Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL)

Hodgkin Lymphoma

Lymphoma Research Foundation

Hodgkin lymphoma (HL), also known as Hodgkin disease, represents about 10 percent of all lymphomas in the United States. It is estimated that 8,570 new cases of HL will be diagnosed in the United States in 2024. HL can occur in both children and adults, but it is most common in young adults between the ages of 20 and 29 years, with an average age of 39 years at diagnosis.

HL is often characterized by the presence of very large cells called Reed-Sternberg (RS) cells (Figure 1) and usually starts in the lymph nodes (small bean-shaped structures that help the body fight disease, Figure 2). It can spread to other lymph nodes and, rarely, to other organs.

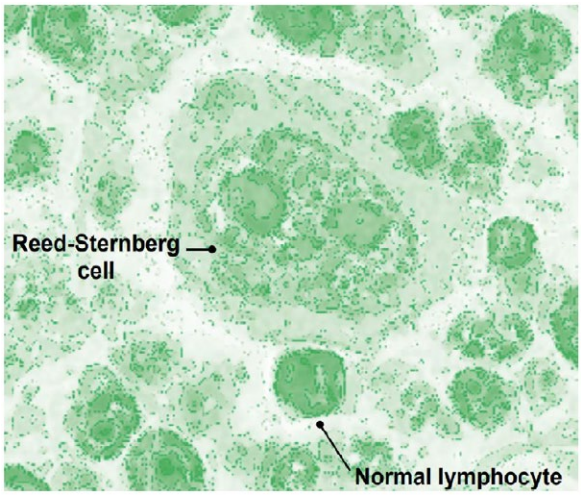

Figure 1: Example of a normal *lymphocyte* (a type of white blood cell that fights infection and cancer) and a Reed-Sternberg cell found in HL. HL, Hodgkin lymphoma.

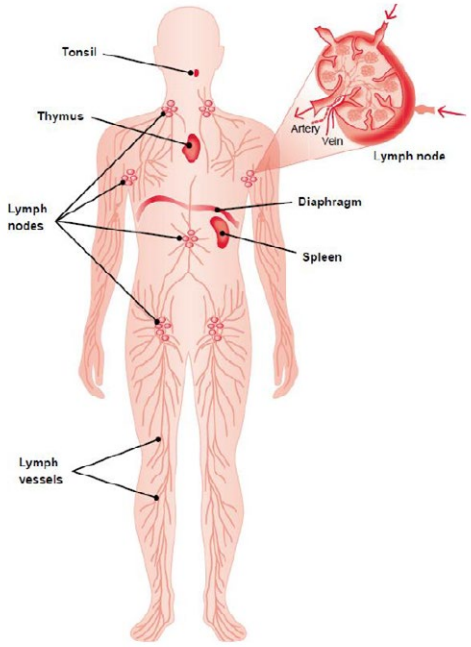

Figure 2: The lymphatic system and lymph nodes.

The exact cause of HL is not fully understood, and most cases of HL are not explained by any clear cause. Certain factors may increase the risk of developing it, such as a weakened immune system, certain infections (like Epstein-Barr virus [EBV]), genetic factors, or exposure to certain chemicals. Biological siblings of patients with HL have a slight increased risk of also developing HL.

Common signs and symptoms of HL include:

- Swelling of the lymph nodes (usually painless).
- Fever.
- Night sweats.
- Unexplained weight loss.
- Itching.
- Lack of energy.

While most people who have these symptoms do not have HL, anyone with persistent symptoms should see a physician to make sure that lymphoma is not present.

Common Types of HL

HL is divided into two main classifications: classical HL (cHL), which accounts for the majority of cases, and nodular lymphocyte-predominant HL (NLPHL) which accounts for 5-10% of all cases. The type of HL a patient has affects their treatment options.

Classical HL

Nodular Sclerosis cHL is the most common subtype of cHL in the US. The involved lymph nodes contain a lot of scar tissue, which is where the name nodular *sclerosis* (scarring) comes from. The disease is more common in women than in men, and it usually affects adolescents and adults under the age of 50 years. The majority of patients are cured with current treatments.

Mixed Cellularity cHL is the second most prevalent form of cHL cases. The disease is more common in men than in women, and primarily affects young children and is associated with EBV also known as mononucleosis and in older adults and people with human immunodeficiency virus (HIV) infection. This is also more common in underdeveloped countries such as sub-Saharan Africa and is associated with EBV in these cases. Due to the mixed cellularity, patients often present with disease above and below the diaphragm (middle of the body). Because of this, patients might present a more advanced stage (III or IV) of this subtype at diagnosis.

Lymphocyte-Rich cHL is a less common subtype of cHL. This subtype of HL is usually diagnosed at an *early stage* (cancer is small and has not spread) in older adults and has a low risk of *relapse* (disease returns after treatment).

Lymphocyte-Depleted cHL is a rare form of cHL and occurs mainly in older people and those with human immunodeficiency virus (HIV) infection. This subtype is *aggressive* (grows rapidly) and usually not diagnosed until it is widespread throughout the body.

