

Hodgkin lymphoma: tests, treatment by setting, regimens and problems during treatment

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A. Diagnosis and staging tests and what they change

Reading the immunostains: classic HL, NLPHL and the lymphomas that imitate them

	Classic HL (HRS cells)	NLPHL (LP or "popcorn" cells)
CD30	+ (virtually all)	- (rarely +)
CD15	+ in 75-85%	-
CD45	-	+
CD20 and B-cell program	absent or weak in a subset	+ (strong)
PAX5	weak +	+
BOB1, OCT2	reduced or lost	+
EBV (EBER)	variable; most cases in India	rare
Background	mixed inflammatory cells, fibrosis	small B cells, CD57+ T-cell rosettes

ALCL

- CD30 strong, CD15 -, PAX5 -
- T-cell antigens +, ALK ±, cytotoxic +

PMBL

- Pan-B +, CD30 weak, CD15 rare
- Primary mediastinal B-cell lymphoma

THRLBCL

- B-cell +; CD15, CD30, EBV -
- T-cell/histiocyte-rich LBCL

Grey-zone lymphoma

- CD15 + strong CD30 + B markers
- Worse outlook than cHL, PMBL

Immunostains. A diagnosis rests on morphology plus phenotype in an excised node; ask for an expert haematopathologist when the pattern is unusual. Marker patterns from the UpToDate cHL and NLPHL diagnosis reviews.

Table A. Diagnosis and staging tests and what they change

Test	When	What it changes	Pitfalls
Excision (or incision) node biopsy; multiple cores if not feasible	Every suspected case	Diagnosis and subtype; separates cHL from NLPHL, ALCL, PMBL, grey zone and THRLBCL	FNAC is not enough; inguinal nodes are often reactive; CT-guided or endobronchial mediastinal needles crush the tissue
Immunohistochemistry (CD30, CD15, CD45, CD20, PAX5, BOB1/OCT2, CD3) and EBER	Every biopsy	HRS phenotype CD30+, CD15+ (75–85%), CD45–, CD3–; LP cells CD20+, CD30–, CD15–	CD15–negative cHL exists; absence of both CD15 and CD30 points elsewhere
PET-CT, skull base to mid-thigh	Staging; after 2 cycles (PET2); end of treatment	Lugano stage, bulk, marrow and extranodal disease; response–adapted decisions (Deauville)	Inflammation, infection and thymic rebound take up FDG; too early after treatment reads falsely positive
CBC, ESR, albumin, LFT, renal function, LDH	Baseline	ESR defines early–stage risk group; albumin, Hb, WBC, lymphocytes feed the IPS	Microcytic anaemia from cytokines is not iron deficiency
HBsAg, anti–HBc, HCV, HIV	Before any treatment	Antiviral prophylaxis; HIV changes management and is common in EBV–positive cases	Anti–HBc alone still needs a plan when rituximab is used (NLPHL)
Echocardiogram (LVEF)	Before anthracycline	LVEF ≥50% generally needed for doxorubicin; baseline for survivorship	Statins may slow EF decline (STOP–CA); no proven fall in heart failure
Pulmonary function with DLCO	Before bleomycin	DLCO ≥60% generally needed; repeat before extra ABVD cycles	Older age, smoking and kidney impairment raise bleomycin toxicity
Bone marrow biopsy	Only for unexplained cytopenias with a marrow–negative PET	Stage IV if involved	Homogeneous marrow uptake on PET is usually reactive
Pregnancy test; fertility counselling; sperm banking	Before treatment	Choice of regimen and timing; oocyte or tissue preservation where escalated therapy is likely	ABVD rarely causes infertility; BEACOPP–type regimens and transplant do

B. Treatment by setting

From stage to treatment group

Early favourable

- Stage I–II with none of the risk factors of the chosen group
- GHSG favourable (strictest): ≤2 regions, no E, ESR <50 (or <30 with B), mediastinum <1/3
- Only GHSG-favourable patients qualify for the shortest course (2 ABVD + 20 Gy)

