



CONSULTATION WITH THE SPECIALIST

Author Disclosure

Drs Pearce and Sills did not disclose any financial relationships relevant to this article.

Childhood Leukemia

Jennifer M. Pearce, MD,* Richard H. Sills, MD*

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

1. Understand the similarities in presentation of aplastic anemia and childhood leukemia.
2. Know that the absence of blasts in the peripheral blood of a patient who has pancytopenia does not rule out the diagnosis of leukemia.
3. Recognize bone pain as a symptom of leukemia.
4. Delineate the percentage of patients who have standard-risk acute lymphoblastic leukemia and enter remission with initial treatment.
5. Identify the important sites of relapse of acute lymphoblastic leukemia.
6. Identify the relationship of Down syndrome and leukemia.
7. Recognize the potential for a second malignancy following acute lymphoblastic leukemia.

Case 1

A 3-year-old boy develops pallor, bruising, and intermittent fever over 3 weeks. Laboratory findings include: hemoglobin, 6.8 g/dL (68 g/L); white blood cell (WBC) count, $1.8 \times 10^3/\text{mcL}$ ($1.8 \times 10^9/\text{L}$) with 2% neutrophils and 98% lymphocytes; platelet count, $25 \times 10^3/\text{mcL}$ ($25 \times 10^9/\text{L}$); mature lymphocytes on blood smear; and normal prothrombin and partial thromboplastin times. He is referred to a pediatric hematologist with the concern of aplastic anemia. The bone marrow is hypercellular and replaced with large blasts; immunophenotyping is consistent with acute myeloid leukemia (AML) (Figs. 1 and 2).

Case 2

A 13-year-old girl presents with malaise and intermittent fever for 1 week. She has bilateral 2- to 3-cm firm, nontender anterior cervical lymph nodes, and her spleen is palpable 3 cm below the left costal margin. Epstein-Barr virus titers are reported as equivocally positive. Two days later, she is vomiting repeatedly and appears mildly dehydrated. Specimens for other studies are sent to an outside laboratory. Based on a presumptive diagnosis of mononucleosis, she

is given promethazine and a single 40-mg intramuscular dose of methylprednisolone. Study results available the following morning include: hemoglobin, 10.5 g/dL (105 g/L); WBC count, $135 \times 10^3/\text{mcL}$ ($135 \times 10^9/\text{L}$); platelet count, $40 \times 10^3/\text{mcL}$ ($40 \times 10^9/\text{L}$); potassium, 5.2 mEq/L (5.2 mmol/L); bicarbonate, 19 mEq/L (19 mmol/L); blood urea nitrogen (BUN), 25 mg/dL (8.9 mmol/L); creatinine, 1.3 mg/dL (114.9 $\mu\text{mol/L}$); lactate dehydrogenase, 4,500 U/L; uric acid, 11 mg/dL (0.7 mmol/L); calcium, 9 mg/dL (2.25 mmol/L); and phosphorus, 4 mg/dL (1.3 mmol/L).

She now reports no urine output for 18 hours and is referred emergently to a pediatric hematologist. New findings include: WBC differential count, greater than 95% blasts; potassium 6.7 mEq/L (6.7 mmol/L); bicarbonate, 17 mEq/L (17 mmol/L); BUN, 60 mg/dL (21.4 mmol/L); creatinine, 4.5 mg/dL (398 $\mu\text{mol/L}$); uric acid, 23 mg/dL (1.4 mmol/L); calcium, 5.5 mg/dL (1.4 mmol/L); and phosphorus, 9.9 mg/dL (3.2 mmol/L). Chest radiography reveals mild mediastinal widening. Hemodialysis is initiated to correct the electrolyte abnormalities. Oral urate oxidase is administered to block uric acid formation, and aluminum hydroxide is administered orally to bind phosphate. Bone marrow aspirate reveals replacement

*Department of Pediatrics, Albany Medical College, Albany, NY.

