

Pediatric Lymphoma

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Education Gaps

Painless lymphadenopathy is one of the commonest presentations of pediatric lymphoma. Absence of the absolute lymphoma-specific signs and symptoms makes it a particular diagnostic challenge. Lack of systemic symptoms does not preclude a malignant transformation. High level of suspicion is critical for timely patient referral to a pediatric oncologist. Outstanding survival rates may be compromised by a substantial prevalence of the therapy-related side effects.

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

1. Recognize genetic and environmental factors contributing to development of lymphoma.
2. Identify clinical parameters that can be used to predict the nonbenign nature of lymphadenopathy.
3. Recognize lymphoma-associated oncologic emergencies.
4. Diagnose tumor lysis syndrome and propose prophylactic and therapeutic interventions.
5. Discuss therapeutic options and recognize therapy-related side effects.

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INTRODUCTION

Lymphoma is the third most frequent childhood malignancy (prevalence rate of 12%–15%), closely following acute leukemia and central nervous system (CNS) tumors. Most pediatric patients with lymphoma will survive their disease into adulthood. Having a high threshold of clinical suspicion at the time of first assessment, along with performing problem-oriented initial tests, followed by prompt referral to the pediatric lymphoma expert for further evaluation and specialized treatment, are the pillars of therapeutic success. This review will serve to update the readership on pediatric lymphoma epidemiology and known predisposition factors, clinical presentation, diagnostic tests, and therapeutic options, as well as treatment-related side effects that may need to be recognized while taking care of lymphoma survivors.

Lymphoma is a neoplasm caused by malignant transformation of lymphoid cells. Advances in the understanding of lymphoma biology led to development of

ABBREVIATIONS

CAR	chimeric antigen receptor
CHL	classic Hodgkin lymphoma
CNS	central nervous system
CT	computed tomography
EBV	Epstein-Barr virus
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HRSC	Hodgkin Reed-Sternberg cell
HSCT	hematopoietic stem cell transplantation
Ig	immunoglobulin
LN	lymph node
NHL	non-Hodgkin lymphoma
NLPD	nodular lymphocyte-predominant
SVC	superior vena cava
TLS	tumor lysis syndrome
UA	uric acid

risk- and response-adapted therapies, which caused lymphomas to be one of the most curable pediatric cancers. The disease-free survival after completion of therapy exceeds 85% for most patients with lymphoma.

BIOLOGY AND EPIDEMIOLOGY OF LYMPHOMA

There are 2 clinicopathologic lymphoma types: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), with distinct clinical subtypes within each of those types. Variations in lymphoma incidence, age, and sex distribution occur in different pediatric populations according to geographic location and socioeconomic environment.

HL accounts for approximately 6% to 8% of all pediatric neoplasms. In developed countries, HL is the most prevalent lymphoma, as well as the most prevalent neoplasm in patients aged 10 to 19 years (Table 1 [1]). In developing countries, the overall HL prevalence in older children is about the same but occurs significantly more frequently in younger patients (aged 0–9 years). HL incidence has a bimodal age distribution: the early peak occurs in the mid-20s, with the second peak in the late 50s; however, in developing countries, the early peak occurs before adolescence. In early childhood, HL is more frequent in boys (male to female ratio of approximately 5:1), whereas in adolescents, it is more frequent in girls (male to female ratio of approximately 0.8:1.0). In younger patients, the increased HL prevalence correlates with larger family size and socioeconomically disadvantaged status. For the older group, the greater HL risk correlates with higher socioeconomic status, smaller sibship size, and late birth order. These patients commonly experience fewer childhood infections or experience them at older ages, which potentially affects the timing of immune system maturation. HL incidence is similar among young African American and

white patients; it is less frequent among African American adolescents (ratio of 0.8:1.0).

There are 2 biologically distinct HL variants: classic HL (cHL) and nodular lymphocyte-predominant (NLPD) HL. The diagnostic hallmark of cHL is the multinucleated (at least 2 nuclei in 2 separate lobes) Reed-Sternberg cell or its mononuclear variant, the Hodgkin cell (Fig 1A). These malignant cells of B-cell origin constitute less than 1% of the tumor bulk; most of the tumor mass is a variable mixture of nonneoplastic reactive leukocytes of a certain lymphoma-specific architecture. Hodgkin Reed-Sternberg cells (HRSCs) express B-cell lineage-specific antigens CD30 and CD15. On the basis of characteristics of the reactive infiltrate and HRSC morphology, 4 cHL subvariants are recognized: nodular sclerosis (most frequent in older patients [>10 years of age]); mixed cellularity (more frequent in younger children [<10 years of age]), lymphocyte rich (rare), and lymphocyte depleted (also rare). These histologic variants have some prognostic implications; patients with the mixed cellularity cHL seem to have a better outcome.

NLPD HL accounts for approximately 10% of all HL cases and affects girls more frequently than boys (female to male ratio of 3:1). The malignant cells of NLPD HL are called *lymphocyte-predominant cells* (Fig 1B). They are large cells with single, folded, multilobulated nuclei with small nucleoli. Unlike classic HRSC, the lymphocyte-predominant cells uniformly express CD20 but not CD30 or CD15.

After the onset of HL at a single lymphoid organ, the HRSC contiguously spreads to the adjacent lymphoid tissues and to distant lymphoid and nonlymphoid organs through both lymphatic and hematogenous routes. Since HRSCs are terminally differentiated cells with a limited proliferation and extravasation potential, the role of HRSC “precursors” homing into “metastatic niches” is being debated. (2)

TABLE 1. Pediatric Lymphoma Incidence (Per 100,000 Person-Years)

	MALE PATIENTS				FEMALE PATIENTS			
	<5 Y	5–9 Y	10–14 Y	15–19 Y	<5 Y	5–9 Y	10–14 Y	15–19 Y
Hodgkin lymphoma	<1	6	12	28	<1	2	9	31
Non-Hodgkin lymphoma	3.2	6	6.1	2.8	0.8	1.1	0.8	1.2
Burkitt lymphoma								
Lymphoblastic	1.6	2.2	2.8	2.2	0.9	1.0	0.7	0.9
Diffuse large B-cell lymphoma	<1	1.2	2.5	6.1	0.6	<1	1.4	4.9
Anaplastic large-cell lymphoma and other	2.3	3.3	4.3	7.8	1.5	1.6	2.8	3.4

According to reference 1. Data are number of patients.

