All About Non-Hodgkin Lymphoma

What is the lymph system, and what are lymph nodes?

The lymph system is essentially the "housekeeping system" of the body. It is a network of vessels (tubes), which connect the lymph nodes. These nodes can vary in size, but are normally up to about 2 centimeters in width. They contain cells that clear bacteria and other foreign debris from the body. Lymph is a watery liquid that flows between cells in the body, picking up foreign debris and taking it into the lymph node for filtering. From the lymph node, the debris may pass through several more nodes in the system before being dumped into the bloodstream to ultimately be cleared by the liver. The lymph system flows throughout the body, and also includes the spleen and thymus gland.

What is a lymphocyte?

Lymphocytes are a type of white blood cell. These cells (called B cells and T cells) are important in fighting infection and mount what is called the "immune response." B cells produce proteins called antibodies, which move through the bloodstream and attack a specific target as directed by the B cell. They start their lives in the bone marrow and then develop fully in the lymph nodes. T cells are developed in the thymus gland and directly attack the cells identified as foreign by the B cells. In addition, both of these cells are able to remember bacteria from previous infections, and thus respond quicker to future infections.

What are the Non-Hodgkin's lymphomas?

Non-Hodgkin lymphomas (NHL) are a group of cancers that affect the immune system; the very system that is supposed to protect our body against disease. NHLs begin in the lymph nodes and are made up of malignant (cancerous) lymphocytes (either B cells or T cells). In 2001, the World Health Organization developed a comprehensive classification system for the 30+ different types of NHLs, which are then further divided according to the cell type involved (either B cell or T cell). These 30+ types of NHLs are different in their growth rates and aggressiveness, and are often treated differently. The full, 2016 version of the WHO classification is located in the appendix.

Non-Hodgkin lymphoma makes up about 4.3% of the cancer diagnoses in the United States with about 72,240 people (both adults and children) diagnosed annually. About 95% of these cases are in adults, with the median age of diagnosis being 67. The disease is slightly more common in men than women. Rates are much higher among persons over the age of 65 (68 for every 100,000 people). NHL occurs more often in whites than in blacks.

Rates have been increasing 3-4% annually in the U.S. since the 1950's, but incidence varies widely throughout the world. For instance, in the United Kingdom, there are approximately 10 cases for every 100,000 people, whereas in Asia there are only 2 cases for every 100,000 people, compared to approximately 20 per 100,000 in the U.S.

Non-Hodgkin lymphomas should not be confused with Hodgkin's disease, as these are two distinct diseases. Although Hodgkin lymphoma also occurs in the lymph system, providers are able to differentiate between the two because of the presence of Reed-Sternberg cells in Hodgkin's tumors. (Read about Hodgkin lymphoma in adults or in children).

What causes NHL and am I at risk?

The actual cause of NHLs is still unknown in most cases, but there are some factors known to increase a person's risk. These factors are related to the immune system, and cause either a chronic decrease or chronic increase in immune response. Certain viruses and bacteria increase the risk of certain types of NHLs, possibly because they cause a long-term increase in immune response. For instance, MALT lymphoma is associated with Helicobacter pylori infection, the same bacteria that causes stomach ulcers. Epstein-Barr (EBV) virus is associated with 30% of Burkitt's lymphoma cases in the U.S., but 95% of Burkitt's
cases are in Africa, and nearly all of these cases are associated with EBV. This points to the fact that there are genetic differences in the types of Burkitt's (and probably all NHLs) found in different areas of the world. Other viruses thought to increase risk include: human T-cell leukemia/lymphoma virus 1 (HTLV-1), human herpes virus 8 (HHV-8), and hepatitis C virus.

Suppression of the immune system appears to cause increased risk of NHLs. This includes infection with the human immunodeficiency virus (HIV), organ or bone marrow transplant (requiring immune suppression medications), rheumatoid arthritis, and inherited immune deficiencies. The use of pesticides and herbicides was studied by the National Academy of Sciences (NAS) as a risk factor because agricultural workers had higher rates of NHLs. The NAS found a "positive association" between exposure to herbicides and NHL, meaning there is an increased risk with herbicide exposure. It is thought that the use of protective equipment (gloves, jumpsuits, and face protection) can decrease this risk.

**How can I prevent NHL?**

Because no one knows exactly what causes NHLs, there are no specific steps anyone can take to prevent it. The factors that increase risk are generally not things that can be avoided, making it difficult to decrease risk in people affected by these viruses, bacteria, and immune suppression.

**What screening tests are used for NHL?**

Unfortunately, there is no screening test available for NHLs. Because there are so many different types of NHLs, it would be difficult to develop a single effective test that could screen for all types.

