

Facts About Lymphoma

Introduction

The lymphomas are a diverse group of blood cancers broadly categorized into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Significant distinctions between these two entities in clinical features, signs and symptoms, and prognosis translate into important differences in treatment strategy, supportive care, outcomes, and survivorship needs. This Leukemia & Lymphoma Society (LLS) Fact Sheet provides a practical overview of lymphoma incidence and survival trends, classification, risk factors, clinical features, diagnosis and workup, treatment, and the management of treatment-related side effects. This fact sheet also provides details on the expected long-term and late effects of therapy, as well as a broader overview of survivorship needs in the years and even decades following diagnosis and treatment. Resources from LLS and other organizations that provide quality information on lymphomas are also included. With these resources, healthcare providers can help support lymphoma patients and their families and caregivers not only through diagnosis and treatment but also through years and often decades of survivorship.

Highlights

- Approximately 5% of all cancer diagnoses are some subtype of lymphoma, most of which originate from B cells, though some originate from T or natural killer (NK) cells.
- Nearly 90% of cases are non-Hodgkin lymphoma (NHL), of which there are numerous subtypes, though the two most common are diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).
- The majority of Hodgkin lymphoma (HL) cases (about 95%) are “classic” HL, of which the nodular sclerosis subtype is the most common.
- Lymphoma risk factors depend on the subtype but can include age, sex, specific infections, immunodeficiency, underlying autoimmune diseases, chemical exposure, and family history (although genetic screening of relatives is neither actionable nor recommended).
- Patients with lymphoma often present with adenopathy (lymph node swelling) and may have fever, night sweats, and unexplained weight loss.
- A key first step in evaluating the patient is a core, incisional, or excisional biopsy of the lymph nodes to obtain a definitive pathologic diagnosis.
- Treatment approaches vary substantially based on lymphoma subtype and other factors. However, the foundation of initial therapy for many patients is combination chemotherapy with immunotherapy, sometimes with radiation.
- Patient outcomes are improving due to the introduction of novel therapies such as CAR T-cell therapy, bispecific antibodies, and antibody-drug conjugates.
- Lymphoma patients may experience a wide variety of treatment-related side effects ranging from mild to severe and life-threatening.
- Patients may also experience long-term side effects that persist for years, as well as late effects that may appear years or decades later, such as heart disease and secondary cancers.
- Fertility issues are critically important for patients and providers to discuss, as some treatments can affect an individual’s ability to conceive.
- More people than ever are surviving lymphoma. Healthcare providers need to recognize the challenges lymphoma survivors face and intervene early to improve physical health, psychosocial well-being, and quality of life.

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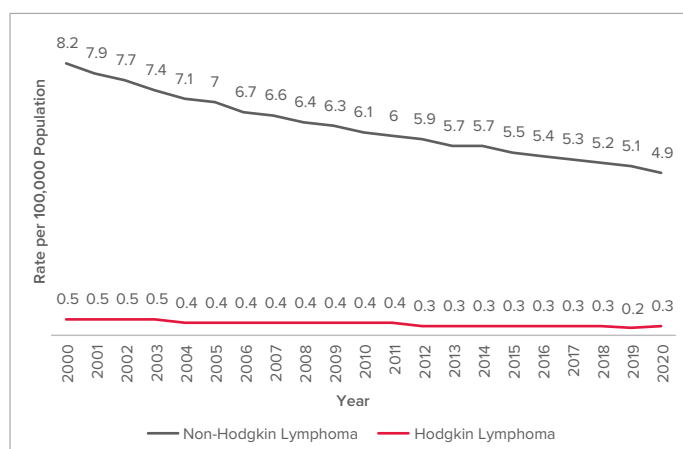
Overview of Lymphomas

The term “lymphoma” refers to a heterogeneous group of hematologic malignancies characterized by the clonal proliferation of lymphocytes. Collectively, lymphomas account for approximately 5% of all cancer diagnoses.¹ Many lymphomas originate from B cells, though some subtypes arise from T cells or natural killer (NK) cells. These malignancies are classified as either Hodgkin lymphoma (HL) named after Dr. Thomas Hodgkin, who in 1832 described several cases of patients with cancer involving the lymph nodes and spleen,² or non-Hodgkin lymphoma. Nearly 90% of lymphoma cases are NHL, while about 10% are HL.¹ Altogether, there were an estimated 80,550 new cases of NHL and 8,830 cases of HL in the United States in 2023.¹

While NHL and HL are similar in many respects, important differences exist in histopathology, stage at diagnosis, prognosis, and treatment. The primary differentiator between NHL and HL is the presence of Reed-Sternberg lymphocytes, which are the hallmark of HL.³ Patients with HL are often diagnosed with earlier-stage disease, whereas NHL cases tend to be more advanced at diagnosis.^{4,5} Finally, treatment approaches for NHL and HL are overwhelmingly similar with substantial differences in standards of care depending on the subtype, as discussed later in this fact sheet.