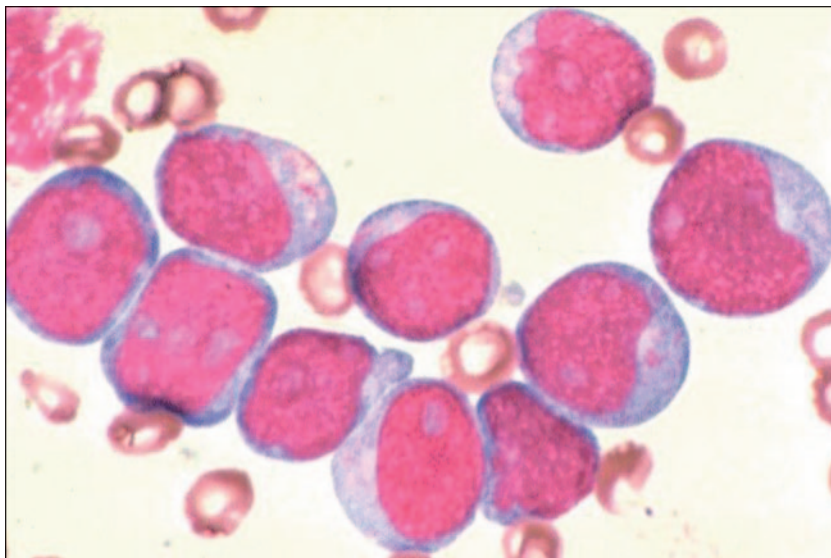


Figure 1. Photomicrograph of bone marrow aspirate smear from Case 1, showing marrow replaced completely with myeloblasts. Identifying features include the very fine nuclear chromatin, large distinct nucleoli, an irregular nuclear shape, and relatively abundant cytoplasm with red granules. Flow cytometry demonstrates that these cells are myeloid in origin because they are positive for the immunophenotypic markers CD13 and CD33.

with lymphoblasts immunophenotyped as T cells (Fig. 3).

Case 3

A 5-year-old girl presents with intermittent bilateral leg and wrist pain, irritability, and a temperature as high as 103°F (39.5°C) for 3 weeks. Findings on her physical examination are normal except for a slight limp. Results of laboratory tests include: hemoglobin, 10.9 g/dL (109 g/L); mean corpuscular volume, 77 fL; WBC count, $4.1 \times 10^3/\text{mcL}$ ($4.1 \times 10^9/\text{L}$) with a differential count of 21% neutrophils and 79% mature lymphocytes; platelet count, $190 \times 10^3/\text{mcL}$ ($190 \times 10^9/\text{L}$); and erythrocyte sedimentation rate, 35 mm/hr. She is referred to a rheumatologist, who diagnoses juvenile rheumatoid arthritis (JRA) and initiates aspirin therapy. She improves for 2 days, but her pain subsequently worsens, and she refuses to bear weight. A 2-week trial of naproxen also fails. Plain radiographs show normal-appearing legs and wrists. Additional laboratory tests reveal similar blood counts; lactate dehydrogenase, 1,200 U/L; and uric acid, 6.9 mg/dL (0.4 mmol/L). A bone marrow aspirate documents replacement with early

pre-B-cell lymphoblasts. After 2 days of induction chemotherapy, her pain resolves and she bears weight.

Epidemiology

Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood, accounting for 25% of cancers in those younger than age 15 years. The peak incidence is at 2 to 5 years. It is more common in males and in whites compared with blacks. In contrast, AML and its variants account for 4% of childhood cancers, and its incidence does not vary with sex, age, or ethnicity. Predisposing factors include exposure to chemotherapy and ionizing radiation.

Chronic myelogenous leukemia is a myeloproliferative disease characterized by the predominance of relatively mature myeloid cells (Fig. 4). It accounts for less than 1% of childhood cancers and is not discussed further.

The incidence of acute leukemias

is increased in certain genetic syndromes, most strikingly the 15- to 20-fold increased risk in individuals who have Down syndrome. Children who have other syndromes, such as Fanconi, Klinefelter, and Shwachman-Diamond, as well as neurofibromatosis, are at risk.

Presentation

ALL and AML have similar, often nonspecific, presenting symptoms (Table 1). The patient in Case 1 presented with pancytopenia without blasts in the peripheral blood that mimics aplastic anemia, requiring bone marrow examination to establish the diagnosis. Although many think of leukemia as presenting with high WBC counts and blasts on the blood smear, almost 50% of children who have ALL and 20% to 30% of those who have AML present with WBC counts of less than $10 \times 10^3/\text{mcL}$ ($10 \times 10^9/\text{L}$). Blasts commonly are absent in the peripheral blood when the WBC count is not elevated.

The child described in Case 2 is typical of high-risk ALL, with a rapid onset and a high tumor burden due to the marked leukocytosis and mediastinal involvement. The approximately 20% of children who have WBC counts greater than $50 \times 10^3/\text{mcL}$ ($50 \times 10^9/\text{L}$) often have “bulky” disease manifested by lymphadenopathy or hepatosplenomegaly from leukemic infiltration. The temporary misdiagnosis of infectious mononucleosis delays the diagnosis, and the use of corticosteroids dramatically worsens the accompanying tumor lysis syndrome (Table 2).