**What are the signs of NHL?**

Oftentimes, the first sign of NHL is the swelling of lymph nodes, but this symptom is easily ignored because the enlargement in many cases is painless. Only about 20% of patients have systemic symptoms (symptoms throughout the body). When they do occur, symptoms include: persistent fever, drenching night sweats, or weight loss. These are sometimes referred to as "B symptoms". Other symptoms may include fatigue, itchy skin, and alcohol intolerance.

Because there are so many forms of NHL that can involve all different organs, signs and symptoms can vary depending on the areas of the body that are affected. For instance, MALT lymphoma affects the stomach lining and can cause nausea, vomiting, and abdominal pain. Cutaneous T-cell lymphoma affects the skin and can cause redness, itching, or raised patches on the skin.

**How is NHL diagnosed?**

When a patient presents with signs or symptoms of NHL, a healthcare provider will perform a complete medical health history and a physical exam. A biopsy of the enlarged lymph node is necessary to determine if lymphoma is present, and if so, what type. This can be done by inserting a needle into the affected lymph node to remove some tissue, but more often the entire node is removed for examination.

Once NHL is found, a series of other tests are done to determine if the lymphoma has spread, where it has spread to, and other prognostic information. These tests may include further blood tests (complete blood count, sedimentation rate, LDH, albumin and beta-2 microglobulin), chest x-ray, CT scan or MRI of the chest, abdomen and pelvis, PET scan, and bone marrow biopsy.

**How is NHL staged?**

After your full work-up is complete your care team will stage your cancer. Staging is important because it classifies your cancer by how much disease you have and if/where it has spread. Staging helps guide your treatment plan. The staging system used for NHL is the Costwolds Modification of Ann Arbor Staging System.

- Stage I indicates that the cancer is located in a single lymph node group.
- Stage II indicates that multiple lymph node groups are involved and that both areas are on the same side of the diaphragm (the muscle located at the bottom of the lungs) - that is, both are above the diaphragm or both are below the diaphragm.
- Stage III indicates that multiple lymph nodes on both sides of the diaphragm are involved.
- Stage IV Indicates involvement of lymph node regions on both sides of the diaphragm and involvement of the organs such as the bones, liver or lungs.

**These letters can be added to all stages: (ex: stage IIIB)**

- A: No symptoms
- B: Presence of "B symptoms" (fever, night sweats, weight loss > 10% of body weight)
- E: Used if the disease is "extranodal" meaning it has spread from lymph nodes to adjacent tissue/organs
- X: is used if the largest tumor is >10 cm large (also called "bulky disease")

(Note: Cutaneous T-cell Lymphoma, mycosis fungoides staged differently)

In addition to staging, the subtype of NHL must be taken into consideration. Some types are classified as aggressive because they grow more quickly and require immediate treatment. The good news is that chemotherapy works by attacking fast-growing cells, so aggressive lymphomas are more sensitive to treatment. Indolent lymphomas are those that are considered slow-growing. In some cases, indolent lymphomas may not be treated immediately but rather followed with a "watch and wait" methodology. These lymphomas may respond to treatment, but they often return, requiring more treatment.

**How is NHL treated?**

Chemotherapy is the most commonly used treatment. Other therapies include immunotherapy and radioimmunotherapy. Radiation therapy is only able to treat limited areas, and is typically used after chemotherapy, though certain early stage and low grade lymphomas can be treated with radiation alone. Surgery is generally only used to establish a diagnosis; an exception to this is testicular lymphoma, since most suspicious testicular masses require removal of the testicle.

**Chemotherapy**

Chemotherapy is a medication that targets quickly-growing and dividing cells, such as cancer cells. It may be taken in a pill form, given through an intravenous (IV) infusion and when necessary it can be given directly into your spinal fluid. Chemotherapy is considered a systemic therapy, meaning it travels throughout the body. This is in contrast to radiation therapy, which is a local treatment that targets a limited area. Chemotherapy medications can be used alone or in combination with other chemotherapies. This combination of different medications is called a "regimen". The regimen combines medications that work to kill cancer cells in different ways, thereby hopefully maximizing the number of cells killed. These regimens are given names based on the medications used. For instance, CHOP, a common regimen for NHL, is made up of **cytoxan**, **adriamycin (hydroxydoxorubicin)**, **vincristine**, and **prednisone**. This combination is given in "cycles" (blocks of time). A cycle may be 21 days, with cytoxan, adriamycin and oncovin being given on day 1, prednisone on days 1-5, followed by 16 days off, and then start over again with the next cycle.

Some other chemotherapies used in NHL therapy include: **chlorambucil, methotrexate, etoposide, cytarabine, fludarabine**, and **cladribine**.

If the lymphoma is affecting the tissues around your brain and spinal cord you may be treated with **intrathecal chemotherapy**. Intrathecal chemotherapy is chemotherapy that is given directly into the spinal fluid through a procedure called a lumbar puncture. The two chemotherapies commonly given intrathecally are methotrexate and cytarabine.