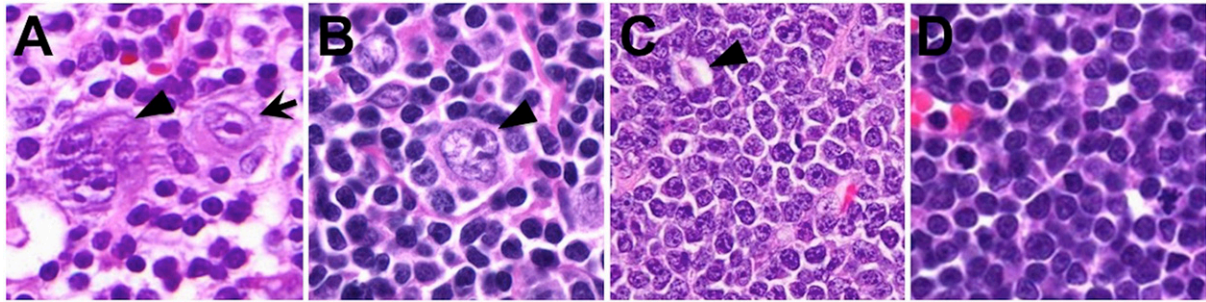


Figure 1. Photomicrographs (H&E stain; original magnification, $\times 40$) demonstrate the histomorphology of different types of lymphoma. A. Classic Hodgkin lymphoma is shown. The arrowhead indicates the Reed-Sternberg cell; the arrow indicates the Hodgkin cell, surrounded by reactive lymphocytes. B. Nodular lymphocyte-predominant Hodgkin lymphoma is shown. The arrowhead indicates the lymphocyte-predominant “popcorn” cell, which is the cell surrounded by reactive lymphocytes. C. Burkitt lymphoma is shown. The arrowhead indicates a macrophage surrounded by morphologically uniform malignant lymphoma cells (also known as “the starry sky” appearance). D. T-cell lymphoblastic lymphoma is shown. Morphologically uniform malignant cells form the bulk of the tumor.

Although early exposure to pediatric infections has a protective effect, Epstein-Barr virus (EBV) has been implicated in HL development; EBV positivity can be observed in approximately 70% to 80% cases of mixed-cellularity HL, the commonest histologic cHL subvariant of early childhood. Children with a medical history of infectious mononucleosis have increased risk of developing EBV-positive cHL; EBV can still be detected in the tumors of more than 50% of these patients. However, such patients are not at increased risk for EBV-negative cHL. (3) In contrast, NLPD HL has no strong association with EBV.

Familial HL comprises approximately 4% of all cHL cases. HL history in a parent or a sibling is a recognized risk factor. Age (<45 years) of the affected parent or sibling is critical and results in a sevenfold increased risk of HL development. Brother-brother and sister-sister pairs have the highest risks for developing cHL. Monozygotic twins of patients with HL demonstrate the greatest risk. (4) In many cases of familial cHL, certain inherited or acquired immune system abnormalities exist, such as autoimmune lymphoproliferative syndrome, ataxia-telangiectasia, sarcoidosis, juvenile rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, ulcerative colitis, immune thrombocytopenic purpura, acquired immune deficiencies caused by EBV, and human immunodeficiency virus (HIV) infections. A long latency from the onset of the autoimmune condition (mean, 15.4 years) to HL diagnosis has been observed. This underscores the role of long-term immunologic dysregulations as a pathogenetic factor in HL.

In children without underlying immunologic disarrays, the recessively inherited human leukocyte antigen-linked susceptibility genes may be found in approximately 60% of cases. Familial HL cases demonstrate only 1 major incidence peak between 15 and 34 years of age. The aforementioned factors seem to play a minimal role in NLPD HL development.

Secondary HL—that is, HL that develops after therapy administered for another malignancy—is extremely rare and, in reported cases, follows the treatment of acute lymphoblastic leukemia.

NHL is a heterogeneous group of neoplasms that accounts for approximately 7% of all pediatric malignancies; it originates from either immature (lymphoblastic) or mature B, T, or natural killer cells: lymphoblastic lymphoma; mature B-cell NHL (Burkitt lymphoma, diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma); and anaplastic large-cell lymphoma. There are several other infrequent types, including primary CNS NHL. Similar to HL, there is a variability in NHL incidence rates according to sex, age, and ethnicity. The overall incidence rate appears to be increasing with age (Table 1). Male patients are affected more frequently than female patients (male to female ratio 3.5:1). (1) NHL incidence in white children is the highest when compared to other ethnic groups.

In NHL, the bulk of the tumor is composed predominantly of the uniform malignant cells (Fig 1 C and D). Conceptually, any lymphoma that lacks the morphologic features of HL should be classified as NHL, although in some cases, the distinction is challenging to make.

The spreading of NHL to different sites and organs is a phylogenetically conserved phenomenon that relies on lymphocyte biology; it uniquely depends on lymphoma cells' expression of various adhesion molecules and the reciprocal receptors expressed in the target organs. (5)

Previous exposure to pediatric infections does not affect NHL incidence. However, there is a strong association of endemic Burkitt lymphoma with EBV and malaria (and possibly schistosomes and arbovirus) in some African countries (Uganda, Malawi, Congo, and Nigeria, known as the “African lymphoma belt”). Exposure to *Euphorbia tirucalli* spurge, also known as “milk bush,” which is used in many rituals, has been attributed to reactivation of latent

EBV infection. Poor socioeconomic conditions lower the age of initial EBV infection, which could be the trigger for Burkitt lymphoma. However, EBV can be isolated in only 10% to 15% of cases of sporadic Burkitt lymphoma. The aforementioned factors play no role in the incidence of other NHL types.

The retrospective studies performed by the International Lymphoma Epidemiology Consortium demonstrated increased NHL risk for patients with a first-degree relative with previous NHL history, a first-degree relative with history of cHL, or a first-degree relative with acute leukemia. Prospective cohort studies confirmed the association of B-cell NHL with a history of lymphoma in first-degree relatives. Unlike cHL, no human leukocyte antigen class I or II alleles were characterized as having NHL risk-modifying effects. Recently, certain genetic variations within or near the candidate genes have been identified. (6)

Similar to cHL, congenital or acquired immune deficiencies are strong risk factors for childhood NHL. Patients with ataxia-telangiectasia, Wiskott-Aldrich syndrome, severe combined immune deficiency, X-linked lymphoproliferative disease, autoimmune lymphoproliferative syndrome, common variable immune deficiency, and X-linked hyperimmunoglobulin (Ig) M syndrome have a 10- to 200-fold increased risk of NHL development. Many children demonstrate evidence of preceding EBV infection. HIV infection is one of the commonest acquired immune deficiencies that increases risk of NHL by more than 150 times. Sjögren syndrome, systemic lupus erythematosus, and hemolytic anemia are associated with increased risk of B-cell lineage NHL, whereas psoriasis was reported to increase the risk for cutaneous T-cell lymphoma by 3.5-fold. Juvenile rheumatoid arthritis and the concomitant use of corticosteroids or other immunosuppressants are also associated with increased NHL risk.