Due to improvements in therapy and supportive care, prognosis has improved and many patients are living longer with lymphoma. Survival rates for both NHL and HL have seen remarkable increases in recent decades. These improvements are clear in age-adjusted death rates for NHL, which fell by an average of 2.2% per year from 2011 to 2020; death rates for HL, already quite low in comparison to NHL, dropped an average of 4.0% per year during that same 10-year period (see Figure).^{4,5}

Figure 1. Trends in Death Rates for Non-Hodgkin Lymphoma and Hodgkin Lymphoma, 2000-2020



Source: National Cancer Institute, Cancer Stat Facts. Accessed December 2, 2023.

Lymphoma Classification

To date, more than 90 subtypes of NHL have been identified, though many are extremely rare. These and other NHL subtypes are broadly outlined in the World Health Organization Classification of Hematolymphoid Tumors.⁶ Two subtypes account for more than 50% of cases, namely, diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (FL).⁷ The NHLs can also be differentiated in terms of the rate of progression: either aggressive (also known as high grade), such as DLBCL; or indolent, meaning slow-growing (also known as low grade), meaning slow-growing (such as FL). The most common aggressive NHL is DLBCL, accounting for an estimated 31% of all cases, and the most common indolent NHL is FL, accounting for an estimated 22% of cases (Table 1).

Subtypes can also be classified by cell of origin; about 85% to 90% of NHLs are due to clonal proliferation of B cells, while 10-15% derive from T or NK cells.⁸ The more common and notable NHL subtypes and their defining characteristics are described in Table 1.

In contrast to NHL, HL classification is considerably simpler. About 95% of cases are categorized as classic HL (cHL), and about 5% are nodular lymphocyte-predominant HL (NLPHL). Classic HL further breaks down into four different subtypes, the most common of which is nodular sclerosis HL, accounting for about 70% of cases in developed countries.⁹ All subtypes are more common in males than in females except for nodular sclerosis HL, where the sex distribution is roughly equal. Further details on HL subtypes and their characteristics are provided in Table 2.

Table 1. Common Non-Hodgkin Lymphoma Subtypes

Subtype	% of NHLs*	Features/Characteristics	Most Common in:
B-Cell Lymphomas (Aggressive)			
Diffuse Large B-Cell Lymphoma (DLBCL)	31%	<ul style="list-style-type: none"> Divided into 2 subtypes by immunohistochemistry: GCB and non-GCB Patients usually present with advanced-stage disease Aggressive, but responsive to treatment and often curable 	<ul style="list-style-type: none"> Older adults (median age at diagnosis in mid-60s) Young women (for DLBCL subtype, primary mediastinal B-cell lymphoma)
Mantle Cell Lymphoma (MCL)	6%	<ul style="list-style-type: none"> Develops in one of the outer edges of a lymph node follicle (the mantle zone) Patients usually present with advanced-stage disease Often classified as aggressive but also has an indolent variant Most aggressive variants can be treated successfully with prolonged remission Indolent variants may be appropriate for surveillance 	<ul style="list-style-type: none"> Males Individuals over 60 years of age
Burkitt Lymphoma (BL)	2%	<ul style="list-style-type: none"> Three major subtypes include endemic (localized to Africa), sporadic, and immunodeficiency-related, though EBV+ cases across subtypes are genetically similar Endemic form is associated with EBV and malaria; typically found in Africa Sporadic form is more common, and not linked to EBV; mostly seen in North America and Europe Highly aggressive but also highly responsive to chemoimmunotherapy 	<ul style="list-style-type: none"> Children and young adults Peak in older patients
B-Cell Lymphomas (Indolent)			
Follicular Lymphoma	22%	<ul style="list-style-type: none"> Originates from germinal/follicular center B cells Usually indolent, though some can progress rapidly May transform into more aggressive DLBCL Often responds to treatment but tends to relapse Overall survival now likely approximates the general population 	<ul style="list-style-type: none"> Older adults (average of ~60 years at diagnosis)
Marginal Zone Lymphoma (MZL)	8%	<ul style="list-style-type: none"> Originates in the margin of the lymph node or lymphoid tissue follicle Major subtype is extra-nodal including primarily mucosa-associated lymphoid tissue (MALT) lymphoma: <ul style="list-style-type: none"> Can be gastric in origin or non-gastric (e.g. lung, thyroid, salivary gland, others) Gastric subtypes still dependent on Helicobacter pylori bacteria can be eradicated with antibiotics Rare subtypes: splenic marginal zone B-cell lymphoma and even more rare nodal marginal zone B-cell lymphoma Treatment is particular to stage and subtype Prognosis is excellent 	<ul style="list-style-type: none"> MALT lymphomas: older adults (~60 years of age at diagnosis)
Chronic Lymphocytic Leukemia/Small-Cell Lymphocytic Lymphoma (CLL/SLL)	6%	<ul style="list-style-type: none"> CLL and SLL are variants of the same process presenting as lymphocytosis, marrow, lymphadenopathy and hepatosplenomegaly. Many patients can be surveilled without therapy. Treatments have largely evolved to target therapies and away from chemoimmunotherapy with an excellent prognosis. 	<ul style="list-style-type: none"> Adults over 60 (median 72 years at diagnosis)