Early unfavourable

- EORTC: age >50, mediastinum >1/3, high ESR*, ≥4 sites
- GHSG: mediastinum >1/3, high ESR*, ≥3 sites, extranodal disease
- NCCN adds any mass >10 cm
- *ESR ≥50, or ≥30 with B symptoms

Advanced

- Stage III–IV (some trials include IIB with bulk or E)
- International Prognostic Score, 1 point each: albumin <4 g/dL, Hb <10.5 g/dL, male, age >45, stage IV, WBC ≥15,000, lymphocytes <600 or <8%
- A-HIPI calculator also available

IPS and 5-year freedom from progression with ABVD: 0 factors 88% · 1: 84% · 2: 80% · 3: 74% · 4: 67% · 5 or more: 62% (Moccia 2012).

Treatment groups. Use the prognostic system of the trial whose regimen you follow; the three systems label about 55% of early-stage patients as unfavourable (UpToDate staging review).

Table B. Treatment by setting (adults)

Setting	Usual plan	Alternatives and notes
Early favourable, PET2 Deauville 1–3, all GHSG favourable criteria	ABVD × 2 then 20 Gy involved-site RT (HD16)	Not tested with other groups' criteria; if RT unsuitable, chemotherapy only as below
Early favourable, PET2 1–3, other criteria	Chemotherapy only: ABVD × 2 more (≤60, healthy lungs) or AVD × 2 (>60 or lung disease), up to 4 more for Deauville 3 or bulk	Or CMT: ABVD × 1 more + 30 Gy (H10 : fewer relapses, same survival)
Early unfavourable, PET2 1–3	CMT: ABVD × 2 more + 30 Gy ISRT, or chemotherapy only: AVD × 4 (RATHL)	Bulky mediastinum: ABVD × 6 without RT worked in CALGB 50801 ; alternatives N-AVD, BV-AVD, BrECADD
Early stage, PET2 Deauville 4–5	ABVD × 2 or BrECADD × 2, then PET4: 1–4 → 30 Gy; 5 → biopsy	Persistent cHL on biopsy = primary refractory
Early stage, no PET available	ABVD × 3 + 30 Gy ISRT (GHSG favourable: ABVD × 2 + 20 Gy)	CMT preferred over chemotherapy only when response cannot be measured
Advanced (III–IV)	N-AVD × 6 (S1826)	BrECADD for fit ≤60 with adverse features (HD21); BV-AVD if nivolumab contraindicated; RATHL when neither is possible
Advanced, over 60	N-AVD; or sequential BV → AVD → BV	No bleomycin; geriatric assessment; dexrazoxane if cardiac risk; frail: BV-dacarbazine, BV-nivolumab, PD-1 alone, palliative RT

Setting	Usual plan	Alternatives and notes
Bulky advanced disease in complete response	No consolidation RT (HD0607)	RT for a single PET-positive residual site, or biopsy it first
First relapse or refractory, transplant-eligible	Biopsy → checkpoint-based salvage → PET complete response → autologous transplant (BEAM)	BV maintenance if BV-naïve and high risk (AETHERA); RT to bulky unirradiated sites
Relapse, not transplant-eligible	BV-nivolumab; PD-1 inhibitor ± gemcitabine	Bendamustine, gemcitabine, vinblastine, lenalidomide, everolimus; RT for symptoms
Relapse after autologous transplant	Checkpoint inhibitor (if not already failing one); BV if not given	Allogeneic transplant (reduced intensity) for fit patients with less than CR to a checkpoint inhibitor
NLPHL stage IA or contiguous IIA	Involved-site RT 30–36 Gy (adults)	Watch after complete excision; rituximab alone relapses more; children: watch or R-CVbP
NLPHL symptomatic or higher-risk advanced	R-CHOP, R-CVbP or R-B (about 6 cycles)	Asymptomatic low-risk: watch or rituximab; biopsy every relapse (transformation)