Interestingly, patients who were previously treated for HL are at risk for developing secondary NHL, the risk of which is higher after treatment than that of any other cancer. The biology of such a phenomenon is unclear. Chromosomal instability documented in patients with HL before any therapy might render these patients particularly sensitive to the genotoxic effect of chemotherapy and radiation. Risk of secondary NHL increases after the first 5 years after completion of chemotherapy and persists for decades.

Exposure to various environmental factors prenatally or in early childhood has always been considered one of the putative key elements of lymphomagenesis. Thus, it was found that maternal consumption of heavy liquors (ie, alcoholic beverages other than wine and beer) (7) during pregnancy might be associated with NHL but not HL. However, no statistically significant relationship between

alcohol dose and lymphoma incidence was documented. Preconception paternal smoking but not maternal smoking before or during pregnancy was also observed to be associated with NHL; this had a tendency to increase with the number of cigarettes smoked. However, parental smoking history was not associated with increased frequency of HL. (7) In addition, residential exposure to household pesticides, (8)(9) paternal preconception exposure to organic solvents and petrol exhaust, (10) and in utero exposure to benzene and nitrogen dioxide (11) have been proposed as possible causative factors for lymphoma development.

Similarly, in utero exposure to ionizing radiation (diagnostic radiography, computed tomography [CT]), although extremely rare, has also been suggested to be associated with increased frequency of lymphoma. (12) In contrast, exposure to ionizing radiation in early childhood or exposure to diagnostic ultrasonography in utero has not been found to be associated with increased lymphoma incidence later in life. (12) Exposure to chemotherapy agents used for other malignancies, as discussed previously, also increases the risk of lymphoma development.

Hence, both genetic susceptibility and environmental factors may play a role in the development of lymphoma. However, it is unclear if there is any cross-potential between different factors. It remains to be elucidated whether additional pathogenetic factors, resulting in postnatal genetic alterations, are necessary to trigger lymphomagenesis, as pediatric lymphoma remains an infrequent condition. Similarly, it remains to be studied if active avoidance of exposure to the aforementioned environmental factors could have a prophylactic effect on development of pediatric lymphoma.

CLINICAL PRESENTATION

Lymphoma is traditionally perceived as a malignancy that predominantly involves the lymph nodes (LNs). Whereas this is true for most cases, there are occurrences where lymphoma originates from primary lymphoid tissues (bone marrow and thymus) or various secondary lymphoid tissues other than LN (spleen, mucosa-associated lymphoid tissue) or nonlymphoid organs (skin, bone, brain, lungs, liver, salivary glands, etc). It is extremely important to remember that there are no lymphoma-specific signs or symptoms other than those related to growth of the lymphoma mass. It is also difficult to distinguish HL from NHL solely on the basis of clinical presentation.

Lymphadenopathy in a well-appearing child is always a diagnostic challenge. In many patients, lymphadenopathy is secondary to self-limited transient processes that resolve without interventions (Table 2). Regardless, despite the

TABLE 2. Common Causes of Lymphadenopathy

CAUSE	SOURCE
Infection	Bacterial: <i>Staphylococcus aureus</i> , group A <i>Streptococcus</i> , <i>Brucella</i> spp, <i>Borrelia</i> spp, <i>Bartonella henselae</i> , <i>Francisella tularensis</i> , <i>Mycobacterium</i> spp Viral: Epstein-Barr virus, cytomegalovirus, HIV, herpes simplex virus, human papillomavirus, human herpesvirus-8, measles, rubella Fungal: <i>Histoplasma capsulatum</i> , <i>Cryptococcus</i> spp, <i>Coccidioides</i> spp Protozoan: <i>Toxoplasma gondii</i> , <i>Plasmodium</i> spp
Autoimmune disease	Juvenile rheumatoid arthritis, systemic lupus erythematosus, autoimmune lymphoproliferative syndrome
Storage disease	Gaucher disease, Niemann-Pick disease
Drug reaction	Allopurinol, atenolol, captopril, carbamazepine, cephalosporins, hydralazine, penicillins, phenytoin, quinidine, sulfonamides
Malignancy	Lymphoma, leukemia, solid tumor metastases
Miscellaneous	Postvaccination reaction, Langerhans cell histiocytosis, Kawasaki disease, sarcoidosis, Castleman disease, Kikuchi disease, Rosai-Dorfman disease

relative infrequency of childhood cancers, careful consideration must be made to rule out lymphadenopathy as an initial presentation of malignancy. There is no agreement on what LN size should indicate an abnormality. In pediatric oncology practice, a persistently enlarged LN larger than 1 cm should merit further investigation. However, it also depends on the age of the child, as well as anatomic location. For example, epitrochlear LNs, which are usually not palpable, are considered enlarged if larger than 0.5 cm; inguinal LNs are considered enlarged if larger than 1.5 cm. Localized lymphadenopathy involves a single nodal area; generalized lymphadenopathy involves at least 2 noncontiguous nodal groups. Chronic lymphadenopathy is the LN enlargement that persists for more than 3 weeks.

A diagnostic approach to lymphadenopathy includes the following:

- History: duration, associated symptoms, contact with ill persons, infections, medications, vaccinations, and site of vaccine inoculation (Table 2)
- Physical examination: size, number, anatomic location, pain and/or tenderness, consistency, matting (ie, forming conglomerates that feel and move together during lymph node palpitation), overlying skin changes
- Minimally invasive testing, including the following:
 - Laboratory tests: complete blood cell count; serum lactate dehydrogenase, alkaline phosphatase, uric acid (UA), and C-reactive protein levels; and erythrocyte sedimentation rate
 - Radiologic imaging: chest radiography, LN ultrasonography, CT

The ultimate goal is to determine whether biopsies of LNs should be performed. Patients with unremarkable clinical history and physical examination findings do not require

immediate biopsy; such patients should be re-evaluated in 3 to 4 weeks. Children with chronic or generalized lymphadenopathy or those with new-onset systemic symptoms should be advised to undergo biopsy without delay.

Factors that have high predictive value for the nonbenign nature of lymphadenopathy are as follows (13):

- Age of more than 10 years
- Duration of lymphadenopathy longer than 6 weeks
- LN size larger than 2.5 cm
- Supraclavicular site (left side in particular)
- Matting and limited motility to palpation
- More than 1 noncontiguous LN area involved

HL commonly appears with an LN conglomerate at presentation, which is frequently located in the cervical or supraclavicular area. It is usually painless, unless the mass compresses other anatomic structures, and has “rubbery” firmness, with no inflammatory changes of overlying skin. Involvement of other organs may be symptomatic on the basis of the anatomic compartment: chest discomfort, superior vena cava (SVC) syndrome, tachypnea and orthopnea in the case of large mediastinal masses; abdominal discomfort due to hepatomegaly or splenomegaly or large intra-abdominal tumor; musculoskeletal pains; and headaches or focal neurological signs in cases of CNS involvement.

