Non-Hodgkin's Lymphoma

Chapter 113 | Part 4: Oncology and Hematology

KEY CLINICAL POINTS

1. NHL incidence has nearly doubled over the past 20–40 years and continues to rise by 1.5–2% each year.
2. Approximately 90% of all lymphomas are of B-cell origin; ~80–85% of HL patients are cured, whereas NHL prognosis is more variable.
3. The International Prognostic Index (IPI) uses 5 risk factors: Age ≥60, elevated LDH, Performance status ≥2 (ECOG) or ≤70 (Karnofsky), Stage III/IV, and >1 extranodal site.
4. Burkitt's lymphoma has a doubling time of <24 hours and requires immediate intensive chemotherapy with CNS prophylaxis.
5. DLBCL is the most common NHL subtype (30% of cases), with median age at diagnosis of 64.
6. Gene expression profiling identifies GCB and ABC subtypes of DLBCL, with GCB-like having a better prognosis.
7. Infectious agents like EBV, HTLV-1, HIV, HCV, and H. pylori are associated with specific NHL subtypes.
8. FDG-PET is useful for aggressive lymphomas (DLBCL, BL) but PET during therapy is recommended only as part of clinical trials.
9. Relapsed DLBCL may be treated with CD79b ADC polatuzumab, tafasitamab, loncastuximab, or bispecific antibodies.
10. Approximately 30% of NHLs in immunosuppressed patients arise as polyclonal B-cell proliferation evolving into clonal malignancy.

1. DEFINITION & OVERVIEW

- **Definition:** Non-Hodgkin's lymphomas (NHLs) are cancers of mature B, T, and natural killer (NK) cells.
- **Distinction from HL:** Characterized by the absence of Reed-Sternberg cells and distinct biological features.
- **Classification Basis:** Classification depends on cell lineage: B-cell or T/NK-cell origin.
- **Clinical Behavior:** Aggressive subtypes grow rapidly, while indolent subtypes progress slowly.
- **Prognosis:** Prognosis is more variable in NHL than in Hodgkin's lymphoma (HL), which has an ~80–85% cure rate.

1.1 WHO Classification

The WHO-HAEM5 classification categorizes lymphoid neoplasms into B-cell and T-cell mature (peripheral) neoplasms.

2. EPIDEMIOLOGY

- **Incidence:** In 2023, ~80,550 new NHL cases in the US (~4% of all cancers).
- **Comparison:** Incidence is 10x higher than HL, plasma cell disorders, or lymphoid leukemias.
- **Trends:** Rising by 1.5–2%/year since the 1980s.
- **Demographics:** Slight male predominance; higher incidence in Caucasians. Age-related: peaks after 40 but also common in adolescents.
- **Risk Factors (Immunodeficiency):** Immunodeficiency states (HIV, post-transplant) increase risk.

2.1 Risk Factors

- **Environmental:** Agricultural chemicals, prior HL treatment (radiation), immunosuppression (organ transplant, HIV).
- **Genetic/Inherited:** Inherited immunodeficiencies (XLP, Wiskott-Aldrich); ~9% of lymphoma patients have a first-degree relative with NHL/HL/CLL.
- **Autoimmune Association:** Autoimmune diseases (Sjögren's, celiac) associate with MALT lymphoma.

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3. ETIOLOGY & PATHOPHYSIOLOGY

- **Developmental Origin:** Lymphoid cells derive from hematopoietic progenitors.
- **B-cell Path:** Commitment occurs via PAX5 expression and immunoglobulin gene rearrangement. Errors in somatic hypermutation and class switching contribute to oncogenesis.
- **T-cell Path:** Development involves NOTCH-1 and TCR gene rearrangement.
- **Genetics of DLBCL:** Gene expression profiling identifies GCB (better prognosis) vs ABC (worse prognosis).
- **High-Risk Features:** Double-hit lymphoma (MYC+BCL2 rearrangements) has poor outcomes.

3.1 B-cell Differentiation Pathway

- **Mantle zone B cells:** HLA-DR+, CD19+, CD10+/- , CD20+, CD22+, CD21+, CD5+ → correlates with Mantle zone lymphoma.
- **Intermediate transition (IgM+):** Indicates progression toward marginal zone.
- **Secretory B cells:** CD19+, CD20+, CD38+, PCA-1+, IgM+ or IgM+/IgD+ → correlates with SL and LL.
- **Developmental Progression:** Mantle zone B cells → [Transition via IgM expression] → Secretory B cells.

