

Childhood Leukemias and Lymphomas

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Faculty

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Faculty Disclosure

Contributing faculty, **Lori L. Alexander, MTPW, ELS, MWC**, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This advanced course is designed for psychologists in the pediatric or family medicine setting.

Accreditations & Approvals



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Course Objective

All healthcare professionals should understand how pediatric leukemia and lymphoma and their treatment affect growth and development and routine preventive measures and be skilled in discussing emotional well-being and psychosocial issues and in recommending psychosocial interventions. The purpose of this course is to enhance psychologists understanding of treatment options for childhood leukemias and lymphomas, the effects of treatment on normal growth and development, and the psychosocial effect of cancer on a child and his or her family.

Learning Objectives

Upon completion of this course, you should be able to:

1. Discuss the prevalence and types of childhood leukemia and lymphoma.
2. Identify the clinical signs and symptoms associated with childhood leukemia.
3. Describe the diagnostic testing for and classification of childhood leukemias.
4. Discuss the prognostic variables for childhood leukemias.
5. Describe the clinical presentation, diagnosis, and prognostic variables of Hodgkin lymphoma.
6. Discuss the signs and symptoms, diagnosis, and prognostic variables associated with non-Hodgkin lymphomas.
7. Explain the principles of communicating a diagnosis of childhood cancer.
8. Discuss the importance of clinical trials and the issues unique to trials involving children.
9. Outline the treatment approaches for childhood leukemia and lymphoma.
10. Discuss the various means of supportive care needed for children/adolescents with leukemia or lymphoma.
11. Describe the elements of effective palliation of symptoms in the end of life for children/adolescents with cancer.
12. Recognize the psychosocial and spiritual needs of children/adolescents with cancer and their families.
13. Discuss coping mechanisms of children/adolescents with cancer and their effect on psychosocial adjustment.
14. Explain the psychosocial effect of childhood cancer on family dynamics.
15. Define the most common long-term effects of childhood leukemias and lymphomas and their treatment.
16. Outline recommendations for necessary surveillance and long-term monitoring specific for a child's or adolescent's cancer and treatment.



Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Cancer is the leading cause of death among children 14 years of age and younger, and leukemia and lymphoma are among the most prevalent cancers in children/adolescents [1; 2]. Two types of leukemia—acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML)—and two types of lymphoma—Hodgkin and non-Hodgkin—occur in this population. Each of these diseases is distinct, with variations in etiology, patient characteristics, signs and symptoms, treatment approaches, and outcomes. Primary care practitioners should be able to identify the clinical signs and symptoms that may be indicative of these diseases and have knowledge of diagnostic testing, staging, and prognostic variables. A discussion of all of these aspects is included here, as well as a broad overview of treatment options.

A diagnosis of cancer in a child/adolescent creates devastating effects on him or her, as well as the family. As a result of the key relationship between primary care practitioners and children/adolescents and their families, these clinicians are often an important resource for emotional support, guidance, and referrals. Clinicians should be skilled in discussing emotional well-being and psychosocial issues and in recommending psychosocial interventions to help the patient and family develop coping mechanisms and deal with the disruption to normal family dynamics. Interventions can also help children/adolescents with cancer through problems with social interactions and school-related issues.

Primary pediatric care should continue during treatment for cancer, and clinicians in this setting should understand the effects of leukemia and lymphoma and their treatments on the child's/adolescent's growth and development and on routine preventive measures. In addition, studies have shown higher rates of morbidity and mortality among childhood cancer survivors compared with healthy siblings and the overall (age-matched) population [3; 4; 5; 6; 7].

The specific findings of these studies point to the need for heightened awareness of the health risks for survivors and the value of creating survivorship care plans. A discussion of late effects of childhood cancer and its treatment, the maintenance of health documentation, and appropriate follow-up care offers information to help clinicians provide optimal primary care to their patients with childhood leukemia or lymphoma.

OVERVIEW OF CHILDHOOD LEUKEMIAS AND LYMPHOMAS

The term “childhood cancer” is used to describe cancers that affect individuals from birth to 19 years of age. Although this age range is wide, cancers that occur throughout these ages have many similarities; however, the physical and psychosocial needs of infants differ greatly from those of young children as well as those of adolescents (defined as 15 to 19 years of age). The incidence of childhood leukemias and lymphoma vary among age groups, as do outcomes. Treatment varies as well, and some adolescents are treated in pediatric clinical practice, while others are treated in adult practices; this difference makes it difficult to evaluate the efficacy of certain treatment protocols and also creates challenges in improving survival rates [8]. In addition, issues related to dependency, access to care, treatment compliance, and decision making differ between children and adolescents with cancer [8; 9]. In sum, adolescents represent a distinct population of individuals with cancer, and their unique needs have been recognized, as evidenced by several recent articles and, especially, the 2011 launch of the peer-reviewed journal, the *Journal of Adolescent and Young Adult Oncology* [10].

In 2023, cancer will be diagnosed in an estimated 15,190 children/adolescents 0 to 19 years of age and will be the cause of 1,590 deaths [2]. Among children 5 to 9 years of age in the United States, cancer is the second leading cause of death (behind

unintentional injuries), and it is the third leading cause for older children, representing approximately 8.5% of all deaths among individuals 10 to 24 years of age [11]. Hematologic cancers are among the most common childhood cancers in children 1 to 4 years of age; brain and central nervous system tumors and lymphomas are the most common types of cancer diagnosed in adolescents 15 to 19 years of age [2]. Hematologic cancers are classified as leukemia when they involve primarily blood and bone marrow and as lymphoma when they arise from lymph nodes or other organs. Over the years, several systems have been developed to classify hematologic cancers. The uniform standard now used is the World Health Organization (WHO)/Revised European-American Lymphoma (REAL) system, now in its fifth (revised) edition, published in 2022 [12; 13; 14]. This system differentiates hematologic cancers into four broad categories: myeloid, lymphoid, mast cell, and histiocytic neoplasms. Specific disease entities are further defined within these categories on the basis of morphologic, immunophenotypic, genetic, biologic, and clinical criteria. The hematologic cancers occurring in childhood are predominantly lymphoid or myeloid. For the first time, in an effort to prevent the over-diagnosis of lymphoma and to improve the recognition of clinicopathologically distinct entities, non-neoplastic conditions mimicking lymphoma or representing an important differential diagnosis have been included [14].

Lymphoid and myeloid leukemias are further classified as acute or chronic, depending on the maturity of the cells affected and the pace of disease progression; acute leukemia affects immature cells (lymphoblasts) and progresses rapidly, whereas chronic leukemia affects mature cells and progresses more slowly. According to the International Classification of Childhood Cancer (ICCC), leukemia is categorized according to five diagnostic groups. Two of these groups—lymphoid leukemia and acute myeloid leukemia—account for approximately 85% of all leukemias [1].

Acute leukemia is the leading type of childhood cancer, representing 25.4% of all new childhood cancer cases [15]. Lymphoid leukemia is more common in both children and adolescents, with acute lymphocytic leukemia (ALL) accounting for 25% of leukemias in children and adolescents, compared with acute myeloid leukemia (AML), which accounts for 20% of leukemias in children and adolescents [15]. Chronic lymphocytic leukemia and chronic myeloid leukemia occur primarily in individuals who are at least 50 years of age and are rare in children/adolescents [16]. Because of the rarity of the chronic forms of leukemia in children, the focus in this course is on ALL and AML.

According to the National Cancer Institute's Childhood Cancer Data Initiative, 2,860 children and adolescents were diagnosed with lymphoma in 2020 [1]. Hodgkin lymphoma is the most prevalent cancer among adolescents and young adults 15 to 19 years of age, representing 13% of all childhood cancers in this age group; non-Hodgkin lymphoma accounts for 7% [1]. Among children 14 years of age and younger, non-Hodgkin lymphoma is the more prevalent lymphoma, accounting for 7% of cancers, with Hodgkin lymphoma representing less than 6% [17; 18].

The incidence of pediatric ALL and AML increased significantly between 1999 and 2019. The incidence of non-Hodgkin lymphoma showed no measurable increase, while the incidence of Hodgkin lymphoma has decreased [18]. Mortality associated with pediatric leukemia and lymphoma has also decreased, with the greatest decreases in ALL and AML [2].

RISK FACTORS

Unlike other types of cancers in adults, childhood leukemia and lymphoma are not associated with lifestyle risk factors, but the etiology is unclear. The only clear risk factor for childhood hematologic cancer is an inherited genetic syndrome, especially Down syndrome, which is associated with a 10-fold to 20-fold increased risk of leukemia [19; 20; 21; 22].

| GENETIC SYNDROMES ASSOCIATED WITH PEDIATRIC LEUKEMIA AND LYMPHOMA | |
|---|--|
| Genetic Syndrome | Type of Pediatric Leukemia or Lymphoma |
| Inherited Syndromes | |
| Ataxia-telangiectasia | ALL, AML |
| Bloom syndrome | ALL, AML |
| Diamond-Blackfan anemia | AML |
| Down syndrome | ALL, AML |
| Familial monosomy 7 | AML |
| Fanconi anemia | AML |
| Klinefelter syndrome | ALL |
| Kostmann syndrome (severe congenital neutropenia) | AML |
| Langerhans cell histiocytosis | ALL |
| Neurofibromatosis type 1 | ALL, AML |
| Severe combined immunodeficiency syndrome | NHL |
| Shwachman syndrome | ALL, AML |
| Acquired Syndromes | |
| Acquired monosomy 7 | AML |
| Amegakaryocytic thrombocytopenia | AML |
| Human immunodeficiency virus (HIV) infection | NHL |
| Immunocompromise (drug-related) | NHL |
| Paroxysmal nocturnal hemoglobinuria | AML |
| ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; NHL = non-Hodgkin lymphoma. | |
| Source: [20; 21; 22] | Table 1 |

Increased risk is associated with several other genetic syndromes as well (**Table 1**) [20; 21; 22].

Many factors have been investigated for their role in the development of childhood leukemia and lymphoma, including infection and environmental factors. The combination of genetic susceptibility and an abnormal response to infection is thought to be one cause of leukemia in children 2 to 5 years of age [23; 24; 25]. In addition, infection with the Epstein-Barr virus (EBV) in the presence of an immunodeficiency condition has been linked to an increased risk of Hodgkin lymphoma, and a history of serologically confirmed infectious mononucleosis significantly increases the risk for EBV-positive

Hodgkin lymphoma among young adults [26; 27; 28; 29]. A Children's Oncology Group study found that parental history of autoimmunity and parent or sibling with an allergy is associated with increased risk for EBV-positive Hodgkin lymphoma [30]. Infection in early childhood may reduce the risk of Hodgkin lymphoma, as the incidence is lower for children with many siblings or many playmates [31; 32]. With regard to non-Hodgkin lymphoma, the prevalence ranges from 1% to 25% among children/adolescents with primary or acquired immunodeficiency disorders, and a Swedish study demonstrated a significant increase in the risk of non-Hodgkin lymphoma in association with infections in infancy [26; 33]

| INCIDENCE OF PEDIATRIC LEUKEMIA AND LYMPHOMA ACCORDING TO RACE/ETHNICITY | | | | |
|--|---------------------------|--------------------|----------|------------------------|
| Cancer Type | Incidence (per 1 million) | | | |
| | Non-Hispanic White | Non-Hispanic Black | Hispanic | Asian/Pacific Islander |
| Leukemia (all types) | 46 | 32 | 62 | 47 |
| Acute lymphoblastic leukemia | 34 | 19 | 47 | 32 |
| Acute myeloid leukemia | 8 | 8 | 9 | 10 |
| Hodgkin lymphoma | 14 | 19 | 19 | 9 |
| Non-Hodgkin lymphoma | 19 | 11 | 10 | 10 |

Source: [15] Table 2

Radiation has emerged as a causal factor of hematologic cancers. Exposure to large doses of radiation, as from such catastrophes as atomic bombs or nuclear reactor accidents, has been associated with higher rates of leukemia and a slightly higher risk for non-Hodgkin lymphoma [34]. Low-dose radiation, from x-rays or radiation therapy, has also been found to be associated with a slight increase in risk for leukemia and lymphoma [34]. However, because of the time needed for disease to develop from such exposure, this cause is not as common in children as it is in adults. Prenatal exposure to radiation has been linked to the development of leukemia, but this cause has been rare since the routine use of preventive measures in performing radiographs on women. In one study, researchers evaluated three types of exposure to radiation: parental exposure before conception, intrauterine exposure, and postnatal exposure. None was found to increase leukemogenesis for children with Down syndrome [35].

Maternal exposure to chemicals and carcinogens during pregnancy has also been evaluated as an etiologic factor for hematologic cancer. Gestational exposure to petroleum products has been associated with an increased risk of infant leukemia, particularly AML and leukemia without mixed lineage leukemia gene rearrangements [36]. In the same study, eight other classes of household chemicals were not found to

increase the risk of leukemia. One study explored a possible association between residential proximity to oil and gas development and increased risk for ALL [37]. A meta-analysis found that maternal smoking during pregnancy was associated with a modest increase in risk for non-Hodgkin lymphoma [38].

A family history of Hodgkin lymphoma increases the risk of pediatric Hodgkin lymphoma, with a sevenfold increase in risk for children who have a sibling with the disease [39]. The risk of non-Hodgkin lymphoma is not higher for children who are born to parents who are survivors of non-Hodgkin lymphoma, unless the cancer was associated with a congenital disorder [39].

For reasons that are unclear, the risk of non-Hodgkin lymphoma has been higher among children/adolescents in families with higher parental incomes and educational levels and lower in families with large numbers of children [40]. Other demographic variables may also be risk factors, as the prevalence of childhood leukemia and lymphoma varies according to age, sex, and race/ethnicity, as will be discussed.

The risk factors for childhood hematologic cancers continue to be explored, and it currently appears that a complex set of factors is involved in the development of these diseases.

**FIVE-YEAR OBSERVED SURVIVAL RATES FOR PEDIATRIC LEUKEMIA AND LYMPHOMA
AMONG CHILDREN/ADOLESCENTS (BIRTH TO 19 YEARS OF AGE)**

| Cancer Type | 1975–1977 | 2013–2019 |
|----------------------------|-----------|----------------|
| Acute lymphocytic leukemia | 41% | 91% |
| Acute myeloid leukemia | 6% | 70% |
| Hodgkin lymphoma | 72% | 98% |
| Non-Hodgkin lymphoma | 47% | 89% |
| <i>Source: [15]</i> | | <i>Table 3</i> |

LONG-TERM SURVIVAL IN PEDIATRIC LEUKEMIA AND LYMPHOMA

| Cancer Type | 5-Year Survival | |
|------------------------------|-----------------|----------------|
| Acute lymphoblastic leukemia | 91% | |
| Acute myeloid leukemia | 70% | |
| Hodgkin lymphoma | 98% | |
| Non-Hodgkin lymphoma | 89% | |
| <i>Source: [1]</i> | | <i>Table 4</i> |

TYPES OF LEUKEMIA

Acute leukemia occurs in approximately 4,920 children and adolescents each year, with most cases occurring in children 1 to 4 years of age. The median age at diagnosis is 6 years of age [1; 15]. The incidence is higher for male than female children/adolescents for all races/ethnicities (5.4 per 100,000 vs. 4.4 per 100,000, respectively) [15]. Among racial/ethnic populations of children/adolescents, the incidence of leukemia (all types) is highest for the Asian/Pacific Islander population and lowest for the non-Hispanic Black population (*Table 2*) [1; 15].

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

ALL represents a heterogeneous group of biologic subtypes of leukemia and is classified into two principal types depending on the lymphocytes from which it develops. Most cases of B-lymphocyte ALL originate in cells early in the development of B cells and are therefore designated as precursor B-cell type [41]. Research has demonstrated that childhood ALL is initiated in utero, with another event required for full malignant transformation [42; 43].

DNA injury leads to the uncontrolled development of leukemic lymphoblasts in the marrow, which causes a deficiency of normally functioning blood cells. As a result, anemia, thrombocytopenia, and neutropenia occur.

ALL accounts for 82% of leukemias in children and adolescents [1]. The incidence of ALL varies according to sex, age, and race/ethnicity. ALL is more common among male children/adolescents (40 per million) than among female children/adolescents (31 per million) [1]. ALL typically develops in children between 1 and 9 years old, with a sharp peak in the incidence for children 1 to 3 years old [1]. The incidence of ALL is highest in the American Indian/Alaska Native population and lowest in the Black population [1].

Advances in treatment since the mid-1970s have improved survival rates for ALL [18]. According to SEER data, the five-year relative survival rate for ALL improved from 62% in 2000 to 71% in 2016 (*Table 3*) [1]. The observed long-term survival for ALL is 90% at 5 years, with an 88% probability of 10-year survival for children/adolescents who have 5-year survival (*Table 4*) [1].

ACUTE MYELOID LEUKEMIA (AML)

Pediatric myeloid leukemia refers to a spectrum of hematopoietic malignant diseases, but AML accounts for the majority of cases. Although AML is less prevalent than ALL, AML is more lethal, accounting for approximately 30% of childhood leukemia-related deaths [44]. AML involves the malignant transformation of stem cells or progenitor cells in the bone marrow.

As noted, AML accounts for 20% of leukemias in children and adolescents [1]. As with ALL, the incidence of AML varies according to age, but the pattern differs. The incidence of AML is highest for infants and lowest for children 5 to 9 years of age [1]. After 9 years of age, the rate slowly increases throughout adolescence [1]. Unlike ALL, the incidence of AML is similar for male and female children/adolescents (10.8 vs. 11.9 per million, respectively) [1]. The incidence is highest in the Asian/Pacific Islander and White populations, but the range across race/ethnicities is narrow [1].

The five-year survival rate for AML has consistently been the lowest of all childhood cancers. Based on SEER data, from 2013 to 2019, 31.7% of AML patients were alive five years after diagnosis [45]. The observed long-term survival is 75% at five years [1]. A review of data from two AML studies conducted by the Children's Cancer Group (now part of the Children's Oncology Group [COG]) showed that overall survival was substantially higher for White children/adolescents than for Black or Hispanic children/adolescents [46]. Because treatment was given according to established cooperative group treatment protocols, compliance rates, access to therapy, type of supportive care, or leukemia phenotype were not likely to be factors in the differences.

TYPES OF LYMPHOMA

Lymphomas arise from lymphoid cells. The distinction between Hodgkin and non-Hodgkin lymphoma is defined by the presence of Reed-Sternberg cells in Hodgkin lymphoma [27]. The two types of lymphoma differ from each other in several ways, including clinical behavior, biology, and histopathologic features.

Hodgkin and non-Hodgkin lymphoma occur in approximately 2,300 children and adolescents, and the incidence increases with age, with significant peaks in adolescence [1]. In the United States, the incidence of Hodgkin lymphoma is age-related and is highest among adolescents 15 to 19 years (of age 33.3 cases per 1 million per year). Children aged 10 to 14 years, 5 to 9 years, and 0 to 4 years have approximately threefold, tenfold, and 20-fold lower rates of Hodgkin lymphoma, respectively, than do adolescents. In developing countries, there is a similar incidence rate in young adults but a much higher incidence rate in childhood [47]. Among racial/ethnic groups, the incidence of Hodgkin lymphoma is highest for non-Hispanic White children/adolescents and lowest for American Indian/Alaska natives. The incidence of non-Hodgkin lymphoma is highest for Black children/adolescents and lowest for American Indian/Alaskan children/adolescents [1].

As with leukemia, advances in treatment options have improved survival for children/adolescents with lymphoma [47].

HODGKIN LYMPHOMA

Hodgkin lymphoma was first described in 1832 by Thomas Hodgkin as a “peculiar enlargement” and “affection” of the lymph nodes of the neck and other areas of the body, along with enlargement of the spleen and possibly the liver; there were often

deposits of firm tubercle-like nodules in the spleen and liver [27]. The malignant cells, subsequently named Reed-Sternberg cells, arise from B lymphocytes and exist with Hodgkin cells (large, mononuclear cell variants) within an immunoreactive background consisting of lymphocytes, eosinophils, neutrophils, histiocytes, plasma cells, fibroblasts, and collagen [27]. According to the WHO/REAL system, Hodgkin lymphoma may be categorized as classical and nonclassical [14]. Classical Hodgkin lymphoma is further categorized into four subtypes: lymphocyte predominant, nodular sclerosis, mixed cellularity, and lymphocyte depleted [14; 48; 49]. Two of the four subtypes of classical Hodgkin lymphoma account for most cases in children. Lymphocyte-predominant Hodgkin lymphoma and lymphocyte-depleted Hodgkin lymphoma are both rare in children.

In the United States, the incidence of Hodgkin lymphoma is much lower for children up to 4 years of age than for older children and adolescents [47]. In children younger than 10 years of age, the incidence of Hodgkin lymphoma is twofold to threefold higher in boys than in girls. In children 10 to 14 years of age, the incidence is approximately 1.2-fold higher in boys than in girls. In adolescents 15 to 19 years of age, the incidence is similar for males and females [47]. Hodgkin lymphoma is the most curable childhood cancer, with a five-year survival rate of 98% in 2013–2019, an increase from 88% in 1975–1983 [1].

NON-HODGKIN LYMPHOMA

Pediatric non-Hodgkin lymphoma is a heterogeneous group of malignant tumors of lymphoreticular cells that arise from both mature and blastic B cells and T cells [50]. Non-Hodgkin lymphomas in children/adolescents differ from those in adults in that adult lymphomas are more clinically aggressive.

As with Hodgkin lymphoma, the incidence of non-Hodgkin lymphoma increases with age and remains relatively constant across all ages for both boys and girls [1; 17]. Non-Hodgkin lymphoma develops nearly twice as often in male than female children/adolescents across all age-groups (15 vs. 6 per million) [15]. The incidence is highest among White Americans and lowest among Hispanic Americans [1; 17].

The five-year survival rate for non-Hodgkin lymphoma improved from approximately 74% in 1975–1979 to 89% in 2013–2019 [1].

There are nearly 30 different types of non-Hodgkin lymphoma, but only four are predominant in children: small noncleaved cell lymphoma (Burkitt lymphoma and Burkitt-like lymphoma), lymphoblastic lymphoma, diffuse large B-cell lymphoma, and anaplastic large-cell lymphoma (systemic or cutaneous). Burkitt lymphoma and diffuse large B cell lymphomas both develop from B lymphocytes; anaplastic large-cell lymphoma and lymphoblastic lymphoma typically arise from T cells.

Burkitt Lymphoma

Burkitt lymphoma is the most prevalent type of non-Hodgkin lymphoma among children/adolescents, accounting for approximately 23% of pediatric non-Hodgkin lymphoma in the United States [1]. It most commonly develops in males 15 to 19 years of age [1]. It is more common in non-Hispanic White adolescents than in Hispanic White adolescents [17]. This type of lymphoma was first noted by Denis Burkitt, who was studying children in Africa [50]. Burkitt lymphoma is endemic in Africa, where it occurs at a very high rate [17; 51].

There are clinicopathologic differences between the endemic and sporadic forms of the disease [50]. Burkitt lymphoma most commonly affects the jaw and maxilla of African children, whereas the abdomen is the most common site in children in the United States [51].

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma is the second most common non-Hodgkin lymphoma, representing 10% to 20% of pediatric non-Hodgkin lymphoma. It occurs most frequently in adolescents 15 to 19 years of age [17]. This type of lymphoma differs from other types of non-Hodgkin lymphoma in that it grows more slowly and does not usually spread to the bone marrow, central nervous system (CNS), or skin.

Diffuse large B-cell lymphoma is further categorized as nonmediastinal or primary mediastinal. Nonmediastinal disease is more common; primary mediastinal occurs predominately in adolescents [52]. The gene expression profile of this type of non-Hodgkin lymphoma is distinct and suggests a close association with Hodgkin lymphoma [53; 54].

Lymphoblastic Lymphoma

Lymphoblastic lymphoma represents approximately 16% of pediatric non-Hodgkin lymphoma [17]. It develops most often in boys, especially in the 15 to 19 year age group [17]. The malignant lymphoblasts are the same as those involved with childhood ALL. If the lymphoblasts involve more than 25% of the bone marrow, the disease is reclassified as leukemia and is treated accordingly. Lymphoblastic lymphoma can arise from early T cells or B cells; precursor B-cell lymphoblastic lymphoma occurs less frequently, representing 2.5% of all non-Hodgkin lymphoma [55].

Anaplastic Large-Cell Lymphoma

Anaplastic large-cell lymphoma accounts for approximately 10% of pediatric non-Hodgkin lymphoma, occurring most often among male adolescents [1; 17]. This type of non-Hodgkin lymphoma varies substantially in its clinical presentation, with possible involvement of lymph nodes and extranodal sites, typically bone and skin.

IDENTIFYING LEUKEMIAS AND LYMPHOMAS

Leukemia and lymphoma are often not suspected during the evaluation of children because of the rarity of the diseases. This low level of suspicion can make diagnosis in the primary care setting a challenge. In addition, the symptoms associated with these hematologic cancers are typically vague or nonspecific and are similar to those of common childhood conditions. Clinicians in the pediatric and family medicine settings must recognize early signs and symptoms and make appropriate referrals to ensure timely diagnosis and treatment, which are essential for enhancing survival.

Diagnosis begins with a history and physical examination. The subsequent course of diagnostic testing varies among patients and may include:

- Laboratory testing
- Imaging studies
- Evaluation of bone marrow aspirate
- Analysis of cerebrospinal fluid (CSF)
- Biopsy of lymph nodes
- Immunophenotyping
- Cytogenetic testing
- Molecular genetic testing

Some diagnostic procedures are uncomfortable, and children may be fearful and distressed at the prospect of diagnostic testing. Bone marrow aspiration and lumbar puncture are the most feared procedures, and care should be taken to ensure that the child is not in pain during either procedure [56]. The goal of pain intervention in this setting is unconsciousness, amnesia, and analgesia. The drugs used should be available in oral and/or intravenous form, have a rapid onset of action, and be of short duration [57]. Optimum anesthesia will provide the

maximum amount of comfort for the child and help him or her cooperate with the procedure. A review demonstrated that mind-body interventions, such as hypnosis, distraction, and imagery, may be useful, either alone or in combination with pharmacologic interventions, in managing procedure-related pain [58]. Preventing pain in diagnostic procedures also has important implications for future care. Children who have a painful experience will be distressed about further diagnostic or therapeutic procedures and will be reluctant to undergo such procedures. The distress related to a painful experience can also manifest several years later, as a painful diagnostic procedure is often recalled as a traumatic event in childhood cancer survivors who experience post-traumatic stress [57].

Specialized testing, such as immunophenotyping, cytogenetic testing, and molecular genetic testing, is complex and beyond the scope of this course. In brief, immunophenotyping is carried out with use of flow cytometry, immunohistochemical assay, or immunophenotyping panel. The results demonstrate the cell lineage of the leukemia or lymphoma (T or B cell origin). Immunophenotyping also demonstrates associations between specific clusters of differentiation antigens and subtypes of disease and is used to diagnose and classify leukemia and lymphoma [59].

Cytogenetic testing identifies chromosomal abnormalities with respect to either number or structure [60]. In addition to conventional cytogenetic methods, molecular cytogenetic methods, such as fluorescent in situ hybridization (FISH); molecular genetic methods, such as reverse transcriptase polymerase chain reaction (RT-PCR) or Southern blot analysis; or DNA probes are used to identify chromosome abnormalities. Molecular studies are expensive and not necessary in all cases. However, they may help to detect translocations involving parts of chromosomes that are too small to be seen with conventional cytogenetic techniques.

The accurate diagnosis of leukemia and lymphoma requires careful evaluation and interpretation of the results of these studies, which, in turn, necessitates consultation with pediatric oncologists with expertise in hematologic malignancies. For this reason, the American Academy of Pediatrics (AAP) recommends that diagnostic testing be carried out in pediatric cancer centers, where the availability of appropriate technology and subspecialists helps to ensure an accurate diagnosis [61; 62].

DIAGNOSIS OF LEUKEMIAS

CLINICAL SIGNS AND SYMPTOMS

There is a wide variation in the signs and symptoms of leukemia, and the onset is usually acute. However, in some cases, symptoms are insidious and persistent [41]. On average, symptoms are present for four to six weeks before diagnosis and are associated primarily with leukemia-related pancytopenia [22; 41]. The clinical manifestations of ALL and AML are similar, although there are some distinctions (*Table 5*) [22; 41; 63]

In taking a history from the child and/or a parent or caregiver, the clinician should determine if any of the following symptoms have been present:

- Fever
- Fatigue or weakness
- General malaise or loss of well-being
- Easy bruising or increased bleeding
- Anorexia or weight loss
- Dyspnea on exertion
- Discomfort in bones and/or joints
- Headache
- Seizures
- Vomiting

| CLINICAL MANIFESTATIONS OF ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) AND ACUTE MYELOGENOUS LEUKEMIA (AML) | | |
|--|-------------------------|--------------------------------|
| Clinical Sign/Symptom | ALL | AML |
| Involvement of central nervous system | Yes (20% to 25%) | Yes (5% to 30%) |
| History | | |
| Low-grade fever; fatigue/weakness | Most common symptom | Yes |
| Anorexia or weight loss | Yes | Yes |
| Discomfort in bones and/or joints | Yes | Yes |
| Easy bruising or increased bleeding | Yes (33%) | Uncommon |
| Infection | No | Often first presenting symptom |
| Physical Examination | | |
| Pallor | Yes | Yes |
| Lymphadenopathy | Yes | Yes |
| Splenomegaly/hepatomegaly | Yes (60%) | Yes (<50%) |
| Mediastinal mass | Yes (10% to 18%) | Rare |
| Ecchymoses of skin or mucous membranes | Yes | No |
| Petechiae | Yes | No |
| Inflammation/bleeding of gums | No | Yes |
| Cutaneous rash | No | Yes |
| Laboratory Values (Median) | | |
| Hemoglobin | 8 g/dL | 8 g/dL |
| White blood cell count | 12 x 10 ⁹ /L | 20 x 10 ⁹ /L |
| Platelet count | 53 x 10 ⁹ /L | 70 x 10 ⁹ /L |
| Source: [22; 41; 63] | | Table 5 |

A low-grade fever of unknown etiology is the most common symptom associated with ALL [41]. If fever has persisted for more than two weeks, further evaluation for leukemia is warranted. Findings on physical examination that should prompt diagnostic testing for leukemia include pallor, petechiae, ecchymoses of the skin or mucous membranes, or lymphadenopathy (enlargement of more than 2 centimeters). Splenomegaly or hepatomegaly is evident at the time of diagnosis in approximately 60% of children with ALL and in less than half of children with AML [41].

The first sign of AML is often severe infection. Other common signs include swelling, pain, and bleeding of the gums; inflammation of the mucous membranes of the upper airways; and cutaneous rash (reddish papules, plaques, or nodules or maculopapular rash).

A mediastinal mass is rare in children with AML and is found in a small percentage (10% to 18%) of children with ALL [22; 41]. With ALL, an enlarged thymus may lead to compression of the trachea or the superior vena cava, which can cause coughing and dyspnea or superior vena cava syndrome, respectively. A chest x-ray should be done if a cough persists for more than two weeks without an identifiable cause [63]. Overt testicular disease is rare (2%) at the time of diagnosis of ALL, but testicular leukemia is identified on evaluation of biopsy specimen in as many as 25% of male children/adolescents [41].

There are some differences between the initial laboratory values for ALL and AML. Although the median hemoglobin is approximately 8 g/dL for both types of leukemia, a higher percentage of children/adolescents with ALL have a hemoglobin of less than 8 g/dL. In addition, AML is associated with higher white blood cell (WBC) and platelet counts [22; 41].

Involvement of the CNS is present at the time of the initial diagnosis of leukemia in approximately 20% to 25% of cases of ALL and 5% to 30% of cases of AML [22; 41]. Signs of CNS involvement include headache, seizures, vomiting, asthenia, blurred vision, slurred speech, imbalance, cranial nerve palsy, and poor performance in school [22; 41].

Many of the symptoms related to leukemia are associated with other diseases and conditions, and care is needed in making a differential diagnosis. Lymphadenopathy may be related to infectious mononucleosis or other infection, but a lack of a response to a routine course of antibiotics should prompt laboratory testing consisting of a complete blood cell count (CBC) with differential and a reticulocyte count. The likelihood of leukemia is high when such testing demonstrates anemia, thrombocytopenia, leukopenia, high mean corpuscular volume, and reticulocytopenia [63]. Light microscopy of stained blood cells can demonstrate leukemic blast cells; blast cells may also be present on the peripheral blood smear. However, blast cells are often present in the bone marrow only.

Children with ALL often have bone and/or joint pain before leukemic blast cells are evident in the peripheral blood, which can prompt evaluation for juvenile rheumatoid arthritis before leukemia. A study showed that for children with bone or joint pain, three factors predicted the diagnosis of ALL: a low WBC count (less than 4,000/mcL), a low-normal platelet count (150,000–250,000/mcL), and a history of nighttime pain [64]. When all three of these factors were present, the sensitivity of a diagnosis of ALL was 100% and the specificity was 85% [64].

DIAGNOSTIC TESTING

Computed tomography (CT), ultrasonography, and magnetic resonance imaging (MRI) can be helpful in detecting leukemic involvement of organs, bone, joints, soft tissue, or brain. Examination of CSF obtained through lumbar puncture can also help to determine whether leukemia involves the CNS [65]. A trephine biopsy should be performed if the tap is dry to differentiate between AML and myelodysplastic syndrome. Differentiation is important for treatment decision making, as myelodysplastic syndrome can only be cured by hematopoietic stem cell transplantation (HSCT) [65].

When the suspicion of leukemia is high on the basis of laboratory testing and/or imaging studies, the child should be referred to a pediatric hematologist or oncologist. Further diagnostic testing begins with bone marrow aspiration. The presence of leukemic blast cells on examination of a bone marrow sample confirms a diagnosis of leukemia. Cells obtained through bone marrow aspiration are also used for cytogenetic examination, immunophenotyping, and other special studies to determine whether the leukemia is lymphocytic or myeloid and to identify the specific leukemia subgroup. Determining this information is important for planning appropriate treatment and providing prognostic information about response to treatment.

CLASSIFICATION

The French-American-British (FAB) Cooperative Group developed a comprehensive classification system for acute leukemias, with three subtypes of ALL based solely on morphologic features and eight subtypes of AML based on morphology and findings of immunohistochemical analysis [66]. However, the discovery that immunophenotypic, cytogenetic, and molecular features of ALL are better than morphology alone for stratifying risk has led to the abandonment of the FAB classification of ALL [67]. The FAB classification for AML is widely accepted (**Table 6**), but it has been noted that strict application of the system will not allow for the diagnosis and classification of a considerable number of childhood cases [22].

| FRENCH-AMERICAN-BRITISH (FAB) COOPERATIVE GROUP CLASSIFICATION SYSTEM FOR ACUTE MYELOGENOUS LEUKEMIA AND PREVALENCE OF SUBTYPES | | |
|---|--|------------|
| Subtype | Description | Prevalence |
| M0 | Acute myeloblastic leukemia without differentiation; no expression of myeloperoxidase (MPO) at light microscopy level | - |
| M1 | Acute myeloblastic leukemia with minimal differentiation; expression of MPO detected by immunohistochemistry or flow cytometry | 18% |
| M2 | Acute myeloblastic leukemia with differentiation | 26% |
| M3 | Acute promyelocytic leukemia (APL) hypergranular type | 6% |
| M3v | APL, microgranular variant; cytoplasm of promyelocytes demonstrates a fine granularity, and nuclei are often folded | - |
| M4 | Acute myelomonocytic leukemia (AMML) | 17% |
| M4Eo | AMML with eosinophilia | - |
| M5a | Acute monocytic leukemia (AMoL) without differentiation (monoblastic) | 21% |
| M5b | AMoL with differentiation | - |
| M6 | Acute erythroid leukemia (AEL) | - |
| M7 | Acute megakaryocytic leukemia (AMKL); flow cytometry is helpful to distinguish blasts from lymphoblasts | 7% |

Source: [22; 66] Table 6

Although a comprehensive discussion of the cytogenetic characteristics of leukemia is beyond the scope of the course, an overview of the most common features is helpful in understanding risk, as chromosomal abnormalities are among the most important factors for classifying risk in leukemia [60]. Hyperploidy (more than 50 chromosomes in a tumor cell) is evident in approximately 25% of pediatric ALL but is extremely rare in AML [60]. The most frequent numerical abnormalities in AML are trisomy 8 (three copies of chromosome 8) and acquired trisomy 21 [60].

In infant leukemia (both ALL and AML), abnormality of the mixed-lineage leukemia (MLL) gene at 11q23 is found in nearly 80% of cases [34]. Across all pediatric age groups, the most common structural abnormality in ALL, occurring in approximately 20% to 25% of cases of B-cell ALL, is reciprocal translocation of t(12;21)(p13;q22), which results in fusion of the TEL and AML1 genes. However, TEL-AML1 fusion is rare in T-cell ALL [68]. Several other common abnormalities occur frequently in ALL (*Table 7*) [60].

Structural abnormalities are found in approximately 60% of pediatric AML cases and are usually linked to specific subtypes. The most common translocations are t(8;21), which is associated primarily with the M2 subtype, and t(15;17), which is strongly linked to the M3 subtype [60; 69]. Other common abnormalities associated with AML are aberrations of 11q23 and inv(16) [60].

PROGNOSTIC VARIABLES

The use of prognostic variables has been of more value in ALL than in AML. Several factors predictive of outcome have enabled the stratification of ALL into high-risk and standard-risk groups, and treatment is planned according to risk [41]. However, studies have been inconsistent in identifying factors present at or shortly after the time of diagnosis of AML that are predictive of outcome [22; 70; 71; 72; 73; 74; 75]. The greatest prognostic factor is the response to treatment [76].

| COMMON CYTOGENETIC FINDINGS IN LEUKEMIA | |
|---|---|
| Type of Leukemia | Cytogenetic Abnormality |
| Acute lymphoblastic leukemia (ALL) | Hyperploidy t(12;21)(p13;q22) <i>TEL-AML1</i> fusion t(1;19) t(17;19)(q22;p13.3) t(9;22)(q34;q11.2) (Philadelphia chromosome) Aberrations of 12p |
| Acute myelogenous leukemia (AML) | Trisomy 8 Acquired trisomy 21 t(8;21) t(15;17) Aberrations of 11q23 inv(16) |
| Infant leukemia (ALL and AML) | Abnormality of the <i>MLL</i> gene at 11q23 |
| Source: [60; 68; 69] | |

Table 7

Acute Lymphoblastic Leukemia (ALL)

The following factors have been found to have prognostic significance for children with ALL [76; 77]:

- Age at the time of diagnosis
- WBC count at the time of diagnosis
- CNS status at the time of diagnosis
- Subtype of ALL
- Sex
- Race/ethnicity
- Cytogenetic findings

Age at the time of diagnosis is a strong prognostic factor, and the variation in outcome reflects differences in the underlying biology of ALL in different age groups [78; 79]. For example, there is a high percentage of favorable cytogenetic features, such as high hyperdiploidy and t(12;21), in children who are 1 to 9 years of age, and the disease-free survival is better for that age group than for infants and older children and adolescents [80; 81; 82; 83]. In addition, the risk of treatment failure is high for infants with ALL, especially infants younger than 3 months of age [84; 85; 86].

The risk of treatment failure is also high for children with precursor B-cell ALL who have an increased WBC count (more than 50,000/mcL) at the time of diagnosis [77; 83]. In turn, a high WBC count is associated with other high-risk prognostic factors, such as t(4;11) and t(9;22).

The CNS status at the time of diagnosis is described according to results of a nontraumatic diagnostic lumbar puncture, specifically, the number of WBCs and the presence or absence of blasts on cytospin of the CSF sample. CNS3, which is defined as a WBC count of ≥ 5 /mcL and the presence of blasts on cytospin, is associated with a higher risk of treatment failure compared with patients who do not have CNS involvement at the time of diagnosis. CNS2 status (WBC count less than 5/mcL and the presence of blasts) may be associated with a higher risk of relapse, but this risk may depend on treatment [87; 88; 89]. With respect to the sex of the patient, the prognosis has been slightly better for girls than for boys [90; 91; 92; 93]. Although testicular relapse is one reason for this difference, relapse in bone marrow and CNS is also more frequent among boys [90; 91; 92]. Male sex has not been a risk factor in studies in which the event-free survival rate is more than 80% [94; 95]. Studies that have examined sex differential for etiologic clues have identified several sex-specific genetic markers for childhood ALL risk [96; 97; 98; 99].

The role of race/ethnicity as a prognostic variable is unclear. Early studies indicated better survival rates for White children than for Black children, and later studies demonstrated lower survival rates for Black, Hispanic, and American Indian/Alaska Native children compared with White and Asian/Pacific Islander children/adolescents [100]. However, studies done at St. Jude Children's Research Hospital have indicated no racial/ethnic differences in survival, leading researchers to believe that survival depended instead on access to the same treatment protocols [86; 101]. Social, biologic, and pharmacokinetic factors should be explored in an effort to better understand racial/ethnic variations in outcome [102; 103]. Clinical and public health strategies can help improve access to health care, clinical trial enrollment, treatment, and survivorship care for children with ALL [104].

With regard to cytogenetic findings, hyperdiploidy is associated with a highly favorable prognosis and is also associated with other favorable prognostic factors, including an age of 1 to 9 years, a low WBC count, and $t(12;21)$ with the *TEL-AML1* fusion gene [77; 80; 81; 105; 106; 107; 108]. Hypodiploidy has been associated with progressively worse outcomes as the number of chromosomes decreases, with the worst outcome associated with near haploidy (24 to 28 chromosomes) [76; 77; 106]. Extreme hypoploidy and presence of the Philadelphia chromosome has been an indicator of very poor prognosis in B-cell ALL [77; 109].

Chromosome translocations may influence prognosis, but other prognostic factors and the type of treatment may determine the effect of a specific translocation. *TEL-AML1* fusion has been associated with an excellent outcome [68; 81; 110]. In contrast, the Philadelphia chromosome is related to an unfavorable prognosis, especially when it occurs in children who have a high WBC count or in whom the response to initial therapy is slow [60; 111]. The $t(4;11)$ has also been related to a high risk of treatment failure, and the event-free and overall survival rates are lower for children with Down syndrome and ALL [112; 113; 114].

Acute Myeloid Leukemia (AML)

The first prognostic factors identified for AML were age, WBC count, and FAB classification at the time of diagnosis, but their ability to predict outcome has been inconsistent [71; 72]. A report of 61 children treated between 1976 and 1984 indicated that an age of younger than 2 years at the time of diagnosis, a WBC count of less than 100,000/ μL , and an FAB subtype of M4 or M5 were predictive of an increased risk of relapse and a decreased overall survival [72]. Adolescent patients are at higher risk for treatment-related mortality compared with younger children [115].

In another study of nearly 500 patients treated between 1986 and 1989, univariate and multivariate analyses demonstrated several clinical, morphologic, and cytogenetic factors associated with a lower rate of complete remission, including hepatomegaly, low platelet count (20,000/ μL or less), FAB subtype M5, and trisomy 8 [71]. In addition, a higher platelet count (more than 20,000/ μL) and absence of hepatomegaly were independent prognostic factors of better overall survival [71].

Data for a series of nearly 300 patients treated at St. Jude Children's Research Hospital from 1980 to 1996 indicated that the five-year event-free survival was slightly better for an age of 2 years or younger, an initial WBC count of less than 50,000/ μL , and an FAB subtype of M3 or M5 [22]. Although sex has not been used as a prognostic factor, several studies have suggested that the outcome is more favorable for girls than boys [22; 71].

The ability of cytogenetic findings to predict outcome has varied, but they appear to be the best prognostic factors in AML [70; 116; 117]. In one study, trisomy 8 was the strongest predictor of poor prognosis, and in another, abnormalities of 11q23, q3, or chromosomes 5 or 7 were associated with a high rate of treatment failure [82]. In the series of patients treated at St. Jude, the best outcome was associated with $t(9;21)$, and a favorable outcome has also been associated with $t(8;21)$, $t(15;17)$, and $inv(16)$ [22; 70]. Aberrations of chromosome 16q

have also been shown to be a prognostic indicator of complete remission and better overall survival [69; 71]. For children with monosomy 7, AML progresses rapidly and the response to treatment is poor [60; 77]. In contrast to the situation in ALL, children with Down syndrome and AML have a good response to treatment [71; 116]. Advances in technology are allowing researchers to identify other factors associated with outcome, and further studies are needed to confirm the usefulness of these factors as prognostic variables [118].

DIAGNOSIS OF LYMPHOMA

The clinical presentation of lymphoma is similar to that of leukemia in several ways, and the course of diagnostic testing is also similar. However, some signs and symptoms of lymphoma are distinct from those of leukemia. Furthermore, there are differences even between the two types of lymphoma, especially with regard to the sites of disease.

Imaging studies are done not only to determine or confirm the presence of lymphoma but also to assess the extent of disease, which assists in staging as well as in establishing a baseline for monitoring response to treatment. As with leukemia, immunophenotyping and cytogenetic analysis are done to determine the cell lineage of disease, evaluate the pattern of CD antigen expression, and identify chromosomal abnormalities. The role of these studies in the diagnosis of lymphoma is not discussed here, as other factors currently play a more significant role in prognosis.

HODGKIN LYMPHOMA

Clinical Signs and Symptoms

Children and adolescents with Hodgkin lymphoma are often asymptomatic, and the disease is frequently an incidental finding during a routine examination or evaluation of an injury. Approximately 25% to 30% of children will have one of three archetypal constitutional symptoms, known as B symptoms:

unexplained, intermittent fever of 38 degrees Centigrade; drenching night sweats; or unintentional loss of more than 10% of body weight within the past six months (**Table 8**) [119]. The suspicion of Hodgkin lymphoma is increased when B symptoms are present with lymphadenopathy or splenomegaly. Patients may also have nonspecific systemic symptoms, such as fatigue and anorexia. In some patients, generalized pruritus may be present for months before lymphadenopathy is found, and excoriations may be evident as a result of excessive scratching [119]. On physical examination, the most common finding is a persistent, painless adenopathy, usually in the supraclavicular or cervical area [63; 119]. As noted, reactive lymphadenopathy is common in children/adolescents, making it necessary to carefully evaluate patients to first rule out other infectious or inflammatory conditions. Involvement of the supraclavicular nodes should prompt earlier evaluation for Hodgkin lymphoma, as the cervical nodes are most commonly involved in infection and inflammatory conditions. Infectious mononucleosis can be distinguished from Hodgkin lymphoma by the presence of symmetrical cervical lymphadenopathy with pharyngitis. A tuberculin test may be helpful to rule out tuberculosis, which also may have similar clinical characteristics.

Involvement of only lymph nodes and/or the spleen is present in most patients [119]. In general, enlarged lymph nodes are firm and nontender. In advanced disease, enlarged nodes may grow together to form aggregate masses that become attached to underlying tissues [119]. Approximately 15% to 20% of patients will have noncontiguous extranodal involvement, and the lung, liver, bone marrow, and bone are the most common sites of extranodal involvement [123; 124]. Extranodal involvement is more commonly associated with the mixed cellularity subtype of Hodgkin lymphoma, whereas involvement of the cervical, supraclavicular, and mediastinal lymph nodes is most often associated with the nodular sclerosis subtype [119].

| CLINICAL MANIFESTATIONS OF HODGKIN AND NON-HODGKIN LYMPHOMA | | | | |
|---|---|---|--|------------------------------------|
| Clinical Sign/Symptom | Hodgkin Lymphoma | Non-Hodgkin Lymphoma | | |
| | | B-Cell | Lymphoblastic | Anaplastic Large Cell |
| History | | | | |
| Presence of symptoms | Usually asymptomatic | - | - | Wax and wane for weeks |
| B symptoms (unexplained fever, night sweats, weight loss) | Occurs in approximately 28% | Occurs in approximately 50% | - | Occurs in approximately 42% to 68% |
| Other | Pruritus | - | - | - |
| Physical Examination | | | | |
| Lymphadenopathy | Cervical or supraclavicular, painless | Peripheral Relatively uncommon | Cervical or axilla, painless | Peripheral (occurs in 88% to 97%) |
| Most common extranodal site(s) | Lung, liver, bone | Abdomen (Burkitt); neck, mediastinum, throat (DLBCL) | Mediastinum (T cell); head and neck (B cell) | Skin, soft tissue |
| Splenic involvement | 30% to 40% | - | - | 11% to 23% |
| Hepatic involvement | Rare | - | - | 15% to 27% |
| Mediastinal involvement | 66% | - | 75% | 19% to 52% |
| Other | - | - | Pallor, petechiae, ecchymoses | - |
| Abnormal laboratory values | Elevated erythrocyte sedimentation rate | Elevated erythrocyte sedimentation rate and lactate dehydrogenase | - | - |
| DLBCL = Diffuse large B-cell lymphoma. | | | | |
| Source: [119; 120; 121; 122] | | | | |

Table 8

The mediastinum is involved in about two-thirds of patients [119]. Symptoms accompanying mediastinal involvement may include a persistent, nonproductive cough, dyspnea, or chest pain. Evaluation for Hodgkin lymphoma should be carried out if these symptoms are present, especially if accompanied by B symptoms. It is important to distinguish involvement of the mediastinum from a large, normal thymus or from other mediastinal tumors [27; 119]. Morphology, clinical signs, radiographic findings, and immunophenotyping findings must all be evaluated closely to make the distinction.

