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(Eds.)

Pediatric Oncology Nursing

**Advanced Clinical
Handbook**

Second Edition

 Springer

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Dedication

To all pediatric nurses. Your contribution to our world's future is beyond words.

To Chris and our children, Vivian, Sam, Suzanne and Angus – for giving me reason.
Deborah Tomlinson

To my parents, and my husband Michael. Thank you for your unwavering support throughout this endeavor.
Nancy E. Kline

Preface

Pediatric Oncology Nursing: Advanced Clinical Handbook is a joint effort between nurses in Canada, the United Kingdom, and the United States. This is the second edition, and has been another wonderful opportunity to bring together the expertise of hematology and oncology nurses from two continents. The book is designed to be a comprehensive clinical handbook for nurses in advanced practice working with pediatric hematology/oncology patients. Specific issues related to young children and adolescents with cancer and hematologic disorders are discussed.

Thirty-one contributors and two editors participated in the writing of this text. Individuals in advanced practice and academic roles – nurse practitioners, clinical nurse specialists, nutritionists, clinical instructors, lecturers, academicians, and educators – were involved. One of the most appealing features of this text is the vast experience represented by our authors from different countries and different educational backgrounds.

The book is divided into 5 sections: pediatric cancers, hematologic disorders, treatment of childhood cancer, side effects of treatment and disease, and supportive and palliative care. Many tables and illustrations are included for quick reference in the clinical setting. Future perspectives and opportunities for new treatment options and research are discussed.

Part I focuses on pediatric cancers – the leukemias, lymphomas, and solid tumors. The most common pediatric tumors as well as some rare tumors are discussed in regards to epidemiology, etiology, molecular genetics, symptoms and clinical signs, diagnostic and laboratory testing, staging and classification, treatment, prognosis, and follow up care.

Part II focuses on pediatric hematology. The anemias, bleeding disorders, neutropenia, thrombocytopenia, and bleeding disorders are discussed in detail. Epidemiology, etiology, symptoms and clinical

signs, diagnostic and laboratory procedures, treatment, prognosis, and follow up care are included for each of the disorders.

Part III covers cancer treatment, including chemotherapy, radiation therapy, hematopoietic stem cell transplantation, surgery, gene therapy, biotherapy, complementary and alternative medicine, and clinical trials. The principles and description of treatment, method of treatment delivery, potential side effects, and special considerations for each type of treatment are discussed.

Part IV focuses on the side effects of cancer treatment in relation to metabolic processes and gastrointestinal, hematologic, respiratory, renal, cardiovascular, neurologic, musculoskeletal, integumentary, endocrine, and auditory systems. The incidence, etiology, treatment, prevention, and prognosis are included for each side effect reviewed.

Part V includes the essential information regarding supportive and palliative care of pediatric cancer patients. Nutrition, hydration, pain, blood transfusion therapy, growth factors, and care of the dying child and the family are covered. The principles of treatment for these conditions, method of delivery, and special considerations for certain conditions are included.

The Editors of *Pediatric Oncology Nursing: Advanced Clinical Handbook* want to recognize, thank, and acknowledge everyone who participated in the development of this text. We are profoundly aware of the personal time and commitment that was devoted to make this an outstanding resource and we are grateful. It is our hope that nurses in advanced clinical practice will find this publication useful, and that it will enrich knowledge and improve care for children and adolescents with cancer and hematologic disorders.

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Leukemia

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1.1 Introduction

Leukemia is the most common malignancy that affects children, accounting for approximately one-third of cancer diagnoses. It may be defined as a neoplastic disease that affects the blood-forming tissues of the bone marrow, lymph nodes, and spleen.

Normal hematopoiesis occurs in these blood-forming tissues; the development of blood cells is shown in Fig. 1.1. A range of extracellular protein factors regulate the growth and differentiation of pathways of developing cells. This ensures that the

mature blood cell types are produced in appropriate proportions. Leukemia is a clonal disease that results from genetic mutations and transformation of a single early progenitor myeloid or lymphoid cell during hematopoiesis. Therefore, the type of leukemia that results is dependent on the cell lineage that is affected by the mutation. Table 1.1 shows the blood cells that can be affected from either lineage. In leukemia, there is an overproduction of immature white blood cells that cannot function effectively. These immature white blood cells are commonly called “blasts,” such as the myeloblasts, lymphoblasts, and monoblasts. An