The child in Case 3 presented with fever and bone pain, which occurs most commonly in younger children. The fever usually is due to cytokine release by the lymphoblasts, but it also can herald a life-threatening infection due to associated neutropenia. Bone pain (from

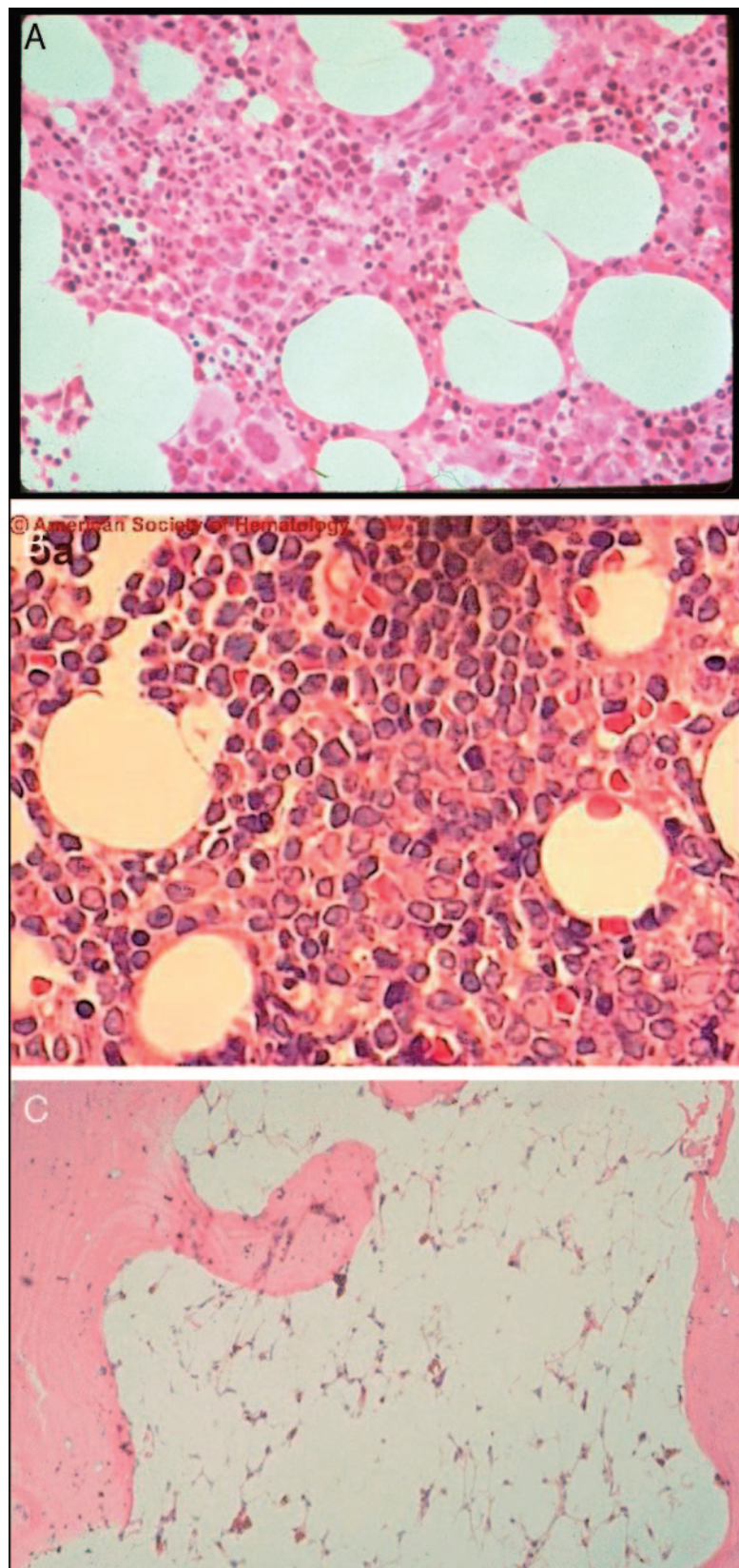


Figure 2. A. Normal section of bone marrow biopsy with the typical heterogeneous appearance due to the presence of the different hematopoietic precursors. The clear areas represent the expected amount of fat. B. Biopsy from Case 1, demonstrating replacement of normal marrow with a monotonous population of blasts. C. Marrow biopsy (at reduced magnification) from a patient who has aplastic anemia, demonstrating very rare hematopoietic precursors and a substantial increase in fat. The pink areas represent normal bony spicules. Bone marrow biopsies provide a better overview of the marrow in situ, but cellular detail is better in bone marrow aspirate smears.

marrow expansion) occurs in 30% of children who have ALL and can mimic toxic synovitis, osteomyelitis, trauma, bone metastases from other malignancies, or as in Case 3, JRA. Leukemia presenting with bone pain can have an insidious onset, with blood counts that initially are normal. Nonsteroidal anti-inflammatory drugs may relieve the pain temporarily. Failure of anti-inflammatory agents and refusal to walk necessitate consideration of leukemia, particularly if the use of corticosteroids is contemplated. Mild anemia is common in JRA, but leukopenia, thrombocytopenia, and elevations in lactate dehydrogenase or uric acid are clues to underlying leukemia.