Non-Hodgkin lymphoma should be considered in the differential diagnosis of Hodgkin lymphoma. One distinguishing feature is the rate of disease progression; involved lymph nodes will grow more rapidly in non-Hodgkin lymphoma than in Hodgkin lymphoma. In addition, abnormal laboratory values are more common with non-Hodgkin lymphoma [119].

Diagnostic Testing

The diagnostic work-up for suspected Hodgkin lymphoma includes laboratory testing and imaging studies to evaluate the site and extent of disease. Laboratory testing should begin with a CBC with differential and an erythrocyte sedimentation rate.

The results of the CBC may be nonspecific, demonstrating neutrophilia, eosinophilia, and thrombocytosis [27; 119]. Lymphopenia and normochromic normocytic anemia are indicators of extensive disease [125; 126]. In the presence of other signs of Hodgkin lymphoma, elevations of the erythrocyte sedimentation rate, lactate dehydrogenase level, and ferritin level may be further indicators of Hodgkin lymphoma [63]. An elevated level of alkaline phosphatase may indicate metastatic bone disease, and further testing should be done to determine if there is skeletal involvement [119].

Evaluation of a bone marrow sample is usually not routinely done. Bone marrow involvement is a characteristic of primarily lymphocyte-depleted Hodgkin lymphoma, which is rare in the pediatric population; approximately 10% to 15% of children/adolescents will have bone marrow involvement at the time of the initial diagnosis [27]. The frequency of bone marrow involvement is higher for older male children who have constitutional symptoms. Bone marrow biopsy should be limited to patients who have B symptoms and in whom advanced disease is suspected [119].

A diagnosis of Hodgkin lymphoma can be confirmed only through evaluation of a specimen from an involved lymph node, and biopsy should be done when there is no response to a course of antibiotics. The biopsy technique depends on the site of the involved node. Excisional biopsy is often the preferred technique, as it allows for better determination of the histologic subtype [119]. However, the least invasive procedure should be used [127; 128]. Thus, fine-needle aspiration may be more appropriate if the involved node is in the thoracic or abdominal cavity, and CT can be used to guide biopsy in these situations.

Classification and Staging

As noted, Hodgkin lymphoma is classified histologically according to four subtypes. Nodular sclerosis is the most common subtype, representing approximately 72% of the cases of pediatric Hodgkin lymphoma. This subtype occurs most frequently in adolescents, and the mediastinum is involved in

80% of cases [27]. Mixed cellularity Hodgkin lymphoma accounts for approximately 25% of pediatric Hodgkin lymphoma, most frequently developing in children younger than 10 years of age [27]. It is usually associated with the peripheral lymph nodes of the upper part of the body.

The American Joint Committee on Cancer has adopted the Lugano classification system to evaluate and stage lymphoma. The Lugano system replaces the Ann Arbor classification system (which was adopted in 1971). The Lugano system categorizes the disease as stage I through IV according to the extent of lymph node involvement (**Table 9**) [129]. The system is based on the premise that Hodgkin lymphoma progresses along contiguous lymph nodes [130]. Within this classification system there are additional designations that are applied to further define symptoms and disease [130].

Prognostic Variables

Prognostic variables have less importance in Hodgkin lymphoma because of advances in treatment, but some variables are helpful in predicting outcome. The most significant prognostic indicator is stage of disease. The outcome associated with stage I, II, or III disease is better than that for stage IV disease [47; 123; 131]. Studies in which prognostic factors were evaluated in multivariate analysis have demonstrated the following factors to be of import [131; 132]:

- Presence of B symptoms
- Mediastinal disease bulk
- Results of laboratory studies



According to the National Comprehensive Cancer Network, there is no uniform risk stratification for pediatric Hodgkin lymphoma. However, several factors are considered to confer poor prognosis, including B symptoms, extranodal disease, Ann Arbor stage, gender, and response to initial chemotherapy.

(https://www.nccn.org/professionals/physician_gls/pdf/ped_hodgkin.pdf. Last accessed August 22, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

| LUGANO SYSTEM FOR STAGING OF HODGKIN LYMPHOMA | |
|---|---|
| Stage | Criteria |
| I (limited stage) | Involvement of a single lymph node region or single extranodal site |
| II (limited stage) | Involvement of two or more lymph node regions (number to be stated) on the same side of the diaphragm, and may include limited contiguous extranodal involvement |
| III (advanced stage) | Involvement of lymph node regions in the spleen or on both sides of the diaphragm |
| IV (advanced stage) | Noncontiguous involvement of one or more extralymphatic organs or tissues with or without associated lymph node involvement |
| Subclassifications | |
| A | Asymptomatic |
| B | Displaying specific symptoms of unexplained loss of more than 10% of body weight in the six months before diagnosis, unexplained fever with temperatures greater than 38 degrees Centigrade for more than three days, or drenching night sweats |
| E | Single extranodal site involvement in stage I or limited contiguous extranodal involvement in stage II. Involvement of noncontiguous extranodal sites is considered stage IV. |
| Source: [129] | |

Table 9

The presence of B symptoms (low-grade fever, night sweats, and weight loss) reflects aggressive disease and has been associated with a worse prognosis [131; 132; 133]. High tumor burden is also predictive of a worse prognosis; a ratio of mediastinal mass-to-thoracic cavity of more than one-third has been associated with a greater risk of recurrence and with a slightly lower survival rate in several studies [131; 133; 134]. The number of disease sites may also play a role in predicting outcome. Patients who have fewer than four sites of involvement generally have a better outcome [129; 135].

Several laboratory studies, including the WBC count, hemoglobin, erythrocyte sedimentation rate, and serum ferritin level, have also been correlated with a poor prognosis [129; 131; 136]. In one study, a WBC of more than 13,500/mcL and a hemoglobin level of less than 11.0 g/dL were significantly associated with shorter disease-free survival [131].

The predictive value of patient-related factors such as sex and age is unclear. One study indicated that disease-free survival was better for girls than for boys [131]. Age has been an important indicator in some

studies, with 5-year and 10-year survival rates being higher for children 10 years of age or younger than for older children and adolescents (11 to 16 years of age) or young adults [137].

The rate of response to initial cycles of chemotherapy appears to be prognostically important and is being used in the research setting to tailor subsequent therapy, avoid treatment-associated risks that compromise long-term health, and achieve high cure rates [47; 138].

NON-HODGKIN LYMPHOMA

Clinical Signs and Symptoms

The clinical evaluation and diagnostic testing for non-Hodgkin lymphoma is similar to that for Hodgkin lymphoma. Lymphadenopathy should be evaluated, and infectious or inflammatory conditions should be ruled out before a biopsy is performed. The sites of disease and associated symptoms vary according to the histopathologic type of non-Hodgkin lymphoma [120; 121; 122]. Most children/adolescents will have advanced disease at the time of presentation [17; 121].

B-Cell Lymphoma (Burkitt, Burkitt-like, and Diffuse Large B-Cell)

Diffuse large B-cell lymphoma and Burkitt or Burkitt-like lymphoma may appear clinically similar, but the former is more often localized [139; 140]. The most common site of B-cell lymphoma is the abdomen, and involvement of peripheral lymph nodes is relatively uncommon [17; 120]. When present, peripheral lymph node involvement is more likely to be associated with diffuse large B-cell lymphoma, with sites in the neck, mediastinum, or throat [120]. Symptoms associated with B-cell lymphoma in the abdomen include abdominal pain, nausea, vomiting, and diarrhea. A mass may be palpable on physical examination of the abdomen [63; 120]. Persistent abdominal pain with vomiting or diarrhea, especially when accompanied by significant weight loss, should prompt further diagnostic testing. Intussusception of the small bowel is common.

Lymphoblastic Lymphoma

In comparison with B-cell lymphoma, the abdomen is rarely involved with lymphoblastic non-Hodgkin lymphoma. Instead, the mediastinum is involved in nearly 75% of children/adolescents with T-cell lymphoblastic lymphoma, as a result of development of the lymphoma from the thymus [17]. The mass forms in the anterior mediastinum. Dyspnea is often the first symptom [121]. Coughing, wheezing, stridor, dysphagia, and superior vena cava syndrome may also be presenting symptoms. Because mediastinal involvement with non-Hodgkin lymphoma progresses more rapidly than with Hodgkin lymphoma, these symptoms may be more severe. Pleural effusion may also occur [17]. Localized lymphoblastic lymphoma may occur in lymph nodes, bone, and subcutaneous tissue. Other lymph nodes, such as the tonsils or neck nodes, are less commonly the primary site of T-cell lymphoblastic lymphoma. Disease spread can be rapid, with the brain, pleura, pericardium, and bone marrow being the most common sites of metastases. Disease is in an advanced stage (stage III or IV) at the time of diagnosis in most cases [121].

In the case of precursor B-cell lymphoblastic lymphoma, disease is usually more limited and involves skin, soft tissue, bone, tonsil, or a sole peripheral nodal region [121].

Anaplastic Large-Cell Lymphoma

The course of symptoms with anaplastic large-cell lymphoma may be indolent, with fever and a waxing and waning of lymphadenopathy [141; 142]. Nearly 50% of patients have B symptoms, and 88% to 97% of patients have lymphadenopathy, with the peripheral nodes being involved most often. CNS and bone marrow involvement occur less frequently with anaplastic large-cell lymphoma than with other types of non-Hodgkin lymphoma [17; 122; 142].

Soft tissue and skin are the most frequent sites of extranodal involvement [17; 122; 142; 143; 144]. Cutaneous manifestations may be single or multiple nodules, multiple or disseminated red-yellow papillomatous lesions, or large ulcerated lesions [122]. Other extranodal sites include the gastrointestinal tract, lung, pleura, and muscle.

Diagnostic Testing

As with Hodgkin lymphoma, the diagnostic work-up for suspected non-Hodgkin lymphoma includes laboratory testing, diagnostic imaging, and biopsy of suspicious nodes. A CBC can help distinguish non-Hodgkin lymphoma from infectious or inflammatory adenopathy [121]. A high level of serum lactate dehydrogenase level is often indicative of a large mass, but the level is increased less often in patients with anaplastic large-cell lymphoma than in patients with B-cell lymphoma or lymphoblastic lymphoma [122]. A CSF sample should be examined, and evaluation of biopsy specimens should include histopathologic analysis, immunophenotyping, and cytogenetic and molecular analysis [120; 121; 122; 142].

The use of imaging studies is similar for all types of suspected lymphoma. The choice of study is based on the suspected site of involvement. A chest x-ray or CT of the chest is indicated if a mediastinal mass is suspected, which is often associated with T-cell lymphoblastic lymphoma or diffuse large B-cell lymphoma [120]. MRI of the head and neck should be done if signs or symptoms are suggestive of involvement of neck nodes. The abdomen is the most frequent site of involvement for B-cell lymphoma, making CT of the abdomen perhaps the most valuable imaging study in that setting. CT also is useful for staging the lymphoma and for differentiating the primary cutaneous form from the systemic form [120; 145]. Skeletal scintigraphy is useful for detecting bone involvement, such as with anaplastic large-cell lymphoma [142]. Positron emission tomography (PET)/CT scanning has largely supplanted scintigraphy and is highly recommended for patients with suspected non-Hodgkin lymphoma [146; 147; 148]. PET/CT scanning is also useful for assessing response to treatment and for identifying occult sites of disease. Whole-body scanning may be helpful in detecting disease sites that would otherwise be unidentified [120; 145]. If advanced disease is suspected, MRI or CT of the brain should be done [145].

Classification and Staging

Pediatric non-Hodgkin lymphoma is classified as stage I through IV according to the St. Jude staging system, which is similar to the Ann Arbor staging system for Hodgkin lymphoma [149; 150]. These stages are [17; 149; 150]:

- Stage I: Involvement of a single node or single tumor outside of the abdomen or chest
- Stage II: Single extranodal tumor with involvement of regional lymph nodes
 - Involvement of two nodal regions or more on the same side of the diaphragm
- Two single extranodal tumors, with or without involvement of regional lymph nodes, on the same side of the diaphragm
- Primary tumor (completely resectable) in the gastrointestinal tract, with or without involvement of associated mesenteric lymph nodes
- Stage III: Two single extranodal tumors on opposite sides of the diaphragm
 - Involvement of two or more nodal regions above and below the diaphragm
 - Primary intrathoracic tumor (mediastinal, pleural, or thymic)
 - Extensive primary intra-abdominal disease
 - Paraspinal or epidural tumor, with or without involvement of other sites
- Stage IV: Any finding of stage I, II, or III disease with initial involvement of the CNS, bone marrow, or both

Prognostic Variables

As with Hodgkin lymphoma, advances in treatment for non-Hodgkin lymphoma have made prognostic variables less significant [120]. In addition, factors predictive of outcome vary according to the histologic subtype of non-Hodgkin lymphoma.

For B-cell lymphomas, the most important prognostic factor is tumor burden, as determined by either stage of disease or the serum lactate dehydrogenase level [120]. The tumor burden is high for patients with extensive bone marrow involvement (more than 25%) [120]. Serum lactate dehydrogenase level is a well-recognized risk factor that correlates with tumor burden, and a level of more than 1,000 IU/L has been associated with a poor prognosis [52; 151; 152].

Age and sex have also been evaluated as prognostic factors in B-cell lymphoma; many studies have not found them to be predictive of outcome [120]. In one study involving children/adolescents with diffuse large B-cell lymphoma, the event-free survival was significantly better for male patients than for

female patients and the outcome was better for younger girls than for adolescent girls [139]. Again, the universal applicability of these findings is not established.

In an analysis of pooled data from three multicenter studies of prognostic variables in anaplastic large-cell lymphoma, multivariate analysis demonstrated that the following factors were significantly associated with a risk for treatment failure [120; 144; 152; 153; 154; 155]:

- Presence of a mediastinal mass
- Involvement of the lung
- Focal lesions of the liver or spleen (and/or hepatomegaly or splenomegaly)
- Skin involvement

There was no significant effect of age, sex, or stage of disease in any of the studies [17].

In a comprehensive analysis of potential prognostic factors for outcome in lymphoblastic lymphoma, no factor was found to be associated with outcome [156].

COMMUNICATION WITH THE PATIENT AND FAMILY

The primary care provider is often in the position to tell parents that the clinical findings and initial testing may indicate a diagnosis of leukemia or lymphoma. Primary care practitioners who have established a relationship with their patients and families are the healthcare professionals most likely to understand the overall health status of the family, family dynamics, and cultural context of the family. They should draw on all of this information to help present the diagnosis in a way that the family can understand. Further diagnostic testing in a pediatric cancer center will help to refine the diagnosis by identifying a specific type of leukemia or lymphoma, and prognosis and treatment options will then be discussed by oncology specialists. Primary care providers should have familiarity with key aspects of the diseases, as they may become a resource for the

family during the child's/adolescent's treatment in a pediatric cancer care center. Primary care providers must be able to communicate effectively with parents as well as the child/adolescent with leukemia or lymphoma. Effective communication requires basic physician communication skills as well as specialized skills in delivering bad news.

COMMUNICATING EFFECTIVELY

Effective communication is a cornerstone of the family-physician relationship. Some physician communication behaviors that have been found to be positively associated with health outcomes include empathy, reassurance and support, explanations, positive reinforcement, humor, discussion of psychosocial issues, health education and information sharing, courtesy, and summarization and clarification [157]. Other factors essential for effective communication and a successful relationship are knowledge of the language preference of the patient and family; an understanding of and respect for the family's cultural values, beliefs, and practices (referred to as cultural and linguistic competency); and an awareness of the family's health literacy level [158; 159; 160].

Language, cultural competency, and health literacy are significant issues, given the growing percentages of racial/ethnic populations. According to U.S. Census Bureau data from 2022, approximately 69.2 million Americans (22% of the population) speak a language other than English in the home, with more than 16.7 million of them (5.3% of the population) reporting that they speak English less than "very well" [161]. Clinicians should ask their patients' parents what language they prefer for their medical care information, as some individuals prefer their native language even though they have said they can understand and discuss such information in English [162]. An example of the effect of limited English proficiency is a study of children/adolescents hospitalized for infections, in which a primary caregiver with limited English proficiency was found to be an important independent risk factor for both a longer hospital stay and fewer home health care referrals [163].

The national standards on Culturally and Linguistically Appropriate Services (CLAS) include four standards related to communication and language access services that are mandated for healthcare organizations [164]. Although these standards are not mandated for individual health care providers, the Office of Minority Health encourages clinicians to meet the standards to make their practices more culturally and linguistically accessible [164]. These standards are:

- Offering and providing language assistance services, including bilingual staff and interpreter services, at no cost to each patient/consumer with limited English proficiency at all points of contact, in a timely manner during all hours of operation
- Providing patients with both verbal offers and written notices (in their preferred language) that inform them of their right to receive language assistance services
- Ensuring the competence of language assistance provided to limited English proficient patients by interpreters and bilingual staff and avoiding the use of the patient's family and friends as interpreters
- Making easily-understood patient-related materials available and posting signage in the languages of the commonly encountered groups and/or groups represented in the practice area

Studies have demonstrated that the use of professional interpreters rather than “ad hoc” interpreters (family members, bilingual staff, etc.) leads to better outcomes [165; 166; 167]. In addition, individuals with limited English language skills have indicated a preference for professional interpreters rather than family members [168]. Despite this clear benefit and preference, a survey of more than 900 pediatricians showed that professional interpreters were the third most commonly used resource; bilingual family members were used most often [169]. According to one study, this practice has only modestly improved since 2004 [170]. Professional interpreters have recommended that clinicians can further enhance the

quality of care by meeting with interpreters before discussions of bad news and by explicitly discussing with the interpreter whether strict interpretation or cultural brokering is expected [171].

Knowledge of the family's health literacy is important for achieving treatment goals and good outcomes, yet most individuals lack adequate health literacy. According to the 2003 National Assessment of Health Literacy, 14% of individuals in the United States have “below basic” health literacy, which means they lack the ability to understand health information and make informed health decisions [172]. According to the Center for Health Care Strategies, nearly 9 of 10 adults enrolled in Medicaid in the United States struggle with health literacy [173]. A systematic review of more than 300 studies showed that an estimated 26% of patients had inadequate literacy and an additional 20% had marginal literacy [174]. Health literacy varies widely, according to race/ethnicity, level of education, and gender, and clinicians are often unaware of the literacy level of their patients and family [160; 175]. Predictors of limited health literacy are poor self-rated reading ability, low level of education, male sex, and non-White race [175; 176].

Several instruments are available to test the literacy level, and they vary in the amount of time needed to administer and reliability in identifying low literacy. A review demonstrated that the two most accurate tools for identifying literacy are the Rapid Estimate of Adult Literacy in Medicine (REALM) and the shortened version of the Test of Functional Health Literacy in Adults (S-TOFHLA) [160; 173]. REALM takes 3 minutes to administer, whereas S-TOFHLA takes 7 to 12 minutes to administer [160; 173]. More rapid testing is available since the development of the Newest Vital Sign (NVS), an instrument named to promote the assessment of health literacy as part of the overall routine patient evaluation [173]. The NVS takes fewer than three minutes to administer, has correlated well with more extensive literacy tests, and has performed moderately well at identifying limited literacy [160; 175]. Two questions have also been found to perform moderately well in identify-

KEY TALKING POINTS TO ASSESS CULTURAL INFORMATION

- What behaviors and symptoms of the child are of most concern to the parents?
- Why do the parents believe cancer occurred in the child?
- How do the parents believe the child is affected by the cancer?
- What are the family's beliefs and fears about cancer?
- What measures did the parents take to control the symptoms before diagnosis?
- What do the parents expect of the medical team?
- What are the expected roles of various family members in the healthcare setting?
- What are the family's dietary practices?
- What are the religious beliefs and/or affiliations and significant religious persons in the family's lives?

Source: [178]

Table 10

ing patients with inadequate or marginal literacy: “How confident are you in filling out medical forms by yourself?” and “How often do you have someone help you read health information?” [160].

Clinicians should adapt their discussions and educational resources to a family's identified health literacy level and degree of language proficiency. The use of plain language (free of medical jargon), asking parents to repeat pertinent information, regularly assessing recall and comprehension, providing educational resources in a variety of formats (e.g., print, oral, web-based, video), and using culturally appropriate and translated educational materials, can all help ensure that parents better understand the diagnosis and other aspects of their child's disease and its management, ultimately leading to higher quality care.

Cultural competency is essential for addressing healthcare disparities among minority groups, in whom limited health literacy is prevalent [158; 173]. The AAP Task Force on the Family noted that “nonjudgmental, culturally sensitive, family-oriented care” should be provided by all pediatricians [177]. The task force further noted that providing such care requires that the “family's history, interactions, and preferred solutions are considered, used, and supported” [177]. To that end, primary care providers should assess the family's beliefs and values associated with illness and health care (*Table 10*).

The status of children within the family and community differs among cultures and is a factor in how parents and other family members will respond to a child's illness [179]. Respect for cultural health beliefs and practices is important for many patients from non-Western cultures, and clinicians should be sensitive to culturally defined beliefs about health care [168]. These beliefs may underlie the degree or quality of the parents' involvement in the child's care or noncompliance with treatment or recommendations [179].

Another factor that varies across cultures is the role of decision-makers; an understanding of the family dynamics with respect to decision making is essential [180]. In most cases of children/adolescents with cancer, the parents will be the primary decision-makers. There are three options for decision making: clinician-centered (the clinician makes the decision), informed (the patient/family makes the decision after becoming informed by the clinician and through other sources), and shared (the clinician and patient/family collaborate in the process). Parents differ in their preferences regarding the level of involvement [181; 182; 183]. The physician should explore the issue of decision making with parents to ensure that their preferred level of involvement is attained.

GUIDELINES FOR BREAKING BAD NEWS

- Formulate a plan. Mentally rehearse the steps of the conversation.
- Schedule a time for the discussion to allow all important family members and medical staff to be present.
- Meet in a quiet and private setting.
- Make arrangements for a professional translator if English is not the first language of the family. Meet with the professional translator before the discussion to discuss expectations.
- Preface bad news with a phrase to prepare the family, such as “I wish the results were different, but...”
- Communicate clearly and minimize use of technical language.
- Let the patient’s and family’s reactions guide the flow of the conversation. Allow silence.
- Be empathetic and acknowledge the family’s emotions.
- Explain to parents who are worried about the child hearing bad news that age-appropriate, open communication with children allows the practitioner and family to provide the child with comfort and reassurance while removing uncertainty.
- Determine the family’s level of understanding of the illness/situation to assess misconceptions, aspects of news that will be surprising, and their unique information needs.
- Determine if any family members are “numbers people” so they can be provided the type of information with which they feel most comfortable.
- Make parents feel that they are part of the team to help their child and that their efforts will help the medical team take care of their child.
- Explain to patient and family that they are not to blame for the child’s cancer.
- Schedule a future meeting to discuss the bad news and options (e.g., in an hour, the next day, the next week).

Source: [184; 185; 186]

Table 11

One study has underscored the need to engage in the preferred decision-making process; the study found that parents’ unhappiness with the decision-making process was correlated with optimism about cure [184]. In the study, 61% of parents were more optimistic than their child’s physician about the likelihood of cure. Parents who were unhappy with the decision-making process were more apt to be overly optimistic [184]. Studies have also shown that satisfaction with treatment choices is increased when communication in the diagnosis phase has been effective [181].

Delivering Bad News

A cancer diagnosis presents the dual challenge of being both emotionally and intellectually overwhelming. These feelings are heightened for parents of a child/adolescent with cancer. Parents differ in how much information they want or feel they can handle about the diagnosis. Clinicians should ask how much detail the parents wish to hear [181].

Important points for communicating the diagnosis include:

- Use clear, jargon-free language.
- Check often for understanding.
- Offer reassurance and support.
- Encourage questions.

Clinicians should address parents’ and patients’ fears and reassure them that they will be available throughout the course of treatment [181]. Eliciting and validating emotional reactions at this time will help parents and patients better understand and comply with further diagnostic testing [181].

Guidelines are available to help clinicians deliver bad news in the childhood cancer setting with sensitivity (*Table 11*) [184; 185; 186]. However, the stress of receiving bad news, even if the clinician is compassionate and speaks clearly, can prevent patients and family members from retaining needed information [185]. After relating bad news, clinicians can build

a partnership by allowing parents to express their feelings and opinions [187]. A pediatric psychologist or family therapist can assist both the child and family in coping with the impact of the diagnosis.

Clinicians should also determine parents' preference for the type and amount of information to be shared with the child. Many parents wish to protect their child by withholding information. This is especially true among some cultures—for example, among Chinese, Japanese, and Greek populations [188]. However, studies have shown that children often recognize the seriousness of their illness and prefer open communication about their disease and prognosis [188; 189; 190]. Such open exchange of information can help to avoid the fear of the unknown and to preserve the child's trust in his or her parents and/or family and caregivers [188; 190]. Even if the child is to be included in the discussion, the best approach may be to sequence some information; that is, to communicate information to parents in separate meetings before communicating it to the child. Parents of children with leukemia have acknowledged the benefits of communicating openly with children, but they noted that their child's presence during discussions of such topics as prognosis, treatment options, and adverse events, restricted their own communication with physicians, made it difficult to concentrate, and interfered with their efforts to care for their child emotionally [191]. Parents also said that separate meetings allowed them to absorb information and to convey it to their child at an appropriate time and in a reassuring way [191].

Parents and clinicians should involve the child in the discussion of the diagnosis using language that is developmentally appropriate for the child, checking often to make sure the child understands. Having the child repeat the information in his or her own words is one way to assess comprehension [188]. The child should also be encouraged to express feelings and concerns. Adolescents and children who are mature enough to understand and reason should be allowed to express their opinions, and

healthcare professionals should be advocates for the child's preferences and decisions [183]. Adolescents especially, because of their need for independence, should be given choices about their care, whenever possible, as well as about privacy issues, such as with whom information can be shared [8].

Clinicians should explore ways to best communicate with and educate children/adolescents. Computer-assisted and multimedia educational programs have been shown to enhance cancer-related knowledge among children/adolescents and improve their feelings of control over their health [192].

TREATMENT APPROACHES

The goals for treatment of pediatric leukemia and lymphoma have evolved dramatically since the early 1960s, when palliative care was considered to be the rational approach to treatment of leukemia and extensive radiation therapy was used for lymphoma. The search for better curative therapies that do not yield long-term side effects has led to a variety of approaches based on prognostic factors, as well as independent host-related or disease-related factors.

The treatment protocols for pediatric leukemia and lymphoma have been developed and refined by several cooperative groups in the United States and Europe, the most notable of which are COG, the National Cancer Institute, St. Jude Children's Research Hospital, Dana-Farber Cancer Institute Consortium, Medical Research Council Working Party on Childhood Leukemia, European Organisation for Research and Treatment of Cancer—Children's Leukaemia Cooperative Study Group, the French Society for Pediatric Oncology, and the Berlin-Frankfurt-Munster Cooperative Groups. The investigators in these groups are at the forefront of evaluating chemotherapy and radiation doses and combinations to achieve the overall goal of maximizing the potential for cure while minimizing treatment-related toxicity.

The treatment of pediatric leukemia and lymphoma is a complex process that requires the expertise of several pediatric subspecialists, including hematologists/oncologists, diagnostic radiologists, pathologists, radiation oncologists, and surgeons, as well as pediatric nurses, social workers, and other allied healthcare professionals experienced in the care of children with cancer. Superior results have been achieved when treatment is provided at pediatric cancer centers with specialized multidisciplinary teams. Due to these superior results, the AAP developed guidelines recommending that all children and adolescents with cancer be referred to a pediatric cancer center for treatment [61; 62]. The AAP notes that, in many cases, all aspects of care should be given at the center but acknowledges that “after diagnosis has been established and the treatment plan has been determined by the pediatric cancer center, certain aspects of care that are not investigational may be continued in the office of a primary care pediatrician for selected children when mandated by distance from the cancer center or other individual specific circumstances” [193].

Over the years, the treatment of adolescents with leukemia or lymphoma has been the topic of some debate because of the decreased event-free and overall survival among adolescents compared with children [194]. Some adolescents have been treated according to adult protocols, while others have been treated according to pediatric protocols. Almost all retrospective studies comparing outcomes for adult and pediatric protocols have shown a significant benefit to pediatric protocols [74; 133; 194]. These differences are thought to be related to the substantial differences between adult and pediatric protocols [194].

IMPORTANCE OF CLINICAL TRIALS

Retrospective reviews of data from pediatric cancer clinical trials have demonstrated that the treatment protocols in clinical trials offer a significant survival benefit compared with other treatment approaches [195; 196]. Virtually all children with leukemia or lymphoma are eligible for treatment in a clinical trial, yet 40% to 60% do not participate [195; 197].

This rate of nonparticipation is even higher outside pediatric cancer centers. In one study of more than 5,000 children/adolescents (birth to 21 years of age), the rate of clinical trial participation was 25% for institutions other than pediatric cancer centers [195]. Participation of children/adolescents in clinical trials, both within and outside of pediatric cancer centers, is higher for leukemia than for lymphoma and for younger children (birth to 5 years) than for older children [195]. The rate of participation among adolescents is substantially lower, ranging from 10% to 15%, and this low rate is of special concern [194]. The paucity of adolescents treated in clinical trials is itself the result of several elements of the healthcare landscape in the United States. On the local level, these factors include referral patterns and facilities available; on the national level, related factors include the number of clinical trials available for this age group and healthcare provider education in the care of these patients [198].

One systematic review sought to identify the perceptions and attitudes toward clinical trial participation among adolescents and young adults (15 to 39 years of age) [199]. Major themes identified for acceptability of clinical trials included hope for positive clinical affect, altruism, and having autonomy, while potential deterrents included prolonged hospitalization, worry about side effects, and discomfort with experimentation [199]. The findings of one qualitative study suggest that caregivers and providers have work to do in overcoming factors that limit patients' involvement in clinical trial enrollment decision-making [200]. Data from a retrospective study suggest that establishing a joint pediatric/adult oncology program can improve adolescent/young adult enrollment in clinical trials. Fifty-seven patients were referred to an oncology program from 2006 to 2010. Eight were referred for consultation only and not treated. Five of 22 patients (23%) who received treatment at the pediatric cancer center were enrolled onto a clinical trial; 9 of 27 patients (33%) who received treatment at the adult cancer center were enrolled, an increase from the previous three years [201].

Clearly, more children/adolescents should participate in clinical trials to provide the maximum opportunity for cure and long-term survival. Health-care professionals should encourage parents to seek care at a pediatric cancer center and to ask about clinical trials if the issue is not raised. This is particularly important for older children and adolescents [202]. Assent for clinical trial participation in the pediatric setting differs from its counterpart in the adult setting (informed consent) in many ways and is a complicated issue. The obvious and primary difference between the two settings is the patient's capacity for decision making. It is generally believed that children/adolescents should be involved in the discussion and decision making about medical treatment (including participation in a clinical trial) if the discussion is developmentally appropriate [188; 203; 204]. Various ages have been suggested as the threshold for sufficient capacity to reason and understand a discussion about a clinical trial and make a decision to participate. The National Commission for Protection of Human Subjects of Biomedical and Behavioral Research, the California legislature, and the AAP have set the threshold for participating in the assent discussion at 7 years of age [203; 204]. However, others have argued that a child at this age cannot understand all aspects of a research trial, and the ages of 9 years, 11 years, and 14 years have all been suggested as thresholds [204; 205; 206]. The age range of 9 to 14 years has been noted as the "transition period," or the ages at which there is the most variability in the capacities of individual children [204]. Studies involving focus groups of healthy adolescents have shown that research concepts such as placebo and randomization are difficult to understand even for teenagers [207]. Clearly, age is but one of several factors that should be considered when determining the appropriateness of engaging a child in the decision-making process; other factors include level of maturity, physiologic and psychological state, and the child's reasons for his or her preferences [206; 208].

In a study of assent discussions involving children/adolescents with leukemia and their parents, the fewest number of clinicians considered the patient alone to be the primary decision-maker [209]. Most clinicians noted that the parents were the primary decision-makers; others indicated that it was a "family" decision to be made jointly between parents and the patient [209]. According to guidelines established by COG, the clinician and parents should seek the child's perspective in a "developmentally, contextually, and culturally sensitive fashion," and the clinician should encourage the parents and patient to make the decision jointly as a family unit [204]. Furthermore, clinicians should advocate for the child if the parents disregard the child's preferences and should ask to speak to the child alone if they think the child is not expressing his or her true perspective in the presence of the parents [204].

Another factor in the issue of clinical trial assent is the high levels of emotion, stress, and anxiety associated with a diagnosis of cancer in a child. These psychosocial factors have been shown to have an effect on comprehension, which, in turn, influences the ability to make a decision [197]. The complexity of treatment options for pediatric cancer and the swiftness with which most decisions must be made also add to the challenge of decision making about clinical trials. Because of these factors, effective clinician-parent communication is essential [181]. In many cases, the intervention of a psychologist or therapist may also be helpful. A study showed that race and socioeconomic status were associated with less information-sharing and partnership-building cues from clinicians and with less participation in the assent discussion by parents [197].

The importance of respect in obtaining assent has been emphasized. Respectful assent involves providing sufficient information about the trial and encouraging the patient and family to ask questions and express concerns [204; 206]. Respectful assent also involves responding to dissent [204; 206]. The child's participation in a trial should be monitored, and persistent expressions of distress about continued participation should be addressed [204].

In a study to gain the perspective of parents about clinical trial decision making, parents offered several suggestions to improve the process. The most common suggestion was to give parents more time to decide [210]. Parents also suggested that clinicians should [210]:

- Provide more information and repeat it for understanding
- Offer other resources, such as videos and books
- Communicate honestly and with empathy
- Arrange for parents to speak with other parents who have been through the clinical trial decision-making process

Parents who were not native English speakers noted the importance of having a professional interpreter available during the process [210].

Discussion of the trial should be comprehensive and address all facets of treatment, including side effects, long-term effects, and survival expectancy (**Table 12**). A focus on providing information in the context of informed consent may come at the expense of other communication exchanges that are important to patients, especially in the context of end-of-life decisions [211]. Many parents wish to avoid these topics in an effort to protect their children, but research has shown that children tend to pose these questions themselves and that they benefit from the assent process [188; 209; 211].

Parents have also noted a need for clearer explanations of the randomization process and of the difference between the clinical trial treatment and standard treatment [212]. Specifically, parents have noted a need to better understand that a clinical trial involves several possible treatment options, one of which is the treatment their child would receive outside of the clinical trial [212]. One analysis identified suggestions for improving the informed consent process by interviewing 57 parents and 20 young adult patients (14 to 21 years of age). A total of 21 suggestions for improvement emerged in three main themes: provision of more information; structure and presentation of the informed consent process;

| KEY ELEMENTS TO BE DISCUSSED ABOUT PARTICIPATING IN A CLINICAL TRIAL | |
|---|-----------------|
| <ul style="list-style-type: none"> • Goals of the trial and treatment • Rationale for treatment • Prognosis (survival and cure) • Importance of the child’s best interests • Randomization procedure • Procedures necessary for the research • Anticipated risks and benefits of both experimental and standard treatments • Inconveniences associated with the trial • Alternative procedures or treatments • Voluntariness • Confidentiality | <i>Table 12</i> |
| <i>Source: [210; 212]</i> | |

and suggestions for physicians conducting the process. Common suggestions included providing more specific information about the trial, allowing more time for decision making, and using different methods to deliver information [213]. Multimedia approaches to describe research procedures have been shown to enhance overall understanding of both parents and children/adolescents [214].

Although signed assent is not usually required legally, clinicians should document the assent process, including whether the child was invited to participate in the discussion and, if so, the role he or she played in the decision-making process [204].

DISEASE-DIRECTED TREATMENT

As mentioned, treatment regimens for leukemia and lymphoma continue to be refined as the findings of long-term studies demonstrate late effects. For example, high rates of neurocognitive disorders and other effects have been associated with radiation exposure resulting from prophylactic cranial radiation therapy in children with leukemia or radiation to the thorax or head and neck area in children with lymphoma. This has led to the reduction of radiation doses in treatment protocols and/or the use of radiation only for high-risk patients [215; 216].

Another well-recognized late effect, anthracycline-related cardiac toxicity, has led to the use of lower doses of anthracycline as well as the use of cardioprotectants (dexrazoxane or enalapril) during anthracycline treatment [217; 218; 219]. The effects of cardioprotectants require the results of long-term studies, which will not be available for several years.

A detailed discussion of the various protocols that have become standard for the treatment of leukemia and lymphoma is beyond the scope of this course. An overview of the goals and approaches to treatment and the chemotherapy agents used is provided here (*Table 13*).

TREATMENT OF LEUKEMIAS

The treatment of leukemia varies according to the type and is risk-adapted. This approach prevents overtreatment of children at low risk for relapse and provides sufficient cytotoxicity for children at high risk for relapse or treatment failure. Investigators continue to explore both different doses of chemotherapy agents, timing and intensity, and different drug combinations to achieve better rates of remission, disease-free survival, and overall survival for children/adolescents with ALL and AML.

With one exception, all types of ALL are treated with an approach that includes the following phases [220]:

- Remission induction therapy (at the time of diagnosis)
- Postinduction therapy (after achieving complete remission), including:
 - Consolidation/intensification therapy
 - Continuation (maintenance) therapy
 - CNS prophylaxis

The exception to this approach is B-cell ALL. B-cell ALL is histologically similar to Burkitt lymphoma, and it is, therefore, treated according to protocols for advanced Burkitt lymphoma without marrow involvement, which consists of short-term intensive chemotherapy (high-dose methotrexate, cytarabine, and cyclophosphamide) [151; 221].

| CHEMOTHERAPY AGENTS USED IN REGIMENS TO TREAT PEDIATRIC LEUKEMIA AND LYMPHOMA | |
|---|---|
| Class of Drug | Name of Drug |
| Alkylating agents | Busulfan Carmustine (BCNU) Chlorambucil Cyclophosphamide Ifosfamide Mechlorethamine Melphalan Procarbazine |
| Antimetabolites | Cytarabine Mercaptopurine (6-MP) Thioguanine (6-TG) Methotrexate Clofarabine Cladribine Fludarabine |
| Antitumor antibiotics | Bleomycin Dactinomycin |
| Anthracyclines | Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone |
| Corticosteroids | Dexamethasone Prednisone |
| Enzymes | Asparaginase Asparaginase (<i>Erwinia asparaginase</i> [recombinant]) Pegaspargase |
| Epipodophyllotoxins | Etoposide Teniposide Topotecan |
| Heavy metals | Carboplatin Cisplatin |
| Plant alkaloids | Vinblastine Vincristine Vinorelbine |
| <i>Source: Compiled by Author</i> | |

Table 13

The biologic and molecular characteristics of childhood leukemia are becoming better understood with the advent of genetic technology. As this enhanced knowledge leads to further distinction of subgroups according to molecular characteristics, research is focusing on the development of novel therapies to target molecular abnormalities, a type of treatment that has dramatically changed treatment and outcomes for several types of cancers in adults. Several such drugs are in early studies of children/adolescents with leukemia [222]. Imatinib (an oral drug that has been successful in adults) received FDA approval in 2013 for treatment of pediatric Philadelphia chromosome-positive (Ph+) ALL [223].

Acute Lymphoblastic Leukemia (ALL)

Risk-adapted treatment protocols developed in the 1990s have achieved a cure rate of 80% [101; 224]. Most pediatric study groups classify patients with ALL according to three risk categories: standard, high, and very high; COG uses a fourth category for very low probability of relapse [223; 225].

In general, treatment of pediatric T-cell or precursor B-cell ALL consists of intensive multidrug chemotherapy for standard-risk patients, allogeneic HSCT for high-risk patients, and antimetabolites for low-risk or very-high-risk patients [41]. All children with ALL receive CNS prophylaxis, primarily with intrathecal chemotherapy [74; 220]. Prophylaxis with cranial radiation is reserved for patients at very high risk of relapse, such as patients with CNS involvement at diagnosis or with T-cell ALL [74; 220].

Remission Induction

The goals of remission induction therapy are to induce complete remission (defined as eradication of 99% of the initial burden of leukemia cells), to restore normal hematopoiesis, and to regain a normal performance status [41; 220]. This phase of treatment typically lasts four weeks [220]. The rate of complete remission after induction therapy is high, ranging from 96% to 99% [74; 220]. Of the patients in whom complete remission is not achieved within the first four weeks of treatment,

approximately 50% will experience a toxic death during induction (usually due to infection) and the remaining 50% will have resistant disease [94; 156; 220; 226; 227]. The protocols for children with high-risk or very-high-risk ALL and all adolescents with ALL involve treatment with at least four chemotherapeutic agents. These agents most often include a corticosteroid (prednisone or dexamethasone), vincristine, and asparaginase and/or an anthracycline (doxorubicin or daunorubicin) [220; 228]. The COG protocols reserve the use of a four-drug induction for patients with high-risk B-cell ALL and T-cell ALL and do not include administration of anthracycline during induction to patients with standard-risk ALL [220; 228]. Patients treated by three other study groups receive an induction regimen with four or more drugs regardless of presenting features [220]. A meta-analysis of studies comparing the use of dexamethasone or prednisone showed that dexamethasone was more efficacious, with lower rates of events (death from any cause, refractory or relapsed leukemia, second malignancy, and CNS relapse) but no difference in bone marrow relapse or overall mortality [229]. Dexamethasone was associated with higher rates of toxicity, however, and it is not clear whether the short-term benefits found will translate to better overall survival [229]. A randomized trial comparing doxorubicin and daunorubicin given during induction found no difference in efficacy between the agents in early response measures [230]. In June 2021, the U.S. Food and Drug Administration (FDA) approved Rylaze (*Erwinia asparaginase* [recombinant]) as a component of the multi-agent chemotherapy regimen to treat ALL (and lymphoblastic lymphoma) in adult and pediatric patients (one month and older) who have developed hypersensitivity to *Escheria coli*-derived asparaginase products [231]. Rylaze was found to maintain a clinically meaningful level of asparaginase activity throughout the entire duration of treatment [231]. In 2022, the FDA approved a new dosing regimen for Rylaze in adult and pediatric patients with ALL who are 1 month of age or older and who have developed hypersensitivity to *E. coli*-derived asparaginase [232].

The emergence of targeted therapies for treatment of Philadelphia chromosome-positive (Ph+) disorders with tyrosine kinase inhibitors (TKIs) represents an important advancement in ALL therapy. Imatinib mesylate and dasatinib are inhibitors of BCR-ABL tyrosine kinase and approved by the FDA for treatment-naïve patients with pediatric Ph+ ALL [228]. In one study of early response to TKIs during remission induction in children with Ph+ ALL, TKIs (imatinib and dasatinib) produced a marked drop in minimal residual disease levels. At the end of remission induction, 9 of 11 patients who received imatinib or dasatinib and conventional induction chemotherapy had remission, compared with two of 16 patients who received chemotherapy alone. The five-year event-free survival rate was 68.6% for the 11 patients who received TKIs compared with 31.6% for the 19 patients who did not [233].

Consolidation/Intensification Therapy

Consolidation/intensification therapy begins after normal hematopoiesis has been restored. The most commonly used intensification regimen was first introduced by the Berlin-Frankfurt-Munster (BFM) clinical trials group and usually includes methotrexate with 6-mercaptopurine (6-MP) and high-dose asparaginase, followed by reinduction treatment (the same regimen given during the first few months of remission induction therapy). Maintenance typically includes 6-MP, weekly low-dose methotrexate, and sometimes administration of vincristine and a corticosteroid, as well as continued intrathecal therapy [74; 220; 228]. This regimen, with variations (e.g., intensification for higher-risk patients, use of escalating doses of methotrexate without leucovorin rescue, elimination or truncation of some phases for lower-risk patients), has been adopted by COG and has been associated with favorable outcomes in children with standard-risk ALL [234; 235].

The doses of drugs are increased according to risk, and studies have been done to evaluate the efficacy of higher doses in preventing relapse. Research reported in 2011 demonstrated a significant

improvement in event-free survival for children/adolescents with high-risk B-cell ALL when high-dose methotrexate without asparaginase was used compared with standard-dose methotrexate and asparaginase (82% vs. 75%) [236]. Similarly, compared with standard-dose methotrexate, high-dose methotrexate led to significantly better 5-year and 10-year event-free survival for children/adolescents with high-risk T-cell ALL, with rates of 80% vs. 68% and 77% vs. 66%, respectively [237].

In a landmark multicenter COG study of 92 children (1 to 21 years of age) with Ph+ ALL, investigators evaluated whether imatinib (340 mg/m² per day) with an intensive postinduction chemotherapy regimen improved outcome. Continuous imatinib exposure improved outcome in patients treated with imatinib for 280 continuous days, with a three-year event-free survival of approximately 80%, more than twice that of historical controls. Three-year event-free survival was similar for patients treated with chemotherapy plus imatinib or sibling donor blood and marrow transplantation. There were no significant toxicities associated with adding imatinib to intensive chemotherapy [238]. A follow-up study found that five-year disease-free survival was similar for patients treated with chemotherapy plus imatinib (70%), sibling donor blood and marrow transplantation (65%), and unrelated donor blood and marrow transplantation (59%). The reinduction rate following relapse was similar to other higher-risk ALL groups [239].

Another study assessed the safety and efficacy of oral imatinib in association with a Berlin-Frankfurt-Munster intensive chemotherapy regimen and allogeneic stem-cell transplantation for patients (1 to 18 years of age) with pediatric Ph+ ALL [240]. Patients were enrolled by 10 study groups between 2004 and 2009, and were classified as either good risk or poor risk according to early response to induction treatment. Good-risk patients were randomly assigned to receive postinduction imatinib with chemotherapy or chemotherapy alone. All poor-risk patients received postinduction imatinib with chemotherapy.

All patients received four postinduction blocks of chemotherapy, after which they became eligible for stem-cell transplantation. Four-year disease-free survival was 72.9% in the good-risk/imatinib group compared with 61.7% in the good-risk/no imatinib group. Four-year event-free survival for poor-risk patients was 53.5% [240].

Continuation (Maintenance) Therapy

Continuation therapy usually consists of weekly methotrexate and daily 6-MP for a period of 2 to 3 years [74; 220; 228]. A review of trials involving more than 10,000 children demonstrated that shorter durations of treatment were associated with a higher risk of relapse and death [241; 242].

CNS Prophylaxis

Before the routine use of CNS prophylaxis, relapse involving the CNS occurred in approximately 80% of all patients with complete remission [243]. Preventing relapse of disease in the CNS has led to significant improvement in the rate of isolated CNS relapse, which now ranges from less than 2% to 10% [22; 101]. Radiation was first used for CNS prophylaxis, but this approach was associated with significant acute and late morbidity, including neurocognitive impairment, second cancers, and endocrinopathy [74; 215]. As such, the use of intrathecal chemotherapy, usually methotrexate or cytarabine, is now used in most cases [220]. Children/adolescents with very-high-risk disease may still benefit from cranial radiation, and most treatment protocols limit the use of radiation to these instances, with the use of lower doses [156; 220; 244].