C. Regimens: evidence and best fit

First-line choices for advanced classic HL (no doses: follow your protocol)

N-AVD (preferred)

- 6 cycles, about 6 months
- S1826: 2-yr PFS 92% vs 83% over BV-AVD
- Neutropenia; thyroid and other immune effects
- Not if autoimmune disease needs immunosuppression
- Suits all ages from 12, including over 60

BrECADD

- 4 or 6 three-week cycles (12 weeks if PET2-negative)
- HD21: better PFS than escBEACOPP; 4-yr OS 98.6%
- Febrile neutropenia 28%; transfusions common
- Fit adults ≤60 with adverse features

BV-AVD

- 6 cycles with G-CSF
- ECHELON-1: 6-yr OS 93.9% vs 89.4% over ABVD
- Neuropathy in two-thirds (mostly reversible)
- When nivolumab is contraindicated; usually ≤60

RATHL (ABVD → AVD)

- 2 ABVD, PET2; if negative, 4 AVD
- 7-yr PFS about 80%, OS 93%
- Drops bleomycin early: less lung toxicity
- When nivolumab and BV are unsuitable or unaffordable

Over 60: N-AVD, or sequential BV → AVD → BV; avoid bleomycin (ABVD in E2496: 9% treatment deaths, lung toxicity in 43%).

Four evidence-based starts. No trial has compared N-AVD with BrECADD; inclusion criteria and endpoints differ (S1826, HD21, ECHELON-1, RATHL; UpToDate advanced-stage review).

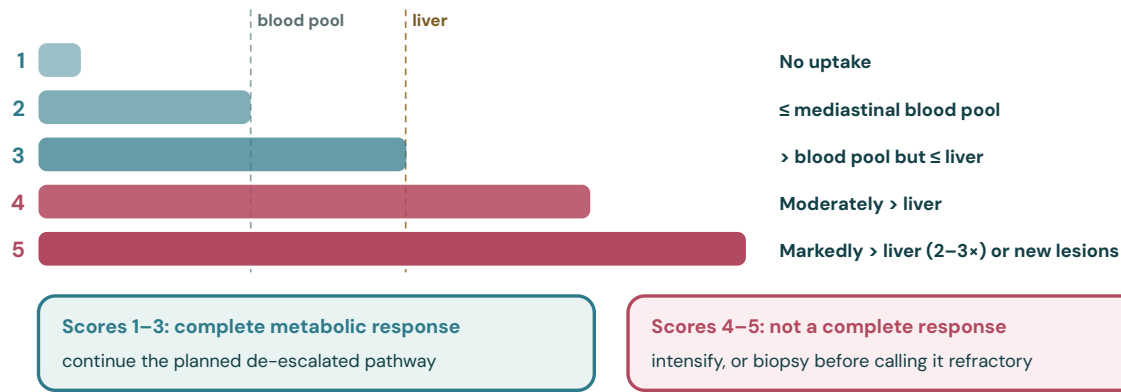
Table C. Regimens: evidence and best fit (no doses)

Regimen	Key evidence	Best fit	Watch for
ABVD (PET-adapted)	H10, HD16, RATHL, RAPID	Early-stage backbone; advanced when newer drugs are unavailable (drop bleomycin after PET2-negative)	Bleomycin lung injury, neuropathy, high emetic risk (dacarbazine), vesicants (doxorubicin, vinblastine); no G-CSF or dose delays for neutropenia alone
N-AVD (nivolumab + AVD)	S1826: 2-yr PFS 92% vs 83% over BV-AVD; older patients 89% vs 64%	Advanced stage, age 12 and above, including over 60	Neutropenia (G-CSF optional), thyroid dysfunction, rare severe immune effects; contraindicated with active autoimmune disease on immunosuppression
BV-AVD	ECHELON-1: 6-yr OS 93.9% vs 89.4% over ABVD	Advanced stage when nivolumab is contraindicated; usually ≤60	Peripheral neuropathy (two-thirds), febrile neutropenia: G-CSF is mandatory
BrECADD	HD21: better PFS than escBEACOPP, 4-yr OS 98.6%, fewer severe AEs (42% vs 59%)	Fit adults ≤60 with advanced or high-risk stage II disease; shortest course (12 weeks if PET2-negative)	Febrile neutropenia 28%, transfusions; G-CSF every cycle