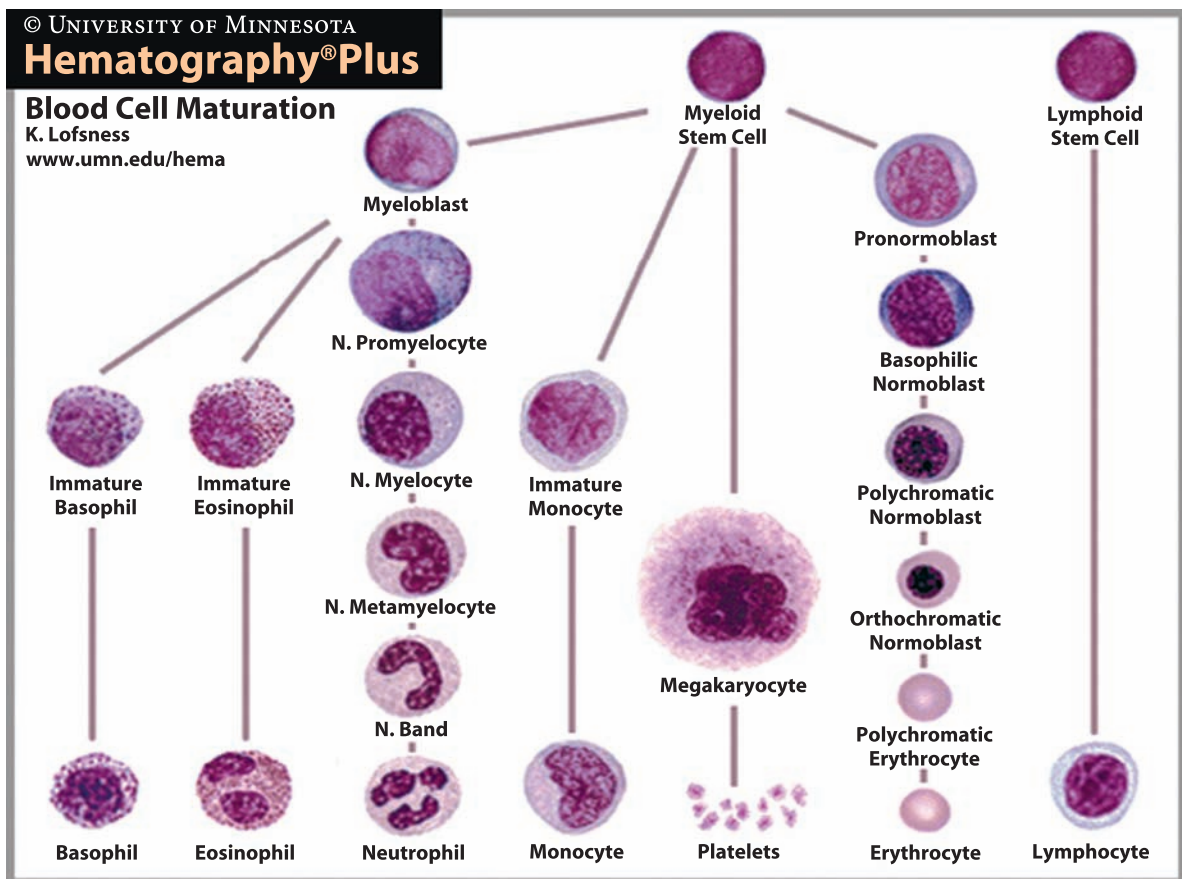


Figure 1.1

Hematopoiesis: The lymphoid stem cell differentiates into T-lymphocytes and B-lymphocytes. Natural Killer (NK) cells are also thought to be derived from the lymphocyte stem cells. Image credit: K. Lofsness, University of Minnesota

Table 1.1. Lineage and function of major types of blood cells

Blood cell	Lineage	Function	Half life
Red blood cells (erythrocytes)	Myeloid	Transport oxygen from lungs to tissue Transport some carbon dioxide from tissues to lungs	About 120 days
Platelets (thrombocytes)	Myeloid	Repair blood vessels and participate in clotting mechanism	7–10 days
White blood cells (leucocytes)		Crucial in immunity	
Monocytes	Myeloid	Can differentiate into macrophages, phagocytosis, antigen presentation, immune regulation	1–3 days in blood 3 months in tissues
Granulocytes			
Neutrophils	Myeloid	Phagocytosis, killing bacteria	6–12 h in blood
Eosinophils	Myeloid	Detoxify products from allergic response, phagocytosis	2–3 days in tissues
Basophils	Myeloid	Involved in allergic response, source of immune inhibitors (e.g., histamine)	Minutes to hours in blood, then in tissue for about 12 days
Lymphocytes	Lymphoid	Role in immunity	Undetermined cells can move between blood and lymphoid tissues
T-lymphocytes		Attack invaders directly	
B-lymphocytes		Production of antibodies	
Others			
Null cells, natural killer cells, lymphokine-activated killer cells, and tumour-infiltrating lymphocytes			

abnormal population of immature white blood cells decreases the space available for the production of other healthy blood cells produced by the bone marrow. The blast cells can also enter the blood and may infiltrate the central nervous system (CNS), testicles in males, bones, and other tissues or organs.