Leukemia can have other presentations. WBC counts greater than $200 \times 10^3/\text{mcL}$ ($200 \times 10^9/\text{L}$) can lead to the formation of microemboli in the brain or lungs, causing symptoms similar to those of stroke or pulmonary emboli. These life-threatening complications, which are more common in AML, may be reversed or prevented with urgent intervention. Respiratory distress, cough, and facial edema are signs of superior vena cava syndrome due to

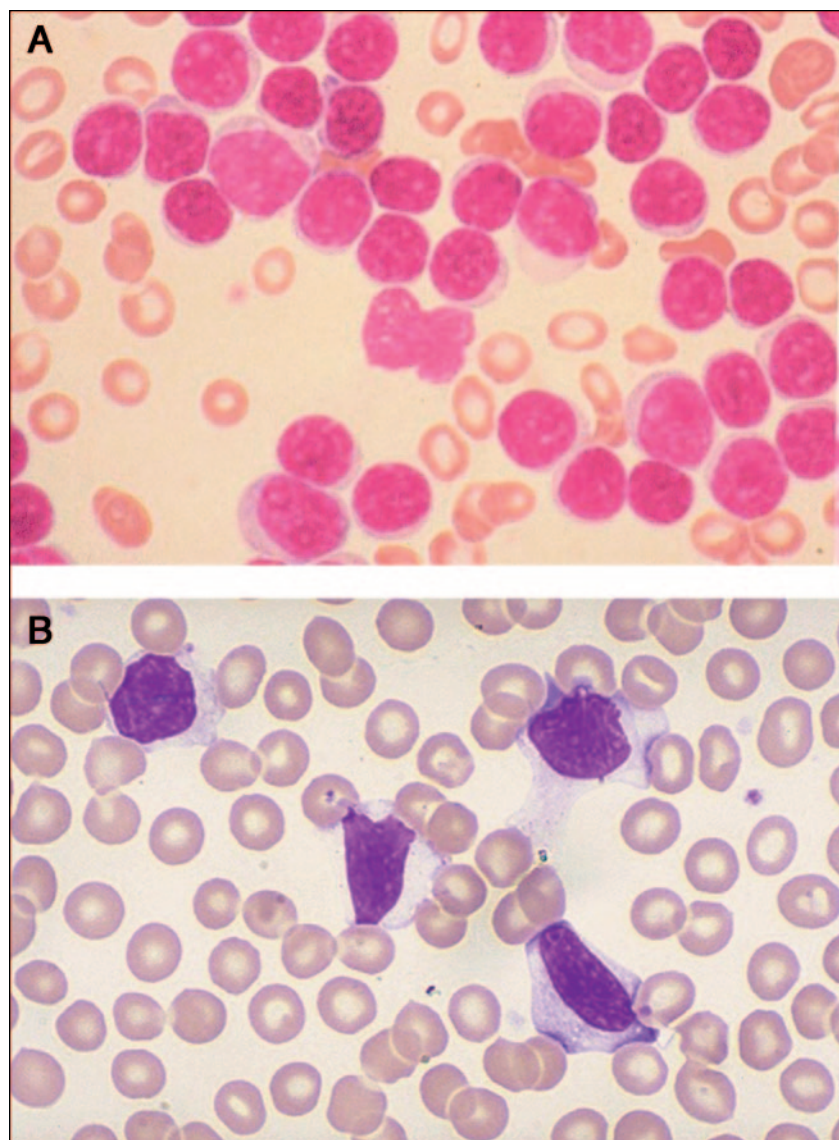


Figure 3. A. Bone marrow aspirate smear from Case 2, with the typical replacement of normal marrow by lymphoblasts. Compared with the myeloblasts in Case 1, these cells have less cytoplasm, coarser nuclear chromatin, and less prominent nucleoli. Flow cytometry is positive for CD2 and CD7 and identifies the T-cell origin of this acute lymphoblastic leukemia subtype. B. Atypical lymphocytes from a child who has infectious mononucleosis. The pale blue cytoplasm with a darker blue rim indented by the surrounding erythrocytes and an elongated nucleus with a more mature, clumped chromatin pattern distinguishes it from the malignant blasts seen in leukemia.

mediastinal compression of the airway or major vessels in ALL. Life-threatening bleeding occurs in the promyelocytic variants of AML due to disseminated intravascular coagulation. Because the initial symptoms of leuke-

mia often are nonspecific, the differential diagnosis is extensive (Table 3).