Regimen	Key evidence	Best fit	Watch for
Sequential BV-AVD-BV	Evens 2018: 2-yr PFS 84% in patients ≥60	Older adults who cannot have N-AVD	Neutropenia, infection, neuropathy
Checkpoint-based salvage (pembrolizumab-GVD, pembrolizumab- or nivolumab-ICE)	CR 87–95%, 2-yr PFS 88–100% after transplant (phase 2)	First relapse before autologous transplant	Immune effects; pseudoprogression or sarcoid-like reactions: biopsy before calling failure; GVHD risk if allogeneic transplant follows
BV-nivolumab	Advani 2021: CR 67%; 3-yr PFS 91% in transplanted patients	Outpatient salvage; transplant-ineligible patients	Neuropathy (continue nivolumab alone if it limits), infusion reactions
BV maintenance after autologous transplant	AETHERA: 5-yr PFS 59% vs 41%	BV-naïve patients with a high-risk feature	Neuropathy in over half, mostly reversible; neutropenia
Rituximab-based (NLPHL)	R-CHOP , R-B, R-CVbP series	Symptomatic or higher-risk NLPHL	HBV reactivation (screen first), infusion reactions

D. Managing problems during treatment

Reading interim and end-of-treatment PET: the five-point (Deauville) scale



X = new uptake unlikely to be lymphoma (infection, inflammation, thymic rebound, sarcoid-like reaction to immunotherapy).
Time the end-of-treatment PET 6–8 weeks after chemotherapy or 3 months after radiotherapy, once inflammation has settled.

Deauville scale. It compares the hottest residual site with the patient's own blood pool and liver, so scans from different machines can be read the same way (Lugano 2014).

Table D. Managing common problems during treatment

Problem	Likely cause	First steps	When to act fast
New cough, breathlessness, falling DLCO on ABVD	Bleomycin lung injury (worse with age, smoking, kidney impairment)	Stop bleomycin for good; imaging; steroids per pulmonology	Hypoxia: admit
Fever while neutropenic	Infection (more after 60, BrECADD, BV-AVD)	Febrile neutropenia protocol; G-CSF for later cycles where indicated	Hypotension, rigors: emergency
Tingling, numbness, constipation	Vinblastine or brentuximab neuropathy	Grade it each visit; dose change by protocol; laxatives	Weakness or adynamic ileus: stop the drug
Tiredness, weight change, palpitations on nivolumab	Thyroiditis (immune effect)	TSH and free T4; replace or treat	Severe diarrhoea, breathlessness, jaundice: suspect colitis, pneumonitis, hepatitis
Nodes enlarge or PET lights up early on immunotherapy	Pseudoprogression (flare) or sarcoid-like reaction	Do not stop at once; repeat imaging; biopsy if in doubt	Organ compression
Pain or swelling at the drip site	Extravasation (doxorubicin, vinblastine are vesicants)	Stop infusion; local protocol; central line for long courses	Blistering or necrosis

Problem	Likely cause	First steps	When to act fast
Severe nausea	Dacarbazine-containing regimens are highly emetogenic	Guideline antiemetics before each dose	Dehydration, kidney injury
Breathlessness or swelling years after treatment	Late cardiac effect (anthracycline, mediastinal RT)	Echo, ECG; cardiology	Chest pain, syncope
Swelling of face and arms, stridor at diagnosis	Large mediastinal mass (SVC or airway compression)	Urgent biopsy plan with anaesthetist; steroids may hamper diagnosis	Airway compromise: emergency