The two broad classifications of leukemia are acute and chronic. The most common types of leukemia are:

- Acute lymphoblastic leukemia (ALL), which accounts for 75–80% of childhood leukemia
- Acute myeloid leukemia (AML), also known as acute nonlymphoblastic leukemia (ANLL), which accounts for 20–25% of childhood leukemia

The most common type of chronic leukemia is:

- Chronic myeloid (or myelocytic) leukemia (CML), which accounts for less than 5% of childhood leukemia

1.2 Acute Lymphoblastic Leukemia

1.2.1 Epidemiology

ALL affects slightly more males than females (1.2:1) and peaks between the ages of 2 and 5 years. In infants, higher number of females are observed to be affected.

Globally, the highest incidence of ALL appears to be in Europe and North America, with about 5 cases in 100,000 of 0–14-year-old children. The lowest incidence, of about 0.9 in 100,000, has been observed in Kuwait and Mumbai. There may be a lack of clarity regarding some incidence figures, owing to the lack of true population-based registration of cancer. A recent study has shown that the incidence of leukemia has increased in Europe in the last decades with an average 0.6% annual increase (Kaatsch and Mergenthaler 2008). Generally, higher incidence of ALL is observed in the affluent industrialized nations among white populations. The incidence tends to be lower among the black populations of the same nations.

1.2.2 Etiology

The factors involved in the cause of childhood cancers are still unclear. Many different etiologies have been suggested and investigated, but few are well established. It would be misleading to entirely associate the cause of any childhood malignancy to genetic or environmental factors, but the study of various factors can improve the understanding of events that may lead to leukemia in children.

1.2.2.1 Genetic Factors

Syndromes that have a component of hereditary or genetic predisposition to leukemia have been identified and are listed in Table 1.2. A study by Mellema et al. (2000) has shown that children of parents with autoimmune disease are slightly more susceptible to leukemia. Family cancer history does not appear to be associated with an increased risk of childhood acute leukemia (Rudant et al. 2007). If one monozygotic twin is diagnosed with leukemia, the other twin will have a 5–25% risk of developing leukemia (Greaves et al. 2003; Kadan-Lottick et al. 2008; Couto et al. 2005).

1.2.2.2 Environmental Factors

It has been accepted that ionizing radiation is a causal factor of leukemia. Following the explosion of atomic bombs in Japan, the exposed children acquired an increased risk of developing leukemia. However, those individuals exposed in utero showed no increase in

Table 1.2. Syndromes with a predisposition to leukemia

Genetic bone marrow failure syndromes predisposed to leukemia

- Fanconi anemia
- Diamond-Blackfan anemia
- Shwachman-Diamond syndrome
- Dyskeratosis congenita
- Kostmann severe congenital neutropenia

Genetic syndromes predisposed to leukemia as one of the illnesses

- Chromosomal abnormality
- Down's syndrome (trisomy 21)
- Chromosome 8 trisomy syndrome
- Klinefelter syndrome

DNA repair/tumor suppressor deficiency

- Ataxia telangiectasia
- Li-Fraumeni syndrome
- Neurofibromatosis type 1
- Bloom syndrome
- Nijmegen/Berlin breakage syndrome

(Table compiled from Mizutani, 1998)

the incidence of leukemia. This finding is in contrast to the suggested results of various studies that showed an increased risk of leukemia and other cancers (by about 40%) among children exposed in utero to diagnostic radiography (Doll and Wakeford 1997). There is no doubt that ionizing radiation is a causal factor in leukemia; however, there are uncertainties regarding various aspects of its effect on leukemogenesis.

Kinlen's theory (1995) states that population mixing, herd immunity, and abnormal response to infection of unusually susceptible children increases the risk of ALL. The "delayed infection" or "hygiene" hypothesis suggests that ALL in children is caused by a lack of exposure to infection in infancy, with an abnormal response to a later common infection incurred after mixing with other children in playgroups or schools. This hypothesis is consistent with Greaves's theory that childhood ALL results from at least two mutations, with the second one more likely to occur in children with a delayed exposure to infection leading to increased immunological stress (Stiller et al. 2008). Therefore, circumstances that alter the pattern of infections in infants may contribute to the etiology of ALL (Stiller et al. 2008).