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Subtype	% of NHLs*	Features/Characteristics	Most Common in:
Lymphoplasmacytic Lymphoma (LPL)	1%	<ul style="list-style-type: none"> • Also known as Waldenström macroglobulinemia • Uncommon lymphoma with cells primarily in lymph nodes, spleen, bone marrow and characterized by an elevated IgM monoclonal gammopathy which can become symptomatic and typically dictates therapy initiation versus surveillance. • Initial treatments T have largely evolved to target therapies and away from chemoimmunotherapy with an excellent prognosis. 	<ul style="list-style-type: none"> • Adults over 60 (median age of 63 years at diagnosis) • Male predominance.
T-Cell Lymphomas			
Peripheral T-Cell Lymphoma, not otherwise specified (PTCL-NOS)	6%	<ul style="list-style-type: none"> • Systemic; tend to be aggressive • Typically diagnosed in advanced stages • Challenging to manage due to relapses after initial response though more than half are cured with initial therapy • Commonly nodal with additional areas in the spleen, liver, bone marrow, digestive tract, or skin 	<ul style="list-style-type: none"> • Adults over 60
Anaplastic Large Cell Lymphoma (ALCL)	2%	<ul style="list-style-type: none"> • Subtyped based on positivity for the anaplastic large cell kinase (ALK) protein • ALK-positive ALCL usually occurs in younger patients and responds better to treatment as compared to ALK-negative ALCL • Can be systemic or cutaneous • Often aggressive but also often curable 	<ul style="list-style-type: none"> • Median age ~34 for ALK-positive ALCL; mid-50s for ALK-negative and primary cutaneous ALCL • Males
Lymphoblastic Lymphoma (LBL)	2%	<ul style="list-style-type: none"> • Systemic and aggressive • Can be either T-cell or B-cell in origin • Usually grouped with acute lymphoblastic leukemia (ALL) and treated accordingly • Lymphoblasts are the characteristic cell type; usually seen in lymph nodes (LBL) or bone marrow/blood (ALL) 	<ul style="list-style-type: none"> • Individuals under 35; mostly children and teenagers; median age of 20 years at diagnosis • Somewhat more prevalent in men vs. women
Cutaneous T-Cell Lymphoma (CTCL)	4%	<ul style="list-style-type: none"> • Primarily affects the skin but can progress to lymph nodes and organs • Often indolent but can be aggressive (especially in older adults) • Approximately 50% of CTCLs are Mycosis Fungoides (MF) • In advanced cases, the morbidities of skin breakdown and infection predominate 	<ul style="list-style-type: none"> • Adults 50 and older • Men and non-Hispanic Black patients

* Approximate. Based on statistics from Western countries.

Abbreviations: EBV = Epstein-Barr Virus; GCB = germinal center B-cell.

Sources: Thandra KC, et al. *Med Sci (Basel)*. 2021;9(1):5; American Cancer Society. Last revised February 15, 2024.

<https://www.cancer.org/cancer/types/non-hodgkin-lymphoma/about/b-cell-lymphoma.html>; American Cancer Society. Last revised March 29, 2018.

<https://www.cancer.org/cancer/types/skin-lymphoma/about/types-of-skin-lymphoma.html>; Leukemia Foundation. Last updated December 15, 2023.

<https://www.leukaemia.org.au/blood-cancer/lymphoma/non-hodgkin-lymphoma/lymphoblastic-lymphoma>; Cai ZR, et al. *JAMA Oncol*. 2022;8(11):1690-1692.

