## Lymphoma

### Non-Hodgkin’s Lymphoma

**Introduction**

*Non-Hodgkin’s lymphoma* is a type of cancer that originates in the lymphatic system. It is estimated to be the sixth most common cancer in the United States.

<table>
<thead>
<tr>
<th>Lymphatic system component</th>
<th>Lymph vessels</th>
<th>Lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
<td>These vessels branch out throughout the body similar to blood vessels</td>
<td>The lymph vessels are interconnected to small masses of lymph tissue called lymph nodes. Lymph nodes are found throughout the body. Collections of lymph nodes are found in the neck, underarms (axillae), chest, abdomen, and groin. Lymph nodes store white blood cells. When you are ill and the lymph nodes are active, they will swell and be easily palpable</td>
</tr>
</tbody>
</table>

| **Lymph** | The lymph vessels carry a clear fluid called lymph. Lymph contains white blood cells, especially lymphocytes such as B cells and T cells |

| **Additional parts of the lymphatic system** | The tonsils, thymus, and spleen are additional components of the lymphatic system. Lymphatic tissue is also found in other parts of the body, including the stomach, skin, and small intestine. Because lymphatic tissue is found in many parts of the body, non-Hodgkin's lymphoma can start almost anywhere |

| **nb** | The lymphatic system is part of the body’s immune system and helps fight infections and other diseases. In addition, the lymphatic system filters out bacteria, viruses, and other unwanted substances. |

| **Statistics** | 6th most common cause of cancer death in United States. Increasing in incidence and mortality. Since 1970, the incidence of lymphoma has almost doubled. **Estimated new cases and deaths** from non-Hodgkin lymphoma in the United States in 2014: New cases: 70,800, Deaths: 18,990 |

| **Overview** | The types of non-Hodgkin’s lymphoma reflect the developmental stages of lymphocytes. Each type of lymphoma can be viewed as a lymphocyte arrested at a certain stage of development and transformed into a malignant cell. 85% B cell origin, the rest T or null cell |

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### B Cell Differentiation

**Cell Surface Markers**

- CD20
- CALLA (CD10)
- CD22
- CD38

**Precursors**

- Precursor B Cell
- Leukemias
- CLL, B Cell Lymphomas
- Waldenström’s, Myeloma

**Maturation in Lymphoid Follicle**

- B lymphocyte
- T lymphocyte
- Immunoblast

- Small cleaved
- Large cleaved
- Small non-cleaved
- Large non-cleaved

- Follicular lymphoma
- Burkitt’s lymphoma
- Chronic lymphocytic leukemia
- Sézary syndrome
- Mycosis fungoides
- Peripheral T cell lymphoma
- Waldenström’s macroglobulinemia

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How is NHL staging determined?

1. Bone marrow biopsy
2. CT scan
3. MRI
4. Ultrasound
5. PET scan: Radioactive material is injected, and a CT scan is performed to determine the metabolism of this material. Lymphoma cells show faster metabolism than normal cells, and areas with lymphoma look brighter on the pictures.

Pathophysiology

- Non-Hodgkin’s lymphoma (NHL). NHL occurs when your body produces too many abnormal lymphocytes.
- In the normal life cycle of lymphocytes, old lymphocytes die and your body creates new ones to replenish the supply.
- In NHL, lymphocytes grow indefinitely, so the number of circulating lymphocytes increases, filling up the lymph nodes and causing them to swell.

Cells involved

- In NHL, either B cells or T cells are involved in this process. These are the two subtypes of lymphocytes.
- B cells produce antibodies that fight infections. This is the most common type of cell involved in NHL.
- T cells kill the foreign substances directly. NHL less frequently originates from T cells.

Risk factors

1. Medications that suppress your immune system: Using immunosuppressive agents (such as after an organ transplant) is a risk factor as it reduces your body ability to fight infection.
2. Weakened immune system: The risk of developing lymphoma may be increased by having a weakened immune system.
3. Certain infections: Certain viral and bacterial infections increase the risk of NHL. Examples are HIV, hepatitis C virus, and Epstein-Barr virus. A type of bacteria sometimes linked to NHL is the ulcer-causing H. pylori.