Constitutional signs include fatigue, anorexia, and so-called B symptoms:

- Fever of at least 100.4°F (38°C) for 3 consecutive days, occurring mostly at night in an undulant pattern and progressively becoming worse (Cardarelli-Pel-Ebstein fever)
- Drenching night sweats
- Unexplained body weight loss of 10% or more over the preceding 6 months

These signs, present in about one-third of patients, usually signify advanced-stage disease and are secondary to inflammatory cytokine release by the tumor. Fever is an independent prognostic factor for bone marrow involvement. The “B symptoms” are uncommon in patients with NLPD HL. Absence of “B symptoms” does not rule out HL.

NHL clinical presentation greatly varies because of biological difference of distinct NHL variants, and depends on the NHL type; any organ, tissue, and anatomic area can be involved. Unlike HL, NHL frequently manifests with a rapidly enlarging mass (Burkitt lymphoma doubling time is approximately 5 days vs approximately 30 days for HL). The most common presenting sites are the abdomen, the head and neck region (parotid glands, Waldeyer ring of lymphoid tissue, cervical LN), and the mediastinum; bones, kidneys, and skin may also be involved. Gonadal involvement is present in approximately 5% of cases, with no sex-related differences. CNS and bone marrow involvement are more common than in patients with HL; these patients require more intensive treatment to attain the same survival rate. The bone marrow involvement in patients with Burkitt lymphoma and lymphoblastic lymphoma may become a source of diagnostic confusion; patients with fewer than 25% lymphoma cells in the bone marrow are still considered to have Burkitt lymphoma or lymphoblastic lymphoma, whereas those who have at least 25% bone marrow lymphoma cells will be classified as having the Burkitt type or acute lymphoblastic leukemia with extramedullary disease, respectively.

ONCOLOGIC EMERGENCIES IN NEWLY DIAGNOSED LYMPHOMA

Children with newly diagnosed lymphoma may present with life-threatening conditions that necessitate immediate therapeutic interventions:

- Anterior mediastinal mass presenting as SVC syndrome, airway obstruction, or pleural effusion with resultant acute cardiorespiratory insufficiency
- Abdominal masses complicated with intestinal obstruction, intussusception, inferior vena cava syndrome, ureteral obstructions, or postrenal failure
- CNS lymphoma manifesting with cranial nerve palsies, spinal cord compression, or lymphomatous meningitis
- Metabolic derangements due to rapid tumor cell breakdown in the settings of compromised renal function, also known as tumor lysis syndrome (TLS)

Other infrequent life-threatening conditions are acute hemolytic anemia and coagulopathy. This review will focus only on the most frequent oncologic emergencies.

Respiratory distress (stridor, shortness of breath, orthopnea) is a frequent initial presentation of a rapidly enlarging mediastinal mass. When children initially present to a pediatrician’s office with these signs, the frequent first therapeutic interventions are β -adrenergic agonists and glucocorticoids. Since lymphoma cells are exquisitely sensitive to glucocorticoids, the rapid tumor size reduction, followed by transient symptomatic improvement, can soon be seen. It has to be remembered that therapy with glucocorticoids in a patient with atypical presentation (asymmetrical chest wall anatomy and excursion, as well as asymmetrical air entry, concomitant neck vein distention, lymphadenopathy, and other systemic signs or symptoms, including “B symptoms”) should be preceded by chest radiography, which might demonstrate the mediastinal mass with or without pleural effusion (Fig 2).

SVC syndrome appears at presentation with dilated neck veins, asymmetrical facial swelling, plethora, and altered mental status; children with SVC syndrome are at high risk for venous thrombosis and strokes.

For patients with the aforementioned conditions, (a) emergency cytoreduction chemotherapy with prednisone or cyclophosphamide or (b) radiation therapy should be initiated. The staging and diagnostic evaluation, including tumor biopsy, can be completed within 48 to 72 hours from onset of the treatment; the quality of the specimen will not be substantially compromised, but the risk of severe cardiorespiratory morbidity would be markedly reduced.

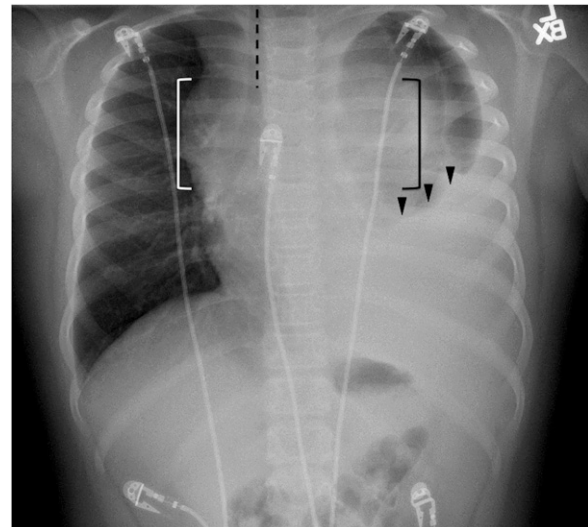


Figure 2. A chest radiograph of a 8-year-old male with newly diagnosed NHL is shown. The child was initially treated with nebulized albuterol and enteral prednisolone for presumed exacerbation of reactive airway disease. The black and white brackets indicate a mediastinal mass; the dashed vertical line highlights the airways that deviate from midline; the arrowheads indicate left hemithorax pleural effusion.

Cranial nerve or spinal cord compression (direct invasion occurs rarely) appears at presentation with focal neurological deficits, paraplegias, or generalized convulsions; emergency chemotherapy or surgical decompression via vertebral laminectomy and intracanal tumor resection are therapeutic alternatives.

TLS is a life-threatening condition that can be seen in patients with Burkitt lymphoma, diffuse large B-cell lymphoma, and B-cell lymphoblastic lymphoma—that is, neoplasms with both high proliferation rate and large tumor burden. TLS occurs when the intracellular components of the tumor cell cytoplasm (nucleic acids, which are metabolized into UA, phosphorus, and potassium) are released into the blood after the lymphoma cell breakdown, either spontaneously or after the onset of treatment. Under normal physiological circumstances, these substances are excreted in the urine. In patients with bulky lymphomas, the amount of the released content overwhelms the excretory kidney capacity. This becomes an even greater problem when the kidneys are already infiltrated by malignant cells or compressed by the intra-abdominal tumor. The acute kidney injury, which leads to progressively worsening electrolyte and fluid imbalance, is the pathogenetic cornerstone of TLS.