**Immunotherapy/Targeted Therapy**

Immunotherapy (sometimes called targeted therapy) is aimed at using the body's own immune system to attack the cancer cells and includes several different types of agents. **Interferon-alpha** is one type of immunotherapy that works by targeting certain receptors on the cancer cells, interfering with cell replication and causing the immune system to attack the cells. Interferon alpha is used in follicular and cutaneous T-cell lymphomas.

Monoclonal antibodies are man-made antibodies. They are designed to target a specific marker found on the tumor cell – this marker varies depending on the particular medication and the cancer it is treating. Once the medication is administered, the monoclonal antibody finds and attaches itself to the cancer cell, activating the body's immune system to attack it. This therapy is used alone or in combination with chemotherapy. **Rituxan** is the most commonly used monoclonal antibody for NHL and targets the CD20 antigen. This means the lymphoma must express the CD20 antigen for this therapy to work. Since monoclonal
antibodies target only specific cells, they may cause less toxicity to normal healthy cells than chemotherapy. Rituxan is frequently combined with CHOP chemotherapy, and in such cases, is known as "R-CHOP."

**Idelalisib** is a type of targeted therapy that works by targeting a protein called phosphoinositide 3-kinase (PI3K) delta, which is important in the activation and proliferation of B cells. PI3K is seen in higher than normal levels in many B-cell cancers. **Ibrutinib** is a type of targeted therapy that works by interfering with the function of Bruton's tyrosine kinase (BTK), which is found in excess on cancerous B cells. **Bortezomib** works by inhibiting the 26S proteasome, stopping cancer cells from growing and dividing and is used in the treatment of mantle cell lymphoma. Venetoclax (link) targets the BCL-2 inhibitor.

Many new targeted therapies have recently been approved for the treatment of various subtypes of NHL. These include, **obinutuzumab**, **brentuximab vedotin**, **acalabrutinib**, **copanlisib**, and **rituximab + hyaluronidase human**. Your healthcare provider will determine the most appropriate therapies for you given your stage and subtype of NHL.

Recently, a new type of immunotherapy, called adoptive cell transfer (ACT) approved. In this treatment, the patient’s own immune cells are used to treat their cancer. Axicabtagene ciloleucel is a type of ACT therapy called CAR-T cell therapy. It is CD19- directed and can be used in the treatment of relapsed or refractory large B cell lymphomas.

**Radioimmunotherapy** combines the technology of monoclonal antibodies and radiation. Man-made antibodies with a form of radiation (called a radioisotope) attached to them are designed to target the CD20 antigen. The antibody seeks out the tumor cells (by finding the antigen), attaches to them, exposes these cells to the radiation, and thus kills them along with any nearby cancer cells. Again, since these agents target specific cells, side effects may be less than those typically seen with chemotherapy. Currently, the only available radioimmunotherapy agent is Zevalin.

**Radiation**

Radiation therapy uses high-energy rays (similar to x-rays), delivered from an external source, to kill cancer cells. Unlike chemotherapy, which goes everywhere in the body, radiation therapy is a local treatment. It is targeted only to small areas. There are two main types of radiation used to treat non-Hodgkin lymphoma: photon (traditional radiation) and proton therapy. **Proton therapy** is only available at a certain centers. You should discuss with your provider which type of radiation therapy is right for you.

Radiation therapy has evolved in the last few decades, as concern has grown over the long-term affects of having radiation that involves important organs, like the heart and lungs. In patients who need radiation, there is considerable effort to make sure the surrounding healthy tissues receive the least amount of radiation exposure as possible. Advanced radiation techniques and methods, such as IMRT (can link), respiratory gating, breath holding and advanced simulation techniques (4D imaging), allow for highly conforming doses. This means the radiation beams are shaped tightly around the tumor and spare surrounding tissue as much as possible. In addition, the area treated has evolved over time. Many radiation oncologists now choose to treat just the lymph nodes that were involved and the surrounding areas where tumor had spread (called involved site radiation therapy, ISRT). This has largely replaced treating an entire field surrounding the involved lymph nodes (involved field radiation therapy). In the past, even larger fields were treated, including large areas of healthy tissue (called extended field radiation therapy). As you can see, the field of radiation has evolved as it has learned the dangers of exposing healthy tissue to radiation.

Radiation therapy typically requires patients to come to a radiation therapy treatment center 5 days a week, for several weeks. The radiation team will take scans and measurements to determine the number of doses needed and exactly where the radiation beams should be aimed. The treatment takes just a few minutes, and it is painless. You shouldn’t feel anything, though you may see some lights on the machines and hear them as they move around. Most radiation providers see patients weekly while they are receiving treatment to monitor for side effects and answer questions.

