



Facing the Challenge of CHILDHOOD LEUKEMIA

By Robin C. Kanarek, BSN, RN, CDE

A nurse recalls what she learned about acute lymphocytic leukemia after her 11-year-old son received the diagnosis.

Life was going well for me before it all began. My husband and I had just celebrated our 14th anniversary, I was looking forward to completing my last semester at Fairfield University's RN-to-BSN program, and I found my work as a diabetes nurse educator at a local hospital fulfilling. My son, David, had just turned 11. Sarah, my five-year-old daughter, was flourishing in kindergarten. Then it happened, and my world began to crumble.

One afternoon, David told me that his legs had just "given out" and that he'd fallen. I asked if he was hurt, and since he said he wasn't, the incident was soon forgotten. Over the next several days, however, I noticed that he was walking strangely—with his shoulders hunched over as if he were an old man. I also noticed that he'd begun putting his right hand on his hip as if to give it support. When I asked him about it, David couldn't explain why he walked like that, but told me it was "no big deal."

Five days passed. As I was putting my daughter to bed one

night, I heard David screaming for me. I ran to his room and found him on the floor crying and scared. He couldn't get up. He was in pain. I knew something was wrong when he told me he wanted to go to the pediatrician's office. When I called the pediatrician, he told me to give him children's acetaminophen and bring him to the office the next morning.

Everyone at the pediatrician's office seemed perplexed by the situation. David was in obvious pain and had difficulty walking, but he had no other symptoms. While awaiting results of various lab studies, we were to watch him closely, monitor his temperature, and notify the office of any new symptoms.

Over the next several days, David's condition deteriorated. Walking became more difficult, and the pain, which he could neither

describe nor pinpoint, began to intensify. Meanwhile, his lab results had come back within normal limits, though some of his white blood cells were atypical in size or shape (as commonly occurs with viral infections). Serologic tests for Lyme disease and mononucleosis were negative.

Several days later, as David was urinating, his legs gave out again. He fell and urinated on the bathroom floor. I began to panic. We notified our pediatrician and rushed David to the emergency department. David was given a complete physical and neurologic exam, a bone scan, an MRI of the lumbosacral region, and various X-rays. All tests came back normal.



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Meanwhile, David's pain intensified daily. To get around, he had to crawl. His abdomen was becoming increasingly tender. An abdominal CT scan taken two days later revealed an enlarged spleen. The pediatrician advised me to take David to a pediatric hematologist-oncologist that afternoon for bone marrow aspiration.

At 3:15 PM, my world caved in. David was diagnosed with acute lymphocytic leukemia (see *One Day at a Time: David's Story* on page 49).

What the diagnosis means

Terror engulfed me. I cried hysterically. I blurted out questions to the physician—how? What? When? Where? I was inconsolable. Then I had to compose myself and face David. That was the toughest moment in my life.

The physician and I told him that the leukemia was causing his intense pain and that he'd be given special medication to remove it. That was all we told him. That was enough. David seemed relieved. "At least now we know what the problem is," he replied.

The problem, acute lymphocytic (also known as lymphoblastic) leukemia (ALL), is a malignant, rapidly progressive hematologic disease characterized by the uncontrolled proliferation of immature lymphocytes (lymphoblasts). These cells infiltrate the bone marrow and, subsequently, the lymph nodes, spleen, liver, circulating blood, and other body tissues.

Before the advent of chemotherapy, a diagnosis of ALL meant inevitable death for the child, usually within two to three months. During the 1940s and 1950s, however, chemotherapeutically induced remission was reported using methotrexate (and later, with combination therapy: methotrexate, cortisone, and prednisone). In the 1960s, multidrug regimens and central nervous system therapy were introduced. Since then, other antineoplastic drugs (such as doxorubicin) and cranial irradiation have been used successfully. Today, more than two-thirds of children diagnosed with ALL can be cured.

Representing approximately 80% of all childhood leukemias, ALL is the most common of childhood cancers. Each year in the United States, about 2,000 children are diagnosed with the disease. The incidence rate is 3.4 per 100,000 under the age of 15, with peak incidence occurring between the ages of three and four. In the United States, incidence is 20% higher in boys than girls and 80% higher in Caucasians than African Americans.