Table 1.3 highlights the studies that have been undertaken to investigate the various possible factors in the

Table 1.3. Reported environmental links to childhood leukemia and current conclusions

Possible environmental link	Current conclusions
Parental use of tobacco	Studies on parental smoking are controversial. However, several studies support the hypothesis that paternal smoking is associated with an increased risk of ALL (MacArthur et al. 2008; Rudant et al. 2008; Lee et al. 2009; Menegaux et al. 2007; Pang et al. 2003)
Vitamin K prophylaxis in infants	Now disproved; initially inconsistent associations reported. However, confirmed benefits of vitamin K outweigh the hypothetical association with any childhood cancer (American Academy of Pediatrics Committee on Fetus and Newborn 2003; Roman et al. 2002; Ross and Davies 2000; Parker et al. 1998; Passmore et al. 1998)
Living near landfill sites	No excess risk of any cancer reported (Jarup et al. 2002)
Proximity to railways and roads	No association reported between risk of childhood leukemia and railway proximity (Dickinson et al. 2003). Small association with railway density assumed to be the consequence of population mixing and proximity of railways in deprived urban areas. Child cancer initiations may be determined by prenatal or early postnatal exposures to engine exhaust gas (Knox 2006)
In vitro fertilization	No increased risk of childhood cancer reported in studies published (Bergh et al. 1999; Klip et al. 2001). Underlying cause of infertility may be a predisposing factor which may account for some case control studies reporting increased risk of specific cancers (Lightfoot et al. 2005)
Prenatal ultrasound	No association with childhood leukemia found (Naumburg et al. 2000)
Supplementary oxygen	Resuscitation with 100% oxygen immediately postpartum is associated with childhood ALL; further studies warranted (Naumburg et al. 2002a)
Breastfeeding	Contradicting reports of association with a reduced risk of acute leukemia (Bener et al. 2008; Lancashire et al., 2003; UK Childhood Cancer Study Investigators 2001; Shu et al. 1999)
Pet (healthy or sick) ownership	No relationship (Swensen et al. 2001)
Electromagnetic fields (EMF) and power lines	Consensus of available studies does not support hypothesis of an association (Skinner et al. 2002; Schüz et al. 2007)
Natural radionuclides in drinking water, including uranium and arsenic	Results do not indicate increased risk of leukemia (Auvinen et al. 2002; Engel and Lamm 2008)
In utero exposure to metronidazole	No reported increased risk (Thapa et al. 1998)
Allergies or family history of allergies	Reduced risk of ALL; no such pattern seen with AML (Schuz et al., 2003). The reduced risk may be due to an increased infection rate associated with a positive allergy history (Rosenbaum et al. 2005)
Exposure to pesticides	May increase risk (Rudant et al. 2007; Ma et al. 2002)
Perinatal exposure to infection	Some association reported between maternal infection in utero and risk of childhood leukemia (Kwan et al. 2007; Naumburg et al. 2002b)
Population mixing	Increased risk of ALL in children 1–6 years old in high tertile of population mixing (Alexander et al. 1999; Boutou et al. 2002). Further support for the hypothesis of infectious agents involved in etiology of ALL
Parental alcohol consumption	Some studies indicate an increased risk of ALL and increased maternal alcohol consumption (MacArthur et al. 2008; Menegaux et al. 2007)
Parental caffeine consumption	No significant reports of increased risk of childhood ALL and maternal coffee consumption (Menegaux et al. 2007)

etiology of childhood leukemia and other cancers. All the theories surrounding the causes of ALL, or indeed the majority of childhood cancers, are for the most part unexplained, and further studies are necessary to confirm or reject the conclusions of those available.

Because of the public interest that surrounds the majority of these potential risk factors, parents will continue to form theories regarding their children's illnesses (Ruccione et al. 1994). Nurses have a role in eliciting parents' causal explanations so that the content of these concerns can be related to the parents' adjustment and management of their experience of childhood cancer.

1.2.3 Molecular Genetics

Clonal chromosomal abnormalities (originating in a single cell) are detectable in around 90% of childhood ALL cases. The leukemia then evolves by the accrual of mutations within a clone. The abnormalities are responsible for a loss of controlled cell growth, division, and differentiation.

The following is a review on the biology of chromosomes:

- Genes carry instructions to make proteins essential for cell growth, division, and differentiation.
- A deoxyribonucleic acid (DNA) molecule carries the genetic information in coded form.
- DNA is a nucleic acid made of chains of nucleotides.
- Nucleotides have three components – a phosphate group, a pentose sugar, and a base.
- In DNA, the sugar is deoxyribose, and the bases are adenine, guanine, thymine, and cytosine.
- DNA consists of two chains of nucleotides linked across their bases by weak hydrogen bonds. These two complementary strands of nucleotides are linked in a double-helix formation.
- The bases have specific affinities toward each other, and thymine pairs only with adenine, and cytosine pairs only with guanine.
- The base sequence is the key to the control of the cell and is referred to as the genetic code.
- The length of DNA in cells is so great that there is a significant risk of mutations. DNA is packaged into 46 compact manageable chromosomes (23 pairs).