**Bone Marrow and Stem Cell Transplants**

Transplants can be done using a donor's bone marrow or stem cells (**allogeneic**) or a patient's own bone marrow or stem cells (**autologous**). Autologous transplants are used to maximize the amount of chemotherapy that a patient can safely receive. The problem with giving large doses of chemotherapy is that this can kill the patient's bone marrow, which would lead to death. However, a patient can tolerate this high dose of chemotherapy if the bone marrow (or stem cells) is replaced soon after the chemotherapy, using cells that have been stored ahead of time. In an allogeneic transplant this is also true, but in NHL the role...
of graft-versus-lymphoma effect is the key to its efficacy. This is the ability of the donor's cells and immune system to attack any remaining cancer cells in the recipient.

Clinical Trials

Clinical trials are extremely important in furthering our knowledge of this disease. It is through clinical trials that we know what we do today, and many exciting new therapies are currently being tested. Talk to your healthcare provider about participating in clinical trials in your area. You can also explore currently open clinical trials using the OncoLink Clinical Trials Matching Service.

Follow-up care and Survivorship

Once a patient has been treated for NHL, they need to be closely followed for a recurrence. At first, follow-up visits will be fairly frequent, usually every couple of months. The longer a patient is free of disease, the less often the checkups are needed. The oncologist will tell you when he or she wants to perform follow-up blood tests, CT scans or PET scans. Follow-up schedules and the tests ordered will vary depending on the type of NHL. It is very important to attend all of your follow-up appointments and to discuss any new symptoms or side effects you are experiencing with your provider.

Fear of recurrence, the financial impact of cancer treatment, employment issues, and coping strategies are common emotional and practical issues experienced by Hodgkin lymphoma survivors. Your healthcare team can identify resources for support and management of these challenges faced during and after cancer.

Cancer survivorship is a relatively new focus of oncology care. With some 15 million cancer survivors in the US alone, there is a need to help patients transition from active treatment to survivorship. What happens next, how do you get back to normal, what should you know and do to live healthy going forward? A survivorship care plan can be a first step in educating yourself about navigating life after cancer and helping you communicate knowledgeably with your healthcare providers. Create a survivorship care plan today on OncoLink.

Resources for More Information

Leukemia and Lymphoma Society

Provides disease information and support resources.

http://www.lls.org/

Lymphoma Research Foundation

Offers education and patient services, information on research and stories of hope.

http://www.lymphoma.org/

American Society of Hematology

The official website of providers who treat blood disorders such as lymphoma.

http://www.hematology.org/Patients/Cancers/Lymphoma.aspx

LymphomaInfo.net

Aim to bring people together around lymphoma-related issues by providing concise, up-to-date information and a meeting place for lymphoma patients and those who care about them.

http://www.lymphomainfo.net/

Cutaneous Lymphoma Foundation

An independent, non-profit patient advocacy organization dedicated to supporting every person with cutaneous lymphoma by
promoting awareness and education, advancing patient care, and facilitating research.

http://www.clfoundation.org

Appendix: The 2016 revision of the World Health Organization classification of lymphoid neoplasms

NHL subtypes

Mature B cell type

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- Splenic marginal zone lymphoma
- Splenic B-cell lymphoma/leukemia, unclassifiable
  - Splenic diffuse red pulp small B-cell lymphoma
- Lymphoplasmacytic lymphoma
- Waldenstrom macroglobulinemia
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
  - Pediatric nodal marginal zone lymphoma
- Follicular lymphoma
  - In situ follicular neoplasia
  - Duodenal type follicular lymphoma
- Large B cell lymphoma with IRF4 rearrangement
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
  - In situ mantle cell neoplasm
- Diffuse large B-cell lymphoma (DLBCL), NOS
  - Germinal center B-cell type
  - Activated B-cell type
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system (CNS)
- Primary cutaneous DLBCL, leg type
- EBV+ DLBCL, NOS
- DLBCL associated with chronic inflammation
- Intravascular large B-cell lymphoma
- ALK+ large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- HHV8+ DLBCL, NOS
- Burkitt lymphoma
- Burkitt-like lymphoma with 11a aberration
- High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements
- High grade B-cell lymphoma, NOS
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Mature T and NK Neoplasms

- Systemic EBV+ T cell lymphoma of childhood
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-Cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Indolent T-cell lymphoproliferative disorder of the GI tract
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis like T-cell lymphoma
- Cutaneous T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30+ T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous γδ T-cell lymphoma
- Primary cutaneous CD8+ aggressive eipdermotropic cytotoxic T-cell lymphoma
- Primary cutaneous acral CD8+ T-cell lymphoma
- Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma
- Nodal peripheral T-cell lymphoma with TFH phenotype
- Anaplastic large-cell lymphoma, ALK+
- Anaplastic large-cell lymphoma, ALK-
- Breast implant associated anaplastic large cell lymphoma

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