Treatment for Relapsed or Refractory Disease

Relapse occurs in approximately 25% of patients with ALL [245]. The most common sites of relapse in ALL are bone marrow, the CNS, and the testicles [245]. For bone marrow relapse, reinduction

therapy (usually a four-week course of prednisone, vincristine, and an anthracycline, with perhaps the addition of asparaginase) is followed by postremission chemotherapy [245]. Treatment of CNS relapse usually involves intensive systemic therapy, with cranial or craniospinal radiation delayed for six months [246].

In 2017, the FDA approved the first gene therapy for the treatment of B-cell precursor ALL in children and young adults [247]. Tisagenlecleucel is a genetically modified autologous T-cell immunotherapy used in the treatment of refractory or relapsed disease. With this approach, the patient's T cells are collected and modified to include a chimeric antigen receptor that directs T cells to kill leukemias cells, then infused back into the patient. In one study, the three-month remission rate was 83% [247]. However, tisagenlecleucel is associated with potentially severe side effects, including cytokine release syndrome, neurologic events, serious infections, acute kidney injury, and hypoxia [248].

Isolated testicular relapse usually occurs later than either bone marrow or CNS relapse and is treated with intensive chemotherapy that includes high-dose methotrexate. Patients who do not have a complete remission after induction also receive local radiation therapy [220]. Orchiectomy of the clinically involved testis is performed in some European clinical trial groups, with biopsy of the contralateral testis to determine whether additional local control (i.e., surgical removal or radiation) is needed. One study that examined testicular biopsy at the end of frontline therapy failed to demonstrate a survival benefit for patients with early detection of occult disease [249]. While there are limited clinical data concerning outcome without the use of radiation therapy or orchiectomy, the use of chemotherapy (e.g., high-dose methotrexate) to achieve antileukemic levels in the testes is being tested in clinical trials [220].

Hematopoietic Stem Cell Transplantation

In 2012, the American Society for Blood and Marrow Transplantation (ASBMT) published an update to its 2005 recommendation that HSCT be done after first complete remission of Ph⁺ ALL when a matched related donor is available [250; 251]. Allogeneic HSCT is recommended for children who [251]:

- Are in their second complete remission following an early marrow relapse for B-cell ALL
- Have had failure of primary induction therapy but subsequent complete remission
- Have T-cell ALL in their second complete remission
- Have ALL in their third or greater remission

Allogeneic HSCT is not recommended for patients with T-cell ALL in their first complete remission; patients with the MLL gene plus ALL when it is the sole adverse risk factor; and patients with isolated CNS relapse in B-cell ALL [251]. In general, HSCT approaches benefit only children at high risk for relapse with standard chemotherapy approaches [252].

Infection prophylaxis during HSCT includes confinement in a HEPA-filtered, positive-air-pressure sealed room, strict hand hygiene, antibacterial prophylaxis with fluoroquinolone, and antifungal prophylaxis with fluconazole [253].

Follow-Up and Surveillance

Several organizations have published consensus guidelines for follow-up for late effects following HSCT; however, these guidelines do not address all pediatric-specific challenges to HSCT [254]. The Pediatric Blood and Marrow Transplant Consortium (PBMTTC) published six detailed papers to address the lack of detailed pediatric-specific late effects and guidelines for long-term follow-up after HSCT. The PBMTTC summary and guideline recommendations provide the most current outline for following up children for late effects after HSCT (**Table 14**) [255].

Acute Myeloid Leukemia (AML)

As noted earlier, the event-free and overall survival rates are lower for children/adolescents with AML than for those with ALL. Due to lack of consistent prognostic factors in AML, risk-adapted treatment is not regularly used as it is for ALL; however, risk-adapted and biologically targeted therapies are being tested to improve treatment while sparing normal tissues [44; 256]. Optimal treatment of AML requires control of bone marrow and systemic disease [45]. The four-phase approach is not always followed, as the efficacy of the continuation (maintenance) phase has not been proven for the treatment of AML [22; 44; 45]. The approach to the treatment of AML is similar for all types except for the M3 subtype (acute promyelocytic leukemia), for which chemotherapy is combined with all-trans retinoic acid (ATRA) [22].

The drugs used to treat AML have primarily remained the same, but regimens and timing of treatment have been refined, with current rates of 80% to 90% for complete remission, 30% to 40% for relapse, 45% to 55% for event-free survival, and 55% to 65% for overall survival [44; 45].

Induction Therapy

The most effective chemotherapy regimen for induction in AML has been an anthracycline, cytarabine, and etoposide [44; 45]. Although the regimens used have differed in many ways, including the cumulative doses of drugs, the choice of anthracycline, and the number of treatment cycles, the results have been relatively similar [44; 45].

Consolidation/Intensification Therapy

Studies and one phase III clinical trial have demonstrated that intensive treatment during the consolidation phase leads to decreased relapse rates and better event-free and overall survival for younger patients with AML [22; 257]. High-dose cytarabine, usually given with mitoxantrone, has led to improved outcomes for children with high-risk disease [45].

**SELECTED SCREENING RECOMMENDATIONS FOR
LATE EFFECTS AFTER HSCT IN PEDIATRIC POPULATION**

| Effects | Screening | Management |
|-----------------------|---|---|
| Immune reconstitution | Monitor T-cell reconstitution; high content B cell immunophenotyping 6 months after HCT | Neoantigen challenge for patients with poor/incomplete immune reconstitution based on immunophenotyping |
| Iron overload | Annual serum ferritin; if elevated, consider T2-weighted MRI | Phlebotomy or chelation |
| Gastrointestinal | Annual screening for chronic GVHD and hepatitis virus infection Annual hepatocellular carcinoma screening for high-risk patients (i.e., those with hepatitis C or B infection, obesity, diabetes, or low platelet count) | — |
| Renal | Monitor urine for albumin:creatinine ratio at day 80 and then annually. If ratio is >30 and <300 mg/g, confirm with two or more tests in 3 to 6 months and monitor every 3 to 6 months. If ratio is >300 mg/g, monitor every 3 to 6 months. | Treat with ACE inhibitor or ARB if albumin:creatinine ratio is >300 mg/g on one occasion or if patient has persistent ratio >30 g/kg on three occasions in a 6-month period and has hypertension. |
| Pulmonary | Pulmonary function testing for allogeneic recipients twice per year for two years, with consideration for more frequent screening in recipients of mismatched or unrelated donor grafts, or patients with active chronic GVHD. After two years, consider yearly follow-up pulmonary function tests based on symptoms and past measurements. | With a >15% decrease in pulmonary function test values or new pulmonary infiltrate, evaluate for infection/GVHD. Refer to pulmonologist for disease-specific care as needed. |
| Cardiac | Annual cardiovascular risk assessment Blood pressure each visit and at least annually Electrocardiogram/echocardiogram at least every five years, more frequently if patient received anthracycline, total body radiation, or chest radiation | Refer to cardiologist for abnormal or declining cardiac function. |
| Thyroid dysfunction | Thyroid-stimulating hormone and free thyroxine annually for 10 years after busulfan and for at least 30 years after total body radiation. Physical examination of thyroid yearly to screen for tumors after total body radiation. | If thyroid-stimulating hormone is high and free thyroxine is normal, either treat or repeat in two months. Replace thyroid as indicated for low levels. Rare secondary thyroid tumors post-TBI can be cured with surgery. |
| Growth | Accurate measurement of growth yearly through full growth (age 17 years for girls and 19 years for boys). Bone age as needed. | Bone age and referral to an endocrine specialist for a patient not growing appropriately. GH therapy may unmask hypothyroidism. |

Table 14 continues to next page.

**SELECTED SCREENING RECOMMENDATIONS FOR
LATE EFFECTS AFTER HSCT IN PEDIATRIC POPULATION (Continued)**

| Effects | Screening | Management |
|---|---|---|
| Reproductive risks | Women: monitor for ovarian failure (FSH, assess cycling) Men: semen analysis | Women: Anti-Müllerian hormone may assess ovarian reserve. Treat ovarian failure with hormone replacement therapy. Men: If oligospermia noted, may offer intracytoplasmic sperm injection |
| ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; FSH = follicle-stimulating hormone; GH = growth hormone; GVHD = graft-versus-host disease; MRI = magnetic resonance imaging. | | |
| Source: [255] | | Table 14 |

CNS Prophylaxis

Intrathecal chemotherapy is considered by most to be a standard component of treatment of AML, although no studies have compared CNS prophylaxis with no CNS prophylaxis, and it has not been shown to contribute directly to improved survival [22; 45]. Cytarabine, methotrexate, or both, along with hydrocortisone, are the preferred agents for prophylaxis [45]. The rate of isolated CNS relapse is reported to be 2% [44]. Cranial radiation is not used for prophylaxis [44; 45].

Treatment for Relapsed or Refractory Disease

Most relapses occur during the first year, and the most common site of relapse is the bone marrow (92%) [258]. Relapse occurs in the CNS in 10% to 20% of patients and in the skin in 4%.

Remission induction chemotherapy regimens have included high-dose cytarabine in combination with fludarabine or mitoxantrone [44; 45]. Anthracyclines are effective, but the increased risk for cardiotoxicity limits their use in the relapse setting if they have been used for primary treatment [258]. Liposomal daunorubicin has been added to fludarabine plus cytarabine in an attempt to limit cardiotoxicity [44].

However, cure is unlikely with chemotherapy alone for relapsed AML [44]. In 2020, the FDA extended the indication for gemtuzumab ozogamicin to include newly diagnosed CD33-positive AML in pediatric patients 1 month of age and older [259]. The drug was previously approved for children 2 years of age and older with relapsed or refractory AML [45; 260]. Efficacy and safety information for the extended indication was supported by data from a multicenter randomized study of 1,063 patients, 0 to 29 years of age, with newly-diagnosed AML. The estimated percentage of patients free of induction failure, relapse, or death at five years was 48% in the gemtuzumab ozogamicin plus chemotherapy arm versus 40% in the chemotherapy alone arm. No difference in overall survival was found between treatment arms. The most common adverse events included cardiotoxicity, hepatotoxicity, infection, fatigue, and fever [260]. In a report from the COG on the efficacy of clofarabine in combination with cytarabine in pediatric patients with recurrent AML, the combination yielded an acceptable response rate without excess toxicity. The nearly 50% survival rate reported suggests that this combination is an effective bridge to HSCT [261]. HSCT is thought to be the only curative treatment for relapse [44; 45; 257; 258; 262].

Stem Cell Transplantation

The issue of HSCT in AML, especially with regard to when it should be done, remains a topic of some debate. A meta-analysis demonstrated that transplantation reduced the risk of relapse and significantly improved disease-free and overall survival among many children/adolescents with AML [263]. The review of evidence by the ASBMT led to its recommendation of transplantation after either first or second remission if a matched related donor is available [264]. However, a later meta-analysis showed that transplantation after first complete remission did not lead to significant differences in relapse or disease-free or overall survival compared with no transplantation [265]. Current application of allogeneic HSCT involves incorporation of risk classification to determine whether transplantation should be pursued in first remission [45]. Due to improved outcomes in patients with favorable prognostic features and lack of demonstrated superiority of HSCT, this patient population typically receives matched-family donor HSCT only after first relapse and achievement of a second complete remission [264; 266; 267; 268].

The absence of published recommendations specific for pediatric AML motivated an international group of pediatric hematologists and oncologists to develop evidence- and expert opinion-based consensus recommendations for the management of AML in children [65]:

- For patients with initial hyperleukocytosis and symptomatic coagulopathy and/or leukostasis, emergency strategies should be initiated to reduce the risk of fatal hemorrhage and leukostasis.
- Antifungal prophylaxis (including trimethoprim-sulfamethoxazole for prophylaxis of *Pneumocystis jirovecii*) should be administered to all children.
- The use of fluoroquinolones may be considered as prophylaxis against *Streptococcus viridans* and gram-negative sepsis.

Follow-Up and Surveillance

The improved outcome in children with AML over the last 10 years is probably associated with better supportive care strategies [65]. Children with AML who receive treatment with contemporary therapy and remain in remission four years from diagnosis probably are cured. Although late relapses and late deaths from other causes are rare, long-term follow-up of survivors is necessary for the timely management of late adverse effects [269].

TREATMENT OF LYMPHOMA

Hodgkin Lymphoma

Standard treatment options achieve cure in approximately 80% to 90% of children/adolescents with Hodgkin lymphoma. The rates have been better for children 10 years of age and younger than for children older than 10 years of age [119; 270]. Between 2011 and 2017, the five-year overall survival rate was 98% for patients younger than 20 years of age [47]. The German Hodgkin Study Group found that adult treatment protocols were safe and effective treatment options for adolescents with Hodgkin lymphoma [271]. No single treatment approach is ideal for all pediatric and young adult patients due to differences in age-related developmental status and sex-related sensitivity to chemotherapy toxicity. The general treatment strategy for children and adolescents with Hodgkin lymphoma is chemotherapy, with or without radiation [47].



EVIDENCE-BASED
PRACTICE
RECOMMENDATION

The National Comprehensive Cancer Network recommends that treatment of patients with favorable-risk pediatric Hodgkin lymphoma typically involve participation in an ongoing clinical trial.

(https://www.nccn.org/professionals/physician_gls/pdf/ped_hodgkin.pdf. Last accessed August 22, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

The risk-adaptive approach to the treatment of Hodgkin lymphoma involves planning treatment according to prognostic variables such as stage of disease, presence of B symptoms, and tumor bulk [272]. Disease is classified as being low, intermediate, or high risk. Low-risk disease is defined as localized Hodgkin lymphoma (stage I or II and sometimes IIIA) with no B symptoms or tumor bulk. Intermediate-risk disease usually includes stage I or II disease with unfavorable features (B symptoms, tumor bulk, involvement of three or more lymph node regions, and/or extranodal extension to contiguous structures) [119]. Stages III and IV typically represent high-risk disease.

Ongoing trials for patients with favorable-risk (low-risk) disease are evaluating the effectiveness of treatment with fewer cycles of combination chemotherapy alone that limit doses of anthracyclines, alkylating agents, and radiation therapy. Contemporary trials for patients with intermediate/unfavorable disease are testing whether chemotherapy and radiation therapy can be limited in patients who achieve a rapid early response to dose-intensive chemotherapy regimens. Trials are also testing the efficacy of regimens integrating novel, potentially less-toxic agents such as brentuximab vedotin [47].

Favorable-risk (low-risk) disease is defined differently by different clinical trial groups, but for the most part it encompasses patients with localized stage I and II disease without adverse prognostic features (e.g., “B” symptoms, extranodal extension, mediastinal bulky disease). Favorable-risk disease can be treated with reduced therapy, which consists of two to four cycles of multiagent chemotherapy and low-dose (15–25 Gy), involved-field radiation [47; 272; 273]. The regimens used most often include etoposide, which has commonly replaced alkylating agents and anthracyclines, in an effort to reduce gonadal toxicity and enhance antineoplastic activity [47].

Intermediate-risk disease is treated with three to six cycles of compacted, dose-intensive chemotherapy and low-dose, involved-field radiation, usually as consolidation therapy. For high-risk disease, four to six compacted, dose-intensive cycles of chemotherapy in addition to low-dose (15–25 Gy) involved-field radiation therapy to involved sites of disease are recommended [272]. The dose-intensive regimen of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone led to response within four weeks in 74% of children/adolescents with stage IIB or IIIB Hodgkin lymphoma with bulk disease or stage IV disease [274]. When followed by guideline-directed consolidation therapy, the treatment led to overall survival of 97% and five-year event-free survival of 94% [274]. More recent pediatric trials conducted in North America and Europe have used procarbazine-free standard backbone regimens, which represent dose-dense therapies that use six drugs to maximize intensity without exceeding thresholds of toxicity [47]. Early response to therapy may be considered in determining the need for radiation in those who have complete remission. Advanced radiation techniques, such as intensity-modulated radiation therapy and proton therapy, may be considered depending on the clinical scenario and if an improvement is expected [272; 275].

In addition to disease-related factors, the patient’s age and sex are primary considerations. A younger age at the time of diagnosis has implications for musculoskeletal and soft-tissue deformities and cardiovascular dysfunction after radiation and/or chemotherapy with an anthracycline [119]. With respect to the patient’s sex, the risk of breast cancer is increased for teenage girls who have radiation to the thorax, and girls are at higher risk of cardiomyopathy as a result of anthracycline use [119]. Alkylating agents lead to a higher prevalence of gonadal dysfunction in boys. The German Paediatric Oncology and Haematology Society pioneered risk- and gender-adapted therapy featuring the vincristine, etoposide, prednisone, and doxorubicin regimen

for boys to limit the amount of alkylating agents; girls received vincristine, procarbazine, prednisone, and doxorubicin. The HD-95 trial investigated whether radiation therapy could be omitted in patients achieving a complete remission to chemotherapy. Early results (median follow-up time: three years) indicate a 97% event-free survival rate for favorable-risk patients. There was no difference in outcome between favorable-risk patients treated with chemotherapy alone and those treated with combined-modality therapy [276].

Randomized trials have compared chemotherapy alone with chemotherapy plus low-dose radiation for advanced stage Hodgkin lymphoma. The results have primarily indicated that there is no benefit to the addition of radiation in terms of event-free or overall survival, with one study indicating that the addition of radiation was comparable to the addition of a second chemotherapy regimen [123; 277]. Researchers continue to debate the issue of adding low-dose radiation to chemotherapy because of the toxicity associated with each modality [278; 279; 280]. However, the use of radiation therapy may allow for lower doses of chemotherapy agents. In an effort to cure children with Hodgkin lymphoma with minimal side effects, most treatment approaches entail combined-modality therapy with reduced dose radiation. A number of combined-modality therapy protocols exist, and the decision as to how to incorporate radiation therapy should be made within the context of the protocol followed [272].

Treatment for Relapsed/Refractory Disease

Relapse will occur after first-line treatment in approximately 10% to 20% of children with advanced-stage Hodgkin lymphoma [270]. Relapse occurs most often within four years, but late relapse is not rare [272]. Chemotherapy is the recommended second-line therapy. The choice of specific agents, dose intensity, and number of cycles is determined by the initial therapy, disease characteristics at progression/relapse, and response to second-line therapy [47]. Although chemotherapy with ifosfamide, carboplatin, and etoposide in combination or as single agents is effective, the toxicity profiles of the drugs have led

investigators to search for alternative treatments. Vinorelbine, ifosfamide, and high-dose methotrexate have been found to be acceptable, but subsequent relapse after high-dose methotrexate has occurred in as many as 50% of children/adolescents [270]. Nonmyeloablative stem cell transplantation has been used in selected patients with high-risk disease [270]. In addition, two cycles of chemotherapy with dexamethasone, etoposide, cisplatin, high-dose cytarabine, and asparaginase (DECAL) plus maintenance therapy and stem cell transplantation was found to be effective for relapsed Hodgkin lymphoma, with a five-year event-free survival of 26% and five-year overall survival of 31% [281]. The COG has evaluated ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide) and its derivatives across all risk groups [282; 283; 284]. Benefits of this regimen include lower cumulative doses of anthracyclines, alkylating agents, and bleomycin compared with MOPP and ABVD regimens used in prior decades. Lower cumulative doses are expected to translate into long-term reductions in second malignant neoplasms and fewer cardiovascular, pulmonary, and fertility complications [285; 286; 287].

COG investigated treatment of relapsed/refractory disease with brentuximab vedotin and gemcitabine in 46 children and young adults [288]. Twenty-four of 42 patients treated at the recommended phase II dose of 1.8 mg/kg experienced a complete response within the first four cycles. Four of 13 patients (31%) with partial response or stable disease had all target lesions with Deauville scores of 3 or less after cycle four. By modern response criteria, these are also complete responses, increasing the complete response rate to 28 of 42 patients. There were no treatment-related deaths. The most common adverse events among all patients treated were neutropenia, rash, transaminitis, and pruritus [288]. Trials are ongoing to determine the efficacy and toxicity of combining brentuximab vedotin with chemotherapy. Additionally, phase I/II trials of immune checkpoint inhibitor therapy (with nivolumab and pembrolizumab) for use in childhood refractory/relapsed disease are ongoing [289; 290].

Stem Cell Transplantation

HSCT is usually limited to patients who have relapse or in whom disease is refractory to primary conventional therapy [47; 119; 252].

Follow-Up and Surveillance

Most pediatric patients with Hodgkin lymphoma have a favorable outcome; however, there is increasing concern about risks of carcinogenesis from diagnostic and therapeutic radiation therapy and from post-treatment surveillance imaging. In one study, cumulative radiation dosage from diagnostic imaging examinations and the frequency of relapse detection by these examinations were recorded. In the first two years after therapy, patients in remission received a median of 11 examinations. In 13 of 99 patients who relapsed, approximately 1% of surveillance imaging examinations (e.g., CT scan, positron emission tomography [PET] scan, chest radiographs) identified relapsed disease. Given this very low rate, the financial burden of the tests themselves, the high cure rate, and risks of second malignancy from ionizing radiation exposure, modification of the surveillance strategy is recommended [291].

Non-Hodgkin Lymphoma

With standard treatment options, approximately 75% to 80% of children/adolescents with non-Hodgkin lymphoma will survive at least five years, although the survival rate varies according to subtype [17; 139; 292]. Age may also be a factor. In one study, the five-year event-free survival rate was approximately 79% for adolescents compared with 85% for patients younger than 15 years of age [293]. However, another study found that age was not a factor in increased risk of treatment failure [152]. Instead, the patient's level of lactate dehydrogenase, mediastinal disease, and combined bone marrow-/CNS-positive involvement were independent risk factors in children with mature B-cell non-Hodgkin lymphoma [152]. Response to treatment also is an important prognostic indicator. With the exception of anaplastic large-cell lymphoma, pediatric non-Hodgkin lymphoma that is refractory to first-line therapy has a very poor prognosis, regardless of histology [294; 295; 296].

As with Hodgkin lymphoma, the treatment of non-Hodgkin lymphoma is based on the extent of disease, with the intensity of treatment being increased for more extensive disease [297]. Because non-Hodgkin lymphoma in children is considered to be widely disseminated from the outset, even when apparently localized, combination chemotherapy is recommended for most patients [17]. The event-free survival has been better in some studies in which surgical resection was done. So, there may be some value to this approach if resection can be readily accomplished, especially in cases of large tumor masses [120]. Treatment often consists of a cytoreduction phase to reduce tumor burden, followed by a consolidation phase.

For most studies of treatments done in the United States, patients are categorized into three risk groups: low-risk, which is completely resected stage I disease or stage II abdominal disease; high-risk, which consists of CNS involvement with or without bone marrow involvement; and intermediate-risk, which encompasses disease that is not eligible for the other two groups [120]. Treatment also varies according to the pathologic subtype.

B-cell non-Hodgkin lymphoma can be treated with two or three cycles of combination chemotherapy after surgical resection if there is no measurable tumor burden [17; 297; 298]. The combination of vincristine, cyclophosphamide, doxorubicin, and prednisone has been highly effective in this setting [221]. A single-agent phase II study of rituximab performed by the BFM group showed activity in Burkitt lymphoma [299]. A pilot study from the COG added rituximab to baseline chemotherapy with FAB/LMB-96 therapy in patients with stage III and stage IV B-cell non-Hodgkin lymphoma [300; 301]. For higher risk disease, the addition of two or three courses of chemotherapy, high-dose methotrexate, and high-dose cytarabine was also effective [221; 302; 303].

Good outcomes for treatment of lymphoblastic lymphoma have been achieved with use of ALL-type regimens consisting of an induction phase of multiagent chemotherapy (eight drugs) followed by a consolidation phase and a maintenance phase of two years, with cranial radiation for CNS prophylaxis [55; 304]. This approach was superior to short, intensive pulsed chemotherapy regimens [305; 306; 307]. Good outcomes also have been reported by the COG with use of a Children's Cancer Group (CCG)-modified BFM ALL regimen (prednisone, dexamethasone, vincristine, daunorubicin, doxorubicin, L-asparaginase, cyclophosphamide, cytarabine, methotrexate, 6-mercaptopurine, 6-thioguanine, and reduced number of intrathecal treatments during maintenance) [17]. The study randomized 254 patients to the regimen with intensified intrathecal methotrexate (Arm A1) or an adapted non-Hodgkin lymphoma/BFM-95 therapy with high dose methotrexate in interim maintenance but no intrathecal methotrexate in maintenance (Arm B1). Each cohort was randomized to either more or less intensification (cyclophosphamide/anthracycline) (Arms A2/B2) and CNS radiation therapy for CNS-positive patients only [308]. There was no difference in five-year event-free survival among the four arms. Five-year survival for CNS-positive patients was 63%. There was no difference in outcome based on CNS prophylaxis or intensification for CNS-negative patients [308]. In a COG study of 56 children and adolescents with stages I and II disease who were treated with the modified CCG BFM regimen for two years, the COG reported a five-year event-free survival of 90% and a five-year overall survival of 96% [309].

For patients with a mediastinal mass, radiation targeting the mass is not necessary except as emergency treatment to relieve airway obstruction or superior vena cava syndrome [17; 121]. In such cases, low doses of radiation are used. Cranial radiation may be reserved for patients with CNS involvement at the time of diagnosis [307].

Several treatment strategies have been used for anaplastic large-cell lymphoma, and the outcomes have been comparable [17; 122; 144]. Treatment has been adapted to risk in some cases, usually according to stage of disease [144]. Common agents are corticosteroids, vincristine, doxorubicin, and methotrexate, but the doses have varied substantially. A course of chemotherapy similar to that used for B-cell non-Hodgkin lymphoma, with treatment stratified by stage of disease, was effective for disseminated anaplastic large-cell lymphoma, as was treatment that included a short cytoreduction phase (two chemotherapy cycles) followed by a short maintenance phase (five to seven months) [143; 144]. In an international study of systemic childhood anaplastic large-cell lymphoma, 12 of 463 patients had CNS involvement; three of the 12 had isolated CNS disease. Comparative analysis of CNS-positive and CNS-negative patients showed no difference in anaplastic lymphoma kinase positivity, immunophenotype, presence of B symptoms, or other sites of disease. With multiagent chemotherapy, the event-free and overall survival rates of the CNS-positive group at five years were 50% and 74%, respectively [310]. CNS involvement in anaplastic large-cell lymphoma is rare at diagnosis [17].

CNS Prophylaxis

The use of radiation therapy is limited in children with non-Hodgkin lymphoma. Early studies showed that routine CNS prophylaxis had no benefit for patients with low-risk (stage I or stage II) disease [311]. It has been demonstrated that CNS prophylaxis can be omitted in lymphoblastic lymphoma [307; 312]. It can also be eliminated for patients with anaplastic large-cell lymphoma and B-cell non-Hodgkin lymphoma, even those who present with CNS disease [144; 302]. These findings are supported by data from the Childhood Cancer Survivor Study, which demonstrated that radiation was a significant risk factor for secondary malignancy and death in long-term survivors [313].

Treatment for Recurrent or Refractory Disease

Relapse occurs in approximately 12% of children/adolescents with non-Hodgkin lymphoma [292]. Intensive chemotherapy with drugs that were not used in first-line treatment have been utilized, and stem cell transplantation support has been effective for patients with chemosensitive disease [120; 314; 315; 316; 317]. Two cycles of chemotherapy with DECAL, maintenance therapy, and stem cell transplantation was found to be effective for relapsed non-Hodgkin lymphoma, with a five-year event-free survival of 23% and five-year overall survival of 30% [281].

Although outcomes in pediatric B-non-Hodgkin lymphoma have improved with intensive chemotherapy protocols, the long-term adverse effects of therapy and poor outcomes for patients who relapse continue to be challenges [17; 318]. One study evaluated the potential risks and benefits of routine relapse surveillance imaging after the completion of therapy among 44 patients with non-Hodgkin lymphoma who were diagnosed and treated at Texas Children's Cancer Center between 2000 and 2011 [318]. Only three of the 44 patients had relapse (6.8%) and none of the relapses were initially diagnosed by CT or PET scans. The median effective radiation dose per patient was 40.3 mSv (range: 0–276 mSv). This study highlights the low relapse rate following complete response at the end of therapy among children/adolescents with B-non-Hodgkin lymphoma, the low sensitivity of early relapse detection by surveillance imaging, and the costs and potential increased risk of secondary malignancies from cumulative radiation exposure from surveillance imaging [318].

SUPPORTIVE CARE

Supportive care is integral to the treatment of leukemias and lymphomas and addresses the symptoms and potential complications of both the disease and treatment. Children should be followed closely during active treatment; the primary oncologist usually coordinates this care. However, the child's primary care provider may also be involved, especially if the family's home is far from the pediatric cancer center. In addition, routine visits with the primary care provider should continue for overall health maintenance. These visits provide an opportunity to assess symptom management and the development of complications. Good reciprocal communication between the primary care provider and the primary oncologist is essential. The primary oncologist should send a copy of the patient's treatment plan to the primary care provider, and both clinicians should maintain communication about complications as they occur [319].

Supportive care focuses on the treatment of infection, neutropenia, anemia, thrombocytopenia, and other complications, such as metabolic disturbances and deep vein thrombosis. Also essential is symptom management, which centers on enhancing the quality of life.


INFECTION

Of primary concern during treatment for leukemia or lymphoma is the risk of infection, which is the leading cause of morbidity and mortality among children with cancer [22; 320]. Infection is a result of the severe immunosuppression caused by both treatment (chemotherapy and radiation therapy) and the disease process itself. Immunosuppression and associated neutropenia increase the risk for opportunistic infection with bacterial, viral, fungal, and protozoal organisms [320; 321]. Most infections that occur in children during or after treatment for leukemia or lymphoma are the same as those found in healthy children [321].

Prevention of infection includes general measures such as meticulous hand hygiene (for the patient and all who come in direct contact) and the avoidance of environments where the risk of infection transmission is high. Playing in dirt or gardens or near construction sites may pose a risk of fungal infection [320]. In addition, it is important to protect the integrity of the skin and mucosal surfaces, as they serve as barriers to infectious pathogens [321]. Proper oral hygiene, with daily tooth brushing and use of chlorhexidine mouth rinse, is important, and rectal suppositories and rectal thermometers should not be used [320]. Unless the child is at high risk for fever and neutropenia, routine prophylaxis against viral, bacterial, and fungal agents is not recommended [321; 322; 323]. One exception is prophylaxis for *Pneumocystis jiroveci*, which occurs in 15% to 20% of children treated for ALL [321; 324; 325]. Prophylactic treatment consists of trimethoprim-sulfamethoxazole (TMP-SMZ), given either daily or on three consecutive days per week [260; 325; 326]. Treatment with TMP-SMZ on two consecutive days per week has also been shown to be effective [327].

found that, when compared with placebo or no intervention, antibiotic prophylaxis significantly reduced the occurrence of fever, clinically and microbiologically documented infection, and other indicators of infection. There were no significant differences between prophylaxis with quinolone or TMP-SMZ with regard to death from all causes or infection; however, quinolone prophylaxis was associated with fewer side effects leading to discontinuation and less resistance to the drugs thereafter. The benefits of antibiotic prophylaxis outweighed the harms (e.g., adverse effects, development of resistance) because all-cause mortality was reduced [328].

Children receiving treatment for leukemia or lymphoma who have a fever (38.5 degrees Centigrade or two temperatures of at least 38.0 degrees Centigrade within 24 hours) should be evaluated carefully for infection. Vital signs should be assessed, and physical examination should include evaluation of common sites of infection (respiratory system, ears, sinuses) as well as occult sites (mouth, skin, perianal area) [320]. Laboratory testing should include a CBC, blood cultures, urinalysis, and urine culture [320]. The absolute neutrophil count (ANC) should be determined, as neutropenia is the most significant predisposing factor for infection [320; 329]. Approximately 70% to 80% of bacterial infections occur in children who have moderate neutropenia [329]. The presence of fever and neutropenia requires hospitalization for empiric treatment with intravenous administration of broad-spectrum antibiotics [330]. One randomized controlled trial evaluated the use of ciprofloxacin in children younger than 18 years of age with ALL or lymphoma who were scheduled to undergo chemotherapy [331]. A total of 95 children were randomized to receive oral ciprofloxacin 20 mg/kg/day (45 children) or placebo (50 children) from the beginning of their chemotherapy. Rectal swab cultures were taken before and at one and/or two weeks after the intervention. Of the 71 patients who developed neutropenia, the proportion of children who developed fever was significantly lower in the ciprofloxacin group than in the placebo group.



According to the Advisory Committee on Immunization Practices, the measles, mumps, rubella, and varicella vaccine is contraindicated in children with severe immunocompromise (including as a result of leukemia or lymphoma).

(<https://www.cdc.gov/pinkbook/hcp/table-of-contents/chapter-13-measles.html>. Last accessed August 22, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

Several trials have shown the efficacy of antibiotic prophylaxis in reducing the incidence of bacterial infections but not in reducing mortality rates. One systematic review evaluated whether there remains a benefit of reduction in mortality when compared with placebo or no intervention [328]. The review included 109 trials (involving 13,579 patients) that were conducted from 1973 to 2010. The reviewers


Ciprofloxacin significantly reduced the occurrence of febrile episodes in patients with ALL in the induction phase of chemotherapy, but not in patients with lymphoma or in the consolidation phase of chemotherapy. Adverse effects were not different between the groups [331].

The risk of infection is also increased for children who have an indwelling central venous catheter. Indwelling venous catheters are used in most children/adolescents with cancer to facilitate the administration of medications, fluids, and blood products. The risk of infection related to these catheters has ranged from approximately 3% to 60%, and the risk is greater with external catheters than with implanted ones [332; 333]. Care of external catheters requires strict adherence to aseptic technique, daily flushing of the catheter, and frequent changes of the sterile dressing [321]. If a fever develops, blood for cultures should be obtained through the catheter and from a peripheral site and empiric treatment with antibiotics should be started. Routine removal of the catheter is not necessary, as nearly 75% of catheter-related infections resolve with the catheter intact [334]. However, if signs of septicemia develop and bacteremia persists 48 hours after the start of antibiotic administration, the catheter should be removed [320]. The catheter should also be removed immediately if the infection is fungal.

The presence of a central venous catheter also requires prophylactic antibiotics before invasive procedures, including dental cleaning or procedures. The prophylaxis used is that recommended by the American Heart Association for children with congenital heart disease: amoxicillin, 50 mg/kg (maximum of 3 grams), given one hour prior to the procedure [335].

NEUTROPENIA

Neutropenia is defined as an ANC of less than 1,000/mcL. An ANC of less than 500/mcL is considered to be moderate neutropenia, and an ANC of less than 200/mcL is severe neutropenia [320]. As noted, neutropenia is a significant factor for the development of infection. In the adult setting, neutropenia is prevented and managed with the use of hematopoietic growth factors, such as granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF). In the pediatric population, clinical protocols for leukemia usually include guidelines for the use of CSFs. Research to evaluate their use has been limited, and the results have varied [332; 336; 337]. One meta-analysis of 16 randomized controlled trials involving nearly 1,200 children with cancer, primarily leukemia and lymphoma, demonstrated that the prophylactic use of CSFs was associated with a 20% decrease in febrile neutropenia, a lower number of documented infections, and shorter hospital stays [338]. However, other studies, including a meta-analysis, have indicated that CSFs have no significant effect on the incidence of infection [336; 339]. It is important also to note that the use of CSFs in children with ALL has been associated with an increased risk for secondary myeloid leukemia or myelodysplastic syndrome [340]. Given these findings, the American Society of Clinical Oncology states that the use of CSFs in children with ALL should be “considered with caution” and recommends that primary prophylaxis with CSFs is “reasonable” for children in whom febrile neutropenia is likely [337]. Secondary prophylaxis with CSFs should be limited to children at high risk [337]. The risk of AML has also led to the



The Children's Oncology Group recommends obtaining blood cultures at the onset of fever and neutropenia in children with cancer from all lumens of central venous catheters.

(<https://ascopubs.org/doi/10.1200/JCO.2016.71.7017>. Last accessed August 22, 2024.)

Strength of Evidence/Level of Evidence: Strong recommendation, low-quality evidence

**INTERNATIONAL PEDIATRIC FEVER AND NEUTROPENIA
GUIDELINE PANEL RECOMMENDATIONS FOR THE MANAGEMENT
OF FEVER AND NEUTROPENIA IN CHILDREN WITH CANCER**

| Recommendation | Level of Evidence | Remarks |
|--|---------------------------|---|
| Initial Presentation of Fever and Neutropenia: Initial Management | | |
| Risk stratification: Adopt validated risk stratification strategy and incorporate into routine clinical management | Low-quality evidence | Strategy choice should be determined by validation in similar context; ability to implement based on complexity, availability of required components (e.g., biomarkers) |
| Evaluation: Obtain blood cultures at onset of FN from all CVC lumens | Low-quality evidence | — |
| Evaluation: Obtain chest radiography in patients with respiratory signs/symptoms | Moderate-quality evidence | |
| Patients at High Risk for Fever and Neutropenia: Treatment | | |
| Use monotherapy with antipseudomonal β -lactam, fourth-generation cephalosporin, or carbapenem as empirical therapy | High-quality evidence | Monotherapy may not be appropriate for centers with high rate of resistance, or for patients who present with hemodynamic instability |
| Reserve addition of second gram-negative agent or a glycopeptide for patients who are clinically unstable, when resistant infection is suspected, or for centers with high rate of resistant pathogens | Moderate-quality evidence | Threshold for when rates of resistance are sufficiently high to support empirical combination or glycopeptide therapy has not been established, will vary by institution |
| Ongoing Management (Excluding Empirical Therapy) | | |
| Modification of treatment: In patients who respond to initial empirical antibiotic therapy, discontinue double coverage for gram-negative infection or empirical glycopeptide (if initiated) after 24 to 72 hours if there is no specific microbiologic indication to continue combination therapy | Moderate-quality evidence | Rationale is same as that for recommendation for initial empirical monotherapy. The Panel valued reducing unnecessary antibiotic administration to reduce toxicity, costs, and antibiotic resistance. |
| Modification of treatment: Do not modify initial empirical antibacterial regimen based solely on persistent fever in children who are clinically stable | Low-quality evidence | |
| Modification of treatment: In children with persistent fever who become clinically unstable, escalate initial empirical antibacterial regimen to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria | Very low-quality evidence | |
| Cessation of treatment: In all patients, discontinue empirical antibiotics in patients who have negative blood cultures at 48 hours, who have been afebrile for at least 24 hours, and who have evidence of marrow recovery | Low-quality evidence | — |
| <i>Table 15 continues to next page.</i> | | |

**INTERNATIONAL PEDIATRIC FEVER AND NEUTROPENIA
GUIDELINE PANEL RECOMMENDATIONS FOR THE MANAGEMENT
OF FEVER AND NEUTROPENIA IN CHILDREN WITH CANCER (Continued)**


| Recommendation | Level of Evidence | Remarks |
|--|--|--|
| Empirical Antifungal Therapy | | |
| Risk stratification: Patients at high risk of IFD are those with AML, high-risk ALL, or relapsed acute leukemia, and children undergoing allogeneic HSCT. Children with prolonged neutropenia and children receiving high-dose corticosteroids are also at high risk of IFD. All others should be categorized as low-risk IFD. | Low-quality evidence | Risk stratification rules are not yet available for prediction of IFD. The Panel recognized that high-risk ALL is a heterogeneous group and this risk may be explained by prolonged neutropenia and corticosteroid administration. No data available to specify which ALL patients is at particular risk of IFD. |
| Evaluation: Do not use β -D-glucan. | Low-quality evidence | — |
| Evaluation: Do not use fungal PCR testing in blood | Moderate-quality evidence (new recommendation) | — |
| Evaluation: In terms of imaging for evaluation of prolonged (≥ 96 hours) FN in IFD high-risk patients, perform CT of the lungs | Low-quality evidence | Lungs consistently most commonly affected site. Optimal timing of initial and repeated imaging not known. |
| Treatment: In IFD high-risk patients with prolonged (≥ 96 hours) FN unresponsive to broad-spectrum antibacterial agents, initiate caspofungin or liposomal amphotericin B for empirical antifungal therapy | High-quality evidence | — |
| FN = fever and neutropenia; CVC = central venous catheter; IFD = invasive fungal disease; AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia; HSCT = hematopoietic stem cell transplantation; PCR = polymerase chain reaction; CT = computed tomography | | |
| Source: [323] | | Table 15 |

recommendation to avoid the routine use of CSFs after induction therapy [332; 337]. Pegfilgrastim, a recombinant G-CSF used to prevent neutropenia in adults, has been shown to be safe and effective for children [341].

The International Pediatric Fever and Neutropenia Guideline Panel is a multidisciplinary, multinational group of pediatric oncology and infectious diseases experts. In 2017, the Panel published an updated clinical practice guideline for the management of fever and neutropenia in children with cancer and in HSCT recipients [323]. The Panel addressed risk stratification and evaluation as well as therapeutic interventions, and it made strong or weak recommendations related to initial presentation, ongoing management, and antifungal therapy of pediatric fever and neutropenia. The Panel's strong recommendations are summarized in **Table 15** [323].

ANEMIA OR THROMBOCYTOPENIA

Myelosuppression caused by chemotherapy may lead to anemia and thrombocytopenia. In these cases, blood products may be needed. No hemoglobin level has been established as a threshold for transfusion of blood; the need for transfusion of packed red blood cells (preferred to whole blood) is based on careful evaluation of individual patients [332]. Transfusion was once done for a hemoglobin of less than 10 g/dL, but most clinicians now consider 7–8 g/dL as the threshold due to the risks associated with transfusions [320; 332]. Erythropoietin at a dose of 600 units/kg to 900 units/kg once weekly for 16 weeks has been shown to be safe for increasing the hemoglobin level and decreasing the need for transfusion among children 5 to 18 years of age who were being treated with myelosuppressive chemotherapy for nonmyeloid cancers [342].



According to the Council of Pediatric Hematology/Oncology Centres across Canada, prophylactic platelet transfusions are recommended at a platelet threshold of $10 \times 10^9/L$ for clinically stable pediatric patients receiving chemotherapy for leukemia.

(https://www.c17.ca/application/files/2916/2006/0821/C17_Platelet_Guideline_English_Summary_2011.pdf. Last accessed August 22, 2024.)

Strength of Evidence/Level of Evidence: 1C
(Strong recommendation, poor-quality evidence)

As with transfusion of blood products for anemia, the need for transfusion of platelets is based on the individual case. Platelet transfusion is rarely indicated during remission induction for ALL, but prophylactic platelet transfusions are usually given during treatment for AML when the platelet count declines to less than $10,000/mcL$ [332]. If a child has fever, sepsis, a history of bleeding, severe mucositis, coagulopathy, or hyperleukocytosis, prophylactic transfusion of platelets may be given with the presence of a higher platelet count (for example, $20,000/mcL$) [332]. If a child is to have an invasive procedure, a transfusion should be given to maintain a platelet count of $40,000\text{--}50,000/mcL$ [320].

METABOLIC DISTURBANCES

The rapid destruction of malignant cells can lead to a build-up of chemicals in the bloodstream. This accumulation of biochemicals can cause several metabolic disturbances, including hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia [329; 343]. Collectively, these abnormalities comprise tumor lysis syndrome, which is most commonly associated with high tumor burden [120; 121]. Prompt management of tumor lysis syndrome is necessary to prevent renal failure. The management approach has involved increased hydration with a hypotonic solution and administration of allopurinol; however, recombinant urate oxidase has been shown to be more effective than allopurinol [120; 121; 329; 343].

DEEP VEIN THROMBOSIS

The risk of deep vein thrombosis is increased for children with a central venous catheter (CVC), and the likelihood of thrombosis is higher for children who have had catheter-related infection or occlusion of the catheter [344]. Deep vein thrombosis (DVT) in these cases usually develops without signs or symptoms. In a study of 21 children with a catheter-related deep vein thrombosis, signs or symptoms occurred in only five [344]. Repeated complications, primarily occlusions, should prompt investigation for thrombosis [320; 344]. Treatment consists of a thrombolytic agent, such as tissue plasminogen activator [320; 345]. One prospective registry study found that insertion of peripheral central catheters (specifically, Hickman catheters), insertion in an angiography suite, and proximal-tip location significantly increased the risk of symptomatic CVC-related DVT. Positive family history of thrombosis also significantly increased the risk of CVC occlusion [346].

PALLIATIVE AND END-OF-LIFE CARE

The term palliative care is often used synonymously with end-of-life care. However, palliative care is increasingly being defined as care that focuses on enhancing the quality of life for the patient (child or adult) and family, regardless of whether curative treatment is being undertaken. As optimally defined, pediatric palliative care [178; 347; 348; 349; 350; 351; 352]:

- Begins at the time of diagnosis
- Is family-centered and includes the child and the child's family, including siblings
- Is delivered by a multidisciplinary team
- Addresses physical symptoms and psychosocial issues
- Addresses the family's spiritual issues (e.g., faith, culture, religion, clergy, questions about the meaning of pain/suffering and death/dying)

- Enhances the quality of life for the patient and family
- Provides assistance with advance care planning and practical concerns (e.g., location of end-of-life care)

Recognizing the need for more effective pediatric palliative care, the AAP issued a statement recommending that “the components of palliative care are offered at diagnosis and continued throughout the course of illness, whether the outcome ends in cure or death. Palliative care should be accessible in any setting, including home, hospital, and school” and should be patient- and family-centered [350; 353]. Despite the calls for a family-focused approach to pediatric palliative care, a gap remains between optimal family care and actual practice, due in part to the ambiguity and ambivalence about the meaning of “caring for the family” [352].

Effective communication among all caregivers and between parents and the patient is essential to providing optimum palliative care. The goals of treatment should be clearly articulated among the palliative care team and the family to facilitate collaboration and delivery of care [178]. As much as possible and appropriate, the child should be allowed to participate in discussions about the direction of care [350; 354]. Parents have repeatedly stated that compassionate, honest, and complete information, ready access to staff, emotional expression by staff, and staff support are critically important to their ability to make decisions concerning their children. Family needs in this area are high [355; 356; 357; 358].

ASSESSING AND MANAGING SYMPTOMS

The assessment and management of symptoms represent the cornerstone of palliative care [178; 359]. Symptom management is crucial not only to relieve physical and psychological suffering but also to avoid feelings of mistrust and fear [354]. In general, studies have shown that pain, fatigue, and nausea/vomiting are the most common physical symptoms in children being treated for cancer [178; 354; 360; 361; 362].

Symptoms differ, however, according to age, the type of cancer, the type of treatment, and the degree of distress they cause. For example, in one study, 35% of children/adolescents 10 to 18 years of age had clinically significant pain, lack of energy, drowsiness, nausea, cough, lack of appetite, and psychological symptoms; the most distressing symptoms were pain, insomnia, mouth sores, and difficulty swallowing [363]. A similar study of younger children, 7 to 12 years of age, demonstrated lethargy, pain, or insomnia occurring in approximately 33%, with pain, insomnia, pruritus, nausea, sadness, and worry being the most distressing symptoms [364].

Effective management of symptoms requires careful assessment, physical examination, and functional evaluation, all of which should be repeated at regular intervals to ensure ongoing alleviation. Several tools are available to assess pain. However, such tools are lacking for other symptoms, highlighting the importance of the patient’s self-report of symptoms. A symptom checklist for children can help facilitate monitoring and self-reporting of symptoms [362]. Symptom management should be timely and include both pharmacologic and nonpharmacologic strategies [178; 347; 354]. Because stress and anxiety can exacerbate physical symptoms, attention to psychosocial issues is essential for optimum symptom management.