- The complete chromosome complement of a cell is referred to as the karyotype.

Some genes are associated with the transformation of a normal cell to a malignant cell. These are known as oncogenes (or proto-oncogenes) and tumor suppressor genes. Mutations in the DNA of these genes may cause them to produce an abnormal product, or disrupt their control so that they are expressed inappropriately, making products in excessive amounts or at the wrong time. Some oncogenes may cause extra production of growth factors, which are chemicals that stimulate cell growth. Other oncogenes may cause changes in a surface receptor, causing it to send signals as though it were being activated by a growth factor.

The exact number of mutations required to transform a normal cell into a malignant cell is unknown, but research indicates that two or more mutations, or “hits,” are involved. The first hit is thought to occur in the womb, which in ALL is likely to be a developmental accident affecting a chromosome. This may then suggest that a second hit after birth is necessary before ALL develops. This theory has arisen mainly from the observed high concordance rates of leukemia in infant monozygotic twins (i.e., if one twin has leukemia, so will the other) and the study of neonatal blood spots or Guthrie cards. In twins, the leukemogenic event is considered to arise in one twin, and the cells from the abnormal clone are presumed to spread to the other via shared placental anastomoses. Polymerase chain reaction (PCR) has been used to identify the same fusion gene sequence in neonatal blood spots similar to that in patients' leukemic cells at diagnosis. In almost all cases of infant leukemia with a fusion of the MLL gene and in many cases of childhood ALL with a fusion of the TEL-AML1 gene, these fusions are detectable at birth. These gene fusions would indicate the first hit or mutation. Table 1.4 shows the classification of types of mutation that can occur. In childhood ALL, reciprocal translocations account for approximately 25% of the chromosomal abnormalities. The translocations involve exchanges of tracks of DNA between chromosomes, resulting in the generation of chimeric or fusion genes. There may also be changes in chromosome number (ploidy), gene deletions, or single nucleotide-base changes in

Table 1.4. Types of mutation to genetic code

Mutation	Description	Presentations
Point mutation	Change in DNA sequence Can occur in base substitution, deletion, or addition May result in wrong amino acid being inserted into protein	Mis-sense mutation, usually a decrease in function
Chromosomal mutation	Alteration in the gross structure of chromosomes Result from cell breakage and reunion of chromosomal material during the cell cycle	Translocation Rearrangement
Genomic mutation	Change in the number of chromosomes in the genome	Amplification Aneuploidy (loss or gain of single chromosome)

genes (the chromosome number is also measurable as the DNA index, in which 46 chromosomes equals a DNA index of 1) .

As discussed earlier, the process by which a normal cell transforms into a leukemic cell is unclear. However, improved molecular analysis techniques have assisted in identifying mechanisms regulating cell growth and differentiation. These include the following:

- PCR
- Fluorescence in situ hybridization (FISH)
- Flow cytometry for immunophenotyping
- Digitized karyotype imaging/multicolor spectral karyotyping
- Microarray profiling of all genes active in a given cell population
- Southern blotting

Molecular analysis has proved indispensable for identifying prognostic factors and therapeutically important genetic subtypes of childhood ALL. The ranges of subtypes are based on gene expression, antigens that delineate the cell type, and chromosomal and molecular abnormalities. There is currently a relatively sophisticated understanding of the genetic basis of ALL, which will be discussed further in the following sections.

1.2.4 Symptoms and Clinical Signs

ALL can be either of T-lymphoblastic lineage or of B-lymphoblastic lineage. Both the subtypes of ALL have similar presenting features. However, T-cell ALL can have some associated symptoms related to the

presence of a mediastinal mass. The symptoms and clinical signs of both T-cell and B-cell lineage will be described in the following sections.

ALL usually presents as an acute illness of short onset, but symptoms are occasionally slow and insidious. The symptoms are related to the infiltration of the bone marrow and other affected organs by lymphoblastic cells and the absence of normal blood cells. The presenting features often appear like many childhood illnesses. Parents or children may describe the following:

- Irritability
- Fatigue
- Bone pain, which may present as limping
- Loss of appetite

Initially, symptoms may fluctuate daily, with the child feeling exhausted one day and fine the next day.