Table 2. Hodgkin Lymphoma Subtypes and Classification

Subtype	Frequency	Lymph Node Presentation (Typical)	Disease Characteristics	B Symptoms	Clinical Features	Most Common in:	More Common in Males?
Classical Hodgkin Lymphoma (cHL): ~95% of HL cases*							
Nodular Sclerosis	Most common cHL (~70% of cases)	Mediastinum; later, the neck, upper abdomen, spleen, and above the clavicle	Nodular pattern of growth, fibrosis, lacunar cells (variant of RS cells)	Relatively common (~40% of cases)	Highly curable Usually diagnosed at an early stage	Adolescents, young adults	No (Male to female ratio ~1:1)
Mixed Cellularity	Second most common cHL (~20%-25% of cases)	Neck, axilla, abdomen	Typical RS cells, inflammatory background including eosinophils, histiocytes, and plasma cells	Common	Associated with EBV infection Usually diagnosed in a more advanced stage	Children, older adults HIV-infected individuals	Yes
Lymphocyte-rich	Uncommon (~5% of cHL cases)	Neck, axilla, above the clavicle	Numerous normal-appearing lymphocytes, infrequent but typical RS cells	Rare	Usually diagnosed at an early stage Presents with localized painless peripheral lymphadenopathy	Older adults	Yes
Lymphocyte-depleted	Very rare (<1% of cHL cases)	"It's most often in lymph nodes in the abdomen (belly) as well as in the spleen, liver, and bone marrow."	Variable; few normal lymphocytes, but numerous RS cells (typical RS and variants)	Common	More aggressive than other HL subtypes Often extensive extranodal disease at diagnosis	Older adults	Yes
Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL): ~5% of HL cases*							
		Neck, axilla predominate	Growth pattern is nodular or nodular and diffuse Hallmark is the "popcorn" RS cell variant (based on their appearance); also called L&H cells Typical RS cells infrequently seen	Uncommon (6% to 15%)	Patients often present with localized, painless peripheral lymphadenopathy Indolent, but with tendency for late relapses Elevated risk of transformation to aggressive NHL (up to 17% of cases) as compared to cHL (up to 3% of cases)	Children and adults; median age of 40	Yes

* The subclassifications with of classical Hodgkin lymphoma have little clinical bearing outside of their anatomic proclivities of involvement; they are treated identically. The nodular lymphocyte-predominant subtype is managed according to an indolent B-cell lymphoma paradigm.

Abbreviations: L&H = lymphocytic and histiocytic; RS = Reed-Sternberg.

Sources: American Cancer Society. Last revised May 1, 2018. <https://www.cancer.org/cancer/types/hodgkin-lymphoma/about/what-is-hodgkin-disease.html>; The Leukemia & Lymphoma Society. <https://www.LLS.org/lymphoma/hodgkin-lymphoma/diagnosis/hodgkin-lymphoma-subtypes>; Kaseb H, et al. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK499969>; Sidda A, et al. J Investig Med High Impact Case Rep. 2022;10:2324709622111767. Feldman AL, et al. In: Canellos GP, Lister TA, Young BD, eds. *The Lymphomas (Second Edition)*. Philadelphia: W.B. Saunders; 2006:2-38.

Risk Factors for Lymphoma

Established risk factors for lymphomas include but are not limited to age, sex, certain infections, immunodeficiency, autoimmune disorders, past chemotherapy, geographic location, environmental factors such as chemical exposure, and family history. However, risk factors for lymphoma vary substantially depending on the specific subtype. For example, men are more likely to be diagnosed with MCL, while women are somewhat more likely to be diagnosed with FL. In HL, all subtypes are more common in males than in females, except for nodular sclerosis HL, where the sex distribution is roughly equal (Table 1 [above]).

Similarly, newly diagnosed NHL patients are on average 67 years of age; however, subtypes such as DLBCL and MZL often occur in individuals under 65 years, and BL has two peak ages of incidence—one in childhood, and one in older adults.⁸ In addition, while NHL is more common among individuals of European or Hispanic descent, notable exceptions include the endemic form of Burkitt lymphoma, a childhood cancer seen most often in tropical Africa.¹⁰

Autoimmune diseases such as Sjögren's syndrome are more strongly linked to increased risk of specific lymphoma subtypes such as parotid MZL, but not others.

Immunosuppression (due to solid organ or hematopoietic stem cell transplantation, immunosuppressive therapy, or HIV infection) has also been linked to increased incidence of certain lymphomas including DLBCL, HL, and Burkitt.^{11–13} Some risk factors, such as smoking, obesity, sun exposure, and chemical exposure at work are modifiable, which has important implications for prevention efforts.⁸

Some infections have been associated with specific lymphoma subtypes, though the percentage affected by infection (active or prior) varies by the lymphoma subtype. Pathobiology may be direct (eg. oncogenetic) or indirect (eg. facilitating chronic inflammation). Viral infections associated with subtypes include Epstein-Barr virus (Burkitt lymphoma, diffuse large B-cell lymphoma, peripheral T-cell lymphoma, lymphocyte-depleted HL, post-transplant lymphoproliferative disorders), HIV (DLBCL, Burkitt, primary effusion, primary brain lymphoma and HL), HTLV-1 (adult T-cell leukemia/lymphoma), and hepatitis C virus [DLBCL (in certain geographies), splenic MZL].^{8,13,14} Although rare, infection with the *Helicobacter pylori* bacteria is linked to gastric MALT lymphomas, while other MALT lymphomas have been linked to *Chlamydia* or *Campylobacter* infections.¹⁴

Family history of lymphoma is also an established risk factor across subtypes of NHL and HL; however, having a first-degree relative with a lymphoma adds only a small, incremental increase in an individual's lifetime risk of lymphoma (from 2.1% to 3.6%) and the risk is not actionable; thus, clinical surveillance (i.e., genetic screening) of relatives is not recommended.^{15,16}

