Understanding Hodgkin Lymphoma

A Guide for Patients, Survivors, and Loved Ones
Lymphoma Research Foundation (LRF) Helpline and Clinical Trials Information Service

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Trained staff are available to answer questions and provide support to patients, caregivers and healthcare professionals in any language.

Our support services include:

- Information on lymphoma, treatment options, side effect management and current research findings
- Financial assistance for eligible patients and referrals for additional financial, legal and insurance help
- Clinical trial searches based on patient's diagnosis and treatment history
- Support through LRF's Lymphoma Support Network, a national one-to-one volunteer patient peer program

Monday through Friday, Toll-Free (800) 500-9976 or email helpline@lymphoma.org
This guide is an educational resource compiled by the Lymphoma Research Foundation to provide general information on adult Hodgkin lymphoma. Publication of this information is not intended to replace individualized medical care or the advice of a patient’s doctor. Patients are strongly encouraged to talk to their doctors for complete information on how their disease should be diagnosed, treated, and followed. Before starting treatment, patients should discuss the potential benefits and side effects of cancer therapies with their physician.
ACKNOWLEDGMENTS

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TABLE OF CONTENTS

Abbreviations .......................................................... 4

Introduction ............................................................. 6

Part 1 — Learning the Basics ........................................... 7

Chapter 1: Understanding the Disease ............................. 7
  Table 1.1. Subtypes of Classical Hodgkin Lymphoma .... 16
  Table 1.2. Known Risk Factors For Hodgkin Lymphoma 17

Chapter 2: Seeking Medical Attention ............................. 19
  Table 2.1. Signs and Symptoms Commonly Found in
  Patients With HL .................................................... 20

Chapter 3: Receiving a Diagnosis ................................. 23
  Table 3.1. The Three Main Types of Biopsies .............. 25
  Table 3.2. Immunohistochemistry and Flow
  Cytometry Tests .................................................... 29

Chapter 4: Work-Up Before Treatment Can Begin ............ 31
  Table 4.1. The Eastern Cooperative Oncology Group
  Performance Status Scale ......................................... 33
  Table 4.2. Types of Imaging Tests .............................. 34
Part 2 — Treatment of Hodgkin Lymphoma

Chapter 5: What to Know Before Starting Treatment

Table 5.1. Adverse Prognostic Risk Factors

Chapter 6: Treatments for Hodgkin Lymphoma

Table 6.1. Catheters Used to Administer Chemotherapy
Table 6.2. Methods for Delivering Radiation Therapy
Table 6.3. Terms Used to Describe Treatment and Its Outcomes
Table 6.4. Forms of Complementary Therapy

Chapter 7: Treatments for Classical Hodgkin Lymphoma

Table 7.1. Common Frontline Chemotherapy Regimens for Adults With cHL
Table 7.2. Common Frontline Chemotherapy Regimens for Children With cHL
Table 7.3. Common Secondline Chemotherapy Regimens for Adults With cHL

Chapter 8: Treatments for Nodular Lymphocyte-Predominant Hodgkin Lymphoma

Table 8.1. Treatment for Various Stages of NLPHL
Part 3 — Survivorship and Living With the Side Effects of Treatment ........................................... 84

Chapter 9: Common Treatment Side Effects ................. 84

Table 9.1. Five Common Conditions Caused by Decreased Blood Cell Production .............................. 87

Chapter 10: Managing Life During and After Treatment . . . 110

Table 10.1. Coping Strategies ................................. 110

Part 4 — Hospital Admission ........................................ 116

Chapter 11: Preparing to Go to the Hospital .................. 116

Part 5 — Clinical Trials and Advances in Treatment .............. 123

Chapter 12: Overview of Clinical Trials ......................... 123

Table 12.1. The Four Main Phases of Clinical Trials ...... 124

Chapter 13: Advances in Treatment of Patients With Hodgkin Lymphoma ........................................ 130

About The Lymphoma Research Foundation ................. 136
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABMS</td>
<td>American Board of Medical Specialties</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>ANC</td>
<td>absolute neutrophil count</td>
</tr>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>ASH</td>
<td>American Society of Hematology</td>
</tr>
<tr>
<td>CAR</td>
<td>chimeric antigen receptor</td>
</tr>
<tr>
<td>CBC</td>
<td>complete blood count</td>
</tr>
<tr>
<td>cHL</td>
<td>classical Hodgkin lymphoma</td>
</tr>
<tr>
<td>CPR</td>
<td>cardiopulmonary resuscitation</td>
</tr>
<tr>
<td>CR</td>
<td>complete remission</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DLCO</td>
<td>diffusing capacity of the lungs for carbon monoxide</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid; genetic material</td>
</tr>
<tr>
<td>DNR</td>
<td>do not resuscitate</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>ECHO</td>
<td>echocardiogram</td>
</tr>
<tr>
<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>FNA</td>
<td>fine needle aspiration</td>
</tr>
<tr>
<td>GVHD</td>
<td>graft-versus-host disease</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HL</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>IFRT</td>
<td>involved-field radiation therapy</td>
</tr>
<tr>
<td>IHC</td>
<td>immunohistochemistry</td>
</tr>
<tr>
<td>IMRT</td>
<td>intensity-modulated radiation therapy</td>
</tr>
<tr>
<td>IRB</td>
<td>institutional review board</td>
</tr>
<tr>
<td>ISRT</td>
<td>involved-site radiation therapy</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
</tr>
<tr>
<td>LP</td>
<td>lymphocyte predominant (cell)</td>
</tr>
<tr>
<td>LRF</td>
<td>Lymphoma Research Foundation</td>
</tr>
<tr>
<td>MMAE</td>
<td>monomethyl auristatin E</td>
</tr>
<tr>
<td>MR</td>
<td>minor response</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>mTOR</td>
<td>mammalian target of rapamycin</td>
</tr>
<tr>
<td>MUGA</td>
<td>multigated acquisition</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>NHL</td>
<td>non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NK</td>
<td>natural killer (cell)</td>
</tr>
<tr>
<td>NLPHEL</td>
<td>nodular lymphocyte-predominant Hodgkin lymphoma</td>
</tr>
<tr>
<td>PD-1</td>
<td>programmed cell death-1</td>
</tr>
</tbody>
</table>
PET  positron emission
tomography
PFT  pulmonary function test
PICC peripherally inserted
central catheter
PML progressive multifocal
leukoencephalopathy
PR  partial remission
PS  performance status
RIT radioimmunotherapy
RS Reed-Sternberg
SAB scientific advisory board
TBI total body irradiation
INTRODUCTION

The purpose of this guide is to educate and support patients with Hodgkin lymphoma and their caregivers. It is designed to allow them to familiarize themselves with this disease and to become active participants in their healthcare decisions. Chapters in this guide address different issues faced by patients with Hodgkin lymphoma, including what to expect during diagnosis, work-up, and treatment; how to cope with treatment side effects; and what questions to ask doctors, nurses, physician assistants, social workers, and other members of the healthcare team. In addition to this guide, information is available on the Lymphoma Research Foundation’s (LRF’s) website at www.lymphoma.org and the Foundation’s Hodgkin lymphoma-specific website at www.FocusOnHL.org. The LRF Helpline can also provide additional information and copies of LRF educational and support publications. For Helpline assistance, call (800) 500-9976 or email helpline@lymphoma.org.
Hodgkin lymphoma (HL) is a type of cancer that affects specialized white blood cells called lymphocytes. Lymphocytes work together with other cells in the immune system to defend the body against invasion by bacteria, viruses, parasites, and other foreign substances. Lymphocytes travel in the bloodstream and in another network of vessels called the lymphatic system. Lymphocytes are also found in specialized structures called lymph nodes, in the bone marrow, and in the spleen. Lymph nodes are part of the lymphatic system and typically are the sites in which the body develops an immune response to viruses and bacterial infections.

This chapter explains these and other terms that will help people understand HL and how it affects a person’s health. A better understanding of the disease may allow patients to be active participants in their care.

What Is Cancer?
The body is made up of many different types of specialized cells that are organized into tissues and organs that perform the tasks needed to sustain life. To keep the body running smoothly, cells in the body grow, work, and multiply in a very controlled fashion.

All normal cells have a limited lifespan. A self-destruct mechanism is triggered when cells become senescent (too old) or get damaged; this process is called apoptosis or programmed cell death. However, sometimes damage to the genetic material (DNA) of a cell gives it the ability to override this self-destruct mechanism and allows the cell to continue to live and grow indefinitely, making the cell “immortal” in many ways. Unless the body’s immune system gets rid of these abnormal cells, they can become cancerous.
Cancer, or malignancy, is a disease in which abnormal cells gain the ability to multiply uncontrollably and also may develop defects in apoptosis (programmed cell death). When these cells accumulate, they form a mass called a *tumor* that can interfere with normal organ function.

**HOW CANCER FORMS INSIDE THE BODY**

**Normal cell division**
- Normal cell division
- Groups of abnormal cells may form tumors

**Cancer cell division**
- Damaged or senescent cell
- Programmed cell death (apoptosis)
- Damaged cell does not self-destruct, and starts to multiply
- Groups of abnormal cells may form tumors
Most cancers are named after the organ or cell type of their origin. For example:

- A cancer that started in the pancreas is called pancreatic cancer.
- A cancer of the lymphocytes is called a \textit{lymphoma} or \textit{lymphocytic leukemia} depending on whether the cancerous lymphocytes reside primarily in the lymph nodes and other lymphatic tissues (lymphoma) or primarily in the bone marrow and the blood (lymphocytic leukemia).

\textbf{What Are the Different Types of Blood Cells?}

There are three main classes of blood cells:

- Red blood cells (or \textit{erythrocytes}) — Red blood cells carry oxygen from the lungs to all the tissues in the body. Red blood cells also remove the carbon dioxide waste produced by cells and bring it to the lungs to be exhaled. A low number of red blood cells is called \textit{anemia}. A person with anemia may feel tired, weak, and short of breath.

- White blood cells (or \textit{leukocytes}) — White blood cells work as part of the immune system to help the body fight infections. The main types of white blood cells are:
  - Lymphocytes — These are discussed on the following page.
  - Granulocytes — There are three types of granulocytes: neutrophils, basophils, and eosinophils. Neutrophils help fight bacterial infections. A low number of neutrophils in the blood is called \textit{neutropenia}. People with neutropenia are more likely to get infections (mostly bacterial infections) than people with normal numbers of neutrophils. Basophils are cells that take part in inflammatory reactions. Eosinophils also help fight infections— particularly those caused by parasites—and they become plentiful during allergic reactions.
  - Monocytes — These also play an important role in immunity and are usually the first cells to recover after an episode of neutropenia.
Platelets (or *thrombocytes*) — Platelets are cell fragments produced by cells in the bone marrow. They clump together in a blood clot to stop bleeding from broken blood vessels. A low number of platelets is called *thrombocytopenia*. People with thrombocytopenia are more likely to bruise and bleed with minor trauma. They are also more likely to have severe and recurring nosebleeds and bleeding gums.

Because blood cells have a limited lifespan, the body needs to constantly replenish its supply of these cells. Red blood cells live for about 120 days; most white blood cells have a much shorter life, ranging from a few hours to a few weeks. New blood cells are made by *hematopoietic* (blood-forming) stem cells, which are immature (nonspecialized) cells that can develop into any kind of blood cell. Hematopoietic stem cells are found in the *bone marrow* (the spongy, fatty material inside large bones such as the pelvis, vertebrae, and ribs).

**What Are Lymphocytes?**

Lymphocytes are one type of white blood cell. There are three main types of lymphocytes:

- **B lymphocytes (B cells)** — B cells make antibodies to fight infections. They are called “B” cells because they were first discovered in the “Bursa of Fabricius” in birds (similar to the appendix in humans). Later, similar cells were found in humans.

- **T lymphocytes (T cells)** — There are many types of T cells. Some help B cells make antibodies, some attack and kill infected cells, and others help control or regulate the way other parts of the immune system fight infections. They are called “T” cells because they develop in the thymus gland, a small organ in the front of the chest.

- **Natural killer (NK) cells** — NK cells attack and kill cancer cells and virus-infected cells. They also make chemicals called cytokines that help the body get rid of viruses and tumor cells.
What Is the Lymphatic System?
As shown in the image below, the *lymphatic system* is a circulatory system made up of a spidery network of thin tubes called *lymph vessels* or *lymphatic vessels*. Like blood vessels, lymphatic vessels branch out into all tissues of the body. Lymphatic vessels carry *lymph*, a liquid that contains lymphocytes to help fight infection.
Within this huge network of vessels are groups of small, bean-shaped organs called **lymph nodes**, which are also commonly known as “glands.” Lymph nodes filter the lymph fluid, removing bacteria, viruses, and other foreign substances from the body. Hundreds of lymph nodes are found at locations throughout the body, including the neck, underarms, chest, abdomen, and groin. Lymphocytes can mostly be found in lymph nodes, where they monitor the body’s immune system for signs of infection. The lymph nodes can change in size, becoming bigger or smaller depending on the number of lymphocytes inside them.

If large numbers of foreign substances are filtered through a lymph node or series of lymph nodes, swelling may occur and the nodes may become tender to the touch. Most swollen lymph nodes are a reaction to infection and are not cancerous. Lymph nodes can also become enlarged in states of inflammation, such as in autoimmune diseases like rheumatoid arthritis.

**How Does the Immune System Work?**
The immune system is the body's defense against things that might cause it harm. The immune system is made up of a network of cells, tissues, and organs that work together to detect and destroy invaders, such as bacteria, viruses, and parasites, that can make people sick.

The immune system provides two different types of immunity:

- **Innate** (meaning “inborn” or “natural”) immunity — This type of immunity is provided by natural barriers in the body, substances in the blood, and specific cells that attack and kill foreign cells. Examples of natural barriers include skin, mucous membranes, stomach acid, and the cough reflex. These barriers keep germs and other harmful substances from entering the body. **Inflammation** (redness and swelling) is also a type of innate immunity. Blood cells that are part of the innate immune system include neutrophils, macrophages, eosinophils, and basophils.
■ **Adaptive** (meaning adapting to external forces or threats) immunity — This type of immunity is provided by the thymus gland, spleen, tonsils, bone marrow, circulatory system, and lymphatic system. B cells and T cells, the two main types of lymphocytes, carry out the adaptive immune response by recognizing and either inactivating or killing invading organisms. The adaptive immune system can then “remember” the identity of the invader, so that the next time the body is infected by the same invader, the immune response will develop more quickly and strongly.

**What Is Lymphoma?**

A **lymphoma** is a type of cancer that originates from lymphocytes in the lymph nodes and other tissues in the lymphatic system. There are two major categories of lymphomas: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Both of these categories are further subdivided into numerous types that differ in the way they develop and spread, whether they come from B cells or T cells or NK cells, as well as in the way they are treated. Unlike other cancers, therapy and prognosis are not based solely on the stage at which the disease is diagnosed but rather are determined by the lymphoma type, in addition to a variety of other factors like age and other medical issues.

**What Is Hodgkin Lymphoma?**

Hodgkin lymphoma (previously called Hodgkin’s disease or Hodgkin disease) is a type of cancer that starts in the lymphocytes. HL is named after Dr. Thomas Hodgkin, a British physician who first described the disease in 1832. In the United States, approximately 8,260 people a year are diagnosed with HL. Although both children and adults can develop HL, the disease is most common among young adults aged 20 to 34.
How Does HL Develop?
HL develops when abnormal (cancerous) B cells called Reed-Sternberg (RS) cells start to multiply and grow in an unregulated manner. Most patients with HL have either RS cells or RS-cell variants in their lymphatic tissue. When examined under a microscope, RS cells are usually surrounded by large numbers of inflammatory cells such as T cells, histiocytes, eosinophils, and neutrophils. For this reason, HL was not initially recognized as a cancer; for years doctors thought of HL as a type of infection.

A REED-STERNBERG CELL

The presence of cells that look like RS cells does not necessarily mean that a person has HL. In fact, RS-like cells can be found in many other conditions, some of which are benign (not cancerous). However, one characteristic that is unique to most types of HL is that the RS cells have an antigen (marker) on their surfaces called CD30. To make an HL diagnosis, a hematopathologist (a doctor who specializes in the
diagnosis of blood diseases) examines a sample of lymphatic tissue under a microscope and uses tests to determine whether (1) the RS cells are surrounded by inflammatory cells, and (2) the CD30 antigen and CD15 antigen are present on the RS cells. The hematopathologist may also use more sophisticated molecular tests to help confirm the diagnosis.

HL usually starts in the lymph nodes, and the first signs a patient notices may be swelling in the neck, above or below the collarbone, under the arms, in the chest, or in the groin. The lymphoma can then spread throughout the body via lymphatic vessels. HL may also spread to other areas and organs outside of the lymphatic system.

**What Distinguishes HL From NHL?**
The RS cells seen in patients with HL are not present in patients with NHL. Also, unlike NHL, HL tends to spread from one group of lymph nodes to adjacent nodes, while NHL may spread to lymph nodes anywhere in the body in an unpredictable manner.

The different types and subtypes of HL are distinguished by how they look under a microscope. The two main forms are classical HL (cHL) and nodular lymphocyte-predominant HL (NLPHL).

**Classical Hodgkin Lymphoma and Its Subtypes**
About 95 percent of patients with HL have cHL. Classical Hodgkin lymphoma is further divided into four subtypes, as described in Table 1.1. However, it is important to remember that these four subtypes are generally treated similarly.
Table 1.1. Subtypes of Classical Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular Sclerosis HL</td>
<td>- Affects 70 percent of patients with cHL</td>
</tr>
<tr>
<td></td>
<td>- Often causes involved lymph nodes to form nodules (lumps) separated by broad bands of fibrotic (fiber-like) or sclerotic (hardened) tissue</td>
</tr>
<tr>
<td></td>
<td>- Typically affects young adults and is more common in women</td>
</tr>
<tr>
<td></td>
<td>- Most frequently involves lymph nodes in the chest</td>
</tr>
<tr>
<td>Mixed Cellularity HL</td>
<td>- Affects 20 to 25 percent of patients with cHL</td>
</tr>
<tr>
<td></td>
<td>- Characterized by many classic RS cells mixed with various other types of inflammatory cells</td>
</tr>
<tr>
<td></td>
<td>- Primarily affects older adults, children under 10 years, and people with underlying immunodeficiency disorders</td>
</tr>
<tr>
<td>Lymphocyte-Rich HL</td>
<td>- Affects five percent of patients with cHL</td>
</tr>
<tr>
<td></td>
<td>- Characterized by many normal lymphocytes and relatively few RS cells</td>
</tr>
<tr>
<td></td>
<td>- More common in men</td>
</tr>
<tr>
<td>Lymphocyte-Depleted HL</td>
<td>- Affects less than one percent of patients with cHL</td>
</tr>
<tr>
<td></td>
<td>- Characterized by very few normal lymphocytes and many RS cells</td>
</tr>
<tr>
<td></td>
<td>- More common in older adults</td>
</tr>
<tr>
<td></td>
<td>- Often not diagnosed until the disease is in an advanced stage</td>
</tr>
</tbody>
</table>

**Nodular Lymphocyte-Predominant Hodgkin Lymphoma**

NLPHL, which makes up about five percent of HL cases, is characterized by variants of RS cells called lymphocyte-predominant (LP) cells. These are also called “popcorn cells,” because the cell nuclei resemble popped kernels of corn. LP cells have different antigens on their cell surfaces than the RS cells in cHL. For example, LP cells are positive for the CD20 antigen, which is common in B-cell NHL, and they are negative for the CD30 antigen. This form of HL is often found in the lymph nodes of the neck, groin, or underarms. It is *indolent* (slow-growing). The approach to treatment for NLPHL differs...
from the treatment for cHL, as discussed in Chapter 8. NLPHL should not be confused with lymphocyte-rich HL, which is a subtype of cHL described in Table 1.1.

**Why Do Certain People Develop HL?**

The reasons why certain people develop HL are not totally understood. However, scientists have found that people with particular characteristics called “risk factors,” have a slightly higher chance of developing HL compared with people who do not have these risk factors. Having one or more HL risk factors does not mean a person will definitely develop the disease. In fact, most people with the known risk factors never develop HL, and many people diagnosed with HL do not have any of these risk factors. However, there does seem to be a correlation between the risk factors described in Table 1.2 and the development of HL.