The distinction should be made between laboratory TLS and clinical TLS. Laboratory TLS is asymptomatic metabolic disarray; it includes 2 or more of the following, occurring simultaneously within 3 days prior to and up to 7 days after therapy onset (14):

- Hyperuricemia (>8.0 mg/dL [>475.88 μ mol/L])
- Hyperkalemia (>6.0 mmol/L)
- Hyperphosphatemia (>4.5 mg/L)
- Hypocalcemia (corrected calcium <7.0 mg/dL [<1.75 mmol/L], ionized calcium <1.12 mg/dL [<0.28 mmol/L]).

Unlike all other abnormalities, hypocalcemia results from excess of serum UA and phosphorus precipitating calcium into calcium urate and calcium phosphate crystals in the kidneys. The clinical TLS is laboratory TLS, along with laboratory and clinical evidence of end-organ damage, including neuromuscular symptoms secondary to hypocalcemia, uremia, increased creatinine level, oliguria, hypertension, cardiac dysrhythmia, pulmonary edema, altered mental status, seizures, and death.

It should be assumed that any patient with lymphoma is at high risk for TLS, especially before the histopathologic variant and the extent of the disease are established. Serum lactate dehydrogenase level can be regarded as the surrogate marker of the tumor bulk; patients with lactate dehydrogenase level more than 2 times the upper limit of normal are at high risk for TLS. Once the histologic variant is confirmed, the patients may be restratified according to risk: Burkitt

lymphoma, diffuse large B-cell lymphoma, and B-cell lymphoblastic lymphoma are the conditions with high risk for TLS, whereas anaplastic large-cell lymphoma and HL are the conditions with low risk for TLS.

TLS management should be initiated without delay. The evolution of TLS must be monitored via serial measurement of serum potassium, creatinine, UA, calcium, and phosphorus levels. In the absence of any electrolyte disarrays, all patients must receive prophylactic therapy with xanthine oxidase (the rate-limiting enzyme that metabolizes purines into UA) inhibitors allopurinol or febuxostat, as well as intravenous hydration to facilitate removal of the breakdown metabolites by urine. Until recently, aggressive urine alkalinization was recommended to prevent tubular precipitation of calcium urate crystals; nowadays, this practice is discouraged, since calcium phosphate, as well as hypoxanthine and xanthine (intermediate metabolites of nucleic acid degradation, increased in concentration when allopurinol is used) are poorly soluble in the alkalinized urine. Hence, the neutral or minimally alkalinized urine pH level is preferred.

Patients who demonstrate a picture of laboratory TLS must be treated more aggressively to prevent organ damage. Rasburicase, the recombinant urate oxidase, is used to rapidly degrade UA in serum. It is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency. Because rasburicase does not inhibit UA formation, it should be administered in parallel with allopurinol.

Hyperkalemia should be treated aggressively, as it may precipitate fatal arrhythmia. Bedside electrocardiographic monitoring must be established without delays. Serum potassium concentration above 5.5 mEq/L (5.5 mmol/L) is associated with myocardial repolarization abnormalities. Peaked T waves on an electrocardiogram are the earliest sign of hyperkalemia. Serum potassium level higher than 6.5 mEq/L (6.5 mmol/L) is associated with imminent paralysis of the atria and manifests as progressive P wave widening and flattening, as well as PR segment lengthening. Calcium gluconate should be administered promptly to protect myocardial excitability. Other pharmacological interventions to decrease potassium concentration in serum must also be implemented, including administration of β -adrenergic agonists (inhaled or enteral), insulin and sodium bicarbonate (both intravenous) to shift potassium into the intracellular compartment, loop diuretics (intravenous; may not be feasible in patients with kidney lymphomatous infiltration), and sodium polystyrene sulfonate (enteral) to facilitate renal or intestinal potassium excretion.

Hyperphosphatemia is managed by limiting the dietary phosphorus absorption (calcium acetate, sevelamer).

Hypocalcemia does not need to be managed pharmacologically unless the patient is symptomatic; serum calcium level usually normalizes once the UA and phosphorus concentrations are under control. Patients with clinical TLS and renal failure require hemodialysis, which improves hyperkalemia, azotemia, and fluid balance.

APPROACHES TO DIAGNOSIS

As mentioned previously, there are no lymphoma-specific signs or symptoms, laboratory tests, or imaging tests. Hence, the differential diagnosis can be broad and includes infectious, autoimmune, and lymphoproliferative disorders, as well as nonspecific reactive conditions (Table 2). Only pathomorphologic evaluation of the tissue (excisional biopsy is preferred over fine-needle aspiration or core-needle biopsy, as it allows evaluation of the histologic architecture of the LN or tumor) can be used to reliably establish the diagnosis. Additional tests may be used to identify all body sites involved, stratify the disease risk, and assign correct treatment. Table 3 summarizes suggested investigations.

LYMPHOMA THERAPY: RISK- AND RESPONSE-ADAPTED THERAPEUTIC APPROACHES

When patients with limited disease (serum lactate dehydrogenase concentration increase less than two-fold above upper normal limit; lower stage, Table 4) and rapid early response to initial chemotherapy (as determined by tumor viability and/or size decrease measured with fluorine 18 (¹⁸F) fluorodeoxyglucose positron emission tomography/CT) receive less intensive treatment, this usually results in unprecedented reduction of the treatment-related adverse

effects while maintaining a high survival rate (>85%) in the patients with lymphoma across all age groups. (15)(16)

Multiagent chemotherapy is the mainstay of treatment for both HL and NHL; it is based on the clinical protocols proven to be effective in multi-institutional clinical trials. The protocols differ in the number (4)(5)(6)(7)(8) and duration (21–28 days) of cycles, various agents used together, doses of the agents, and frequency of their use within the cycle. There may be some variability between the cycles within 1 protocol, too. Traditionally, chemotherapy is delivered during the first 8 to 15 days; the remainder of the days within the cycle is allowed for recovery from treatment-related immediate (nausea, vomiting, fatigue, fever, etc; 1–2 days from receiving the drug) and prompt (suppressed blood cell counts, loss of appetite, mucositis, diarrhea, constipation, etc; 1–2 weeks) side effects. Late side effects (any time after completion of the therapy) are discussed herein. Lymphoblastic lymphomas are treated by using acute lymphoblastic leukemia protocols, which are completely different. All patients undergoing chemotherapy receive prophylactic therapy with antifungal azoles and with trimethoprim/sulfamethoxazole or pentamidine for *Pneumocystis jirovecii*. In addition, patients frequently require blood product (packed red blood cells, platelets) transfusions, as well as granulocyte colony-stimulating growth factor (for neutrophil recovery) and recombinant human keratinocyte growth factor (palifermin, for treatment-induced mucositis) support to ensure uncomplicated transition through the treatment cycles.