Note: Lymphoma is not contagious. You cannot catch lymphoma from another person.
### Etiology

| Immune suppression                          | 1. Congenital (Wiskott-Aldrich)  
2. Organ transplant (cyclosporine)  
3. AIDS  
4. Increasing age |
|--------------------------------------------|---------------------------------------------------------------------|
| DNA repair defects                         | 1. Ataxia telangiectasia  
2. Xeroderma pigmentosum |
| Chronic inflammation and antigenic stimulation | 1. Helicobacter pylori inflammation, stomach  
2. Chlamydia psittaci inflammation, ocular adnexal tissues  
3. Sjögren's syndrome |
| Viral causes                      | 1. EBV and Burkitt's lymphoma  
2. HTLV-I and T cell leukemia-lymphoma  
3. HTLV-V and cutaneous T cell lymphoma  
4. Hepatitis C |
| Age                                      | Although non-Hodgkin's lymphoma can occur in young people, the chance of developing this disease increases with age. Most people with non-Hodgkin's lymphoma are older than 60 years of age. |
| Other possible links                    | • People who work with herbicides or certain other chemicals may be at increased risk of this disease.  
• Researchers are also looking at a possible link between using hair dyes before 1980 and non-Hodgkin's lymphoma. None of these possible links have definitely been proven. |

**Note:** Having one or more risk factors does not mean that a person will develop non-Hodgkin's lymphoma.

### Epidemiology

- Can occur at any age
- Overall incidence, and incidence of subtypes, varies with location:
  - Burkitt’s in tropical Africa
  - Adult T cell leukemia-lymphoma in Japan and Caribbean
- Indolent lymphomas are rare in young people and increase in incidence with age.
- Large cell lymphoma (DHL) is less age related, and is among most common cancers affecting the young.
- Burkitt’s and lymphoblastic lymphoma are common in adolescents.
- AIDS patients develop aggressive, high grade lymphomas.

### Clinical feature

| Signs and symptoms | 1. Swollen, painless lymph nodes in the neck, armpits, or groin  
2. Unexplained weight loss  
3. Fever  
4. Night sweats  
5. Coughing, trouble breathing, or chest pain  
6. Weakness and tiredness that don’t go away (fatigue)  
7. Abdominal pain or swelling, or a feeling of fullness in the abdomen  
8. Itching of the skin |
|-------------------|---------------------------------------------------------------------|
| Diagnosis of NHL  | • Excisional biopsy is preferred to show nodal architecture (follicular vs diffuse).  
• Immunohistochemistry to confirm cells are lymphoid  
  ➢ LCA (leukocyte common antigen)  
  ➢ Monoclonal staining with Igk or Ig|  
• Flow cytometry:  
  ➢ CD 19, CD20 for B cell lymphomas  
  ➢ CD 3, CD 4, CD8 for T cell lymphomas  
• Chromosome changes  
  ➢ t(8;14), t(2;8), t(8;22) in Burkitt’s lymphoma  
  ➢ bcl-2 oncogene  
  ➢ c-myc oncogene  
  ➢ t(11;14) in mantle cell lymphoma  
  ➢ cyclin D1 gene |
How is NHL diagnosed?

<table>
<thead>
<tr>
<th>Physical exam</th>
<th>• Your doctor will complete a physical examination with a special emphasis on palpating your lymph nodes in your neck, underarms, and groin and establishing if they are swollen. He will also try to find out if your spleen or liver are swollen. In most cases, swollen lymph nodes are signs of infection (rather than lymphoma), and your doctor will try to establish if you have any other signs of infection and what the source of the infection could be.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history</td>
<td>• You will be asked questions in regards to your past medical history and about risk factors for NHL.</td>
</tr>
<tr>
<td>Blood tests</td>
<td>• A complete blood count (CBC) will usually be performed to check the number of white blood cells. Additional tests might include a lactate dehydrogenase level (can be elevated in lymphoma). Additional tests might be performed to rule out an infection causing the swollen lymph nodes.</td>
</tr>
<tr>
<td>Imaging procedures</td>
<td>• A chest X-ray or CT scan of the chest or neck might help detect the presence of tumors or more enlarged lymph nodes. Positron emission tomography (PET) scanning is a newer modality to help detect NHL.</td>
</tr>
</tbody>
</table>

Biopsy

| Stage I | The cells are found in only one lymph node area (such as in the neck or axilla). Or, if the abnormal cells are not in the lymph nodes, they are in only one part of a tissue or organ (such as the lung, but not the liver or bone marrow). |
| Stage II | The lymphoma cells are found in at least two lymph node areas on the same side of the body or only above or below the diaphragm. Or the cells are in one organ and the lymph nodes affected are near that organ. |
| Stage III | The lymphoma is in lymph nodes above and below the diaphragm. There might be spread into an organ near this lymph node group. |
| Stage IV | In addition to lymph cell spread, lymphoma cells are found in several parts of one or more organs or tissues. |

A | No symptoms (You have not had weight loss, fever or night sweats) |
| B | Presence of any of the following symptoms: weight loss (10% or more in the last six months), fever (greater than 101.5°F) night sweats, or severe itching |

Bone marrow biopsy

<table>
<thead>
<tr>
<th>Staging workup</th>
<th>A bone marrow biopsy can establish the spread of the disease. This involves the insertion of a needle into bone to obtain bone marrow. In adults, the most common site for this biopsy is the pelvic bone</th>
</tr>
</thead>
</table>
| Staging: Ann Arbor | • CBC, chemistries, urinalysis  
• CT scans of chest, abdomen and pelvis  
• Bone marrow biopsy and aspirate  
  (Lumbar puncture)  
  – AIDS lymphoma  
  – T cell lymphoblastic lymphoma  
  – High grade lymphoma with positive marrow |