Pain

Pain may be related to treatment, diagnostic procedures, and/or progressive disease. The patient’s self-report of pain, when possible, is the most reliable indicator [57; 354]. Assessment of pain must be appropriate for each child’s age, developmental level, and cultural context. Pain assessment tools have been developed for several different age groups among children/adolescents, from birth to 18 years of age, and for nonverbal or cognitively impaired children (**Table 16**) [57; 365; 366; 367; 368; 369; 370; 371; 372; 373; 374]. These tools are designed to either provide a score according to a set of behavioral cues, as in the case of infants and young children, or allow the child to self-report on the intensity and

| INSTRUMENTS USED FOR PAIN ASSESSMENT IN CHILDREN AND ADOLESCENTS | |
|---|--|
| Age of Child | Assessment Tool |
| Birth to 3 years of age | FLACC (Face, Legs, Activity, Cry, Consolability) CRIES ^a Neonatal Infant Pain Scale Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) |
| 3 to 7 years of age | Faces Scale Oucher Pain thermometers Body maps |
| Older than 7 years of age | Visual analog scale Verbal response scale |
| ^a The five parameters are crying, requires oxygen to maintain saturation greater than 95%, increased vital signs, expression, and sleepless. | |
| Source: [57; 365; 366; 367; 368; 369; 370; 371; 372; 373; 374] | |

Table 16

location of pain. Several tools have been modified and validated for use among children/adolescents of different races/ethnicities, including Black, Hispanic, Asian, and Alaska Native populations [375; 376; 377; 378].

It is also helpful to evaluate behaviors to determine if a young child has pain. Indicators of pain in infants include facial expressions such as frowning, a furrowed brow, a quivering chin, crying, sucking, flexing of fingers and toes, and breath-holding. Behavioral indicators are also important for older children, as they may not admit to having pain because of fear of an injection. Indicators in older children include decreased energy level; decreased eating; lack of interest in usual activities; holding or protecting part of the body; seeking comfort or closeness; and whining or groaning [365; 366; 367; 368; 369].

Physical examination and functional evaluation are other components of pain assessment. During the examination, the clinician should watch closely for nonverbal cues that suggest pain. These cues are especially important when examining patients who are unable to verbally communicate. To evaluate how pain may be influencing function, the clinician should watch the patient to see how pain limits movements and should ask the patient or family how the pain interferes with normal activi-

ties. Determining functional limitations can help enhance patient compliance in reporting pain and adhering to pain-relieving measures, as clinicians can discuss compliance in terms of achieving established functional goals.

As with adults, using the WHO ladder to manage pain is effective for children [379; 380; 381]. The WHO ladder involves a three-step approach, with the strength of the analgesic agent increasing according to the severity of pain. There are two important underlying principles of the WHO ladder. First, analgesics should be administered on a regular schedule rather than on an as-needed basis. This approach is not only more effective at controlling pain but also avoids unnecessary pain as a prompt for the next dose. The second principle is that treatment should correspond to the intensity of pain as reported by the patient, regardless of whether treatment at a previous step was carried out [379].

The WHO ladder calls for the use of nonopioid and opioid analgesic agents (*Table 17*). Rotation of opioids has been found to be effective and can help avoid dose-limiting toxicity [178]. Medications for pain should be given by the easiest, least painful route (oral, sublingual, or parenteral for children with a central venous catheter), avoiding intramuscular injections whenever possible [178; 354].

| PHARMACOLOGIC APPROACHES TO PAIN RELIEF IN CHILDREN AND ADOLESCENTS | | | |
|--|---------------------------------------|-------------------------------------|--|
| Drug (Route) | Typical Initial Dose, Interval | Maximum Dose | Notes |
| Nociceptive Pain | | | |
| Acetaminophen (PO, PR) | 10–15 mg/kg every 4 to 6 hrs | 1.0 g/dose, 4 g/day | Oral form available as tablets, chewable tablets, liquid, and drops |
| Ibuprofen (PO) | 5–10 mg/kg every 8 to 12 hrs | 400 mg/dose, 1.2 g/day | Oral form available as tablets, chewable tablets, liquid, and drops |
| Choline magnesium trisalicylate (PO) | 7.5–15 mg/kg every 12 hrs | 1.0 g/dose | Oral form available as tablets and liquid |
| Naproxen (PO) | 5–10 mg/kg every 12 hrs | 1.0 g/dose | Oral form available as tablets and liquid |
| Ketorolac (PO, IV, IM) ^a | 0.5 mg/kg every 6 hrs | 10 mg/dose (PO); 30 mg/dose (IV) | – |
| Codeine (PO, SQ, IM) | 0.5–1 mg/kg every 3 to 4 hrs | 60 mg/dose | Oral form available as tablets and liquid |
| Tramadol (PO) | 1–2 mg/kg every 6 hrs | Titrate | – |
| Morphine (PO, SL, PR) | 0.15–0.3 mg/kg every 3 to 4 hrs | Titrate | Oral form available as tablets and liquid |
| Morphine (IV, SQ, IM) | 0.1 mg/kg every 2 to 4 hrs | Titrate | – |
| Hydromorphone (PO, PR) | 0.03–0.08 mg/kg every 3 to 4 hrs | Titrate | Oral form available as tablets and liquid |
| Hydromorphone (IV, SQ, IM) | 0.015 mg/kg every 2 to 4 hrs | Titrate | – |
| Methadone (PO) | 0.2 mg/kg every 8 to 12 hrs | Titrate | Oral form available as tablets and liquid |
| Methadone (IV, SQ, IM) | 0.1 mg/kg every 8 to 12 hrs | Titrate | – |
| Fentanyl (Transdermal) | 0.5–1 mcg/kg/hr every 48 to 72 hrs | Titrate | – |
| Fentanyl (Lozenge [sedative]) | 5–15 mcg/kg every 4 to 6 hrs | Titrate | – |
| Fentanyl (IV, SQ) | 1–2 mcg/kg every 1 to 2 hrs | Titrate | – |
| Oxycodone (PO) | 0.1 mg/kg every 3 hrs | Titrate | Oral form available as tablets and liquids |
| Neuropathic Pain | | | |
| Gabapentin (PO) | 5 mg/kg every 6 to 8 hrs | 3.6 g/day | – |
| Amitriptyline (PO) | 0.2 mg/kg at night | 1 mg/kg/night | – |
| ^a Give for no more than five days. PO = by mouth; PR = per rectum; IV = intravenously; IM = intramuscularly; SL = sublingually; SQ = subcutaneously. | | | |
| Source: [57; 354] | | | Table 17 |

There are no randomized controlled trials addressing the management of breakthrough pain in children with cancer. Limited data and considerable experience indicate that breakthrough pain in this patient group is common, underassessed, and undertreated [382]. Clinicians and parents should also be alert to breakthrough pain, which occurred in 57% of children with cancer in one study [383]. The risk of breakthrough pain was higher for younger children (7 to 12 years of age) than older children (13 to 18 years of age). The high rate of breakthrough pain reflects the importance of pain assessment as an ongoing process, with assessment and documentation at regular intervals. The optimum interval varies. In general, patients with more severe disease should be evaluated more frequently. Measures of pain relief should also be documented, especially with regard to efficacy.

An ideal therapeutic agent would be easy to administer and rapid in onset with short duration. The most common and effective strategy seems to be multimodal analgesia that includes an immediate-release opioid (e.g., morphine, fentanyl, hydromorphone) administered intravenously by a patient-controlled analgesia pump, ensuring an onset of analgesic action within minutes. Intranasal fentanyl (or hydromorphone) may be an alternative, but no pediatric data have been published for commercially available fentanyl transmucosal application systems, and these products cannot yet be recommended for use with children with cancer and breakthrough pain [382].

Pain medication should be complemented by non-pharmacologic interventions that are begun early in the course of treatment. These interventions should be age-appropriate. Touch, massage, stroking, and rocking work well for infants, toddlers, and young children; distraction is effective for older children, as are guided imagery, music and art therapy, play therapy, controlled breathing, and relaxation techniques [57].

Fatigue

Fatigue is often described by children as “drowsiness,” feeling “sluggish,” or having a loss of energy. As many as 70% to 80% of children/adolescents with cancer note one of these feelings, which can be caused by many factors, including medications (chemotherapy agents and opioids), pain, anemia, progressive disease, and psychological issues [348; 354; 362]. Tools to assess fatigue, for use by patients (7 to 12 years of age), parents, and healthcare staff, have been developed but require evaluation and validation in prospective studies [384; 385]. Signs and symptoms of fatigue include asthenia, sleep disturbances, low energy level, and decreased participation in activities. Gradual increases in exercise and school activities and cognitive-behavioral approaches to improve coping skills may be helpful.

One study evaluated the change in children’s and adolescents’ fatigue scores during cancer treatment and described possible causes of fatigue [386]. Forty children 7 to 12 years of age, 29 adolescents 13 to 15 years of age, and one parent were included in the study. Cancer-related fatigue was measured using the Child Fatigue Scale, the Adolescent Fatigue Scale, and the Parent Fatigue Scale. Children, adolescents, and parents reported a statistically significant increase in fatigue scores during their treatment, with medical procedures and the hospital environment reported as major causative factors of the fatigue experienced [386]. Results of another study indicate that cancer-related fatigue results in a low health-related quality of life for pediatric patients [387].

Gastrointestinal Symptoms

Nausea and vomiting are the most common gastrointestinal symptoms in the pediatric cancer setting; other symptoms include constipation, diarrhea, and anorexia/cachexia. Nausea and vomiting can be a challenge to assess, especially in young children who are unable to articulate the feeling of nausea.

Inactivity, signs of weakness, and/or lack of appetite may indicate nausea. The choice of antiemetic is based on the likely cause of nausea and vomiting [178; 354]. The best agents for nausea and vomiting caused by chemotherapy or radiation therapy are 5-HT₃ receptor antagonists, such as ondansetron and granisetron. Other choices are prochlorperazine, scopolamine, dronabinol, and metoclopramide [119; 178; 354; 388]. Anticipatory nausea may be alleviated by benzodiazepines and the use of relaxation techniques [329; 354]. Use of a hydration fluid may be necessary to prevent dehydration in a child who is vomiting excessively [354]. Taking medications after meals, when possible; eating small, frequent meals; and avoiding strong smells may also help ease nausea [178].

Constipation is also common among children/adolescents with cancer and is usually related to medications, particularly opioids and vincristine [354]. This symptom is often under-recognized or undertreated by clinicians [178]. The optimum treatment for constipation is prevention through a variety of measures, including movement/exercise, adequate fluid intake, and increased fiber intake. Regular use of laxatives is recommended during treatment with opioids [57].

Mucositis

Mucositis occurs in as many as 50% of children/adolescents receiving chemotherapy. It is often associated with radiation therapy to the head and neck area [329; 343]. Mucositis can affect the mouth, esophagus, stomach, duodenum, and colon, and the severity depends on the type of chemotherapy used. High-dose methotrexate and high-dose cytarabine are considered the most damaging to mucosa [343]. Small studies have shown that chlorhexidine is beneficial for alleviating mucositis in children, but the results must be confirmed by larger trials [389]. One literature review focused on randomized clinical trials to evaluate the effectiveness of chlorhexidine mouthwash in alleviating mucositis

in children receiving chemotherapy [390]. Control groups consisted of placebo, no intervention, or another intervention group. Mucositis was scored using either the WHO scale or the modified Oral Assessment Guide. Five studies fulfilled the inclusion criteria, in which chlorhexidine was evaluated. Four of the five showed a significant preventive effect on the development or severity of mucositis when chlorhexidine mouthwash was used. The remaining study showed no benefit compared with the placebo group [390]. Other helpful measures include the use of ice chips during administration of chemotherapy, excellent oral hygiene, analgesic agents, and avoidance of irritating foods or fluids, such as citrus fruits and juices [329; 343].

Pruritus

Pruritus usually occurs as a side effect of medications, especially morphine and other opiates, and may also be associated with progressive lymphoma [57]. Physical manifestations of pruritus include excoriation, erythema, and lichenification; rubbing of the eyes, nose, or skin may also indicate pruritus [256]. Discontinuing use of the causative medication, if possible, is the preferred treatment approach. Moisturizing creams may be used for dry skin, and systemic corticosteroids or antihistamines may be helpful for more severe cases [256].

PSYCHOSOCIAL AND SPIRITUAL ISSUES

Anxiety, worry, and sadness are among the most frequently occurring psychological symptoms for children/adolescents with cancer [178; 354; 363]. These emotions are a normal response to many effects of cancer and its treatment, including pain and other symptoms, disease progression, impaired function, isolation, loss of control, concern about parents and other family members, and loss of a “normal” life [178]. Clinicians and other caregivers should address such fears and concerns honestly and should encourage family members to discuss them openly with each other and the patient.

Specially trained members of the palliative care team can play an important role in helping patients and their families deal with psychosocial issues. Child-life specialists and creative art therapists are available in hospital settings to guide patients in expressing their feelings through creativity and imagination [178]. This process can help foster the patient's sense of control and independence and enhance self-esteem [178]. Psychologists on the palliative care team can assess the psychological needs of both the patient and family and implement interventions as appropriate.

Spiritual support for the child and family is an important component of palliative care and is usually the primary responsibility of a pastoral care worker on the palliative care team. However, all professional caregivers should provide spiritual support. Spirituality transcends religion and involves such concerns as hope, forgiveness, love, and sense of meaning [354]. Caregivers should talk with the patient about his or her dreams and hopes for the future and encourage the patient and family to express spiritual concerns and engage in their religious traditions [351].

PROVIDING END-OF-LIFE CARE

The high survival rates for children with leukemia and lymphoma has of course led to a decreasing number of childhood deaths. Still, 10% to 30% of patients will have relapsed disease and die. Despite the fact that these children would benefit from hospice care delivered by a multidisciplinary palliative care team, studies have shown that most children with cancer die in the hospital [391]. However, one report indicated a significant increase in the number of children/adolescents who died at home since the late 1990s, and a survey of bereaved parents and pediatric oncologists ranked home as their first choice for end-of-life pediatric cancer care [392; 393]. Still, hospice care is used by only 5% to 25% of eligible children in the United States and Canada [394].

The movement to formally develop high-quality palliative care programs began in the late 1990s. The AAP issued the first policy statement on pediatric palliative care in 2000. Then in 2003, the Institute of Medicine recommended specialty training in pediatric palliative care and development of collaborative guidelines and protocols tailored to children [395; 396]. In 2006, St. Jude Children's Research Hospital (St. Jude) made development of a pediatric palliative care program an institutional priority, with the mission to "provide each child living with or dying from a catastrophic illness with state-of-the-art patient- and family-centered physical, emotional, and spiritual care with the goal to attend suffering, promote healing, and improve quality of life" [397; 398; 399]. In 2007, St. Jude initiated a one-year pilot project to evaluate the role of pediatric palliative care expertise as part of the interdisciplinary care team. The pilot program was a success, and in 2008, St. Jude fully implemented the Quality of Life Service (QoLS) program throughout the hospital. The program functioned on a consultative basis, working together with patients' primary care teams. QoLS consults included advanced care planning; symptom control; care coordination and continuity; emotional, social, and spiritual support; end-of-life care; and bereavement support in inpatient, outpatient, and home-based settings. The QoLS also provided more than 200 educational offerings across all professions in the institution and partnered with medical and psychosocial providers [400].

In 2016, members of the St. Jude Department of Oncology, Division of Quality of Life and Palliative Care, in collaboration with others, published results of a study that described the institution's eight-year experience integrating palliative care with cancer care for pediatric patients [400]. According to the results, new consults per year increased from 17 in the pilot year to 115 in 2014. Patient encounters increased from 58 in the pilot year to 1,297 in 2014, indicating that the QoLS not only saw more patients but also followed them more regularly and for longer periods of time. Mean encounters per

BARRIERS TO PEDIATRIC END-OF-LIFE CARE

- Rarity of death among children
- Immeasurable parental distress at loss of child
- Unrealistic expectations or denial of parents
- Association of palliative care with “giving up” or hopelessness
- Provider sense of failure when a child dies
- Difficulty in determining prognosis
- Lack of symptom assessment tools
- Lack of knowledge regarding pediatric dosing of symptom-relief medications
- Fragmentation of medical and psychosocial/spiritual services for children
- Lack of adequately trained pediatric hospice professionals
- Lack of comprehensive, coordinated pediatric palliative care programs
- Inadequate education for providers and families about palliative care

Source: [178; 349; 352; 354; 400; 404; 407; 408; 410; 411; 412]

Table 18

patient by year of initial consult more than tripled, from 5.1 in 2007 to 16.1 in 2014, substantiating that patients were seen with increasing regularity and sustained continuity from the time of consultation [400]. In the early years of the program, the primary patients’ goal of care at initial consultation was focused on “comfort only,” but this shifted over time to a “goal of cure,” which increased from 25% of patients in 2008 to 58% in 2014. Following the pilot year, there was also a shift in patients’ location of death from primarily inpatient settings to increased use of outpatient settings. The authors were unable to determine the preferred location of death, but increased use of outpatient locations suggest that increased availability of palliative care services facilitated outpatient end-of-life care and a greater ability to satisfy the preferences of patients and their families [400]. This led the American Society of Clinical Oncology to recommend palliative care services for all high risk oncology patients. Yet, as stated, both adult and pediatric oncologists refer only a small proportion of patients to palliative care services, and then it is late in the disease course when the goal of cure is no longer an option [401; 402; 403; 404].

There is a significant association between race/ethnicity and hospice enrollment, with Latinos enrolled in hospice significantly more often than patients of other races. However, by the time of death, 34% of Latinos and 50% of non-Latinos had withdrawn from hospice [405]. The lack of appropriate end-of-life care has a high price; one study indicated that 89% of dying children suffered “a lot” or “a great deal” from at least one symptom in their last month of life [406]. The findings of that study and others, including the Institute of Medicine (IOM) report *When Children Die: Improving Palliative and End-of-Life Care for Children and Their Families*, have prompted further research on the topic [349; 359; 364].

Several barriers to pediatric end-of-life care have been identified (**Table 18**) [178; 349; 354; 407; 408]. Because of the low rate of mortality, the lack of relevant educational programs, and the paucity of palliative care services across the United States, particularly in pediatric facilities, many healthcare professionals are left inexperienced with pediatric end-of-life care [407; 408; 409; 410]. In addition, the availability of sufficiently trained pediatric hospice professionals is limited because of the low rate of

hospice admissions for children/adolescents. One survey found that pediatric palliative care is only offered in 58% of Children's Oncology Group institutions caring for children with cancer [408]. Other challenges to providing high-quality care include growing demands for expansive care, discomfort in providing mental health/bereavement services to families, and reimbursement models that do not support comprehensive care [352]. The increasing demand for expansive care, including palliative care services, led St. Jude to expand the QoLS resources, which included: more clinical and research staff; a hospice and palliative medicine fellowship training program; and creation of a home-based palliative care and hospice program in collaboration with the local children's hospital and community hospice [400].

The potential death of a child goes against the natural order and is associated with feelings of distress and failure for parents as well as clinicians. Parents and family members continue to hope for a cure and often see the end of curative therapy as "giving up" [354; 413]. In a survey of pediatric oncologists, the most frequently reported barrier to end-of-life care was unrealistic expectations of the family, noted by approximately 48% of respondents [414]. Family denial was another commonly reported barrier, noted by 36% of respondents [414]. Paradoxically, the high rates of cure and long-term survival associated with most pediatric leukemias and lymphomas foster parents' hope for cure [349; 413]. Feelings of denial and hope are also factors in late hospice referrals. Most hospice referrals are made at the time of disease progression (44%), at the end of therapeutic options (26%), or at the time of imminent death (20%) [407]. Earlier hospice referral, such as at the time of disease relapse, would enhance the quality of care for children and their families, yet only 2.5% of referrals are made at that time [407]. A survey of pediatric oncologists found that they were less likely to refer patients after chemotherapy had been stopped and more likely to refer at the time of diagnosis of cancer/incurable cancer. They also preferred that "supportive care" be used in place of "palliative care," because the term was negatively perceived by their patients [404].

Clinicians usually recognize the lack of a realistic chance for cure before parents and should talk openly with parents about discontinuing aggressive treatment and directing attention to enhancing the quality of life that remains for the child [415]. At this point, it is helpful to emphasize the importance of alleviating pain and other symptoms and making the child comfortable [178]. In addition, the family should understand that the primary oncologist and/or primary care provider will remain involved in the child's care [178]. Members of the palliative care team should discuss goals of treatment with the family, outline choices for interventions as the end of life draws near, and establish limits of care as the health status changes [178; 347].

The symptoms present at the end of life are similar to those that occur during treatment, although research has shown that some are more common or more intense in the end-of-life period [359]. Pain, nausea, drowsiness, and energy loss have been reported by more than half of children/adolescents (6 to 17 years old) with advanced cancer [359; 416]. Other common symptoms include dyspnea, weight loss and anorexia, vomiting, and constipation [359]. Bone marrow failure may occur as a result of progressive disease, leading to infection, fatigue, and bleeding [359]. Transfusion of blood products can provide symptomatic relief, and their use should be considered on an individual basis.

In a study in which symptoms among various types of cancer were evaluated, the symptoms most commonly associated with pediatric leukemia and lymphoma during the end-of-life period were pain (95%), weakness (83%), anemia (76%), bleeding (66%), infection (59%), and weight loss and anorexia (56%) [359]. Overall, symptom management was more effective for children with leukemia or lymphoma than for children with solid tumors, but weakness and anorexia remained intractable among all patients [359]. How aggressively symptoms are treated will depend on many factors, including how close the child is to death and the defined limits of care. The underlying goal is to keep the child as comfortable as possible. In addition to the management of symptoms, "comfort interventions" should be integrated into care (*Table 19*) [417].

| COMFORT CARE INTERVENTIONS | |
|---|--|
| Intervention | Description |
| Quiet presence | Sit quietly to provide calming influence and comfort that family is near |
| Massage | Ask the child what he or she would like massaged (e.g., feet, back); play quiet music to aid in relaxation |
| Touch | Hold hand or gently touch or stroke the child in familiar comforting manner |
| Music/television/DVD | Play child's favorite music, television show, cartoon, movies for familiar comfort and distraction |
| Toys/blanket | Provide the child with his or her favorite item for comfort |
| Picture board | Have family and friends gather pictures of fun past events shared with the child and place the pictures on a bulletin board or poster board near the bed |
| Books | Ask the child which book he or she would like to hear and read aloud |
| Family, friends, spiritual support person, pets | Honor the child's requests to see family members, pets, etc. |
| Source: [417] | |

Table 19

Dyspnea is particularly present near the end of life, occurring in approximately 30% of children with leukemia and lymphoma [359; 406]. Objective measures of dyspnea do not correlate well with subjective sensation. But because the symptom is extremely distressing and frightening to both the patient and the family, treatment should be directed at alleviating the patient's discomfort and distress promptly [354]. The use of oxygen, opiates, and/or benzodiazepines can provide symptomatic relief [178; 354]. Nonpharmacologic interventions include relaxation techniques and the use of fans to blow air across the child's bed [178].

The need for spiritual support is heightened during the end of life as children and family prepare for dying [354]. Faith and the involvement of clergy play a critical role in decision making about end-of-life care [351]. A survey of pastoral care workers indicated that more than half of patients and 60% to 80% of parents had spiritual needs [418]. Because the illness experience, primary fears, and concept of death range according to the child's developmental age, appropriate spiritual interventions vary (**Table 20**) [178; 347; 354]. Patients grieve because of the isolation and loss associated with the disease, and the palliative care team should provide support for this process [419]. Many parents avoid talking with their ill child about death for many reasons,

primarily because they do not wish to acknowledge the fact to themselves or the child. However, most dying children are aware that they are dying, and talking about it with family can help them to express important feelings and to say good-bye [178; 349]. One retrospective study showed that parents who talked with their child about death did not regret it, whereas more than 25% of parents who did not talk to their child about death regretted that decision [419]. In addition, levels of anxiety were higher among parents who did not discuss death with their child. Another retrospective study investigated the rationale and consequences of a parent's decision to discuss death with their child [420]. The study involved bereaved parents of a child who died of cancer. Eighty-six parents of 56 children responded to questions about the topic. Of these, 55 parents of 35 children did not discuss the impending death. Their reasons for not discussing death were varied and included: parents' inability to discuss the impending death; their desire to protect their child; their general views about talking with children; their perceptions of their child's characteristics; the child's unwillingness to discuss death; a lack of opportunity to have the discussion; and the child's disability. The parents who did discuss death with their child generally used symbolic and/or religious narratives, or they discussed the subject directly and briefly. A majority of the parents interviewed felt

| FEARS, CONCEPTS OF DEATH, AND SPIRITUAL INTERVENTIONS ACCORDING TO DEVELOPMENTAL AGE OF CHILDREN AND ADOLESCENTS | | | |
|---|--|---|--|
| Age | Primary Fears | Concept of Death | Spiritual Interventions |
| Infant | Separation; strangers | Unable to differentiate death from temporary separation or abandonment | Provide consistent caretakers Minimize separation from parents and significant others Decrease parental anxiety Maintain crib/nursery as “safe place” (no invasive procedures) Encourage parental presence Encourage/facilitate use of spiritual support system for the family |
| Toddler | Separation; loss of control | Recognizes death in terms of immobility Often viewed as reversible, temporary, or foreign | Minimize separation from parents and significant others Keep security objects at hand Provide simple, brief explanations Explain and maintain consistent limits Encourage participation in daily care Provide opportunities for play and play therapy Reassure the child that disease is not punishment (by God, Higher Power, or other authority figure) |
| Early school-age child | Bodily injury and mutilation; loss of control; the unknown; the dark; being left alone | Recognizes death in terms of immobility Often viewed as reversible, temporary, or foreign Begins to question and develop a mature concept | Do not underestimate level of comprehension Provide simple, concrete explanations Provide advance preparation (days for major events, hours for minor events) Use pictures, models, actual equipment, medical play when providing explanations When appropriate, initiate discussion of love and caring from Higher Power to relieve anxiety and loneliness Show behavioral qualities of love, trust, respect, caring, and setting of firm limits and disciplining without anger |
| School-age child | Loss of control; bodily injury and mutilation; failure to live up to expectations of important others; death | Recognizes all the components of irreversibility, universality, nonfunctionality, and causality | Provide choices whenever possible Stress contact with school or organized religious peer group Use diagrams, pictures, and models for explanations Emphasize the “normal” things the child can do Reassure child that he/she has done nothing wrong; hospitalization is not punishment Be alert to anxiety about being punished by deity Provide appropriate concrete explanations in response to questions regarding spiritual beliefs Continue spiritual rituals; if appropriate, promote prayer and relationship with child’s concept of God Model behaviors that show forgiveness and acceptance |
| Adolescent | Loss of control; altered body image; separation from peer group | Speculates on the implications and ramifications of death Understands effect of death on other people and society as a whole Future-oriented, difficult to understand reality of death as a present possibility | Allow adolescent to be an integral part of decision making regarding care Give information sensitively Allow as many choices and as much control as possible Be honest about treatment and consequences Stress what the adolescent can do for himself or herself and the importance of cooperation and compliance Assist in maintaining contact with peer group Provide answers without bias and enable participation in discussions of illness in terms of philosophical or spiritual beliefs Encourage contact with friends and use of spiritual rituals if appropriate Observe and document verbalizations of adolescent’s values and beliefs |

Source: [178; 347; 354]

Table 20

positive about their ultimate decision [420]. Parents should be encouraged to talk to their spiritual or religious advisor for guidance in how to talk with their child [178]. Strict adherence to Western ethical norms may not always be the best choice for migrant or immigrant patients and their families. Instead, an approach that is based on cultural humility may allow for a greater understanding and improved communication between patient/family and caregivers [421].

Bereavement and Grieving

Bereavement and grieving support are other essential components in end-of-life care [178; 352; 419]. Bereavement care may best address grief by providing family members with outlets to communicate feelings and memories about a dying or deceased child [422; 423]. It is important to provide support for siblings, who report often feeling left out and abandoned [352; 419]. Despite a growing body of literature substantiating the needs of siblings, they continue to be unmet [424; 425; 426; 427]. Siblings also may experience post-traumatic stress symptoms, poor quality of life, and a sense of aloneness [428]. Healthcare providers can address the needs of siblings by [428; 429; 430; 431]:

- Engaging them in discussions about care
- Providing them with specific caregiving tasks
- Ensuring that they have adequate support (e.g., child life specialist, social worker, support group) and education
- Encouraging them to remain active in activities important to them
- Identifying a “safe adult” in which the sibling can confide
- Making mental health referrals when appropriate
- Asking sibling directly about his or her experiences

Grief can be prolonged and exacerbated by several factors, including the loss of the child’s quality of life, the family’s dissatisfaction with the provider-family rapport and communication, cultural insen-


sitivity, and lack of follow-up [178]. This finding underscores the need for effective end-of-life care and open, honest, empathic communication from the palliative care team. In addition, caregivers should respect the family’s cultural context when designing and discussing treatment plans and goals. Also, it is imperative that family members be allowed to hold their child during and after death and to carry out family, religious, and cultural rituals.

In most cases, the grieving process is considered to be in its end stages when bereaved individuals are comfortable with a restructured lifestyle [432]. However, parental grief related to the loss of a child is generally experienced more intensely and differently than other forms of grief because a child’s death is atypical in developed countries [433]. Parents can maintain healthy bonds with their deceased children by sharing memories about their children, writing biographies, performing annual religious rituals, and establishing monetary memorials [434; 435]. The maintenance of the connection through conversation appears to aid in healing for grieving parents [435].

Grieving is relieved by the continued involvement and support of the palliative care team and the primary care provider after a child’s death [436]. Attendance at a memorial service and handwritten notes of sympathy from the clinician and medical team are valued highly by grieving families [429; 437]. The clinician should emphasize the personal strengths of the family that will help them cope with the loss and should offer help with specific issues. The note should also invite the patient to contact the physician or other members of the palliative care team with questions. Provision of bereavement services varies. Programs usually involve contacting the family at regular intervals to provide resources on grieving, coping strategies, professional services, and support groups. Frequent contact with family after death can ensure that families are adjusting to the loss [352]. Referrals for psychosocial and spiritual interventions should be made as early as possible to optimize their efficacy. Bereavement services should extend for at least one year after the patient’s death, but a longer period may be necessary.

PSYCHOSOCIAL ISSUES FOR THE PATIENT AND FAMILY

In the 1960s, psychosocial interventions focused on bereavement during palliative care because of the low survival rates for common childhood cancers. Today, the excellent survival rates produced by advances in treatment challenge clinicians with more complicated familial psychosocial issues and increase the need for a variety of intervention strategies.



The Psychosocial Standards of Care Project for Childhood Cancer recommends that youth with cancer and their family members should routinely receive systematic assessments of their psychosocial health care needs.

(<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6397048>. Last accessed August 22, 2024.)

Strength of Recommendation/Level of Evidence:
Strong/High

Addressing psychosocial issues is an integral component of comprehensive cancer care not only to help patients and their families cope with a cancer diagnosis and the stress related to treatment, but also to help alleviate latent psychosocial distress. The diagnosis and course of a child's cancer can detrimentally affect family members' interactions with one another and their social environment. Yet, responding to childhood cancer can prompt positive growth if psychosocial issues are managed effectively. Although many families are resilient, the negative psychosocial consequences for one or more family members touched by a child's cancer can be lasting and severe. Studies have found that the psychological distress experienced by family members is often greater than that experienced by the patient [438]. For example, parents, who are already distressed by their child's illness also often struggle with conflicted feelings when their role as parent means they must manage the competing needs of various family members. The authors of one qualitative analysis sought to identify parental expectations of support from healthcare providers during a child's life-threatening

illness [439]. Based on thematic analyses conducted with data from 31 semi-structured interviews of parents, the authors identified three themes and one overall expectation [439]:

- "Help us survive this."
- "Let's fight together. Please fight with me, not against me, to care for my family."
- "Guide me through the darkness. I am suffering."

The overall expectation was for mutuality with the healthcare providers and healthcare system in order to keep fighting together for the family's survival [439].

Clinicians in the pediatric and family medicine setting are well-positioned to monitor family members' coping abilities and psychosocial states during the trajectory of the illness. Most parents believe that psychosocial issues should be discussed with the child's physician and would find that discussion to be valuable [177]. However, less than 50% of parents raise such topics, and parents report that only 15% to 20% of physicians assess the family's psychosocial issues [177]. Clinicians may be able to provide the auxiliary emotional support and guidance the child and his or her family needs [439; 440]. If necessary, they can refer at-risk family members to intervention programs/specialists to improve coping strategies and promote healthy psychological adjustment.

PSYCHOSOCIAL ISSUES FOR THE PATIENT

The anxiety and stress associated with cancer and its treatment require that patients use effective coping mechanisms. Due to the wide range in age of patients with childhood leukemia and lymphoma, coping mechanisms vary according to a child's level of understanding and stressors. Similarly, the potential late effects and the actions to promote well-being also differ. In addition to disrupting a child's psychological well-being, the period of cancer treatment affects a child's relationships with peers and school performance. The psychosocial issues discussed in this section focus primarily on issues arising during treatment.

Coping Mechanisms

Coping has been defined as the “constantly changing cognitive and behavioral efforts to manage the specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person” [441]. The two main types of coping are problem-focused and emotion-focused [441]. The goal of problem-focused coping is to change aspects of an event to relieve distress. If the individual cannot manage a stressful event, emotion-focused coping is used to regulate feelings or alter his or her interpretation of the situation. Emotion-focused coping mechanisms intended to alter interpretations are categorized into four control strategies: predictive control, vicarious control, illusory control, and interpretative control [360]. These control strategies are used commonly by children and their parents when coping with cancer [361; 362]. Using combinations of problem-solving and emotion-regulating mechanisms to meet each cancer-related challenge decreases short-term distress and promotes healthy social and cognitive development and adaptation [442].

The majority of studies have shown that the psychological profile of childhood leukemia or lymphoma survivors is similar to population norms, suggesting that most children with leukemia or lymphoma will cope effectively with their cancer experience [443; 444]. However, subgroups of these patients are at special risk for poor psychological outcomes [445; 446; 447].

As children learn and grow, they construct the world around them differently. Thus, the developmental age at the time of a cancer diagnosis defines the type and complexity of coping mechanisms available to the patient throughout the course of the disease [448; 449]. The level of understanding and stressors, coping mechanisms, potential long-term effects, and actions a medical team can take to promote well-being vary according to the developmental age [450; 451].

Infants (Birth to 12 Months of Age)

Level of understanding and stressors: The infant’s understanding of treatment is limited to pain and comfort. Infants undergoing cancer treatment can have a difficult time developing trust and bonding with parents because medical procedures often separate infants from their parents, disrupt household routines, and cause pain. An infant frequently separated from parents may experience feelings of abandonment [452].

Coping mechanisms: Infants are limited to certain aspects of emotion-focused coping because crying is an emotional release. With few available coping mechanisms, the infant’s emotional development and future coping abilities can be affected adversely by cancer.

Potential long-term effects: A child diagnosed with cancer during infancy may experience cognitive delay. Difficulty bonding with parents may affect subsequent developmental stages.

Actions to promote well-being: To offset cancer-related developmental disruptions, the medical team should allow parents to stay in the infant’s room and attend to his or her needs, such as feeding, diaper changing, comforting, and bathing. In addition, minimizing the number of staff caring for the child may promote trust and a sense of routine.

Toddler (18 Months to 3 Years of Age)

Level of understanding and stressors: A toddler diagnosed with cancer has different developmental challenges than an infant. However, a toddler still has limited understanding of cancer-related cause and effect and has limited access to coping mechanisms. Because a toddler’s sense of time is restricted to the present, the child will likely not grasp that staying still reduces the time and pain associated with treatment. The toddler’s level of understanding may exceed his or her ability to communicate, which is another barrier to coping. During this stage of development, a toddler explores his or her sense of self, property, and security. Cancer therapy, however, challenges a toddler’s autonomy and feeling of safety. For instance, a toddler will likely say “no” to treatment, only to be vetoed. In addition, the

toddler may perceive that his or her parents cannot protect him or her from pain associated with treatment. Although a toddler's understanding of death is minimal, he or she likely has some concept of loss and separation and may fear abandonment when parents are out of sight. The health-related quality of life for toddlers with cancer is significantly worse than that of healthy age-matched controls. Cancer most strongly affects a toddler's sleep, appetite, behavior, and liveliness [453].

Coping mechanisms: A toddler has access to more emotion-focused coping strategies to regulate stress than an infant and has developed some problem-focused strategies. Communication skills, although limited, can be used to express emotions and seek parental support and solace. To gain more control over his or her environment, a child may hold a parent's hand during a painful procedure to know that the parent is near. Pain endured during a procedure may be associated with the staff member providing the respective treatment.

Potential long-term effects: During this stage, a cancer diagnosis may postpone language and motor development as well as bladder and bowel control. Toddlers' development in these areas may regress.

Actions to promote well-being: Parental handling of a toddler's cancer-independent needs should be made routine to minimize the child's feelings of abandonment or insecurity. Motor skill development accelerates at this age; therefore, safe levels of physical activity should be promoted. Also, giving a toddler limited choices, even in the smallest matters, supports their sense of autonomy. For instance, a provider could ask a toddler, "Would you like a bandage with cartoon characters or a regular one?"

Early School-Age (4 to 7 Years of Age)

Level of understanding and stressors: Although the degree of development of a child at 4 years of age may be much different from that of a child at 7 years of age, children of these ages have surpassed the cognitive and emotional development of toddlers. Concepts of empathy and guilt are developing.

Injury and death may be believed to be magically reversible, as in many children's cartoons. Patients who are 6 to 7 years of age at the time of a cancer diagnosis have been shown to have poor health-related quality of life with respect to autonomy, motor skills, and cognitive functioning two months after treatment [453].

Coping mechanisms: Early school-age children can cope using emotion-focused methods and some problem-focused strategies. A child in this age category can communicate feelings and needs more clearly than a toddler and has a better understanding of cause and effect. Both of these factors elevate the child's ability to cope actively with stressors and express negative emotions. Children understand the concept of hopefulness during this stage, which can promote a positive outlook and adaptive coping [454]. Regardless of the cancer stressors experienced, patients with a high sense of humor have better psychosocial adjustment and fewer infections [455].

Potential long-term effects: Experiencing leukemia can interfere with the proper development of an early school-age child's social and academic skills [456; 457; 458; 459]. Without honest, age-appropriate discussions about the child's prognostic information and death, the development of thinking based on logic rather than fantasy may be delayed [460]. Children in whom cancer is diagnosed after 5 years of age are more likely to experience post-traumatic stress symptoms because they are able to understand the seriousness of their illness. However, they are also more likely to experience post-traumatic growth, characterized by a positive shift in perspective and priorities, because they can appreciate their inner strength and others' support [461].

Actions to promote well-being: A child may believe that his or her cancer diagnosis and treatments are punishments for bad behavior. Parents should be advised that rewarding good behavior during and after procedures with praise and small rewards (e.g., stickers) can promote a child's healthy development and ability to cope with cancer. Negative behaviors should not receive extra attention. To avoid devel-

opmental delay of reality-based thinking, parents should also be advised to answer a child's questions about the cancer honestly and in an age-appropriate manner [460]. Role-play discussions should be performed to assist in understanding how to best tell an individual child distressing news [185]. Discussions should be tempered by the expression of hope, which is a very important coping strategy in any pediatric cancer situation. School attendance should be encouraged because social and academic skills can be developed and peers can serve as an important support system for children with cancer [457]. Animal therapy programs may reduce a young child's emotional distress and promote socialization [462].

School-Age (8 to 12 Years of Age)

Level of understanding and stressors: Compared with self-reports in other developmental age groups, self-reports of children with cancer who are 8 to 12 years of age and secondary assessments were more likely to emphasize emotional distress over physical distress. Emotional stressors include confinement, feelings of alienation, and worries before medical procedures. The pain associated with diagnostic procedures and treatments is the most frequently mentioned physical aspect of cancer-related distress [463]. By 9 years of age, children understand that death is irreversible; however, their concept of the future is still very limited [464]. Some children may try to "protect" their parents from fearing death by avoiding conversations about the subject. However, avoidance of these discussions causes a child to suffer in isolation [190; 460].

Coping mechanisms: Communication and logical reasoning skills available to children in this age range promote the development of problem-focused coping. Children may be more interested in learning about their cancer and its treatment because they want to master social and cognitive skills; intellectualizing the problem is one coping strategy children of this age may use. Emotion-focused coping skills are also more advanced because a school-age child is more likely to communicate emotions to seek others' support [463].

Potential long-term effects: Intensive treatments may interrupt the development of social and academic skills. Although the child's communication skills are more sophisticated, sharing concepts that are "too adult" for the child can affect socialization with peers and personality development.

Actions to promote well-being: A cancer diagnosis poses a challenge to a child's desire for equality and fairness. Its effects on schoolwork and physical activity may leave the child feeling inferior to peers, angry, and frustrated [457]. Such emotions may manifest as withdrawal or depression; the child may hide these feelings from parents. Thus, listening carefully and discussing feelings is imperative to understanding the child's problems. Art, writing, music, and dance/movement therapy can provide the child with expressive outlets [465; 466; 467]. Although children may desire to know all about their illness, parents and the treatment team must provide age-appropriate education. Too much exposure to decision making and adult responsibilities may disrupt a child's socialization with peers. As for any school-age child, school attendance is beneficial for social and academic development, and children should therefore be given the tools necessary to transition back into a school routine [457].

Adolescent (13 to 18 Years of Age)

Level of understanding and stressors: During this stage, adolescents are attempting to individualize themselves. However, identity formation in adolescents with cancer may revolve around their illness. Although adolescents understand death, they may feel it only happens to others. The most frequently reported emotional stressors are worries before medical procedures and feelings of alienation [363; 463; 468]. Compared with age-matched controls, children 12 to 15 years of age with cancer have a significantly lower health-related quality of life with respect to motor functioning [453].

Coping mechanisms: Coping strategies commonly used by adolescents during treatment include positive thinking, avoiding thoughts of treatment, keeping busy, focusing on positive outcomes, and staying relaxed [468; 469; 470]. One study found that better problem-solving skills were associated with lower adolescent distress [471]. A systematic review analyzed how childhood cancer patients and survivors communicate about their cancer with family and peers [472]. Participants were adolescents and young adults 16 to 34 years of age. Communication occurred on a spectrum with variations in who the youth shared information with, how often they shared information, and the amount and type of information they shared. The reviewers found that communicating about cancer was a beneficial coping strategy and that it prompted social support and appeared central to significant relationships. Barriers to communication (e.g., fear of stigma, poor peer reactions) hindered the participants' willingness to disclose [472]. Post-treatment coping strategies include negotiating to regain/gain autonomy, cognitive reliving of the cancer experience with peers or the medical team, and forgetting the negative aspects of treatment [469]. Potential long-term effects: One large, retrospective study has suggested that adolescents with cancer achieve autonomy, psychosexual development, and social development at an older age than peers [473]. Diagnosis at adolescence has been linked to an increased risk for the development of post-traumatic stress disorder [446]. However, one study found that personality factors, such as adaptive style, were a stronger determinant of post-traumatic stress than health history [474]. Another study of 435 youth (253 with cancer, 182 healthy controls) found that the relationship between post-traumatic stress symptoms and post-traumatic growth depended on contextual factors and that the majority of the youth (83%) were resilient and able to find benefit from stressful life events [475].

Actions to promote well-being: The physical and emotional changes of this final stage of childhood are conjoined with a desire for private space. However, honoring an adolescent's desire for privacy can be difficult during hospitalizations. A sense of privacy and respect, as well as cooperation, can be maintained by knocking before entering an adolescent's room, asking permission when introducing new people, and being mindful of the adolescent's physical modesty during examinations. To promote treatment compliance in older adolescents, equal medical information should be provided to patients and their parents. Adolescents should have the option to lead treatment discussions in order to enhance feelings of respect, control, and independence. Getting to know others with the same disease, treatment, or situation—especially those who are cured—may help adolescents cope, and emerging technology, cancer-related video games, and social networking are helping adolescents with cancer to better understand their disease, comply with treatment, and connect with one another [9; 468; 476]. Parents should be dissuaded from controlling treatment discussions and decision making without the adolescent's approval, which can lead to acting-out (externalizing) or internalizing behaviors in the patient.

Gender Differences in Coping Mechanisms

Some studies have shown differences in the coping styles of male and female children/adolescents with cancer. One study found that older female children (12 to 18 years of age) use a wider repertoire of emotion-focused and problem-focused coping strategies than their male counterparts [477]. Among male participants in the study, use of emotion-focused coping was linked to a disposition to experience anger and anxiety but not depression. Emotion-focused coping in the female participants was not associated with these variables. Depressive symptoms were less likely to develop in female participants who used problem-focused strategies.

In another study, male children 11 to 18 years of age were found to use disengagement coping strategies, such as problem avoidance, wishful thinking, social withdrawal, and self-criticism, more often than female children did [478; 479]. Engagement coping strategies include problem-solving, cognitive-restructuring, social support, and expression of emotions. Male children were also found to use humor coping significantly more often than girls in a study of children 7 to 14 years of age who had ALL [455; 480]. Healthy psychosocial adjustment was strongly correlated to humor coping [455].

Relationships with Peers

Mothers are the most commonly reported source of social support by children/adolescents with cancer. As a child with cancer develops into an adult, however, his or her social support needs extend beyond the family. Socialization with peers contributes to coping abilities and psychological adjustment of children/adolescents with cancer [481; 482; 483]. For adolescents 12 to 14 years of age, family-independent social networks are significantly smaller than those of adolescents 15 to 18 years of age, which may contribute to less effective coping. The emotional support of peers is particularly important for continued participation in school and social activities [483]. Hospitalizations, poor physical health/appearance, academic difficulties, and poor parental coping skills can also limit the patient's development of relationships with peers [457; 484].

School-Related Issues

Regular attendance at school is difficult during cancer treatment, but clinicians should emphasize to patients and their parents that going to school is an important part of normal life. School can help to reduce the social isolation associated with cancer and enhance the child's self-esteem [320]. School reintegration programs have been found to improve children's psychosocial well-being (anxiety and depression), social well-being (social competence and social support), behavioral problems, and physical competence, but more research is needed to investigate the effects of these and other related interventions [192; 485].

In preparing for the child/adolescent to re-enter school, the primary care provider should guide parents in developing questions and issues to discuss with teachers and other personnel at the school. Topics that should be addressed with school personnel include [486]:

- Child's diagnosis and treatment plan
- Information on low blood counts and the risk of infection
- Central venous line issues
- Importance of contacting the parents when the child has a fever
- Immunization restrictions
- Attendance issues
- Administration of medicine
- Activities that the child cannot participate in
- Whether special permission is required to wear a hat or scarf in school
- Whether the child may take extra time to move between classrooms
- Possibility of tutors in specific subjects

Cancer and its treatment are often associated with learning problems, and parents should be aware for the potential for difficulties with handwriting or spelling, reading comprehension, remembering math facts, copying information after seeing it, and completing tasks on time [486].

Psychosocial Interventions

A meta-analysis of the effects of psychosocial interventions on psychological outcomes in children with cancer showed that patient-oriented therapies do not effectively reduce child distress or improve child adjustment [487]. The authors of the study suggested several reasons for this finding: children with cancer have psychological outcomes similar to those of healthy children; the average length of follow-up of the studies analyzed was only four months; and most studies used a waitlist/standard care control group instead of a control group with a generic psychosocial intervention providing non-specific support or attention. Waitlist control groups

do not control for nonspecific treatment variables such as social support from other group members or facilitators. One systematic review identified a broad range of psychosocial interventions that could benefit cancer survivors and their families, but concluded that more high-quality studies are needed to optimize the healthcare services that can best support children and their families [488].

PSYCHOSOCIAL ISSUES FOR THE FAMILY AND FAMILY DYNAMICS

Childhood cancer can place every family member at risk for the development of psychosocial problems. Several studies have been conducted to explore the psychosocial dynamics within family units.

Patient and Parents

Parental factors linked to the psychological outcomes and quality of life for a child with cancer include education, communication styles, and coping strategies [457; 478; 485; 489; 490; 491; 492; 493].

