with similar degrees of severe anemia, neutropenia, or thrombocytopenia and similar clinical signs and symptoms produced by the cytopenias.

Many initial signs and symptoms of leukemia are related to decreased production of normal blood cells (Table 2). The major life-threatening complication in a child who has acute leukemia remains overwhelming infection, often sepsis or severe pneumonia. The risk of sepsis can be correlated directly with the severity of neutropenia; other alterations of host immunity produced by leukemia also contribute to infection risk. Bleeding manifestations in a child who has leukemia most frequently are due to severe thrombocytopenia. On occasion, severe coagulation factor deficiencies can augment the bleeding tendency; coagulation factor abnormalities are most pronounced in a rare subtype of ANLL known as acute promyelocytic leukemia.

In addition to possibilities of overwhelming infection and severe bleeding, other leukemia manifestations may be life-threatening. Severe airway obstruction with respiratory distress may result from massive mediastinal

**Table 2. Relationship of Leukemia Pathophysiology to Clinical Manifestations**

Leukemia Abnormality	Clinical Signs, Symptoms, or Complications
Anemia	Pallor, fatigue, decreased appetite; congestive heart failure with extremely severe anemia
Neutropenia	Fever; risk of overwhelming infection increases with severity of neutropenia
Thrombocytopenia	Petechiae, ecchymoses, mucosal and other bleeding
Coagulation factor deficiencies	Increased bleeding; disseminated intravascular coagulation with severe factor deficiencies occurs frequently in the acute promyelocytic subset of acute nonlymphocytic leukemia
Leukemia in bone	Bone pain

lymphadenopathy. The risk of massive mediastinal lymphadenopathy is greatest in T-cell ALL, a subset of ALL that occurs most often in adolescent boys. Hyperleukocytosis, defined as a white blood cell leukemia blast count more than  $100 \times 10^3/\text{mL}$  ( $100 \times 10^9/\text{L}$ ), can result in damage to vital organs in children who have ANLL. The elevated numbers of leukemia blast cells may sludge in the vascular supply of the brain, lungs, and liver, producing infarction within these organs. Children who have ALL are at much lower risk of developing vascular sludging from hyperleukocytosis, in part because the ALL malignant blast cells are more deformable than those of ANLL.

Kidney function during leukemia onset may be compromised for several reasons, including leukemia infiltration of the renal parenchyma. Breakdown of leukemia cells frequently results in elevated serum concentrations of uric acid, which may impair renal function further. Children who have the rare B-cell subtype of ALL also may present with severe acute renal failure with normal blood uric acid values. Abnormal calcium metabolism with either hypercalcemia or hypocalcemia occurs in some children who have leukemia. Due to the potential for metabolic abnormalities, initial evaluation of an affected child should include not only a blood count but also measurement of serum sodium, potassium, chloride, bicarbonate, creatinine, calcium, phosphate, and uric acid.

### Treatment and Prognosis

The past 50 years has seen a marked improvement in outcome for children who have leukemia. Steady improvements in continuous complete remission and survival rates have resulted primarily from the development of effective combination chemotherapy regimens. In the era before chemotherapy, the median survival for a child who had newly diagnosed acute leukemia was 3 months, with the cause of death predominantly due to massive

bleeding or overwhelming infection. Five-year survival rates for children receiving new diagnoses of ALL in the United States and other developed countries are now in excess of 80%. (8) Hematopoietic stem cell transplantation used for certain types of leukemia and for salvage of children whose leukemia has relapsed after conventional chemotherapy also has contributed to improved survival.

Certain sites of leukemia involvement have required particular attention in the development of treatments. During the early periods of development of combination chemotherapy, some children were found to develop leukemia recurrences in the CNS or the testes at a time when the bone marrow showed disease remission. CNS leukemia most frequently involves the meninges, with associated signs and symptoms of increased intracranial pressure of headache, vomiting, or papilledema. Testicular leukemia usually manifests as painless, firm enlargement of one or both testes, although microscopic leukemia testicular involvement can occur without any overt clinical signs or symptoms. Extramedullary leukemia recurrences in the CNS and testes, for the most part, have been due to inherent barriers to the delivery of effective chemotherapy to these sites. CNS and testicular recurrence rates have been reduced by chemotherapy strategies that result in enhanced drug delivery to these organs. For treatment of CNS leukemia, delivery of chemotherapeutic agents directly into the cerebrospinal fluid often is required. Accordingly, lumbar punctures usually are performed for children who have newly diagnosed acute leukemia, both to assess for the possibility of leukemia involvement of the meninges and to administer chemotherapeutic agents directly into the cerebrospinal fluid.