3.2 T-cell Differentiation Pathway

- **Stage I Prothymocyte:** CD: 2, 7, 38, 71.
- **Stage II Thymocyte:** CD: 1, 2, 4, 7, 8, 38.
- **Stage III Thymocyte:** CD: 2, 3, 4/8, 5, 6, 7; TCR (T-cell receptor) → marks transition to mature-capable cell.
- **Mature T Helper Cell:** CD: 2, 3, 4, 5, 6, 7; TCR.
- **Mature T Cytotoxic/Suppressor Cell:** CD: 2, 3, 5, 6, 7, 8; TCR.

- **Developmental Progression:** Prothymocyte → Stage II Thymocyte → Stage III Thymocyte → Mature T cells (Helper or Cytotoxic).

3.3 Genetic Features

- **B-cell Translocations:**

→ t(8;14) (MYC/IgH) → Burkitt's lymphoma

→ t(14;18) (BCL2/IgH) → Follicular lymphoma, DLBCL

→ t(11;14) (CCND1/IgH) → Mantle cell lymphoma, multiple myeloma

→ t(11;18) (API2/MALT1) → MALT lymphoma

→ t(9;14) (PAX5/IgH) → Lymphoplasmacytic lymphoma

- **T-cell Translocations:**

→ inv(14), t(14;14) (TCRα/TCL1) → Peripheral T-cell lymphoma, T-PLL

→ t(2;5), t(1;2), t(2;3), t(2;17), inv(2) → Various ALK-related lymphomas (e.g., ALCL).

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4. CLINICAL FEATURES

- **General Presentation:** Symptoms vary by progression rate (aggressive vs. indolent).
- **B symptoms:** Fever, night sweats, weight loss.
- **Localizing symptoms:** Chest, abdomen, CNS involvement.
- **Physical Exam:** Lymphadenopathy, hepatosplenomegaly, Waldeyer's ring, effusions, masses, cutaneous lesions.
- **Laboratory Workup:** CBC, chemistries, LDH, β-microglobulin, serum protein electrophoresis.

4.1 Specific Subtypes

- **Burkitt's lymphoma:**

→ Rapid doubling time (<24h)

→ Requires immediate CNS prophylaxis

→ 80–90% cure rate with intensive chemotherapy (Magrath, EPOCH-R).

- **DLBCL:**

→ Most common NHL (~30% of cases)

→ Median age at diagnosis: 64

→ Advanced stage in 60–70% of patients

→ Prognostic factors: IPI score, LDH, extranodal sites.

→ Subtypes: GCB (better prognosis) vs ABC (worse prognosis).

→ Double-hit lymphoma (MYC+BCL2): Poor outcomes.

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5. DIFFERENTIAL DIAGNOSIS

- **Primary Differentials:** Hodgkin's lymphoma, reactive lymphadenopathy, infectious mononucleosis, autoimmune disorders (Sjögren's, lupus), other hematologic malignancies (CLL, myeloma).

- **Distinguishing Features:** Absence of Reed-Sternberg cells in NHL, immunophenotype, genetic abnormalities, and PET/CT findings.

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6. INVESTIGATIONS & DIAGNOSIS

1. **Initial Laboratory Evaluation:**

→ CBC, chemistries, LDH, β-microglobulin, serum protein electrophoresis.

2. **Imaging Studies:**

→ CT scan (standard for all)

→ FDG-PET/CT (preferred for aggressive NHL like DLBCL and Burkitt's).

3. **Tissue Diagnosis:**

→ Biopsy with immunohistochemistry (CD19, CD20, CD79a for B-cell; TCR expression for T-cell).

4. **Staging & Site Assessment:**

→ Bone marrow biopsy (standard staging).

→ Lumbar puncture (required for high-risk cases: Burkitt's, DLBCL with positive marrow, or involvement of testes, breast, paranasal sinuses).

5. **Ann Arbor Staging (Table 113-6):**

→ Stage I: Single lymph node region or single extranodal site.

→ Stage III: Involvement of lymph node regions on both sides of the diaphragm (may include spleen, or limited, contiguous, extralymphatic organ/tissue, or both).

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7. MANAGEMENT & TREATMENT

1. **General Strategy:** Treatment depends on subtype and stage.
2. **Aggressive NHL (e.g., DLBCL):**

→ First-line: R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for 6 cycles.

→ High-risk/Double-hit: More aggressive approaches required.

3. **Burkitt's Lymphoma:**

→ Immediate intensive chemotherapy (Magrath, EPOCH-R).

→ Mandatory CNS prophylaxis.

4. **Relapsed/Refractory DLBCL:**

→ CD79b ADC (polatuzumab)

→ Tafasitamab

→ Loncastuximab

→ Bispecific antibodies (epcoritamab).

5. **Indolent NHL:**

→ Early-stage: Watchful waiting.

→ Advanced disease: Rituximab-based chemotherapy.