- **Parental education:** Children with cancer are more likely to experience poor psychological adjustment if their parents' education level does not exceed high school.
- **Parental communication styles:** Most healthcare professionals agree that parents should talk openly, honestly, and age-appropriately to a child about his or her illness. Open lines of communication protect children with cancer from suffering emotional distress in isolation and promote high-quality care. In addition, poor cancer-related communication is linked to children's and adolescents' noncompliance with cancer treatments.
- **Parental coping strategies:** Coping mechanisms of parents can be reflected by children with cancer. A correlation study demonstrated similarities in the use of disengagement coping—in particular, problem avoidance—by parents and their adolescent child. Three months after diagnosis, parental differences in information-seeking were correlated with lower quality of life for children with cancer.

However, other dissimilarities in maternal and paternal coping mechanisms, such as religious or support-seeking coping styles, do not appear to affect patients' quality of life.

Patient and Siblings

From the diagnosis through the course of a child's cancer, cancer-free siblings of all ages are affected emotionally and often physically. Siblings may suffer from unattended emotional responses, including anger, anxiety, jealousy, resentment, depression, and loneliness; difficulties related to the absence of their parents; and reduced school achievement [494]. Immature thinking in young children can lead to thoughts that they caused their sibling's illness. Adverse physical problems experienced by cancer-free siblings are headaches, sleep disruption, and poor eating habits [495]. Most siblings who experience these emotional and physical responses do not suffer long-term problematic outcomes; however, a subset of siblings does experience difficulties [496].

Risk Factors for Poor Psychological Outcomes for Cancer-Free Siblings

A meta-analysis of 50 studies involving siblings of children with chronic illness showed that internalizing behaviors, especially anxiety and depression, placed healthy siblings at a higher risk of poor psychological adjustment [497]. The risk of unhealthy psychological adjustment is also amplified if the ill sibling's cancer alters day-to-day family function. Warmth or closeness between cancer-free siblings (8 to 15 years of age) and their siblings with cancer increases the risk of poor psychological adjustment; these intimate relationships are associated with decreases in social competence [498]. In addition, the incidence of poor psychological outcomes in response to guilt and heightened fear of death increases if the sibling with cancer dies [499]. The psychological adjustment of cancer-free siblings, however, improves with age as a result of the development of protective factors such as increased maturity and capacity to empathize [498; 500].

A post-traumatic stress model may best fit the potential psychological outcomes of cancer-free siblings up to five years after treatment. As a component of the Surviving Cancer Competently Intervention Program randomized trial, 78 sibling participants completed a Post-traumatic Stress Disorder Reaction Index [501; 502]. Post-traumatic stress symptoms were experienced by almost half of cancer-free siblings. Moderate-to-severe post-traumatic stress disorder was reported by one-third of cancer-free siblings. Cancer-free siblings who were 7 years of age or older at the time of their sibling's cancer diagnosis reported more severe post-traumatic stress symptoms than those who were 6 years of age or younger at the time of diagnosis. In the same study, cancer-free female siblings indicated more post-traumatic stress symptoms than cancer-free male siblings.

One study explored bereaved siblings' advice to healthcare professionals working with children with cancer and their families [503]. Of the 174 siblings that participated, 108 answered an open-ended question about what advice they would give. The most common advice (given by 56% of siblings) related to their own support. Another one-third wanted professionals to provide them with better medical information. Some siblings wanted to be more involved in their brother's/sister's care and asked that healthcare professionals provide their parents with guidance on how to achieve this. Other common threads were related to psychosocial aspects, for example, siblings' wish for professionals to mediate hope without sacrificing realism and understanding the importance of asking the ill child about the kind of care they wanted [503].

Factors that promote healthy psychological outcomes in cancer-free siblings are related to support and functioning of the entire family. Specifically, these factors include [504; 505; 506]:

- More family cohesion and adaptability with less family disruption
- Increased family support resources
- Enhanced communication within the family

Cancer-Free Siblings' Feelings During Treatment

Cancer-free siblings tend to identify themselves through the experiences of other family members during the course of their ill siblings' cancer [507]. When encouraged to discuss their personal experiences and feelings, cancer-free siblings focused primarily on their ill siblings' or parents' experiences, diminishing their sense of self. These patterns were more evident during the ill siblings' hospitalizations and as the physical appearance of their ill siblings worsened. Although cancer-free siblings experience stress similar to their brothers or sisters with cancer, most participants reinforced that their suffering was not justified because they were not experiencing the illness. Healthy siblings worried about the physical and emotional needs and abilities of their ill brothers or sisters following a cancer diagnosis. They said that they often "felt good" during the times they helped the ill sibling feel more comfortable. Yet, most of the cancer-free siblings also indicated that they experienced guilt because they had minimal involvement in taking care of their ill sibling. Although feelings of guilt in cancer-free siblings have not been correlated to negative psychological outcomes, these feelings should be addressed by parents and clinicians [507].

Parents and Siblings

Numerous studies have shown that cancer-free siblings of children with cancer have the most unmet emotional needs relative to all other members of the family [508]. For children, the family is the primary social support system, and cancer-free siblings receive the least attention when childhood cancer disrupts everyday household life. Cancer-free siblings' emotional responses (e.g., fear, anger, guilt, jealousy, sadness) and health-related responses (e.g., sleeping difficulties, eating problems) are often overlooked or underestimated by parents [495]. These responses are compounded by cancer-free siblings' sensitivities to the parents' cancer-related emotional and practical burdens.

Parental and Self-Reports of Cancer-Free Siblings' Health

Parental and self-reports regarding cancer-free siblings' emotional and physical states also differ. Parents generally report better statuses for their cancer-free children than the children report themselves [509]. However, parents of children with cancer also report that their cancer-free children are "less healthy" than age-matched and sex-matched controls. Despite these reports, parents utilized health care for their cancer-free children less than the parents of matched controls [495]. The relative health of a cancer-free sibling to that of a child with cancer may cause parents to minimize the significance of the cancer-free sibling's health issues. Lack of time, energy, and financial resources may also reduce the parent's efforts to seek health care for a cancer-free child. Furthermore, most cancer-free children attempt to protect their parents' emotions by hiding their own negative emotions and health issues. The findings of a qualitative study suggested that cancer-free siblings valued keeping the family together and the survival of the sibling with cancer similarly [507].

Compared with matched controls, cancer-free siblings of children with cancer report significantly more trouble sleeping (72% compared with 53%) and problems eating (42% compared with 26%) [495]. These complaints are reported more frequently by cancer-free siblings who also report internalizing behaviors than those who engaged in externalizing coping strategies. Cancer-free siblings who present emotional or behavioral problems before the cancer diagnosis are more prone to somatic symptoms and poor psychological adjustment. Therefore, healthcare practitioners should ask parents if their cancer-free children acted-out or had emotional problems prior to the development of cancer in the ill sibling to help assess the cancer-free child's level of risk for psychosocial issues. Also, clinicians should ask if the cancer-free sibling has

any physical complaints in order to evaluate whether he or she needs additional interventions to avoid long-term psychological repercussions. Parents who understand that their cancer-free child is at risk for psychosocial problems due to a sibling's cancer are more likely to have the child participate in a therapeutic program [509].

Parents

Although parental emotional distress and psychosomatic complaints are high shortly following a child's cancer diagnosis, prospective studies have shown that most survivors' parents adjust within 1 to 10 years [510; 511; 512]. Still, approximately 25% to 33% of parents face long-term psychological issues [365; 510; 512; 513]. Healthcare professionals' attention to the specific needs of the family can enhance the family's resilience [514; 515; 516; 517]. Post-traumatic stress disorder is the most common psychological disturbance for parents of childhood cancer survivors [513; 518].

In a prospective and longitudinal study to assess psychological functioning, parents' somatic symptoms and feelings of anxiety gradually decreased to control group levels by five years after diagnosis [519]. However, 27% of parents still had clinically elevated scores for psychological distress at that time. When the data were analyzed according to the treatment outcome for the child, psychological distress was manifested in 23% and 29% of parents of survivors and deceased children, respectively. Fifty percent of parents of children with relapsed disease continued to experience psychological distress after five years. Higher levels of psychosomatic complaints at the time of the cancer diagnosis and the child's relapse were indicators of higher long-term psychological risk. The same study found that mothers had higher levels of anxious feelings than fathers; however, all other measures were similar between mothers and fathers. Support-seeking coping strategies have been found to significantly reduce anxiety levels in mothers [520].

Psychosocial Interventions for Families

Therapies that holistically address the family's or the parents' emotional distress and coping skills are most effective for curtailing the intensity of unhealthy psychological outcomes caused by childhood cancer [487; 521; 522]. Of interventions that have been studied in randomized trials, two have been shown to offer significant benefit [487]. Mothers of children recently diagnosed with cancer were better able to cope with their cancer-related stressors after receiving problem-solving skills training in conjunction with standard psychosocial care, compared with mothers who received standard psychosocial care alone [521]. The effectiveness of the training was better for Spanish-speaking mothers than English-speaking mothers, and single mothers derived the greatest benefit from the training.

The second intervention with proven efficacy is the Surviving Cancer Competently Intervention Program, a one-day, four-session, family-centered treatment intervention designed to teach coping skills to mothers, fathers, and adolescent survivors [522]. Compared with the control group, fathers derived the most benefit from the program, followed by the adolescent survivors. The coping strategies taught to fathers and survivors allowed them to reframe their reactions to the cancer and to speak more openly with their families about the cancer experience. Mothers did not show improvements with the intervention.

Interventions for siblings have also been effective. A therapeutic peer support camp was shown to improve mental health outcomes for siblings (8 to 13 years of age) of children with cancer [523]. The camp program was designed to decrease stress levels, improve social competence, and enhance knowledge of cancer and its treatment. According to standardized self-report measures, participants in the program demonstrated significantly decreased

anxiety, improved social competence, greater social acceptance, and significantly reduced fear of disease [523]. Another study found that structured teaching and psychosocial sessions at a five-day residential summer camp led to significant improvements in knowledge about the sibling's cancer, behavior, social support, self-esteem, attitude, and mood [524]. The improvements represented increases of 5% to 25% over the baseline values and were sustained over a period of one year. One study surveyed children's pain and distress levels immediately before and after a one-hour Kids Kicking Cancer in-person class [525]. Eligible participants were enrolled in standard classes, diagnosed with a chronic health condition (e.g., cancer), or the sibling of a child diagnosed with a chronic health condition, and between 5 to 17 years of age. Pain and distress were reported using Likert-style scales. Friedman test was used to test for overall changes in pain and distress, and within subgroups. A total of 59 youth (19 cancer patients, 17 non-cancer patients, 23 siblings) completed the study. Overall, pain and emotional distress were significantly reduced following a one-hour class, with 50% and 89% of youth reporting a reduction in pain and distress, respectively. The reduction in pain was most pronounced with cancer and non-cancer patients, whereas, the reduction in distress was most pronounced among healthy siblings. Reductions in pain and distress did not significantly differ among subgroups [525].

Resources for Patients and Their Families

Several resources are available to help patients and their families become more knowledgeable about cancer and treatment options, gain support from other families, and obtain help with practical concerns. Educational materials developed by several advocacy organizations are available online, and a list of potentially useful resources is available at the end of this course.

LONG-TERM HEALTH CARE FOR CHILDHOOD CANCER SURVIVORS

Approximately 1 in 640 adults 20 to 39 years of age is a survivor of pediatric cancer [526]. As of 2020, nearly 496,000 cancer survivors were first diagnosed when they were younger than 20 years of age [527]. Among adolescents 15 to 19 years of age who were diagnosed with cancer from 2013 to 2019 and followed through 2020, 86% had a five-year relative survival rate if diagnosed with leukemia, 90% if diagnosed with non-Hodgkin lymphoma, and 98% if diagnosed with Hodgkin lymphoma [528]. The high (and increasing) number of survivors, as well as the emerging results of myriad late effects of treatment, led to the IOM report *Childhood Cancer Survivorship: Improving Care and Quality of Life*, published in 2003 [529]. Among the recommendations in that report were:

- Develop evidence-based clinical practice guidelines for the care of survivors of childhood cancer.
- Define a minimum set of standards for systems of comprehensive, multidisciplinary follow-up care that link specialty and primary care practitioners and ensure the presence of such a system within institutions treating children with cancer.
- Evaluate alternate models of delivery of survivorship care.
- Improve awareness of late effects and their implications to long-term health among childhood cancer survivors and their families.
- Improve professional education and training regarding late effects of childhood cancer and their management for both specialty and primary care practitioners.

The long-term follow-up care of childhood cancer survivors is important both to maintain routine care and to monitor for the occurrence of late effects of cancer treatment. Children and adolescents need continuity of routine pediatric care throughout and following their cancer treatment. This need has been emphasized by the AAP, which, in 2002, stated that each child must have a “medical home” for maintenance of health care [530]. In 2010, the Patient Protection and Affordable Care Act emphasized the implementation and promotion of the medical home model for children and adults [531]. Pediatricians, family practitioners, and nurses have an important role in the follow-up care for children with cancer [319; 320; 526; 532]. Children with cancer should have regularly scheduled visits for routine preventive care, such as immunizations and the monitoring of growth and development [320]. In addition, routine pediatric care provides the opportunity to assess the effectiveness of symptom management, monitor treatment-related toxicity, confirm cancer remission, evaluate the psychosocial needs of the patient as well as the family, and promote healthy lifestyle behaviors [319]. Lastly, primary care providers are valuable resources for education and support for the patient and family.

Long-term follow-up healthcare is also crucial for ensuring appropriate surveillance, screening, and preventive care for childhood cancer survivors. The advances in survival for pediatric cancer have allowed investigators to evaluate survivors’ health over time. Since the 1980s, long-term studies have identified several, widely varying late adverse effects of treatment. These long-term studies have served two valuable purposes: by identifying the most common treatment-related effects, clinicians can provide better follow-up care and investigators can modify treatment protocols to minimize toxicity for future patients. Many of the studies have involved the Childhood Cancer Survivor Study (CCSS) group, a cohort of more than 20,000 survivors who have survived for more than 5 years after treatment at various institutions and have been followed for 16 to 32 years. The group also includes sibling controls for comparison studies.

Research with the CCSS group has led to the development of evidence-based clinical practice guidelines for childhood cancer survivors [533; 534]. The guidelines were developed by an expert panel within COG and are available online [534]. The guidelines facilitate creating a surveillance and follow-up care plan that is individualized according to treatment exposure and risk [534]. The COG Late Effects Committee, in conjunction with Baylor School of Medicine, has developed a web-based interface, Passport for Care, that generates personalized recommendations based on an individual's specific risks [535]. Updates on this interface will be posted on the guidelines website.

LATE EFFECTS AMONG CHILDHOOD CANCER SURVIVORS

Late effects are usually defined as those occurring at least two years after completion of treatment and are chronic and sometimes progressive [56]. These late effects are primary contributors to mortality and morbidity for survivors. Among 20,483 five-year survivors in the CCSS group, mortality was 8.4 times higher for survivors than for the age-, sex-, and year-matched U.S. population [5]. The overall absolute excess risk of mortality was 7.36, which represents an additional seven deaths per 1,000 individuals who were followed up for one year [5]. The leading cause of mortality was recurrent and/or progressive disease (approximately 58%), followed by subsequent neoplasms (19%), circulatory system diseases (7%), and respiratory system diseases (3%) [5]. The cause of mortality varied by sex, with a higher proportion of deaths related to a subsequent neoplasm among female survivors and a higher proportion of cardiac deaths among male survivors [5]. The morbidity related to pediatric cancer treatment has a substantial impact on the health status and quality of life for survivors. Studies have shown that 63% to 75% of childhood cancer survivors have at least one physical or psychosocial late effect and that 28% to 40% have a severe or life-threatening condition [3; 4].

However, one study found the incidence of severe or life-threatening conditions to be much higher. Researchers evaluated 14,359 five-year survivors in the CCSS cohort for risk of severe, disabling, life-threatening, and fatal events, and 4,301 siblings were included for comparison [536]. The cumulative incidence of a severe, disabling, life-threatening, or fatal health condition was greater among survivors than siblings (53.6% and 19.8%, respectively) by 50 years of age [536]. Correlation of late effects with primary diagnosis has indicated that leukemia and non-Hodgkin lymphoma are associated with lower burdens of adverse events, whereas the burden associated with Hodgkin lymphoma is often higher than the average burden (**Table 21**) [3; 4; 537].

Among the most common late effects are [3; 4; 216; 273; 319; 526; 534; 537]:

- Subsequent neoplasm
- Cardiac abnormalities
- Abnormal growth and development
- Gonadal dysfunction
- Neurocognitive impairment
- Dental problems
- Psychosocial disorders

Many other less common late effects are also associated with cancer treatment, and survivors at risk should be evaluated accordingly (**Table 22** and **Table 23**). The morbidity rates related to these late effects vary substantially according to many factors, primarily the type of treatment and the primary cancer diagnosis. Knowledge of the specific diagnosis and details of treatment can help clinicians provide preventive care, establish early diagnosis, and implement appropriate interventions.

Subsequent Neoplasms

The occurrence of subsequent neoplasms as a late effect among childhood cancer survivors has been well-documented. Multiple studies have demonstrated that these cancers are a major source of morbidity and mortality for 30 years or longer after treatment [3; 273; 526; 544; 545; 546; 547; 548].

| COMPARISON OF LATE EFFECTS ACCORDING TO PRIMARY DIAGNOSIS | | | |
|---|----------------------|----------|--------------|
| Measure of Late Effect | Overall ^a | Leukemia | HL/NHL |
| Moderate or extreme adverse effect in at least 1 of 6 health status domains | 44% | 40% | 44% / 37% |
| Burden of Adverse Events | | | |
| None | 20% | 26% | 19% |
| High or severe | 23% | 12% | 16% |
| Chronic Health Condition (Relative Risk) | | | |
| Any | 3.3% | 2.2% | 4.6% / 3.2% |
| Severe or life-threatening | 8.2% | 4.1% | 10.2% / 6.8% |
| Two or more | 4.9% | 2.8% | 8.7% / 4.3% |
| ^a Includes all childhood cancer diagnoses. HL = Hodgkin lymphoma; NHL = non-Hodgkin lymphoma. | | | |
| Source: [3; 4; 537] | | | Table 21 |

The 30-year cumulative incidence is 20.5% for a subsequent neoplasm and 7.9% for a second malignant neoplasm (excluding nonmelanoma skin cancer) [7]. The highest cumulative incidence is associated with Hodgkin lymphoma (18.4%); the incidence is similar for non-Hodgkin lymphoma and leukemia (5.8% and 5.6%, respectively) [7].

The greatest risk factor for a subsequent neoplasm is radiation therapy (relative risk: 2.7), followed by female sex and childhood Hodgkin disease (relative risk: 1.5 for both), and older age at the time of childhood cancer diagnosis (relative risk: 1.3) [7]. It is important to note, however, that changes to treatment protocols over time (e.g., the move to limited use of radiation therapy) may affect risk among children/adolescents treated within the past decade. Overall, the most frequently occurring subsequent solid tumors among childhood cancer survivors are breast, thyroid, and CNS cancers and soft-tissue sarcoma [7; 543].

The authors of one study sought to find the incidence and excess risk for breast cancer in women after chest radiation; differences between the clinical characteristics of breast cancer and the outcomes after therapy among these women and in the general population; and potential benefits and harms associated with breast cancer surveillance among women exposed to chest radiation. The cumulative incidence of breast cancer by 40 to 45 years of age ranged from 13% to 20%. The risk for breast cancer increased linearly with radiation dose. The evidence suggests that the characteristics of breast cancer in these women and the outcomes after diagnosis are similar to those of women in the general population [542]. Authors of another study evaluated cumulative breast cancer risk in 1,230 female childhood cancer survivors treated with chest radiation. Survivors who were treated with lower delivered doses of radiation (2–20 Gy) to a large volume (i.e., whole-lung field) had a high risk (43.6%) of breast cancer. The cumulative incidence of breast cancer by 50 years of age was 30%, with a 35% incidence among Hodgkin lymphoma survivors. Breast cancer-specific mortality at 5 and 10 years was 12% and 19%, respectively [540].

| NONMALIGNANT ADVERSE EFFECTS ASSOCIATED WITH CHILDHOOD LEUKEMIA OR LYMPHOMA AND ITS TREATMENT | | |
|--|--|---|
| Organ/System Affected | Late Effect | Causative Agent or Therapy |
| Blood | Hepatitis B or C, human immunodeficiency virus (HIV) | Transfusion of contaminated blood product ^a |
| Bone marrow | Myelodysplasia | Alkylating agents |
| | Acute myelogenous leukemia | Epipodophyllotoxins |
| Endocrine glands | Pituitary and/or thyroid dysfunction | Radiation |
| Bones and joints | Abnormal skeletal growth, chronic pain | Radiation |
| | Osteopenia, osteoporosis, avascular necrosis | Radiation, corticosteroids, methotrexate, cyclophosphamide, ifosfamide |
| Reproductive system | Testes/ovaries dysfunction | Alkylating agents, radiation |
| Lungs | Fibrosis | Bleomycin, BCNU, radiation |
| | Diffusion abnormalities | Radiation |
| Cardiovascular System | | |
| Heart | Cardiomyopathy, left ventricular dysfunction (subclinical), congestive heart failure | Anthracyclines |
| | Cardiac failure, cardiac arrhythmias | Cyclophosphamide (high dose) |
| | Myocardial infarction, valve disorders, cardiac arrhythmias, constrictive pericarditis | Radiation |
| Blood vessels | Coronary artery disease | Radiation |
| Central Nervous System | | |
| Brain | Neurocognitive impairment, motor problems, seizures, behavior changes | Methotrexate, cytarabine, radiation |
| Ears | Scarring of eardrum, build-up of ear wax, damage to middle ear (sense of balance) | Radiation |
| | Hearing loss | Cisplatin |
| Eyes | Dry eyes, light sensitivity, keratoconjunctivitis, retinopathy | Radiation |
| | Cataracts | Radiation, corticosteroids, busulphan |
| Nerves | Neuropathy | Cisplatin, vincristine, vinblastine |
| Digestive System | | |
| Oral cavity, teeth | Xerostomia, abnormal dentition, cavities, gingivitis, periodontal disease | Radiation |
| Intestines | Malabsorption, strictures, chronic diarrhea | Radiation |
| Liver | Hepatitis, fibrosis, cirrhosis | Methotrexate, BCNU, 6-mercaptopurine, radiation, contaminated blood products ^a |
| Urinary System | | |
| Bladder | Hemorrhagic cystitis, cancer | Ifosfamide, cyclophosphamide |
| | Scarring | Radiation |
| Kidneys | Nephropathy | Radiation, ifosfamide |
| | Fanconi syndrome | Ifosfamide, cisplatin |
| | Reduced filtration | Cisplatin, carboplatin |
| | Hypertension, renal insufficiency | Radiation |
| | Kidney failure (rare) | BCNU, CCNU, methotrexate (high dose) |
| ^a For transfusions given before 1972 (hepatitis B), between 1977 and 1985 (HIV), and before 1993 (hepatitis C). | | |
| Source: [3; 4; 216; 273; 319; 526; 534; 537; 538; 539; 540; 541; 542; 543] | | Table 22 |

| RECOMMENDED SCREENING FOR SURVIVORS OF CHILDHOOD LEUKEMIA AND LYMPHOMA ACCORDING TO CHILDREN'S ONCOLOGY GROUP GUIDELINES | | |
|--|---|---|
| Late Effect | Therapy or Cause | Recommended Screening |
| Cardiac abnormalities (cardiomyopathy, left ventricular dysfunction [subclinical], congestive heart failure, arrhythmias, myocardial infarction, valve disorders, pericarditis, coronary artery disease) | Anthracyclines, cyclophosphamide (high dose), radiation (mantle, mediastinum, thorax, axilla, abdomen) | Yearly history and physical examination with attention to presence of murmur, S3, S4, increased P2 sound, pericardial rub, rales, wheezes, peripheral edema, jugular vein distention Baseline echocardiography and electrocardiography, repeated as clinically indicated Fasting glucose and lipid profile every three to five years Education about risk of strenuous exercise |
| Cataracts | Alkylating agents, corticosteroids, cranial, orbital, or eye radiation | Yearly eye examination |
| Dental problems (abnormal dentition, cavities, gingivitis, periodontal disease, microdontia) | Cranial radiation, bone marrow transplantation, chemotherapy (any) | Dental cleaning every six months Yearly oral examination |
| Dyslipidemia | Radiation | Baseline fasting lipid profile every two years |
| Testicular hormonal dysfunction/impaired spermatogenesis; ovarian hormone deficiencies/reduced ovarian follicular pool | Alkylating agents, radiation (whole abdomen, pelvis) | Yearly evaluation of puberty stage and pace, sexual function, Tanner assessment, testicular volume (male patients) Baseline levels of FSH, LH, and estradiol (female patients) or testosterone (male patients) at 13 years age (female patients) and 14 years of age (male patients) Monitor growth until mature AM testosterone screening in high-risk patients starting at 18 years of age |
| Hearing loss, tinnitus, vertigo | Heavy metals, radiation | Yearly assessment of hearing difficulties and otoscopic examination Complete audiologic evaluation by audiologist, yearly, for patients age ≤ 5 years Pure tone audiometry testing at 1,000–8,000 Hz every 2 years for patients 6 to 12 years of age, then every 5 years beginning at 13 years of age |
| Hepatic dysfunction | Antimetabolites, methotrexate | Yearly examination with attention to jaundice, ascites, hepatomegaly, splenomegaly Baseline levels of ALT, AST, and bilirubin, repeated as clinically indicated |
| Hepatitis B or C; HIV | Transfusion of blood products before 1972 (hepatitis B), between 1977 and 1985 (HIV), and before 1993 (hepatitis C) | Hepatitis B surface antigen and core antibody once HIV 1 and 2 antibodies once Hepatitis C antibody once Immunization in at-risk patients lacking immunity |
| Neurocognitive deficits | Cranial radiation, methotrexate, cytarabine (high-dose IV), neurosurgery (brain) | Formal neuropsychologic evaluation at baseline Yearly assessment of educational or vocational progress |
| Peripheral sensory neuropathy | Heavy metals, plant alkaloids | Yearly neurologic examination for two to three years after therapy completed |
| Psychosocial disorders | Cancer experience | Yearly assessment for depression, anxiety, post-traumatic stress syndrome, educational and/or vocational progress, and social withdrawal |

Table 23 continues on next page.

**RECOMMENDED SCREENING FOR SURVIVORS OF CHILDHOOD LEUKEMIA
AND LYMPHOMA ACCORDING TO CHILDREN'S ONCOLOGY GROUP GUIDELINES (Continued)**

| Late Effect | Therapy or Cause | Recommended Screening |
|---|---|--|
| Pulmonary toxicity (fibrosis, interstitial pneumonitis, obstructive lung disease) | Alkylating agents, bleomycin, radiation (mantle, mediastinum, thorax), hematopoietic cell transplant, thoracic surgery | Yearly pulmonary examination with attention to history of cough, shortness of breath, dyspnea, wheezing Baseline chest x-ray and pulmonary function tests, repeated as clinically indicated PFTs (including DLCO and spirometry) |
| Renal/bladder damage (glomerular injury, renal insufficiency, hypertension, tubular injury) | Alkylating agents, heavy metals, antimetabolites, radiation (abdomen, pelvis), hematopoietic cell transplant, nephrectomy | Yearly blood pressure, urinalysis Baseline levels of BUN, creatinine, electrolytes, calcium, magnesium, and phosphate, repeated as clinically indicated |
| Sinusitis (chronic) | Cranial radiation | Yearly sinus examination with evaluation for history of rhinorrhea and postnasal discharge |
| Thyroid gland dysfunction | Radiation (head and neck, thorax), thyroidectomy, systemic radiation | Yearly thyroid function studies and evaluation for thyroid hyperplasia |
| Bone Disorders | | |
| Osteopenia, osteoporosis | Radiation, corticosteroids, methotrexate, cyclophosphamide, ifosfamide, hematopoietic cell transplant | Baseline bone density Yearly musculoskeletal examination Yearly musculoskeletal examination |
| Avascular necrosis | Corticosteroids, hematopoietic cell transplant | |
| Abnormal Growth and Development | | |
| Impaired growth | Cranial radiation, corticosteroids, chemotherapy (any), radiation (neck, thorax, whole abdomen) | Yearly height measurements on standardized growth charts Yearly determination of height, weight, body mass index, and blood pressure/BMI every 6 months until growth is completed, then yearly |
| Overweight or obesity | Cranial radiation, diagnosis of acute lymphoblastic leukemia | Fasting glucose, serum insulin, and lipid profile every two years (overweight or obese individuals) or five years (normal-weight individuals) Tanner staging every 6 months until sexually mature |
| Second Cancers | | |
| Acute myelogenous leukemia, myelodysplasia | Epipodophyllotoxins, alkylating agents, hematopoietic cell transplant | Yearly dermatologic examination (pallor, petechiae, purpura) with evaluation for history of fatigue, bleeding, or easy bruising up to 10 years after treatment Yearly CBC with differential up to 10 years after treatment |
| Bladder cancer | Cyclophosphamide, radiation (whole abdomen, pelvis) | Yearly urinalysis and evaluation for history of hematuria, urinary dysfunction |
| Breast cancer | Radiation of 20 Gy or more (mantle, mediastinum, thorax, axilla) | Yearly clinical breast examination beginning at puberty until 25 years of age, then every six months Mammography beginning eight years after radiation or at 25 years of age, whichever occurs last |
| Colorectal cancer | Radiation of 30 Gy or more (whole abdomen, pelvis) | Regular screening (multitarget stool DNA test/colonoscopy) beginning five years after radiation or at 30 years of age, whichever occurs last |
| Lung cancer | Radiation | Yearly pulmonary examination Spiral CT scan (discuss the benefits and risks/harms of spiral CT scanning for patients at highest risk (e.g., smokers)) |

Table 23 continues on next page.

| RECOMMENDED SCREENING FOR SURVIVORS OF CHILDHOOD LEUKEMIA AND LYMPHOMA ACCORDING TO CHILDREN'S ONCOLOGY GROUP GUIDELINES (Continued) | | |
|---|-------------------------------|--|
| Late Effect | Therapy or Cause | Recommended Screening |
| Second Cancers | | |
| Lymphoma | Hematopoietic cell transplant | Yearly physical with attention to lymphadenopathy and splenomegaly |
| Skin cancer | Radiation (any field) | Monthly skin self exam Yearly dermatologic examination of radiated fields with evaluation for history of skin lesions or changing moles |
| Solid tumors | Hematopoietic cell transplant | Monthly skin self exam Yearly evaluation for benign or malignant tumors |
| FSH = follicle-stimulating hormone; LH = luteinizing hormone; AM = hormone levels; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count. | | |
| Source: [534] | | Table 23 |

The rate of cancer screening among childhood cancer survivors has been lower than optimal, and clinicians should emphasize the importance of screening, given the high risks [549]. Second cancers among childhood cancer survivors call for vigilant screening and surveillance according to individual risk [534; 550]. A prospective one-arm study was conducted among a random sample of 72 Hodgkin lymphoma survivors, 27 to 55 years of age, who were at increased risk for breast cancer and/or cardiomyopathy and had not had a screening mammogram or echocardiogram within the prior two years. A one-page survivorship care plan with recommendations for surveillance was mailed to participants. In addition, survivors' primary physicians were contacted and provided patient-specific information. A web-based virtual information center was made available for both survivors and physicians. Outcomes were assessed by telephone six months after the intervention. At six months, 41% of survivors reported having completed the recommended mammogram; 20% reported having an echocardiogram (women 30%, men 10%) [543].

Cardiac Abnormalities

The greatest risk of cardiac abnormality is associated with a high cumulative dose of anthracycline, which is used in treatment regimens for approximately 60% of children and adolescents with cancer [217; 218;

526; 541; 551]. In a study of more than 1,300 childhood cancer survivors, the relative risk of cardiac abnormality was reported to be 3.53 in association with use of an anthracycline and 7.41 in association with the combination of an anthracycline and an alkylating agent [4]. The risk of anthracycline-induced cardiac abnormality is increased further by several factors, including female sex, younger age (younger than 5 years) at the time of treatment, and Black race [534]. Examples of nonanthracycline agents used in pediatric populations that have been associated with cardiotoxicity include cyclophosphamide, cytarabine, cisplatin, and ifosfamide [552].

A wide range of cardiac abnormalities have been noted in survivors [3; 4; 216; 319; 526]. It is well-established that the development of congestive heart failure can occur at any anthracycline dose, but the risk increases with increased cumulative doses, especially doses ≥ 300 mg/m² [553; 554; 555; 556]. A systematic review indicated a rate of subclinical cardiotoxicity of approximately 16% to 28% associated with an accumulated dose of anthracycline of more than 200 mg/m² [4]. Among survivors who had been treated with an anthracycline, cardiomyopathy has been identified in as many as 57% and clinical heart failure (usually asymptomatic) in as many as 39% [216; 526]. In a study of more than 10,000 survivors, the relative risk of congestive heart failure was 15.1 compared with sibling controls [3].

The more time that has passed since a patient has received treatment with an anthracycline, the higher the patient's risk for developing changes in cardiac function [217; 557; 558].

Radiation therapy to the thorax has also been associated with cardiac damage, including decreased left ventricular mass, end-diastolic wall thickness, valve defect, and early, significant decline in left ventricular shortening fraction, with elevated body mass index and Hispanic ethnicity identified as independent risk factors [216; 526; 541]. The use of lower doses of radiation for children with lymphoma has decreased the occurrence of radiation-related cardiac toxicity [216].

The COG guidelines suggest yearly history and physical examination for survivors at risk for cardiac abnormality related to either chemotherapy or radiation [534]. In addition, an echocardiography and electrocardiography should be done at baseline (the beginning of long-term follow-up) and periodically, depending on risk. Survivors should be educated about the risks of strenuous sports or exercise.

Abnormal Growth and Development

The most common abnormalities in growth and development among childhood cancer survivors have been impaired growth (short stature) and obesity.

Impaired Growth

The use of chemotherapy and radiation therapy in children has been associated with impaired growth and short stature as a result of effects on growth centers in the spine and long bones and endocrine organs [273; 559; 560; 561]. Cranial radiation at a dose of more than 18 Gy has been linked to the greatest loss in height. This loss can be caused by several factors, including growth hormone deficiency, precocious or delayed puberty, or hypothyroidism [273; 319; 534]. Other factors, such as age younger than 4 years, female sex, obesity, concomitant use of corticosteroids, and radiation dose, contribute to risk [273; 534; 559].

Cranial radiation alone is not the only causative factor, as final height has been compromised in children with ALL regardless of whether radiation was given in addition to chemotherapy [559; 560]. Growth is impaired primarily during remission induction therapy, and so-called "catch-up growth" will occur in approximately 70% of children after induction therapy has been completed [526; 559; 560; 561]. However, maintenance therapy with methotrexate and 6-MP may prevent catch-up growth [562]. Catch-up growth does not occur with radiation-induced impairment [560].

Radiation therapy to the head and neck or cerebral cortex can cause hypothyroidism, leading to short stature and poor growth [273; 563]. This risk has been somewhat decreased by the use of lower cumulative doses of radiation therapy in treatment protocols for childhood lymphoma [216]. Bone marrow transplantation is also associated with a high risk for severe growth impairment, especially when the conditioning regimen involves total body radiation [273].

Survivors should have regular growth assessment consisting of measurement of height on standardized growth charts [534]. Growth hormone therapy may be beneficial if growth hormone deficiency is found to be the cause of impaired growth [319; 526; 534]. Although the use of growth hormone therapy was once thought to confer an increased risk of second neoplasms, evidence of this risk has not been demonstrated in large studies [273; 319].

Obesity

Obesity is another well-recognized long-term complication in survivors of ALL, occurring in as many as half of long-term survivors [273; 319; 526]. Weight gain is increased the most during the first year after the end of treatment, and gains continue with time. Several factors have been suggested as the cause of obesity, including treatment with corticosteroids (especially dexamethasone) and cranial radiation [273; 526; 534].

A meta-analysis of survivors of pediatric ALL found a high prevalence of obesity in ALL survivors regardless of survivors' receipt of cranial radiation, gender, or age at diagnosis [564]. Another study indicated a relative risk of obesity of 1.97 in association with radiation therapy to the head and neck, cranium, or thorax [4]. However, other investigators found no difference in the prevalence of overweight and obesity among survivors and the general population [565]. In this latter study, an age of younger than 6 years and overweight and obesity at the time of diagnosis were stronger factors than cranial radiation for overweight and obesity in adulthood [565]. Data from a longitudinal analysis of a multiethnic cohort of pediatric ALL survivors suggest that weight gain within the first year after diagnosis is more strongly associated with long-term increased BMI than early (within 30 days) weight gain [566].

Childhood cancer survivors should be weighed yearly at the time of routine history and physical examination and a body mass index should be determined. The patient's height should be considered when reviewing the body mass index, as a high body mass index may be the result of normal weight gain but relative loss of height. Primary care practitioners should emphasize the importance of weight control through healthy eating habits and exercise in preventing the development of such chronic conditions as diabetes, hypertension, dyslipidemia, and cardiovascular disease [319; 526; 534].

Gonadal Dysfunction

Gonadal dysfunction can occur in both boys and girls as a result of alkylating agents or radiation therapy [273; 526; 534]. In boys, testicular dysfunction may include delayed or arrested puberty, oligospermia, azoospermia, or infertility. In girls, ovarian dysfunction may include delayed or arrested puberty, premature menopause, or infertility [216; 273; 319; 526; 534]. The risk is dose-dependent and is increased when an alkylating agent is used in combination with radiation or an anthracycline [216; 534]. The majority of these late effects arise from radiation-induced uterine injury. Such injuries are reported at higher incidence in adult survivors

of childhood cancers who were exposed to uterine radiation (i.e., pelvic, spinal, or total-body) during childhood. Findings from long-term follow-up studies of the reproductive performance of female survivors provides some reassurance to them by documenting that pregnancy and live birth rates were not significantly compromised in survivors, including those who had been treated with alkylating agents and had not received pelvic, cranial, and total-body irradiation [567]. The relative risk for male infertility has been reported to be 9.03 in association with use of an alkylating agent and 10.6 in association with both an alkylating agent and an anthracycline [4]. Cranial radiation is correlated with an increased risk for premature puberty, especially for girls treated before 8 years of age [273]. The risk of infertility is low and is directly related to gonadal exposure to radiation and age at the time of treatment [568; 569]. The possibility of maintaining gonadal function in the presence of higher cumulative doses of alkylating agents is greater in girls than for boys [534].

The annual history and physical for survivors at high risk for gonadal dysfunction should include evaluation of the puberty stage and pace, sexual function, and Tanner assessment [534]. Baseline levels of follicle-stimulating hormone, luteinizing hormone, and estradiol (girls) or testosterone (boys) should be determined at 13 years of age for girls or 14 years of age for boys and as clinically indicated [534].

Neurocognitive Impairment

Neurocognitive impairment is among the most common and distressing late effect of pediatric cancer treatment [4; 319; 457; 526; 570; 571; 572]. In one study, the relative risk of severe cognitive dysfunction among more than 10,000 survivors was 10.5 compared with sibling controls [3]. In another study, cognitive or psychosocial disorders represented approximately 8% of all severe, life-threatening, or disabling events [4]. A cancer experience alone increases the risk for neurocognitive impairment, and the interruption of regular schooling during treatment can have serious effects on academic performance [534]. Cranial radiation is the greatest contributor to the risk for neurocognitive deficits.

The highest risk is associated with cranial radiation in combination with an age of younger than 3 years at the time of treatment or female sex [534]. The intensity of treatment and the time since treatment are also factors [534]. The replacement of prophylactic cranial radiation with intrathecal chemotherapy has led to a decrease in neurocognitive toxicity, but intrathecal chemotherapy (primarily methotrexate) is associated with some level of deficit in approximately 30% of survivors [570; 571; 572].

A variety of impairments have been reported, and the most common deficits are related to [56; 319; 471; 534; 571]:

- Attention
- Memory
- Mathematic reasoning
- Reading comprehension
- Executive function (planning and organization)
- Visual-motor coordination
- Written expression
- Delays in academic achievement

The deficits in survivors of leukemia and lymphoma are more often related to information processing [534].

The findings of studies on the academic status of survivors support the high reported rate of neurocognitive impairment. In a Childhood Cancer Survivor Study involving 12,430 survivors and 3,410 siblings, significantly more survivors used special education services (23% compared with 8% for siblings) [572]. The results indicated that the greatest differences were found for survivors who were younger than 6 years of age at the time of treatment or who had a diagnosis of CNS tumors, leukemia, or Hodgkin lymphoma [572]. Survivors of leukemia and non-Hodgkin lymphoma were among those who were least likely to finish high school [572]. In addition, a Canadian survey of parents of childhood cancer survivors showed that significantly more survivors than controls had educational or other school problems (46% compared with 23%), had repeated a grade (21% compared with 9%), had attended a

learning disability program (19% compared with 7%), or had participated in a special education program (20% compared with 8%) [457]. Leukemia survivors were among the subgroups that were more likely to have educational problems. While there is longstanding recognition that these effects span the whole illness trajectory and continue beyond treatment completion, further clarity is needed on the specific barriers and facilitators to education during cancer treatment and beyond, as well as on the experiences of children and adolescents across the full range of education settings (e.g., hospital, home, virtual, original school of enrollment), in order to determine which interventions are successful in improving access and experience from their perspective [573].

The COG long-term follow-up guidelines recommend that the annual examination for all childhood cancer survivors include an assessment of educational and/or vocational progress [534]. A baseline formal neuropsychologic evaluation is recommended, with follow-up testing for survivors who demonstrate evidence of impaired progress. Primary care practitioners should alert parents to signs of neurocognitive impairment, emphasizing the importance of evaluating any learning-related problems [56]. In addition, primary care practitioners should refer patients with neurocognitive deficits to a school liaison or community service to facilitate access to educational services or vocational rehabilitation.

Dental Problems

Dental abnormalities have been associated primarily with radiation to the head and neck area or brain and also with chemotherapy. Abnormalities include tooth agenesis, enamel dysplasia, blunting of roots, incomplete calcification, high plaque index, arrested tooth development, and tooth discoloration [216; 273; 319; 526]. The maturity of the teeth appear to be a substantial factor, as the most severe abnormalities have been found in children who are younger than 5 years of age at the time of treatment [273]. Dental caries and periodontal disease are also associated with bone marrow transplantation with chronic graft-versus-host disease [534].

Despite the prevalence of dental abnormalities, the rate of routine dentist visits among survivors of childhood cancer is lower than that recommended for the general population [574]. Primary care practitioners should encourage patients and parents to maintain regularly scheduled dentist visits, with dental cleaning every six months and an oral examination yearly [534].

Psychosocial Disorders

Psychosocial disorders are thought to be related to physical function, well-being, and anxiety related to future health needs [444]. As such, survivors of childhood cancers would be vulnerable to such disorders. However, long-term studies have shown contrasting results with respect to the psychological health of childhood cancer survivors. In general, the psychological health of survivors is similar to that of the general population, but a small percentage of survivors and family members have difficulty with coping and with personal and social skills [460].

A meta-analysis of 20 studies showed no deficits in measures of anxiety, depression, and self-esteem when results for survivors were compared with those for population norms or matched controls [444]. Following that study, the CCSS reported on the psychological outcomes for survivors of pediatric leukemia and lymphoma [445]. That study indicated that survivors were approximately 1.7 times more likely to report symptomatic levels of depression or somatic distress compared with sibling controls, but the rate of depression and distress were similar to those among the general population [445; 575].

In another Childhood Cancer Survivor Study, the percentage of leukemia and lymphoma survivors who reported an adverse effect on mental health or anxiety was similar to the overall population of survivors. One exception was a greater likelihood for Hodgkin lymphoma survivors to report cancer-related anxiety [537]. The authors of the report suggested that the older age at the time of Hodgkin lymphoma diagnosis may account for this difference, as the patient is better able to understand

the seriousness of the cancer diagnosis [537]. This rationale supports the finding of post-traumatic stress disorder symptoms in approximately 20% of adolescent survivors [576].

Age and time since diagnosis may be factors in reported levels of post-traumatic stress disorder [577]. In one study, 255 children with cancer, stratified by time since diagnosis, and 101 demographically matched peers were assessed for post-traumatic stress disorder using structured interviews by both child and parent reports and survey measures of post-traumatic stress symptoms by child report. Cancer was identified as a traumatic event by 52.6% of children with cancer, declining to 23.8% in those who were five years or more from diagnosis [577].

The authors of one study sought to estimate the prevalence of emotional distress in a large cohort of adult survivors of childhood cancer and to evaluate the inter-relationship of risk factors, including cancer-related late effects. A total of 1,863 adult survivors of childhood cancer (median age at follow-up: 32 years) completed comprehensive medical evaluations. Elevated global distress was reported by 15.1% of survivors, and childhood cancer-related morbidities, including pain and learning or memory problems, appear to be directly and indirectly associated with elevated distress symptoms decades after treatment [578].

Sociodemographic factors related to psychosocial disorders among childhood cancer survivors are similar to those of the general population, with higher rates associated with female sex, lower level of educational attainment, and lower socioeconomic status [445; 537]. One systematic review assessed unemployment in adult childhood cancer survivors compared with the general population, and its predictors [579]. Overall, approximately one in six survivors was unemployed and survivors were more likely to be unemployed than controls. Survivors of brain tumors were more likely to be unemployed. Younger age, female sex, radiotherapy, and physical late effects were predictors of unemployment [579]. Because the effects of prolonged psychological distress can

be severe, assessment for depression, anxiety, post-traumatic stress, and social withdrawal should be carried out annually [534]. Special attention should be directed toward female survivors, Hispanic survivors, and survivors with low socioeconomic status. Primary care practitioners should refer patients with emotional difficulties for psychological consultation.

Other Late Effects

The CCSS cohort was used to compare the incidence rates of infections among five-year survivors of pediatric cancer with the rates of siblings [580]. Compared with that of the U.S. population, survivors were at an increased risk of death from infectious causes, with girls/women and those exposed to total body radiation being at greatest risk. Survivors also reported higher rates of overall infectious complications than siblings [580]. As part of the Swiss CCSS, a questionnaire was sent to all registered survivors (20 to 40 years of age), all aged younger than 16 years at diagnosis who had survived five or more years [581]. Fewer survivors than siblings had life partners, and fewer survivors were married than siblings and participants in the Swiss Health Survey. Older and female survivors were more likely to have life partners. Survivors who had undergone radiotherapy, bone marrow transplants, or who had a CNS diagnosis were less likely to have life partners [581].

HEALTH PROMOTION AND EDUCATION

Surveys of childhood cancer survivors have shown knowledge deficits regarding the late effects of cancer and cancer treatment [582; 583]. More than half of the participants in a Childhood Cancer Survivor Study survey could not accurately report their anthracycline exposure or site of radiation therapy, information that is essential for appropriate long-term follow-up care [583]. In addition, 46% of respondents said that previous treatment did not pose a serious health issue, and 19% did not know that previous treatment was related to adverse events [583].

Given the lack of knowledge about the risk for adverse effects and the need for long-term follow-up care, education is essential and should focus on the importance of:

- Obtaining documentation of cancer type and treatment
- Understanding the risk of specific late effects according to a specific cancer diagnosis and specific therapies
- Engaging in healthy lifestyle behaviors to reduce the risk of treatment-related morbidity
- Seeking routine follow-up care and recommended screening

When developing or recommending educational resources for patients and family members, clinicians should consider the native language and literacy level, as appropriate materials will facilitate comprehension.