The cause of ALL is unknown, but associated factors include prenatal and postnatal exposure to radiation or toxic chemicals and genetic factors. Some chromosomal abnormalities have been linked to increased risk, including Down's syndrome. (Children with Down's syndrome have 15 times the risk of developing ALL during the first decade of life compared to children without the condition.)

Early findings aren't specific

The presenting signs and symptoms of ALL reflect the degree of bone marrow infiltration with lymphoblasts; the subsequent drop in the number of normal leukocytes, ery-

throcytes, and thrombocytes due to overcrowding of the bone marrow by proliferating lymphoblasts; and the extent of extramedullary leukemic spread. Generally, ALL's onset and progression is abrupt and rapid.

When the lymphoblasts invade the bone marrow, suppressing the body's blood-forming tissues, anemia, neutropenia, and thrombocytopenia ensue. Signs may include pallor, petechiae, ecchymosis, purpura, mucous membrane bleeding, and fever. Early on, the patient may experience joint and leg pain, due to bone marrow expansion, and fatigue and muscle wasting, as the proliferating cells deprive the tissues of nutrients. If these cells invade the spleen, liver, and lymph nodes,

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splenomegaly, hepatomegaly, and adenopathy result. Central nervous system involvement, which may be characterized by headache, vomiting, cranial nerve palsies, convulsions, and visual disturbances, is rarely observed at the time of initial diagnosis.

Neutropenia (less than 500 granulocytes/mm³), often associated with an increased risk of serious infection, is a frequent finding in ALL. Anemia (hemoglobin values below 10 g/dL) is present in about 80% of patients at the time of diagnosis and may be quite severe. About half of patients with ALL have an elevated leukocyte count (above 10,000/mm³) at diagnosis, and 20% have an initial leukocyte count above 50,000/mm³. Many ALL patients, however, have a normal leukocyte count at the time of diagnosis, and there may be no abnormal cells detected on peripheral blood smears.

Diagnosis may be delayed because some of ALL's early, nonspecific signs and symptoms mimic a variety of nonmalignant conditions, including mononucleosis, lymphocytosis, Lyme disease, juvenile rheumatoid arthritis, Legg-Calvé-Perthes disease, and aplastic anemia. A definitive diagnosis of ALL is made by bone marrow aspiration. This procedure reveals lymphoblasts replacing normal blood cells. It also provides data to determine the classification of the leukemia. A lymphoblast count of more than 30% in bone marrow is diagnostic of leukemia.

Two primary classification systems

In 1976, the French-American-British (FAB) Cooperative Group developed criteria for ALL classification based on morphology and cytology. The FAB system recognizes three types

COMMON ADVERSE EFFECTS ASSOCIATED WITH CHEMOTHERAPY

DRUG	ADM	N/V	STOMA	BMD	FEV	ALOP	ANO	WGH	DIA	OTHER
CORTICOSTEROIDS Prednisone or Dexamethasone	IM PO									Moonface, fluid retention, weight gain, gastric irritation, insomnia, nervousness, glucosuria, mood swings, depression, acne, increased risk of infection, muscle weakness, hirsutism
DAUNORUBICIN or DOXORUBICIN	IV	X	X	X	X	X				Local phlebitis, orange urine, severe tissue necrosis if extravasated
ESCHERICHIA COLI L-ASPARAGINASE or ERWINIA ASPARAGINASE	IV IM	X			X		X	X		Clotting tendency, itching, anaphylaxis
MERCAPTOPYRINE	PO	X	X	X						
VINCRIStINE	IV				X	X	X			Constipation, neuropathy, neurotoxicity (difficulty walking, headache, jaw and joint pain, paresthesia, weakness, mental depression, hyporeflexia, hoarseness)
METHOTREXATE	PO IV IM Intrathecal	X	X	X			X		X	Photosensitivity, acne, dry hair, hyperpigmentation

ADM = administration, N/V = nausea/vomiting, STOMA = stomatitis, BMD = bone marrow depression (neutropenia, leukopenia, thrombocytopenia, anemia), FEV = fever, ALOP = alopecia, ANO = anorexia, WGH = weight loss, DIA = diarrhea.

of lymphoblasts: L₁, L₂, and L₃, with L₁ being associated with the most favorable prognosis and L₃ with the least. Approximately 85% of children with ALL have L₁ lymphoblasts, 14% have L₂, and 1% have L₃.