Physical findings may include the following:

- Pallor and lethargy
- Pain at the sites of disease infiltration, especially in long bones
- Petechiae
- Bruising or unusual bleeding (including nose bleeds)
- Enlarged liver or spleen, causing the abdomen to protrude
- Enlarged lymph nodes and fever
- Painless testicular swelling

In less than 10% of the cases, the disease is observed to spread to the CNS at diagnosis. This may cause related symptoms of

- Headache
- Poor school performance
- Weakness
- Vomiting
- Blurred vision
- Seizures
- Difficulty maintaining balance

In 60–70% of children with the T-cell type of ALL, there is involvement of the thymus. Enlargement of the thymus caused by an accumulation of white blood cells can give rise to an anterior mediastinal mass that can cause pressure on the trachea, causing coughing, shortness of breath, pain, and dysphagia. In some cases, the pressure may also compress the superior vena cava and cause swelling of the head and arms.

In rare circumstances, acute leukemia may present with extremely high blast cell counts, known as hyperleukocytosis. This state of the disease can cause respiratory failure, intracranial bleeding, and severe metabolic abnormalities – conditions that are the main causes of early mortality. The process that leads to these complications is known as leukostasis. It had been thought that leukostasis was caused by overcrowding of leukemic blasts. However, it is now evident that leukostasis results from adhesive interactions between blasts and the vascular endothelium. Damage to the endothelium is likely, owing to the cytokines that are released. The adhesion molecules displayed by the blasts and their response to the environment are probably more important factors in leukostasis formation than the numbers of cells. Leukopheresis is sometimes used to reduce the leukocyte count in the initial phase when there is hyperleukocytosis. It remains unclear whether this is the most efficient method of treating leukostasis. It is also important to start cytoreductive therapy as soon as possible, and this requires an expedited diagnosis. Further research should indicate the most appropriate use of leukopheresis and the development of practice guidelines for the management of hyperleukocytosis.

1.2.5 Diagnostics

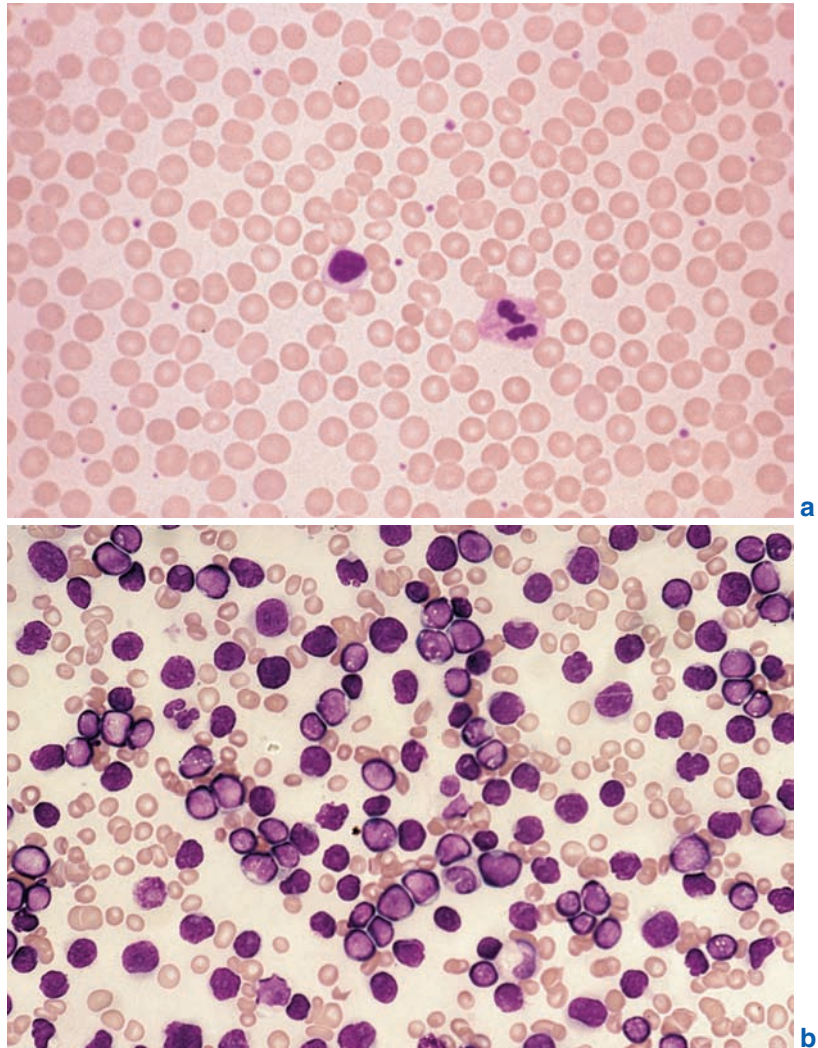
If ALL is suspected following the history and physical examination of the child, then the initial investiga-