Lymphocyte-Predominant HL

Nodular Lymphocyte-Predominant HL (NLPHL), now known as Nodular Lymphocyte Predominant B-cell Lymphoma (NLPBCL), accounts for 5%-10% of all HL cases. It affects men more often than women and is usually diagnosed in young males before the age of 35 years. This subtype is characterized by the appearance of large white blood cells (*lymphocytes* and *histiocytes*, sometimes called popcorn cells) under the microscope as well as small B cells that typically have CD20 protein on their surface. NLPHL is most often diagnosed at an early stage (>70% of patients) and is still curable even at more advance stages (III-IV) or when it involves organs other than lymph nodes.

This form of HL is indolent (grows slowly) and can *relapse* (disease comes back after treatment) many years later regardless of how it is first treated. Prognosis is usually still excellent even at the time of relapse. Transformation of NLPHL to aggressive lymphoma is uncommon (<5% of patients at 10 years after initial diagnosis) and is associated with lower rates of cure and survival. Follow-up is very important because of the possibility of late relapse and the risk of long-term treatment toxicities.

Treatment Options

The majority of patients with newly diagnosed HL can be cured. While the treatment depends on the type of HL and the patient's overall health, most patients receive as their first treatment:

- *Chemotherapy* (drugs that stop the growth of or kill cancer cells).
  - Common chemotherapy regimens used as initial treatment (frontline chemotherapy) for cHL are listed in **Table 1**.
  - Some chemotherapy regimens include steroids (like dexamethasone or prednisone), which treat cancer and help to relieve inflammation (redness, swelling, pain, and/or a feeling of heat in an area of the body).
- *Radiation therapy* (uses high-energy radiation to kill cancer cells) works very well against HL.
- *Immunotherapy* (drugs that use the body's immune system to fight cancer) with antibody-drug conjugates (ADC).
  - An ADC is a monoclonal antibody (a protein made in the laboratory that binds to cancer cells and helps the immune system destroy them) attached to a chemotherapy drug. The monoclonal antibody in the ADC recognizes and binds to a protein on the cancer cell surface. Once the ADC is inside the cell, the chemotherapy drug separates from the ADC and kills the cancer cell by targeting cell multiplication. This targeting helps direct the chemotherapy to the cancer cells and prevent some of the killing of healthy cells in the body.
  - The antibody-drug conjugate (ADC) brentuximab vedotin (Adcetris) can be used as frontline therapy for stage III or IV cHL in combination with other drugs such as doxorubicin, vinblastine, and dacarbazine (BV+AVD).

For more information on ADCs and other types of immunotherapy, please view the *Immunotherapy and Other Targeted Therapies* fact sheet on the Lymphoma Research Foundation's website (**lymphoma.org/publications**).

Patients with NLPHL may not require immediate treatment and can go under observation or watchful waiting (also known as active surveillance), in which the patient is closely monitored to see if or when treatment is needed. The treatments may be used alone or combined, depending on the stage of the disease (how much the cancer has grown and if it has spread in the body) and the *B symptoms* (fever without infection, drenching night sweats and unexplained weight loss).

The most common treatments for NLPHL are radiation therapy, chemotherapy, immunotherapy with rituximab (Rituxan), or surgery. In many situations, multiple treatment approaches are reasonable with no single "best" option, and it is appropriate for patients and families to play an active role in treatment decision-making. It is often preferable to avoid aggressive upfront treatments in NLPHL because of the cumulative side effects of such treatments over time and the curability of the disease even at relapse (>90% survival at 10 years after initial diagnosis).

Table 1: Common frontline chemotherapy regimens used to treat cHL.

Abbreviation	Description
ABVD	Doxorubicin, bleomycin, vinblastine, and dacarbazine
AVD	Doxorubicin, vinblastine, and dacarbazine
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
BV+AVD	Brentuximab vedotin (Adcetris) + doxorubicin, vinblastine, and dacarbazine
BV-AVPC	Brentuximab vedotin, doxorubicin, vincristine, prednisone, cyclophosphamide
AEPA/CAPDac	Vincristine, etoposide, prednisolone, doxorubicin, cyclophosphamide, vincristine, prednisone, and dacarbazine

cHL, classic Hodgkin lymphoma.

Table 2: Common frontline combination therapies used to treat NLPHL.

Regimen	Description
R-ABVD	Doxorubicin, bleomycin, vinblastine, and dacarbazine + rituximab
R-CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone + rituximab
R-CVbP	Cyclophosphamide, vinblastine, and prednisolone + rituximab

In cases where NLPHL is isolated in one lymph node, surgery alone can be used. In other patients with early-stage disease, radiation therapy, rituximab (Rituxan) or combination chemotherapy such as ABVD or CHOP may be used. More advanced disease is usually treated with rituximab (Rituxan) in combination with chemotherapy, as listed in Table 2.