**Table 1.2. Known Risk Factors for Hodgkin Lymphoma**

<table>
<thead>
<tr>
<th>Age</th>
<th>It has a bimodal distribution of age groups: people who are 15 to 40 years of age, as well as those who are older than 55 years, have a higher risk of developing HL than people in other age groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History</td>
<td>People with a family history of HL, especially among first-degree relatives (parent, sibling, or child), have a higher risk of developing HL compared with people who do not have first-degree relatives with the disease.</td>
</tr>
<tr>
<td></td>
<td>Siblings of patients with HL have a three- to seven-fold increased risk of developing this disease, and the risk is higher in identical twins. However, since the incidence of HL in the general population is extremely low, the risk of a first-degree relative developing HL is still very rare.</td>
</tr>
<tr>
<td></td>
<td>Fewer than one percent of patients with HL have a family history of the disease.</td>
</tr>
</tbody>
</table>
Table 1.2. Known Risk Factors for Hodgkin Lymphoma (continued)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Overall, men have a slightly higher risk of developing HL than women; however, women are more likely to be diagnosed with the nodular sclerosis subtype.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunodeficiency Disorders</td>
<td>People with inherited (for example, common variable immunodeficiency disorder, X-linked lymphoproliferative disorder) or acquired (for example, chronic immunosuppression that may occur following a solid organ transplant or treatment of certain immune conditions such as juvenile rheumatoid arthritis) are at an increased risk of developing HL.</td>
</tr>
<tr>
<td>Infection by Certain Viruses</td>
<td>People infected with the Epstein-Barr virus (EBV; the virus that can cause infectious mononucleosis) or the human immunodeficiency virus (HIV; the virus that can cause acquired immunodeficiency syndrome [AIDS]) have a higher risk of developing HL compared with people who have not been infected with these viruses.</td>
</tr>
</tbody>
</table>

HL cannot be caused by injury and cannot be caught from someone who has the disease. While parents, children, and siblings of patients with HL have a slightly increased risk of developing this disease compared with the general population, there are no clearly identifiable genetic or hereditary factors that can predict this slightly increased risk. Therefore, routine screening for HL among the immediate family members of patients with HL is not recommended.
Chapter 2: Seeking Medical Attention

This chapter explains the signs and symptoms of Hodgkin lymphoma (HL) and discusses how a doctor determines whether a person has the disease.

A *sign* is anything unusual that doctors, nurses, or physician assistants notice when they examine their patients or look at their laboratory test results.

A *symptom* is anything unusual in a normal body function, appearance, or sensation that a patient experiences. During a visit with a healthcare practitioner, patients should report all of their symptoms to their doctor, nurse, or physician assistant. Symptoms may indicate the presence of HL or another disease.

What Are the Signs and Symptoms of HL?

Some patients with HL do not have any obvious signs or symptoms of the disease. Their doctors might detect the lymphoma during routine blood tests and/or a physical examination. For others, the lymphoma is discovered when symptoms occur and patients go to the doctor because they are worried, uncomfortable, or not feeling well.

As shown in Table 2.1, HL may cause different signs and symptoms depending on where it is located in the body. Keep in mind that many of these signs and symptoms are not specific to HL and may be due to other conditions.
Table 2.1. Signs and Symptoms Commonly Found in Patients With HL

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>Possible Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumps under the skin on the sides of the neck, above the collarbone, or in the</td>
<td>Lymph nodes, or “glands,” that swell when the lymphocytes respond to an infection</td>
</tr>
<tr>
<td>underarms, elbows, or groin</td>
<td>or because of an increased number of abnormal lymphocytes</td>
</tr>
<tr>
<td>“B symptoms,” including fevers for no known reason, unexplained weight loss,</td>
<td>Increased levels of inflammatory chemicals in the blood that are released by</td>
</tr>
<tr>
<td>and drenching night sweats that soak clothing and sheets</td>
<td>lymphoma cells or by the immune system reacting to the lymphoma cells</td>
</tr>
<tr>
<td>Unexplained itching (sometimes severe)</td>
<td>Unknown cause but often associated with “B symptoms” or reactivation of viruses</td>
</tr>
<tr>
<td>Coughing, trouble breathing, or chest pain or pressure</td>
<td>Lymphoma in the chest, which may press on the windpipe or bronchi (tubes leading</td>
</tr>
<tr>
<td></td>
<td>to the lungs)</td>
</tr>
<tr>
<td></td>
<td><em>Pleural effusion</em> (fluid surrounding the lungs)</td>
</tr>
<tr>
<td>Feeling tired</td>
<td>Anemia (low red blood cell count)</td>
</tr>
<tr>
<td>Increased sensitivity to alcohol, or pain in the lymph nodes after drinking</td>
<td>Poorly understood cause, but thought to be due to increased blood flow through the</td>
</tr>
<tr>
<td>alcohol</td>
<td>lymph nodes in response to alcohol</td>
</tr>
</tbody>
</table>

When Should a Patient Seek Medical Attention?

Anyone who has an enlarged lymph node that does not return to normal size within one month and is greater than one centimeter in size (unless it is located in the groin) and/or persistent symptoms should see a doctor to make sure that lymphoma or another serious condition is not present. A good rule of thumb is to seek medical attention if any of the signs or symptoms listed in Table 2.1 last longer than two weeks, or sooner if the symptoms are severe enough to impact daily life. It is important to note that most patients with these symptoms do not have lymphoma, as diseases or conditions not related to lymphoma may cause many of these symptoms.
What Does the Doctor Look for During the Visit?

During their visit, patients should describe all of their symptoms to the doctor. The doctor will ask questions about their medical history and perform a complete physical examination, during which the doctor is likely to:

- Ask about “B symptoms” (unexplained fever, unexplained weight loss, and night sweats)
- Ask about pain in the lymph nodes after drinking alcohol
- Ask about itching
- Ask about any other pain the patient may be experiencing
- Measure blood pressure and pulse
- Listen to the heart and lungs
- Look for any physical signs of infection or any other cancers, especially on the skin
- Check for swollen lymph nodes under the chin, in the neck and tonsil area, above the shoulders, on the elbows, in the underarms, and in the groin
- Examine other parts of the body to look for swelling or fluid that may be caused by swollen lymph nodes
- Examine the abdomen to see whether the liver and/or spleen are enlarged and to feel for masses

If the doctor suspects HL after reviewing the symptoms reported and the signs discovered during the examination, he or she will order tests to confirm the diagnosis.
These tests include a complete blood count (CBC) with differential and a biopsy; they may also include specific laboratory tests, chest X-rays, computed tomography (CT) scans or other imaging tests, bone marrow evaluation, and heart and lung function tests. Depending on the type and location of the suspected HL, other tests may be required. However, a diagnosis of HL cannot be established without evaluating a sample of the involved tissue. These tests and procedures are discussed in more detail in Chapters 3 and 4.
Chapter 3: Receiving a Diagnosis

Doctors need the results of various diagnostic tests to determine accurately whether a patient has Hodgkin lymphoma (HL). This chapter explains the purpose of each test and describes what to expect during and after the test procedures.

Before agreeing to any procedure, patients should make sure they understand the reasons for the procedure and what will be involved. Here is a list of questions patients may want to ask their doctor.

**Patent Tip: Questions to Ask Before Having a Diagnostic Procedure**

- Why is this procedure necessary?
- What will the procedure tell us about my condition?
- Can the same information be obtained in another way?
- What is involved in this procedure?
- What are the possible risks, complications, and side effects?
- Where will I have the procedure done?
- Will I have to do anything to prepare for the procedure?
- How long will the procedure take? Will I be awake? Will I feel pain?
- How long will it take for me to recover from the procedure?
- May someone else be present when I have the procedure?
- Will I need someone to take me home afterward?
- When will I get the results?
- When will we discuss the results?
How Is HL Diagnosed?
A tissue biopsy is the test required to establish an initial diagnosis of HL. After that, one or more of the following tests may also be used to help with the HL diagnosis:

- Complete blood count (CBC) with differential (a test in which the relative percentages of each type of blood cell are determined)
- Erythrocyte (red blood cell) sedimentation rate (ESR) test
- Comprehensive metabolic panel to check liver and kidney function
- Testing for infection with the human immunodeficiency virus (HIV) and hepatitis B and C viruses
- Positron emission tomography (PET) and computed tomography (CT) scans

What Is a Biopsy?
A biopsy is a procedure in which a piece of tissue from an area of suspected disease is removed from the body and examined under a microscope. The information provided by this tissue sample is crucial to correctly diagnose the disease and to decide on the best course of treatment.

Table 3.1 on the next two pages shows the three main types of biopsies used in patients with suspected HL.
### Table 3.1. The Three Main Types of Biopsies

<table>
<thead>
<tr>
<th>Biopsy Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excisional or Incisional Biopsy</strong></td>
<td>This type of biopsy is generally considered the best to establish an initial diagnosis of HL because it allows the removal of bigger samples than other biopsy procedures. The larger the sample, the more tissue can be examined, which improves the accuracy of the diagnosis.</td>
</tr>
<tr>
<td></td>
<td>A surgeon cuts through the skin to remove an entire lymph node (excisional biopsy) or a large portion of a lymph node or other tissue (incisional biopsy).</td>
</tr>
<tr>
<td></td>
<td>If the lymph node is close to the skin surface, the procedure can be done under local anesthesia to numb the area. If the lymph node is in the chest or abdomen, the patient is sedated and the surgeon removes the tissue either laparoscopically (through a tube inserted in the body) or by performing more extensive surgery.</td>
</tr>
<tr>
<td><strong>Core Needle Biopsy</strong></td>
<td>This procedure is used when the lymph nodes being examined are deep in the chest or abdomen or in other locations that are difficult to reach with excisional biopsy, or when there are medical reasons for avoiding an excisional or incisional biopsy.</td>
</tr>
<tr>
<td></td>
<td>A large needle is inserted into the lymph node and a small tissue sample is withdrawn using a syringe attached to the needle. This can be done under local anesthesia, and stitches are usually not required.</td>
</tr>
<tr>
<td></td>
<td>Sometimes the material collected may not be adequate for diagnosis, so a subsequent excisional or incisional biopsy may be necessary.</td>
</tr>
<tr>
<td></td>
<td>Often the core needle biopsy is guided by an imaging test, such as an ultrasound, CT scan, or PET scan.</td>
</tr>
</tbody>
</table>
After a tissue sample has been removed, it is examined by a pathologist (doctor who specializes in the diagnosis of diseases by studying the cells from a patient’s body fluids and tissue samples). A hematopathologist (pathologist who has undergone additional training in the diagnosis of blood diseases, including lymphoma) may also examine the sample. These specialists identify and classify the lymphoma cells by looking at their shape and size and how they are grouped in the sample.

An oncologist (doctor who specializes in treating patients with cancer) or hematologist (doctor who specializes in treating patients with blood cancers and other blood disorders) uses the pathologist’s report, along with results of other diagnostic tests, to confirm a diagnosis. A pathologic diagnosis and accurate classification of specific lymphoma types can sometimes be difficult to make. If the pathologist’s interpretation of the biopsy is uncertain, the biopsy should be reviewed by an expert hematopathologist.

Biopsies that are interpreted as “normal” may still contain HL cells. This may occur when the sample is small and therefore not representative of the rest of the lymph node. Sometimes a repeat biopsy is needed to establish the diagnosis. It takes an experienced hematopathologist working with the hematologist or oncologist to determine the need for more tissue sampling.
What Are a Bone Marrow Biopsy and a Bone Marrow Aspiration?

*Bone marrow* is the spongy, fatty material inside large flat bones (such as the pelvis, vertebrae, and sternum) where blood cells are generated. A *bone marrow biopsy* involves removing a small amount of bone marrow and examining it for the presence of lymphoma cells. A *bone marrow aspiration* is similar to a bone marrow biopsy, except it involves removing only the liquid portion of the marrow using a fine needle. A bone marrow biopsy or aspiration is not typically used for initial diagnosis, but it is occasionally used at a later stage to determine whether the HL has spread to the bone marrow.

What Happens During a Bone Marrow Aspiration and Biopsy?

- Patients lie on the examination table either on their side or on their stomach.
- Patients may be given a general anesthetic to put them to sleep, or the doctor may inject a local anesthetic to numb the skin over the hip where the needle will be inserted.
- In bone marrow aspiration, the doctor inserts a thin, hollow needle through the skin into the hip bone.
- The doctor then uses a syringe to remove a small amount of liquid from the bone marrow. Even with the numbing local anesthetic, withdrawal of the marrow can briefly cause pain.
- In a bone marrow biopsy, which is often performed immediately after the aspiration, the doctor inserts a slightly larger needle to remove a small piece of bone and marrow. This procedure can also briefly cause pain.
- A pathologist examines the samples under a microscope to look for Reed-Sternberg (RS) cells and other findings that may indicate HL.
What Is a Complete Blood Count (CBC) With Differential Test?
In a CBC with differential test, samples of blood are examined to measure the levels of each different type and subtype of blood cells, including:

- The number of red blood cells
- The amount of hemoglobin (the oxygen-carrying protein) inside the red blood cells
- The number of total white blood cells, as well as the numbers of each subtype of white blood cells (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
- The number of platelets

The results of the CBC with differential test assist in the diagnosis of HL by ruling out other types of blood cancer. The test is often repeated during the course of treatment to help determine how much the therapy has affected the different blood counts and, in some cases, to help gauge how well the treatment is working against the lymphoma.

What Is Erythrocyte Sedimentation Rate (ESR)?
The ESR is the rate at which erythrocytes (red blood cells) settle to the bottom of a tube of blood. The ESR is an indicator of the amount of inflammatory cells in the blood. Patients with an elevated ESR tend to have a worse prognosis so they may be treated more aggressively.

What Is Immunophenotyping?
Immunophenotyping is a process that can be used to distinguish between different types of cells (for example, normal lymphocytes vs. HL cells) based on the presence of antigens (cell markers) on the cell surface. Antigens are specific to different cell types, just as landmarks are specific to different cities. These antigens are recognized by antibodies that have been chemically modified in the laboratory so that they show color or emit fluorescent light.
Two types of analyses, immunohistochemistry (IHC) and flow cytometry, may be performed with these antibodies for accurate immunophenotyping (see Table 3.2).

<table>
<thead>
<tr>
<th>Table 3.2. Immunohistochemistry and Flow Cytometry Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunohistochemistry (IHC)</strong></td>
</tr>
<tr>
<td>■ Thin slices of the biopsy sample (or thin layers of fluid) are treated with sets of antibodies that recognize markers found in different types of lymphoma cells and normal lymphocytes.</td>
</tr>
<tr>
<td>■ The pathologist examines the slides under a microscope to look for the visible color change that happens when the antibodies attach to the antigens.</td>
</tr>
<tr>
<td>■ The pathologist identifies and counts the number of cells that are highlighted by color (meaning that they have the antigen on their surface or inside the cell) with each of the different antibodies.</td>
</tr>
<tr>
<td><strong>Flow Cytometry</strong></td>
</tr>
<tr>
<td>■ Cells from the biopsy sample are placed in a liquid solution and treated with sets of antibodies that recognize antigens found in different types of lymphoma cells.</td>
</tr>
<tr>
<td>■ The cell-antibody mixture is injected into an instrument called a flow cytometer. This machine uses laser beams to detect the different colors of light the cells emit from the antibodies attached to them. This information is measured and analyzed by a computer and interpreted by a hematopathologist or another specialist.</td>
</tr>
<tr>
<td>■ This approach to immunophenotyping is not used in the diagnosis of HL as frequently as it is for other diseases.</td>
</tr>
</tbody>
</table>
It is important for patients to discuss the interpretation of diagnostic tests with their doctor. Here is a list of some important considerations when interpreting diagnostic reports.

**Cautions About Interpreting Diagnostic Reports**

- A biopsy is the only definitive test for HL.
- Some test results may be reported as “normal” even though HL is present.
- Some test results may be reported as “abnormal” even though HL is not present.
- Other conditions can produce signs and symptoms similar to HL.
- The interpretation of test results such as imaging studies and scans can be lengthy and difficult in some situations.
- Follow-up tests are often needed to determine the significance of previous results, and additional biopsies may be needed to clarify the results.
- If patients wish to look at their written test reports, it is important for them to review the findings carefully with their doctor.
After the initial diagnosis of Hodgkin lymphoma (HL), the doctor may order other tests such as blood tests, imaging studies, heart and lung function tests, a bone marrow biopsy or aspiration, and, less frequently, additional biopsies. This process is often called the work-up or staging studies. Some of these tests are needed to determine a patient’s disease stage, which is a measure of whether and how much the disease has spread to other parts of the body. Other tests check how the disease has affected a patient’s overall health and major organ functions.

Together, these test results provide the information needed to help patients and their doctors decide on the best course of treatment. This chapter explains the reasons for the various tests, how these tests work, what to expect, and how HL is staged.

**What Tests Are Used in the Work-Up for HL?**

Patients with HL may undergo some or all of the following work-up tests before starting treatment. Many of these tests may be repeated during the course of treatment.

- Physical examination with special attention to the size of the liver, spleen, and lymph nodes in the neck, underarms, and groin
- Determination of general health status (also called *performance status* or *functional status*) to see how well a patient feels and how well he/she can carry out normal daily activities, such as getting washed and dressed, going to work, and doing chores.
- Questioning about the presence of fever, night sweats, and weight loss (also called “B symptoms”)
- Questioning about the presence of itching and pain, particularly in response to drinking alcohol
- Questioning about human immunodeficiency virus (HIV) and cardiac disease
- Complete blood count (CBC) with differential
- Measurement of the erythrocyte sedimentation rate (ESR)
- Comprehensive metabolic panel
- Testing for infection with human immunodeficiency virus (HIV) and hepatitis viruses
- Chest X-ray
- Computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography (PET) scans of the neck, chest, abdomen, and pelvis
- Echocardiogram (ECHO) or multigated acquisition (MUGA) scan to evaluate heart function
- Pulmonary studies to evaluate lung function
- Excisional, incisional, or core needle biopsy
- Bone marrow aspiration and/or biopsy is not routinely performed in adults (it may be used in select cases), although it is done routinely in pediatric patients with intermediate- and high-risk disease

Many of these tests—including a CBC with differential, ESR, and the different types of biopsies—were described in Chapter 3; the rest are discussed in this chapter.

What Is Performance Status?

Performance status (PS) is a numerical rating of patients’ general health and their ability to carry out normal daily activities (such as getting washed and dressed, going to work/school, and doing chores). As shown in Table 4.1 on the next page, PS is graded on a scale of 0–4, with the lower numbers indicating better health. Note that in younger patients, other PS scales may be used.
What Is a Comprehensive Metabolic Panel?

A comprehensive metabolic panel measures the levels of certain chemicals in the blood to see whether the HL is causing any abnormalities in the main organs of the body. The comprehensive metabolic panel usually includes 14 or more specific tests that measure liver and kidney function, electrolytes, acid/base balance, and the levels of blood sugar and other blood proteins. Testing is also often done for uric acid and lactate dehydrogenase (LDH); high levels of LDH are associated with fast-growing lymphomas.

The results from these tests can help patients and their doctors choose between different treatments. Many of these blood tests may be repeated several times during the course of treatment to see how the treatment and the lymphoma are affecting the patient’s body functions.
What Is the Purpose of Testing For Hepatitis Virus and HIV?
It is important to determine whether patients with HL are infected with hepatitis B virus (HBV), hepatitis C virus (HCV), and/or HIV, because the presence of these viruses in the body may affect the type of treatments given.

What Types of Imaging Tests May Be Used?
A doctor will order imaging tests to help identify areas of the body where the lymphoma has spread, and, later on, to determine how well treatment is working. Most of these tests are painless and require no anesthetic. Several types of imaging procedures (described in Table 4.2) may be needed to thoroughly evaluate the extent of disease.

Table 4.2. Types of Imaging Tests

<table>
<thead>
<tr>
<th>Chest X-Ray</th>
<th>X-rays use radiation to take pictures of areas inside the body. The amount of radiation used in most diagnostic tests is so small that it poses little risk to the patient.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Findings from a chest X-ray may indicate whether a tumor is “bulky” (greater than 10 centimeters in adults or greater than six centimeters in children), located in the mediastinum, or measures more than one-third of the diameter of the chest cavity.</td>
</tr>
</tbody>
</table>
|             | A chest X-ray is the only imaging test conducted while the patient is standing up.  Adamant Anti-Adipogenic Treatment  

<table>
<thead>
<tr>
<th>Computed Tomography (CT) Scan</th>
<th>A CT scan takes X-rays from many different angles around the body. A computer combines the pictures obtained from these different angles to give a detailed image of organs inside the body.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with HL often have CT scans of the neck, chest, abdomen, and pelvis to find out how many lymph nodes are involved and how enlarged they are, as well as whether any internal organs are affected by the disease.</td>
</tr>
<tr>
<td></td>
<td>Before a CT scan, the patient may be asked to drink a contrast liquid and/or get an intravenous (IV) injection of a contrast dye that will more clearly outline any abnormal areas in the body.</td>
</tr>
</tbody>
</table>
### Magnetic Resonance Imaging (MRI)
- An MRI uses magnets and radiofrequency waves to acquire images from different angles throughout the body.
- An MRI can provide important information about tissues and organs, particularly the bones and nervous system that is not available from other imaging techniques.
- MRI scans cannot replace CT scans, because they do not provide clear images of lymph nodes as well as CT scans do.

### Positron Emission Tomography (PET)
- A PET scan evaluates HL activity in all parts of the body.
- Radioactive fluorodeoxyglucose (a type of sugar) is injected into the body. A positron camera is then used to detect the radioactivity and produce cross-sectional images of the body. This test relies on the fact that cancer cells metabolize sugar faster than normal cells, so that more “uptake” on a PET scan indicates more metabolic activity, suggesting the presence of the malignant cells.
- While CT scans provide information about the size of a lymph node, PET scans can better indicate whether the lymph node contains active HL cells.
- PET scans help distinguish active tumors from scar tissue and may be used to assess a patient’s response to treatment.
- PET and CT scans are often combined into a single test (PET-CT), in which the CT procedure is slightly modified from that described above.
Why Is Heart Function Evaluated?
Before beginning some types of lymphoma treatment, the doctor may measure the patient’s baseline heart function to make sure that the patient’s body can withstand treatment. This is especially important because certain lymphoma treatments can occasionally make heart function worse. Depending on the treatment used, the patient’s heart function may be evaluated again during treatment to make sure the heart is tolerating the treatment.