tions include a complete blood count, serum evaluations of kidney and liver function, electrolyte counts, and a chest X-ray. The blood count may point to a diagnosis of leukemia if there are blast cells present or there is evidence of anemia, thrombocytopenia, or leukopenia. At presentation of leukemia, the white blood cell count (WBC) is often elevated; however, it may also be in the normal range or below normal values. [Figure 1.2a](#) shows a normal blood film, and [Fig. 1.2b](#) is a blood film from a child with ALL. Blood counts may raise suspicion of leukemia, but the diagnosis is most often confirmed by bone marrow examination. Occasionally, a diagnosis is made on peripheral blood samples, particularly if there is a high WBC and/or the patient is clinically unstable making sedation for diagnostic procedures dangerous. When bone marrow procedure is done, the marrow is mostly aspirated from the iliac bone at the iliac crest. Despite the new technologies available, ALL is still usually diagnosed by an experienced pediatric oncologist and/or pathologist, by examining a Romanowsky-stained bone marrow smear with a high-powered microscope. A higher than 25% blast-cell count in the marrow confirms a diagnosis of leukemia. A portion of the bone marrow aspirate is then analyzed to detect other features of the leukemic cells to help determine what type of leukemia is present. Bone marrow biopsy/trephine may be required for diagnosis if bone marrow aspirate is inconclusive and leukemia is still suspected.

A lumbar puncture (LP) is performed to determine any CNS involvement; a sample of cerebrospinal fluid (CSF) is examined for blast cells. The bone marrow aspirate (BMA) and LP are most often performed together using sedation or anesthetics. Therefore, because of the potential anesthetic difficulties that could develop, a chest X-ray is vital to assist in diagnosing infection or detecting a mediastinal mass. To minimize the risk of bleeding, platelet transfusion may be required prior to an LP. For males suspected of testicular involvement on clinical examination, an ultrasound is indicated. An echocardiogram is often carried out at diagnosis, and is necessary for all patients who are intended to start an induction therapy that included anthracycline chemotherapy.

Figure 1.2

(a) Normal blood film ($\times 25$),
(b) ALL blood film ($\times 25$).
Image credit: Dr Angela
Thomas, RHSC, Edinburgh



1.2.6 Staging and Classification

1.2.6.1 Risk Classification

Once the diagnosis of ALL has been confirmed, cell morphology, cytogenetics, and immunophenotyping are determined to elicit more defined prognostic factors. Treatment can subsequently focus on “risk-directed” protocols developed through well-designed clinical trials. This strategy uses the child’s likelihood of relapse or resistance to treatment, to intensify or reduce the treatment to ensure adequate cell kill

within acceptable levels of toxicity. The significance of various reported risk factors has led to some debate. Difficulty also arises when comparing the results among different countries and centers using locally-assigned risk categories. However, over the past few decades, several features have been determined to be more favorable prognostic factors. In 1993, following a previous initiative in Rome, collaborative groups met to establish those features that would indicate “standard risk” of ALL. These are known as the Rome/NCI (National Cancer Institute) criteria:

- WBC <50,000/mm³
- 1–9 years of age
- non-T/non-B (mature B-cell ALL)

Although risk classification differs by investigator group, most investigators agree on the four identified risk group classifications. These include:

- Standard risk: low (trisomy 4, 10, and TEL-AML1 t(12:21))
- Standard risk (NCI as mentioned earlier)
- High risk (WBC >50,000/mm³ or age >10 years)
- Very high risk (VHR) (hypodiploid karyotype or presence of BCR-ABL/t(9:22) or poor early response to treatment, high minimal residual disease (MRD) level at the end of induction).

Other factors are also used to determine the risk classification, but the number and array of factors used to classify ALL make it difficult to establish any one system. Consequently, there is a lack of precision within most risk classification systems. Varying conclusions have been reported with regard to the prognostic significance of other characteristics, including the presence of Down's syndrome (DS), liver and spleen size, the presence of an anterior mediastinal mass, French-American-British (FAB) subtype, body mass index, CNS involvement, hemoglobin level, and platelet count. Interestingly, traumatic lumbar puncture at diagnosis of childhood ALL may indicate increased risk of CNS relapse and may be an indication to intensify intrathecal (IT) therapy (Gajjar et al. 2000; Rech et al. 2005). However, subgroups of patients with different outcomes can be predicted by blast karyotype, molecular abnormalities, and early response to treatment, with response to treatment proving to be increasingly more important (Schultz et al. 2007). Response to treatment is usually assessed at the end of induction therapy for ALL, and is now determined by measuring the amount of minimal residual disease (MRD). This very sensitive diagnostic test appears to have the greatest strength to predict prognosis when compared with the other biological and clinical features (Pui and Evans 2006). Currently, investigators continue to determine a cut-off value that is indicative of poor prognosis prompting treatment intensification. Presently, an MRD value of 0.01% appears to be highly prognostic, with