Another classification system is based on the immune properties of the leukemic cells. The three categories said to distinguish ALL in terms of cellular origin and maturity include the B-cell, T-cell, and null-cell types. In this system, ALL is classified from best to worst prognosis as early pre-B (about 57% of childhood cases), pre-B (22% of childhood cases), T-cell type (15% of childhood cases), transitional pre-B (4% of childhood cases), and B-cell type (2% of childhood cases).

Cytogenetic analysis has also been used to classify ALL. Currently, more than 90% of childhood ALL cases can be classified according to specific chromosomal changes, many of which are critical in the leukemic process and have prognostic significance.

In addition to classification, other factors that contribute to the prognosis include leukocyte count, age at the time of diagnosis, and gender. Better outcomes are associated with initial leukocyte counts below 10,000/mm³, being between the ages of two and 10 years at the time of diagnosis, and female gender.

Within three hours of diagnosis, David was admitted to a university children's hospital. He was given morphine, though it didn't seem to provide adequate pain relief. Over the next several hours, he had blood drawn for cytomegalovirus and varicella titers, coagulation studies, and drug levels.

A chest X-ray to rule out any mediastinal mass took an hour and a half to perform because any movement intensified David's pain. Finally, the technician handed me a lead apron and, with tears streaming down my face, I held David's arms above his head in order to complete the radiologic series. He cried in agony the entire time.

The next several days were a blur as more blood, urine, and cerebrospinal fluid tests were performed. I stayed with David during the day and my husband stayed with him at night, so I could stay with our daughter at home. Physicians, nurses, and therapists visited hourly. I bathed, fed, and massaged David but felt totally helpless.

We were told that David's leukemia was classified as early pre-B, which carried the best prognosis. David's pediatric oncologist spent three hours with us one evening describing ALL, David's prognosis, and the treatment he would receive. Friends and colleagues gave me books about leukemia, but I couldn't even open them. I was too scared to learn any more

details about the disease. I was in a constant state of inner turmoil. Though the nurse in me wanted to jump out and take control of the situation, the parent in me wanted to deny that there was a problem. "Let this be a nightmare," I heard myself saying.

The goal of treatment: Cure

The goal of therapy for newly diagnosed childhood ALL is cure. The dramatic increase in ALL's cure rate has been attributed to combination chemotherapy along with central nervous system prophylaxis. Treatment protocols vary and are generally influenced by specific prognostic factors.

Treatment is divided into four phases: induction, CNS prophylaxis, consolidation, and maintenance. The aim of the first phase, induction, is to induce a remission—a state in which the patient exhibits no signs or symptoms of leukemia. Blood values must be normal and bone marrow aspiration must reveal fewer than 5% lymphoblasts. A combination of vincristine and corticosteroids induces remission in most cases. The addition of asparaginase or an anthracycline improves the induction rate to about 95% and prolongs remission. Four or more chemotherapeutic agents are used in many oncology centers but are usually reserved for high-risk patients because of the growing concern over long-term toxic effects (see *Common Adverse Effects Associated with Chemotherapy* on page 44).

Induction usually requires four weeks. Patients who don't achieve remission during that period have a poorer prognosis. Induction therapy succeeds in all but 3% to 5% of cases. Since induction puts the patient at risk for infection and abnormal bleeding, transfusion of red blood cells and platelets is usually necessary during this phase.

Because leukemic cells may circulate in the CNS where they are protected by the blood-brain barrier, CNS prophylaxis is usually started within a few weeks of induction and continues throughout the maintenance phase. Children with good prognostic indicators receive methotrexate alone or in combination with cytarabine and steroids. Initially, these drugs may be administered intravenously, which is usually followed by intrathecal administration every nine weeks. Then, depending on the protocol used, the drugs may be given intramuscularly at a later point. Currently, most treatment centers avoid cranial irradiation out of concern over long-term adverse effects on cognitive development. (It's generally reserved for children who have CNS leukemia at diagnosis or are believed to be at high risk for relapse, and then it's administered in addition to extended intrathecal therapy.)