Two tests are used to evaluate heart function: an echocardiogram (ECHO) or a multigated acquisition (MUGA) scan.

An ECHO is an ultrasound of the heart. An instrument called a transducer is placed on the chest and releases high-frequency sound waves, which are converted into moving images of the heart. This test evaluates the function of the cardiac muscle and provides information about the heart valves. An ECHO can be performed while the patient is resting or after exercise.

A MUGA scan creates video images of the ventricles (lower chambers of the heart) to measure how well they are pumping blood. During the procedure, a tracer (radioactive material) that attaches to red blood cells is injected into the arm. As the tracer moves through the bloodstream, a special camera takes pictures to see how efficiently the heart is pumping the blood.

Why Is Lung Function Evaluated?
Some lymphoma treatments, especially the chemotherapy drug bleomycin (Blenoxane), can put stress on the lungs. For this reason, the doctor may order pulmonary (lung) function tests (PFTs) before beginning treatment and again during treatment to make sure the patient’s lungs are working properly.

Three types of PFTs are typically used. Spirometry measures the amount of air a patient breathes in and out. For this test, the patient is fitted with a mouthpiece and a nose clip and is asked to breathe normally.
Patients may also be told to inhale and exhale as deeply and/or as rapidly as they can for several seconds.

**Plethysmography** measures the volume of air in the lungs. For this test, the patient sits or stands in a small booth and breathes into a mouthpiece. The pressure in the booth is measured to determine lung volume.

A third test, called **diffusing capacity of the lungs for carbon monoxide** (DLCO), measures how well the lungs transfer gas from inhaled air to red blood cells. Patients are asked to inhale air containing a very small amount of carbon monoxide, hold their breath for 10 seconds, and then exhale.

**How Is HL Staged?**

Staging is used to describe how widely the lymphoma has spread in patients with HL. Doctors use the stage of disease, along with test results and other factors, to decide the best time to begin treatment and what treatments are likely to be the most effective for each patient.

For adults, there are two main divisions of HL (limited and advanced disease) and four stages designated by Roman numerals I through IV. Stages I and II are considered limited disease, although Stage II may be considered advanced in patients with *bulky* disease (tumors greater than 10 centimeters [~four inches] wide). Stages III and IV are considered advanced disease. Although some patients have advanced HL at the time they are diagnosed, their disease can often be successfully treated.

The Ann Arbor staging system has traditionally been used for staging HL. Although this older staging system is still in use, a modification of the Ann Arbor staging system called the Lugano Classification was proposed in 2014. This system is shown in the figure on the following page.
STAGING OF HL (LUGANO CLASSIFICATION)

Stage I:
• Involvement of a single lymph node or group of adjacent nodes

Stage II:
• Involvement of two or more groups of lymph nodes on the same side of the diaphragm

Stage III:
• Involvement of lymph nodes on both sides of the diaphragm (muscle that separates the chest from the abdomen), or
• Involvement of lymph nodes above the diaphragm plus spleen involvement

Stage IV:
• Widespread disease in lymph nodes and organ involvement
Stage I–IV HL can be further classified based on whether “B symptoms” (fever, unexplained weight loss of greater than 10 percent of body weight, and drenching night sweats) are present. An “A” designation means that the patient does not have “B symptoms,” while the “B” designation means that the patient does have “B symptoms” (see Chapter 2 for additional discussion of “B symptoms”).

In children, HL is staged using a different system in which the lymphoma is classified as low-, intermediate-, or high-risk.
Chapter 5: What to Know Before Starting Treatment

Receiving a cancer diagnosis can be overwhelming. It is perfectly normal to be shocked by the diagnosis, anxious about the future, and confused about the decisions that need to be made. This chapter will help patients and caregivers prepare for the start of treatment by explaining the next steps and providing tips for talking with doctors about any questions or concerns. Patients can also call the Lymphoma Research Foundation’s (LRF’s) Helpline at (800) 500-9976 or email helpline@lymphoma.org.

First Steps to Take After Receiving a Diagnosis

- Take care of yourself (eat, sleep, rest, and exercise).
- Seek the support of family, friends, and others you trust.
- Learn about the disease and treatment options.
- Find medical care that meets your needs.
- Seek out additional sources of emotional and social support for people with cancer, such as LRF’s Lymphoma Support Network that connects patients and caregivers with volunteers who have experience with Hodgkin lymphoma, similar treatments, or challenges.
- Research the cost of care, what your insurance will cover, and what financial assistance programs may be available to you.
- Maintain a copy of your medical records (paperwork, test results, and your own notes).
- Download and start using LRF’s Focus On Lymphoma app on your mobile device to learn about and manage HL.
**Who Plans and Carries Out the Treatment?**

Treatment is usually overseen by a medical oncologist, hematologist, or hematologist/oncologist. Oncologists are physicians who specialize in diagnosing and treating patients with cancer. Hematologists are physicians who specialize in diagnosing and treating patients with disorders of the blood and lymphatic system. Physicians who treat lymphoma may be certified in one or both specialties. Depending on the patient’s healthcare needs, the primary doctor may refer the patient to other specialists, such as a surgical oncologist or a radiation oncologist. The doctor may also suggest a second opinion at a cancer center with particular expertise in managing patients with a specific type of Hodgkin lymphoma (HL) or for participation in a clinical trial. For more information about clinical trials, contact LRF’s Helpline at (800) 500-9976 or helpline@lymphoma.org and ask about the LRF “Clinical Trials Information Service.”

The healthcare team may also include other healthcare professionals such as an oncology nurse, nurse practitioner, physician assistant, clinical research coordinator, social worker, and registered dietitian. The healthcare team works together and consults with the patient to plan, carry out, and monitor the treatment.

**What Is a Prognosis?**

Prognosis is the medical term for predicting how a disease will progress and the likelihood for recovery, which is often one of the first questions that patients ask their doctor. A prognosis is usually based on information gathered from hundreds or thousands of other patients who have had the same disease. This statistical information provides doctors with a general idea of what to expect when a patient is diagnosed with a specific type of HL, and it helps them select which treatments are most likely to work.
Keep in mind that no two patients are alike and that statistics from large groups of people cannot accurately predict what will happen to an individual patient. The doctor most familiar with the patient’s situation is in the best position to interpret these statistics and understand how well they apply to a patient’s particular situation. Patients should also bear in mind that most published statistics on treatment outcomes do not reflect the benefits of the most recent new therapeutics that might be used in treatment.

What Are Prognostic Factors?
The characteristics that help predict a patient’s prognosis are called prognostic factors. Favorable or good prognostic factors tend to be associated with better outcomes, while unfavorable or adverse prognostic factors tend to be associated with worse outcomes.

To help doctors determine the best course of treatment, patients with classical HL (cHL) are grouped in prognostic categories reflective of their risk factors. Some of the adverse prognostic risk factors are listed in Table 5.1 and are derived from the International Prognostic Score. Note that the risk factors are somewhat different in pediatric patients.

Table 5.1. Adverse Prognostic Risk Factors

<table>
<thead>
<tr>
<th>Stage</th>
<th>Adverse Prognostic Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited Disease</td>
<td>• Bulky disease (a tumor in the chest larger than one-third of the width of the chest, or a tumor at least 10 centimeters wide)</td>
</tr>
<tr>
<td></td>
<td>• Cancer that has spread directly outside the lymph nodes to an adjacent site</td>
</tr>
<tr>
<td></td>
<td>• A high erythrocyte sedimentation rate (ESR)</td>
</tr>
<tr>
<td></td>
<td>• Cancer in three or more nodal areas</td>
</tr>
<tr>
<td></td>
<td>• The presence of “B symptoms” (fever, weight loss, and night sweats)</td>
</tr>
</tbody>
</table>
Table 5.1. Adverse Prognostic Risk Factors (continued)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Adverse Prognostic Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced Disease</td>
<td>• Male</td>
</tr>
<tr>
<td></td>
<td>• Age 45 years or older</td>
</tr>
<tr>
<td></td>
<td>• Stage IV disease</td>
</tr>
<tr>
<td></td>
<td>• Low blood albumin (a type of protein) level (less than four grams per deciliter)</td>
</tr>
<tr>
<td></td>
<td>• Low hemoglobin level (less than 10.5 grams per deciliter)</td>
</tr>
<tr>
<td></td>
<td>• High white blood cell count (15,000 cells per microliter or greater)</td>
</tr>
<tr>
<td></td>
<td>• Low lymphocyte count (fewer than 600 cells per liter, or fewer than eight percent of the total white blood cell count)</td>
</tr>
</tbody>
</table>

How Does Bulky Disease Affect a Patient’s Prognosis?

*Bulky disease* is defined as either (1) a tumor in the chest larger than one-third of the width of the chest, or (2) a tumor greater than 10 centimeters (about four inches) or greater than six centimeters in children located anywhere in the body. Patients with bulky disease may require more aggressive treatment than those with limited disease. However, while smaller tumors are usually easier to treat than larger tumors, patients with bulky HL also have a high chance of being cured.
How to Decide What Treatment Is Best

There are many effective treatment options for patients with HL. To identify which treatments may work best, doctors consider the following factors:

- Type of HL
- Stage, location, and bulkiness of the lymphoma
- Presence or absence of symptoms, especially “B symptoms” (fever, weight loss, and night sweats)
- Results of blood tests and other laboratory tests
- A patient’s overall health, age, and performance status
- A patient’s prognostic factors
- A patient’s preferences and goals for treatment
- Whether the treatment is the first the patient has received or the disease has relapsed (returned after prior therapy)
- Whether the treatment will impact future treatment options
- Availability of a clinical trial

The doctor will discuss the risks, benefits, and side effects associated with the different treatment choices applicable to the patient’s particular situation. Patients and caregivers should share questions and concerns with the doctor so that together they can decide which option is best. It is always helpful for patients to write down their questions and go over them with their treating physician and/or team. The questions on the next page can be used to guide the conversation and help patients make an informed decision about their treatment plan.
Questions to Ask
Before Treatment Begins

- What is my exact diagnosis? May I have a copy of the report from the pathologist?
- What is the stage of my disease? In what area in the body is it specifically located?
- What are my prognostic factors, and what does that mean?
- What are my treatment choices? Which do you recommend for me and why? Would choosing one treatment prevent me from getting a different kind of treatment? How are the different treatment choices administered?
- What is a clinical trial? Are clinical trials available that are studying new treatments for my type of HL? Would a clinical trial be appropriate for me? How would I benefit?
- Do I need more than one type of treatment?
- What is the goal of treatment? What are the expected benefits of each type of treatment?
- How will we know if the treatment is working? What tests will I need to determine if treatment is working, and how often will I need to be tested?
- What are the risks and possible side effects of each treatment? Can these side effects be prevented or controlled?
- What should I do to take care of myself during treatment?
- Are there any late or long-term side effects I should be aware of?
- Will treatment impact my ability to have children in the future? Is there time for sperm banking or egg harvesting before starting treatment?
- How long will the treatment last?
- What are the chances the treatment will be successful?
When to Get a Second Opinion

Before starting any type of treatment, a patient may want to consider getting a second opinion, especially if the diagnosis is rare, complicated, or uncertain. The purpose of the second opinion is not to question the doctor’s expertise but to make sure the suggested treatment plan is the best choice for the patient’s particular case, as well as to evaluate alternative treatment options, including clinical trials.

Most doctors are supportive and helpful if patients tell them they would like to get a second opinion. Patients should ask the doctor if it is safe to briefly delay the start of treatment to provide the time needed to get a second opinion. Some insurance programs require second opinions, and others may pay for a second opinion if a patient or doctor requests it.

When getting a second opinion, patients might want to consider the tips outlined on the following two pages.
Getting a Second Opinion

- Some hematologists/oncologists/lymphoma specialists associated with medical schools or cancer centers may be willing to provide a consultation and work together with a local oncologist to provide treatment and follow-up care.

- As part of the second opinion, another pathologist must review the tissue and blood samples to confirm the diagnosis. The pathology of HL is often complex, and some pathologists may have limited experience analyzing HL cells, so it is valuable to have the pathology results reviewed by an expert hematopathologist with extensive experience in lymphoma.

- To get a second opinion, you will need to provide the consulting doctor with a complete copy of all medical records, pathology samples, images and scans, and reports. When you set up the appointment, ask the office for a list of the materials you need to bring. It will be useful to keep your own copy of all these records in case you have questions or concerns later on.

To identify HL specialists to contact for a second opinion:

- Ask your current doctors, family members, other patients, friends, and coworkers.

- Contact the patient referral service at your local hospital and at the nearest hospital associated with a medical school; many hospitals have online directories that can be searched to find a specialist in your area.

- Visit LRF’s website at www.lymphoma.org or contact the LRF Helpline by phone (800-500-9976) or email (helpline@lymphoma.org). However, note that LRF does not provide a physician referral service.

- Visit the American Society of Clinical Oncology (ASCO) website at www.cancer.net to search their oncologist database.
How to Find an Oncologist and Treatment Center

A patient’s primary care doctor usually makes a referral to a medical oncologist, hematologist, hematologist/oncologist (adult or pediatric). Before agreeing to treatment by any specific doctor or treatment center, patients and caregivers should make sure that they feel comfortable with the healthcare team and the quality of care they provide. Patients need to feel confident that the providers they select can meet their medical and personal needs. The following questions can be used to help patients select the best medical team.

Questions to Ask to Select the Best Medical Team

- What are the credentials of the doctor, the other members of the medical team, and the hospital or cancer center?
- Is the doctor board certified as a medical or pediatric oncologist or hematologist? Has he or she passed qualifying examinations by the American Board of Internal Medicine or American Board of Pediatrics to certify competency in these specialties?
- How much experience do the doctor and treatment center have in treating patients with HL in particular?

Getting a Second Opinion (continued)

- Visit the American Society of Hematology (ASH) web page at www.hematology.org/patients to search for hematologists with expertise in lymphoma.
- Visit the American Board of Medical Specialties (ABMS) Certification Matters website at www.certificationmatters.org to find out if doctors are board certified in a particular specialty.
Patients enrolled in a managed care health insurance program may have limited choices. However, patients have the right to choose another healthcare team if they are not entirely satisfied or comfortable with their first consultation visit. They should talk to other patients and caregivers about their experiences and ask them if they would recommend their doctor and healthcare team. Patients and caregivers who are not satisfied with their healthcare team should also share their concerns with their primary doctor and ask for a referral to a different doctor.

Questions to Ask to Select the Best Medical Team *(continued)*

- How many patients with this type of HL are being treated at this center now?
- Does the doctor and/or center participate in clinical trials?
- Does the clinic or center have modern surgical facilities and diagnostic equipment?
- Is the doctor or clinic affiliated with any major medical center or medical school?
- In case of an emergency, what arrangements are made for medical assistance after hours and on weekends?
- Is my health insurance accepted at this center? Will the treatment center file claims for reimbursement and process the paperwork?
- What kind of patient resources does the clinic or cancer center have for patients with HL?
- If I see other specialists (cardiologist, endocrinologist, etc.), will the doctor coordinate my cancer care with my other doctors?
How to Communicate with the Healthcare Team

Patients and caregivers can ease some of their anxieties by establishing open, honest communication with their healthcare team regarding their diagnosis and treatment. This can help patients and caregivers better understand the prescribed treatment regimen, including how it works, what tests are involved, and what side effects and complications may be associated with it.

A good first step for patients is to write down all the questions that come to mind. Before meeting with a doctor, nurse, or physician assistant either for the first time or for follow-up visits, patients should consider organizing their questions into a list to bring to the visit. Since time with doctors, nurses, or physician assistants may be limited, patients should put the two or three most important questions at the top of their list. However, patients should make sure a member of the medical team reads all the questions, because some may be more important than the patient realizes.

Patients should consider having a family member or close friend accompany them to the doctor’s office or clinic to help ask questions and understand and remember answers. This person could also help by taking notes during the visit. Some patients bring a recording device to record the answers. Patients should ask the doctor, nurse, or physician assistant for permission before recording any conversations.

Most oncology nurses are also very well informed about cancer treatments and are a good source of information on a wide range of topics. Additionally, oncology social workers are available to assist with practical, emotional, and other support needs throughout the diagnosis and treatment process.

Although family members are often very concerned about their loved ones and want information concerning their care, confidentiality rules prohibit doctors from giving out information to anyone without the patient’s permission. For efficiency, one family member should be designated as the family contact, and the healthcare team should
know that person’s identity and contact information. Most importantly, it is essential for patients and their caregivers or family contact person to have the names, addresses, office number and emergency contact information of the physicians involved in their care, so that they can communicate with the oncologist or hematologist regularly or in the event of an emergency. Adding these phone numbers directly to a cell phone may be helpful so patients or caregivers have the numbers directly on hand, if needed.

Open communication between patients and doctors is paramount. The following tips can be used to help patients better communicate with their healthcare team.

**Communicating With Your Doctors**

**At home**

- Keep a journal of your symptoms to help you remember the details you want to discuss with your doctor during your next office visit.
- Ask your doctor or nurse ahead of time which symptoms need to be communicated to them immediately and which can wait for your next visit.
- If your questions are urgent, do not wait for the next visit; call the doctor’s office to discuss your concerns.
- Ask whether your healthcare team has an online “patient portal.” These portals may provide secure email contact and educational materials, and they often allow patients to check benefits and coverage, schedule non-urgent appointments, and order prescription refills.
- Download the free *Focus On Lymphoma* mobile application (app) from LRF to help plan appointments, manage medications and blood work, and document treatment side effects, record doctor visits, and list questions (www.FocusOnLymphoma.org).
Communicating With Your Doctors (continued)

At your next doctor’s visit

- Bring your symptom journal and list of questions to discuss with your doctor or nurse.
- Bring a list of the medications you are currently taking, including the dosage and frequency.
- Ask a family member or friend to come with you to provide emotional support and take notes.
- Do not be afraid to ask questions if you do not understand something. Your doctor will want to know if you are uncertain or confused and will be happy to address your concerns.
- Inquire about whom should be contacted for specific questions or weekend support and how you can reach them.
- Inquire whether members of your healthcare team communicate electronically (by email, patient portals, etc.). Some providers do not use electronic forms of communication with patients because of concerns about security and patient privacy.
- Make sure you understand the next steps in your care before you leave the doctor’s office.
- Request written information that you can take home to help you remember everything your doctor tells you.
How to Be a Self-Advocate

Being a self-advocate and an active participant in healthcare decisions can be a positive experience and may help patients regain a sense of control that they may have lost following the lymphoma diagnosis. Patients and caregivers should remember they are partners in their treatment plan. Patients should ask questions, learn about options, and work closely with their healthcare team.

It is important for patients to be comfortable with the doctors and the approaches they take. If patients or caregivers are not comfortable, they should openly discuss their concerns. Confidence in the medical team often leads to confidence in treatment. If patients feel that the team is not a good match, they should ask for a referral to a different healthcare team.

Although each patient is different and each response to therapy is unique, knowing someone who has been through the same situation and who may have had similar concerns can be a source of great comfort. If patients or caregivers are interested in talking to and learning from people who have had similar experiences, they can ask their healthcare team members about any support groups in the area or contact LRF for more information about the Lymphoma Support Network.

Finally, it is important that patients not be afraid to talk with the healthcare team about nonmedical issues such as transportation, finances, insurance, working through treatment or taking time off, and childcare. The tips on the following page offer self-advocacy strategies for patients.
Self-Advocacy

- Do not be afraid to ask your doctors or nurses questions about your care.
- Learn more about HL by asking your doctor for information and visiting reliable websites, such as LRF at www.lymphoma.org and www.FocusOnHL.org.
- Take advantage of counseling, support groups, nutritional counseling, fitness classes, expressive arts, and other services offered at your doctor’s office, cancer center, or hospital.
- Consider joining LRF’s Lymphoma Support Network, a nationwide buddy program that matches patients and caregivers with people who have had similar experiences. For information about the program, call (800) 500-9976 or email helpline@lymphoma.org.
Chapter 6: Treatments for Hodgkin Lymphoma

This chapter reviews the most common therapies currently used in the treatment of Hodgkin lymphoma (HL). Keep in mind that new therapies may have been approved by the U.S. Food and Drug Administration (FDA) since this guide was printed. Read Chapter 13 to learn more about emerging treatments under investigation.

There are important differences between different types of HL, and a treatment that works for one type of HL may not necessarily be the best treatment choice for another type. There are also small but important differences in the lymphoma cells found in different patients diagnosed with the same type of HL. Because of these differences, a treatment that may work very well in one patient may not have the same positive effect in another.

What Types of Treatments Are Used in Patients With HL?

There are three general types of treatments for patients with HL:

- Drug therapy, including:
  - Chemotherapy, which affects general cell growth and *proliferation* (the ability of cells to multiply)
  - Immunotherapy, which helps the body’s immune system attack lymphoma cells

- Radiation therapy, which uses high-energy radiation to kill lymphoma cells

- Stem cell transplantation, usually in combination with high-dose chemotherapy, which involves replacing a patient’s immune system with healthy immune cells

Each of these types of therapies is described in detail in this chapter.
What Is Chemotherapy?
Chemotherapy drugs work by attacking cells that grow and multiply very quickly, which is a common characteristic of cancer cells. During chemotherapy, patients receive the treatment at certain intervals, such as once every two weeks, followed by a rest period. This regular treatment schedule is called a *cycle*. The length of the rest period and the number of cycles vary depending on the patient’s disease and the types of drugs used.