Radiation therapy plays an important role in the treatment of HL but is reserved for patients who did not demonstrate rapid response after the first several chemotherapy cycles. It is administered only to areas initially

TABLE 3. Recommended Investigations for Lymphoma Evaluation

STUDY TYPE	PROTOCOL
Laboratory studies	Complete blood cell count, renal and liver function tests Erythrocyte sedimentation rate; C-reactive protein, uric acid, lactate dehydrogenase, and alkaline phosphatase levels
Imaging studies	Chest radiography, posteroanterior and lateral views Computed tomography of the neck, chest, abdomen, and pelvis Magnetic resonance imaging of the brain, abdomen, and pelvis Fluorodeoxyglucose positron emission tomography/computed tomography, whole body
Staging tests	Bone marrow biopsy: uniformly for patients with non-Hodgkin lymphoma Patients with classic Hodgkin lymphoma, patients with extensive disease and skeletal involvement by fluorodeoxyglucose positron emission tomography/computed tomography Cerebrospinal fluid studies, only for patients with non-Hodgkin lymphoma
Miscellaneous	Pulmonary function tests, electrocardiography, echocardiography Fertility preservation (sperm banking, ovarian tissue cryopreservation)

TABLE 4. **Pediatric Lymphoma Clinical Staging**

STAGE	HODGKIN LYMPHOMA ANN ARBOR STAGING	NON-HODGKIN LYMPHOMA ST JUDE CHILDREN'S RESEARCH HOSPITAL (MURPHY) STAGING
I	Single lymphatic site or localized single extralymphatic site without regional LN involvement	Single tumor or LN involvement outside of the abdomen and mediastinum
II	≥2 LN regions on the same side of the diaphragm or Localized single extralymphatic site with regional LN involvement on the same side of the diaphragm	Single tumor with regional LN involvement or ≥2 sites on one side of the diaphragm or Primary gastrointestinal tract tumor (completely resected) with or without regional LN involvement
III	LN involvement on both sides of the diaphragm or Localized extralymphatic extension with adjacent LN involvement or Spleen	Tumors or LN involvement on both sides of the diaphragm Primary intrathoracic tumor or primary intra-abdominal disease Paraspinal or epidural tumors
IV	Diffuse involvement of ≥1 extralymphatic site with or without associated LN involvement or with involvement of distant site(s) or Liver, bone marrow, lungs, central nervous system	Bone marrow or central nervous system, with or without any other sites involved

LN=lymph node.

“affected by lymphoma” (so-called involved field radiation), which allows minimizing the exposure of the whole body. Both noncorpuscular (photon) and corpuscular (proton) radiation can be used. For NHL, radiation therapy is used infrequently, usually in patients with lymphoma refractory to first- and second-line therapies and with primary CNS lymphomas. It remains an emergency treatment of choice in patients who present with SVC syndrome, spinal cord compression, and large splanchnic tumors that cause pain or obstruction. The commonest immediate and prompt side effects are radiation-induced dermatitis, transient myelosuppression, malaise, nausea, diarrhea, and xerostomia.

Surgery, in contrast to chemotherapy and radiation therapy, has a limited role in lymphoma treatment. Only patients with stage I NLPD HL and stage I (nodal) and II (primary gastrointestinal) Burkitt lymphoma and anaplastic large-cell lymphoma benefit from primary tumor excision. However, these patients still require chemotherapy and/or radiation therapy to attain stable remission. Total splenectomy, which was used in the past for staging and therapeutic purposes, used to result in overwhelming and frequently fatal infections (17); nowadays, it is not a treatment of choice. Instead, the radiation therapy or low-intensity chemotherapy can be used to attain rapid size reduction and symptomatic relief in patients with extreme splenomegaly.

Hematopoietic stem cell transplantation (HSCT) plays an important role in the therapy of both HL and NHL. It is used in conjunction with second- and third-line therapies for primary treatment-resistant or recurrent lymphoma; HSCT facilitates hematopoietic recovery after highly intensive

chemotherapy and mediates remission consolidation via graft-versus-lymphoma effect, when the cells of the recovered immune system perform immunologic surveillance and destroy residual microscopic lymphoma. Autologous HSCT involves the use of patients’ own hematopoietic stem cells harvested from peripheral blood between chemotherapy cycles after the hematopoietic stem cells’ mobilization with granulocyte colony-stimulating factor with or without plerixafor, a reversible CXCR4 chemokine receptor antagonist that allows the release of hematopoietic stem cells from the bone marrow. Patients with lymphoma who undergo autologous HSCT benefit primarily from accelerated hematologic recovery after extremely aggressive chemotherapy. Autologous HSCT is a preferred stem cell–based therapy for pediatric patients with lymphoma. In contrast, the allogeneic HSCT involves the use of hematopoietic stem cells from human leukocyte factor–matched related or unrelated donors; the source of the hematopoietic stem cells can be either peripheral blood or bone marrow. In addition to hematologic reconstitution, the stem cell–derived immune cells can recognize the residual lymphoma cells as “foreign” and effectively destroy them. This type of HSCT is used for treatment of aggressive, treatment-refractory, and relapsed lymphomas. Patients whose disease progresses after autologous HSCT may still benefit from allogeneic HSCT.

As expected, HSCT-related toxicities uniquely depend on the donor type; allogeneic HSCT is frequently complicated with graft-versus-host disease, when recovered immune cells attack the recipient’s body cells as “foreign.” Therapy for graft-versus-host disease requires prolonged

immunosuppression to mitigate immunologic attack of the recipient's body by alloreactive cytotoxic T-cells. However, the same mechanism underlies the curative graft-versus-lymphoma effect. Patients who undergo autologous HSCT can also develop graft-versus-host disease; however, this disease is milder and has unique clinicobiological characteristics.

Biological therapy has truly revolutionized lymphoma treatment. It involves the use of principles of selective targeting of neoplastic cells that share unique biological characteristics that are distinct from other normal cells. Lymphoma cell antigen-specific monoclonal antibodies and cytotoxic T-cells, as well as small molecules that target intracellular signaling pathways, are now in use. Monoclonal antibodies that target CD19 (denintuzumab mafodotin [CD19a antibody-cytotoxic drug conjugate]; blinatumomab [CD19/CD3 bispecific T-cell engager]), anti-CD20 monoclonal antibodies (rituximab, ofatumumab, obinutuzumab), and anti-CD30 monoclonal antibody (brentuximab vedotin antibody-cytotoxic drug conjugate) are used either as single agents or in combination with conventional chemotherapy. The mechanisms of killing lymphoma cells with the aforementioned biological agents involve direct cytotoxic effect, as well as engaging the activated immune cells to mediate lymphoma cell killing.