Presentation, Diagnosis, and Workup

Patients with lymphoma commonly present with painless adenopathy (i.e. swelling of lymph nodes). In more advanced cases, patients may present with fever, night sweats, and unexplained weight loss, collectively referred to as B symptoms.¹⁷ Adenopathy in more indolent lymphoma subtypes can wax and wane over the course of years, while in more aggressive cases, adenopathy can progress rapidly.¹⁷ In most NHL subtypes, any nodes can be affected, while in HL, typically the nodes above the diaphragm are affected.¹⁸ A substantial proportion of NHL patients will have extranodal involvement (i.e., infiltration of anatomic sites beyond the lymph nodes), most commonly in the stomach, spleen, lung, bone, skin, and central nervous system.¹⁹

The most important first step in lymphoma management is obtaining a definitive pathologic diagnosis; toward that end, a biopsy of the lymph nodes (and sometimes extranodal sites) is required. In clinical practice, an incisional or excisional lymph node biopsy is recommended, while by contrast, fine-needle aspiration biopsy alone is not considered suitable, while core needle biopsy is not optimal, but widely used in practice when combined with pathologic techniques.¹⁶ Immunophenotyping, essential to differentiating NHL subtypes, can be performed via an immunohistochemistry (IHC) panel or flow cytometry. Cytogenetic/genetic molecular analysis is increasingly used in some cases to identify chromosomal translocations characteristic of certain subtypes and acquired mutations reflective of diagnosis. Algorithms to guide immunophenotyping and clinical interpretation of the results are available in clinical practice guidelines.¹⁶ Other essential aspects of workup include laboratory tests (such as complete blood count, lactate dehydrogenase, and liver function tests, among others), imaging (primarily positron emission tomography/computed tomography scans) to support staging, and pregnancy testing/fertility counseling in appropriate patients.¹⁶

Treatment of Lymphomas

Therapeutic approaches in lymphoma have become increasingly complex and nuanced in recent years, particularly with the introduction of numerous targeted therapies and immunotherapeutic options. The National Comprehensive Cancer Network (NCCN) offers continuously updated treatment guidelines, including at least seven separate guidelines that are relevant to the treatment of lymphomas. Altogether, these guidelines encompass 955 pages of content, more than one-third of which is focused on B-cell lymphomas. Other available guidelines cover T-cell lymphomas, HL, pediatric HL, primary cutaneous lymphomas, CLL/SLL, and lymphoplasmacytic lymphoma/Waldenström macroglobulinemia.¹⁶

Treatment of a specific lymphoma depends on numerous factors, including but not limited to disease subtype, stage, and extent; patient factors such as age, fitness, and overall health; previous treatments or lines of therapy; anticipated side effects; and the patient's treatment preferences, values, and goals.^{20,21}

Patients with earlier-stage lymphomas may be adequately managed with observation, therapeutic excision, local radiation, or chemotherapy, highly dependent on the lymphoma subtype. For more advanced lymphomas, the foundation for aggressive lymphomas is often systemic therapy regimens (i.e., combination chemotherapy) plus immunotherapy, with or without radiotherapy. Indolent lymphomas require individualized approaches, as surveillance alone is often appropriate initially and treatment indications are myriad. Depending on the subtype, disease stage, and line of therapy, other treatment approaches may include oral targeted therapies, monoclonal antibodies, antibody-drug conjugates (ADCs), bispecific antibodies, and chimeric antigen receptor (CAR) T-cell therapy, among other approaches.¹⁶ For certain lymphomas, treatment of an infectious cause may be part of standard therapy (e.g., antibiotics for eradication of *H. pylori* in MALT lymphoma).²² Autologous and even allogeneic hematopoietic stem cell transplantation is most often reserved for patients who do not have a good response to initial therapy.

For the various B-cell NHL subtypes, treatment varies widely. In more advanced cases, a core therapy for many patients with newly diagnosed B-cell NHL (most often DLBCL and sometimes FL) is the CD20-specific monoclonal antibody rituximab plus the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Another regimen recently approved for DLBCL combines

polatuzumab vedotin, an ADC that targets CD79b with chemotherapy. In the randomized phase 3 POLARIX trial, polatuzumab vedotin added to R-CHP (note that vincristine is omitted) improved PFS as compared to standard R-CHOP therapy in patients with previously treated intermediate- or high-risk DLBCL.²³

Traditionally, patients with relapsed or refractory DLBCL have been treated with second-line chemotherapy followed by autologous stem cell transplantation for those with chemosensitive disease. However, a growing number of non-chemotherapy approaches have been adopted in recent years. Novel therapies recently incorporated into treatment algorithms include ADCs such as polatuzumab vedotin and loncastuximab tesirine; bispecific antibodies, chimeric antigen receptor (CAR) T-cell therapy; tafasitamab (an anti-CD19 monoclonal antibody) in combination the immunomodulatory drug lenalidomide; and selinexor, an oral inhibitor of XPO1-mediated nuclear export.¹⁶