If no therapy were given beyond the induction and CNS prophylaxis phases, most patients would relapse within weeks or months. That's why these treatment phases are followed by consolidation, a period of intensive treatment in which high doses of previously used agents, or new ones, are used to further eradicate any residual disease. This approach has improved outcomes in childhood ALL, even in patients considered to have poor prognostic indicators.

After consolidation, chemotherapy continues for two to three years at a less intensive maintenance level as long as the

WHAT TO TEACH PATIENTS AND FAMILIES ABOUT CHEMOTHERAPY

The child undergoing chemotherapy needs to:

- Avoid crowds and people who are sick
- Take prescribed antiemetics as needed
- Eat small snacks rather than large meals and avoid foods that are spicy, oily, or have a strong odor
- Be prepared for possible alopecia, which is always reversible after chemotherapy and usually reversible after cranial radiation (consider using hats, scarves, or wigs; use a mild shampoo; discuss with appropriate school personnel)
- Increase fluid intake and maintain good oral hygiene
- Take oral medication as directed for optimal absorption
- Avoid the sun and use highly protective sunscreen (including on the scalp)

Advise their parents to:

- Encourage rest
- Watch for and report any signs or symptoms of infection
- Report any abnormal bleeding or bruising
- Help the child maintain good skin care
- Monitor the child's bowel habits and report any constipation or diarrhea
- Weigh the child daily
- Encourage the child to discuss mood changes and learn age-appropriate relaxation techniques

child remains in remission. The purpose of this maintenance therapy is to destroy small numbers of leftover leukemic cells before they multiply. Protocols vary according to clinical and biologic indicators, but most include daily oral mercaptopurine, and weekly oral or intravenous methotrexate. Periodic short courses of vincristine, corticosteroids, and other medications may be administered to prevent relapse. Maintenance therapy lasts from 18 to 36 months, depending on the protocol used. Patients are monitored closely for relapse after the chemotherapy series is completed.

A major problem for patients on maintenance therapy is decreased resistance to infection. Common minor illnesses become serious threats to children receiving chemotherapy, especially if they are febrile or neutropenic. Administration of live-virus vaccines, such as measles, rubella, mumps, and trivalent oral polio, are contraindicated. Varicella has proven to be a particularly virulent infection in immunosuppressed children, with liver, lung, or CNS involvement occurring in about one-third of those who contract the disease.

Due to the chronic nature of the disease, the need for repeated blood samplings, and the administration of chemotherapy, IV fluids, and blood products, treatment requires adequate venous access. The surgical placement of an indwelling central venous catheter or an implanted venous

The nurse in me wanted to provide David with presurgical instruction. The mother in me wanted to hold him and tell him everything would be okay.

access port spares the patient the pain and anxiety associated with repeated venipuncture, though it increases the risk of infection, embolization, and thrombosis.

Getting David to agree to have a central venous catheter surgically placed in his subclavian vein was our next hurdle. The oncologist told us this was the most appropriate way to administer David's chemotherapy over the next two years, but David was terrified at the thought of surgery. The nurse in me wanted to provide David with presurgical instruction. The mother in me wanted to hold him and tell him everything would be okay. I did both.

David finally agreed to the surgery, but with much resistance. He cried and screamed for us as he was being wheeled into the operating suite. My husband and I were filled with feelings of guilt, helplessness, and despair.

Responding to relapse

A relapse is defined as a recurrence of the leukemic cells in the bone marrow (the most common site) or in extramedullary sites (testicular and CNS involvement account for fewer than 5% of cases). In ALL, relapse following the completion of therapy has decreased by 50% since the 1970s.

Relapse is associated with drug resistance of residual leukemic cells. Children at highest risk during initial remission include those under 12 months of age at diagnosis, those with chromosomal abnormalities, those who fail to achieve remission within 28 days of induction therapy, and those with an initial leukocyte count over 100,000/mm³. When relapse occurs, the child is started on reinduction therapy. Bone marrow or stem cell transplantation may be performed when remission is reestablished.