Children generally are treated at pediatric cancer centers and, when appropriate, offered participation in a clinical trial that evaluates treatment results. Analyses of previous clinical trial results have contributed greatly to subsequent trial designs that resulted in the development of chemotherapy regimens with improved outcomes.

Leukemia chemotherapy regimens are generally divided into three phases: induction, intensification, and maintenance. The goals of induction therapy are to achieve a complete remission of leukemia and to optimize chances that a remission will be maintained. Children who have ALL and are treated with current chemotherapy regimens have a greater than 95% probability of achieving a complete remission within 4 weeks.

In addition to evaluation of overall remission rates, survival, and complications, analyses of clinical trial data have assisted in identifying affected children who have more favorable as well as less favorable outcomes with prior therapy regimens. This resulted in the evolution of different treatments for children based on whether they are considered to have a higher risk of initial treatment failure or leukemia recurrence. For children who have ALL, major clinical determinants of increased risk of leukemia recurrence are the child's age and concentration of circulating blasts in the blood. Those who are younger than 1 year or older than 10 years have worse outcomes, as do those who have higher concentrations of leukemia cells in the blood, particularly with white blood cell counts greater than  $50.0 \times 10^3/\text{mcL}$  ( $50.0 \times 10^9/\text{L}$ ). Certain immunologic, cytogenetic, and molecular abnormalities also were identified as risk factors, most likely because they serve to define specific subtypes of leukemia. The Philadelphia (Ph) chromosome, a cytogenetic translocation involving the long arms of chromosomes 9 and 22, occurs in 3% to 5% of children who have ALL. The translocation site involves the *abl* proto-oncogene, with production of an abnormal fusion protein (named *bcr abl*) that has tyrosine kinase activity. In rare instances, the abnormal *bcr abl* fusion protein may be detected in the absence of a discernible karyotypic change. Children who have ALL and manifest the Ph chromosome (Ph+) currently have a worse response rate to conventional chemotherapy compared with children who do not have this abnormality. The Ph chromosome with abnormal *bcr abl* fusion protein also is present in approximately 50% of children who have CML and rarely occurs in ANLL.

Risk determinations in childhood leukemia are treatment-specific, and children who were considered high risk from previous treatments eventually may have markedly better outcomes with the development of effective treatments for their leukemia subtype. For example, children who have the B-cell ALL subtype would have been considered high risk 25 years ago but now have markedly improved survival due to both chemotherapy regimens that are more effective for this particu-

lar subtype and recognition and management of acute renal failure, which may occur with this subtype.

An emerging therapeutic strategy is the development and use of agents that target molecular abnormalities detected in leukemia subtypes. The tyrosine kinase inhibitor imatinib mesylate, which actively binds to the abnormal *bcr abl* fusion protein and a limited number of other normally occurring tyrosine kinases, has been efficacious in children and adults who have chronic phase CML. Although imatinib therapy for Ph+ ALL or blast crisis CML has resulted in responses, the overall results have been less dramatic than that observed for CML chronic phase. Decreased binding of imatinib to the abnormal *bcr abl* protein in patients who have Ph+ ALL or CML blast crisis compared with those who have CML chronic phase may account for some of the differences in response rates. In addition to the abnormal *bcr abl* tyrosine kinase found in Ph+ leukemia, mutations of other kinase proteins may occur in children who have ALL. A recent study of Janus kinase (*JAK*) in childhood ALL found a greater frequency of mutated *JAK* kinase in children who had high-risk ALL, and they also had worse treatment outcomes with current therapy. (9) An additional success in leukemia therapy directed at specific molecular targets has been the administration of all-trans retinoic acid to children who have acute promyelocytic leukemia. Treatment of such children with all-trans retinoic acid in conjunction with other chemotherapeutic agents has resulted in improved remission rates and overall survival.