Most patients with HL are treated with combination chemotherapy, meaning two or more drugs, instead of a single drug. The purpose of combining drugs is to increase how effectively they damage or kill cancer cells, to diminish the chances of the cancer cells becoming resistant to treatment, and to allow lower doses of each drug to be used to minimize side effects. The chemotherapy drugs are combined to create a *treatment regimen*—a specific schedule that determines which drugs are given on which days of each treatment cycle.

Oncology nurses are usually responsible for administering the chemotherapy prescribed. Most patients receive their chemotherapy treatments in an outpatient clinic, hospital outpatient department, or doctor’s office, but sometimes patients have to stay overnight in the hospital for their treatment.

How Is Chemotherapy Given?
Depending on the drug, chemotherapy can be administered *orally* (as a pill or capsule that is swallowed), *intravenously* (as a liquid that is infused directly into a vein, commonly known as an “IV”), or *intrathecally* (as an injection into the fluid around the spinal cord [lumbar puncture]).
Most HL chemotherapy drugs are given by IV. One reason for this is that IVs provide flexibility in dosing, allowing the medication to be given all at once or slowly over many hours or days. Another reason is that many chemotherapy drugs cannot be given orally, either because they cannot be easily absorbed from the stomach into the bloodstream, or because they are too harsh for the stomach lining to tolerate.

To administer IV chemotherapy, a doctor, nurse, or physician assistant inserts an IV catheter, which is a small flexible tube used to deliver medications. While some catheters are designed for short-term use, others can stay in the patient’s body for weeks or months, making it easier to administer multiple cycles of chemotherapy over time. Several commonly used types of catheters are described in Table 6.1. Patients and caregivers should discuss with their doctor which catheter, if any, would be best for their particular situation.

**Table 6.1. Catheters Used to Administer Chemotherapy**

<table>
<thead>
<tr>
<th>Type of Catheter</th>
<th>Description</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Venous Catheter</td>
<td>A needle is used to insert a small, flexible tube into a small vein in the hand or arm.</td>
<td>Can be inserted quickly and easily by a nurse; no need for surgical insertion. Good for a single infusion or other temporary use.</td>
<td>Cannot be left in place for more than three days at a time due to infection risk. Sterile dressing needs to be kept clean and dry and replaced daily; the line needs to be injected periodically with a blood thinner (heparin) to prevent blockage.</td>
</tr>
<tr>
<td>Type of Catheter</td>
<td>Description</td>
<td>Advantages</td>
<td>Disadvantages</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Peripherally Inserted Central Catheter (PICC Line)</td>
<td>A long, thin plastic tube is inserted into a large vein in the arm, and the tip is guided up through the body into the large vein that enters the heart.</td>
<td>Can be kept in place longer than a peripheral venous catheter. Can be used to draw blood samples as well as to give drugs. Good for patients who need to have many short infusions or continuous infusions in a hospital or at home.</td>
<td>Not intended to remain in place as long as some catheter types.</td>
</tr>
<tr>
<td>Tunneled Catheter (e.g., Hickman, Broviac)</td>
<td>One to three tubes are surgically inserted into the subclavian vein (underneath the collarbone). Six to 12 inches of tubing remain outside the skin in the upper chest wall.</td>
<td>Can be left in place for months or years with low infection risk. Easy to draw blood and give drugs using standard needles without having to pierce the skin each time.</td>
<td>Requires a small surgery to be inserted. Patients must learn to clean and take care of the external tubes to prevent infection and blockage. The tubes on the outside of the body make it more obvious that a catheter is in place.</td>
</tr>
<tr>
<td>Infusaport or Portacath</td>
<td>A catheter is surgically inserted through the subclavian vein and attached to a small reservoir (port) that lies under the skin. Nothing is visible on the outside except for a bump on the upper chest.</td>
<td>Patients do not have to do anything to care for it; a nurse keeps the line open by “flushing” it once a month with a small amount of injected liquid.</td>
<td>Requires surgery to be inserted. Patient must be injected through the skin covering the port with a special needle each time it is used. Can be hard to use to draw blood samples because blood clots often cause clogging. Requires another minor surgical procedure to be removed.</td>
</tr>
</tbody>
</table>
What Other Types of Drugs Are Used to Treat Patients With HL?
In addition to chemotherapy, immunotherapy drugs are used to treat HL. Most of these drugs have been developed relatively recently, and ongoing studies are continually testing new drugs in these categories.

What Is Immunotherapy?
The term immunotherapy refers to treatments that help boost the body’s own immune response. The immune system normally patrols the body for cancer cells, and when a cancer cell is detected, the immune system launches an attack to eliminate it. However, some cancer cells can “hide” from the immune system and continue to grow in an uncontrolled manner until they form tumors or spread through the body. Immunotherapies help the immune system recognize those “hidden” lymphoma cells and eliminate them from the body.

Current FDA-approved immunotherapies for HL can be subdivided into three types: monoclonal antibodies, antibody-drug conjugates, and checkpoint inhibitors as described in the next few pages. For more information, view the Immunotherapy and Lymphoma fact sheet on the Lymphoma Research Foundation’s (LRF’s) website at www.lymphoma.org/publications.

What Are Monoclonal Antibodies?
Plasma cells are specialized white blood cells that make proteins called antibodies. Antibodies help fight infection by recognizing and sticking to viruses, bacteria, or other foreign substances in the body. Each antibody is naturally designed to recognize one specific antigen (identifying molecule on the surface of certain cells).

Monoclonal antibodies are molecules that have been engineered in a laboratory to behave differently than antibodies found naturally in our bodies. Monoclonal antibodies are specifically designed to recognize and stick to a particular antigen on the surface of certain cancer cells. Once injected in the patient, the monoclonal antibodies travel through
the blood and attach themselves to the cells that have the antigen they recognize, most of which are HL cells. This can either stop or slow down the growth of the cancer cell, or it can trigger an “alarm” that makes it easier for other cells in the immune system to recognize and destroy the cancer cell.

Before beginning monoclonal antibody therapy, all patients are tested for active hepatitis infection. In addition, to avoid life-threatening infections, patients being treated with monoclonal antibodies should not be vaccinated with live attenuated virus vaccines, such as those for shingles (herpes zoster), yellow fever, and polio (Sabin vaccine), because the monoclonal antibodies can potentially reactivate these viruses. The monoclonal antibody therapies used to treat HL are given to patients as IV infusions at a doctor’s office or clinic. To prevent serious allergic reactions to the infusion, patients are given an oral antihistamine such as diphenhydramine (Benadryl), acetaminophen (Tylenol), and sometimes steroids before the antibody infusion.

What Are Antibody-Drug Conjugates?
An antibody-drug conjugate is a chemotherapy drug attached to a monoclonal antibody. The monoclonal antibody part of the drug attaches to specific molecules on the surface of HL cells, and the chemotherapy portion enters the HL cell, causing it to stop multiplying and die. Brentuximab vedotin (Adcetris) is the only antibody-drug conjugate that is approved for use in HL. See page 78 for more information on brentuximab vedotin.

What Are Checkpoint Inhibitors?
The body normally uses “checkpoint proteins” such as CTLA-4 and PD-1/PD-L1 to shut down immune responses that are not needed, such as those that occur when immune cells mistakenly attack the body’s own cells. Some lymphoma cells are able to activate these checkpoints to “trick” the body into shutting down the immune response to the cancer cells, effectively “putting the brakes” on our own immune cells. Checkpoint inhibitors are a type of monoclonal
antibody that can block this checkpoint activation, thereby restoring the immune system’s ability to launch an attack against the lymphoma cells and rid them from the body, thus taking the “brakes” off of our immune cells.

What Is Radiation Therapy?

Radiation therapy (also called radiotherapy) uses high-energy X-rays or other types of radiation to kill cancer cells and shrink tumors. The term is generally used to describe external-beam radiotherapy, in which a radiation beam is delivered from a machine. Because of the potential long-term toxicities of this treatment, radiation therapy is only used for patients who require it.

A radiation oncologist is in charge of the radiation therapy. The part of the body selected to receive the radiation is called the radiation field. Doctors usually limit the radiation field to affected lymph nodes, the areas immediately surrounding lymph nodes, or other areas where lymphoma is present. Doctors determine the type of radiation used and the size of the radiation field depending on the type of lymphoma and the extent of disease. In the past, common areas of the body that receive radiation include lymph nodes in the neck, chest, and underarms (called the “mantle field”); lymph nodes in the abdomen and possibly spleen; and lymph nodes in the pelvis and groin. In certain circumstances, extended-field radiation was given to both the mantle and upper abdominal fields. However, these fields are no longer used in the modern treatment of HL.

To prepare for radiation therapy, the healthcare team marks the patient's body with tattoos (tiny ink dots) to make sure that only the targeted areas receive radiation. On the day of treatment, lead shields are used to protect the normal tissues around the radiation field. The radiation team also uses plastic forms, pillows, and rolled blankets to make patients comfortable and keep them in the proper position. Patients lie still on a table beneath a large machine that delivers the radiation painlessly. Once the preparations have been made, it takes only a few minutes to deliver the prescribed dose. The total dose of
radiation is usually divided and given over two to six weeks. During and after the radiation treatment, patients need to carefully protect the radiation site from exposure to sunlight — it is really important to not become sunburned.

Some of the more common types of radiation therapy and delivery methods used for HL are shown in Table 6.2.

Table 6.2. Methods for Delivering Radiation Therapy

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involved-Field Radiation Therapy (IFRT)</td>
<td>This is the main type of external-beam radiation therapy used for HL.</td>
</tr>
<tr>
<td></td>
<td>The radiation field includes the lymph node regions that contain HL.</td>
</tr>
<tr>
<td></td>
<td>IFRT is usually given after chemotherapy; it is only used alone to treat certain patients with nodular lymphocyte-predominant HL.</td>
</tr>
<tr>
<td>Involved-Site Radiation Therapy (ISRT)</td>
<td>The radiation field is narrower compared with that used in IFRT so that nearby tissues and organs are not affected by the radiation.</td>
</tr>
<tr>
<td></td>
<td>ISRT uses newer radiation techniques like intensity-modulated radiation therapy (IMRT), which varies the strength of the radiation to spare surrounding healthy tissues.</td>
</tr>
<tr>
<td>Proton Therapy</td>
<td>Proton therapy uses positively charged particles called protons delivered in an external beam.</td>
</tr>
<tr>
<td></td>
<td>This approach can reduce radiation exposure to normal surrounding tissues, allowing higher doses to be delivered to the tumor.</td>
</tr>
<tr>
<td></td>
<td>Proton therapy may be useful in patients with tumors near the heart, lungs, or esophagus that are difficult to treat with other radiotherapy methods.</td>
</tr>
<tr>
<td>Total Body Irradiation (TBI)</td>
<td>The whole body is exposed to radiation along with high-dose chemotherapy in an attempt to kill the lymphoma cells throughout the body.</td>
</tr>
<tr>
<td></td>
<td>TBI may be given to patients who are preparing for a stem cell transplant.</td>
</tr>
</tbody>
</table>
Patients may wish to use the questions below to ask their doctors about what to expect during and after radiation therapy.

**Questions to Ask Before Starting Radiation Therapy**

- What is the goal of my radiation therapy?
- How will the radiation be given?
- How long will the treatment last, and how often will it be given?
- How will I feel during the therapy?
- What are the side effects of radiation therapy? Is there anything that can be done to prevent them?
- Are there any lasting side effects?
- What can I do to take care of myself during and after therapy?
- How will we know if the radiation therapy is working?
- How will the radiation treatment affect my normal activities (work, school, childcare, driving, sexual activity, and exercise)?

**What Is Stem Cell Transplantation?**

There are two types of stem cell transplantation that differ based on the source of the stem cells. In an *autologous stem cell transplant*, the patient is his or her own donor. In an *allogeneic stem cell transplant*, the donor is another person who is genetically similar to the patient; this person is often a brother or sister. Donor stem cells may also come from the patient’s child, the patient’s parent, an unrelated person, or donated umbilical cord blood.

The primary purpose of stem cell transplantation is to allow patients to receive higher doses of chemotherapy than their bodies could normally withstand. Such high doses of chemotherapy can kill cancer...
cells effectively, but they can also severely damage or destroy the stem cells that the body uses to create new blood cells. Stem cell transplantation replaces the supply of stem cells killed by the high-dose chemotherapy, allowing the body to recover from such an intense treatment.

Allogeneic transplantation also has a second benefit. Because the transplanted cells come from a donor instead of the patient, the donated cells recognize the patient’s lymphoma cells as foreign and attack them, resulting in an immunologic response called the *graft-versus-lymphoma* (GVL) effect. For this reason, allogeneic transplantation generally controls lymphoma better than autologous transplantation. However, the toxicity and risk of complications is also higher in an allogeneic transplant, because the donor cells can recognize the normal organs of the patient as foreign and attack them, resulting in a serious complication known as *graft-versus-host disease* (GVHD). The decision about which treatment to use is a complex one and should involve a detailed discussion with the patient’s doctor and a referral to a major cancer center with expertise in transplantation.

Because high-dose chemotherapy and stem cell transplantation place great strain on a patient’s body, these types of therapies are not options for everyone. For patients who are not candidates for traditional stem cell transplantation, *reduced-intensity transplantation* (also called nonmyeloablative or mini-allogeneic stem cell transplantation) may be an option. This approach uses lower doses of chemotherapy and/or radiation prior to allogeneic transplantation. This option is available only for allogeneic transplantation, because it takes advantage of the GVL effect, in which the transplanted cells recognize the cancerous cells in the patient’s body as foreign and destroy them. Patients receiving reduced-intensity transplants may avoid some of the side effects that occur with higher-dose chemotherapy. However, they are still at risk for serious side effects including GVHD, in which the donor immune cells attack the normal organs of the patient.
In deciding if transplantation is a good option, doctors consider the patient’s subtype of lymphoma, health status, age, medical history, cancer stage, and response to previous therapy. For more information on stem cell transplants, view the *Understanding Stem Cell Transplantation* publication on LRF’s website at www.lymphoma.org/publications.

**AUTOLOGOUS STEM CELL COLLECTION**

*A patient’s own stem cells*

1. **Collection**
   Stem cells are collected from the patient’s bone marrow or blood.

2. **Conditioning and Processing**
   While the patient receives treatment (conditioning), the blood or bone marrow may be processed in the laboratory to concentrate the stem cells. Samples are frozen until needed.

3. **Reinfusion**
   Stem cells are thawed and reinfused into the patient.
ALLOGENEIC STEM CELL COLLECTION
Stem cells from a donor who is genetically similar to the patient

1. **Collection**
   Stem cells are collected from the donor’s bone marrow or blood.

2. **Conditioning and Processing**
   While the patient receives treatment (conditioning), the blood or bone marrow may be processed in the laboratory to concentrate the stem cells.

3. **Infusion**
   Stem cells are infused into the patient.

Suggested questions for patients to ask their healthcare team before deciding to undergo stem cell transplantation are listed on the following page.
Questions to Ask Before Deciding to Undergo Stem Cell Transplantation

- What type of transplantation is most appropriate for me (autologous or allogeneic) and why?
- If an allogeneic transplant is being considered, how will a donor be found?
- What are the risks and benefits associated with this procedure?
- What complications may arise as a result of having a transplant?
- What are the short-term and long-term side effects I might experience after my transplant?
- What can be done to lessen the side effects?
- How do I identify a hospital or transplant center for the transplant?
- How long will I need to be in the hospital?
- How long will I need someone to care for me after the transplant?
- Will my insurance cover this procedure?
- How sick will this treatment make me?
- How will we know if the treatment is working?
- What treatments will be available to me after transplant?
- How and for how long will the treatment affect my normal activities (work, school, childcare, driving, sexual activity, and exercise)?
- What is my chance of making a full recovery?
What Terms Do Doctors Use to Describe Treatment and Its Outcomes?

Doctors who treat patients with lymphoma use certain terms to describe a patient’s treatment and the anticipated outcomes. Some of these terms are defined in Table 6.3.

### Table 6.3. Terms Used to Describe Treatment and Its Outcomes

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cure</strong></td>
<td>This word is used cautiously by doctors for subtypes of lymphoma that are potentially curable when there are no signs of the lymphoma reappearing after many years of continuous complete remission.</td>
</tr>
<tr>
<td><strong>Complete Remission (CR)</strong></td>
<td>This term is used when all signs of the lymphoma have disappeared after treatment. It does not mean that the lymphoma is completely cured; rather, it indicates that the symptoms have disappeared and the lymphoma cannot be detected using current tests. Relapses can occur in patients who experience a CR. If complete remission is maintained for a long period, it is called a <em>durable remission</em>.</td>
</tr>
<tr>
<td><strong>Partial Remission (PR)</strong></td>
<td>This term is used if a lymphoma tumor has responded to treatment and shrunk to less than one-half of its original size.</td>
</tr>
<tr>
<td><strong>Minor Response (MR) or Minor Improvement</strong></td>
<td>This term is used if a lymphoma tumor has shrunk following therapy but is still more than one-half of its original size.</td>
</tr>
<tr>
<td><strong>Stable Disease</strong></td>
<td>This term means the disease has not gotten worse or better following therapy.</td>
</tr>
<tr>
<td><strong>Disease Progression</strong></td>
<td>This term means the disease has worsened or the lymphoma has grown or spread during therapy or observation. Other terms used to describe disease progression are relapse, treatment resistance, or resistant disease.</td>
</tr>
<tr>
<td><strong>Primary or Frontline Therapy</strong></td>
<td>This term is used to describe the first therapy that a patient receives. The choice of primary therapy depends on the type of HL and the characteristics of the disease.</td>
</tr>
<tr>
<td><strong>Refractory Disease</strong></td>
<td>This term is used to describe lymphoma that does not respond to treatment or in which the response to treatment does not last very long.</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>This term refers to disease that reappears or grows again after a period of remission.</td>
</tr>
</tbody>
</table>
What Is Relapsed or Refractory HL?

*Relapsed* HL means that the disease has returned after responding to treatment, which is sometimes also called a *recurrence*. *Refractory* HL means that the patient’s disease does not respond to a specific treatment or that the response to treatment does not last very long. There are many treatment options for patients with relapsed or refractory HL. Exactly what type of treatment is optimal for individual patients with relapsed or refractory HL depends on such factors as the subtype of HL, the patient’s age and overall health, the extent and location of disease, the type of previous therapies received, and the length of response to previous therapies.

The standard secondary treatment for the majority of patients with relapsed or refractory HL consists of systemic therapy, usually followed by autologous stem cell transplantation. Involved-site radiation therapy may also be used. For more information about specific treatments used for relapsed/refractory HL, see Chapters 7 and 8 of this guide and view the *Hodgkin Lymphoma: Relapsed/Refractory* fact sheet on LRF’s website at www.lymphoma.org/publications.

When Should a Clinical Trial Be Considered?

Clinical trials are appropriate for patients at all stages of disease, whether newly diagnosed or at the time of relapse (see Chapter 12 “Overview of Clinical Trials”). The purpose of a clinical trial is to safely monitor the effects of a new drug or new combination of drugs on patients over time and to identify more effective therapies for specific diseases. Some trials randomly assign patients to one of two or more treatment arms, each of which receives a different treatment. By participating in a randomized clinical trial, patients may or may not get access to the newest therapies, but at a minimum, they will receive quality standard care in a very carefully controlled and supportive environment.
Because HL is a rare disease, it is very hard for researchers to find enough patients to enroll in studies that are critical for improving HL treatment. That is why it is particularly important for patients with HL to consider clinical trials as a treatment option. If patients are interested in participating in a clinical trial, they should ask their doctor if there is an appropriate trial for them and what the potential risks and benefits may be. For more information about clinical trials for patients with HL, please contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org and ask about the LRF “Clinical Trials Information Service.”

**What Are Alternative and Complementary Therapies?**

*Alternative therapy* refers to any treatment used instead of a standard therapy. Alternative therapies are not recognized as effective therapy by the medical profession. Currently, there are no proven alternative therapies to conventional cancer care for patients with HL. Patients should not use alternative remedies to replace the care suggested by their doctors.

*Complementary therapy* can be used in addition to standard therapy to help improve a patient’s quality of life and to relieve the effects of drug therapy, radiation, and surgery. Patients and caregivers should talk to their doctor and healthcare team before starting any form of complementary therapy, because a few of these approaches may make their lymphoma treatment less effective.