Diagnosis

Although the diagnosis of leukemia may be evident from the peripheral

blood smear, bone marrow samples for morphology, flow cytometry, and cytogenetics are obtained to delineate the type of leukemia and the appropriate therapy. Morphologic examination of marrow smears is the traditional diagnostic study. Flow cytometry permits more accurate diagnosis. This technique uses monoclonal antibodies directed against specific cell antigens (called cluster designation [CD] markers) to determine the type of leukemia immunologically. The lymphoblasts of ALL are derived from mature B cells, mature T cells, or most often, less differentiated pre-B cells. Most B cells, both mature and pre-B, are positive for CD10 and CD19, but only mature B cells are positive for surface immunoglobulin. Other CD markers identify T cells, with different markers identifying the various subtypes of acute nonlymphoblastic leukemias. Although referred to most commonly as acute myeloid leukemia, the nonlymphoblastic cell of origin also can be monocytic, megakaryocytic, or erythroid. Eight subtypes are identified as M0 through M7. The most common AML subtypes are M1 and M2 (both myelocytic in origin), but in children who have Down syndrome, acute megakaryoblastic leukemia (M7) predominates.

The pediatrician needs to recognize the possibility of underlying leukemia from the clinical presentation, the complete blood count, and blood chemistries. The pediatric hematologist/oncologist should be responsible for obtaining and interpreting the bone marrow studies to establish the diagnosis of leukemia, to identify the subtype, and to determine and implement appropriate treatment.

Cerebrospinal fluid (CSF) is examined to verify that central nervous system (CNS) leukemia is not

present. Because a traumatic lumbar puncture may introduce leukemic cells to the CSF, thereby increasing the risk of CNS relapse, only experienced staff under optimal circumstances, including sedation or anesthesia if necessary, should perform this procedure.

Treatment

Survival rates in childhood leukemia have improved dramatically; 75% to 80% of children who have ALL and nearly 50% who have AML are cured. Much of the recent improvement in ALL survival is attributable to therapy stratification based on risk characteristics at diagnosis; children identified by risk factors as being at higher risk of relapse are treated more aggressively (“intensification of therapy”), and those at lower risk are not exposed to excessively toxic therapy. This approach dramatically improves the prognoses for high-risk children whose survival had been much worse than children who have lower risk factors. Factors associated with a lower risk of relapse include being between 1 and 9 years of age and having a lower peripheral WBC count at the time of diagnosis. Those at higher risk of relapse are children older than 10 years of age, infants, those who have a high WBC count (usually $>50 \times 10^3/\text{mCL}$ [$50 \times 10^9/\text{L}$]), and those who have mature B-cell leukemia. Males have a higher risk of relapse, but prolonging their therapy by 1 year negates this risk.

Cytogenetic studies also help determine the risk of relapse. In ALL, hyperdiploidy (>50 chromosomes per cell) confers a better prognosis than a normal complement of chromosomes. Hypodiploidy is associated with a worse prognosis. More specific chromosomal alterations, such as t(9;22) (Philadelphia chromosome), also confer higher risk.

The initial response to treatment also is an important prognostic fac-

tor. Because 95% of children who have ALL are in remission by the 28th day of induction therapy, this result is not prognostic except for the 5% who fail induction. However, slower-than-expected reductions in the percentage of lymphoblasts in the marrow at 7 or 14 days of induction therapy identify individual children at higher risk of relapse. Their subsequent chemotherapy regimen can be intensified, improving their survival and justifying increasing treatment-related toxicity.

ALL treatment is complex and constantly changing, based on ongoing multi-institutional studies, so this discussion is limited to general therapeutic concepts. First, ALL therapy must be protracted over 2 to 3 years. Girls generally are treated with 2 years of maintenance therapy and boys with 3 years. Second, all patients receive more aggressive (“intensified”) chemotherapy in the first 6 to 12 months. Third, patients who have prognostic factors associated with a higher risk of relapse receive

more aggressive, “intensified” therapy, which allows their survival to approach that of low-risk children treated with less intensive regimens. The exception is infants younger than 6 months of age, whose prognosis remains poor. Fourth, all regimens provide prophylactic treatment of the CNS because systemic chemotherapy may not cross the blood-brain barrier adequately. Because of the many late sequelae of cranial radiation, intrathecal chemotherapy alone is used except in a small subgroup of high-risk patients.