Documentation of Cancer Type and Treatment

It is imperative that every childhood cancer survivor have written documentation of his or her specific diagnosis and all diagnostic and treatment details [534]. The concept of survivorship care plans has been developed as a way to facilitate better follow-up care for all survivors [584; 585]. Among the basic elements of a survivorship care plan are [534; 585]:

- Diagnostic tests performed and results
- Disease characteristics (e.g., histologic type, stage, grade, site)
- Start and end dates of treatment
- Type of treatment (chemotherapy and radiation therapy regimens, including doses and schedules)
- Indicators of treatment response
- Treatment-related toxicities
- Psychosocial and other supportive services provided
- Information on possible late and long-term effects of treatment and symptoms of such effects

- Information on possible signs of recurrence
- Description of recommended cancer screening and other periodic testing and examinations, their performance schedule, and which provider should perform them
- Specific recommendations for healthy behaviors (e.g., diet, exercise, healthy weight, sunscreen use, immunizations, smoking avoidance/cessation, osteoporosis prevention)
- List of cancer-related resources and information (e.g., web-based sources and telephone listings for major cancer support organizations)
- Identifying number and title of clinical trial (if applicable)
- Full contact information on treating institutions and key individual practitioners
- Identification of a key contact and a coordinator of continuing care

One study suggests, however, that a majority of cancer survivors and their physicians have not yet embraced survivor care plans [586]. From April to July 2012, researchers conducted in-depth telephone interviews with 53 adult survivors (average age: 39.1 years) recruited from the Utah Cancer SEER Registry. Participants were randomly selected from sex, age, and rural/urban strata and were younger than 21 years of age at the time of diagnosis. Participants were asked if they had a primary care physician, if they discussed their cancer history with their physician, and if they had interest in a survivor care plan. Most (83%) survivors had a current primary care physician; nearly 50% were not concerned about their health despite having had cancer; and few had a follow-up care plan, although more than half felt that a survivor care plan could empower their medical decision making. However, more than 30% of survivors were skeptical about the usefulness of a survivor care plan and some expressed concern about healthcare costs [586].

The National Children's Cancer Society has introduced a new online Late Effects After Treatment Tool (LEATT), which is available online at <https://leatt.thenccs.org>. The tool was designed to help survivors learn about potential late effects of childhood cancer. The LEATT provides personalized results, based on the information that the survivor enters, and it takes less than 10 minutes to complete. The results describe potential late effects and symptoms to look for, provide recommendations for follow-up care, and offer preventive tips to help reduce the risk of further health issues [587].

Understanding Risks of Late Effects

A valuable resource for patient and family education is Health Links, a series of educational handouts based on the COG guidelines for long-term care of childhood cancer survivors. These handouts are designed to enhance patient follow-up visits and broaden the application of guidelines. The entire set of Health Links is available online [588]. The handouts address more than 40 topics within the guidelines, and each handout contains a brief overall description of a specific late effect, as well as [533; 534]:

- Explanation of risk factors
- Description of common symptoms
- Explanation of exacerbating conditions
- Recommended screening
- Next steps after positive screening
- Brief explanation of the treatment
- Health-promoting behaviors and interventions

Healthy Lifestyle Behaviors

The health behaviors of childhood cancer survivors have not been well-studied, but overall, young cancer survivors report lifestyle behaviors that are at least as healthy as the age-matched population [56; 532]. Behaviors have been shown to vary according to race/ethnicity; overall, Black survivors have reported better preventive practices and have been less likely to engage in risky behaviors such as smoking and

alcohol consumption [589]. In one study, 40% of survivors reported eating a nutritious diet, 64% said they practiced sun protection, and 94% said they did not smoke [590]. In a later and much larger study, the rate of physical inactivity was high (52% to 72%), with the lowest rate for Hispanic male survivors and the highest rate for Black female survivors [589]. In that same study, the rates of smoking among Black and Hispanic survivors were lower than the rates among their peers in the general population [589].

In a case-control study published in 2014, researchers sought to identify factors other than cancer-related treatment and presence/severity of chronic health conditions that might be associated with late mortality risk among adult survivors of pediatric cancer [591]. A total of 445 participants who died from causes other than cancer recurrence/progression or non-health-related events were compared with 7,162 surviving participants matched for primary diagnosis, age at baseline questionnaire, time from diagnosis to baseline questionnaire, and time at risk. Exercising fewer than three days per week, being underweight, increased medical care use, and self-reported fair-to-poor health were associated with an increased risk for all-cause mortality [591]. A report from the Childhood Cancer Survivor Study found that poor physical activity during adolescence, parents with less than a college education, previous treatment with cranial radiation, limitations of activity due to health or mobility restriction, and low self-esteem were associated with level of psychosocial functioning among childhood and young adult cancer survivors [592].

Primary care practitioners should make sure that childhood cancer survivors understand that the risks associated with unhealthy lifestyle behaviors may be increased because of their previous cancer treatment. In addition, clinicians should ensure that survivors know the importance of a healthy diet, regular exercise, routine sun protection, avoidance of tobacco, and moderation in alcohol consumption. Survivors should also be educated about the signs and symptoms of depression and of ways to alleviate stress and anxiety.

Routine Follow-Up Care and Recommended Screening

The cancer screening practices and compliance with healthcare recommendations have been less than optimal among childhood cancer survivors, and most survivors have contact with primary care practitioners rather than oncology specialists or follow-up clinics [532; 550; 569; 584]. These findings indicate the importance of primary care practitioners assuming responsibility for the long-term follow-up care of childhood cancer survivors; however, barriers to doing so remain. In one study, a minority of primary care physicians perceived that their medical training was adequate to recognize late effects of chemotherapy (27.6%), cancer surgery (36.6%), and radiation therapy (38.1%). Most (93%) had never used the COG guidelines, but 86% would follow their recommendations. Most (84% to 86%) stated that they had never received a cancer treatment summary or survivorship care plan, but more than 90% thought these documents would be useful [593]. Although most general internists report involvement in the care of pediatric cancer survivors, many are unfamiliar with surveillance guidelines and uncomfortable caring for survivors, citing access to guidelines and treatment summaries as the most useful resources in caring for survivors and preferring to care for survivors in collaboration with a cancer care center [594]. A survey of U.S. and Canadian family physicians involved in the care of pediatric cancer survivors revealed similar attitudes. Clinicians also cited surveillance recommendations and clinical care guidelines as being the most useful in assisting them with survivor care and were willing to care for survivors in consultation with a cancer care center [595].

Due to their heightened risk of developing late-occurring adverse outcomes, pediatric cancer survivors are advised to receive follow-up care in specialized survivor clinics. Research indicates that most survivors (71%) who do not attend a specialized clinic were “not aware” of their availability [596].

Clinicians should use every opportunity (e.g., acute care visits, parental or sibling visits, annual examinations) to emphasize the importance of long-term follow-up care in a survivor care clinic and adherence to recommended screening guidelines for survivors.

CHALLENGES IN PROVIDING HEALTH CARE

Approximately one in every 640 young adults (20 to 39 years of age) in the United States is a childhood cancer survivor [526]. This large and increasing population, with its increased risk of adverse events, creates a substantial healthcare burden. As such, there are several challenges to providing long-term care for childhood cancer survivors.

The first challenge is related to the overall age of childhood cancer survivors. Because survival rates have improved over the years, the population of survivors is young and will require close follow-up for several years. The primary responsibility for follow-up care has typically been assigned to oncologists, but many have suggested that primary care practitioners are best equipped to provide the full spectrum of health care to cancer survivors [56; 320; 526; 584; 597]. This shift in responsibility may be especially important given the predicted shortage of oncologists by the year 2020, as well as the predisposition of survivors to seek care with primary practitioners [598].

The increasing age of childhood cancer survivors also creates many challenges to maintaining long-term follow-up care. First, over the course of childhood, adolescence, and young adulthood, individuals are more likely to be mobile, which makes continuity of long-term follow-up difficult. Second, as children/adolescents mature, the primary responsibility for their care shifts from their parents to themselves and they begin to make their own decisions. Third, most pediatric cancer centers do not have programs for follow-up into adulthood, which means that when survivors become adults, they must seek follow-up care elsewhere [597]. Lastly, long-term follow-up

centers that are in existence are confronted with many barriers, including inadequate funding, lack of capacity of the growing population of survivors, and lack of awareness or interest among survivors [526].

Models of care that take into account the transition of care into the adult setting are needed. Until such programs are available, it becomes incumbent on pediatric oncologists to share treatment plans with pediatricians and family practitioners and for oncologists and primary care practitioners to collaborate on survivorship care plans. With emerging technology, the use of electronic media to store health information will facilitate maintenance of important documentation in a portable format.

Lack of awareness of diagnosis, treatments, and potential late effects among childhood cancer survivors also presents a challenge. Such information is essential for appropriate long-term care, and primary care practitioners have an important role in providing educational resources to help survivors better understand their health and receive optimal long-term care.

CASE STUDIES

CASE STUDY 1

Patient A, a bright, energetic boy, 8 years of age, had shown less enthusiasm for his normal activities for a few days. He told his mother he felt tired and was sometimes nauseated, and his mother found that he had a low-grade fever (37.8 degrees Centigrade). Mrs. T, the patient's mother, took Patient A to his pediatrician, who noted no abnormalities on physical examination. He told Mrs. T that the patient probably had a virus. A week later, Patient A was still not feeling better, and Mrs. T took him to the pediatrician again. On physical examination, the pediatrician noted that the patient appeared pale and had slight lymphadenopathy. Suspecting infection, the pediatrician prescribed a 10-day course of an antibiotic. After completing the course of

antibiotics, Patient A still did not feel better and continued to have a low-grade fever. At that time, the pediatrician noted ecchymoses of the skin and slight splenomegaly, findings that had not been previously evident. He ordered laboratory and imaging studies to rule out leukemia. The complete blood count demonstrated slight anemia and leukopenia; the chest x-ray was normal, and computerized tomography confirmed splenomegaly.

The signs and symptoms of pediatric leukemia are often insidious and persistent. The most common symptom associated with ALL is a low-grade fever of unknown etiology. Many symptoms related to leukemia are associated with other diseases and conditions, and care is needed in making a differential diagnosis. Reactive lymphadenopathy is common in children and adolescents, and clinicians should first rule out infectious or inflammatory conditions. Because of this, symptoms of ALL are present for an average of four to six weeks before the diagnosis is made. Further evaluation for leukemia is warranted when fever persists for more than two weeks and when findings on physical examination include pallor, petechiae, ecchymoses of the skin or mucous membranes, or lymphadenopathy. Splenomegaly (or hepatomegaly) at the time of diagnosis of ALL is common. Imaging studies should be carried out to determine the presence of leukemic involvement.

The pediatrician talked with Mr. and Mrs. T privately (without Patient A present) and carefully explained that their son may have leukemia and that he was referring Patient A to a pediatric cancer care center in a neighboring city. Patient A's parents were both devastated by the news. The pediatrician encouraged them to express their emotions and to ask questions. He patiently answered all questions, checking often to make sure they understood. He also reassured Mr. and Mrs. T that he would be available to talk with them or their son at any time. Mr. and Mrs. T told the pediatrician that they did not want Patient A to know about the diagnosis until it was confirmed. The pediatrician tried to persuade them to carefully consider this decision.

A cancer diagnosis is overwhelming for parents, and clinicians discussing the diagnosis should use clear language, encourage questions, check often for understanding, and offer reassurance and support. In addition, clinicians should elicit and validate parents' and patients' emotions. The American Academy of Pediatrics recommends that clinicians refer children to pediatric cancer centers for diagnostic testing for leukemia (and lymphoma), where the availability of appropriate technology and subspecialists helps to ensure an accurate diagnosis. Many parents wish to protect their child by withholding information about the diagnosis, but clinicians should encourage parents to share information with their child, as studies have shown that children often recognize the severity of their illness and wish to be included in discussions about diagnosis and treatment. Open discussion can help a child feel less fear about the unknown and feel trust for their family and caregivers.

After much discussion, Mr. and Mrs. T decided not to tell Patient A the suspected diagnosis, but they did tell him he would need to see another physician and possibly have more tests. Patient A was concerned about the tests and wanted to know if they would be painful. The patient and his parents met with the pediatric oncologist, who performed a bone marrow aspiration, ensuring that Patient A was comfortable during the procedure. Examination of the bone marrow sample showed the presence of leukemic blast cells consistent with ALL. A lumbar puncture was performed, again ensuring that the patient was comfortable, and there was no evidence of leukemic involvement of the CNS. Cytogenetic examination of bone marrow cells demonstrated hyperploidy.

Pain interventions during diagnostic procedures are important, and the goal is to achieve unconsciousness, amnesia, and analgesia to ensure optimum comfort and cooperation. Preventing pain during diagnostic procedures is also important to avoid a child's fear of future diagnostic testing and to avoid post-traumatic stress years later. The sample obtained during bone marrow aspiration should be enough for both cytogenetic examination and immunophenotyping.

The pediatric oncologist met with Patient A and his parents to discuss the findings. Before the oncologist could discuss the diagnosis, Patient A's mother requested that the oncologist speak with only her and her husband before telling the patient. Both Mr. and Mrs. T seemed to be masking their emotions. The oncologist noted that Patient A should be included in the conversation, but Mr. and Mrs. T were adamant. Reluctantly, the oncologist discussed the diagnosis and prognostic factors with the parents only; he told them that the prognostic factors were favorable and noted that a clinical trial would be the best option. Mr. and Mrs. T began to express strong emotions, with Mrs. T crying and Mr. T becoming angry. They did not ask any questions, and Mr. T said he did not want his son to be a "guinea pig" in a clinical trial. The oncologist encouraged them to consider the decision carefully and to talk about the diagnosis with Patient A. When the oncologist suggested that Patient A be involved in the decision about participating in a clinical trial, both parents argued that he was too young to make such a decision. The oncologist provided Mr. and Mrs. T with educational resources and the names of some parents who had agreed to talk with parents of children with newly diagnosed leukemia. He also told them that a decision would need to be made quickly, as treatment should begin as soon as possible.

The emotional behavior of Mr. and Mrs. T indicates that they are having a difficult time dealing with their son's diagnosis. It is important for the clinician to be empathic and to encourage them to express their emotions. The clinician should also reiterate the importance of Patient A being involved with discussions about the diagnosis and treatment. Among the favorable prognostic factors are Patient A's age; age at the time of diagnosis is a strong prognostic factor, and disease-free survival is better for children 1 to 9 years of age than for other age groups. In addition, hyperploidy is associated with a highly favorable prognosis. These factors will allow treatment with a standard-risk protocol. Clinical trial participation should always be encouraged, as it provides the maximum opportunity for cure and long-term survival. The age threshold for a child participating in a discussion about a clinical trial has been debated, but most agree that individual decisions should be made on the basis of the child's level of maturity and physi-

ologic and psychological state. The Children's Oncology Group recommends that the clinician and parents seek the child's perspective and that the clinician should encourage the parents and patient to make the decision jointly as a family. During the clinical trial discussion, the clinician should discuss all facets of the clinical trial, emphasizing that a trial involves several possible treatment options, one of which is the treatment their child would receive outside of the clinical trial. Parents of children with cancer have suggested that providing educational resources and arranging for discussions with other parents are helpful for making decisions about a clinical trial.

Mr. and Mrs. T met with other parents and gained support for their emotional reactions. They also decided that Patient A should know about the diagnosis. He had many questions, and they arranged a meeting with the oncologist. The oncologist also discussed the possibility of a clinical trial, and Patient A said he wanted to participate; his parents supported his decision.

Patient A received induction therapy, CNS prophylaxis, consolidation therapy, and three years of maintenance therapy. Throughout his treatment, the patient received support from his extended family, friends, and classmates. He was tutored at home and managed to keep up with his school work. Four years after diagnosis, Patient A has no evidence of disease and he has returned to a "normal" life of school and activities. The pediatric oncologist documented the patient's complete diagnosis and a comprehensive account of treatment in a survivorship care plan, which he forwarded to the patient's pediatrician.

As Patient A continues routine health care, the survivorship care plan will provide the information his pediatrician and subsequent physicians need to understand his health risks according to his cancer type and its treatment. His physicians should also consult the Children's Oncology Group's evidence-based guidelines for the long-term follow-up care of childhood cancer survivor to provide individualized follow-up care and screening. Lastly, Patient A's physicians should use every healthcare visit as an opportunity to educate Patient A (and his parents) about his specific health risks and the importance of appropriate prevention measures, engaging in healthy lifestyle behaviors, and avoiding risky behaviors.

CASE STUDY 2

E is a Puerto Rican girl, 10 years of age, whose brother, Patient M, 5 years of age, is in the second year of his three-year course of chemotherapy for ALL. Before Patient M was diagnosed with cancer, E enjoyed helping her mother with his care and teaching him how to count and to say the alphabet. E also enjoyed taking dance classes, and she and her classmates would visit each other's homes to practice. E's mother, Mrs. P, does not work outside the home and had been very involved in E's activities before the diagnosis. E's father, Mr. P, works full-time on the weekdays and paints houses on the weekends to ensure that the family can live in a nice neighborhood outside of the city. Several Puerto Rican families live in the neighborhood, and the P family enjoys close ties within this community. Both Mr. and Mrs. P speak Spanish as a first language and use English sparingly.

Because of the financial strain and the long drive to the hospital, the family moved into a two-bedroom condominium closer to the hospital. E's family is the only Hispanic family in the complex, and E spends much time at home alone, as Mr. P continues to work two jobs and Mrs. P spends most of each day at the hospital. E's grades begin to drop, and she does not complete assignments or closely follow directions. E's teacher feels that she is disinterested in academics and her classmates. At home and at the hospital, E argues frequently with Mrs. P and cries often, saying that she wants to live with her friends in her former neighborhood because she feels "bored." In general, Mrs. P is embarrassed and frustrated by E's behavior. She often physically handles E following outbursts, resulting in E's crying and embarrassment. Conversely, Mrs. P is very kind to the staff and her son. If E is not present, Mrs. P does not exhibit signs of emotional distress.

E has lost many things that were important to her: dance lessons, familiar school, and friends, and her behavior and outbursts may be indicative of loneliness as well as jealousy and resentment she feels against the time and attention Mrs. P provides Patient M. Cancer-free siblings are often reactive to the loss of day-to-day family routine, restrictions on their social activities, and inability to help their siblings with cancer. In addition, cancer-free siblings receive the least attention in the family, and their parents often overlook or underestimate their emotional and health-related responses [495]. E's feelings and behaviors increase the risk of unhealthy psychosocial adjustment and lower educational achievements.

Noting the emotional behaviors of E and her mother, Patient M's healthcare team seeks to provide psychosocial support for the family. A female member of the medical team who has been involved with Patient M's treatment and a professional interpreter arrange to talk with Mr. and Mrs. P and E independently so that they can share their concerns and express their emotions openly. The team member reassures the parents that E is expressing feelings and behaviors typical of cancer-free siblings. She acknowledges that the move has been difficult for the entire family, and points out that it is particularly so for E because of the social support she lost in addition to the time lost with her family. In the discussion with E, the team member acknowledges how difficult the adjustment is for E and emphasizes that her parents love her. E says that she misses being with her mother and brother and wishes she could be more involved. She also misses her father and wishes he could spend more time with the family. On the basis of the discussions with the family, the team member recommends several interventions, including a problem-solving skills training program for Mrs. P, family therapy, and a sibling program for E. The team member also encourages Mrs. P to involve E in Patient M's care and helps Mr. and Mrs. P seek additional practical resources to help them meet the challenges associated with Patient M's illness.

Family-centered care is essential in pediatric cancer, and the healthcare team must emphasize the importance of family cohesion and communication [504; 505; 506]. Helping Mr. and Mrs. P understand the reasons for E's behavior enhances the likelihood that they will agree to have her participate in a psychosocial intervention [509]. The use of a professional interpreter helps to make Mr. and Mrs. P more comfortable and provides for better comprehension [167]. The recommendation for a problem-solving program for Mrs. P is especially appropriate as such training has been shown to have increased effectiveness for Spanish-speaking mothers [521]. Family therapy will help Mr. and Mrs. P and E communicate more openly with each other, and the therapeutic peer support group can help E with psychosocial adjustment.

Four months after the intervention, E says that she feels she has more of an active role in Patient M's treatment and that she is helping him with pain and emotional management. E is able to speak with her mother and father about problems at school and emotional aspects related to Patient M's cancer and the move. Mrs. P is noticeably affectionate with E. The family has received financial assistance with help from a cancer society, and Mr. P has negotiated with his employer to be off on every Friday and has quit his second job, allowing him to spend more time with his family. The family also makes arrangements to see friends in their former neighborhood occasionally. E is interacting with schoolmates again and is also performing better academically.

CONCLUSION

The diagnosis, treatment, and follow-up care for children and adolescents with leukemia and lymphoma are complex. Although pediatric oncologists and a host of oncology specialists will provide treatment, primary care practitioners should be familiar with the signs and symptoms indicative of the most common types of hematologic cancers to ensure timely detection and early treatment, when the chances for cure are best. The types of leukemia and lymphoma differ from each other according to patient factors (age, sex, and race/ethnicity), clinical features, cancer biology and histology, approaches to treatment, late effects, and rates of overall and disease-free survival.

Diagnosing childhood leukemia and lymphoma is challenging because of the similarity between their symptoms and the symptoms of other common childhood conditions, especially infection. Careful history and physical examination targeted to suspicious symptoms is the first step of testing to confirm the diagnosis and determine the biology and histology of the cancer.

The diagnosis of cancer in a young person is devastating for patients and families. Therefore, clinicians should follow the tenets of "breaking bad news" and use clear, simple language, show empathy, and allow the patient and family to express concerns and emotion. As in all healthcare encounters, communicating the diagnosis should be done with consideration of the family's cultural context, with a professional interpreter used if English is not the family's native language.

Children and adolescents with leukemia or lymphoma should be treated in a pediatric cancer center and should be encouraged to participate in a clinical trial, which provides the opportunity for the most advanced care. The discussion of clinical trial participation should include all the pertinent information necessary for decision making. When possible, the family should make a decision together, with involvement of the patient. Treatment for leukemia and lymphoma is centered on chemotherapy, and several regimens have been evaluated for each type of disease. Radiation therapy is also a cornerstone of treatment, especially for lymphoma. The underlying principle of treatment is to maximize the potential for cure while minimizing the toxic effects of chemotherapy and/or radiation therapy. As such, treatment is risk-adapted according to prognostic variables. Research focused on adverse events related to chemotherapy and radiation therapy has demonstrated a variety of acute and late effects of treatment, and investigators continue to modify treatment regimens to avoid toxicity.

Disease-directed treatment is only one component of the overall treatment of children and adolescents with pediatric leukemia or lymphoma. Treatment also includes supportive, palliative, and psychosocial care. Supportive care involves the evaluation and treatment of potential complications of both the disease and treatment. The most common complications are infection, neutropenia, anemia, and thrombocytopenia. Palliative care focuses on the careful assessment and treatment of symptoms to enhance the quality of life. The prevalence of such symptoms as pain, fatigue, gastrointestinal disturbances, mucositis, and pruritus are high among children/adolescents with leukemia or lymphoma, and clinicians should implement both pharmacologic and nonpharmacologic interventions to relieve discomfort.

As a result of advances in treatment, the five-year overall survival for a child/adolescent with leukemia or lymphoma is approximately 80% [4]. Despite this high rate of success, some children and adolescents will die of the disease or complications. Pediatric

end-of-life care is a challenge for several reasons and does not need to exclude curative therapy. Parents often have unrealistic expectations or optimism about cure, and clinicians should talk openly with the family to ensure that the priority in decision making is the patient's quality of life. Throughout all treatment, children and adolescents with cancer should be allowed to express opinions about the direction of care in a way that is appropriate for their developmental age.

Addressing the psychosocial and spiritual needs of children and adolescents with cancer is an integral component of comprehensive care. Evaluating these needs and providing referrals for interventions help patients and their families cope with the diagnosis and treatment of cancer and help to avoid later psychosocial distress. By definition, pediatric health care is family-centered, and it is important for clinicians to ensure that the psychosocial and spiritual needs of parents, siblings, and other family members are also met.

The advances in treatment for children/adolescents with pediatric leukemia or lymphoma have led to a substantial number of childhood cancer survivors, and the health burden caused by the late effects of treatment is substantial for this growing population. Close follow-up care is essential to ensure the early detection and/or prevention of such late effects as second cancers, cardiac abnormalities, abnormal growth and development, gonadal dysfunction, neurocognitive impairment, and psychosocial disorders. Follow-up care should be individualized according to treatment exposure and risk, and evidence-based guidelines are now available for care.

There are many challenges inherent in providing long-term follow-up care to childhood cancer survivors. Patient and family education is necessary to heighten awareness of the importance of follow-up care and the potential late effects. Primary care practitioners are uniquely poised to provide the full spectrum of care for childhood cancer survivors and can play a pivotal role in ensuring the long-term health of this growing population.

RESOURCES FOR FAMILIES WITH A CHILD OR ADOLESCENT WITH LEUKEMIA OR LYMPHOMA

GENERAL EDUCATION AND ADVOCACY

American Cancer Society

<https://www.cancer.org>

American Childhood Cancer Organization

<https://www.acco.org>

The Leukemia and Lymphoma Society

<https://www.lls.org>

The National Children's Cancer Society

<https://www.thenccs.org>

13Thirty Cancer Connect

<http://13thirty.org>

The Ulman Cancer Fund for Young Adults

<https://ulmanfoundation.org>

SURVIVORSHIP

Cancervive

<https://cancervive.ca>

Children's Oncology Group

<http://www.survivorshipguidelines.org>

Stupid Cancer

<https://stupidcancer.org>

National Coalition for Cancer Survivorship

<https://canceradvocacy.org>

Office of Cancer Survivorship

(of the National Cancer Institute)

<https://cancercontrol.cancer.gov/ocs>

INSURANCE, LEGAL, AND EDUCATIONAL ISSUES

National Organization for Rare Disorders:

International Center for Disability

Resources on the Internet

<https://rarediseases.org/organizations/international-center-for-disability-resources-on-the-internet>

Patient Advocate Foundation

<https://www.patientadvocate.org>

FREE WEEKLONG AND WEEKEND CAMPS

Big Sky Kids

<https://eaglemount.org/camp/big-sky-kids>

Camp Mak-A-Dream

<https://www.campdream.org>

Camp Sunshine

<https://www.campsunshine.org>

First Descents

<https://firstdescents.org>

Special Love for Children

with Cancer Camp Fantastic

<https://speciallove.org/event/camp-fantastic>

Works Cited

1. National Cancer Institute. Childhood Cancer Data Initiative. National Childhood Cancer Registry Explorer. Available at <https://nccrexplorer.ccdi.cancer.gov/application.html>. Last accessed August 5, 2024.
2. National Cancer Institute. Cancer in Children and Adolescents. Available at <https://www.cancer.gov/types/childhood-cancers/child-adolescent-cancers-fact-sheet>. Last accessed August 5, 2024.
3. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355(15):1572-1582.
4. Geenen MM, Cardous-Ubbink MC, Kremer LC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA*. 2007;297(24):2705-2715.
5. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2008;100(19):1368-1379.
6. Mody R, Li S, Dover DC. Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Blood*. 2008;111(12):5515-5523.
7. Friedman DL, Whitton J, Leisenring W, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2010;102(14):1083-1095.
8. Howk T, Wasilewski-Masker K. Palliative care for adolescents and young adults: a pediatric perspective. *J Adolesc Young Adult Oncol*. 2011;1(1):11-12.
9. Kondryn HJ, Edmondson CL, Hill J, Eden TO. Treatment non-adherence in teenage and young adult patients with cancer. *Lancet Oncol*. 2011;12(1):100-108.
10. Sender LS (ed). *Journal of Adolescent and Young Adult Oncology*. Available at <https://home.liebertpub.com/publications/journal-of-adolescent-and-young-adult-oncology/387/overview>. Last accessed August 5, 2024.
11. National Center for Health Statistics. Leading Causes of Death. Available at <https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm>. Last accessed August 5, 2024.
12. Harris NL, Jaffe ES, Diebold J, et al. The World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November, 1997. *Ann Oncol*. 1999;10(12):1419-1432.
13. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-2390.
14. Weijie L (ed). Leukemia: Chapter 1: *The 5th Edition of the World Health Organization Classification of Hematolymphoid Tumors*. Brisbane, AU: Exon Publications; 2022.
15. National Cancer Institute. Cancer Stat Facts: Childhood Leukemia (Ages 0-19). Available at <https://seer.cancer.gov/statfacts/html/childleuk.html>. Last accessed August 5, 2024.
16. National Cancer Institute. Chronic Lymphocytic Leukemia Treatment. Available at https://www.cancer.gov/types/leukemia/hp/clk-treatment-pdq#section/_1. Last accessed August 5, 2024.
17. National Cancer Institute. Childhood Non-Hodgkin Lymphoma Treatment (PDQ). Available at <https://www.cancer.gov/types/lymphoma/hp/child-nhl-treatment-pdq>. Last accessed August 5, 2024.
18. National Cancer Institute. Childhood Hodgkin Lymphoma Treatment (PDQ): Diagnosis and Staging. Available at <https://www.cancer.gov/types/lymphoma/hp/child-hodgkin-treatment-pdq#section/all>. Last accessed August 5, 2024.
19. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *Ca Cancer J Clin*. 2014;64(2):83-103.
20. Zipursky A, Brown E, Christensen H, Sutherland R, Doyle J. Leukemia and/or myeloproliferative syndrome in neonates with Down syndrome. *Semin Perinatol*. 1997;21(1):97-101.
21. Sandler D, Ross JA. Epidemiology of acute leukemia in children and adults. *Semin Oncol*. 1997;24(1):3-16.
22. Rubnitz JE, Inaba H, Ribeiro RC. Acute myeloid leukemia. In: Pui CH (ed). *Childhood Leukemias*. 3rd ed. New York, NY: Cambridge University Press; 2012.
23. Marcotte EL, Ritz B, Cockburn M, Clarke CA, Heck JE. Birth characteristics and risk of lymphoma in young children. *Cancer Epidemiol*. 2014;38(1):48-55.
24. Milne E, Greenop KR, Scott RJ, et al. Parental prenatal smoking and risk of childhood acute lymphoblastic leukemia. *Am J Epidemiol*. 2012;175(1):43-53.
25. Marcotte EL, Ritz B, Cockburn M, Yu F, Heck JE. Exposure to infections and risk of leukemia in young children. *Cancer Epidemiol Biomarkers Prev*. 2014;23(7):1195-1203.
26. Filipovich AH, Mathur A, Kamat D, Shapiro RS. Primary immunodeficiencies: genetic risk factors for lymphoma. *Cancer Res*. 1992;52(19 Suppl):5465s-5467s.
27. Hutchison RE, Uner A. Biology and pathology of Hodgkin's disease. In: Weinstein HJ, Hudson MM, Link MP (eds). *Pediatric Lymphomas*. Berlin: Springer; 2007: 7-18.

28. Hjalgrim H, Rostgaard K, Johnson PCD, et al. HLA-A alleles and infectious mononucleosis suggest a critical role for cytotoxic T-cell response in EBV-related Hodgkin lymphoma. *Proc Natl Acad Sci U S A*. 2010;107(14):6400-6405.
29. Mbulaiteye SM, Pullarkat ST, Nathwani BN, et al. Epstein-Barr virus patterns in US Burkitt lymphoma tumors from the SEER residual tissue repository during 1979–2009. *APMIS*. 2014;122(1):5-15.
30. Linabery AM, Erhardt EB, Fonstad RK, et al. Infectious, autoimmune and allergic diseases and risk of Hodgkin lymphoma in children and adolescents: a Children’s Oncology Group study. *Int J Cancer*. 2014;135(6):1454-1469.
31. Rudant J, Orsi L, Menegaux F, et al. Childhood acute leukemia, early common infections, and allergy: the ESCALE Study. *Am J Epidemiol*. 2010;172(9):1015-1027.
32. Gutensohn N, Cole P. Childhood social environment and Hodgkin’s disease. *N Engl J Med*. 1981;304(3):135-140.
33. Goldin LR, Landgren O, Kristinsson SY, Bjorkholm M, Paltiel O. Infection in infancy and subsequent risk of developing lymphoma in children and young adults. *Blood*. 2011;117(5):1670-1672.
34. Spector L, Charbonneau B, Robison LL. Epidemiology and etiology. In: Pui CH (ed). *Childhood Leukemias*. 3rd ed. New York, NY: Cambridge University Press; 2012.
35. Linabery A, Olshan AF, Gamis AS, et al. Exposure to medical test irradiation and acute leukemia among children with Down Syndrome: a report from the Children’s Oncology Group. *Pediatrics*. 2006;118(5):e1499-e1508.
36. Slater ME, Linabery AM, Spector LG, et al. Maternal exposure to household chemicals and risk of infant leukemia: a report from the Children’s Oncology Group. *Cancer Causes Control*. 2011;22(8):1197-1204.
37. McKenzie LM, Allshouse WB, Byers TE, Bedrick EJ, Serdar B, Adgate JL. Childhood hematologic cancer and residential proximity to oil and gas development. *PLoS One*. 2017;12(2):e0710423.
38. Antonopoulos C, Sergentanis T, Papadopoulou C, et al. Maternal smoking during pregnancy and childhood lymphoma: a meta-analysis. *Int J Cancer*. 2011;129(11):2694-2703.
39. Percy C, Smith MA, Linet M, et al. Lymphomas and reticuloendothelial neoplasms. In: Ries L, Smith MA, Gurney JG, et al. (eds). *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975– 1995; NIH Pub. No. 99-4649*. Bethesda, MD: National Cancer Institute, SEER Program; 1999: 35-50.
40. Grufferman S, Gilchrist GS, Pollock BH, et al. Socioeconomic status, the Epstein-Barr virus and risk of Hodgkin’s disease in children. *Leuk Lymphoma*. 2001;42(Suppl 2):40.
41. Pui C. Acute lymphoblastic leukemia. In: Pui CH (ed). *Childhood Leukemias*. 3rd ed. New York, NY: Cambridge University Press; 2012.
42. Gale K, Ford AM, Repp R, et al. Backtracking leukemia to birth: identification of clonotypic gene fusion sequences in neonatal blood spots. *Proc Natl Acad Sci U S A*. 1997;94(25):13950-13954.
43. Ford A, Bennett CA, Price CM, et al. Fetal origins of the TEL-AML1 fusion gene in identical twins with leukemia. *Proc Natl Acad Sci U S A*. 1998;95(8):4584-4588.
44. Rubnitz JE, Gibson B, Smith FO. Acute myeloid leukemia. *Hematol Oncol Clin N Am*. 2010;24(1):35-63.
45. National Cancer Institute. Childhood Acute Myeloid Leukemia Treatment (PDQ). Available at <https://www.cancer.gov/types/leukemia/hp/child-aml-treatment-pdq>. Last accessed August 5, 2024.
46. Aplenc R, Alonzo TA, Gerbing RB, et al. Ethnicity and survival in childhood acute myeloid leukemia: a report from the Children’s Oncology Group. *Blood*. 2006;108(1):74-80.
47. National Cancer Institute. Childhood Hodgkin Lymphoma Treatment (PDQ). Available at <https://www.cancer.gov/types/lymphoma/hp/child-hodgkin-treatment-pdq>. Last accessed August 5, 2024.
48. Lukes R, Butler JJ. The pathology and nomenclature of Hodgkin’s disease. *Cancer Res*. 1966;26:1063-1081.
49. National Cancer Institute. Rye Classification for Hodgkin Disease. Available at <https://training.seer.cancer.gov/lymphoma/abstract-code-stage/morphology/rye.html>. Last accessed August 5, 2024.
50. Perkins S, Morris SW. Biology and pathology of pediatric non-Hodgkin lymphoma. In: Weinstein HJ, Hudson MM, Link MP (eds). *Pediatric Lymphomas*. Berlin: Springer; 2007: 91-140.
51. Kanbar AH, Sacher RA. Burkitt Lymphoma and Burkitt-like Lymphoma. Available at <https://emedicine.medscape.com/article/1447602-overview>. Last accessed August 5, 2024.
52. Seidemann K, Tiemann M, Lauterbach I, et al. Primary mediastinal large B-cell lymphoma with sclerosis in pediatric and adolescent patients: treatment and results from three therapeutic studies of the Berlin-Frankfurt-Münster Group. *J Clin Oncol*. 2003;21(9):1782-1789.
53. Rosenwald A, Wright G, Leroy K, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. *J Exp Med*. 2003;198(6):851-862.
54. Savage K, Monti S, Kutok JL, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. *Blood*. 2003;102(12):3871-3879.
55. Neth O, Seidemann K, Jansen P, et al. Precursor B-cell lymphoblastic lymphoma in childhood and adolescence: clinical features, treatment, and results in trials NHL-BFM 86 and 90. *Med Pediatr Oncol*. 2000;35(1):20-27.

56. Phipps S, Tyc VL, Conklin H, Kevin K. Psychosocial issues. In: Pui CH (ed). *Childhood Leukemias*. 3rd ed. New York, NY: Cambridge University Press; 2012.
57. Angheliescu DL, Kaddoum R. Pain management. In: Pui CH (ed). *Childhood Leukemias*. 3rd ed. New York, NY: Cambridge University Press; 2012.
58. Landier W, Tse AM. Use of complementary and alternative medical interventions for the management of procedure-related pain, anxiety, and distress in pediatric oncology: an integrative review. *J Pediatr Nurs*. 2010;25(6):566-579.
59. Behm FG. Immunophenotyping. In: Pui CH (ed). *Childhood Leukemias*. 3rd ed. New York, NY: Cambridge University Press; 2012.
60. Raimondi SC. Cytogenetics of acute leukemias. In: Pui CH (ed). *Childhood Leukemias*. 3rd ed. New York, NY: Cambridge University Press; 2012.
61. American Academy of Pediatrics. Guidelines for the pediatric cancer center and the role of such centers in diagnosis and treatment. *Pediatrics*. 1997;99(1):139-141.
62. American Academy of Pediatrics. Guidelines for pediatric cancer centers. *Pediatrics*. 2004;113(6):1833-1835.
63. Young G, Toretsky JA, Campbell AB, Eskenazi AE. Recognition of common childhood malignancies. *Am Fam Phys*. 2000;61(7):2144-2154.
64. Jones L, Saha V. Philadelphia positive acute lymphoblastic leukaemia of childhood. *Br J Haematol*. 2005;130(4):489-500.
65. Creutzig U, van den Heuvel-Eibrink MM, Gibson B, et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel. *Blood*. 2012;120(16):3187-3205.
66. Bennett J, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) cooperative group. *Br J Haematol*. 1976;33(4):451-458.
67. Onciu M, Pui CH. Diagnosis and classification. In: Pui CH (ed). *Childhood Leukemias*. 3rd ed. New York, NY: Cambridge University Press; 2012.
68. McLean T, Ringold S, Neuberg D, et al. TEL/AML-1 dimerizes and is associated with a favorable outcome in childhood acute lymphoblastic leukemia. *Blood*. 1996;88(11):4252-4258.
69. Betts DR, Ammann RA, Hirt A, et al. The prognostic significance of cytogenetic aberrations in childhood acute myeloid leukaemia: a study of the Swiss Paediatric Oncology Group (SPOG). *Eur J Haematol Suppl*. 2007;78(6):468-476.
70. Meshinchi S, Arceci RJ. Prognostic factors and risk-based therapy in pediatric acute myeloid leukemia. *Oncologist*. 2007;12(3):341-355.
71. Wells R, Arthur DC, Srivastava A, et al. Prognostic variables in newly diagnosed children and adolescents with acute myeloid leukemia: Children's Cancer Group Study 213. *Leukemia*. 2002;16(4):601-607.
72. Grier HE, Gelber RD, Camitta BM, et al. Prognostic factors in childhood acute myelogenous leukemia. *J Clin Oncol*. 1987;5(7):1026-1032.
73. Aziz H, Ping CY, Alias H, Ab Mutalib NS, Jamal R. Gene mutations as emerging biomarkers and therapeutic targets for relapsed acute myeloid leukemia. *Front Pharmacol*. 2017;8:897.
74. Farrar JE, Schuback HL, Ries RE, et al. Genomic profiling of pediatric acute myeloid leukemia reveals a changing mutational landscape from disease diagnosis to relapse. *Cancer Res*. 2016;76(8):2197-2205.
75. Tarlock K, Zhong S, He Y, et al. Distinct age-associated molecular profiles in acute myeloid leukemia defined by comprehensive clinical genomic profiling. *Oncotarget*. 2018;9(41):26417-26430.
76. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med*. 2006;354(2):166-178.
77. American Cancer Society. Prognostic Factors in Childhood Leukemia (ALL or AML). Available at <https://www.cancer.org/cancer/leukemia-in-children/detection-diagnosis-staging/prognostic-factors.html>. Last accessed August 5, 2024.
78. Hossain MJ, Xie L, McCahan SM. Characterization of pediatric acute lymphoblastic leukemia survival patterns by age at diagnosis. *J Cancer Epidemiol*. 2014;865979.
79. Wang Y, Huang J, Rong L, et al. Impact of age on the survival of pediatric leukemia: an analysis of 15083 children in the SEER database. *Oncotarget*. 2016;7(50):83767-83774.
80. Trueworthy R, Shuster J, Look T, et al. Ploidy of lymphoblasts is the strongest predictor of treatment outcome in B-progenitor cell acute lymphoblastic leukemia of childhood: a Pediatric Oncology Group Study. *J Clin Oncol*. 1992;10(4):606-613.
81. Mörcke A, Zimmermann M, Reiter A, et al. Prognostic impact of age in children and adolescents with acute lymphoblastic leukemia: data from the trials ALL-BFM 86, 90, and 95. *Klin Padiatr*. 2005;217(6):310-320.
82. Forestier E, Schmiegelow K, Nordic Society of Paediatric Haematology and Oncology. The incidence peaks of the childhood acute leukemias reflect specific cytogenetic aberrations. *J Pediatr Hematol Oncol*. 2006;28(8):486-495.
83. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J Clin Oncol*. 1996;14(1):18-24.
84. Reaman GH, Spoto R, Sensel MG, et al. Treatment outcome and prognostic factors for infants with acute lymphoblastic leukemia/ treated on two consecutive trials of the Children's Cancer Group. *J Clin Oncol*. 1999;17(2):445-455.
85. Kosaka Y, Koh K, Kinukawa N, et al. Infant acute lymphoblastic leukemia with MLL gene rearrangements: outcome following intensive chemotherapy and hematopoietic stem cell transplantation. *Blood*. 2004;104(12):3527-3534.

86. Pui C, Sandlund JT, Pei D, et al. Results of therapy for acute lymphoblastic leukemia in black and white children. *JAMA*. 2003;290(15):2001-2007.
87. Mahmoud HH, Rivera GK, Hancock ML, et al. Low leukocyte counts with blast cells in cerebrospinal fluid of children with newly diagnosed acute lymphoblastic leukemia. *N Engl J Med*. 1993;329(5):314-319.
88. Gilchrist GS, Tubergen DG, Sather HN, et al. Low numbers of CSF blasts at diagnosis do not predict for the development of CNS leukemia in children with intermediate-risk acute lymphoblastic leukemia: a Children's Cancer Group report. *J Clin Oncol*. 1994;12(12):2594-2600.
89. Winick N, Devidas M, Chen S, et al. Impact of initial CSF findings on outcome among patients with National Cancer Institute standard- and high-risk B-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group. *J Clin Oncol*. 2017;35(22):2527-2534.
90. Pui CH, Boyett JM, Relling MV, et al. Sex differences in prognosis for children with acute lymphoblastic leukemia. *J Clin Oncol*. 1999;17(3):818-824.
91. Shuster JJ, Wacker P, Pullen J, et al. Prognostic significance of sex in childhood B-precursor acute lymphoblastic leukemia: a Pediatric Oncology Group Study. *J Clin Oncol*. 1998;16(8):2854-2863.
92. Chessells J, Richards SM, Bailey CC, et al. Gender and treatment outcome in childhood lymphoblastic leukaemia: report from the MRC UKALL trials. *Br J Haematol*. 1995;89(2):364-372.
93. Holmes L Jr, Hossain J, Desvignes-Kendrick M, Opara F. Sex variability in pediatric leukemia survival: large cohort evidence. *ISRN Oncol*. 2012;439070.
94. Pui CH, Sandlund JT, Pei D, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIIB at St Jude Children's Research Hospital. *Blood*. 2004;104(9):2690-2696.
95. Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. *Blood*. 2001;97(5):1211-1218.
96. Singh SK, Lupu PJ, Scheurer ME, et al. A childhood acute lymphoblastic leukemia genome-wide association study identifies novel sex-specific risk variants. *Medicine (Baltimore)*. 2016;95(46):e5300.
97. Do TN, Ucisik-Akkaya E, Davis CF, et al. An intronic polymorphism of IRF4 gene influences gene transcription in vitro and shows a risk association with childhood acute lymphoblastic leukemia in males. *Biochim Biophys Acta*. 2010;1802:292-300.
98. Morrison BA, Ucisik-Akkaya E, Flores H, et al. Multiple sclerosis risk markers in HLA-DRA, HLA-C, and IFNG genes are associated with sex-specific childhood leukemia risk. *Autoimmunity*. 2010;43:690-697.
99. Healy J, Richer C, Bourgey M, et al. Replication analysis confirms the association of ARID5B with childhood B-cell acute lymphoblastic leukemia. *Haematologica*. 2010;95:1608-1611.
100. Kadan-Lottick N, Ness KK, Bhatia S, Gurney JG. Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. *JAMA*. 2003;290(15):2008-2014.
101. Pui CH, Pei D, Sandlund JT, et al. Long-term results of St. Jude Total Therapy studies 11, 12, 13A, 13B and 14 for childhood acute lymphoblastic leukemia. *Leukemia*. 2010;24(2):371-382.
102. Kahn JM, Cole PD, Blonquist TM, et al. An investigation of toxicities and survival in Hispanic children and adolescents with ALL: results from the Dana-Farber Cancer Institute ALL Consortium protocol 05-001. *Pediatr Blood Cancer*. 2018;65(3).
103. Eche IJ, Aronowitz T. A literature review of racial disparities in overall survival of black children with acute lymphoblastic leukemia compared with white children with acute lymphoblastic leukemia. *J Pediatr Oncol Nurs*. 2020;37(3):180-194.
104. Tai EW, Ward KC, Bonaventure A, Siegel DA, Coleman MP. Survival among children diagnosed with acute lymphoblastic leukemia in the United States, by race and age, 2001 to 2009: findings from the CONCORD-2 study. *Cancer*. 2017;123(Suppl 24):5178-5189.
105. Raimondi S, Pui CH, Hancock ML, et al. Heterogeneity of hyperdiploid (51-67) childhood acute lymphoblastic leukemia. *Leukemia*. 1996;10(2):213-224.
106. Raimondi S, Zhou Y, Mathew S, et al. Reassessment of the prognostic significance of hypodiploidy in pediatric patients with acute lymphoblastic leukemia. *Cancer*. 2003;98(12):2715-2722.
107. Moorman AV, Richards SM, Martineau M, et al. Outcome heterogeneity in childhood high-hyperdiploid acute lymphoblastic leukemia. *Blood*. 2003;102(8):2756-2762.
108. Dastugue N, Suciú S, Plat G, et al. Hyperdiploidy with 58-66 chromosomes in childhood B-acute lymphoblastic leukemia is highly curable: 58951 CLG-EORTC results. *Blood*. 2013;121(13):2415-2423.
109. Schultz KR, Pullen DJ, Sather HN, et al. Risk- and response-based classification of childhood B-precursor acute lymphoblastic leukemia: a combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). *Blood*. 2007;109(3):926-935.
110. Kanerva J, Saarinen-Pihkala UM, Niini T, et al. Favorable outcome in 20-year follow-up of children with very-low-risk ALL and minimal standard therapy, with special reference to TEL-AML1 fusion. *Pediatr Blood Cancer*. 2004;42(1):30-35.
111. Heerema N, Harbott J, Galimberti S, et al. Secondary cytogenetic aberrations in childhood Philadelphia chromosome positive acute lymphoblastic leukemia are nonrandom and may be associated with outcome. *Leukemia*. 2004;18(4):693-702.