Table 6.4 outlines some forms of complementary therapy for cancer, also known as integrative medicine or integrative oncology.
**Table 6.4. Forms of Complementary Therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acupuncture</td>
<td>- Acupuncture uses ultra-thin needles applied to specific points on the body. The process is safe and painless, and the needles are disposed of after a single use.</td>
</tr>
<tr>
<td></td>
<td>- Acupuncture may relieve pain, nausea, fatigue, hot flashes, and peripheral neuropathy (numbness or tingling in the hands and feet) associated with chemotherapy. It may also help decrease mild depression and other symptoms and side effects.</td>
</tr>
<tr>
<td>Chiropractic and Massage</td>
<td>- Chiropractic and massage therapies are the most commonly used modalities and can help relieve side effects and stress.</td>
</tr>
<tr>
<td>Therapy</td>
<td>- A special type of massage called oncology massage is designed specifically for patients with cancer to help manage stress, pain, swelling, and other side effects without causing harm or interfering with cancer treatments.</td>
</tr>
<tr>
<td></td>
<td>- Patients should look for a massage therapist who is certified in oncology massage.</td>
</tr>
<tr>
<td>Herbal Therapy</td>
<td>- Patients should talk with their doctor before using herbal therapies, because some herbal therapies such as St. John’s wort may interfere with cancer medications.</td>
</tr>
<tr>
<td>Mind/Body Therapies</td>
<td>- Examples of mind/body therapies include meditation, guided imagery, self-hypnosis, Tai Chi, and yoga.</td>
</tr>
<tr>
<td></td>
<td>- Meditation, guided imagery, and self-hypnosis can help manage stress.</td>
</tr>
<tr>
<td></td>
<td>- Yoga and Tai Chi have been shown to minimize stress and improve balance and flexibility.</td>
</tr>
</tbody>
</table>

For more information about complementary therapies, please view the *Integrative Oncology* fact sheet on LRF’s website at www.lymphoma.org/publications.

**Drug Costs: What to Do If the Insurance Company Will Not Pay**

Many patients today face the problem of how to pay for rising healthcare costs. Cancer organizations like LRF (www.lymphoma.org) offer help in finding financial assistance resources. Most
pharmaceutical companies also have patient assistance programs in place that help provide medications to qualifying patients.

Patients in need of financial assistance should talk to their doctor and social worker about available options and how to enroll in an appropriate program. Before undergoing a medical procedure, patients should check with the insurance carrier to confirm that it is covered. If there is a dispute about coverage or if coverage is denied, patients should ask the insurance carrier about their appeals process. If a claim is repeatedly denied, patients should contact their state’s insurance agency. For more information on financial aid, view the Resources for Financial Assistance fact sheet on LRF’s website at www.lymphoma.org/publications. Patients can also call LRF’s Helpline at (800) 500-9976 or email helpline@lymphoma.org.
Chapter 7: Treatments for Classical Hodgkin Lymphoma

This chapter explores the most common therapies currently used in the treatment of patients with classical Hodgkin lymphoma (cHL). Keep in mind that new therapies may have been approved by the U.S. Food and Drug Administration (FDA) since this guide was printed. See Chapter 12 to learn about new agents under investigation.

What Types of Treatments Are Used in Patients With Classical HL?

There are three general types of treatments for patients with cHL:

- **Drug therapy**, including:
  - Chemotherapy, which affects general cell growth and multiplication
  - Immunotherapy, including antibody-drug conjugates and checkpoint inhibitors, which help the body’s immune system target and kill lymphoma cells

- **Radiation therapy**, which uses high-energy radiation to kill lymphoma cells

- **High-dose chemotherapy followed by stem cell transplantation**, which involves replacing a patient’s immune system with healthy immune cells

These types of therapies are described in detail throughout this chapter and in Chapter 6.

Most patients treated for HL receive some form of chemotherapy, with or without radiation therapy, as their **frontline** (first) treatment. In North America, the standard frontline chemotherapy regimen is known as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine); this regimen
and other common frontline regimens for adults are listed in Table 7.1.

**Table 7.1. Common Frontline Chemotherapy Regimens for Adults With cHL**

<table>
<thead>
<tr>
<th>Regimen Abbreviation</th>
<th>Generic Names of Drugs (Brand Names)</th>
</tr>
</thead>
</table>
| ABVD                | Doxorubicin/hydroxydaunorubicin (Rubex, Adriamycin PFS)  
Bleomycin (Blenoxane)  
Vinblastine (Velban)  
Dacarbazine (DTIC-Dome) |
| Escalated BEACOPP    | Bleomycin  
Etoposide/VP16 (VePesid, Toposar, Etopophos)  
Doxorubicin  
Cyclophosphamide (Cytoxan, Neosar)  
Vincristine (Oncovin and others)  
Procarbazine (Matulane)  
Prednisone |
| MOPP                | Mechlorethamine (Mustargen)  
Vincristine  
Procarbazine  
Prednisone |
| Stanford V           | Mechlorethamine  
Doxorubicin  
Vinblastine  
Vincristine  
Bleomycin  
Etoposide/VP16  
Prednisone |

Patients usually receive one to three chemotherapy cycles, followed by positron emission tomography-computed tomography (PET-CT) imaging to evaluate how the lymphoma is responding to the treatment. The results are used to determine how many additional cycles of chemotherapy will be given, whether one of the chemotherapy drugs
(most often bleomycin) can be eliminated, or whether an alternative treatment regimen should be considered.

The ABVD regimen is currently the most widely used and preferred first line combination chemotherapy regimen for HL. All four agents are given intravenously every two weeks in 28-day cycles. Patients may receive two to six cycles depending on the disease stage, prognosis, other treatments, and tolerability. Bleomycin may be stopped after the third cycle to prevent lung complications.

Common first line chemotherapy regimens used in children with cHL are listed in Table 7.2.

**Table 7.2. Common Frontline Chemotherapy Regimens for Children With cHL**

<table>
<thead>
<tr>
<th>Regimen Abbreviation</th>
<th>Generic Names of Drugs (Brand Names)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVE-PC</td>
<td>Doxorubicin (Adriamycin)</td>
</tr>
<tr>
<td></td>
<td>Bleomycin (Blenoxane)</td>
</tr>
<tr>
<td></td>
<td>Vincristine (Oncovin and others)</td>
</tr>
<tr>
<td></td>
<td>Etoposide (VePesid, Toposar, Etopophos)</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide (Cytoxan, Neosar)</td>
</tr>
<tr>
<td>OEPA/COPDac</td>
<td>Vincristine</td>
</tr>
<tr>
<td></td>
<td>Etoposide</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>Vincristine</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
</tr>
<tr>
<td></td>
<td>Dacarbazine (DTIC-Dome)</td>
</tr>
</tbody>
</table>

Pediatric patients usually receive two chemotherapy cycles, followed by PET-CT imaging to determine whether changes to the chemotherapy and/or radiotherapy regimen are needed.
Treatment of Patients Who Do Not Achieve a Complete Response

Patients with cHL whose disease does not go into complete remission (CR) after initial therapy or whose disease relapses (returns after treatment) after achieving CR are often treated with secondline treatment. The preferred secondline treatment for transplant-eligible patients with relapsed HL is another chemotherapy regimen (typically different from the frontline therapy) or immunotherapy, followed by high-dose chemotherapy with autologous stem cell transplantation (using the patient’s own stem cells). Table 7.3 shows examples of secondline chemotherapy regimens used in patients whose cHL has relapsed or recurred after the initial treatment.

Table 7.3. Common Secondline Chemotherapy Regimens for Adults With cHL

<table>
<thead>
<tr>
<th>Regimen Abbreviation</th>
<th>Generic Names of Drugs (Brand Names)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChlVPP</td>
<td>Chlorambucil (Leukeran)</td>
</tr>
<tr>
<td></td>
<td>Vinblastine (Velban)</td>
</tr>
<tr>
<td></td>
<td>Procarbazine (Matulane)</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
</tr>
<tr>
<td>DHAP</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Cytarabine/high-dose Ara-C (Cytosar-U, Tarabine PFS)</td>
</tr>
<tr>
<td></td>
<td>Cisplatin (Platinol)</td>
</tr>
<tr>
<td>DICE</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide (Ifex)</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
</tr>
<tr>
<td></td>
<td>Etoposide/VP16 (VePesid, Toposar, Etopophos)</td>
</tr>
<tr>
<td>ESHAP</td>
<td>Etoposide/VP16</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
</tr>
<tr>
<td></td>
<td>Cytarabine (high-dose Ara-C)</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
</tr>
<tr>
<td>GCD</td>
<td>Gemcitabine (Gemzar)</td>
</tr>
<tr>
<td></td>
<td>Carboplatin (Paraplatin)</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
</tr>
</tbody>
</table>
Regimens commonly used in the treatment of pediatric cHL include gemcitabine (Gemzar) plus vinorelbine (Navelbine), and ifosfamide (Ifex) plus vinorelbine.

For some patients with relapsed cHL, including those who are not good candidates for a stem cell transplant, other secondline treatment options include the following:

- Radiation therapy alone
- Chemotherapy alone
- Chemotherapy combined with radiation therapy
- An antibody-drug conjugate
- A checkpoint inhibitor
- A clinical trial
**Brentuximab Vedotin (Adcetris)**

An *antibody-drug conjugate* is a chemotherapy drug attached to a monoclonal antibody. The only antibody-drug conjugate approved for use in cHL is brentuximab vedotin (Adcetris), which is a combination of the drug monomethyl auristatin E (MMAE or vedotin) and a monoclonal antibody against CD30 (brentuximab). The CD30 antigen is present on the surface of all Reed-Sternberg (RS) cells. Thus, the monoclonal antibody part of this drug is like a “guided missile” that is directed against and attaches itself to RS cells. Once the antibody is attached to the lymphoma cell, it is taken inside the cell (internalized). The MMAE is then released, where it attacks the HL cell, causing it to stop multiplying and die.

Brentuximab vedotin (Adcetris) is approved by the FDA for the treatment of patients with cHL in the following circumstances:

- After failure of autologous stem cell transplantation
- After failure of at least two previous multi-agent chemotherapy regimens in patients who are not candidates for transplantation
- After autologous stem cell transplantation as consolidation therapy in patients at high risk of relapse or progression

It is also approved for use in systemic anaplastic large cell lymphoma, a type of non-Hodgkin lymphoma (NHL). Brentuximab vedotin is given as an intravenous infusion once every three weeks until disease progression or unacceptable toxicity.

**Checkpoint Inhibitors**

Two checkpoint inhibitors are used in the treatment of cHL: nivolumab (Opdivo) and pembrolizumab (Keytruda). Both agents target the PD-1/PD-L1 immune checkpoint, which is used by some cancers to avoid detection by the body’s immune system. Nivolumab and pembrolizumab are monoclonal antibodies that bind to PD-1, thereby shutting down signaling through the PD-1/PD-L1 checkpoint.
Nivolumab (Opdivo) is approved by the FDA for adult patients with cHL that has relapsed or progressed after autologous stem cell transplantation and post-transplantation treatment with brentuximab vedotin (Adcetris).

Pembrolizumab (Keytruda) is approved by the FDA for adult patients with refractory (does not respond to treatment) cHL or cHL that has relapsed after three or more previous lines of therapy.

Both checkpoint inhibitors are given as an intravenous infusion; nivolumab (Opdivo) is given every two or three weeks, while pembrolizumab (Keytruda) is given every three weeks; both agents are given until disease progression or unacceptable toxicity.

Patients who do not go into complete remission following treatment or who do not respond to treatment should not lose hope. Lasting responses to therapy may be achieved after a diagnosis of relapsed or refractory disease. Many patients seek second opinions at any point from diagnosis onward, and some choose to do so if their disease relapses or is considered refractory. Clinical trials are also a good option for patients at all stages of disease.

Clinical Trials
Many of the novel therapeutic agents being investigated in clinical trials are used specifically for patients with relapsed or refractory disease. Lymphoma research continually evolves as doctors and scientists discover new therapies and more effective ways of giving existing treatments. Chapter 13 describes some of the options currently under investigation. In addition, LRF provides a “Clinical Trials Information Service” to help patients and caregivers find trials that may offer access to investigational therapies for lymphoma, including treatments specifically for relapsed/refractory cHL. For more information about clinical trials, contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org and ask about the LRF “Clinical Trials Information Service.”
Chapter 8: Treatments for Nodular Lymphocyte-Predominant Hodgkin Lymphoma

As discussed in Chapter 1, although nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is considered a form of Hodgkin lymphoma (HL), it differs from classical Hodgkin lymphoma (cHL) in both the absence of Reed-Sternberg (RS) cells and the presence of “popcorn cells.” This form of HL is actually treated more like indolent (slow-growing) non-Hodgkin lymphoma (NHL) than like cHL. Therefore, treatment for NLPHL is presented separately in this chapter.

What Types of Treatments Are Used in Patients With NLPHL?

NLPHL tends to grow slowly and may relapse (disease returns after treatment) late. Table 8.1 shows treatments used for various stages of NLPHL.

Table 8.1. Treatment for Various Stages of NLPHL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Commonly Used Treatment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Disease</td>
<td>- Observation/active surveillance</td>
</tr>
<tr>
<td></td>
<td>- Involved-site radiation therapy (ISRT)</td>
</tr>
<tr>
<td></td>
<td>- Rituximab (Rituxan), a single-agent monoclonal antibody</td>
</tr>
<tr>
<td></td>
<td>- ISRT plus ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy, with or without rituximab</td>
</tr>
<tr>
<td></td>
<td>- AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide) or CVP (cyclophosphamide, vincristine, prednisone) for pediatric patients</td>
</tr>
</tbody>
</table>
Table 8.1. Treatment for Various Stages of NLPHL (continued)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Commonly Used Treatment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced Disease</td>
<td>■ Rituximab (Rituxan)</td>
</tr>
<tr>
<td></td>
<td>■ ABVD chemotherapy plus rituximab, with or without involved-site radiation therapy (ISRT)</td>
</tr>
<tr>
<td></td>
<td>■ CHOP chemotherapy plus rituximab</td>
</tr>
<tr>
<td></td>
<td>■ Local radiation therapy</td>
</tr>
<tr>
<td></td>
<td>■ ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, procarbazine) with or without ISRT for pediatric patients</td>
</tr>
<tr>
<td>Recurrent or Relapsed Disease</td>
<td>■ Clinical trial</td>
</tr>
<tr>
<td></td>
<td>■ Observation/active surveillance if recurrence is limited and there are no symptoms</td>
</tr>
<tr>
<td></td>
<td>■ ABVD chemotherapy, rituximab (Rituxan), or involved-field radiation therapy (IFRT) alone or in any combination</td>
</tr>
<tr>
<td></td>
<td>■ Chemotherapy regimens used for aggressive NHL</td>
</tr>
<tr>
<td></td>
<td>■ Radioimmunotherapy (RIT)</td>
</tr>
</tbody>
</table>

In some cases, NLPHL can transform into aggressive NHL. Rapid growth of one or more lymph nodes is a clear indication for a biopsy to see if such a transformation has occurred. If transformation occurs, treatment of the resulting NHL is necessary.

**What Is Active Surveillance?**

With the active surveillance (watchful waiting) approach, patients do not receive any antilymphoma treatments, but their health and disease are monitored through regular checkup visits and periodic evaluation procedures such as laboratory and imaging tests. These patients continue to remain untreated as long as they do not show any signs or symptoms and there is no evidence that the lymphoma is growing or spreading. Active surveillance is an option for patients who have early-stage or advanced-stage disease that is not bulky (no tumor greater than 10 centimeters) or for pediatric patients with complete resection of a single involved node.
Doctors recommend active surveillance for select patients with early-stage NLPHL. This approach may be used after the initial diagnosis or after relapse, depending on the situation. Patients are switched from active surveillance to active treatment if they begin to develop lymphoma-related symptoms or if there are signs that the disease is progressing.

Active surveillance is not a treatment option for patients with symptomatic NLPHL. Here is a list of questions that patients can ask before starting the active surveillance approach.

**Questions to Ask Before Starting Active Surveillance**

- What happens if I choose active surveillance and then change my mind?
- Will the disease be harder to treat later?
- How often will I have checkups and tests?
- Between checkups, what symptoms and other problems should I report?
- What changes will indicate that I should start active treatment?

**Rituximab (Rituxan)**

Rituximab is a monoclonal antibody that targets the antigen CD20, a specific molecule found on the surface of almost all B cells. In 1997, rituximab became the first monoclonal antibody approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with certain types of NHL. As of 2017, rituximab is approved by the FDA for the treatment of patients with NHL, chronic lymphocytic leukemia, and other diagnoses.
While not approved by the FDA to treat HL, rituximab is sometimes given either as monotherapy (without other drugs) or in combination with chemotherapy to patients with NLPHL. Rituximab treatment is given as an intravenous (IV) infusion usually once weekly for a certain number of cycles, but the schedule varies depending on the type of combination regimen used. When combined with chemotherapy, rituximab is usually given during the first day of each chemotherapy cycle.

In patients with relapsed or refractory (does not respond to treatment) NLPHL whose disease responds well to rituximab monotherapy, rituximab may also be used as maintenance therapy (ongoing treatment to prevent cancer from returning) for up to two years.

Whether used as monotherapy, combination therapy, or maintenance therapy, any use of rituximab for patients with NLPHL is considered off-label, meaning that the FDA has not specifically approved using rituximab for this purpose. However, it is listed as an option in the National Comprehensive Cancer Network (NCCN) guidelines. You may consult with your doctor to determine whether this is an option for you.
Patients being treated for Hodgkin lymphoma (HL) may experience various side effects or toxicities caused by their lymphoma treatment. All treatments have the potential to cause side effects. Fortunately, medications and lifestyle changes can effectively prevent or lessen the severity of most side effects. Before beginning treatment, patients should ask their healthcare team about possible treatment side effects and how to prevent and manage them. In addition, once treatment has begun, patients need to tell their doctor, nurse, or physician assistant about all side effects they experience. This chapter explains why side effects occur, the types of side effects caused by different treatments, and steps for minimizing these side effects.

Why Does Chemotherapy Cause Side Effects or Toxicities?
Chemotherapy drugs cause side effects because of the nonspecific way these drugs attack lymphoma cells. Most chemotherapy drugs work by killing cells that grow and multiply more quickly than typical cells. Cancer cells are one type of cell that multiplies rapidly, which is why chemotherapy can be effective at killing them. However, a few types of normal cells in the body also multiply quickly, including the cells in hair roots, the mouth, the gastrointestinal tract, and bone marrow, so those cells may also be damaged or killed by chemotherapy. Some chemotherapy drugs can also damage cells in the heart, lungs, or other organs and tissues.

The type and severity of side effects caused by chemotherapy vary widely depending on the types of drugs that are given, an individual patient's tolerance, and the length of time therapy is delivered. The same drug may cause no side effects in one patient, while in others it may cause very mild to very serious side effects. Other side effects do not occur until later, and may become worse over time.
What Is the Difference Between Long-Term Effects and Late Side Effects?

*Long-term* effects are toxicities that occur during cancer treatment and continue for months or years. Fatigue, menopausal symptoms, and neuropathy are examples of long-term effects. In contrast, *late effects* of treatment appear only after treatment has ended—sometimes months, years, or even decades after treatment is completed. Infertility, osteoporosis, heart problems, and secondary cancers are examples of late effects.

Radiation therapy is associated with late effects such as secondary cancers, heart attacks, and strokes, particularly if the radiation field used is extensive and/or includes the chest region. For this reason, radiation therapy is used less often than in the past, and when it is used, the dosage, duration, and size of the treatment field are all smaller than those used in the past.

What Side Effects Are Caused by Chemotherapy?

Some of the most common side effects caused by chemotherapy used to treat patients with HL include:

- Changes in taste
- Cognitive problems (trouble concentrating, impaired memory, sometimes called “chemo brain”)
- Constipation
- Decreased blood cell production (decreased hemoglobin, white blood cells, neutrophils, or platelets)
- Diarrhea
- Fatigue
- Hair loss
- Heart damage (cardiotoxicity)
- Increased risk of infections
- Loss of appetite
- Lung toxicity
- Mouth sores
- Nausea or vomiting
- *Peripheral neuropathy* (numbness or tingling in hands and feet)
- Problems with sexual function
- Sterility

**Changes in Taste**
Some patients receiving chemotherapy experience a change in the way foods or beverages taste. Familiar foods may taste different (*dysgeusia*), or the flavors of foods may not taste as strong (*hypogeusia*). Some patients may also notice that foods have a metallic taste. These side effects are temporary and usually disappear after completion of chemotherapy. Sometimes this side effect can be helped by dietary changes, such as eating foods that are frozen, cold, or at room temperature; adding extra seasonings or sugar to enhance taste and reduce bitterness; and avoiding metallic silverware.

**Cognitive Problems**
Chemotherapy can result in mild cognitive impairment, such as trouble concentrating, impaired memory, or issues with motor control. Some patients refer to these side effects as “chemo brain.” Although these side effects can be stressful, they typically disappear over time.

**Constipation**
Constipation is a significant side effect observed in adolescent patients as a result of the higher vincristine (Oncovin and others) doses typically used in pediatric regimens and *nonadherence* (not following directions) to regimens prescribed to prevent constipation.
**Decreased Blood Cell Production**

The bone marrow constantly produces red blood cells, white blood cells, and platelets. Several types of therapies for HL temporarily interfere with the ability of the bone marrow to produce enough of one or more of these different types of blood cells. This is called *myelosuppression*.

To prevent and monitor myelosuppression, samples of a patient's blood are tested with a complete blood count (CBC) with differential, which measures the numbers of red blood cells and platelets, as well as all the different subtypes of white blood cells. These tests are usually done before and sometimes during the treatment process. Table 9.1 describes five of the most common conditions involving a decrease in blood cell production.