patients achieving a value less than 0.01% at the end of the induction phase having a predicted excellent treatment outcome. Alternatively, patients who have a greater end of induction MRD value may have a high risk of relapse and will benefit from intensified therapy (Pui and Evans 2006). Patients who have a high MRD value are considered poor early responders (or slow early responders). MRD can be measured using either flow cytometry or PCR techniques.

A VHR classification is assigned to pediatric patients with ALL, who have clinical or biological features associated with a high risk of relapse. Patients with VHR classification are usually recommended for hematopoietic stem cell transplant (HSCT). MLL rearrangement is also considered an VHR feature, but only if there is evidence of a slow early response to treatment and an associated MRD-positive end of induction finding. The MRD value appears to be so strongly prognostic that it is likely to override other biological features of ALL in future therapies.

1.2.6.2 Cell Morphology

Despite other ways of looking at cells, a morphological classification that is still widely applied is the FAB system. This classification is based on the morphology (appearance, structure, and cytochemistry) and number of cells, and it defines three categories (Table 1.5). However, this system is no longer used for prognosis.

1.2.6.3 Cytochemistry

Several biochemical markers have been identified to assist in the classification of leukemia. However, little is added to the morphology of ALL, with the exception of

- Periodic-acid Schiff positivity, seen in around 15% of cases correlating with common ALL
- Acid phosphatase positivity in T-ALL

1.2.6.4 Immunophenotyping

ALL is probably best classified on the basis of immunophenotyping. Antigens on the surface of normal hematopoietic cells express changes as the cells

Table 1.5. French–American–British classification of acute lymphoblastic leukemia

Category	Definition	Features	Percentage of patients
L1	Small cells with scant cytoplasm	Associated with good treatment response	90
L2	Large cells with abundant cytoplasm	Indicates more refractory to therapy if 10–20% L2 cells are present	9
L3	Large cells with prominent nucleoli	Mature B-cell phenotype, frequently presents as lymphoma, poor prognosis	1

mature in the bone marrow. Technology has produced monoclonal antibodies to many of these cluster-of-differentiation (CD) antigen groups. These are each given a classification number prefixed with CD. Some CD antigen groups are related to lymphocyte sublineage (CDs 1–8 mark various stages of T-cell lineage; CDs 19–22, 24, and 79a mark B cells) and some are related to myeloid lineage, whereas others mark more primitive features (CD10 and CD34). CD10 is known as the common ALL antigen (CALLA). Other useful immunologically defined cell characteristics include the following:

- Cytoplasmic immunoglobulins found in pre-B-cell ALL
- Surface immunoglobulins found in mature B-ALL
- Terminal deoxynucleotidyl transferase (TdT) found in immature lymphoid cells

Using these markers enables the classification of ALL into major categories (Table 1.6). ALL cells occasionally express cell antigens usually associated with myeloid lineage. The myeloid antigens may be weakly expressed and are often considered aberrant expressions. However, opinion is divided as to whether this is clinically significant.

Table 1.6. Categories of acute lymphoblastic leukemia

Category of ALL	Percentage (approximately)
Common or pre-B	80
T-cell	10
Mature B	7
Null (early B-precursor)	3

1.2.6.5 Cytogenetics

Cytogenetic abnormalities are detectable in most cases of childhood ALL. They can be categorized either by the number of chromosomes (ploidy) or by the structural changes and rearrangements based on the detailed analysis of the karyotype. The assessment of ploidy status is clinically useful in predicting prognosis (Table 1.7).

With regard to structural changes, the identification of translocations and marker chromosomes and the delineation of complex chromosome aberrations are possible with multicolor spectral karyotyping. The most significant chromosome (Ch⁷) translocations identified in childhood ALL include the following:

Table 1.7. Outcome prediction associated with ploidy status of acute lymphoblastic leukemia

Ploidy Status	Number of chromosomes per malignant cell	Percentage of childhood ALL cases	Predictive response to treatment
Hyperdiploidy	>50	25–30	Favorable
Hypodiploidy	<44	5–10	Poor
Near-haploid	<30	<1	Very poor

Important: Fewer than 44 chromosomes is a degree of hypodiploidy that is prognostically relevant