There are many other agents that demonstrated effectiveness in preclinical trials but have not yet been included in major pediatric lymphoma protocols. Nivolumab and pembrolizumab, the antagonists of programmed cell death receptor 1—stimulation of which results in intratumoral immune suppression—hold particularly strong clinical promise.

Chimeric antigen receptor (CAR) cytotoxic T-cells, which are capable of recognizing and selectively killing CD19-, CD20-, and CD30-expressing lymphoma cells (ie, virtually all HL and NHL subvariants), are the culmination of targeted immune therapy of lymphoma. The T lymphocytes, harvested from either the patient or a donor via leukapheresis, are transfected in vitro with the virus vector-carrying gene sequence encoding an artificial chimeric receptor that enables high affinity and specificity binding to CD19, CD20, and CD30 antigens on the lymphoma cell surface. The CAR T-cells become activated upon encountering the CD19-, CD20-, or CD30-expressing lymphoma cells, and mediate the lymphoma cell killing in a selective fashion. Of practical importance, the activated CAR T-cells produce large quantities of proinflammatory cytokines (interferon- γ , interleukin-6, interleukin-10), which may lead to the development of toxic side effects that manifest as high fever, myalgia, hypotension, capillary leak and pulmonary edema, cardiac dysfunction,

renal and hepatic failure, and disseminated intravascular coagulation.

The CAR T-cells are most effective in the setting of minimal residual disease and are used for treatment of relapsed lymphomas that are resistant to conventional therapies.

DISEASE SURVEILLANCE AFTER THERAPY COMPLETION

After therapy completion, every 3 months for the first year, patients undergo complete physical examination and laboratory testing (complete blood cell count; comprehensive metabolic panel; erythrocyte sedimentation rate; and C-reactive protein and lactate dehydrogenase levels), in addition to ^{18}F fluorodeoxyglucose positron emission tomography/CT (or just CT). The disease surveillance should be performed every 4 months during the second and third years and every 6 months thereafter until 5 years after therapy, by conducting physical examination and laboratory blood tests. Imaging should be performed only if clinically indicated, given the increasing awareness of the potential risks related to imaging-related radiation exposure. After 5 years, the patients usually follow up with the oncologist at a dedicated long-term follow-up clinic semiyearly. Additional screening tools (echocardiography, pulmonary function tests) aim at timely detection and treatment of the side effects summarized herein.

LATE EFFECTS OF THERAPY

Due to the high rate of cure of lymphoma, the likelihood of treatment-related long-term side effects is considerably high, as well. Much of what is seen today is the result of treatment approaches used in the past; fewer side effects are expected in patients who receive therapy with current protocols. The risk-adapted approaches allow for substantial reduction in exposure to radiation, whereas they introduce some novel therapies upfront. Since these novel therapies are not side effect free, we have yet to learn what the long-term consequences would be. All patients must be screened for late-onset side effects (Table 5) during their follow-up visits. A multidisciplinary (endocrinology, cardiology, etc) approach must be used to provide care for patients with organ-specific side effects.

Premature gonadal failure and infertility are always a big concern. Owing to differences in chemotherapy agents and regimens, fertility in patients with HL is affected more frequently than in patients with NHL. The rate of infertility after chemotherapy is higher in male patients than in female patients and demonstrates dose dependence for certain agents (cyclophosphamide, procarbazine). (18) Regardless,

TABLE 5. Therapy-related Late Side Effects

LATE EFFECT	RADIATION THERAPY	CHEMOTHERAPY
Musculoskeletal side effect	Yes	No
Cardiovascular side effect	Yes	Anthracyclines
Pulmonary side effect	Yes	Bleomycin
Hypersplenism and hypogammaglobulinemia	Splenic irradiation	Rituximab immunotherapy
Thyroid dysfunction	Yes	No
Female gonadal dysfunction	Yes	Yes
Premature ovarian failure	Yes	Alkylating agents
Male infertility	Irradiation of inguinal and pelvic areas	Alkylating agents Procarbazine
Myelodysplastic syndrome and secondary leukemia		Cyclophosphamide, ifosfamide, dacarbazine, procarbazine, etoposide
Secondary cancers (breast, thyroid)	Yes	Yes

every patient with lymphoma should be counseled for sperm banking or egg harvesting and/or ovarian tissue cryopreservation. If gamete procurement is not feasible, administration of leuprolide, the gonadotropin-releasing hormone agonist, to adolescent female patients before or during chemotherapy may also be used; it results in a significantly lower rate (approximately 10%) of premature ovarian failure. At the same time, the use of leuprolide, with or without testosterone, results in sperm count recovery in fewer than 20% of male patients.

Secondary malignancies are a devastating late side effect of lymphoma treatment. Death from secondary malignancies is the second leading cause of mortality after death from the primary disease. Similar to infertility, it occurs more frequently in patients with HL (cumulative risk up to 25%) than in patients with NHL (cumulative risk, 2%–5%) and depends on the therapy that the patient received. Acute leukemia, NHL, and lung cancer are the commonest secondary malignancies in patients with HL who underwent chemotherapy alone; breast cancer becomes the leading secondary malignancy in female patients treated with a combination of chemotherapy and radiation therapy. Acute myelogenous leukemia is the most frequent secondary malignancy in patients with NHL. The peak period of secondary malignancy risk is between 5 and 9 years after therapy but may extend beyond 25 years for patients who underwent concomitant chemotherapy and radiation therapy.

Infection is another cause of morbidity of patients with lymphoma, primarily due to lymphopenia and hypogammaglobulinemia secondary to intensive chemotherapy, spleen irradiation, (19) and biotherapy selectively targeting B-cells. (20) All patients with lymphoma must receive yearly

inactivated influenza vaccine between the chemotherapy cycles, provided they do not have absolute severe leukopenia ($<0.2 \times 10^9/L$). It remains a rule not to administer any live vaccines (measles, mumps, rubella, varicella, live attenuated influenza, rotavirus) during this period. If spleen irradiation is planned, the patient should receive vaccination for *Streptococcus pneumoniae* and meningococcal infections at least 2 weeks before radiation therapy. At treatment completion, the patients should be tested for IgG titers against hepatitis B, measles/mumps/rubella, and *S pneumoniae*. Interestingly, many patients selectively lose their IgG titers to hepatitis B and components of measles, mumps, and rubella. Repeat vaccination is recommended when lymphopenia improves. Patients who received rituximab frequently demonstrate profound hypogammaglobulinemia, which is treated with intravenous IgG.