The treatment of AML is dramatically different, usually requiring extremely intensive chemotherapy for less than 1 year. Bone marrow transplantation from a human leukocyte antigen-identical sibling (found in only 20% of families) is optimal in most subtypes of AML. If a donor is not available, current survival with chemotherapy alone is approaching that associated with transplantation. The eight subtypes of AML (desig-

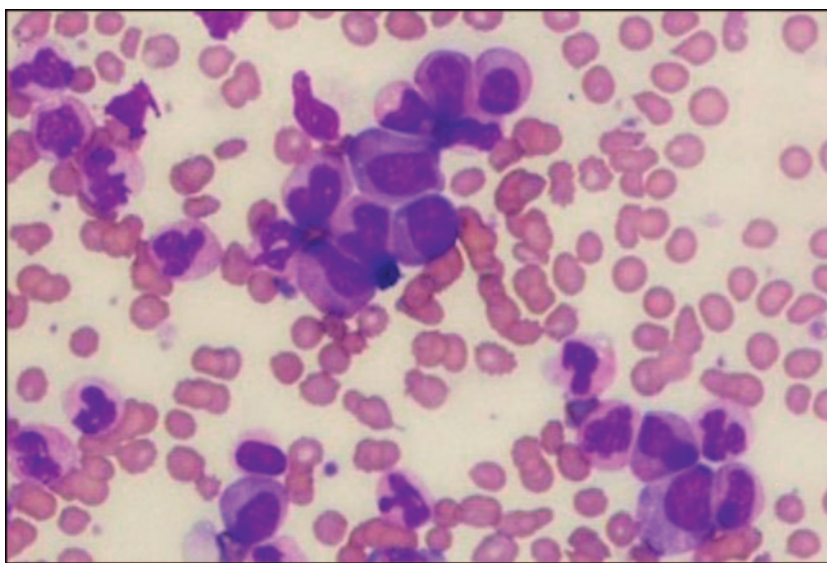


Figure 4. Peripheral smear demonstrating chronic myelogenous leukemia. The greatly increased numbers of myeloid cells in varying stages of development beyond the myeloblast stage are apparent. The monotonous appearance of blasts is absent. The granular appearance of the cytoplasm is typical of maturing granulocytes.

Table 1. Presenting Clinical and Laboratory Features in ALL*

Features	Percentage of Patients
Symptoms and Physical Findings	
Fever	55
Bleeding (eg, petechiae or purpura)	45
Malaise	40
Bone or joint pain	30
Splenomegaly	60
Hepatomegaly	70
Lymphadenopathy	50
Abdominal pain	10
Laboratory Features	
WBC count ($\times 10^3/\text{mcl}$ [$\times 10^9/\text{L}$])	
<10	50
10 to 49	30
>50	20
Hemoglobin (g/dL [g/L])	
<7 (70)	43
7 to 11 (70 to 110)	45
>11 (110)	12
Platelet count ($\times 10^3/\text{mcl}$ [$\times 10^9/\text{L}$])	
<20	30
20 to 99	50
>100	20

*The percentages are approximations, using several sources.

nated M0 through M7) receive similar treatment and have similar prognoses, with some exceptions. Acute promyelocytic leukemia (M3) often is complicated by disseminated intravascular coagulation, but it responds well to a combination of all-*trans*-retinoic acid and chemotherapy without need for bone marrow transplantation. Children who have Down syndrome and AML are treated with less intensive chemotherapy and have a better long-term prognosis; most have the megakaryocytic (M7) variant.

Intensification of both ALL and AML therapy has increased survival, but also morbidity. The greatest risk is from infection. The use of implanted central lines greatly facilitates delivery of therapy and improves quality of life, but increases the risk of infection. Strict guidelines for aggressive evaluation

and management of fever as well as prophylactic therapy (most commonly for *Pneumocystis carinii*) decrease morbidity and mortality.

The constant immunosuppressive therapy depresses lymphocyte function during therapy and for the subsequent 3 to 12 months. Live virus vaccines are contraindicated for children receiving therapy, and their response to inactivated vaccines is impaired. Some patients lose previous vaccine-induced immunity, require reimmunization, and still fail to develop appropriate immunity.

Other supportive care measures beyond the scope of this discussion have improved survival and quality of life. These include the use of hematopoietic growth factors, conscious sedation for painful procedures, psychosocial support for the family under duress, and educational interventions to allow children to remain up-to-date with their education.

Table 2. Tumor Lysis Syndrome**Characteristics**

- Release of intracellular uric acid, potassium, and phosphate from rapid turnover of malignant cells
- Usually precipitated by chemotherapy, but can occur before
- Most often with high tumor burden or T-cell leukemia
- Components of tumor lysis:
 - Hyperuricemia
 - Renal precipitation can progress to acute renal failure
 - Hyperkalemia
 - Can progress to fatal arrhythmia
 - Hyperphosphatemia/Hypocalcemia
 - Increased phosphate can cause hypocalcemia and renal precipitation can progress to renal failure

Management

- Provide hydration and diuresis
- Avoid supplemental potassium
- Treat hyperkalemia emergently, if necessary
- Decrease uric acid with allopurinol or urate oxidase
- Consider oral phosphate binders
- Initiate dialysis for acute renal failure
- Transfer urgently to a pediatric oncology tertiary care center