Novel approaches such as CAR T-cell therapy and bispecific antibody therapy have been increasingly incorporated into the lymphoma treatment toolbox. In CAR T-cell therapy, a patient's T cells are harvested, genetically engineered to recognize CD19, expanded, and then infused back into the patient. Three CAR T cell products (axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel, are approved by the Food and Drug Administration (FDA) for patients with relapsed or refractory large B-cell lymphomas (including DLBCL) refractory to or relapsed within 12 months of one line of therapy or relapsed after least two prior lines of therapy. Another CAR T-cell therapy, brexucabtagene autoleucel, is approved for the treatment of adults with relapsed/refractory MCL. Data from clinical trials demonstrate about one-third of lymphoma patients achieve durable disease control following CAR T-cell therapy; however, the treatment is costly, resource-intensive, and not universally available, presenting barriers to its use.²⁴ Recently, bispecific T-cell engager therapy has become a treatment option following FDA approvals in relapsed/refractory DLBCL (epcoritamab and glofitamab) and FL (mosunetuzumab). These antibodies act as a bridge to bring the targeted CD20-expressing B cells into proximity of CD3-expressing T cells, resulting in T-cell killing and providing an "off the shelf" approach avoiding some of the challenges associated with the engineering of CAR T cells.²⁵

The preferred treatment now for nearly all peripheral T-cell lymphoma histologies expressing the CD30 marker is cyclophosphamide, doxorubicin, and prednisone (CHP) combined with brentuximab vedotin, an ADC consisting of a cytotoxic agent conjugated to an anti-CD30 monoclonal

antibody. Options for second- and subsequent-line therapy vary by histology and whether or not the patient will go on to transplant, though preferred single-agent options in many cases include brentuximab vedotin, belinostat, romidepsin, and pralatrexate. Treatment of cutaneous T-cell lymphomas depends on the stage and may include chemotherapy, targeted therapies, radiation, photodynamic therapy, and extracorporeal photopheresis, among other approaches.¹⁶

In classic HL, combination chemotherapy regimens are also the cornerstone of treatment. For years, a standard of care for patients with advanced-stage disease was the combination of doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD), alone or in combination with radiotherapy. More recently, the combination of brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (BV+AVD) was also recommended as first-line therapy¹⁶ and was shown to provide a survival advantage over ABVD in a phase 3 trial.²⁶ In another phase 3 study recently presented, the immune checkpoint inhibitor (ICI) nivolumab added to AVD significantly improved progression-free survival (PFS) versus A+AVD, with less toxicity than BV+AVD; however, further follow-up is needed to determine whether nivolumab plus chemotherapy improves overall survival (OS) in comparison to the standard-of-care A+AVD regimen.²⁷

Patients with advanced-stage classic HL who relapse or are refractory to initial treatment may receive a second-line systemic therapy followed by high-dose therapy and autologous stem cell transplantation. Nivolumab and pembrolizumab are indicated beyond first-line therapy alone or in combination with chemotherapy, depending on the setting.²⁸

Nodular lymphocyte-predominant HL is a heterogeneous disease with biology similar to an indolent NHL. Most patients with NLPHL present with early-stage disease, which is managed effectively with therapeutic excision and radiotherapy alone or combined with a brief chemotherapy treatment.²⁹ Patients with advanced-stage disease at diagnosis may be appropriate for surveillance or chemotherapy combination regimens used for NHL, again mirroring the approach for indolent NHL.

Treatment-Related Side Effects

During and immediately after treatment, lymphoma patients may experience a wide variety of side effects, each ranging from mild to severe (sometimes requiring hospitalization). What side effects the patient experiences will depend in part on factors such as the medications used, dosages and duration of therapy, age, and individual patient susceptibility due to frailty, impaired performance status, or comorbidities such as diabetes or kidney disease.³⁰

Notable side effects experienced by patients with lymphomas include cytopenias (i.e., decreased blood cell counts), infections, hepatitis B virus (HBV) reactivation (all patients with prior exposure receiving B cell depleting therapies need to be on extended prophylaxis), bone loss/fractures, and neuropathy. Some patients with a high burden of disease and/or rapidly dividing tumors are at an increased risk of tumor lysis syndrome (TLS), which although potentially serious, rarely leads to organ failure and death if managed appropriately.³¹ Other common side effects include nausea/vomiting, diarrhea, alopecia, fatigue, cough, fever, and rash, among others. Use of rituximab can very rarely be associated with an increased risk of progressive multifocal leukoencephalopathy, a typically fatal neurological condition caused by a latent virus.³⁰

Management of these side effects varies, from the use of granulocyte-colony stimulating factor (G-CSF) to stimulate the production of depleted white blood cells and reduce the risk of infection, to preventive antiviral therapy for patients who test positive for HBV. In addition, patients with lymphomas are advised to receive certain vaccinations (including vaccinations for pneumococcal pneumonia, COVID-19, and influenza) preferably before therapy and also once treatment is completed. Immune reconstitution and vaccine efficacy after therapy varies by regimen. The Leukemia & Lymphoma Society (LLS) offers extensive guidance on managing a variety of side effects related to lymphoma treatment (see <https://www.LLS.org/treatment/managing-side-effects>).