7.1 Treatment of DLBCL

- **Standard First-line:** R-CHOP (6 cycles).
- **Risk Stratification:** Based on IPI score, LDH, and extranodal sites.
- **Relapsed/Refractory Options:** CD79b ADC (polatuzumab), bispecific antibodies (epcoritamab), CAR-T therapy.

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8. PROGNOSIS & COMPLICATIONS

- **Prognosis by Subtype:**

→ DLBCL: 5-year survival ~60–70%.

→ Burkitt's lymphoma: 80–90% cure rate with timely treatment.

- **Complications:** Infection (immunodeficiency), tumor lysis syndrome, CNS relapse (especially in BL or testicular NHL), and secondary malignancies.

International Prognostic Index (IPI)

- **Risk Factors:** Age ≥60; LDH elevated; Performance status ≥2 (ECOG) or ≤70 (Karnofsky); Ann Arbor stage III/IV; >1 extranodal site.
- **DLBCL Outcomes (Standard):**

→ 0-1 factor: Low risk (35% of cases; 5-year survival 73%).

→ 2 factors: Low-intermediate risk (27% of cases; 5-year survival 51%).

→ 3 factors: High-intermediate risk (22% of cases; 5-year survival 43%).

→ 4-5 factors: High risk (16% of cases; 5-year survival 26%).

- **DLBCL Outcomes (R-CHOP):**

→ 0 factor: Good (10% of cases; 4-year survival 94%).

→ 1-2 factors: Intermediate (45% of cases; 4-year survival 80%).

→ 3-5 factors: Poor (45% of cases; 4-year survival 53%).

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9. SPECIAL CONSIDERATIONS

- **Immunocompromised Patients:**

→ 30% of NHLs arise from polyclonal B-cell proliferation evolving into clonal malignancy.

→ EBV association is common in these patients.

- **HIV-related NHL:** More aggressive, higher LDH, poorer prognosis.
- **Post-transplant Lymphoma:** High risk for CNS involvement.

9.1 Immunodeficiency

- **Risk Factors:** HIV, post-transplant, genetic disorders (XLP, Wiskott-Aldrich).
- **Associations:** MALT lymphoma in autoimmune diseases (Sjögren's, Hashimoto's).

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10. KEY PEARLS & CLINICAL TRAPS

- **IPI Score:** Critical for determining prognosis and treatment intensity in DLBCL.
- **Imaging Choice:** FDG-PET is standard for aggressive NHL (DLBCL, BL); CT is used for indolent types.
- **DLBCL Subtypes:** GCB-like has a better prognosis than ABC-like.
- **Burkitt's Alert:** Requires immediate CNS prophylaxis and intensive chemotherapy due to <24h doubling time.
- **Clinical Trap:** Avoid over-treatment of indolent NHL; recognize 'double-hit' (MYC+BCL2) as high-risk.

REFERENCE TABLES

TABLE 113-1

WHO-HAEM5 Classification of Lymphoid Malignancies B CELL Mature (peripheral) B-cell neoplasms

B CELL	T CELL
Mature (peripheral) B-cell neoplasms	Mature (peripheral) T-cell neoplasms
L ymphoplasmacytic lymphoma (Waldenström's macroglobulinemia) **Hairy cell leukemia** **S plenic marginal zone B-cell lymphoma** **E xtranodal marginal zone B-cell lymphoma of MALT type** **N odal marginal zone B-cell lymphoma** **Follicular lymphoma** **Mantle cell lymphoma** **D iffuse large B-cell lymphoma (including subtypes)** **H igh-grade B-cell lymphoma with MYC and BCL2 rearrangements** **High-grade B-cell lymphoma NOS** **H igh-grade B-cell lymphoma with 11q aberrations** **B urkitt's lymphoma/Burkitt's cell leukemia** **P rimary mediastinal large B-cell lymphoma** **Mediastinal grey zone lymphoma** **P rimary large B-cell lymphoma of immune-privileged sites**	T-cell granular lymphocytic leukemia
	Adult T-cell leukemia/lymphoma (HTLV-1+)
	Extranodal NK/T-cell lymphoma, nasal type
	Enteropathy-associated T-cell lymphoma
	Hepatosplenic T-cell lymphoma
	Subcutaneous panniculitis-like T-cell lymphoma

B CELL	T CELL
	Mycosis fungoides
	Sezary syndrome
	Peripheral T-cell lymphoma NOS
	Angioimmunoblastic T-cell lymphoma
	Anaplastic large-cell lymphoma, ALK+
	Anaplastic large-cell lymphoma, ALK–
Plasmablastic lymphoma	
Primary effusion lymphoma	
HHV8+ DLBCL NOS	
Intravascular large B-cell lymphoma	
ALK+ large B-cell lymphoma	

TABLE 113-2

Infectious Agents Associated with the Development of Lymphoid Malignancies

INFECTIOUS AGENT	LYMPHOID MALIGNANCY
Epstein-Barr virus	Burkitt's lymphoma
	Post–organ transplant lymphoma
	Primary CNS diffuse large B-cell lymphoma
	Hodgkin's lymphoma
	Extranodal NK/T-cell lymphoma, nasal type

TABLE 113-3

Diseases or Exposures Associated with Increased Risk of Development of Malignant Lymphoma
Inherited immunodeficiency...