Table 3. Differential Diagnosis of Leukemia

Nonmalignant Conditions

- Aplastic anemia
- Juvenile rheumatoid arthritis
- Viral infection
 - Infectious mononucleosis
 - Cytomegalovirus
- Autoimmune thrombocytopenic purpura
- Autoimmune pancytopenia/Evan syndrome
- Sepsis
- Leukemoid reaction
 - Pertussis
 - Acute infectious lymphocytosis
- Langerhans cell histiocytosis
- Osteomyelitis
- Hypersplenism
- Megaloblastic anemia

Malignancies

- Neuroblastoma
- Retinoblastoma
- Rhabdomyosarcoma

Patterns of Relapse

Despite therapeutic advances, 20% to 25% of children who have ALL and 50% of those who have AML experience relapses, occurring most commonly in the marrow. The aggressiveness of the retreatment depends on the intensity of the initial therapy and the timing of the relapse; earlier relapses, defined as within 18 months of initial diagnosis, have a worse prognosis. Successful therapy often involves a subsequent bone marrow transplant. If the patient received a transplant as part of his or her initial treatment (usually for AML), successful retreatment is very unlikely. The CNS and testes, as sanctuary sites of ALL more resistant to therapy, frequently are sites of relapse. Regular testicular examinations are critical during and long after therapy because a relapse at this site presents

Table 4. Long-term Sequelae of Leukemia Therapy*

Sequela	Therapy
Brain tumors	• Cranial radiation ± antimetabolite chemotherapy
AML	• Epipodophyllotoxin chemotherapy • Alkylating chemotherapeutic agents • Anthracycline chemotherapy
Learning disabilities	• Cranial radiation • Intrathecal chemotherapy
Cardiomyopathy	• Anthracycline chemotherapy • Mediastinal radiation
Avascular necrosis of joints	• Corticosteroids
Osteoporosis	• Corticosteroids
Hormone deficiencies (growth, thyroid)	• Cranial or neck radiation
Obesity	• Cranial radiation • Corticosteroids
Fertility	• Ovarian/testicular radiation • Cranial radiation • Alkylating chemotherapeutic agents

*All of these toxicities depend on the degree of exposure to the causative treatment. Additional late effects can complicate the treatment of malignancies other than leukemia, but are not included here. Details are available in Shusterman S, Meadows AT. Long-term survivors of childhood leukemia. *Curr Opin Hematol*. 2000;7:217–222.

as painless enlargement that often is unnoticed. If a CNS or testicular relapse occurs without a marrow relapse, systemic retreatment without bone marrow transplant has a high success rate.

Long-term Sequelae of Therapy

Leukemia therapy can cause significant long-term sequelae that may not manifest for decades (Table 4). Although most pediatric oncology programs have long-term follow-up programs to identify such complications proactively, many of the problems present initially to the pediatrician. Early identification of such “late effects” may allow for more effective intervention, including early institution of cardiac medication for those who have anthracycline cardiomyopathy and hormonal replacement for children who develop endocrine deficiencies. The occurrence of avascular necrosis, primarily in the hip, is

most common in adolescent girls treated for ALL. Detection of this complication requires close monitoring for leg pain and early intervention. Second malignancies induced by either chemotherapy or radiation occur in a small but as yet not well-defined percentage of patients. They occur most often in those receiving the most intensive chemotherapy. More subtle late effects include cognitive impairment, causing learning disabilities that may go undetected without detailed neurocognitive testing. Pediatricians may need to advocate for affected children to help them obtain appropriate assessments and special resources from the schools. Long-term surveillance after therapy is a vital long-term component of health maintenance for these survivors.

Suggested Reading

Childhood ALL Collaborative Group. Duration and intensity of maintenance che-

- motherapy in acute lymphoblastic leukaemia: overview of 42 trials involving 12,000 randomised children. *Lancet*. 1996;347:1783–1788
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PIR Quiz

Quiz also available online at www.pedsinreview.org.