Radiation-specific side effects can include sore, dry, or painful skin in the treated area. In the head and neck area, these side effects could also include mouth sores, dry mouth, or changes in taste, while in the chest, radiation can cause cough or difficulty swallowing.

Patients undergoing hematopoietic stem cell transplantation may experience nausea, skin rashes, or other side effects during high-dose chemotherapy and the transplant procedure, while delayed side effects may include loss of appetite, nausea and vomiting, vision changes, mouth sores, diarrhea, infection, alopecia, and problems sleeping.³² In addition, patients who undergo allogeneic transplant (i.e., transplant using donor cells instead of the patient's own cells) are at risk for graft-versus-host disease, which can range from mild to severe and life-threatening.³⁰

The expansion of treatment options in lymphoma in recent years has increased the range of potential adverse events that a patient may experience. Checkpoint inhibitors are associated with mild to severe forms of autoimmune effects. Toxicities characteristic of CAR T-cell therapy include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which are often mild to moderate but can be more severe and potentially life-threatening. Management of these toxicities may include the use of corticosteroids, tocilizumab (for CRS), and other supportive care measures. All patients experience longer-term toxicities until immune reconstitution.²⁴

Long-Term and Late Effects

Patients who receive lymphoma therapy may experience both *long-term effects*, meaning side effects that persist months or years after the end of treatment (e.g., fatigue), as well as *late effects*, which refers to side effects that may not be evident until years or decades later (e.g., heart disease). The risk of long-term and late effects is variable and depends on patient age, fitness, and overall health, as well as the specific treatments received.

Key late effects of therapy that healthcare providers should make patients aware of include fertility issues (see “Fertility Issues” box, inset), heart disease, and secondary cancers. Patients may be at increased risk of cardiovascular toxicities including heart disease (coronary and valvular), heart failure, and pericarditis. Increased cardiovascular toxicity risks are related to both chemotherapy (particularly alkylating agents such as cyclophosphamide and anthracyclines such as doxorubicin) and radiotherapy to the chest.³³ Secondary malignancies, which may appear several decades following lymphoma treatment, can include cancers of the bone marrow, lung, breast, skin, and others. In NHL, treatment with chemotherapy is associated with an increased risk of secondary malignancies and is likely amplified when

combined with radiation.³³ Infertility risk varies depending on treatment type, dose, location (in the case of radiotherapy), and duration, as well as factors such as patient age. Older women who receive certain treatments (such as CHOP chemotherapy) are also at risk of early menopause even if they regain fertility after treatment.³⁴

Not all lymphoma survivors will develop significant long-term or late effects. However, focused patient-provider discussions on long-term and late effects will help ensure proper planning, evaluation, and follow-up care. Toward that end, healthcare providers should inform patients of any potential long-term or late effects. To aid in these discussions, providers can refer to the LLS Survivorship Workbooks for adults, young adults, and children/adolescents (www.LLS.org/managing-your-cancer/survivorship-workbook) and provide them to patients as a resource. By fostering greater awareness, healthcare providers can increase the chances that these long-term and late effects can be identified early and managed promptly.

Fertility Issues

While many lymphoma treatments have no or little adverse impact on future fertility, some treatments can limit a person's ability to conceive or father a child. The risk of infertility depends on a number of factors, including the type of chemotherapy drug used, the dosages and duration of treatment, whether the patient is male or female, and the patient's age at the start of treatment. Many options are available to help preserve the ability to have biological children in the future. The methods with the highest likelihood of success are sperm freezing (sperm banking) and egg or embryo freezing.

Healthcare providers should speak to adult lymphoma patients of childbearing age and parents of children diagnosed with lymphoma about the potential effects of treatment, and provide information on options to preserve fertility at diagnosis. Patients should also be informed of any potential risks they face regarding conception or pregnancy. Freezing of eggs or embryos requires collaboration with a fertility specialist before therapy is started.

More details on fertility counseling and preservation can be found in the free LLS booklet, *Fertility and Cancer*: <https://www.LLS.org/booklet/fertility-and-cancer>

Survivorship Care

With survival rates increasing in NHL and already quite high in HL, the overall number of lymphoma survivors is growing with each passing year. Accordingly, healthcare providers need to be increasingly focused on the challenges faced by survivors. Key issues in survivorship care include not only the long-term and late effects of therapy (as previously discussed) but also issues such as quality of life and uncertainty about the future.

In the years following diagnosis and treatment, survivors can have poorer general health and vitality in comparison to the general population, and many report practical issues with their work and with obtaining health insurance, life insurance, and even mortgages.³⁵ Multiple studies have demonstrated some patients experience negative physical, mental, and psychosocial effects even in remission. The negative effects may stem from the disease itself, the treatments that were used, and the fear of cancer recurrence.³⁶ Patients may also have social, spiritual, and financial issues that need to be addressed.