**Table 9.1. Five Common Conditions Caused by Decreased Blood Cell Production**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anemia</strong></td>
<td><em>Anemia</em> is caused by a decrease in the number of red blood cells.</td>
</tr>
<tr>
<td></td>
<td>Many chemotherapy drugs cause mild or moderate anemia.</td>
</tr>
<tr>
<td></td>
<td>Anemia can make people feel tired and short of breath, especially when it is severe.</td>
</tr>
<tr>
<td></td>
<td>Although seldom needed, drugs or red blood cell transfusions can be used to treat severe anemia.</td>
</tr>
<tr>
<td><strong>Leukopenia</strong></td>
<td><em>Leukopenia</em> refers to a decrease in the number of leukocytes, or white blood cells. Leukocytes include lymphocytes (B cells and T cells), neutrophils, basophils, eosinophils, and monocytes.</td>
</tr>
<tr>
<td></td>
<td>Patients with low levels of neutrophils and lymphocytes are at increased risk of infections.</td>
</tr>
</tbody>
</table>

---

87 Understanding Hodgkin Lymphoma
### Table 9.1. Five Common Conditions Caused by Decreased Blood Cell Production (continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Lymphopenia** | - *Lymphopenia*, also called lymphocytopenia, refers to a decrease in the number of lymphocytes. Lymphocytes produce antibodies that fight bacterial and viral infections. About 20 to 40 percent of white blood cells are lymphocytes.  
  - Patients with low levels of lymphocytes (notably neutrophils [see below]) are at increased risk for infections.                                                                                                                                                                                                                                                                                                                                                                    |
| **Neutropenia** | - *Neutropenia* refers to a decrease in neutrophils, the primary type of white blood cells that fight bacterial or other infections.  
  - Patients with low neutrophil counts are at higher risk for serious and even life-threatening infections. Symptoms of infection include fever, chills, and night sweats.  
  - During chemotherapy doctors regularly monitor the patient’s *absolute neutrophil count* (ANC), the number of neutrophils in the peripheral blood. Because patients with an ANC below 500 cells per microliter are at particularly high risk for infections, doctors may decrease the chemotherapy dosage or delay the next treatment until the ANC returns to 500 or greater.  
  - Some patients require treatment with antibiotics and hospitalization to prevent or treat infections.  
  - To avoid a patient missing a dose of chemotherapy, doctors sometimes prescribe drugs like filgrastim (*Neupogen, Granix, Zarxio*) and pegfilgrastim (*Neulasta*) to reduce the duration and severity of neutropenia. These drugs can sometimes cause bone pain, which is usually temporary. Bone pain in the chest can simulate heart disease, so patients taking these drugs might think they are having a heart attack.  
  - Bone pain can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (*Advil and others*) or naproxen (*Aleve, Naprosyn*), as well as the antihistamine loratadine (*Claritin, Alavert*).  

### Table 9.1. Five Common Conditions Caused by Decreased Blood Cell Production *(continued)*

<table>
<thead>
<tr>
<th><strong>Neutropenia (continued)</strong></th>
<th>For patients with HL, pegfilgrastim, filgrastim, and other white blood cell growth factors SHOULD ALMOST NEVER BE GIVEN to patients receiving frontline chemotherapy treatment (usually ABVD). Although these drugs can help to raise the ANC, they can also increase the chances that one of the chemotherapy drugs (for example, bleomycin) will cause lung problems. However, these growth factors can be given to patients who do not receive or who stop receiving bleomycin. Note that this is not generally a problem in the treatment of pediatric cHL due to the timing of drug administration.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td><em>Thrombocytopenia</em> refers to a decrease in the number of platelets in the blood. Platelets help start the clotting process when bleeding occurs.</td>
</tr>
<tr>
<td></td>
<td>Patients with low platelet counts may bruise easily; have cuts that bleed more or longer than usual; have nosebleeds or bleeding gums; or bleed from places that have not been injured.</td>
</tr>
<tr>
<td></td>
<td>A platelet transfusion may be needed if thrombocytopenia is severe or if the patient develops bleeding.</td>
</tr>
</tbody>
</table>
Diarrhea

Some types of chemotherapy may cause diarrhea. While most patients do not experience severe diarrhea, the most important point to remember is to stay hydrated. Signs of dehydration include dry mouth or skin, decreased urine, and feeling dizzy or lightheaded after standing up. The doctor should be contacted if the patient has bloody diarrhea or fever with diarrhea. Patients may follow the tips below.

Avoiding Dehydration From Diarrhea or Vomiting

- Drink plenty of liquids (eight glasses a day), such as electrolyte replacement drinks like Gatorade, Pedialyte, and Powerade.
- Sometimes it helps to sip small amounts very frequently rather than to drink a full glass at once.
- Soup, especially broth, is a good source of both water and nutrients.
- Do not drink or eat dairy products because they can worsen diarrhea.
- Do not eat foods that are high in fiber or hard to digest because they can worsen diarrhea.
- Eat plenty of bananas and other high-potassium foods (after checking with your doctor or dietitian to make sure these foods will not interfere with your chemotherapy or other medications).
- Take the medicines that your doctor recommends to control diarrhea or vomiting, and call your doctor if symptoms persist.
Fatigue
Fatigue is a common side effect of many therapies for HL. Fatigue usually decreases after patients have completed their lymphoma treatment, but it can take weeks or months for patients’ energy levels to return to normal. Patients may use the tips below to help them cope with fatigue.

Coping With Fatigue

- Keep a diary to help keep track of when you have the most energy and which activities make you feel tired or give you energy. Use this information to plan your activities for the times when you have the most energy.
- Ask for help with housework and other daily activities that are tiring.
- Exercise if your doctor says it is okay to do so, but do not overdo it. Try simple stretching and range-of-motion exercises or a short walk; these activities may energize you without tiring you out. Start slowly and build up to the level that is right for you. Ask your doctor, nurse, or physical therapist to help you create a personalized exercise plan.
- Rest and sleep during therapy are very important, but too much rest may actually decrease your energy levels. An afternoon nap helps some patients feel less tired for the rest of the day, but other patients cannot sleep at night if they nap during the day. If you have trouble sleeping, talk to your healthcare team to find out what you can do to get more rest.
- Be patient. These symptoms usually improve once treatment is completed.
**Hair Loss**

Certain chemotherapy drugs can cause *alopecia* (thinning or loss of hair) anywhere on the body, including the scalp, eyebrows, eyelashes, arms, legs, and pelvis. The amount of hair loss varies.

When hair loss occurs, it usually starts two to six weeks after the first chemotherapy treatment. Remember that hair loss caused by chemotherapy is usually temporary; hair will most likely grow back after the end of treatment. When the hair first grows back, it may have a slightly different texture or color than it had before treatment. Over time, the texture and color often return to normal. Loss of hair in the nose and nasal passages may lead to symptoms of *rhinorrhea* (runny nose).

Patients may follow the tips below for managing chemotherapy-induced hair loss. However, it is important to understand that none of these measures have been shown to prevent hair loss.

---

**Managing Chemotherapy-Induced Hair Loss**

- After washing your hair, pat it dry instead of rubbing it with a towel.
- Brush your hair with a soft-bristle brush or a wide-tooth comb.
- Do not use curlers or hair dryers.
- Do not color or perm your hair or treat it with other chemicals.
- Use a hat or scarf to protect your scalp when you are out in the sun and to help keep you warm when you are indoors or outside in the cold.
- Many patients choose to wear a wig, scarf, turban, soft cotton hat, or head wrap to disguise hair loss. Some health insurance companies cover the cost of wigs with a doctor’s prescription. Check your policy to see if it covers this cost.
Heart Damage (Cardiotoxicity)

Cardiotoxicity refers to damage to cells in the heart or heart muscle. Long-term use of certain chemotherapy agents such as doxorubicin can cause cardiotoxicity in a small number of patients.

In general, most patients with HL treated with potentially cardiotoxic chemotherapy, such as doxorubicin, receive these drugs at dosages that are not likely to cause cardiotoxicity. In addition, patients only generally receive doxorubicin during frontline chemotherapy and not later during treatment. This helps reduce their risk for developing chemotherapy-related cardiovascular disease.

A patient’s history of heart disease, high cholesterol, or high blood pressure, as well as obesity and lifestyle choices (such as smoking and lack of exercise), may increase the chance of developing chemotherapy-related or radiation-related cardiotoxicity.

Careful monitoring by the healthcare team can reduce the chances of patients developing cardiotoxicity. Before deciding to treat patients with a cardiotoxic drug, most doctors order either an echocardiogram (ECHO) or a multigated acquisition (MUGA) scan to measure the patient’s cardiac function. These tests ensure that patients are prescribed a safe chemotherapy dosage given their current heart function. Patients with underlying conditions that put them at high risk of cardiotoxicity may also have their heart function monitored more intensively during the course of treatment for HL. See Chapter 4 for more information about tests used to evaluate heart function.
Infections

Some HL treatments can lower a patient’s ability to fight infections. Patients with a fever of 100.5°F or greater should call the doctor. Chills or a chilly sensation often precede fever. Patients should ask their provider what to do if they have a sore throat, rash, diarrhea, cough, or redness, swelling, or pain around a wound. The doctor should also be contacted if the patient experiences any painful local rash with or without blisters, as this could indicate an infection with shingles (herpes zoster).

To reduce the risk of infections, patients may be prescribed antibiotic, antiviral, or antifungal medications. Patients may be at increased risk for viral infections such as shingles, and sometimes doctors prescribe medication to prevent a shingles outbreak during therapy. Other ways to reduce the risk of infections are included below.

Reducing Infection Risk During Chemotherapy

- Check with your doctor to make sure your vaccinations are up to date before starting treatment.
- Wash your hands diligently and regularly.
- Avoid crowds, especially during influenza season (October–May in North America).
- Make sure all foods are thoroughly washed and/or cooked; avoid raw foods that may carry germs.
- Do not sleep with pets.
**Loss of Appetite**

Loss of appetite is sometimes a symptom of lymphoma itself, but it can also be a side effect of chemotherapy. Patients may eat less than normal, not feel hungry, or feel full after eating only a small amount of food. Ongoing loss of appetite can lead to weight loss and poor nutrition, which can become serious. Side effects from chemotherapy and other treatments, such as nausea and vomiting, mouth sores or pain, fatigue, depression, dry mouth, and difficulty swallowing can all contribute to a patient’s loss of appetite.

The patient’s healthcare team should be notified about lack of appetite to determine the underlying cause. Loss of appetite can sometimes be treated with drugs or by changing eating habits, such as eating several small meals each day and making nutritious food choices. Patients may wish to visit a nutritionist for additional tips. For more information about nutrition, please view the *Nutrition* fact sheet on LRF’s website at [www.lymphoma.org/publications](http://www.lymphoma.org/publications).

**Lung (Pulmonary) Toxicity**

Damage to the lungs is a serious side effect of the chemotherapy drug bleomycin (Blenoxane). Patients who are receiving ABVD, escalated BEACOPP, Stanford V, ABVE-PC or any other chemotherapy regimen that contains bleomycin should tell their doctor immediately if they experience any changes in lung function such as cough, chest pain, or shortness of breath. Some doctors monitor patients’ lung health by regularly performing pulmonary (lung) function tests (PFTs) during the course of any chemotherapy regimen that contains bleomycin. It is important that patients tell their doctor immediately if they develop a cough or shortness of breath on exertion. The sooner that this is detected, the more favorable the outcome.
**Mouth Sores**

Some chemotherapy drugs can cause a patient's mouth to become red, sore, or irritated, which is called *mucositis*. Additionally, some patients undergoing chemotherapy become more susceptible to viral or fungal infections of the mouth and throat. Doctors may prescribe antiviral and antifungal medications to prevent this type of infection.

The doctor should be informed if a patient develops a sore throat. The doctor may examine the patient's throat and take a swab that is sent to the laboratory to check for infection. Several medications are available to treat different types of infections. To help decrease chances of mouth infections, patients should have a complete dental checkup and cleaning before starting chemotherapy. Other tips for preventing and caring for mouth sores caused by HL treatment are listed below.

### Preventing and Caring for Mouth Sores

- Clean your mouth and teeth regularly. Use a soft-bristle toothbrush, a nonabrasive toothpaste, and lip moisturizer.
- Do not use mouthwashes that contain alcohol. Your doctor may prescribe a mouth rinse that cleans mouth sores without irritating them.
- Do not eat citrus fruits (such as oranges, grapefruit, lemons, or clementines) or drink citrus juices, and avoid other acidic foods and sodas. The acids in these foods and drinks can further damage the lining of the mouth.
- Swish and spit warm salt water (1/4 teaspoon of salt mixed in a coffee cup of warm water) four to six times per day to soothe mouth irritation.
- Do not eat spicy foods.
- Eat soft foods to avoid bruising your gums and other soft tissues in your mouth.
- Do not floss your teeth if your blood counts are low, as this may cause your gums to bleed.
Nausea or Vomiting

Many chemotherapy drugs can cause nausea or vomiting. This typically occurs on the day chemotherapy is administered, but it may also occur one or two days later. Doctors prescribe an antiemetic (a drug that prevents nausea and vomiting) before chemotherapy. Examples of antiemetics include aprepitant (Emend), ondansetron (Zofran, Zuplenz), granisetron (Kytril and others), metoclopramide (Reglan and others), prochlorperazine (Compazine, Procomp, Compro), dolasetron (Anzemet), and a variety of corticosteroids such as prednisone and dexamethasone. In most cases, these antiemetics can partially or completely prevent nausea and vomiting. Tips for controlling or minimizing nausea and vomiting are listed below.

Controlling or Minimizing Nausea and Vomiting

- Before chemotherapy, drink a liquid diet consisting of water-based items such as broth, gelatin, ice pops, tea, and water. Do not drink milk or have a meal in which the main ingredients are dairy products.
- Do not eat foods that are too hot or too cold, greasy or fatty, or sweet or spicy.
- Eat smaller, more frequent meals instead of fewer large meals each day.
- Avoid strong or offensive smells. Get plenty of fresh air.
- Take prescribed antiemetics before chemotherapy to prevent nausea.
- If you vomit, make sure to avoid becoming dehydrated (see tips on page 90).
- Finding the best approach is often a process of trial and error. Try different approaches to determine what works best for you.
Peripheral Neuropathy

Some chemotherapy drugs may damage the nervous system, causing *peripheral neuropathy* in the hands and feet (sometimes extending to the arms and legs). Symptoms of peripheral neuropathy include pain, numbness, a tingling or prickling sensation, sensitivity to cold and touch, and muscle weakness that can impair fine motor skills such as buttoning a shirt or picking up small objects.

Peripheral neuropathy can be a difficult side effect for patients to manage, and it is a common cause of treatment delays. Furthermore, while neuropathy improves or resolves in most patients after completion of therapy, the symptoms can last beyond the end of the treatment period. Patients should notify their doctor as soon as symptoms begin to develop so the treatment regimen and dosing can be modified appropriately. Specific chemotherapy agents may be discontinued or the dosages may be reduced to prevent further complications.

Although no medications have been specifically approved by the U.S. Food and Drug Administration (FDA) to treat chemotherapy-induced peripheral neuropathy, there are several different classes of drugs that doctors may prescribe to help alleviate patients’ symptoms. These include antiepileptic agents such as pregabalin (Lyrica) and gabapentin (Neurontin, Gralise, Horizant); local anesthetics such as lidocaine patches; opioid pain relievers; and antidepressants that also target pain such as duloxetine (Cymbalta). Complementary therapy techniques such as acupuncture and massage may also help with neuropathy symptoms (see Table 6.4). Finally, patients should avoid tight-fitting shoes or clothes and exposure to cold, as these may exacerbate neuropathy symptoms in the hands and feet.

A specific type of neuropathy called Raynaud phenomenon may occur in some patients receiving treatment for HL, particularly bleomycin (Blenoxane). This condition is characterized by signs of poor red blood cell circulation in the blood vessels near the nose, ears, fingers, and toes in response to cold temperatures (including cool weather);
symptoms include feelings of cold, numbness, tingling, discoloration of affected areas, and pain in the hands and feet in cool temperatures. Raynaud phenomenon may be managed with a class of medications called calcium channel blockers.

**Problems With Sexual Function**
Psychological factors such as fear about illness, altered body image due to hair loss and depression, and the physical side effects of treatment on the body and the brain, often cause a drop in *libido* (sex drive). However, a normal libido usually returns after treatment is finished. Patients should not be embarrassed to talk with their doctor about any problems or concerns they have about changes in their libido or sexual function. The doctor might order tests to track hormone levels or recommend seeing a specialist. Doctors can also prescribe medications to restore erectile function in men, or hormone therapy to alleviate vaginal dryness and other menopausal symptoms in women. It is important for patients to discuss this issue openly with their spouses or partners.

**Sterility**
Because chemotherapy and radiation may damage sperm and egg cells, these treatments can sometimes cause temporary or permanent sterility (the inability to have children) in both men and women. The potential for developing sterility depends on the treatment type and dosage, the number of therapies given, and the patient’s age at the time of treatment. Options for preserving fertility both before and during treatment include protection of the ovaries or testes, freezing of sperm cells and egg cells, and in vitro creation and freezing of fertilized embryos. Patients should speak with their doctor about fertility preservation as early as possible before beginning treatment. For more information and resources about sterility, visit LRF’s web page on “Fertility” available at [www.lymphoma.org/fertility](http://www.lymphoma.org/fertility).

Despite these risks, it is still possible for female HL patients to become pregnant and for male HL patients to impregnate their female partners during the course of treatment and after cancer treatment. Because
chemotherapy and radiation treatments can cause severe birth defects and other pregnancy complications, it is critical that patients receiving these treatments always use reliable birth control methods during treatment and for several months after completion of therapy. The exact duration of this precaution depends in part on the treatment regimen administered. Patients should discuss fertility concerns and pregnancy prevention with their doctor and, if needed, with a fertility specialist.

Other Possible Side Effects
Chemotherapy can cause other side effects, such as skin rashes, general weakness, and loss of balance or coordination. Many of these side effects are temporary, but some may last for an extended period. The doctor should be contacted immediately if the patient experiences any painful local rash with or without blisters, as this may be a sign of shingles (herpes zoster).

Can the Chemotherapy Treatment Schedule Be Changed to Reduce Side Effects?
Some treatment-related side effects are unpleasant but tolerable. Other side effects may be more serious, but they can often be anticipated and prevented. Occasionally, side effects may be severe enough that doctors may reduce the dosage of chemotherapy or delay one or more treatment cycles until the side effects improve. However, it is important that chemotherapy treatment schedules be maintained to the greatest extent possible, because changing the regimen to reduce short-term side effects can be harmful in the long run. A full course of chemotherapy given on time works best for the treatment of HL. Research has shown that reducing the dosage or delaying chemotherapy cycles can reduce the chance of complete remission and long-term survival for patients with certain types of lymphomas. Patients and their doctors should work together to anticipate and manage short-term side effects, in order to maximize the chances that patients can complete the entire chemotherapy regimen exactly as prescribed.
What Side Effects Are Caused by Steroids?

*Corticosteroids* (often called simply “steroids”) are commonly given along with chemotherapy. This type of steroid is not the same as androgens and anabolic steroids that can be used to enhance athletic performance. Steroids can serve several purposes in HL treatment, including helping to treat the lymphoma, reducing inflammation, relieving nausea, and stimulating appetite. However, dexamethasone, prednisone, and other corticosteroid drugs can cause side effects such as *insomnia* (the inability to fall or stay asleep), increased appetite, mood or personality changes, anxiety, high blood pressure, fluid retention, and weight gain. Prednisone can also trigger diabetes in patients prone to that disease or worsen diabetes in patients who already have it. Long-term steroid use can also cause osteoporosis, cataracts, and changes in appearance.

Mood and personality changes from steroids can range from mild to severe. Common reactions include irritability, anger, and depression. Patients should alert their family members and friends that these personality changes may occur during their treatment so that they can watch for changes in the patient’s behavior. If personality changes do occur, the doctor should be informed right away, as the steroid dosage may need to be reduced.

What Side Effects Are Caused by Monoclonal Antibodies?

The monoclonal antibodies used to treat patients with HL may cause side effects such as low blood cell counts and infusion reactions, although monoclonal antibodies are less likely than chemotherapy to cause low blood cell counts. These side effects are usually mild, but they can sometimes be severe. Other rare but potentially very serious side effects include infections.
Infusion Reactions

An infusion reaction is a reaction that typically occurs during or within 24 hours after infusion of an intravenous (IV) drug. Symptoms include dizziness, fainting, headache, feeling warm or flushed, fever or chills, hives, itching, shortness of breath, changes in heart rate and blood pressure, pain in the back or abdomen, and swelling of the face, tongue, or throat. Some infusion reactions are true allergic reactions that can cause low blood pressure, difficulty breathing, and anaphylactic shock.

To prevent infusion reactions, patients are given an antihistamine such as diphenhydramine (Benadryl), acetaminophen (Tylenol), and sometimes corticosteroids before or during the antibody infusion. Nurses closely monitor patients during the infusions for signs of an infusion reaction. Patients should immediately report any new symptom they experience during or after an infusion.