Inherited immunodeficiency disease **Klinefelter's syndrome** **Chédiak-Higashi syndrome** **Ataxia-telangiectasia syndrome** **Wiskott-Aldrich syndrome** **Common variable immunodeficiency disease** **Acquired immunodeficiency diseases** **Iatrogenic immunosuppression** **HIV-1 infection** **Acquired hypogammaglobulinemia**	**Autoimmune disease** **Sjögren's syndrome** **Celiac sprue** **Rheumatoid arthritis and systemic lupus erythematosus** **Chemical or drug exposures** **Phenytoin** **Dioxin, phenoxy herbicides** **Radiation** **Prior chemotherapy and radiation therapy** **Anti-TNF drugs**
HIV	Diffuse large B-cell lymphoma
	Burkitt's lymphoma
Helicobacter pylori	Gastric MALT lymphoma

TABLE 113-4

Genetic Features of B- and T-Cell Lymphomas

GENETIC FEATURE	GENES	LYMPHOMA
t(8;14) **t(2;8)** **t(8;22)**	MYC/IgH MYC/Igκ MYC/Ig λ	Burkitt's lymphoma
	BCL1 (CCND1)/IgH	
t(14;18) **t(3;14)**	BCL2/IgH BCL6/IgH	Follicular lymphoma, diffuse large B-cell lymphoma (DLBCL)
	API2/MALT1 BCL10/IgH MALT1/IgH FOXP1/IgH	
Trisomy 3 **7q21 deletion**	Unknown CDK6	Splenic marginal zone lymphoma
	PAX5/IgH Unknown	
inv(14) **t(14;14)**	TCRα/TCL1	Peripheral T-cell lymphoma, NOS; T-PLL
	NPM1/ALK TPM3/ALK TFG/ALK CTLC/ALK ATIC/ALK	
Trisomy 3 **Trisomy 5**	Unknown Unknown	Angioimmunoblastic T-cell lymphoma
	Unknown	
THYMUS		

GENETIC FEATURE	GENES	LYMPHOMA
CD: 2, 7, 38, 71		
CD: 1, 2, 4, 7, 8, 38		
CD: 2, 3, 4/8, 5, 6, 7; TCR		
CD: 2, 7, 38,		
CD: 1,		
4, 7, 8, 38		
RAL BLOOD		
2, 3, 4, 5, 6,		

TABLE 113-6

Ann Arbor Staging for Lymphoma a STAGE I II

STAGE	DESCRIPTION
I	Involvement of a single lymph node region (I) or single extranodal site (IE)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS), or limited, contiguous, extralymphatic organ or tissue (IIIE), or both (IIIES)

TABLE 113-7

International Prognostic Index for NHL Five Clinical Risk Factors Age ≥60 years Serum lactate dehydrogenase levels...

Five Clinical Risk Factors	
Age ≥60 years	
Serum lactate dehydrogenase levels elevated	
Performance status ≥2 (ECOG) or ≤70 (Karnofsky)	
Ann Arbor stage III or IV	
>1 site of extranodal involvement	
For Diffuse Large B-Cell Lymphoma	
0, 1 factor = low risk	35% of cases; 5-year survival, 73%
2 factors = low-intermediate risk	27% of cases; 5-year survival, 51%
3 factors = high-intermediate risk	22% of cases; 5-year survival, 43%
4, 5 factors = high risk	16% of cases; 5-year survival, 26%
For Diffuse Large B-Cell Lymphoma Treated With R-CHOP	

0 factor = good	10% of cases; 4-year survival, 94%
1, 2 factors = intermediate	45% of cases; 4-year survival, 80%
3, 4, 5 factors = poor	45% of cases; 4-year survival, 53%

TABLE 113-5

Staging Evaluation for Non-Hodgkin's Lymphoma Physical examination Documentation of B symptoms Laboratory evaluation

- Physical examination
- Documentation of B symptoms
- Laboratory evaluation
- Complete blood counts
- Liver function tests
- Uric acid
- Calcium
- Serum protein electrophoresis
- Serum β-microglobulin 2
- Chest radiograph
- CT scan of abdomen, pelvis, and usually chest
- Bone marrow biopsy
- Lumbar puncture in lymphoblastic, Burkitt's, and diffuse large B-cell lymphoma with positive marrow biopsy
- Gallium scan (SPECT) or PET scan in large-cell lymphoma