112. Gaynon PS, Angiolillo AL, Carroll WL, et al. Long-term results of the children's cancer group studies for childhood acute lymphoblastic leukemia 1983–2002: a Children's Oncology Group Report. *Leukemia*. 2010;24(2):285-297.
113. Chessells J, Harrison G, Richards SM, et al. Down's syndrome and acute lymphoblastic leukaemia: clinical features and response to treatment. *Arch Dis Child*. 2001;85(4):321-325.
114. Bassal M, La MK, Whitlock JA, et al. Lymphoblast biology and outcome among children with Down syndrome and ALL treated on CCG-1952. *Pediatr Blood Cancer*. 2005;44(1):21-28.
115. Canner J, Alonzo TA, Franklin J, et al. Differences in outcomes of newly diagnosed acute myeloid leukemia for adolescent/young adult and younger patients: a report from the Children's Oncology Group. *Cancer*. 2013;119(23):4162-4169.
116. Ravindranath Y, Chang M, Steuber CP, et al. Pediatric Oncology Group (POG) studies of acute myeloid leukemia (AML): a review of four consecutive childhood AML trials conducted between 1981 and 2000. *Leukemia*. 2005;19(12):2101-2116.
117. Braoudaki M, Tzortzatu-Stathopoulou F. Clinical cytogenetics in pediatric acute leukemia: an update. *Clin Lymphoma Myeloma Leuk*. 2012;12(4):230-237.
118. Radhi M, Meshinch S, Gamis A. Prognostic factors in pediatric acute myeloid leukemia. *Curr Hematol Malig Rep*. 2010;5(4):200-206.
119. Hudson M, Schwartz C, Constine LS. Treatment of pediatric Hodgkin lymphoma. In: Weinstein HJ, Hudson MM, Link MP (eds). *Pediatric Lymphomas*. Berlin: Springer; 2007: 35-66.
120. Magrath I. B-cell lymphoma/Burkitt lymphoma. In: Weinstein HJ, Hudson MM, Link MP (eds). *Pediatric Lymphomas*. Berlin: Springer; 2007: 141-174.
121. Sandlund JT. Precursor B and precursor T-cell lymphoblastic lymphoma. In: Weinstein HJ, Hudson MM, Link MP (eds). *Pediatric Lymphomas*. Berlin: Springer; 2007: 199-213.
122. Reiter A. Anaplastic large-cell lymphoma. In: Weinstein HJ, Hudson MM, Link MP (eds). *Pediatric Lymphomas*. Berlin: Springer; 2007: 175-197.
123. Nachman JB, Spoto R, Herzog P, et al. Randomized comparison of low-dose involved-field radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to chemotherapy. *J Clin Oncol*. 2002;20(18):3765-3771.
124. Rühl U, Albrecht M, Dieckmann K, et al. Response-adapted radiotherapy in the treatment of pediatric Hodgkin's disease: an interim report at 5 years of the German GPOH-HD 95 trial. *Int J Radiat Oncol Biol Phys*. 2001;51(5):1209-1218.
125. Roddie C, Peggs KS. Hodgkin's lymphoma. *Medicine*. 2009;37(4):208-211.
126. Ratkin G, Presant CA, Weinderman B, Reinhard EH. Correlation of anemia with infradiaphragmatic involvement in Hodgkin's disease and other malignant lymphomas. *Can Med Assoc J*. 1974;111(9):924-927.
127. King DR, Patrick LE, Ginn-Pease ME, McCoy KS, Klopfenstein K. Pulmonary function is compromised in children with mediastinal lymphoma. *J Pediatr Surg*. 1997;32(2):294-299, 299-300.
128. Raab CP, Gartner JC Jr. Diagnosis of childhood cancer. *Prim Care*. 2009;36(4):671-684.
129. Merck Manual Online. Hodgkin Lymphoma. Available at <https://www.merckmanuals.com/professional/hematology-and-oncology/lymphomas/hodgkin-lymphoma>. Last accessed August 5, 2024.
130. Carbone P, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res*. 1971;31(11):1860-1861.
131. Smith R, Chen Q, Hudson MM, et al. Prognostic factors for children with Hodgkin's disease treated with combined-modality therapy. *J Clin Oncol*. 2003;21(10):2026-2033.
132. Schellong G. Treatment of children and adolescents with Hodgkin's disease: the experience of the German-Austrian Paediatric Study Group. *Baillieres Clin Haematol*. 1996;9(3):619-634.
133. Nachman J. Clinical characteristics, biologic features and outcome for young adult patients with acute lymphoblastic leukaemia. *Br J Haematol*. 2005;130(2):166-173.
134. Dieckmann K, Potter R, Hofmann J, et al. Does bulky disease at diagnosis influence outcome in childhood Hodgkin's disease and require higher radiation doses? Results from the German-Austrian Pediatric Multicenter Trial DAL-HD-90. *Int J Radiat Oncol Biol Phys*. 2003;56(3):644-652.
135. Maity A, Goldwein JW, Lange B, D'Angio GJ. Mediastinal masses in children with Hodgkin's disease: an analysis of the Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania experience. *Cancer*. 1992;69(11):2755-2760.
136. Montalban C, Garcia JF, Abaira V, et al. Influence of biologic markers on the outcome of Hodgkin's lymphoma: a study by the Spanish Hodgkin's Lymphoma Study Group. *J Clin Oncol*. 2004;22(9):1664-1673.
137. Cleary S, Link MP, Donaldson SS. Hodgkin's disease in the very young. *Int J Radiat Oncol Biol Phys*. 1994;28(1):77-83.
138. Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk Hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. *J Clin Oncol*. 2014;32(32):3651-3658.
139. Burkhardt B, Zimmermann M, Oschlies I, et al. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. *Br J Haematol*. 2005;131(1):39-49.

140. Lones MA, Perkins SL, Sposto R, et al. Large-cell lymphoma arising in the mediastinum in children and adolescents is associated with an excellent outcome: a Children's Cancer Group report. *J Clin Oncol*. 2000;18(22):3845-3853.
141. Reiter A, Schrappe M, Tiemann M, et al. Successful treatment strategy for Ki-1 anaplastic large-cell lymphoma of childhood: a prospective analysis of 62 patients enrolled in three consecutive Berlin-Frankfurt-Munster group studies. *J Clin Oncol*. 1994;12(5):899-908.
142. Johnston JM. Pediatric Non-Hodgkin Lymphoma: Clinical Presentation. Available at <https://emedicine.medscape.com/article/987540-clinical>. Last accessed August 5, 2024.
143. Brugières L, Deley MC, Pacquement H, et al. CD30(+) anaplastic large-cell lymphoma in children: analysis of 82 patients enrolled in two consecutive studies of the French Society of Pediatric Oncology. *Blood*. 1998;92(10):3591-3598.
144. Seidemann K, Tiemann M, Schrappe M, et al. Short-pulse B-non-Hodgkin lymphoma-type chemotherapy is efficacious treatment for pediatric anaplastic large-cell lymphoma: a report of the Berlin-Frankfurt-Münster Group Trial NHL-BFM 90. *Blood*. 2001;97(12):3699-3706.
145. Delong L, Furqan M, Urbanski C, Krishnan K. Anaplastic Large-Cell Lymphoma. Available at <https://emedicine.medscape.com/article/208050-overview#a21>. Last accessed August 5, 2024.
146. Paes FM, Kalkanis DG, Sideras PA, Serafini AN. FDG PET/CT of extranodal involvement in non-Hodgkin lymphoma and Hodgkin disease. *Radiographics*. 2010;30(1):269-291.
147. Weiler-Sagie M, Bushelev O, Epelbaum R, et al. (18)F-FDG avidity in lymphoma readdressed: a study of 766 patients. *J Nucl Med*. 2010;51(1):25-30.
148. Bakhshi S, Radhakrishnan V, Sharma P, et al. Pediatric nonlymphoblastic non-Hodgkin lymphoma: baseline, interim, and posttreatment PET/CT versus contrast-enhanced CT for evaluation—a prospective study. *Radiology*. 2012;262(3):956-968.
149. Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. *Semin Oncol*. 1980;7(3):332-339.
150. National Cancer Institute. Childhood Non-Hodgkin Lymphoma Treatment: Stage Information for Childhood NHL. Available at https://www.cancer.gov/types/lymphoma/hp/child-nhl-treatment-pdq#section/_24. Last accessed August 5, 2024.
151. Shankland KR, Armitage JO, Hancock BW. Non-Hodgkin lymphoma. *Lancet*. 2012;380(9844):848-857.
152. Cairo MS, Sposto R, Gerrard M, et al. Advanced stage, increased lactate dehydrogenase, and primary site, but not adolescent age (≥ 15 years), are associated with an increased risk of treatment failure in children and adolescents with mature B-cell non-Hodgkin's lymphoma: results of the FAB LMB 96 study. *J Clin Oncol*. 2012;30(4):387-393.
153. Williams DM, Hobson R, Imeson J, et al. Anaplastic large-cell lymphoma in childhood: analysis of 72 patients treated on The United Kingdom Children's Cancer Study Group chemotherapy regimens. *Br J Haematol*. 2002;117(4):812-820.
154. Le Deley MC, Reiter A, Williams D, et al. Prognostic factors in childhood anaplastic large cell lymphoma: results of a large European intergroup study. *Blood*. 2008;111(3):1560-1566.
155. Mussolin L, Damm-Welk C, Pillon M, et al. Use of minimal disseminated disease and immunity to NPM-ALK antigen to stratify ALK-positive ALCL patients with different prognosis. *Leukemia*. 2013;27(2):416-422.
156. Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. German-Austrian-Swiss ALL-BFM Study Group. *Blood*. 2000;95(11):3310-3322.
157. Beck RS, Daughtridge R, Sloane PD. Physician-patient communication in the primary care office: a systematic review. *J Am Board Fam Pract*. 2002;15(1):25-38.
158. Office of Minority Health. Cultural and Linguistic Competency. Available at <https://minorityhealth.hhs.gov/cultural-and-linguistic-competency>. Last accessed August 5, 2024.
159. Paez K, Allen JK, Beach MC, Carson KA, Cooper LA. Physician cultural competence and patient ratings of the patient-physician relationship. *J Gen Intern Med*. 2009;24(4):495-498.
160. Powers BJ, Trinh JV, Bosworth HB. Can this patient read and understand written health information? *JAMA*. 2010;304(1):76-84.
161. U.S. Census Bureau. American Community Survey Data: Selected Social Characteristics in the United States. Available at <https://data.census.gov/table?q=DP02>. Last accessed August 5, 2024.
162. Karliner LS, Napoles-Springer AM, Schillinger D, Bibbins-Domingo K, Pérez-Stable EJ. Identification of limited English proficient patients in clinical care. *J Gen Intern Med*. 2008;23(10):1555-1560.
163. Levas MN, Cowden JD, Dowd MD. Effects of the limited English proficiency of parents on hospital length of stay and home health care referral for their home health care-eligible children with infections. *Arch Pediatr Adolesc Med*. 2011;165(9):831-836.
164. Office of Minority Health. Think Cultural Health. Available at <https://minorityhealth.hhs.gov/think-cultural-health>. Last accessed August 5, 2024.
165. Flores G. The impact of medical interpreter services on the quality of health care: a systematic review. *Med Care Res Rev*. 2005;62(3):255-299.
166. Flores G, Abreu M, Barone CP, Bachur R, Lin H. Errors of medical interpretation and their potential clinical consequences: a comparison of professional versus ad hoc versus no interpreters. *Ann Emerg Med*. 2012;60(5):545-553.

167. Karliner LS, Jacobs EA, Chen AH, Mutha S. Do professional interpreters improve clinical care for patients with limited English proficiency? A systematic review of the literature. *Health Serv Res.* 2007;42(2):727-754.
168. Ngo-Metzger Q, Massagli MP, Clarridge BR, et al. Linguistic and cultural barriers to care: perspectives of Chinese and Vietnamese immigrants. *J Gen Intern Med.* 2003;18(1):44-52.
169. Kuo DZ, O'Connor KG, Flores G, Minkovitz CS. Pediatricians' use of language services for families with limited English proficiency. *Pediatrics.* 2007;119(4):e920-e927.
170. DeCamp LR, Zuo DZ, Flores G, O'Connor K, Minkovitz CS. Changes in language services use by US pediatricians. *Am Acad Pediatr.* 2013;132(2):e396.
171. Norris W, Wenrich MD, Nielsen EL, Treece PD, Jackson JC, Curtis JR. Communication about end-of-life care between language-discordant patients and clinicians: insights from medical interpreters. *J Palliat Med.* 2005;8(5):1016-1024.
172. Kutner M, Greenberg E, Jin, Y, Paulsen C, White S. The Health Literacy of America's Adults: Results from the 2003 National Assessment of Adult Literacy. Available at <https://nces.ed.gov/pubs2006/2006483.pdf>. Last accessed August 5, 2024.
173. Center for Health Care Strategies. Health Literacy Fact Sheets. Available at <https://www.chcs.org/resource/health-literacy-fact-sheets/#>. Last accessed August 5, 2024.
174. Paasche-Orlow MK, Parker RM, Gazmararian JA, Nielsen-Bohlman LT, Rudd RR. The prevalence of limited health literacy. *J Gen Intern Med.* 2005;20(2):175-184.
175. Shah LC, West P, Bremmeyer K, Savoy-Moore RT. Health literacy instrument in family medicine: the "newest vital sign" ease of use and correlates. *J Am Board Fam Med.* 2010;23(2):195-203.
176. Jeppesen KM, Coyle JD, Miser WF. Screening questions to predict limited health literacy: a cross-sectional study of patients with diabetes mellitus. *Ann Fam Med.* 2009;7(1):24-31.
177. American Academy of Pediatrics. Family pediatrics: report of the Task Force on the Family. *Pediatrics.* 2003;111(6):1541-1571.
178. Kang T, Hoehn KS, Licht DJ, et al. Pediatric palliative, end-of-life, and bereavement care. *Pediatr Clin North Am.* 2005;52(4):1029-1046.
179. De Trill M, Kovalcik R. The child with cancer: influence of culture on truth-telling and patient care. *Ann NY Acad Sci.* 1997;809(1):197-210.
180. Surbone A. Family, autonomy, and cultural differences. In: Perry MC (ed). *ASCO 2006 Educational Book*. Alexandria, VA: American Society of Clinical Oncology; 2006: 156-159.
181. Epstein R, Street RL Jr. *Patient-Centered Communication in Cancer Care: Promoting Healing and Reducing Suffering*. Bethesda, MD: National Cancer Institute; 2007.
182. Eden LM, Callister LC. Parent involvement in end-of-life care and decision making in the newborn intensive care unit: an integrative review. *J Perinat Educ.* 2010;19(1):29-39.
183. Whitney S, Ethier AM, Fruge E, Berg S, McCullough LB, Hockenberry M. Decision making in pediatric oncology: who should take the lead? The decisional priority in pediatric oncology model. *J Clin Oncol.* 2006;24(1):160-165.
184. Mack JW, Wolfe J, Grier HE, Cleary PD, Weeks JC. Communication about prognosis between parents and physicians of children with cancer: parent preferences and the impact of prognostic information. *J Clin Oncol.* 2006;24(33):5265-5270.
185. Mack JW, Grier HE. The day one talk. *J Clin Oncol.* 2004;22(3):563-566.
186. Buckman R, Kason Y. *How to Break Bad News: A Guide for Health Care Professionals*. Baltimore, MY: The Johns Hopkins University Press; 1992.
187. Roter D. The enduring and evolving nature of the patient-physician relationship. *Patient Educ Couns.* 2000;39(1):5-15.
188. Stillion J, Papadatou D. Suffer the children: an examination of psychosocial issues in children and adolescents with terminal illness. *Am Behav Sci.* 2002;46(2):299-315.
189. Hilden JM, Watterson J, Chrastek J. Tell the children. *J Clin Oncol.* 2003;21(9 Suppl):37s-39s.
190. Beale EA, Baile WF, Aaron J. Silence is not golden: communicating with children dying from cancer. *J Clin Oncol.* 2005;23(15):3629-3631.
191. Young B, Ward J, Salmon P, Gravenhorst K, Hill J, Eden T. Parents' experiences of their children's presence in discussions with physicians about leukemia. *Pediatrics.* 2011;127(5):e1230-e1238.
192. Ranmal R, Prictor M, Scott JT. Interventions for improving communication with children and adolescents about their cancer. *Cochrane Database Syst Rev.* 2008;(4):CD002969.
193. Hale G, Mueller B, Rogers Z, Shearer P, Werner E. Standards for pediatric cancer centers. *Am Acad Pediatr.* 2014;134(2):410-414.
194. Mohan SR, Advani AS. Treatment of acute lymphoblastic leukemia in adolescents and young adults. *J Adolesc Young Adult Oncol.* 2011;1(1):19-24.
195. Shochat SJ, Fremgen AM, Murphy SB, et al. Childhood cancer: patterns of protocol participation in a national survey. *CA Cancer J Clin.* 2001;51(2):119-130.
196. Peppercorn J, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet.* 2004;363(9405):263-270.

197. Miller VA, Drotar D, Burant C, Kodish E. Clinician-parent communication during informed consent for pediatric leukemia trials. *J Pediatr Psychol*. 2005;30(3):219-229.
198. Shaw PH, Hayes-Lattin B, Johnson R, Bleyer A. Improving enrollment in clinical trials for adolescents with cancer. *Pediatrics*. 2014;(Suppl 3):S109-S113.
199. Forcina V, Vakeesan B, Paulo C, et al. Perceptions and attitudes toward clinical trials in adolescent and young adults with cancer: a systematic review. *Adolesc Health Med Ther*. 2018;9:87-94.
200. Barakat LP, Schwartz LA, Reilly A, Deatrick JA, Bailis F. A qualitative study of phase III cancer clinical trial enrollment decision-making: perspectives from adolescents, young adults, caregivers, and providers. *J Adolesc Young Adult Oncol*. 2014;3(1):3-11.
201. Shaw PH, Boyiadzis M, Tawbi H, et al. Improved clinical trial enrollment in adolescent and young adult (AYA) oncology patients after the establishment of an AYA oncology program uniting pediatric and medical oncology divisions. *Cancer*. 2012;118(14):3614-3617.
202. Collins CL, Malvar J, Hamilton AS, Deapen DM, Freyer DR. Case-linked analysis of clinical trial enrollment among adolescents and young adults at a National Cancer Institute-designated comprehensive cancer center. *Cancer*. 2015;121(24):4398-4406.
203. Committee on Bioethics. Informed consent, parental permission, and assent in pediatric practice. *Pediatrics*. 1995;95(2):314-317.
204. Joffe S, Fernandez CV, Pentz RD, et al. Involving children with cancer in decision-making about research participation. *J Pediatr*. 2006;149(6):862-868.
205. Ondrusek N, Abramovitch R, Pencharz P, Koren G. Empirical examination of the ability of children to consent to clinical research. *J Med Ethics*. 1998;24(3):158-165.
206. Wendler DS. Assent in paediatric research: theoretical and practical considerations. *J Med Ethics*. 2006;32(4):229-234.
207. Blake DR, Lemay CA, Kearney MH, Mazor KM. Adolescents' understanding of research concepts: a focus group study. *Arch Pediatr Adolesc Med*. 2011;165(6):533-539.
208. U.S. Congress. Title 45 Subpart A: Basic HHS Policy for Protection of Human Research Subjects. Available at https://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title45/45cfr46_main_02.tpl. Last accessed August 5, 2024.
209. Olechnowicz JQ, Eder M, Simon C, Zyzanski S, Kodish E. Assent observed: children's involvement in leukemia treatment and research discussions. *Pediatrics*. 2002;109(5):806-814.
210. Eder ML, Yamokoski AD, Wittmann PW, Kodish ED. Improving informed consent: suggestions from parents of children with leukemia. *Pediatrics*. 2007;119(4):e849-e859.
211. Miller VA, Baker JN, Leek AC, Drotar D, Kodish E. Patient involvement in informed consent for pediatric phase I cancer research. *J Pediatr Hematol Oncol*. 2014;36(8):635-640.
212. Simon CM, Siminoff LA, Kodish ED, Burant C. Comparison of the informed consent process for randomized clinical trials in pediatric and adult oncology. *J Clin Oncol*. 2004;22(13):2708-2717.
213. Baker JN, Leek AC, Salas HS, et al. Suggestions from adolescents, young adults, and parents for improving informed consent in phase I pediatric oncology trials. *Cancer*. 2013;119(23):4154-4161.
214. O'Lonergan TA, Forster-Harwood JE. Novel approach to parental permission and child assent for research: improving comprehension. *Pediatrics*. 2011;127(5):917-924.
215. Hertzberg H, Huk WJ, Ueberall MA, et al. CNS late effects after ALL therapy in childhood. Part I. Neuroradiological findings in long-term survivors of childhood ALL: an evaluation of the interferences between morphology and neuropsychological performance. The German Late Effects Working Group. *Med Pediatr Oncol*. 1997;28(6):387-400.
216. Friedman D, Meadows AT. Late effects following lymphoma treatment. In: Weinstein HJ, Hudson MM, Link MP (eds). *Pediatric Lymphomas*. Berlin: Springer; 2007: 259-280.
217. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2005;23(12):2629-2636.
218. Hancock SL, Donaldson SS, Hoppe RT. Cardiac disease following treatment of Hodgkin's disease in children and adolescents. *J Clin Oncol*. 1993;11(7):1208-1215.
219. Dong J, Chen H. Cardiotoxicity of anticancer therapeutics. *Front Cardiovasc Med*. 2018;5:9.
220. National Cancer Institute. Childhood Acute Lymphoblastic Leukemia Treatment (PDQ). Available at <https://www.cancer.gov/types/leukemia/hp/child-all-treatment-pdq>. Last accessed August 5, 2024.
221. Patte C, Auperin A, Michon J, et al. The Société Française d'Oncologie Pédiatrique LMB89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. *Blood*. 2001;97(11):3370-3379.
222. Brown P, Hunger SP, Smith FO, Carroll WL, Reaman GH. Novel targeted drug therapies for the treatment of childhood acute leukemia. *Expert Rev Hematol*. 2009;2(9):145.
223. Cancer Network. FDA Approves Imatinib (Gleevec) for Pediatric ALL. Available at <https://www.cancernetwork.com/view/fda-approves-imatinib-gleevec-pediatric-all>. Last accessed August 5, 2024.

224. Mörücke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood*. 2008;111(9):4477-4489.
225. Jeha S, Pui CH. Risk-adapted treatment of pediatric acute lymphoblastic leukemia. *Hematol Oncol Clin N Am*. 2009;23(5):973-990.
226. Moghrabi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. *Blood*. 2007;109(3):896-904.
227. Prucker C, Attarbaschi A, Peters C, et al. Induction death and treatment-related mortality in first remission of children with acute lymphoblastic leukemia: a population-based analysis of the Austrian Berlin-Frankfurt-Münster study group. *Leukemia*. 2009;23(7):1264-1269.
228. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Pediatric Acute Lymphoblastic Leukemia Version 6.2024. Available at https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf. Last accessed August 5, 2024.
229. Teuffel O, Kuster SP, Hunger SP, et al. Dexamethasone versus prednisone for induction therapy in childhood acute lymphoblastic leukemia: a systematic review and meta-analysis. *Leukemia*. 2011;25(8):1232-1238.
230. Escherich G, Zimmermann M, Janka-Schaub G, CoALL Study Group. Doxorubicin or daunorubicin given upfront in a therapeutic window are equally effective in children with newly diagnosed acute lymphoblastic leukemia: a randomized comparison in trial CoALL 07-03. *Pediatr Blood Cancer*. 2013;60(2):254-257.
231. U.S. Food and Drug Administration. FDA News Release. FDA Approves Component of Treatment Regimen for Most Common Childhood Cancer. Available at <https://www.fda.gov/news-events/press-announcements/fda-approves-component-treatment-regimen-most-common-childhood-cancer>. Last accessed August 5, 2024.
232. U.S. Food and Drug Administration. FDA Approves a New Dosing Regimen for Asparaginase Erwinia Chrysanthemi (Recombinant). Available at <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-new-dosing-regimen-asparaginase-erwinia-chrysanthemi-recombinant>. Last accessed August 5, 2024.
233. Jeha S, Coustan-Smith E, Pei D, et al. Impact of tyrosine kinase inhibitors on minimal residual disease and outcome in childhood Philadelphia chromosome-positive acute lymphoblastic leukemia. *Cancer*. 2014;120(10):1514-1519.
234. Mörücke A, Zimmermann M, Reiter A, et al. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1982 to 2000. *Leukemia*. 2010;24(2):265-284.
235. Matloub Y, Bostrom BC, Hunger SP, et al. Escalating intravenous methotrexate improves event-free survival in children with standard-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood*. 2011;118(2):243-251.
236. Larsen EC, Salzer WL, Devidas JB, et al. Comparison of high-dose methotrexate (HD-MTX) with Capizzi methotrexate plus asparaginase (C-MTX/ASNase) in children and young adults with high-risk acute lymphoblastic leukemia (HR-ALL): a report from the Children's Oncology Group Study AALL0232. *J Clin Oncol*. 2011;29(Suppl):abstract 3.
237. Asselin BL, Devidas M, Wang C, et al. Effectiveness of high-dose methotrexate in T-cell lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the Children's Oncology Group (POG 9404). *Blood*. 2011;118(4):874-883.
238. Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a Children's Oncology Group study. *J Clin Oncol*. 2009;27(3):5175-5181.
239. Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group Study AALL0031. *Leukemia*. 2014;28(7):1467-1471.
240. Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. *Lancet Oncol*. 2012;13(9):936-945.
241. Childhood ALL Collaborative Group. Duration and intensity of maintenance chemotherapy in acute lymphoblastic leukaemia: overview of 42 trials involving 12,000 randomized children. *Lancet*. 1996;347(9018):1783-1788.
242. Pui CH, Pei D, Campana D, et al. A revised definition for cure of childhood acute lymphoblastic leukemia. *Leukemia*. 2014;28(12):2336-2343.
243. Evans A, Gilbert ES, Zandstra R. The increasing incidence of central nervous system leukemia in children (Children's Cancer Study Group A). *Cancer*. 1970;26(2):404-409.
244. Gibbs IC, Tuamokumo N, Yock TI. Role of radiation therapy in pediatric cancer. *Hematol Oncol Clin North Am*. 2006;20(2):455-470.
245. Henze G, von Stackelberg V. Relapsed acute lymphoblastic leukemia. In: Pui CH (ed). *Childhood Leukemias*. 3rd ed. New York, NY: Cambridge University Press; 2012.
246. Ritchey A, Pollock BH, Lauer SJ, Andejski Y, Buchanan GR. Improved survival of children with isolated CNS relapse of acute lymphoblastic leukemia: a Pediatric Oncology Group study. *J Clin Oncol*. 1999;17(12):3745-3752.
247. U.S. Food and Drug Administration. FDA News Release: FDA Approval Brings First Gene Therapy to the United States. Available at <https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states>. Last accessed August 5, 2024.
248. Liu Y, Chen X, Han W, Zhang Y. Tisagenlecleucel, an approved anti-CD19 chimeric antigen receptor T-cell therapy for the treatment of leukemia. *Drugs Today (Barc)*. 2017;53(11):597-608.

249. Trigg ME, Steinherz PG, Chappell R, et al. Early testicular biopsy in males with acute lymphoblastic leukemia: lack of impact on subsequent event-free survival. *J Pediatr Hematol Oncol.* 2000;22(1):27-33.
250. Hahn T, Wall D, Camitta B, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in children: an evidence-based review. *Biol Blood Marrow Transplant.* 2005;11(11):823-861.
251. Oliansky DM, Camitta B, Gaynon P, et al. Role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of pediatric acute lymphoblastic leukemia: update of the 2005 evidence-based review. *Biol Blood Marrow Transplant.* 2012;18(4):505-522.
252. National Cancer Institute. Pediatric Hematopoietic Cell Transplant and Cellular Therapy for Cancer. Available at <https://www.cancer.gov/types/childhood-cancers/hp-stem-cell-transplant>. Last accessed August 5, 2024.
253. Perumbeti A, Sacher RA. Hematopoietic Stem Cell Transplantation. Available at <https://emedicine.medscape.com/article/208954-overview#a13>. Last accessed August 5, 2024.
254. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Biol Bone Marrow Transplant.* 2012;(18):348-371.
255. Dietz AC, Duncan CN, Alter BP, et al. The second pediatric blood and marrow transplant consortium international consensus conference on late effects after pediatric hematopoietic cell transplantation: defining the unique late effects of children undergoing hematopoietic cell transplantation for immune deficiencies, inherited marrow failure disorders, and hemoglobinopathies. *Biol Blood Marrow Transplant.* 2017;(23):24-29.
256. Arceci RJ. Progress and controversies in the treatment of pediatric acute myelogenous leukemia. *Curr Opin Hematol.* 2002;9(4):353-360.
257. National Cancer Institute. Intensive Pre-Stem Cell Transplant Regimen May be Best for Younger Patients with AML, MDS. Available at <https://www.cancer.gov/news-events/cancer-currents-blog/2017/aml-stem-cell-transplant>. Last accessed August 5, 2024.
258. Creutzig U. Relapsed acute myeloid leukemia. In: Pui CH (ed). *Childhood Leukemias*. 3rd ed. New York, NY: Cambridge University Press; 2012.
259. U.S. Food and Drug Administration. FDA Approves Gemtuzumab Ozogamicin for CD33-Positive AML in Pediatric Patients. Available at <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-gemtuzumab-ozogamicin-cd33-positive-aml-pediatric-patients>. Last accessed August 5, 2024.
260. Lexicomp Online. Available at <https://online.lexi.com>. Last accessed August 5, 2024.
261. Cooper TM, Alonzo TA, Gerbing RB, et al. AAML0523: A report from the Children's Oncology Group on the efficacy of clofarabine in combination with cytarabine in pediatric patients with recurrent acute myeloid leukemia. *Cancer.* 2014;120(16):2482-2489.
262. Kassim AA, Savani BN. Hematopoietic stem cell transplantation for acute myeloid leukemia: a review. *Hematol/Oncol Stem Cell Ther.* 2017;10(4):245-251.
263. Bleakley M, Lau L, Shaw PJ, Kaufman A. Bone marrow transplantation for paediatric AML in first remission: a systematic review and meta-analysis. *Bone Marrow Transplant.* 2002;29(10):843-852.
264. Oliansky DM, Rizzo D, Aplan PD, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myeloid leukemia in children: an evidence-based review. *Biol Blood Marrow Transplant.* 2007;13(1):1-25.
265. Wang J, Ouyang J, Zhou R, Chen B, Yang Y. Autologous hematopoietic stem cell transplantation for acute myeloid leukemia in first complete remission: a meta-analysis of randomized trials. *Acta Haematol.* 2010;124(2):61-71.
266. Horan JT, Alonzo TA, Lyman GH, et al. Impact of disease risk on efficacy of matched related bone marrow transplantation for pediatric acute myeloid leukemia: the Children's Oncology Group. *J Clin Oncol.* 2008;26(35):5797-5801.
267. Creutzig U, Reinhardt D. Current controversies: which patients with acute myeloid leukaemia should receive a bone marrow transplantation? A European view. *Br J Haematol.* 2002;118(2):365-377.
268. Niewerth D, Creutzig U, Bierings MB, et al. A review on allogeneic stem cell transplantation for newly diagnosed pediatric acute myeloid leukemia. *Blood.* 2010;116(13):2205-2214.
269. Rubnitz JE, Inaba H, Leung WH, et al. Definition of cure in childhood acute myeloid leukemia. *Cancer.* 2014;120(16):2490-2496.
270. Trippett T, Chen A. Treatment of relapsed/refractory Hodgkin lymphoma. In: Weinstein HJ, Hudson MM, Link MP (eds). *Pediatric Lymphomas*. Berlin: Springer; 2007: 67-84.
271. Eichenauer DA, Bredenfeld H, Haverkamp H, et al. Hodgkin's lymphoma in adolescents treated with adult protocols: a report from the German Hodgkin study group. *J Clin Oncol.* 2009;27(36):6079-6085.
272. Terezakis SA, Metzger ML, Hodgson DC, et al. ACR Appropriateness Criteria: pediatric Hodgkin lymphoma. *Pediatr Blood Cancer.* 2014;61(7):1305-1312.
273. Hudson MM. Late complications after leukemia therapy. In: Pui CH (ed). *Childhood Leukemias*. 3rd ed. New York, NY: Cambridge University Press; 2012.
274. Kelly KM, Sposto R, Hutchinson R, et al. BEACOPP chemotherapy is a highly effective regimen in children and adolescents with high-risk Hodgkin lymphoma: a report from the Children's Oncology Group. *Blood.* 2011;117(9):2596-2603.
275. Hodgson DC, Dieckmann K, Terezakis S, et al. Implementation of contemporary radiation therapy planning concepts for pediatric Hodgkin lymphoma: guidelines from the International Lymphoma Radiation Oncology Group. *Pract Radiat Oncol.* 2015;5(2):85-92.

276. Mauz-Korholz C, Hasenclever D, Dorffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. *J Clin Oncol*. 2010;28(23):3680-3686.
277. Hutchinson RJ, Fryer CJ, Davis PC, et al. MOPP or radiation in addition to ABVD in the treatment of pathologically staged advanced Hodgkin's disease in children: results of the Children's Cancer Group Phase III Trial. *J Clin Oncol*. 1998;16(3):897-906.
278. Metzger ML, Weinstein HJ, Hudson MM, et al. Association between radiotherapy vs no radiotherapy based on early response to VAMP chemotherapy and survival among children with favorable-risk Hodgkin lymphoma. *JAMA*. 2012;307(24):2609-2616.
279. Appel BE, Chen L, Buxton AB, et al. Minimal treatment of low-risk, pediatric lymphocyte-predominant Hodgkin lymphoma: a report from the Children's Oncology Group. *J Clin Oncol*. 2016;34(20):2372-2379.
280. Ozuah NW, Marcus KJ, LaCasce AS, Billett AL. Excellent outcomes following response-based omission of radiotherapy in children and adolescents with intermediate or high-risk Hodgkin lymphoma. *J Pediatr Hematol Oncol*. 2018;40(6):e338-e342.
281. Kobrinsky NL, Sposto R, Shah NR, et al. Outcomes of treatment of children and adolescents with recurrent non-Hodgkin's lymphoma and Hodgkin's disease with dexamethasone, etoposide, cisplatin, cytarabine, and L-asparaginase, maintenance chemotherapy, and transplantation: Children's Cancer Group Study CCG-5912. *J Clin Oncol*. 2001;19(9):2390-2396.
282. Kelly KM. Hodgkin lymphoma in children and adolescents: improving the therapeutic index. *Blood*. 2015;126:2452-2458.
283. Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk Hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. *J Clin Oncol*. 2014;32(32):3651-3658.
284. Dharmarajan KV, Friedman DL, Schwartz CL, et al. Patterns of relapse from a phase 3 study of response-based therapy for intermediate-risk Hodgkin lymphoma (AHOD0031): a report from the Children's Oncology Group. *Int J Radiat Oncol Biol Phys*. 2015;92(1):60-66.
285. Tebbi CK, Mendenhall NP, London WB, et al. Response-dependent and reduced treatment in lower risk Hodgkin lymphoma in children and adolescents, results of P9426: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2012;59(7): 1259-1265.
286. Keller FG, Nachman J, Constine L, et al. A phase III study for the treatment of children and adolescents with newly diagnosed low risk Hodgkin Lymphoma (HL). *Blood*. 2010;116:767.
287. Schwartz CL, Constine LS, Villaluna D, et al. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: the results of P9425. *Blood*. 2009;114(10):2051-2059.
288. Cole PD, McCarten KM, Pei Q, et al. Brentuximab vedotin with gemcitabine for paediatric and young adults patients with relapsed or refractory Hodgkin's lymphoma (AHOD1221): a Children's Oncology Group, multicentre single-arm, phase 1-2 trial. *Lancet Oncol*. 2018;19(9):1229-1238.
289. Davis KL, Fox E, Merchant MS, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours of lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1-2 trial. *Lancet Oncol*. 2020;21(4):541-550.
290. Georger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1-2 trial. *Lancet Oncol*. 2020;21(1):121-133.
291. Rathore N, Eissa HM, Margolin JF, et al. Pediatric Hodgkin lymphoma: are we over-scanning our patients? *Pediatr Hematol Oncol*. 2012;29(5):415-423.
292. Müller J, Csóka M, Jakab Z, Ponyi A, Erlaky H, Kovács G. Treatment of pediatric non-Hodgkin lymphoma in Hungary: 15 years' experience with NHL-BFM 90 and 95 protocols. *Pediatr Blood Cancer*. 2008;50(3):633-635.
293. Burkhardt B, Oschlies I, Klapper W, et al. Non-Hodgkin's lymphoma in adolescents: experiences in 378 adolescent NHL patients treated according to pediatric NHL-BFM protocols. *Leukemia*. 2011;25(1):153-160.
294. Attarbaschi A, Dworzak M, Steiner M, et al. Outcome of children with primary resistant or relapsed non-Hodgkin lymphoma and mature B-cell leukemia after intensive first-line treatment: a population-based analysis of the Austrian Cooperative Study Group. *Pediatr Blood Cancer*. 2005;44(1):70-76.
295. Burkhardt B, Reiter A, Landmann E, et al. Poor outcome for children and adolescents with progressive disease or relapse of lymphoblastic lymphoma: a report from the Berlin-Frankfurt-Muenster Group. *J Clin Oncol*. 2009;27(20):3363-3369.
296. Knörr F, Brugières L, Pillon M, et al. Stem cell transplantation and vinblastine monotherapy for relapsed pediatric anaplastic large cell lymphoma: results of the International, Prospective ALCL-Relapse trial. *J Clin Oncol*. 2020;38(34):3999-4009.
297. Woessmann W, Seidemann K, Mann G, et al. The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the BFM Group Study NHL-BFM95. *Blood*. 2005;105(3):948-958.
298. Gerrard M, Cairo MS, Weston C, et al. Excellent survival following two courses of COPAD chemotherapy in children and adolescents with resected localized B-cell non-Hodgkin's lymphoma: results of the FAB/LMB 96 international study. *Br J Haematol*. 2008;141(6):840-847.
299. Meinhardt A, Burkhardt B, Zimmermann M, et al. Phase II window study on rituximab in newly diagnosed pediatric mature B-cell non-Hodgkin's lymphoma and Burkitt leukemia. *J Clin Oncol*. 2010;28(19):3115-3121.

300. Barth MJ, Goldman S, Smith L, et al. Rituximab pharmacokinetics in children and adolescents with de novo intermediate and advanced mature B-cell lymphoma/leukaemia: a Children's Oncology Group report. *Br J Haematol.* 2013;162(5):678-683.
301. Goldman S, Smith L, Anderson JR, et al. Rituximab and FAB/LMB 96 chemotherapy in children with stage III/IV B-cell non-Hodgkin lymphoma: a Children's Oncology Group report. *Leukemia.* 2013;27(5):1174-1177.
302. Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. *Blood.* 2007;109(7):2736-2743.
303. Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. *Blood.* 2007;109(7):2773-2780.
304. Grenzebach J, Schrappe M, Ludwig WD, et al. Favorable outcome for children and adolescents with T-cell lymphoblastic lymphoma with an intensive ALL-type therapy without local radiotherapy. *Ann Hematol.* 2001;80(Suppl 3):B73-B76.
305. Reiter A, Schrappe M, Ludwig WD, et al. Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: a BFM group report. *Blood.* 2000;95(2):416-421.
306. Anderson JR, Jenkin RD, Wilson JF, et al. Long-term follow-up of patients treated with COMP or LSA2L2 therapy for childhood non-Hodgkin's lymphoma: a report of CCG-551 from the Children's Cancer Group. *J Clin Oncol.* 1993;11(6):1024-1032.
307. Burkhardt B, Woessmann W, Zimmermann M, et al. Impact of cranial radiotherapy on central nervous system prophylaxis in children and adolescents with central nervous system-negative stage III or IV lymphoblastic lymphoma. *J Clin Oncol.* 2006;24(3):491-499.
308. Termuhlen AM, Smith LM, Perkins SL, et al. Disseminated lymphoblastic lymphoma in children and adolescents: results of the COG A5971 trial: a report from the Children's Oncology Group. *Br J Haematol.* 2013;162(6):792-801.
309. Termuhlen AM, Smith LM, Perkins SL, et al. Outcome of newly diagnosed children and adolescents with localized lymphoblastic lymphoma treated on Children's Oncology Group trial A5971: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2012;59(7):1229-1233.
310. Williams D, Mori T, Reiter A, et al. Central nervous system involvement in anaplastic large cell lymphoma in childhood: results from a multicentre European and Japanese study. *Pediatr Blood Cancer.* 2013;60(10):E118-E121.
311. Link MP, Shuster JJ, Donaldson SS, et al. Treatment of children and young adults with early-stage non-Hodgkin's lymphoma. *N Engl J Med.* 1997;337(18):1259-1266.
312. Sandlund JT, Pui CH, Zhou Y, Behm FG, et al. Effective treatment of advanced-stage childhood lymphoblastic lymphoma without prophylactic cranial irradiation: results of St Jude NHL13 study. *Leukemia.* 2009;23(6):1127-1130.
313. Bluhm EC, Ronckers C, Hayashi RJ, et al. Cause-specific mortality and second cancer incidence after non-Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. *Blood.* 2008;111(8):4014-4021.
314. Sandlund J, Bowman L, Heslop HE, et al. Intensive chemotherapy with hematopoietic stem-cell support for children with recurrent or refractory NHL. *Cytotherapy.* 2002;4(3):253-258.
315. Attias D, Weitzman S. The efficacy of rituximab in high-grade pediatric B-cell lymphoma/leukemia: a review of available evidence. *Curr Opin Pediatr.* 2008;20(1):17-22.
316. Griffin TC, Weitzman S, Weinstein H, et al. A study of rituximab and ifosfamide, carboplatin, and etoposide chemotherapy in children with recurrent/refractory B-cell (CD20+) non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2009;52(2):177-181.
317. Woessmann W, Zimmermann M, Lenhard M, et al. Relapsed or refractory anaplastic large-cell lymphoma in children and adolescents after Berlin-Frankfurt-Muenster (BFM)-type first-line therapy: a BFM-group study. *J Clin Oncol.* 2011;29(22):3065-3071.
318. Eissa HM, Allen CE, Kamdar K, et al. Pediatric Burkitt's lymphoma and diffuse B-cell lymphoma: are surveillance scans required? *Pediatr Hematol Oncol.* 2014;31(3):253-257.
319. Heath JA. Monitoring after childhood cancer: an update for GPs. *Aust Fam Phys.* 2005;34(9):761-767.
320. Golden E, Beach B, Hastings C. The pediatrician and medical care of the child with cancer. *Pediatr Clin North Am.* 2002;49:1319-1338.
321. Hakim H, Flynn PM. Infectious disease complications in leukemia. In: Pui CH (ed). *Childhood Leukemias.* 3rd ed. New York, NY: Cambridge University Press; 2012: 805-828.
322. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;52(4):e56-e93.
323. Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. *J Clin Oncol.* 2017;35(18):2082-2094.
324. Shankar SM, Nania JJ. Management of *Pneumocystis jirovecii* pneumonia in children receiving chemotherapy. *Paediatr Drugs.* 2007;9(5):301-309.
325. Centers for Disease Control and Prevention. *Pneumocystis Pneumonia Basics.* Available at <https://www.cdc.gov/pneumocystis-pneumonia/about>. Last accessed August 5, 2024.
326. Pizzo P, Rubin M, Freifeld A, Walsh TJ. The child with cancer and infection. II. Nonbacterial infection. *J Pediatr.* 1991;119(6):845-849.

327. Lindemulder S, Albano E. Successful intermittent prophylaxis with trimethoprim/sulfamethoxazole 2 days per week for *Pneumocystis carinii* (jiroveci) pneumonia in pediatric oncology patients. *Pediatrics*. 2007;120(1):e47-e51.
328. Gaftner-Gvili A, Fraser A, Paul M, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database Syst Rev*. 2012;1:CD004386.
329. Mulne AF, Koepke JC. Adverse effects of cancer therapy in children. *Pediatr Rev*. 1985;6(9):259-268.
330. Pizzo P. Management of fever in patients with cancer and treatment-induced neutropenia. *N Engl J Med*. 1993;328(18):1323-1332.
331. Laoprasopwattana K, Khwanna T, Suwankeeree P, Suijanunt T, Tunyapanit W, Chelae S. Ciprofloxacin reduces occurrence of fever in children with acute leukemia who develop neutropenia during chemotherapy. *Pediatr Infect Dis J*. 2013;32(3):e94-e98.
332. Navid F, Santana VM. Hematologic supportive care. In: Pui CH (ed). *Childhood Leukemias*. 3rd ed. New York, NY: Cambridge University Press; 2012.
333. La Quaglia M, Lucas A, Thaler HT, Friedlander-Klar H, Exelby PR, Groeger JS. A prospective analysis of vascular access device-related infections in children. *J Pediatr Surg*. 1992;27(7):840-842.
334. Flynn P. Vascular access device infections. In: Patrick CC (ed). *Clinical Management of Infections in Immunocompromised Infants and Children*. Philadelphia, PA: Lippincott, Williams & Wilkins; 2001: 212-223.
335. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116:1736-1754.
336. Wittman B, Horan J, Lyman GH. Prophylactic colony-stimulating factors in children receiving myelosuppressive chemotherapy: a meta-analysis of randomized controlled trials. *Cancer Treat Rev*. 2006;32(4):289-303.
337. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212.
338. Sung L, Nathan PC, Lange B, Beyene J, Buchanan GR. Prophylactic granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor decrease febrile neutropenia after chemotherapy in children with cancer: a meta-analysis of randomized controlled trials. *J Clin Oncol*. 2004;22(16):3350-3356.
339. Heath J, Steinherz PG, Altman A, et al. Human granulocyte colony-stimulating factor in children with high-risk acute lymphoblastic leukemia: a Children's Cancer Group Study. *J Clin Oncol*. 2003;21(8):1612-1617.
340. Relling M, Boyett JM, Blanco JG, et al. Granulocyte colony-stimulating factor and the risk of secondary myeloid malignancy after etoposide treatment. *Blood*. 2003;101(10):3862-3867.
341. André N, Kababri ME, Bertrand P, et al. Safety and efficacy of pegfilgrastim in children with cancer receiving myelosuppressive chemotherapy. *Anticancer Drugs*. 2007;18(3):277-281.
342. Razzouk BI, Hord JD, Hockenberry M, et al. Double-blind, placebo-controlled study of quality of life, hematologic end points, and safety of weekly epoetin alfa in children with cancer receiving myelosuppressive chemotherapy. *J Clin Oncol*. 2006;24(22):3583-3589.
343. Howard SC, Ribeiro RC, Pui CH. Acute complications. In: Pui CH (ed). *Childhood Leukemias*. 3rd ed. New York, NY: Cambridge University Press; 2012.
344. Journeycake JM, Buchanan GR. Catheter-related deep venous thrombosis and other catheter complications in children with cancer. *J Clin Oncol*. 2006;24(28):4575-4580.
345. Choi M, Massicotte M, Marzinotto, Chan AK, Holmes JL, Andrew M. The use of alteplase to restore patency of central venous lines in pediatric patients: a cohort study. *J Pediatr*. 2001;139(1):152-156.
346. Revel-Vilk S, Yacobovich J, Tamary H, et al. Risk factors for central venous catheter thrombotic complications in children and adolescents with cancer. *Cancer*. 2010;116(17):4197-4205.
347. Himelstein BP, Hilden JM, Boldt AM, Weissman D. Pediatric palliative care. *N Engl J Med*. 2004;350(17):1752-1762.
348. Harris M. Palliative care in children with cancer: which child and when? *J Natl Cancer Inst Monogr*. 2004;(32):144-149.
349. Field MJ, Behrman RE (eds). *When Children Die: Improving Palliative and End-of-Life Care for Children and Their Families*. Washington, DC: National Academies Press; 2003.
350. American Academy of Pediatrics. Palliative care for children. *Pediatrics*. 2000;106(2):351-357.
351. Wiener L, McConnell DG, Latella L, Ludi E. Cultural and religious considerations in pediatric palliative care. *Palliat Support Care*. 2013;11(1):47-67.
352. Jones BL, Contro N, Koch KD. The duty of the physician to care for the family in pediatric palliative care: context, communication, and caring. *Pediatrics*. 2014;133:S8-S15.
353. Committee on Hospital Care and Institute for Patient- and Family-Centered Care. Patient- and family-centered care and the pediatrician's role. *Pediatrics*. 2012;129(2):394-404.
354. Johnson LM, DeLario M, Baker JN, Kane JR. Palliative care in pediatrics. In: Berger AM, Shuster JL Jr, Von Roenn JH (eds). *Principles & Practice of Palliative Care & Supportive Oncology*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.