11. You are seeing an 11-year-old boy for a health supervision visit. He had ALL diagnosed at age 2 years and successfully completed therapy at age 5 years. He has been well since. On physical examination, the only abnormality is a mild enlargement and firmness of the right testes. Of the following, the *most* likely cause of this finding is:
 - A. Development of a secondary testicular malignancy.
 - B. Normal testicular asymmetry.
 - C. Relapse of ALL in the testes.
 - D. Testicular enlargement due to enhanced follicle-stimulating hormone and luteinizing hormone secretion triggered by chemotherapy-induced gonadal failure.
 - E. Testicular torsion.
12. A 4-year-old girl presents with a 4-week history of vague, diffuse bone pain followed by increasing bruising over the past week. Her physical examination reveals no abnormality other than moderate bruising and some scattered petechiae. A complete blood count reveals: WBC count, $3.1 \times 10^3/\text{mCL}$ ($3.1 \times 10^9/\text{L}$); hemoglobin, 8.5 g/dL (85 g/L); platelet count, $23 \times 10^3/\text{mCL}$ ($23 \times 10^3/\text{L}$); mean corpuscular volume, 77 fL; and differential count, 10% polymorphonuclear neutrophils, 83% lymphocytes, 5% monocytes, and 2% eosinophils. No blasts are seen. Of the following, the *most* likely diagnosis is:
 - A. ALL.
 - B. AML.
 - C. Aplastic anemia.
 - D. Infectious mononucleosis.
 - E. Juvenile rheumatoid arthritis.

(Continued)

13. A 6-year-old girl presents with a 3-week history of low-grade fever, malaise, bruising, and pallor. Her physical examination reveals pallor, mild generalized lymphadenopathy, and a spleen palpable 2 cm below the left costal margin. She is afebrile. You suspect a diagnosis of leukemia and obtain the following studies: WBC count, $86 \times 10^3/\text{mCL}$ ($86 \times 10^9/\text{L}$); differential count, 95% blasts, 5% lymphocytes; hemoglobin, 7.6 g/dL (76 g/L); platelets, $49 \times 10^3/\text{mCL}$ ($49 \times 10^9/\text{L}$); sodium, 145 mEq/L (145 mmol/L); chloride, 105 mEq/L (105 mmol/L); BUN, 8 mg/dL (2.9 mmol/L); creatinine, 0.6 mg/dL (53 mcmmol/L); uric acid, 9.9 mg/dL (0.59 mmol/L); lactate dehydrogenase, 1,200 IU/dL; phosphorus, 4.5 mg/dL (1.5 mmol/L); and calcium, 9.2 mg/dL (2.3 mmol/L). While arranging for transfer to the regional pediatric hematology/oncology center, the *most* appropriate therapy to begin is:
- A. Allopurinol and hydration.
 - B. Broad-spectrum antibiotic coverage.
 - C. Platelet transfusion.
 - D. Prednisone.
 - E. Red cell transfusion.
14. You are seeing a 19-year-old girl because of left hip pain. The pain began 4 months ago with exercise, but gradually has increased so that she has pain upon bearing weight. The pain affects no other joints, and there is no prior history of joint pain. The complete blood count is normal. Her history included the development of ALL at age 15 years that was treated with a protocol for a higher risk of relapse because of her age and WBC count ($65 \times 10^3/\text{mCL}$ [$65 \times 10^9/\text{L}$]) at the time of diagnosis. She has remained in continuous remission, having completed her chemotherapy at age 10 years. Of the following, the *most* likely cause of her hip pain is:
- A. Aseptic necrosis of the femoral head due to corticosteroids and chemotherapy.
 - B. Hip fracture due to chronic calcium loss as a result of her chemotherapy.
 - C. Osteogenic sarcoma as a secondary malignancy.
 - D. Osteomyelitis related to her immune suppression.
 - E. Recurrent ALL.
15. A 7-year-old boy presents with a 1-week history of fever, sore throat, and malaise. Findings include pharyngitis; lymphadenopathy; spleen palpable 6 cm below the right costal margin; WBC count, $24 \times 10^3/\text{mCL}$ ($24 \times 10^9/\text{L}$); hemoglobin, 11.6 g/dL (116 g/L); platelet count, $123 \times 10^3/\text{mCL}$ ($123 \times 10^9/\text{L}$); uric acid, 3 mg/dL (0.29 mmol/L); potassium, 4.2 mEq/L (4.2 mmol/L); bilirubin, 0.8 mg/dL (13.7 mcmmol/L); aspartate aminotransferase, 80 U/L; alanine aminotransferase, 95 U/L; BUN, 10 mg/dL (3.6 mmol/L); and phosphorus, 3.9 mg/dL (1.3 mmol/L). Peripheral smear reveals 25% polymorphonuclear neutrophils and 35% lymphocytes, and 40% of the cells are monocytic with some nucleoli, a somewhat open immature nuclear chromatin pattern, and bluish cytoplasm. Of the following, the *most* likely diagnosis is:
- A. ALL.
 - B. Cytomegalovirus infection.
 - C. Infectious mononucleosis.
 - D. Juvenile rheumatoid arthritis.
 - E. Langerhans cell histiocytosis.
16. The expected overall long-term survival rate of children who have ALL is *closest* to:
- A. 90%.
 - B. 75%.
 - C. 50%.
 - D. 25%.
 - E. 10%.