Bone marrow transplants fall into three categories: syngeneic (which use marrow from an identical twin sibling), allogeneic (which use marrow from a histocompatible donor, often a sibling), or autologous (which use disease-free marrow that's been collected from the patient and frozen).

Bone marrow transplantation (BMT) is usually reserved for children who have relapsed during any of the four phases of active therapy or within a year of completing maintenance therapy, or who are at high risk for relapse (because they have an initial WBC count above 100,000/mm³, chromosomal abnormalities, or are under 12 months of age). Allogeneic transplantation performed in the second complete remission of ALL has

lengthened leukemia-free survival when compared with chemotherapy alone, especially following an early relapse. Variables affecting the outcomes of BMT include the child's age and clinical status, number of remissions, duration of the first complete remission, prior therapy, the preparatory chemotherapy regimen, and posttransplantation and supportive care.

Prognosis is excellent

The prognosis for childhood ALL is excellent. In 1968, it was reported that fewer than 1% of children with ALL were long-term survivors. Today, using intensive regimens, the complete response rate exceeds 90%, and 65% to 75% of pediatric patients (about 1,500 children in the United States each year) achieve prolonged disease-free survival (more than five years after diagnosis). These children are generally considered cured.

Although vigorous treatment has dramatically improved survival rates, there is growing concern about delayed effects of therapy. Development of intellectual and motor function is of particular concern because treatment is often administered before brain maturation is complete. Although the potential for adverse effects on all bodily systems is enormous, the risk-benefit ratio overwhelmingly favors chemotherapy. Protocols are continually revised and updated to reduce the duration of therapy and to minimize toxicity without compromising efficacy. There are no indications at this time of an increase in birth defects or cancer among offspring of adult survivors of childhood ALL.

David was discharged from the hospital one week after being admitted. Chemotherapy was in progress and the severe pain he had experienced one week earlier had diminished considerably. He was weak and uncomfortable, but he was glad to go home. Most important, we were all together.

Several weeks went by before he lost his hair. He had been informed of the adverse effects of the chemotherapy and had said he was prepared. It took several days for his hair to fall out. My husband and I took turns bathing him. (It would have been too difficult for either one of us to see the clumps of hair fall out in our hands night after night.) David never complained.

Throughout the entire ordeal, David has maintained a wonderful attitude. Initial feelings of disbelief and anger over his leukemia were replaced by gradual acceptance. He occasionally verbalized confusion over why he got leukemia (his father and I wondered about that ourselves), but he's learned not to dwell on the question.

At this writing, David has been in remission for 30 months. He completed maintenance chemotherapy in mid-January of 1998. He will be monitored by his oncologists for many years for signs of relapse or any long-term adverse effects of chemotherapy.

David has endured chemotherapy, spinal taps, spinal infusions, and bone marrow aspirations. If he remains in remission for five years, he'll be considered cured of leukemia.

Throughout this period I've learned many tough lessons, the most crucial of which is the importance of family and love. This allowed us a sense of normalcy when the disease took

over our lives. It gave us the courage to go on and to think more clearly about what needed to be done.

This became clear to me one week after David was discharged from the hospital. He was still quite uncomfortable and having difficulty walking. The nurse in me wanted to intervene. I asked him what I could do to make him more comfortable. David looked at me with his big, beautiful, blue eyes and said that all he wanted was "for us all to be a family."

That statement made me realize that what my child needed from me most was not a nurse but a mother. As a result of his simple request, my husband and I reprioritized our lives. We learned to push aside the outside influences that had somehow found ways of stealing our time together. Our children became the central focus of our lives. Simple things—bringing the children to school, putting them to bed, eating together, or playing a game—took on new meaning for us.

I realized I was doing something right when David came up to me one evening, put his arms around my neck, hugged me, and thanked me for taking such good care of him. My eyes welled up with tears of joy. He was thanking me, his mom, not the nurse. □

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After reading this article and taking the test on the next page, you will be able to:

- Distinguish at least five early signs of ALL from five advanced manifestations.
- Explain the four phases of ALL treatment.
- Identify three types of bone marrow transplantation.
- Recall at least three points to teach parents of children with ALL.

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