Infections

Reactivation of hepatitis B virus (HBV) infection is a rare but very serious side effect of treatment with the monoclonal antibody rituximab (Rituxan), which is used in patients with nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Reactivation of HBV may also occur with steroid or chemotherapy treatment. Patients may not know they are infected with HBV, because a healthy immune system can force the virus to hide without causing noticeable symptoms. However, treatment with CD20-directed monoclonal antibodies or chemotherapy can trigger immune system changes that reactivate HBV, which can cause acute liver failure. To prevent HBV from reinitiating, patients are screened for HBV infection before treatment. Patients who have the virus are closely monitored during and after treatment and may be given antiviral medications to control HBV infection. Patients should be mindful of signs of an active HBV infection, such as increasing fatigue and yellowing of the skin or eyes.
Very rare cases of a serious and usually fatal central nervous system infection called J C virus infection (progressive multifocal leukoencephalopathy [PML]) can also occur with any of the monoclonal antibodies. Patients should be mindful of neurological symptoms, such as difficulty thinking, loss of balance, changes in speech or walking, weakness on one side of your body, or blurred or lost vision.

**What Side Effects Are Caused by Immunotherapy?**

**Brentuximab V edotin (Adcetris)**
Brentuximab vedotin (Adcetris) shares many similarities to standard chemotherapy, including similar side effects. The most common side effects reported in patients treated with brentuximab vedotin include a depressed immune system, low blood counts, peripheral neuropathy (usually not until the third or fourth cycle of treatment), fatigue, nausea, upper respiratory tract infection, diarrhea, fever, rash, cough, and vomiting. Patients may also experience reactions at the site of the treatment infusion. Hair loss is possible. Rarely, brentuximab vedotin can be associated with inflammation of the pancreas, and patients with severe abdominal pain or diarrhea should seek medical attention immediately.

**Checkpoint Inhibitors**
In patients with HL who are treated with the checkpoint inhibitors nivolumab (Opdivo) or pembrolizumab (Keytruda), the most common side effects include fatigue, upper respiratory tract infection, fever, diarrhea, cough, itching, decreased appetite, rash, shortness of breath, muscle and bone pain, constipation, and nausea.
What Side Effects Are Caused by Radiation Therapy?

Radiation therapy itself is painless, but it can cause short-term and long-term side effects that vary depending on the type of radiation, the dosage, and the area of the body treated. Side effects are usually worse when radiation therapy and chemotherapy are given at the same time. It is important to remember that radiation only affects the area that is treated, much like a flashlight only illuminates the area it shines upon.

Some of the short-term side effects caused by radiation therapy used to treat patients with HL include:

- Dry mouth
- Fatigue
- Loss of appetite and taste
- Nausea
- Skin reactions
- Throat irritation

Dry Mouth

Patients who receive radiation therapy to the mouth may experience a temporary decrease in saliva production causing xerostomia (dry mouth). Dry mouth may result in difficulty swallowing foods or thick liquids. It can also cause food particles to stick to the teeth and gums. Because saliva helps prevent cavities, doctors may advise patients to visit the dentist for fluoride treatments before they start radiation therapy to reduce the risk of tooth decay. Depending upon the involvement of the salivary glands in the radiation field and the total dosage of radiation, xerostomia can occasionally be permanent.

Fatigue

The likelihood of patients experiencing fatigue as a result of radiation therapy depends on their disease and their specific radiation plan. Patient tips for coping with fatigue are included on page 91.
**Loss of Appetite and Taste**

During radiation treatment, patients might lose their appetite for foods they normally enjoy, or their sense of taste may become diminished. The loss of appetite and taste are usually short-term problems. Patients should remember to eat healthy diets, because their bodies need energy and good nutrition to maximize healing. Eating four or five small meals a day may be more comfortable than eating two or three larger meals. Patients should ask their healthcare team for information about how to maintain a healthy diet during treatment.

**Nausea**

Radiation treatment can cause nausea, especially in patients who receive radiation to the abdomen. Not eating (especially sweet, spicy, or fatty foods) a few hours before radiation therapy may help avoid nausea. The doctor may also prescribe an *antiemetic* (antinausea) medication to be taken before each radiation therapy session. Patient tips for coping with nausea are included on page 97.

**Skin Reactions**

Radiation therapy can cause skin changes to the affected area such as redness, itchiness, dry and peeling skin, sores or ulcers, swelling, and puffiness. These skin changes usually decrease and disappear over a few weeks after the radiation therapy ends. However, some skin changes, such as darker and blotchy skin, very dry skin, or thicker skin, may last much longer or be permanent. The radiated area can also sunburn more easily than other parts of the body. Patients should avoid tanning beds and protect their skin from sunlight with a wide-brimmed hat, long sleeves, long pants, and sunscreen with an SPF of at least 30.

Patients should speak with their doctor, nurse, or physician assistant if they experience any skin changes. A list of tips to help patients care for their skin during and after radiation therapy is provided on the following page.
Skin Care During and After Radiation Therapy

- Be gentle with your skin; do not rub, scrub, or scratch.
- Use lotions and other skin products that your doctor prescribes or your nurse suggests.
- Do not put anything on your skin that is very hot or cold (such as heating pads or ice packs).
- Shower or bathe in lukewarm water, and limit your bathing to less than 30 minutes every other day. Use a mild, unscented soap and pat your skin dry after bathing. Be sure not to wash off the ink markings needed for radiation therapy.
- Check with your doctor or nurse before using bubble bath, cornstarch, cream, deodorant, hair removers, makeup, oil, ointment, perfume, powder, and sunscreen.
- Wear soft, loose clothes that allow your skin to breathe.
- Use soft sheets, such as those made with cotton.
- Add moisture (humidity) to the rooms in your home by placing a bowl of water on the radiator or using a properly cleaned and maintained humidifier.
- Do not sunbathe or use tanning beds, and protect your skin from the sun every day.
- Do not put adhesive tape or bandages on your skin. Ask your nurse about ways to bandage without tape.
- Ask your doctor or nurse if you may shave the affected area. Shave only with an electric razor, and do not use preshave lotion.
- Report any skin changes you notice to your doctor or nurse.
Throat Irritation

Radiation therapy to the neck, throat, or chest may cause sore throat, dry mouth, nausea, and/or cough. Patients may have difficulty eating or swallowing, especially toward the end of their treatment regimen. Patients should tell their doctor if swallowing becomes difficult, as there are treatments for the discomfort. Patients should take precautions to avoid becoming dehydrated during treatment (see page 90 for tips on avoiding dehydration). Difficulty swallowing usually goes away a few weeks after treatment is completed. Sometimes a viral infection such as oral herpes or a fungal infection such as thrush can contribute to throat irritation. Patients should notify their doctor if they are experiencing throat irritation, so that the doctor can take a throat swab to test for these infections and prescribe antiviral or antifungal medications if needed.

The tips listed below may help ease throat irritation during radiation therapy.

**Easing Throat Irritation During Radiation Therapy**

- Eat bland foods that are soft, smooth, and easy to digest, such as pudding, yogurt, and milkshakes.
- Take small bites and swallow each bite completely before taking another one.
- Puree foods in a blender to make them easier to swallow.
- Avoid citrus fruits and citrus juices.
- Ask your doctor whether lidocaine hydrochloride solution (Xylocaine Viscous) may be appropriate.
What Long-Term and Late Side Effects Are Caused by Radiation Therapy?

In addition to the short-term side effects caused by chemotherapy or radiation, these treatments can cause long-term and late side effects that may not show up for years or even decades after the initial treatments.

Cardiovascular Damage
Radiation therapy to the chest has three major effects on the heart: it damages arteries, most commonly those in the neck (carotid arteries) and the heart (coronary arteries), which can increase the risk of heart attack and stroke; it damages the valves of the heart; and it causes pericarditis (inflammation of the membrane that surrounds the heart). Patients who receive radiation therapy are also at risk for cardiomyopathy (damage to the heart muscle), especially if they are also receiving doxorubicin. Every five years, patients who have been treated with radiation therapy to the chest should undergo a complete cardiovascular examination that includes a Doppler ultrasound to examine the carotid arteries, an echocardiogram (ECHO) to measure valves, and a stress test to look for coronary artery disease. Statin drugs (a class of drugs used to manage cholesterol) are recommended for patients who have received radiation therapy to prevent coronary artery disease.

Secondary Cancers
The risk of developing secondary cancers from radiation therapy depends on factors such as the amount of radiation given and the part of the body treated. In particular, younger female patients in their teens and 20s who receive chest radiation are more susceptible to developing breast cancer. All the currently available information about secondary cancer risk comes from studies that were performed in the past, when higher doses of radiation were used and larger areas of the body were treated with radiation. Newer methods of radiation therapy limit the amount of healthy tissue exposed to radiation, which reduces but does not eliminate the risk of secondary cancers after these treatments. It is imperative that patients protect irradiated skin from direct sun exposure, no matter how long ago the radiation was administered.
What Side Effects Are Caused by Stem Cell Transplantation?

Patients treated with high doses of chemotherapy and/or radiation before undergoing a stem cell transplant are at increased risk for developing infection, bleeding, and other side effects as described previously (see the previous sections “What Side Effects Are Caused by Chemotherapy?” on page 85 and “What Side Effects Are Caused by Radiation Therapy?” on page 104).

Patients receiving high-dose chemotherapy with autologous stem cell transplantation are followed carefully for the first three to four weeks because of the risks of mouth sores, infection, anemia, and uncontrollable bleeding (for example, nose bleeds, bleeding in the gums when brushing teeth, and blood in the urine or feces) due to the inability of the blood to clot. Transfusions and antibiotics may be necessary, which are often administered in the hospital.

Patients receiving stem cells from a relative or unrelated donor are also at risk of developing graft-versus-host disease (GVHD), a serious condition in which the donated stem cells attack the patient’s tissues. GVHD can affect the digestive system, resulting in symptoms such as diarrhea, abdominal pain, nausea, and vomiting. GVHD can occur at any time after the transplant. Drugs can be used to reduce the risk of developing GVHD or to treat the condition once it develops.

For more information, view the Understanding Stem Cell Transplantation publication on LRF’s website at www.lymphoma.org/publications.

When Should a Patient’s Doctor Be Contacted?

Patients should talk with their doctor about which symptoms and side effects they should watch for. As a general rule, a patient’s doctor should be contacted if the patient experiences:

- A side effect that is unexpected or lasts longer than expected
- A medical problem—such as fever/chills, shortness of breath, prolonged or constant nausea and vomiting, chest pain, and/or dizziness—that cannot wait for a regularly scheduled appointment
Chapter 10: Managing Life During and After Treatment

This chapter discusses some general issues that patients may encounter in their daily lives during and after treatment for Hodgkin lymphoma (HL).

Coping Strategies

Each person’s experience with cancer is different, and the way an individual copes with the physical and emotional impacts of HL is unique to each patient's personality and situation. Table 10.1 lists some suggestions for coping with common issues that patients may face.

Table 10.1. Coping Strategies

<table>
<thead>
<tr>
<th>Building a Strong Support System</th>
<th>Getting Help for Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Communicate your fears and concerns about your disease by talking to your family, friends, doctors, and counselors.</td>
<td>▪ Feeling sad or having a depressed mood from time to time is not unusual in patients living with cancer, but this is not the same as having a psychiatric diagnosis of depression, known as “Major Depressive Disorder.”</td>
</tr>
<tr>
<td>▪ Write down your concerns in a journal.</td>
<td>▪ Watch for signs such as sleeping more or less than usual, a loss of interest in preferred activities, crying, or an inability to concentrate.</td>
</tr>
<tr>
<td>▪ Find a support group (such as the Lymphoma Research Foundation’s Lymphoma Support Network) or other individuals who are also coping with cancer.</td>
<td>▪ If these symptoms last more than two weeks, ask for a referral to a psychiatrist, social worker, psychologist, or counselor who can help you cope with your feelings through talk therapy, medications, or both.</td>
</tr>
</tbody>
</table>
Table 10.1. Coping Strategies (continued)

| Dealing With Physical Changes |  
|-------------------------------|---|
|     ▪ If desired, plan ahead and buy a wig or head covering if hair loss is a possibility. Some patients with lymphoma may feel unattractive because of hair loss and other changes in appearance caused by their treatment. |  
|     ▪ Seek advice from a beautician about makeup if you are concerned about a blotchy complexion. |  
|     ▪ Ask your healthcare team for advice on how to manage other temporary changes such as dry skin and brittle nails. |  

| Maintaining a Healthy Lifestyle |  
|--------------------------------|---|
|     ▪ Eat a healthy diet that includes fruits, vegetables, proteins, and whole grains. |  
|     ▪ Engage in regular physical exercise, which can help improve mood and reduce anxiety, depression, and fatigue. |  
|     ▪ Get sufficient rest to help combat the stress and fatigue of your disease and its treatment. |  
|     ▪ Quit smoking and reduce alcohol consumption. |  

| Set Reasonable Goals |  
|---------------------|---|
|     ▪ Set goals for how you want to live your life during and after treatment to help you maintain a sense of purpose. |  
|     ▪ Avoid setting unreasonable goals, such as working full-time if you do not yet have the energy or stamina to do so. |  
|     ▪ Stay as active and involved as you can in work and other activities that interest you. |  

The Importance of Pain Control

Patients may experience pain from the lymphoma itself or from the treatments and procedures. Pain is very treatable, and there is no reason for a patient to endure this pain without help. Patients should tell their doctors, nurses, or physician assistants if they have any pain, because the healthcare team can offer advice regarding medications and other ways to reduce and manage the pain.
Different types of pain are best controlled by different types of pain relievers, and some medications may not be appropriate for patients with HL. Patients should ask their healthcare team which options are best to help manage their pain. The tips below may help also.

**Managing Pain**

- Be specific when you describe your pain to the doctor or nurse.
  - Where do you feel the pain?
  - When did the pain start?
  - What type of pain is it (sharp, dull, throbbing)?
  - Does the pain come and go, or is it steady? How long does it last?
  - How strong is the pain? Does the intensity change at different times?
  - Does anything make the pain feel better or worse?
  - Which drugs have you taken for the pain? Do they help? If so, for how long?
- Take your pain medication on a regular schedule even if the pain seems to be better. Do not skip doses.
- Tell your family and friends about your pain so they can help you and understand why you may be acting differently.
- Try deep breathing, yoga, or other ways to relax.
- Ask to meet with a pain specialist or palliative care specialist to help you find better ways to control your pain.
- Tell your doctor or nurse of any changes in your pain.
Maintain a Healthy Lifestyle

Regular physical activity helps keep the cardiovascular system strong and the body muscles flexible. Exercise can also help patients alleviate breathing problems, constipation, and mild depression. Additionally, it may help reduce stress and fatigue. Patients should talk to their doctor before starting an exercise program and consider visiting a physical therapist for advice. The most important point to remember is to avoid overexertion. Patients dealing with cancer do not need to perform activities at the same level of intensity that they did before their lymphoma diagnosis, and they should not push themselves to their limit.

Several types of exercise may be particularly helpful, including:

- General physical activity, such as swimming, dancing, household chores, and yard work
- Aerobic activity to improve cardiovascular fitness, such as walking, jogging, and bicycling
- Resistance training to strengthen muscles, protect joints, and help prevent osteoporosis by building bone mass
- Flexibility exercises such as stretching and yoga to improve range of motion, balance, and stability

Eating a healthy diet is especially important during treatment for HL because it helps patients keep up their strength and energy, tolerate treatment-related side effects, decrease the risk of infections, and heal and recover more quickly. Patients should aim for a diet high in fruits and vegetables, protein (such as poultry, fish, and eggs), and whole grains. During or after treatments that can lower white blood cell counts, such as chemotherapy and stem cell transplantation, patients may be instructed to follow a neutropenic diet, which involves temporarily avoiding raw fruits and vegetables that may increase the risk of infection. The healthcare team can help develop an eating plan that is appropriate. Patients should talk to their doctor before taking any dietary supplements such as multivitamins or individual vitamin supplements, as well as any herbal or “natural” supplements, because they may interfere with treatments or have unexpected side effects.
The Importance of Follow-up Care
At the first visit following the completion of treatment, patients should discuss their follow-up schedule with the doctor. This schedule is different for each patient depending on his or her lymphoma type and stage, age, and overall health. It is critical that patients adhere to their schedule of follow-up visits—these are very important for monitoring disease recurrence, as well as detecting and treating any new health problems that might arise.

During these follow-up visits, the doctor asks about any medical changes since the last appointment and conducts a physical examination. The doctor may also prescribe blood, imaging, or other laboratory tests.

Be Proactive in Healthcare Decisions
To stay proactive in healthcare decisions, patients should write out their questions and bring them to their appointments and take notes during their visits. They may also download and start using the Lymphoma Research Foundation’s (LRF) Focus On Lymphoma app on their mobile devices to learn about and manage HL. Patients should also obtain and save the following information from their medical team:

- Copies of all medical records and a written summary of their treatment(s) in case the patient switches doctors or needs to see a physician who is not familiar with the patient’s lymphoma history and treatment
- A list of things to watch for, including signs of disease recurrence and late side effects from treatment
At the follow-up care appointments, patients should inform their doctor of:

- Any new symptoms
- Pain
- Physical problems that disrupt their daily life, such as fatigue, insomnia, sexual dysfunction, and weight gain or loss
- Any new health problems such as heart disease, diabetes, and high blood pressure
- Any new medications and vitamins they are taking, including over-the-counter medications
- Emotional problems, such as anxiety and depression
- Any other questions or concerns
Chapter 11: Preparing to Go to the Hospital

What Are Some Reasons That Patients May Be Admitted to the Hospital?
Hospital admission usually occurs either from the emergency room or through direct admission by the patient’s doctor. In the case of a direct admission, the doctor decides that the patient needs to be admitted and calls ahead to reserve a bed for the patient. If the patient is admitted by a doctor in the emergency room, the patient’s doctor is contacted and informed that the patient is in the hospital.

Most doctors make daily visitation rounds to check on their patients at about the same time each day. The nurse can tell patients when their doctor usually makes rounds. It is a good idea for family members to know when the doctor is likely to be coming so they can be there to ask questions.

Whether admitted through the emergency room or a direct admission, patients are usually first evaluated by a hospitalist or resident physician. Hospitalists are doctors employed by or consulting for the hospital. Their specialty is typically internal medicine or in some cases for pediatric patients, they are pediatricians. Patients are also assigned a case manager (usually a nurse) who works with the patient’s healthcare team.

What Should Patients Bring With Them to the Hospital?
When being admitted to the hospital, being prepared can ease the process of admission and positively impact patients’ care. The following page provides a brief list of items for patients to take with them.
If patients have access to an up-to-date and complete medical record through a patient portal, flash drive, or phone app, they should bring the security code and the name of the website, or the flash drive, phone app, or other device that contains the health information.

**What to Bring if You Are Being Admitted to the Hospital**

- Identification (driver’s license, student ID) and emergency contact information (relatives and friends’ names and phone numbers)
- List of all allergies and the reaction that occurs in response to exposure (especially important for latex and pharmaceutical allergies)
- List of all current prescription medications (name, dosage, and frequency) as well as other products taken such as over-the-counter medications and vitamins (instead of making a list, you can also place all medications in a bag and bring them with you)
- List of all medical conditions other than HL, such as hypertension, epilepsy, or active ulcer
- List of all surgeries (even elective plastic surgeries) regardless of how long ago they occurred
- List of all physicians currently treating you
- Copy of any completed advance directives (for more information see the following section describing advance healthcare directives)
- All insurance cards, a checkbook, a credit card, and a minimal amount of cash

**Do not bring valuables. Leave most money and jewelry at home.**
What Is the Purpose of an Advance Healthcare Directive and Appointing a Healthcare Proxy?

Creating an advance healthcare directive (a living will) and appointing a healthcare proxy is important for all adults to consider, not just people with cancer, because accidents and other unforeseen circumstances can happen at any time.

Writing down wishes for critical medical care in an advance healthcare directive is a way for individuals to communicate their preferences about what medical treatments they do or do not want if they become critically ill or injured and are unable to communicate their desires.

Besides stating medical care instructions, patients may also consider naming a healthcare proxy, or a decision maker, in an advance healthcare directive. This person should be someone who is willing to carry out the patient’s healthcare-related wishes, including any do-not-resuscitate (DNR) instructions. It is best to have both an advance healthcare directive and a healthcare proxy.

Before writing an advance healthcare directive, it is important to understand patients’ rights and laws regarding advance healthcare directives in each state. Consulting an attorney can provide legal information, but it is not necessary to hire an attorney to prepare an advance directive. An advance healthcare directive may include:

- Specific instructions on medical care, including the type of special treatment that is or is not desired, such as cardiopulmonary resuscitation (CPR), artificial respiration, drugs to make the heart function, kidney dialysis, artificial feeding, and certain surgical procedures
- A choice of a healthcare proxy

For more information about advance healthcare directive laws in each state, please visit the “Advance Care Planning” section of the National Hospice and Palliative Care Organization website at www.caringinfo.org.
What Are Patients’ Rights?

Patients’ rights are listed in the hospital’s Patient’s Bill of Rights. See the tips below for more information about these rights.

Your Rights As a Patient

- You must be given a medical screening examination and be evaluated for care whenever you are admitted to a hospital.
- You have the right to considerate and respectful care.
- You have the right to complete information regarding all aspects of your current condition.
- You have the right to know the names of all doctors and healthcare personnel providing your care.
- You have the right to sufficient information about the benefits and risks for all treatments or procedures to enable you to provide informed consent.
- You have the right to refuse any treatment.
- You have the right to privacy—no members of your healthcare team may talk about your condition or care to anyone outside of that team.
- If you must be transferred to another facility, information about why you require transfer must be provided, and the institution that you are being transferred to must have accepted responsibility for your care prior to transfer.
- You have the right to know whether the hospital has any relationship to other healthcare or educational institutions and if/how this relationship impacts your care.
- You have the right to be informed about your continuing healthcare requirements after you are discharged.
- You have the right to examine and receive an explanation of your bill.
- You have the right to know what hospital rules and regulations apply to your conduct.
- You have the right to have a translator present if English is not your first language.
What Do Patients Need to Know About Informed Consent Documents When in the Hospital?