Advances in supportive care and management of leukemia complications also have contributed to better leukemia remission rates and survival. The availability of blood components prepared with minimal risk of transfusion-induced infection has been an important adjunct in the treatment of a child who has newly diagnosed leukemia. Platelet transfusion therapy has reduced the risk of mortality in children who have leukemia and severe bleeding manifestations. Recognition of the importance of the expeditious implementation of effective broad-spectrum antibiotic coverage in the neutropenic febrile child also has helped to reduce morbidity and mortality from infections. Adequate nutrition support also has been essential, particularly when children who have leukemia require intense therapy such as that used in hematopoietic stem cell transplant regimens.

Improved survival rates have resulted in an expanding population of children who have completed treatment of their leukemia. Many pediatric cancer centers have established specific programs dedicated to the long-term follow-up of childhood cancer survivors, but childhood leukemia survivors also receive care in the pediatrician's

office. It is important for the pediatrician to be familiar with issues pertinent for leukemia survivors and to coordinate care with the pediatric cancer center. (10) Particular areas of concern in children who have completed treatment for leukemia include risk of relapse, sequelae of cancer or its treatment, transient immunosuppression in patients whose therapy recently was discontinued, and administration of immunizations that may have been delayed or rendered ineffective due to intensive treatment. The timing and schedule of immunizations for childhood leukemia survivors are provided through the American Academy of Pediatrics *Red Book* or specific recommendations from the pediatric cancer center.

After completion of therapy, children are at varying risk for both leukemia recurrence and long-term treatment complications, depending on the type of leukemia and treatments employed. Some children who have ALL may develop leukemia relapse after initial therapy completion, including recurrences in the extramedullary CNS or testicular sites when the bone marrow remains in remission. Avascular necrosis of the femoral head, which presents as hip pain, can be a complication of therapy, presumably because of effects of corticosteroids.

When compared with sibling controls, childhood leukemia survivors exhibit a greater number of potential problems in the areas of general and mental health, functional impairment, and activity limitations. (11) The highest level of education and subsequent employment achieved by survivors tended to be lower than that of siblings; issues also were observed in the survivor's ability to obtain and maintain health and life insurance. The risk of treatment-related sequelae is related to the type and intensity of therapies employed, with children who received radiation therapy or intensive therapy for relapsed leukemia more likely to develop long-term complications. The prevalence of certain late effects in childhood leukemia survivors frequently can be related to a specific treatment modality: growth abnormalities and precocious puberty in children who received CNS irradiation, secondary malignancies after treatment with radiation therapy or large cumulative doses of alkylating agents or epipodophyllotoxins, and cardiomyopathy related to high cumulative doses of anthracyclines. Children who received gonadal irradiation or intensive chemotherapy are at increased risk for impaired fertility. Treatment-related infertility risks are greater for boys and for adolescents compared with prepubertal children. Whenever feasible, cryopreservation of sperm should be offered to older adolescent male patients prior to administration of treatment modalities that may impair fertility. (12) The younger age of many patients and necessity for prompt

institution of leukemia therapy often preclude the use of fertility preservation interventions.

The prevalence of second malignancies occurring within the first 25 years after treatment for childhood leukemia is at least 3%, with the CNS being the most frequent site of involvement. (11) Because this rate of malignancy occurrence exceeds that observed for children and young adults of similar age in the general population, it is recommended that survivors of childhood leukemia be counseled to minimize exposures to known carcinogens, such as cigarette smoke or excessive sunlight without sun block protection.

Survivors of childhood leukemia, particularly those who received intensive therapy to the CNS at a young age, are at increased risk of developing neuropsychological abnormalities with cognitive defects that can affect subsequent school performance. Such children require monitoring of school performance and achievement, with appropriate educational interventions when indicated.