There are a number of *single-agent* (a drug that is used alone) and combination treatments available for patients with *relapsed* (disease returns after treatment) or *refractory* (disease does not respond to treatment) HL, including:

- *Stem cell transplantation* (the patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells or stem cells, and then receives healthy stem cells to restore the immune system and the bone marrow's ability to make new blood cells). This helps by restarting the immune system so it will catch any cancer cells made in the future and clear them.
- Immunotherapy, including:
  - Brentuximab vedotin (Adcetris).
  - Monoclonal antibodies such as nivolumab (Opdivo) and pembrolizumab (Keytruda)
- Other chemotherapy regimens
- Radiation therapy

For more information on relapsed and refractory HL, view the *Hodgkin Lymphoma: Relapsed/Refractory* fact sheet on the Lymphoma Research Foundation's website (**lymphoma.org/publications**).

Patients with relapsed or refractory NLPHL may enroll in a clinical trial or be treated with a combination of rituximab (Rituxan) and chemotherapy such as:

- Bendamustine
- DHAP (dexamethasone, cisplatin, and high-dose cytarabine)
- ICE (ifosfamide, carboplatin, and etoposide)
- IGEV (ifosfamide, gemcitabine, and vinorelbine)

Treatments Under Investigation

Although many individuals diagnosed with HL are cured after treatment, researchers continue to develop new therapies that are more effective and have less side effects during therapy and for years after. New drugs being studied include immune checkpoint inhibitors (drugs that block proteins that help cancer cells evade immune response).

Investigators (experts who run clinical research) are also looking for ways to treat those patients who are not cured and in need of more treatment. These include new combinations of targeted therapies (drugs that target specific molecules that cancer cells use to survive and spread) or immunotherapies (drugs that help the immune system fight cancer). Table 3 (below) lists some of these investigational drugs that can be accessed through a clinical trial. For more information on clinical trials, view the Understanding Clinical Trials publication on the Lymphoma Research Foundation's website at lymphoma.org/publication. It is also very important that patients with HL consult with their doctor to clear up any questions they may have.

Table 3: Investigational drugs for cHL.

Treatments	Class	Condition
Ipilimumab (Yervoy)	Immunotherapy; immune checkpoint inhibitor	cHL
Avelumab (Bavencio)	Immunotherapy; immune checkpoint inhibitor	cHL
Azacitidine (Vidaza)	Chemotherapy; pyrimidine nucleoside analog	NLPHL
Camrelizumab (SHR-1210)	Immunotherapy; immune checkpoint inhibitor	cHL
Sintilimab (Tyvyt)	Immunotherapy; immune checkpoint inhibitor	cHL
Lenalidomide (Revlimid)	Immunotherapy; Immunomodulatory drug	cHL
Mosunetuzumab (Lunsumio)	Immunotherapy; bispecific antibody; anti-CD20	NLPHL
Tislelizumab (BGB-A317)	Immunotherapy; immune checkpoint inhibitor	cHL
Zimberelimab (GLS-010)	Immunotherapy; immune checkpoint inhibitor	cHL

cHL, classical Hodgkin lymphoma; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma.

Clinical Trials

Clinical trials are crucial in identifying effective drugs and optimal treatment for patients with lymphoma. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on the Foundation's website (**lymphoma.org/publications**), talk to their physician, or contact the Foundation's Helpline for an individualized clinical trial search by calling **(800) 500-9976** or emailing **helpline@lymphoma.org**.

Follow-up

Patients with lymphoma should have regular visits with a physician who is familiar with their medical history and the treatments they have received. During these visits, medical tests (like computed tomography [CT] or positron emission tomography [PET] scans) may be required to evaluate the need for additional treatment.

Some treatments can cause long-term side effects (occur **during** treatment and continue for months or years) or late side effects (appear only months, years or decades **after** treatment has ended). These can vary depending on the following factors:

- Duration of treatment (how long the treatment has lasted)
- Frequency of treatment (how often the treatment was administered)
- Type of treatment given
- Patient's age and gende
- Patient's overall health of at the time of treatment.

A physician will check for these effects during follow-up care. Visits may become less frequent the longer the patient stays in remission (lack of signs and symptoms of disease).

Patients and their care partners are encouraged to keep copies of all medical records. This includes test results as well as information on the types, amounts, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrences. The Foundation's award-winning *Focus On Lymphoma* mobile app and *Lymphoma Care Plan* (**lymphoma.org/publications**) can help patients manage this documentation.

Lymphoma Care Plan

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time.

The Foundation's Lymphoma Care Plan document organizes information on your health care team, treatment regimen, and follow-up care. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The *Lymphoma Care Plan* document can be accessed by visiting **lymphoma.org/publications**.

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit **lymphoma.org/programs**.

Helpline

The Foundation's Helpline staff are available to answer your general questions about lymphoma and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. The Foundation also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Clinical Trials Information Service. For more information about any of these resources, visit our website at **lymphoma.org**, or contact the Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Para información en Español, por favor visite **lymphoma.org/es**. (For Information in Spanish please visit **lymphoma.org/es**).

Focus on Lymphoma Mobile App

Focus on Lymphoma is the first app to provide patients and their care partners with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment. Comprehensive lymphoma management, conveniently in one secure and easy-to-navigate app, no matter where you are on the care continuum. Get the right information, first, with resources from the entire Lymphoma Research Foundation content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more about this resource, visit our website at **lymphoma.org/mobileapp**, or contact the Foundation's Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Lymphoma Research Foundation

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