Patients who are admitted to a teaching hospital may be asked to sign informed consent documents. These documents enable patients to make an educated decision about which treatments and procedures they are willing to receive. Patients should read the informed consent documents carefully and request an explanation of anything they do not completely understand. Signing these documents indicates that the patient understands and agrees to the risks and benefits of the treatments/procedures being performed. The tips below may help patients know what to look for in an informed consent document.

### What to Look For On the Hospital Informed Consent Document

- Indication of whether you are being enrolled in research
- Alternatives to the proposed treatment
- Names of the physician(s) performing your treatments/procedures
- Risks and benefits of the treatments/procedures you are agreeing to
- An explanation of what will be done with any tissue or fluid samples removed and any photos or videos taken
What Do Patients Need to Know at Discharge?
When the patient is ready to be discharged, make sure the case manager addresses the subjects identified in the following Patient Tip. Patients should receive a list of symptoms that will prompt them to contact their doctors if they develop.

Topics for the Case Manager to Address Before Discharge

- Are there any new limitations to what you can do at work or at home? If so, your doctor can provide a note for your employer if needed.
- Will you need physical therapy?
- If you need any new medical equipment, where can it be obtained? Who will order it? Obtain a phone number to ensure you can follow up if there are any problems with equipment delivery.
- Will you need home nursing care or other arrangements?
- What new medications will you need to take, and for how long?
- Does your insurance cover the new medication as an outpatient prescription? If not, or if you do not have insurance, what will the cost be?
- If you do not have insurance, does the hospital have a sliding-scale fee or charity care?
- Are there alternative medications if the cost is beyond your capacity to pay?
- What are the side effects of the new medications?
- Will they interact with any medications you are currently taking?
- Are there other instructions from your doctor or the hospital physician?
- With whom should you follow up and when?
- If you are to schedule your own follow-up, whom do you call?
Itemized hospital bills should be examined carefully to make sure no mistakes were made. If there are discrepancies between the bill and the care the patient received, they should be brought to the attention of both the hospital and the insurance company.

**Should Patients Provide Feedback on Their Stay?**

Hospitals may send patient satisfaction surveys to patients after discharge. This survey is an opportunity for patients to report problems they had with their care during their stay and/or to recognize staff members whose care and support were exceptional. Hospital administrators pay close attention to these survey responses, so it is worth the time to complete and return the survey so that problems can be addressed and staff members who provided excellent care can be acknowledged. If no survey is sent and patients want to report problems or satisfaction with their care, they can write a letter to the hospital administrator or the appropriate department director.
Chapter 12: Overview of Clinical Trials

There are numerous Hodgkin lymphoma (HL) clinical trials now underway in hospitals, cancer centers, and doctors’ offices around the country. The government, pharmaceutical and biotechnology companies, universities, and doctor groups often sponsor clinical trials.

What Is a Clinical Trial?

A clinical trial is a carefully designed research study that involves patients who volunteer to participate. The purpose of cancer clinical trials is to answer specific questions about new ways to prevent, diagnose, treat, or manage a disease or the side effects caused by a new or existing treatment. The investigators in clinical trials want to determine the safety and effectiveness of the treatment being investigated by making specific assessments before, during, and after the trial. Strict rules and oversight procedures make sure that clinical trials are designed and run in a way that protects the rights and safety of the people who volunteer to participate. It can sometimes take years for a clinical trial to be completed and for the results to be compiled and published.

In the United States, a new drug must pass through a strict approval process governed by the U.S. Food and Drug Administration (FDA) before it can become a standard therapy for use in humans. The FDA-regulated approval process for drugs includes preclinical studies (done in laboratories) and clinical trials (done in hospitals and clinics). In addition to the FDA, all trials must be approved by an institutional review board (IRB) consisting of experts and lay persons to ensure that the study is conducted in an appropriate and ethical manner that does not endanger patients in any way.

As shown in Table 12.1, there are four main types or phases of clinical trials. The first three (Phase I, Phase II, and Phase III) are usually required before a drug is considered for approval by the FDA. Phase IV
Clinical trials, sometimes called postmarketing studies, are conducted after a drug has received FDA approval. Each phase is designed to find out certain information, building upon the information learned from the previous phase. Patients may be eligible to participate in different types of clinical trials depending on their health status, type and stage of HL, and the types of treatments, if any, they have previously received.

**Table 12.1. The Four Main Phases of Clinical Trials**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Purpose</th>
<th>Typical Number of Volunteer Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>To identify a safe dose of a new drug or combination of drugs (which may or may not be approved)</td>
<td>6–30 patients with one or more different types of cancer</td>
</tr>
<tr>
<td></td>
<td>To decide on a dosing schedule for the drug</td>
<td></td>
</tr>
<tr>
<td></td>
<td>To see what side effects are related to the therapy</td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>To see if a new treatment is effective against a certain type of cancer at the dose determined in Phase I</td>
<td>Usually less than 100 patients with the same type of cancer</td>
</tr>
<tr>
<td></td>
<td>To confirm and learn more about the side effects identified in Phase I</td>
<td>More than 100 people in two study arms for randomized Phase II studies</td>
</tr>
<tr>
<td>Phase III</td>
<td>To compare the new treatment or new use of an existing treatment with the current standard treatments</td>
<td>Several hundred to several thousand patients with the same type of cancer</td>
</tr>
<tr>
<td></td>
<td>To obtain detailed information about how well the treatment works and the types and severity of side effects it causes</td>
<td>Patients are randomly assigned to a treatment group; one group receives the standard therapy, and the other group receives the experimental treatment</td>
</tr>
</tbody>
</table>
Table 12.1. The Four Main Phases of Clinical Trials (continued)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Purpose</th>
<th>Typical Number of Volunteer Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase IV</td>
<td>To find out more information about the long-term safety and efficacy of a new treatment after it has already been approved by the FDA and is being used by patients outside of a clinical trial</td>
<td>Several hundred to several thousand patients with the same type of cancer</td>
</tr>
</tbody>
</table>

Why Is a Placebo Sometimes Used in Phase III Trials?

A *placebo*, or sugar pill, is an inactive ingredient that is used as a comparator in some randomized clinical trials. We know from past studies that sometimes patients in a clinical trial treated with placebo experience benefits from participation. This may happen because patients enrolled in clinical trials have extra people involved in their care, may have more frequent visits, or other reasons. For these reasons and others, having a group who receives the placebo for comparison can help researchers to better understand the additional benefits of the new treatment being tested. The placebo is made to have the same appearance as the experimental pill, or to have the same appearance as the experimental intravenous agent, so that patients cannot tell whether they have been randomized to the control group receiving the placebo or the experimental group receiving the new treatment. In some trials known as double-blind studies, the doctors and nurses also do not know who is receiving which type of treatment.

In clinical trials for cancer therapies, patients are never given a placebo in place of an effective standard therapy. In Phase III cancer trials that use a placebo, the placebo is given in addition to, not instead of, the standard treatment regimen. Clinical trials are never conducted in a way that would deny patients an effective therapy.
Should a Patient Participate in a Clinical Trial?

Clinical trials are not a “last resort” for patients. Every drug available today had to be tested in clinical trials before it was approved for general use, and all new and emerging treatments for HL must be tested this way before patients can use them in the future. Participating in a clinical trial can help to improve the treatment options for HL patients for many years to come. Patients with all stages of HL can participate in clinical trials, whether at the time of initial diagnosis or at relapse (disease returns after treatment).

Clinical trials offer both benefits and risks. Patients in clinical trials who are randomized to the experimental group may be able to benefit from a new treatment that is not otherwise available to all patients. However, this new treatment may or may not be more effective than the standard therapy. At the very least, patients who are randomized to the control group receive the standard therapy that they would have received if they had not enrolled in the trial. Another advantage of clinical trials is that the health of enrolled patients is monitored very closely. The healthcare team studying the new treatment can explain all the possible benefits and risks of a specific clinical trial.

Every clinical trial is led by a principal investigator who is a medical doctor. Clinical trials also have a research team that may include doctors, nurses, physician assistants, social workers, and other healthcare professionals. Patients usually continue regular visits with their current healthcare provider, who may work with the research team to ensure that any investigational treatment does not interfere with their current medications or treatments. Clinical trials are carefully supervised by safety monitoring boards, monitoring processes, audits, and other activities to ensure ongoing safety assessments.
What Is Informed Consent in a Clinical Trial?

*Informed consent* is a process in which patients learn about the clinical trials they are interested in joining. During this process, members of the clinical trial research team explain:

- The purpose of the study
- The factors used to decide if a patient is allowed to participate in the study
- The tests, procedures, and visits participants are expected to undergo
- The type of treatments provided in the study
- The possible risks, benefits, and alternatives
- The rights of patients to decide whether or not to participate and to leave the study at any time

The research team answers questions and provides written information about the trial. After the team explains all of the details and the patient does not have any more questions, the patient is asked to read and sign an informed consent document before entering the study that details all the trial information discussed, describes how his or her records are kept private, and confirms that the patient was given information on the potential risks and benefits and the alternatives to enrolling in the trial.

It is important for patients to remember that even after signing the consent form, they can leave the study at any time. If a patient leaves the study or decides not to take part in the study, the doctor can discuss other treatment options available. A list of questions patients might ask their doctor about clinical trials is provided on the following page.
Questions to Ask About a Clinical Trial

- What is the purpose of this clinical trial?
- Why are you recommending this clinical trial for me?
- Who is sponsoring this trial (the National Cancer Institute [NCI], a cancer center, an international study group, other state or national study group, or a pharmaceutical/biotechnology company)?
- Who has reviewed and approved this clinical trial?
- Does this clinical trial include the additional use of a *placebo* (no active ingredient/no intervention)?
- How long will the study last? Where will it take place?
- What are the risks involved?
- What are the possible benefits? If I benefit from the intervention, will I be allowed to continue receiving it after the trial ends?
- What are my responsibilities during the clinical trial?
- What kinds of tests, procedures, or treatments will be performed? How many and how often?
- Will I be in any discomfort or pain?
- Will I be able to see my own doctor during the clinical trial?
- What type of long-term follow-up care is part of this trial?
- What costs will I be responsible for? Who will pay for my participation? Will I be reimbursed for other expenses?
- What happens if my health gets worse during the clinical trial?
What Is the Cost of Participating in a Clinical Trial?
Clinical trials are very expensive for the study sponsor. However, the cost to the patient varies depending on the trial, who is sponsoring the trial, what portion of the trial-related expenses the sponsor has agreed to cover, and the patient’s health insurance coverage. Patients should ask their doctor about the potential costs of participating in any clinical trial under consideration.

Patients should ask their doctor what clinical trials may be most appropriate for them. Here are some additional sources of clinical trial information:

- The Lymphoma Research Foundation’s Helpline at (800) 500-9976 or helpline@lymphoma.org
- The NCI’s Cancer Information Center at (800) 4-CANCER or the NCI’s Clinical Trials Referral Office at (888) NCI-1937
- Local cancer centers and institutions affiliated with universities
Chapter 13: Advances in Treatment of Patients With Hodgkin Lymphoma

Doctors and scientists around the world are working very hard to improve currently available treatment options and find better and safer drugs to treat patients with Hodgkin lymphoma (HL). Advances are being made in different areas including genetics, molecular biology, immunology, treatments, and supportive care. In particular, recent developments have provided a better understanding of the biology of the disease.

Drugs that are not yet approved for sale by the U.S. Food and Drug Administration (FDA) are said to be investigational. Some of these investigational drugs are being studied in laboratory experiments. This stage is often referred to as the preclinical phase. The drugs in more advanced stages of research are being studied in patients in clinical trials; these are referred to as being in the clinical phase of development.

The most common way for a patient to receive an investigational drug is through a clinical trial. To find out more about getting access to investigational drugs, visit the National Cancer Institute’s (NCI’s) website at www.cancer.gov and search for “access to investigational drugs.” Alternatively, visit www.clinicaltrials.gov to search for trials using a particular drug or to find clinical trials nearby.

Today’s science is moving quickly. Patients should check with their doctor or the Lymphoma Research Foundation (LRF) Helpline/“Clinical Trials Information Service” for additional information and recent updates.

For a detailed discussion of currently approved treatment options, please see Chapters 7 and 8 of this guide.
Chemotherapy
Researchers are trying to develop new chemotherapy drugs, improve existing drugs, and find better ways to combine different dosages and sequences of existing drugs. The goal is to develop treatment regimens that are better at killing HL cells while leaving healthy cells alone, decreasing the chance of side effects. Researchers are also investigating the best way to use imaging techniques to evaluate responses to therapy and to determine future doses.

Stem Cell Transplantation
Ongoing research in stem cell transplantation is focused on finding better ways to collect stem cells from the bone marrow or peripheral blood; reducing or eliminating graft-versus-host disease (GVHD) in allogeneic (donor) transplants; improving ways to remove all lymphoma cells from stem cell samples used for autologous (self) transplants; and developing more effective regimens for reduced-intensity stem cell transplantation.

Immunotherapy
Monoclonal Antibodies
Some types of monoclonal antibodies that are currently being investigated in clinical trials for HL are called bispecific antibodies. These are actually two different monoclonal antibodies attached to one another that can bind to two different antigens (targets) at once and bring together cells that harbor these two targets. For example, AFM13 is a bispecific antibody that binds to both natural killer (NK) cells (cells of the immune system) and HL cells that express CD30. It is in clinical trials for the treatment of patients with HL that is relapsed (disease returns after treatment) or refractory (disease does not respond to treatment).
**Antibody-Drug Conjugates**

ADCT-301 is an antibody-drug conjugate that is in development for the treatment of HL. The monoclonal antibody is directed against the CD25 receptor on the surface of HL cells, to which it delivers a toxic drug.

**Checkpoint Inhibitors**

Just like the HL therapies nivolumab (Opdivo) and pembrolizumab (Keytruda), two other checkpoint inhibitors that target the PD-1/PD-L1 pathway—avelumab (Bavencio) and PF-06801591—are currently being investigated for use in patients with HL. Another checkpoint inhibitor called ipilimumab (Yervoy) that targets the CTLA-4 checkpoint is also in clinical trials for the treatment of HL. Ipilimumab is currently approved by the FDA to treat melanoma (skin cancer), but it has also shown promise as an HL therapy.

**Radioimmunotherapy**

Radioimmunotherapy (RIT) consists of a source of radiation (a radioactive isotope) attached to a monoclonal antibody. The monoclonal antibody portion of the drug attaches to lymphoma cells, and then the radioactive particle delivers radiation right to the cell, triggering its destruction. An additional benefit of this approach is that the radiation destroys nearby cells in addition to those that have the antigen, giving RIT a “cross-fire” effect.

**Immunomodulatory drugs**

Immunomodulatory agents (IMiDs) interact with the immune system to encourage the destruction of cancer cells. The IMiD agent lenalidomide (Revlimid), which is already approved for the treatment of other blood cancers such as multiple myeloma and mantle cell lymphoma (MCL), is currently being evaluated for use in the treatment of patients with HL, both alone and in combination with other therapies such as checkpoint inhibitors.
**Targeted Therapies**

A better understanding of the biology and genetics of HL is helping researchers identify specific molecules in lymphoma cells that may be good targets for new drugs. These molecules usually have important roles in controlling the growth and survival of lymphoma cells. The drugs that target these molecules are called *targeted therapies*. Targeted therapies attack cancer cells in a more specific way than chemotherapy drugs and are less likely to kill or damage healthy cells, making it less likely for these agents to cause serious side effects.

Examples of targeted therapies, some of which have been FDA-approved for use in other types of lymphoma, leukemia, and solid cancers, that are being studied for HL in clinical trials include:

- **Histone deacetylase (HDAC) inhibitors** that interfere with the functioning of tumor DNA such as romidepsin (Istodax), mocetinostat (MGCD0103), and EDO-S101

- **Kinase inhibitors**, including:
  - Aurora A kinase inhibitors such as alisertib (MLN8237)
  - Bruton tyrosine kinase (BTK) inhibitors such as ibrutinib (Imbruvica)
  - Janus-associated kinase (JAK) inhibitors such as ruxolitinib (Jakafi)
  - Mammalian target of rapamycin (mTOR) inhibitors such as everolimus (Afinitor)
  - PI3K inhibitors such as TGR-1202
Proteasome Inhibitors

Carfilzomib (Kyprolis) and bortezomib (Velcade), two proteasome inhibitors that interfere with protein breakdown which are already approved for the treatment of patients with multiple myeloma, are being tested in clinical trials for the treatment of HL.

CAR T-Cell Therapy

Researchers have treated patients with HL using genetically engineered T cells in clinical trials. In this process, T cells are removed from a patient and genetically modified to produce special receptors on their surface called chimeric antigen receptors (CARs), which allow them to recognize and kill malignant cells. The genetically engineered CAR T cells are grown in the laboratory and then infused back into the patient. Once in the body, the genetically modified CAR T cells can grow to large numbers and amplify the antitumor response, persisting for long periods of time and providing ongoing tumor control and possible protection against recurrence.

Some patients have had very good responses to CAR T-cell therapy, with no malignant tumor cells detected after treatment. However, this therapy can sometimes result in serious side effects such as cytokine release syndrome, which is characterized by mild to moderate flu-like symptoms, reduced blood pressure, heart arrhythmias, and difficulty breathing, as well as neurologic toxicity. Medicines are now available to abrogate or alleviate many of these symptoms. Research is ongoing to improve this novel therapy.
Other Systemic Therapies
Ongoing investigation of many novel nonchemotherapeutic agents may lead to the development of HL treatments that may attack HL cells that are resistant to conventional chemotherapy and radiation therapy. These therapies are being tested for use in both newly diagnosed and relapsed/refractory HL. The research being conducted today is changing the entire landscape of lymphoma treatment now and in the future. The promise of this research is a compelling reason for patients with HL to consider participating in a clinical trial at any stage of treatment.

Radiation Therapy
Researchers are working to continue reducing the size of radiation therapy treatment fields and the dose of radiation delivered, with the goal of limiting radiation exposure to normal organs and tissues and hopefully reducing long-term risks of radiation therapy.
ABOUT THE LYMPHOMA RESEARCH FOUNDATION

The Lymphoma Research Foundation (LRF) is the largest lymphoma-specific non-profit organization in the United States; the Foundation’s mission is to eradicate lymphoma and serve those touched by this disease. Through a national education program, innovative research portfolio and numerous outreach and awareness opportunities, we remain dedicated to serving patients with lymphoma and to finding a cure.

Awareness and Outreach
LRF offers numerous advocacy, awareness, and fundraising programs—including the signature Lymphoma Walk program and Team LRF—which allow members of the lymphoma community to become involved with the organization and support the LRF mission. The LRF Advocacy Program provides volunteer advocates with the resources necessary to raise attention and support for those public policies most important to the lymphoma community. There are currently more than 5,000 LRF advocates in all 50 states and the District of Columbia.

Education Resources and Support Services
LRF provides a comprehensive series of expert programs and services for people with lymphoma and their caregivers, including: Clinical Trials Information Service; Publications focused on lymphoma subtypes and different treatment options; Financial Assistance Resources; In-Person Education Conferences; LRF Lymphoma Helpline; Lymphoma Support Network; Mobile App (www.FocusOnLymphoma.org); Teleconferences; and Videos, Webcasts and Podcasts. All programs and materials are offered free of charge. Learn more at www.lymphoma.org.
Professional Education
LRF is committed to educating healthcare professionals on the latest developments in lymphoma diagnosis and treatment. The Foundation offers a wide range of lymphoma-focused continuing education activities for nurses, physicians, and social workers, including workshops, conference symposia, and webcasts.

Research
LRF is focused on finding a cure for lymphoma through an aggressively-funded research program and by supporting the next generation of lymphoma investigators. LRF supports Clinical Investigator Career Development Awards, Lymphoma Fellowships, and several disease-specific research initiatives. These efforts are led by the Foundation’s Scientific Advisory Board (SAB), comprised of 45 world-renowned lymphoma experts. The Foundation has funded nearly $60 million in lymphoma-specific research.

Contact Information
Helpline: (800) 500-9976
Websites: www.lymphoma.org
            www.FocusOnHL.org
Email: LRF@lymphoma.org
The Lymphoma Research Foundation’s mobile app, *Focus on Lymphoma*, is a great tool and resource for lymphoma patients to manage their disease. *Focus on Lymphoma* is the first mobile app that provides patients and caregivers comprehensive content based on their lymphoma subtype and tools to help manage their diagnosis, including a medication manager, doctor sessions tool and side effects tracker.

The *Focus on Lymphoma* mobile app was recently named Best App by PR News and is available for free download for iOS and Android devices in the Apple App Store and Google Play.

For further information on LRF’s award winning mobile app or any of our programs and services, call the LRF Helpline toll free (800) 500-9976, email helpline@lymphoma.org or visit us at lymphoma.org.
Understanding Hodgkin Lymphoma

This patient guide is supported through unrestricted educational grants from:

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- Genentech
- Biogen
- Seattle Genetics

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