As such, healthcare team members need to be vigilant in recognizing survivorship challenges and intervene early to improve physical health, psychosocial health, and quality of life. The LLS Survivorship Workbook can aid patients in collecting important information throughout their lymphoma survivorship journey and sharing that information with their healthcare provider. In addition, a lifestyle that includes adequate exercise and appropriate nutrition may help improve quality of life, well-being, and overall health.

Patient and Provider Resources

LLS Resources

LLS Disease Information for Patients and Caregivers: Lymphoma

www.LLS.org/lymphoma

Information Booklets on Lymphomas for Patients and Caregivers

www.LLS.org/publications?field_booklets_language_target_id_1=351&field_booklets_category_target_id=344&sort_by=title&view-type=card

Fact Sheet on Fertility and Cancer

www.LLS.org/booklet/fertility-and-cancer

Patient/family Education Webcasts on Lymphoma

www.LLS.org/patient-education-webcasts/lymphoma

Other Helpful Resources

Living as a Non-Hodgkin Lymphoma Survivor (American Cancer Society)

www.cancer.org/cancer/types/non-hodgkin-lymphoma/after-treatment/follow-up.html

The ASCO Answers Guide to Cancer Survivorship

www.society.asco.org/news-initiatives/current-initiatives/cancer-care-initiatives/survivorship-compendium/information-survivors

Lymphoma Research Foundation: Fact Sheets and Guides, Education Programs, and Webinars

www.lymphoma.org/resources/educationresources

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We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has regions throughout the United States and Canada. To find the region nearest to you, visit our website at www.LLS.org/ChapterFind or contact:

The Leukemia & Lymphoma Society

3 International Drive, Suite 200 Rye Brook, NY 10573
Phone Number: (800) 955-4572
(M-F, 9 a.m. to 9 p.m. ET)
Website: www.LLS.org

LLS offers free information and services for patients and families touched by blood cancers as well as for healthcare professionals. The resources listed below are available to you and your patients.

Consult with an Information Specialist. Information Specialists are highly trained social workers and nurses who assist through treatment, financial, and social challenges. They offer up-to-date disease and treatment information. Language services are available. For more information, please:

- Call: (800) 955-4572 (M-F, 9 a.m. to 9 p.m. ET)
- Visit: www.LLS.org/IRC
- Email or Live chat: www.LLS.org/InformationSpecialists

Clinical Trials Support Center (CTSC)

Work one-on-one with an LLS clinical trial nurse navigator who will personally assist throughout the entire clinical trial process. A nurse navigator will help identify potential clinical trials and overcome the barriers to enrollment (navigators help HCPs and patients). For more information about this free service, please:

- Call an Information Specialist: (800) 955-4572 to be referred to the CTSC
- Visit: www.LLS.org/CTSC
- Complete a referral form for your patient at: www.LLS.org/CTSCreferral

Nutrition Consultations. Nutrition Education Services Center (NESC) provides one-on-one *free* nutrition education and consultations to patients and caregivers of all cancer types with registered dietitians who have expertise in oncology nutrition.

- Visit: www.LLSnutrition.org

Free Information Booklets. LLS offers free education and support publications that can either be read online or downloaded. Free print versions can be ordered. For more information, please:

- Visit: www.LLS.org/booklets.

Información en Español. (LLS information in Spanish.) Para mayor información por favor:

- Visite: www.LLS.org/espanol.

LLS Community. LLS Community is an online social network and registry for patients, caregivers, and healthcare professionals. It is a place to ask questions, get informed, share your experience, and connect with others. To join:

- Visit: www.LLS.org/community

LLS Regions. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, and other great resources. For more information about these programs or to contact your region, please:

- Call: (800) 955-4572
- Visit: www.LLS.org/ChapterFind

Patti Robinson Kaufmann First Connection®

Program. A free peer-to-peer support program that connects patients and their loved ones to a trained peer volunteer who has gone through a similar experience.

- www.LLS.org/FirstConnection

LLS Disease Information for Patients and Caregivers: Lymphoma

- www.LLS.org/lymphoma

Resources for Healthcare Professionals: Webinars, Podcasts, In-person Education Programs, Videos, and Fact Sheets

- www.LLS.org/CE (free accreditation)
- www.LLS.org/HCPpodcast
- www.LLS.org/HCPvideos
- www.LLS.org/HCPbooklets

Resources for your Patients

- www.LLS.org/programs
- www.LLS.org/EducationVideos
- www.LLS.org/podcast

Additional Resource

The National Cancer Institute (NCI)

www.cancer.gov
(800) 422-6237

The National Cancer Institute, part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer. The NCI also provides a clinical trial search feature, the PDQ® Cancer Clinical Trials Registry, at <https://www.cancer.gov/research/participate/clinical-trials-search>, where healthcare professionals and patients can look for clinical trials.

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