355. Meert K, Briller S, Myers S, Thurston C, Kabel A. Examining the needs of bereaved parents in the PICU: a qualitative study. *Death Stud.* 2009;33(8):712-740.
356. Longden JV. Parental perceptions of end-of-life care on paediatric intensive care units: a literature review. *Nurs Crit Care.* 2011;16(3):131-139.
357. Meyer E, Ritholz M, Burns J, Truog R. Improving the quality of end-of-life care in the PICU: parent priorities and recommendations. *Pediatrics.* 2006;117(3):649-657.
358. Stevenson M, Achille M, Lugasi T. Pediatric palliative care in Canada and the United States: a qualitative metasummary of the needs of patients and families. *J Palliat Med.* 2013;16(5):566-577.
359. Goldman A, Hewitt M, Collins GS, Childs M, Hain R, for the United Kingdom Children's Cancer Study Group/Paediatric Oncology Nurses' Forum Palliative Care Working G. Symptoms in children/young people with progressive malignant disease: United Kingdom Children's Cancer Study Group/Paediatric Oncology Nurses Forum Survey. *Pediatrics.* 2006;117(6):e1179-e1186.
360. Hockenberry M. Symptom management research in children with cancer. *J Pediatr Oncol Nurs.* 2004;21(3):132-136.
361. Kestler SA, LoBiondo-Wood G. Review of symptom experiences in children and adolescents with cancer. *Cancer Nurs.* 2012;35(2):E31-E49.
362. Williams PD, Williams AR, Kelly KP, et al. A symptom checklist for children with cancer: the Therapy-Related Symptom Checklist—Children. *Cancer Nurs.* 2012;35(2):89-98.
363. Collins JJ, Byrnes ME, Dunkel IJ, et al. The measurement of symptoms in children with cancer. *J Pain Symptom Manage.* 2000;19(5):363-377.
364. Collins J, Devine TD, Dick GS, et al. The measurement of symptoms in young children with cancer: the validation of the Memorial Symptom Assessment Scale in children aged 7–12. *J Pain Symptom Manage.* 2002;23(1):10-16.
365. Buchholz M, Karl HW, Pomietto M, Lynn A. Pain scores in infants: a modified infant pain scale versus visual analogue. *J Pain Symptom Manage.* 1998;15(2):117-124.
366. McGrath P, Seifert CE, Speechley KN, Booth JC, Stitt L, Gibson MC. A new analogue scale for assessing children's pain: an initial validation study. *Pain.* 1996;64(3):435-443.
367. McGrath P, Rosmus C, Canfield C, Campbell MA, Hennigar A. Behaviours caregivers use to determine pain in nonverbal, cognitively impaired children. *Develop Med Child Neurol.* 1998;40(5):340-343.
368. Chambers C, Reid GJ, McGrath PJ, Finley GA. Development and preliminary validation of a postoperative pain measure for parents. *Pain.* 1996;68(2-3):307-313.
369. Savedra M, Holzemer WL, Tesler MD, Wilkie DJ. Assessment of postoperation pain in children and adolescents using the adolescent pediatric pain tool. *Nurs Res.* 1993;42(1):5-9.
370. Wong D, Baker C. Pain in children: comparison of assessment scales. *Pediat Nurs.* 1988;14(1):9-17.
371. Beyer JE, Villarruel AM, Denyes MJ. *The Oucher: A User's Manual and Technical Report.* Evanston, IL: Hospital Play Equipment; 2009.
372. Choinière M, Amsel R. A visual analogue thermometer for measuring pain intensity. *J Pain Symptom Manage.* 1996;11(5):299-311.
373. Krechel SW, Bildner J. CRIES: a new neonatal postoperative pain measurement score: initial testing of validity and reliability. *Paediatr Anaesth.* 1995;5(1):53-61.
374. Lawrence J, Alcock D, McGrath P, Kay J, MacMurray SB, Dulberg C. The development of a tool to assess neonatal pain. *Neonatal Netw.* 1993;12(6):59-66.
375. Newman CJ, Lolekha R, Limkittikul K, Luangxay K, Chotpitayasunondh T, Chanthavanich P. A comparison of pain scales in Thai children. *Arch Dis Child.* 2005;90(3):269-270.
376. Luffy R, Grove SK. Examining the validity, reliability, and preference of three pediatric pain measurement tools in African-American children. *Pediatr Nurs.* 2003;29(1):54-59.
377. Yeh C. Development and validation of the Asian version of the Oucher: a pain intensity scale for children. *J Pain.* 2005;6(8):526-534.
378. Beyer J, Knott CB. Construct validity estimation for the African-American and Hispanic versions of the Oucher Scale. *J Pediatr Nurs.* 1998;13(1):20-31.
379. World Health Organization. *Cancer Pain Relief and Palliative Care in Children.* Geneva: World Health Organization; 1998.
380. Monteiro Caran EM, Dias CG, Seber A, Petrilli AS. Clinical aspects and treatment of pain in children and adolescents with cancer. *Pediatr Blood Cancer.* 2005;45(7):925-932.
381. Zernikow B, Smale H, Michel E, Hasan C, Jorch N, Andler W. Paediatric cancer pain management using the WHO analgesic ladder—results of a prospective analysis from 2265 treatment days during a quality improvement study. *Eur J Pain.* 2006;10(7):587-595.
382. Friedrichsdorf SJ, Postier A. Management of breakthrough pain in children with cancer. *J Pain Res.* 2014;7:117-123.
383. Friedrichsdorf S, Finney D, Bergin M, Stevens M, Collins JJ. Breakthrough pain in children with cancer. *J Pain Symptom Manage.* 2007;34(2):209-216.
384. Hockenberry M, Hinds PS, Barrera P, et al. Three instruments to assess fatigue in children with cancer: the child, parent and staff perspectives. *J Pain Symptom Manage.* 2003;25(4):319-328.

385. Crichton A, Knight S, Oakley E, Babl FE, Anderson V. Fatigue in child chronic health conditions: a systematic review of assessment instruments. *Pediatrics*. 2015;135(4):e1015-e1031.
386. Perdikaris P, Merkouris A, Patiraki E, Tsoumakas K, Vasilatou-Kosmidis E, Matziou V. Evaluating cancer related fatigue during treatment according to children's, adolescents' and parents' perspectives in a sample of Greek young patients. *Eur J Oncol Nurs*. 2009;13(5):399-408.
387. Nunes MDR, Jacob E, Bomfim EO, et al. Fatigue and health related quality of life in children and adolescents with cancer. *Eur J Oncol Nurs*. 2017;29:39-46.
388. Santucci G, Mack JW. Common gastrointestinal symptoms in pediatric palliative care: nausea, vomiting, constipation, anorexia, cachexia. *Pediatr Clin North Am*. 2007;54(5):673-689.
389. Cheng KK, Chang AM, Yuen MP. Prevention of oral mucositis in paediatric patients treated with chemotherapy; a randomised crossover trial comparing two protocols of oral care. *Eur J Cancer*. 2004;40(8):1208-1216.
390. Nashwan AJ. Use of chlorhexidine mouthwash in children receiving chemotherapy: a review of literature. *J Pediatr Oncol Nurs*. 2011;28(5):295-299.
391. Feudtner C, Silveira MJ, Christakis DA. Where do children with complex chronic conditions die? Patterns in Washington state, 1980-1998. *Pediatrics*. 2002;109(4):656-660.
392. Feudtner C, Feinstein JA, Satchell M, Zhao H, Kang TL. Shifting place of death among children with complex chronic conditions in the United States, 1989-2003. *JAMA*. 2007;297(24):2725-2732.
393. Kassam A, Skiadaresis J, Alexander S, Wolfe J. Parent and clinician preferences for location of end-of-life care: home, hospital or freestanding hospice? *Pediatr Blood Cancer*. 2014;61(5):859-864.
394. Widger K, Davies D, Drouin DJ, et al. Pediatric patients receiving palliative care in Canada: results of a multicenter review. *Arch Pediatr Adolesc Med*. 2007;161(6):597-602.
395. Field M, Cassel CK, (eds). *Approaching Death: Improving Care at the End of Life*. Washington, DC: National Academy Press; 1997.
396. American Academy of Pediatrics. Committee on Bioethics and Committee on Hospital Care. Palliative care for children. *Pediatrics*. 2000;106(2 Pt 1):351-357.
397. Johnson LM, Snaman JM, Cupit MC, Baker JN. End-of-life care for hospitalized children. *Pediatr Clin N Am*. 2014;61(4):835-854.
398. Baker JN, Barfield R, Hinds PS, Kane JR. A process to facilitate decision making in pediatric stem cell transplantation: the individualized care planning and coordination model. *Biol Blood Marrow Transplant*. 2007;13(3):245-254.
399. Harper J, Hinds PS, Baker JN, Hicks J, Spunt SL, Razzouk BI. Creating a palliative and end-of-life program in a cure-oriented pediatric setting: the zig-zag method. *J Pediatr Oncol Nurs*. 2007;24(5):246-254.
400. Levine DR, Johnson LM, Snyder A, et al. Integrating palliative care in pediatric oncology: an evolving paradigm for comprehensive cancer care. *J Natl Compr Canc Netw*. 2016;14(6):741-748.
401. Smith TJ, Temin S, Alesi ER, et al. American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. *J Clin Oncol*. 2012;30(8):880-887.
402. Bauman J, Temel J. The integration of early palliative care with oncology care: the time has come for a new tradition. *J Natl Compr Canc Netw*. 2014;12(12):1763-1771.
403. Johnston D, Vadeboncoeur C. Palliative care consultation in pediatric oncology. *Support Care Cancer*. 2012;20:799-803.
404. Wentlandt K, Krzyanowska MK, Swami N, et al. Referral practices of pediatric oncologists to specialized palliative care. *Support Care Cancer*. 2014;22(9):2315-2322.
405. Thienprayoon R, Lee SC, Leonard D, Winick N. Racial and ethnic differences in hospice enrollment among children with cancer. *Pediatr Blood Cancer*. 2013;60(10):1662-1668.
406. Wolfe J, Grier HE, Klar N, et al. Symptoms and suffering at the end of life in children with cancer. *N Engl J Med*. 2000;342(5):326-333.
407. Fowler K, Poehling K, Billheimer D, et al. Hospice referral practices for children with cancer: a survey of pediatric oncologists. *J Clin Oncol*. 2006;24(7):1099-1104.
408. Johnston DL, Nagel K, Friedman DL, Meza JL, Hurwitz CA, Friebert S. Availability and use of palliative care and end-of-life services for pediatric oncology patients. *J Clin Oncol*. 2008;26(28):4646-4650.
409. Collins JJ. Palliative care and the child with cancer. *Hematol Oncol Clin North Am*. 2002;16(3):657-670.
410. Levine D, Lam CG, Cunningham MJ, et al. Best practices for pediatric palliative cancer care: a primer for clinical providers. *J Support Oncol*. 2013;11(3):114-125.
411. Jones BL, Sampson M, Greathouse J, Legett S, Higgerson RA, Christie L. Comfort and confidence levels of health care professionals providing pediatric palliative care in the intensive care unit. *J Soc Work End Life Palliat Care*. 2007;3(3):39-58.
412. Rapoport A, Obwanga C, Sirianni G, Librach SL, Husain A. Not just little adults: palliative care physician attitudes toward pediatric patients. *J Palliat Med*. 2013;16(6):675-679.
413. Foley KM, Gelband H (eds). *Improving Palliative Care for Cancer*. Washington, DC: National Academies Press; 2001.
414. Hilden JM, Emanuel EJ, Fairclough DL, et al. Attitudes and practices among pediatric oncologists regarding end-of-life care: results of the 1998 American Society of Clinical Oncology survey. *J Clin Oncol*. 2001;19(1):205-212.

415. Wolfe J, Klar N, Grier HE, et al. Understanding of prognosis among parents of children who died of cancer: impact on treatment goals and integration of palliative care. *JAMA*. 2000;284(19):2469-2475.
416. Van Cleve L, Muñoz CE, Savedra M, et al. Symptoms in children with advanced cancer: child and nurse reports. *Cancer Nurs*. 2012;35(2):115-125.
417. Fulton R, Moore CM. Spiritual care of the school-age child with a chronic condition. *J Pediatr Nurs*. 1995;10(4):224-231.
418. Feudtner C, Haney J, Dimmers MA. Spiritual care needs of hospitalized children and their families: a national survey of pastoral care providers' perceptions. *Pediatrics*. 2003;111(1):e67-e72.
419. Himelstein BP. Palliative care in pediatrics. *Anesthesiol Clin North Am*. 2005;23(4):837-856.
420. van der Geest IM, van den Heuvel-Eibrink MM, van Vliet LM, et al. Talking about death with children with incurable cancer: perspectives from parents. *J Pediatr*. 2015;17(6):1320-1326.
421. Cochran D, Saleem S, Khawaja-Punjwani S, Lantos JD. Cross-cultural differences in communication about a dying child. *Pediatrics*. 2017;140(5):e20170690.
422. Davies B, Collins J, Steele R, Cook K, Distler V, Brenner A. Parents' and children's perspectives of a children's hospice bereavement program. *J Palliat Care*. 2007;23(1):14-23.
423. Davies R. New understandings of parental grief: literature review. *J Adv Nurs*. 2004;46(5):506-513.
424. Knapp CA, Contro N. Family support services in pediatric palliative care. *Am J Hosp Palliat Care*. 2009;26(6):476-482.
425. Contro N, Sourkes BM. Opportunities for quality improvement in bereavement care at a children's hospital: assessment of interdisciplinary staff perspectives. *J Palliat Care*. 2012;28(1):28-35.
426. Contro NA, Larson J, Scofield S, Sourkes B, Cohen HJ. Hospital staff and family perspectives regarding quality of pediatric palliative care. *Pediatrics*. 2004;114(5):1248-1252.
427. Spinetta JJ, Jankovic M, Eden T, et al. Guidelines for assistance to siblings of children with cancer: report of the SIOP Working Committee on Psychosocial Issues in Pediatric Oncology. *Med Pediatr Oncol*. 1999;33(4):395-398.
428. Alderfer MA, Long KA, Lown EA, et al. Psychosocial adjustment of siblings of children with cancer: a systematic review. *Psychooncology*. 2010;19(8):789-805.
429. Steele AC, Kaal J, Thompson AL, et al. Bereaved parents and siblings offer advice to health care providers and researchers. *J Pediatr Hematol Oncol*. 2013;35(4):253-259.
430. Jones BL. The challenge of quality care for family caregivers in pediatric cancer care. *Semin Oncol Nurs*. 2012;28(4):213-220.
431. Jones B, Levetown M, Hellsten M. Pediatric care: transitioning goals of care in the emergency department, intensive care unit, and in between. In: Ferrell BR, Coyle N, Paice J (eds). *Oxford Textbook of Palliative Nursing*. 4th ed. Oxford University Press; Oxford, NY: 2015: 873-893.
432. Lindstrøm TC. "It ain't necessarily so..." Challenging mainstream thinking about bereavement. *Fam Community Health*. 2002;25(1):11-21.
433. Papadatou D. Training health professionals in caring for dying children and grieving families. *Death Stud*. 1997;21(6):575-600.
434. Meert KL, Thurston CS, Brillier SH. The spiritual needs of parents at the time of their child's death in the pediatric intensive care unit and during bereavement: a qualitative study. *Pediatr Crit Care Med*. 2005;6(4):420-427.
435. Riches G, Dawson P. Lost children, living memories: the role of photographs in processes of grief and adjustment among bereaved parent. *Death Stud*. 1998;22(2):121-140.
436. Meert KL, Thurston CS, Thomas R. Parental coping and bereavement outcome after the death of a child in the pediatric intensive care unit. *Pediatr Crit Care Med*. 2001;2(4):324-328.
437. Macdonald ME, Liben S, Carnevale FA, et al. Parental perspectives on hospital staff members' acts of kindness and commemoration after a child's death. *Pediatrics*. 2005;116(4):884-890.
438. Baidar L. Cancer and the family: a journey to the unknown. In: Perry MC (ed). *ASCO 2006 Educational Book*. Alexandria, VA: American Society of Clinical Oncology; 2006: 160-163.
439. Mooney-Doyle K, Dos Santos MR, Szylyt R, Deatrck JA. Parental expectations of support from healthcare providers during pediatric life-threatening illness: a secondary, qualitative analysis. *J Pediatr Nurs*. 2017;36:163-172.
440. Lerwick JL. Minimizing pediatric healthcare-induced anxiety and trauma. *World J Clin Pediatr*. 2016;5(2):143-150.
441. Lazarus RS, Folkman S. *Stress, Appraisal, and Coping*. 15th ed. Berlin: Springer; 2011.
442. Skinner EA, Zimmer-Gembeck MJ. The development of coping. *Annu Rev Psychol*. 2007;58:119-144.
443. Pastore G, Mosso ML, Magnani C, Luzzatto L, Bianchi M, Terracini B. Physical impairment and social life goals among adult long-term survivors of childhood cancer: a population-based study from the childhood cancer registry of Piedmont, Italy. *Tumori*. 2001;87(6):372-378.
444. Eiser C, Hill JJ, Vance YH. Examining the psychological consequences of surviving childhood cancer: systematic review as a research method in pediatric psychology. *J Pediatr Psychol*. 2000;25(6):449-460.
445. Zebrack BJ, Zeltzer LK, Whitton J, et al. Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma: a report from the Childhood Cancer Survivor Study. *Pediatrics*. 2002;110(1 Pt 1):42-52.

446. Schwartz L, Drotar D. Posttraumatic stress and related impairment in survivors of childhood cancer in early adulthood compared to healthy peers. *J Pediatr Psychol*. 2006;31(4):356-366.
447. Smitherman AB, Mohabir D, Wilkins TM, Blatt J, Nichols HB, Dusetzina SB. Early post-therapy prescription drug usage among childhood and adolescent cancer survivors. *J Pediatr*. 2018;195:161-168.
448. Peterson L. Coping by children undergoing stressful medical procedures: some conceptual, methodological, and therapeutic issues. *J Consult Clin Psychol*. 1989;57(3):380-387.
449. Langston H. *The Child with Cancer: Family-Centered Care in Practice*. New York, NY: Elsevier Health Sciences; 2000.
450. Giammona AJ, Malek DM. The psychological effect of childhood cancer on families. *Pediatr Clin North Am*. 2002;49(5):1063-1081.
451. Erikson EH. *Children and Society*. 2nd ed. New York: WW Norton & Co.; 1963.
452. UCSF Benioff Children's Hospital Oakland. Services: Child Life. Available at <https://www.ucsfbenioffchildrens.org/services/child-life>. Last accessed August 5, 2024.
453. Stam H, Grootenhuys MA, Brons PP, Caron HN, Last BF. Health-related quality of life in children and emotional reactions of parents following completion of cancer treatment. *Pediatr Blood Cancer*. 2006;47(3):312-319.
454. Landier W. Childhood acute lymphoblastic leukemia: current perspectives. *Oncol Nurs Forum*. 2001;28(5):823-833; quiz 834-825.
455. Dowling JS, Hockenberry M, Gregory RL. Sense of humor, childhood cancer stressors, and outcomes of psychosocial adjustment, immune function, and infection. *J Pediatr Oncol Nurs*. 2003;20(6):271-292.
456. Stam H, Grootenhuys MA, Caron HN, Last BF. Quality of life and current coping in young adult survivors of childhood cancer: positive expectations about the further course of the disease were correlated with better quality of life. *Psychooncology*. 2006;15(1):31-43.
457. Barrera M, Shaw AK, Speechley KN, Maunsell E, Pogany L. Educational and social late effects of childhood cancer and related clinical, personal, and familial characteristics. *Cancer*. 2005;104(8):1751-1760.
458. Andersen KK, Duun-Henriksen AK, Frederiksen MH, Winther JF. Ninth grade school performance in Danish childhood cancer survivors. *Br J Cancer*. 2017;116(3):398-404.
459. Ghaderi S, Engeland A, Gunnes MW, et al. Educational attainment among long-term survivors of cancer in childhood and adolescence: a Norwegian population-based cohort study. *J Cancer Surviv*. 2016;10(1):87-95.
460. Patenaude AF, Kupst MJ. Psychosocial functioning in pediatric cancer. *J Pediatr Psychol*. 2005;30(1):9-27.
461. Barakat LP, Alderfer MA, Kazak AE. Posttraumatic growth in adolescent survivors of cancer and their mothers and fathers. *J Pediatr Psychol*. 2006;31(4):413-419.
462. Gagnon J, Bouchard F, Landry M, Belles-Isles M, Fortier M, Fillion L. Implementing a hospital-based animal therapy program for children with cancer: a descriptive study. *Can Oncol Nurs J*. 2004;14(4):217-222.
463. Hedstrom M, Haglund K, Skolin I, von Essen L. Distressing events for children and adolescents with cancer: child, parent, and nurse perceptions. *J Pediatr Oncol Nurs*. 2003;20(3):120-132.
464. Leleszi JP, Lewandowski JG. Interfacing pediatric psychiatry and pediatric palliative care. Paper presented at: 48th Annual Meeting of the American Academy of Child & Adolescent Psychiatry; 2001.
465. Cohen SO, Walco GA. Dance/Movement therapy for children and adolescents with cancer. *Cancer Pract*. 1999;7(1):34-42.
466. Devlin B. The art of healing and knowing in cancer and palliative care. *Int J Palliat Nurs*. 2006;12(1):16-19.
467. Mechtel M, Stoeckle A. psychosocial care of the pediatric oncology patient undergoing surgical treatment. *Semin Oncol Nurs*. 2017;33(1):87-97.
468. Enskar K, Carlsson M, Golsater M, Hamrin E. Symptom distress and life situation in adolescents with cancer. *Cancer Nurs*. 1997;20(1):23-33.
469. Weekes DP, Kagan S. Adolescents completing cancer therapy: meaning, perception, and coping. *Oncol Nurs Forum*. 1994;21(4):663-670.
470. Compas BE, Desjardins L, Vannatta K, et al. Children and adolescents coping with cancer: self- and parent reports of coping and anxiety/depression. *Health Psychol*. 2014;33(8):853-861.
471. Viola A, Taggi-Pinto A, Sahler OJZ, Alderfer MA, Devine KA. Problem-solving skills, parent-adolescent communication, dyadic functioning, and distress among adolescents with cancer. *Pediatr Blood Cancer*. 2018;65(5):e26951.
472. Janin MWH, Ellis SJ, Wakefield CE, Fardell JE. Talking about cancer among adolescent and young adult cancer patients and survivors: a systematic review. *J Adolesc Young Adult Oncol*. 2018;7(5):515-524.
473. Stam H, Hartman EE, Deurloo JA, Groothoff J, Grootenhuys MA. Young adult patients with a history of pediatric disease: impact on course of life and transition into adulthood. *J Adolesc Health*. 2006;39(1):4-13.
474. Phipps S, Jurbergs N, Long A. Symptoms of post-traumatic stress in children with cancer: does personality trump health status? *Psychooncology*. 2009;18(9):992-1002.
475. Tillery R, Howard Sharp KM, Okado Y, Long A, Phipps S. Profiles of resilience and growth in youth with cancer and healthy comparisons. *J Pediatr Psychol*. 2016;41(3):290-297.
476. Kato PM, Cole SW, Bradlyn AS, Pollock BH. A video game improves behavioral outcomes in adolescents and young adults with cancer: a randomized trial. *Pediatrics*. 2008;122(2):e305-e317.

477. Burgess ES, Haaga DAF. Appraisals, coping responses, and attributions as predictors of individual differences in negative emotions among pediatric cancer patients. *Cogn Ther Res.* 1998;22(5):457-473.
478. Trask PC, Paterson AG, Trask CL, Bares CB, Birt J, Maan C. Parent and adolescent adjustment to pediatric cancer: associations with coping, social support, and family function. *J Pediatr Oncol Nurs.* 2003;20(1):36-47.
479. Tobin DL, Holroyd KA, Reynolds RV, Wigal JK. The hierarchical factor structure of the coping strategies inventory. *Cogn Ther Res.* 1989;13(4):343-361.
480. Hockenberry-Eaton M, Manteuffel B, Bottomley S. Development of two instruments examining stress and adjustment in children with cancer. *J Pediatr Oncol Nurs.* 1997;14(3):178-185.
481. Katz ER, Varni JW. Social support and social cognitive problem-solving in children with newly diagnosed cancer. *Cancer.* 1993;71(10 Suppl):3314-3319.
482. Neville K. The relationships among uncertainty, social support, and psychological distress in adolescents recently diagnosed with cancer. *J Pediatr Oncol Nurs.* 1998;15(1):37-46.
483. Ritchie MA. Sources of emotional support for adolescents with cancer. *J Pediatr Oncol Nurs.* 2001;18(3):105-110.
484. Levin Newby W, Brown RT, Pawletko TM, Gold SH, Whitt JK. Social skills and psychological adjustment of child and adolescent cancer survivors. *Psychooncology.* 2000;9(2):113-126.
485. Ranmal R, Prictor M, Scott JT. Interventions for improving communications with children and adolescents about their cancer. *Cochrane Database Syst Rev.* 2008;(4):CD002969.
486. National Children's Cancer Society. *The Mountain You Have Climbed. A Parent's Guide to Childhood Cancer Survivorship.* St. Louis, MO: National Children's Cancer Society; 2006.
487. Pai AL, Drotar D, Zebracki K, Moore M, Youngstrom E. A meta-analysis of the effects of psychological interventions in pediatric oncology on outcomes of psychological distress and adjustment. *J Pediatr Psychol.* 2006;31(9):978-988.
488. Peikert ML, Inhestern L, Bergelt C. Psychosocial interventions for rehabilitation and reintegration into daily life of pediatric cancer survivors and their families: a systematic review. *PLoS One.* 2018;13(4):e0196151.
489. Suzuki LK, Kato PM. Psychosocial support for patients in pediatric oncology: the influences of parents, schools, peers, and technology. *J Pediatr Oncol Nurs.* 2003;20(4):159-174.
490. Goldbeck L. Parental coping with the diagnosis of childhood cancer: gender effects, dissimilarity within couples, and quality of life. *Psychooncology.* 2001;10(4):325-335.
491. Spinetta JJ, Masera G, Jankovic M, et al. Valid informed consent and participative decision-making in children with cancer and their parents: a report of the SIOP Working Committee on psychosocial issues in pediatric oncology. *Med Pediatr Oncol.* 2003;40(4):244-246.
492. Frank NC, Blount RL, Brown RT. Attributions, coping, and adjustment in children with cancer. *J Pediatr Psychol.* 1997;22(4):563-576.
493. Sanger MS, Copeland DR, Davidson ER. Psychosocial adjustment among pediatric cancer patients: a multidimensional assessment. *J Pediatr Psychol.* 1991;16(4):463-474.
494. Prchal A, Landolt MA. How siblings of pediatric cancer patients experience the first time after diagnosis: a qualitative study. *Cancer Nurs.* 2012;35(2):133-140.
495. Zeltzer LK, Dolgin MJ, Sahler OJ, et al. Sibling adaptation to childhood cancer collaborative study: health outcomes of siblings of children with cancer. *Med Pediatr Oncol.* 1996;27(2):98-107.
496. Van Dongen-Melman JE, De Groot A, Hahlen K, Verhulst FC. Siblings of childhood cancer survivors: how does this "forgotten" group of children adjust after cessation of successful cancer treatment? *Eur J Cancer.* 1995;31A(13-14):2277-2283.
497. Sharpe D, Rossiter L. Siblings of children with a chronic illness: a meta-analysis. *J Pediatr Psychol.* 2002;27(8):699-710.
498. Labay LE, Walco GA. Brief report: empathy and psychological adjustment in siblings of children with cancer. *J Pediatr Psychol.* 2004;29(4):309-314.
499. Murray JS. Attachment theory and adjustment difficulties in siblings of children with cancer. *Issues Ment Health Nurs.* 2000;21(2):149-169.
500. Sargent JR, Sahler OJ, Roghmann KJ, et al. Sibling adaptation to childhood cancer collaborative study: siblings' perceptions of the cancer experience. *J Pediatr Psychol.* 1995;20(2):151-164.
501. Kazak AE, Simms S, Barakat L, et al. Surviving cancer competently intervention program (SCCIP): a cognitive-behavioral and family therapy intervention for adolescent survivors of childhood cancer and their families. *Fam Process.* 1999;38(2):175-191.
502. Alderfer MA, Labay LE, Kazak AE. Brief report: does posttraumatic stress apply to siblings of childhood cancer survivors? *J Pediatr Psychol.* 2003;28(4):281-286.
503. Lövgren M, Bylund-Grenklo T, Jalmsell L, Wallin AE, Kreicbergs U. Bereaved siblings' advice to health care professionals working with children with cancer and their families. *J Pediatr Oncol Nurs.* 2016;33(4):297-305.
504. Cohen DS, Friedrich WN, Jaworski TM, Copeland D, Pendergrass T. Pediatric cancer: predicting sibling adjustment. *J Clin Psychol.* 1994;50(3):303-319.
505. Sloper P. Experiences and support needs of siblings of children with cancer. *Health Soc Care Community.* 2000;8(5):298-306.

506. Murray JS. A qualitative exploration of psychosocial support for siblings of children with cancer. *J Pediatr Nurs*. 2002;17(5):327-337.
507. Woodgate RL. Siblings' experiences with childhood cancer: a different way of being in the family. *Cancer Nurs*. 2006;29(5):406-414.
508. Wilkins KL, Woodgate RL. A review of qualitative research on the childhood cancer experience from the perspective of siblings: a need to give them a voice. *J Pediatr Oncol Nurs*. 2005;22(6):305-319.
509. Ballard KL. Meeting the needs of siblings of children with cancer. *Pediatr Nurs*. 2004;30(5):394-401.
510. Hoekstra-Weebers JE, Jaspers JP, Kamps WA, Klip EC. Gender differences in psychological adaptation and coping in parents of pediatric cancer patients. *Psychooncology*. 1998;7(1):26-36.
511. Dahlquist LM, Czyzewski DI, Jones CL. Parents of children with cancer: a longitudinal study of emotional distress, coping style, and marital adjustment two and twenty months after diagnosis. *J Pediatr Psychol*. 1996;21(4):541-554.
512. Kupst MJ, Natta MB, Richardson CC, Schulman JL, Lavigne JV, Das L. Family coping with pediatric leukemia: ten years after treatment. *J Pediatr Psychol*. 1995;20(5):601-617.
513. Kazak AE, Alderfer M, Rourke MT, Simms S, Streisand R, Grossman JR. Posttraumatic stress disorder (PTSD) and posttraumatic stress symptoms (PTSS) in families of adolescent childhood cancer survivors. *J Pediatr Psychol*. 2004;29(3):211-219.
514. Hinds PS, Kelly KP. Helping parents make and survive end of life decisions for their seriously ill child. *Nurs Clin North Am*. 2010;45(3):465-474.
515. Cadell S, Kennedy K, Hemsworth D. Informing social work practice through research with parent caregivers of a child with a life-limiting illness. *J Soc Work End Life Palliat Care*. 2012;8(4):356-381.
516. Meert K, Eggly S, Pollack M, et al. Parents' perspectives regarding a physician-parent conference after their child's death in the pediatric intensive care unit. *J Pediatr*. 2007;151(1):50-55, e52.
517. Liben S, Papadatou D, Wolfe J. Paediatric palliative care: challenges and emerging ideas. *Lancet*. 2008;371(9615):852-864.
518. Brown RT, Madan-Swain A, Lambert R. Posttraumatic stress symptoms in adolescent survivors of childhood cancer and their mothers. *J Trauma Stress*. 2003;16(4):309-318.
519. Wijnberg-Williams BJ, Kamps WA, Klip EC, Hoekstra-Weebers JE. Psychological adjustment of parents of pediatric cancer patients revisited: five years later. *Psychooncology*. 2006;15(1):1-8.
520. Norberg AL, Lindblad F, Boman KK. Support-seeking, perceived support, and anxiety in mothers and fathers after children's cancer treatment. *Psychooncology*. 2006;15(4):335-343.
521. Sahler OJ, Fairclough DL, Phipps S, et al. Using problem-solving skills training to reduce negative affectivity in mothers of children with newly diagnosed cancer: report of a multisite randomized trial. *J Consult Clin Psychol*. 2005;73(2):272-283.
522. Kazak AE, Alderfer MA, Streisand R, et al. Treatment of posttraumatic stress symptoms in adolescent survivors of childhood cancer and their families: a randomized clinical trial. *J Fam Psychol*. 2004;18(3):493-504.
523. Sidhu R, Passmore A, Baker D. The effectiveness of a peer support camp for siblings of children with cancer. *Pediatr Blood Cancer*. 2006;47(5):580-588.
524. Williams PD, Williams AR, Graff JC, et al. A community-based intervention for siblings and parents of children with chronic illness or disability: the ISEE study. *J Pediatr*. 2003;143(3):386-393.
525. Marusak HA, Iadipalo AS, Cohen C, et al. Martial arts-based therapy reduces pain and distress among children with chronic health conditions and their siblings. *J Pain Res*. 2020;13:3467-3478.
526. Dickerman JD. The late effects of childhood cancer therapy. *Pediatrics*. 2007;119(3):554-568.
527. National Cancer Institute. Childhood Cancer Survivor Study: An Overview. Available at <https://www.cancer.gov/types/childhood-cancers/ccss>. Last accessed August 5, 2024.
528. American Cancer Society. Childhood and Adolescent Cancer Statistics. Available at <https://cancerstatisticscenter.cancer.org/childhood-and-adolescent-cancer>. Last accessed August 5, 2024.
529. Hewitt M, Weiner SL, Simone JV (eds). *Childhood Cancer Survivorship. Improving Care and Quality of Life*. Washington, DC: National Academies Press; 2003.
530. American Academy of Pediatrics. Policy statement: the medical home. *Pediatrics*. 2002;110:184-186.
531. American Academy of Pediatrics. What is Medical Home? Medical Home History. Available at <https://www.aap.org/en/practice-management/medical-home/medical-home-overview/what-is-medical-home/#>. Last accessed August 5, 2024.
532. Eiser C. Beyond survival: quality of life and follow-up after childhood cancer. *J Pediatr Psychol*. 2007;32(9):1140-1150.
533. Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group long-term follow-up guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. *J Clin Oncol*. 2004;22(24):4979-4990.
534. Children's Oncology Group. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. Version 6.0. Available at http://www.survivorshipguidelines.org/pdf/2023/COG_LTFU_Guidelines_Comprehensive_v6.pdf. Last accessed August 5, 2024.
535. Passport for Care with the Children's Oncology Group. Available at <https://cancersurvivor.passportforcare.org/en/>. Last accessed August 5, 2024.

536. Armstrong GT, Kawashima T, Leisenring W, et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. *J Clin Oncol*. 2014;32(12):1218-1227.
537. Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor study. *JAMA*. 2003;290(12):1583-1592.
538. De A, Guryev I, Lariviere A, et al. Pulmonary function abnormalities in childhood cancer survivors treated with bleomycin. *Pediatr Blood Cancer*. 2014;61(9):1679-1684.
539. Venkatramani R, Kamath S, Wong K, et al. Pulmonary outcomes in patients with Hodgkin lymphoma treated with involved field radiation. *Pediatr Blood Cancer*. 2014;61(7):1277-1281.
540. Moskowitz CS, Chou JF, Wolden SL, et al. Breast cancer after chest radiation therapy for childhood cancer. *J Clin Oncol*. 2014;32(21):2217-2223.
541. Orgel E, Zung L, Ji L, et al. Early cardiac outcomes following contemporary treatment for childhood acute myeloid leukemia: a North American perspective. *Pediatr Blood Cancer*. 2013;60(9):1528-1533.
542. Henderson TO, Amsterdam A, Bhatia S, et al. Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. *Ann Intern Med*. 2010;152(7):444-455.
543. Oeffinger KC, Hudson MM, Mertens AC, et al. Increasing rates of breast cancer and cardiac surveillance among high-risk survivors of childhood Hodgkin lymphoma following a mailed, one-page survivorship care plan. *Pediatr Blood Cancer*. 2011;56(5):818-824.
544. Bhatia S, Yasui Y, Robison LL, et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. *J Clin Oncol*. 2003;21(23):4386-4394.
545. Hijiya N, Hudson MM, Lensing S, et al. Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukemia. *JAMA*. 2007;297(11):1207-1215.
546. Henderson TO, Whitton J, Stovall M, et al. Secondary sarcomas in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2007;99(4):300-308.
547. Kenney LB, Yasui Y, Inskip PD, et al. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Intern Med*. 2004;141(8):590-597.
548. Bassal M, Mertens AC, Taylor L, et al. Risk of selected subsequent carcinomas in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2006;24(3):476-483.
549. Sunga A, Eberl MM, Oeffinger KC, Hudson MM, Mahoney MC. Care of cancer survivors. *Am Fam Phys*. 2005;71(4):699-706.
550. Yeazel M, Oeffinger KC, Gurney JG, et al. The cancer screening practices of adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer*. 2004;100(3):631-640.
551. Lipshultz SE, Adams MJ, Colan SD, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. *Circulation*. 2013;128(17):1927-1995.
552. Fulbright JM. Review of cardiotoxicity in pediatric cancer patients: during and after therapy. *Cardiol Res Pract*. 2011;2011:942090.
553. Green DM, Grigoriev YA, Nan B, et al. Congestive heart failure after treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol*. 2001;19(7):1926-1934.
554. Pein F, Sakiroglu O, Dahan M, et al. Cardiac abnormalities 15 years and more after adriamycin therapy in 229 childhood survivors of a solid tumour at the Institut Gustave Roussy. *Br J Cancer*. 2004;91(1):37-44.
555. Pinarli FG, Oğuz A, Tunaoglu FS, Karadeniz C, Gökçora N, Elbeg S. Late cardiac evaluation of children with solid tumors after anthracycline chemotherapy. *Pediatric Blood Cancer*. 2005;44(4):370-377.
556. Sorensen K, Levitt GA, Bull C, Dorup I, Sullivan ID. Late anthracycline cardiotoxicity after childhood cancer: a prospective longitudinal study. *Cancer*. 2003;97(8):1991-1998.
557. Hudson MM, Rai SN, Nunez C, et al. Noninvasive evaluation of late anthracycline cardiac toxicity in childhood cancer survivors. *J Clin Oncol*. 2007;25(24):3635-3643.
558. Rathe M, Carlsen NLT, Oxhøj H, Nielsen G. Long-term cardiac follow-up of children treated with anthracycline doses of 300 mg/m or less for acute lymphoblastic leukemia. *Pediatric Blood Cancer*. 2010;54(3):444-448.
559. Vilela M, Viana MB. Longitudinal growth and risk factors for growth deficiency in children treated for acute lymphoblastic leukemia. *Pediatric Blood Cancer*. 2007;48(1):86-92.
560. Haddy T, Mosher RB, Nunez SB, Reaman GH. Growth hormone deficiency after chemotherapy for acute lymphoblastic leukemia in children who have not received cranial radiation. *Pediatric Blood Cancer*. 2006;46(2):258-261.
561. Viana MB, Viela MI. Height deficit during and many years after treatment for acute lymphoblastic leukemia in children: a review. *Pediatric Blood Cancer*. 2008;50(2 Suppl):509-516.
562. Groot-Loonen JJ, Otten BJ, van t'Hof MA, Lippens RJ, Stoelinga GB. Chemotherapy plays a major role in the inhibition of catch-up growth during maintenance therapy for childhood acute lymphoblastic leukemia. *Pediatrics*. 1995;96(4 Pt 1):693-695.
563. Adams J, Lipshultz SE. Pathophysiology of anthracycline- and radiation-associated cardiomyopathies: implications for screening and prevention. *Pediatric Blood Cancer*. 2005;44(7):600-606.

564. Zhang FF, Kelly MJ, Saltzman E, et al. Obesity in pediatric ALL survivors: a meta-analysis. *Pediatrics*. 2014;133(3):e704-715.
565. Razzouk BI, Rose SR, Hongeng S, et al. Obesity in survivors of childhood acute lymphoblastic leukemia and lymphoma. *J Clin Oncol*. 2007;25(10):1183-1189.
566. Foster KL, Kern KD, Chambers TM, et al. Weight trends in a multiethnic cohort of pediatric acute lymphoblastic leukemia survivors: a longitudinal analysis. *PLoS One*. 2019;14(5):e0217932.
567. Oktem O, Kim SS, Selekc U, Schatmann G, Urman B. Ovarian and uterine functions in female survivors of childhood cancers. *Oncologist*. 2018;23(2):214-224.
568. Horning S, Hoppe RT, Kaplan HS, Rosenberg SA. Female reproductive potential after treatment for Hodgkin's disease. *N Engl J Med*. 1981;304(23):1377-1382.
569. Oeffinger KC, Mertens AC, Hudson MM, et al. Health care of young adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Fam Med*. 2004;2(1):61-70.
570. Nathan PC, Patel SK, Dilley K, et al. Guidelines for identification of, advocacy for, and intervention in neurocognitive problems in survivors of childhood cancer: a report from the Children's Oncology Group. *Arch Pediatr Adolesc Med*. 2007;161(8):798-806.
571. Butler RW, Mulhern RK. Neurocognitive interventions for children and adolescents surviving cancer. *J Pediatr Psychol*. 2005;30(1):65-78.
572. Mitby P, Robison LL, Whitton JA, et al. Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer*. 2003;97(4):1115-1126.
573. Bryan G, Kelly P, Chesters H, et al. Access to and experience of education for children and adolescents with cancer: a scoping review protocol. *Syst Rev*. 2021;10(1):167.
574. Yeazel M, Gurney J, Oeffinger K, et al. An examination of the dental utilization practices of adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Public Health Dent*. 2004;64(1):50-54.
575. Mertens AC, Brand S, Ness KK, et al. Health and well-being in adolescent survivors of early childhood cancer: a report from the Childhood Cancer Survivor Study. *Psychooncology*. 2014;23(3):266-275.
576. Hobbie WL, Stuber M, Meeske K, et al. Symptoms of posttraumatic stress in young adult survivors of childhood cancer. *J Clin Oncol*. 2000;18(24):4060-4066.
577. Phipps S, Klosky JL, Long A, et al. Posttraumatic stress and psychological growth in children with cancer: has the traumatic impact of cancer been overestimated? *J Clin Oncol*. 2014;32(7):641-646.
578. Oancea SC, Brinkman TM, Ness KK, et al. Emotional distress among adult survivors of childhood cancer. *J Cancer Surviv*. 2014;8(2):293-303.
579. Mader L, Michel G, Roser K. Unemployment following childhood cancer. *Dtsch Arztebl Int*. 2017;114(47):805-812.
580. Perkins JL, Chen Y, Harris A, et al. Infections among long-term survivors of childhood and adolescent cancer: a report from the Childhood Cancer Survivor Study. *Cancer*. 2014;120(16):2514-2521.
581. Wengenroth L, Rueegg CS, Michel G, et al. Life partnerships in childhood cancer survivors, their siblings, and the general population. *Pediatric Blood Cancer*. 2014;61(3):538-545.
582. Bashore L. Childhood and adolescent cancer survivors' knowledge of their disease and effects of treatment. *J Pediatric Oncol Nurs*. 2004;21(2):98-102.
583. Kadan-Lottick NS, Robison LL, Gurney JG, et al. Childhood cancer survivors' knowledge about their past diagnosis and treatment: Childhood Cancer Survivor Study. *JAMA*. 2002;287(14):1832-1839.
584. Earle C, Schrag D, Woolf SH, Ganz PA. The survivorship care plan: what, why, how, and for whom. In: Perry MC (ed). *ASCO 2006 Educational Book*. Alexandria, VA: American Society of Clinical Oncology; 2006.
585. Earle CC. Failing to plan is planning to fail: improving the quality of care with survivorship care plans. *J Clin Oncol*. 2006;24(32):5112-5116.
586. Kirchoff AC, Montenegro RE, Warner EL, et al. Childhood cancer survivors' primary care and follow-up experiences. *Support Care Cancer*. 2014;22(6):1629-1635.
587. The National Children's Cancer Society. Late Effects After Treatment Tool. Available at <https://leatt.thencs.org>. Last accessed August 5, 2024.
588. Children's Oncology Group. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers: Appendix II: Patient Education Materials "Health Links". Available at http://www.survivorshipguidelines.org/pdf/2023/COG_LTFU_Guidelines_Appendix_II_All_Lang_v6.pdf. Last accessed August 5, 2024.
589. Castellino SM, Casillas J, Hudson MM, et al. Minority adult survivors of childhood cancer: a comparison of long-term outcomes, health care utilization, and health-related behaviors from the childhood cancer survivor study. *J Clin Oncol*. 2005;23(27):6499-6507.
590. Hudson M, Tyc VL, Srivastava DK, et al. Multi-component behavioral intervention to promote health protective behaviors in childhood cancer survivors: the Protect Study. *Med Pediatric Oncol*. 2002;39(1):2-11.
591. Cox CL, Nolan VG, Leisenring W, et al. Noncancer-related mortality risks in adult survivors of pediatric malignancies: the Childhood Cancer Survivor Study. *J Cancer Surviv*. 2014;8(3):460-471.

592. Devine KA, Mertens AC, Whitton JA, et al. Factors associated with physical activity among adolescent and young adult survivors of early childhood cancer: a report from the Childhood Cancer Survivor Study (CCSS). *Psychooncology*. 2018;27(2):613-619.
593. Sima JL, Perkins SM, Haggstrom DA. Primary care physician perceptions of adult survivors of childhood cancer. *J Pediatric Hematol Oncol*. 2014;36(2):118-124.
594. Suh E, Daugherty CK, Wroblewski K, et al. General internists' preferences and knowledge about the care of adult survivors of childhood cancer: a cross-sectional survey. *Ann Intern Med*. 2014;160(1):11-17.
595. Nathan PC, Daugherty CK, Wroblewski, et al. Family physician preferences and knowledge gaps regarding the care of adolescent and young adult survivors of childhood cancer. *J Cancer Surviv*. 2013;7(3):275-282.
596. Ford JS, Chou JF, Sklar CA. Attendance at a survivorship clinic: impact on knowledge and psychosocial adjustment. *J Cancer Surviv*. 2013;7(4):535-543.
597. Meadows A. Pediatric cancer survivorship: research and clinical care. *J Clin Oncol*. 2006;24(32):5160-5165.
598. Erikson C, Salsberg E, Forte G, Bruinooge S, Goldstein M. Future supply and demand for oncologists: challenges to assuring access to oncology services. *J Oncol Pract*. 2007;3(2):79-86.

Evidence-Based Practice Recommendations Citations

- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Pediatric Hodgkin Lymphoma. Version 1.2024. Available at https://www.nccn.org/professionals/physician_gls/pdf/ped_hodgkin.pdf. Last accessed August 22, 2024.
- Centers for Disease Control and Prevention. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. Atlanta, GA: Centers for Disease Control and Prevention; 2021. Available at <https://www.cdc.gov/pinkbook/hcp/table-of-contents/chapter-13-measles.html>. Last accessed August 22, 2024.
- Lehrnbecher T, Robinson PD, Ammann RA, et al. Guideline for the management of fever and neutropenia in pediatric patients with cancer and hematopoietic cell transplantation recipients: 2023 update. *J Clin Oncol*. 2023;41(9):1774-1785. Available at <https://ascopubs.org/doi/10.1200/JCO.2016.71.7017>. Last accessed August 22, 2024.
- Barnard D, Portwine C, Members of the C17 Standards and Guidelines Group. *Guideline for Platelet Transfusion Thresholds for Pediatric Hematology/Oncology Patients*. Edmonton: C17 Council, Children's Cancer & Blood Disorders; 2011. Available at https://www.c17.ca/application/files/2916/2006/0821/C17_Platelet_Guideline_English_Summary_2011.pdf. Last accessed August 22, 2024.
- Wiener L, Kazak AE, Noll RB, Patenaude AF, Kupst MJ. Standards for the psychosocial care of children with cancer and their families: an introduction to the special issue. *Pediatr Blood Cancer*. 2015;62(Suppl 5):S419-S424. Available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6397048>. Last accessed August 22, 2024.