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1 lymph node region or structure</td>
</tr>
<tr>
<td>II</td>
<td>&gt;1 lymph node region or structure, same side of diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Both sides of diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Extranodal sites beyond “E” designation</td>
</tr>
</tbody>
</table>

subscripts: A, B, E, S
### Classification of Non-Hodgkin Lymphoma

**Indolent (low grade)**
1. Life expectancy in years, untreated
2. 85-90% present in Stage III or IV
3. Incurable

**Intermediate**

<table>
<thead>
<tr>
<th>Working formulae</th>
<th>Rappport</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Grade</td>
<td>Small lymphocytic</td>
</tr>
<tr>
<td>Intermediate Grade</td>
<td>Diffuse well-differentiated lymphocytic (DWDL or WDLL)</td>
</tr>
<tr>
<td>High Grade</td>
<td>Follicular small cleaved</td>
</tr>
<tr>
<td></td>
<td>Nodular poorly differentiated lymphocytic (NPDL)</td>
</tr>
<tr>
<td></td>
<td>Follicular mixed</td>
</tr>
<tr>
<td></td>
<td>Nodular mixed lymphocytic-histiocytic (NM)</td>
</tr>
<tr>
<td></td>
<td>Follicular large cell</td>
</tr>
<tr>
<td></td>
<td>Nodular histiocytic (NH)</td>
</tr>
<tr>
<td></td>
<td>Diffuse small cleaved cell</td>
</tr>
<tr>
<td></td>
<td>Diffuse poorly differentiated lymphocytic (DPDL)</td>
</tr>
<tr>
<td></td>
<td>Diffuse mixed</td>
</tr>
<tr>
<td></td>
<td>Diffuse mixed lymphocytic-histiocytic (DM)</td>
</tr>
<tr>
<td></td>
<td>Diffuse large cell</td>
</tr>
<tr>
<td></td>
<td>Diffuse histiocytic (DHL)</td>
</tr>
</tbody>
</table>

**Commonly used classification**

Not included in these classification:
- Mycosis fungoides
- Marginal zone B cell lymphoma → MALT lymphoma
- Mantle cell lymphoma
- Peripheral T cell lymphoma
- Angioimmunoblastic lymphoma

**The REAL Classification (Revised European-American Lymphoma Classification)**

1. Precursor B-lymphoblastic lymphoma/leukemia
2. B cell CLL/prolymphocytic leukemia/small lymphocytic leukemia
3. Lymphoplasmacytoid lymphoma
4. Mantle cell lymphoma
5. Follicular center lymphoma, follicular
6. Follicular center lymphoma, diffuse
7. Extranodal marginal zone B cell lymphoma (MALT type)
8. Nodal marginal zone B cell lymphoma
9. Splenic marginal zone B-cell lymphoma
10. Hairy cell leukemia
11. Plasmacytoma/myeloma
12. Diffuse large B cell lymphoma
13. Primary mediastinal large B cell lymphoma
14. Burkitt’s lymphoma
15. High grade B cell lymphoma, Burkitt-like
16. Precursor T lymphoblastic lymphoma/leukemia
17. T cell CLL/prolymphocytic leukemia
18. Large cell granular lymphocytic leukemia: T cell type, NK cell type
19. Mycosis fungoides/ Sézary syndrome
20. Peripheral T cell lymphomas, unspecified
21. Hepatosplenic T cell lymphoma
22. Angioimmunoblastic T cell lymphoma

**Burkitt lymphoma**
- This lymphoma has two major subtypes, an African type closely associated with an infection with the Epstein-Barr virus and the non-African, or sporadic, form that is not linked to the virus.

**Diffuse large cell lymphoma**
- This represents the most common lymphoma (approximately 30% of NHL) and can be rapidly fatal if not treated.

**Follicular lymphoma**
- These lymphomas exhibit a specific growth pattern when viewed under the microscope (follicular or nodular pattern); they are usually advanced at the time of diagnosis.

**MALT lymphoma**
- This is a B cell lymphoma that usually affects individuals in their 60s.
- The most common area for this lymphoma to develop is the stomach.

**Mantle cell lymphoma**
- One of the rarest of the NHL, mantle cell lymphoma accounts for about 6% of cases.
- This NHL is difficult to treat and is a subtype of B cell lymphoma.

**nb**

The guidelines also say that a GP should investigate and possibly refer anyone with combinations of the following symptoms:
- Tiredness (fatigue)
- Weight loss
- High temperature (fever)
- Night sweats
- Itching
- Being short of breath
- Bruising easily or bleeding
- Having infections that keep coming back
- Bone pain or nerve pain
- Abdominal pain
- An enlarged spleen or lymph nodes