Cardiovascular morbidity, which most frequently manifests as myocardial infarction or valvular structural changes, is prevalent in lymphoma patient survival, as much as 45.5% (95% confidence interval, 36.6%–54.3%); high-dose radiation therapy but not exposure to anthracyclines is associated with the most severe complications. (21)

CONCLUSIONS AND FURTHER DIRECTIONS

Advances in understanding of cellular biology of lymphoma, a risk-adapted approach to therapy, refining of elements of supportive care, and use of novel therapeutics results in outstanding survival outcomes for patients with lymphoma. However, many important questions have yet to be answered. Clarification of interaction of genetic predisposition to

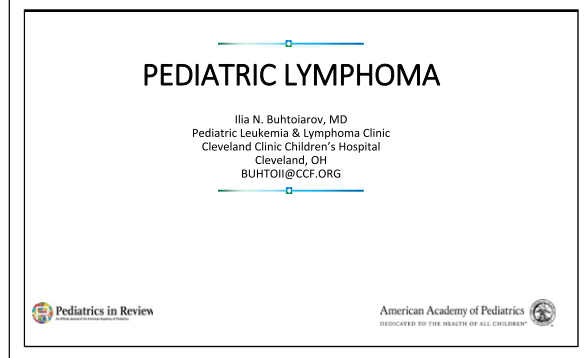
lymphoma and environmental factors merits further investigations. Rapid development of the concept of precision medicine and targeted cancer therapy widens the potential of making lymphoma therapy even more efficient, with potentially minimal late side effects.

- On the basis of strong research evidence (level A) in the form of multiple clinical studies, treatment of patients with lymphoma with contemporary protocols results in fewer treatment-related side effects; however, these late adverse effects require life-long monitoring and multidisciplinary medical management. (17)(18)(19)(20)(21)

Summary

- On the basis of strong research evidence (level A) in the form of numerous epidemiological retrospective studies, (2)(4)(5)(6)(7)(8)(9)(10)(11)(12) both inherited genetic predisposition and exposure to various potentially genotoxic environmental factors may contribute to increased incidence of lymphoma in children.
- On the basis of strong research evidence (level A) in the form of published reports of thorough analysis of lymphadenopathy-associated signs and symptoms, (13) certain lymph node clinical features could be predictive of a possible malignant process. However, it remains to be understood that there are no absolute lymphoma-specific symptoms or signs. Of utmost importance, absence of systemic symptoms does not rule out the diagnosis of lymphoma.
- On the basis of strong research evidence (level A) in the form of multiple clinical observations, tumor lysis syndrome, either spontaneous or treatment induced, remains one of the commonest emergency presentations of lymphoma. (14)

To view teaching slides that accompany this article, visit <http://pedsinreview.aappublications.org/content/38/9/410.supplemental>.



References and Suggested Readings for this article are at <http://pedsinreview.aappublications.org/content/38/9/410>.

Additional Resources for Pediatricians

AAP Textbook of Pediatric Care, 2nd Edition

- Chapter 225: Cancers in Childhood - <https://pediatriccare.solutions.aap.org/chapter.aspx?sectionid=124994555&bookid=1626>

Point-of-Care Quick Reference

- Cancers in Childhood - <https://pediatriccare.solutions.aap.org/content.aspx?gbosid=165492>

Parent Resources from the AAP at HealthyChildren.org

- <https://www.healthychildren.org/English/health-issues/conditions/cancer/Pages/Childhood-Cancer.aspx>

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at <http://patiented.aap.org>.

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1. A 14-year-old African American female adolescent presents to your office with fever, weight loss, and neck swelling. Her father is concerned because his brother recently received a diagnosis of non-Hodgkin lymphoma (NHL) at 48 years of age after a similar presentation. The patient's past medical history includes systemic lupus erythematosus, which was initially managed with corticosteroids; asthma, for which she has undergone multiple chest radiographic examinations; and recurrent ear infections during early childhood. Which of the following factors is most likely to increase the risk for development of NHL in this child?
 - A. Ethnicity.
 - B. Exposure to diagnostic radiography in childhood.
 - C. Family history of lymphoma.
 - D. History of autoimmune disease.
 - E. History of recurrent infections.
2. A 7-year-old boy presents to your office with a mass near his neck. His mother first noticed the mass when he received a diagnosis of group A streptococcal pharyngitis 1 month ago. Since then, the mass has doubled in size. There is no history of fever, night sweats, or weight loss. On physical examination, the patient is well appearing and in no distress. There is a 2-cm nontender, fixed lymph node (LN) in the left supraclavicular region. There are no other enlarged LNs observed. Which of the following factors is most predictive of the nonbenign nature of lymphadenopathy in this child?
 - A. Age of the patient.
 - B. Duration of LN enlargement.
 - C. Lack of lymphadenopathy in other areas.
 - D. Location of lymphadenopathy.
 - E. Size of the LN.
3. A 16-year-old male adolescent presents to the emergency department with fever and respiratory distress. He has had intermittent fever for several weeks and 20-pound weight loss. On physical examination, he is lethargic and has decreased breath sounds on the right side, with ipsilateral neck vein distention and facial swelling. Which of the following is the most likely cause of the neck and facial findings in this patient?
 - A. Bacterial lymphadenitis.
 - B. Pulmonary embolism.
 - C. Septic thrombophlebitis.
 - D. Superior vena cava syndrome.
 - E. Tumor lysis syndrome (TLS).
4. A 7-year-old boy, who is a recent refugee from the Congo, presents with fever for 1 week and a 10-cm jaw mass. You suspect Burkitt lymphoma and order initial laboratory tests. Which of the following findings is most consistent with TLS?
 - A. Decreased serum uric acid level and increased lactate dehydrogenase level.
 - B. Hyperkalemia, hypocalcemia, and increased creatinine level.
 - C. Hyperleukocytosis, anemia, and thrombocytopenia.
 - D. Increased erythrocyte sedimentation rate and C-reactive protein and alkaline phosphatase levels.
 - E. Increased liver transaminase and serum bilirubin levels.

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5. A 15-year-old male adolescent has just completed therapy for stage 2 Hodgkin lymphoma with rapid early response and is now in remission. Which of the following late effects is he at the highest risk for experiencing?
- A. Graft-versus-host disease due to hematopoietic stem cell transplantation.
 - B. Growth failure due to radiation therapy.
 - C. Infertility due to chemotherapy.
 - D. Secondary leukemia due to immunotherapy.
 - E. Sepsis due to splenectomy.
-

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