Although a greater frequency of late complications occurs in survivors of childhood leukemia, many children treated for leukemia do well without any major difficul-

## Summary

- Based on strong research evidence, leukemia is a heterogeneous group of disorders that can be classified according to morphologic, immunologic, karyotypic, biochemical, or molecular criteria.
- Based on strong research evidence, children who have certain congenital disorders such as Down syndrome are at increased risk for leukemia.
- Based on strong research evidence, many initial clinical manifestations of leukemia (eg, pallor, fever, purpura) are a consequence of decreased production of normal red blood cells, white blood cells, and platelets.
- Based on strong research evidence, severe bone pain occurs in approximately 25% of children at the onset of leukemia, with some children also exhibiting abnormalities on bone radiographs or radionuclide bone scan.
- Based on strong evidence and practice guidelines, a bone marrow test is essential in the diagnosis and classification of leukemia.
- Based on strong research evidence, greater than 95% of newly diagnosed children who have ALL achieve a complete remission of leukemia, with subsequent 5-year survival rate in excess of 80%. (8)
- Based on strong research evidence, long-term leukemia survivors, when compared with sibling controls, have a greater incidence of general and mental health functional impairment. (11)

ties. Some survivors have selected and completed training for careers in health-care-related fields, such as social work, nursing, or medicine. Continuing research in the treatment of childhood leukemia with novel regimens and therapeutic agents hopefully will result not only in defining regimens with improved survival success but also in developing treatment regimens that eliminate or greatly reduce the severity of complications.

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## PIR Quiz

Quiz also available online at <http://pedsinreview.aappublications.org>

- The genetic disorder *most* commonly associated with an increased risk of leukemia is:
  - Ataxia telangiectasia.
  - Down syndrome.
  - Fanconi anemia.
  - Klinefelter syndrome.
  - Neurofibromatosis.
- A previously well 5-year-old girl presents with pallor and bone pain of 3 weeks' duration. Physical examination reveals pallor, increased bruising, and scattered petechiae. She is afebrile and has neither lymphadenopathy nor hepatosplenomegaly. Her hemoglobin is 3.5 g/dL (35 g/L), white blood cell count is  $1.1 \times 10^3/\text{mCL}$  ( $1.1 \times 10^9/\text{L}$ ), and platelet count is  $17 \times 10^3/\text{mCL}$  ( $17 \times 10^9/\text{L}$ ). No blasts are seen on her peripheral blood smear. You are most concerned about acute leukemia and aplastic anemia. Pending a bone marrow examination, which should establish the diagnosis, the clinical feature that is *most* helpful in pointing to the correct diagnosis is:
  - Absence of blasts on the peripheral blood smear.
  - Absence of hepatosplenomegaly.
  - Presence of bone pain.
  - Presence of fever.
  - Presence of petechiae and purpura.



8. A patient in your practice was diagnosed with acute lymphoblastic leukemia 2 weeks ago and is undergoing treatment at the regional pediatric oncology center. His parents are concerned that the oncologists are being too optimistic in stating his prognosis. The overall 5-year survival rate for newly diagnosed acute lymphoblastic leukemia in developed countries is *best* described as being at least:
- A. 40%.
  - B. 50%.
  - C. 60%.
  - D. 70%.
  - E. 80%.
9. The family of a 15-year-old boy who was treated successfully 5 years ago for acute lymphoblastic leukemia recently read about the long-term consequences of therapy. They want to know the likelihood of his developing a second malignancy. The prevalence of second malignancies occurring within the first 25 years after treatment of childhood leukemia is *closest* to:
- A. 0.01%.
  - B. 0.05%.
  - C. 0.3%.
  - D. 3%.
  - E. 7%.
10. An 18-year-old boy comes to your office with complaints of fatigue, pallor, bruising, cough, and difficulty doing any exercise. His physical examination reveals pallor, mild bruising, occasional petechiae, and moderate respiratory distress. He is afebrile, but his respiratory rate is 35 breaths/minute. His chest is clear. He has diffuse cervical adenopathy and moderate hepatosplenomegaly. The results of a complete blood count are hemoglobin of 8.9 g/dL (89 g/L), white blood cell count of  $44.0 \times 10^3/\text{mL}$  ( $44.0 \times 10^9/\text{L}$ ), and platelet count of  $19 \times 10^3/\text{mL}$  ( $19 \times 10^9/\text{L}$ ). The *most* likely cause of his respiratory distress is:
- A. Congestive heart failure due to anemia.
  - B. Intrapulmonary hemorrhage.
  - C. Mediastinal lymphadenopathy.
  - D. Pneumonia.
  - E. Pulmonary hyperleukocytosis.

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