

Aggressive B-cell lymphomas: tests, treatment by setting, regimens and problems during treatment

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A. Diagnosis and staging tests and what they change

From the biopsy to a complete diagnosis

Cell of origin: Hans algorithm (positive = ≥30% of cells)

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graph LR; CD10 -- "+" --> GCB1[GCB]; CD10 -- "-" --> BCL6; BCL6 -- "+" --> MUM1; BCL6 -- "-" --> nonGCB1[non-GCB]; MUM1 -- "+" --> nonGCB2[non-GCB]; MUM1 -- "-" --> GCB2[GCB];
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Order on every case

- CD20, CD19, CD79a, CD10, BCL6, MUM1, Ki-67
- MYC and BCL2 IHC; CD5, CD30
- FISH: MYC, then BCL2 and BCL6 if MYC is rearranged
- EBER (EBV); HHV-8 if an effusion

Tissue: excision or incision biopsy preferred; several cores if not possible. FNA can neither diagnose nor exclude lymphoma.
Biopsy before steroids. MYC FISH even when MYC staining is low: some mutations hide the epitope. Some centres reserve FISH for MYC IHC above 40%.
IHC agrees with gene-expression profiling in about 80%; cell of origin is prognostic and helps choose Pola-R-CHP, but is not essential to start.

Pathology work-up (Hans 2004; UpToDate DLBCL diagnosis and prognosis reviews). Review by an expert haematopathologist improves diagnostic accuracy.

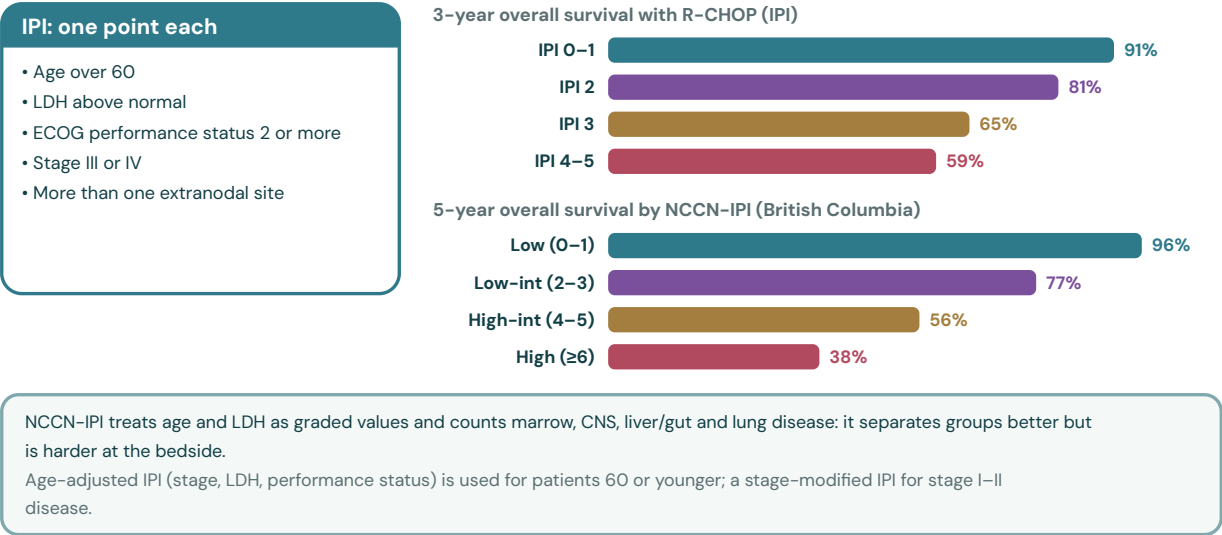
Table A. Diagnosis and staging tests and what they change

Test	When	What it changes	Pitfalls
Excision or incision biopsy (several cores if not feasible)	Every suspected case, urgently, before steroids	Diagnosis and entity	FNA cannot diagnose or exclude lymphoma; avoid inguinal nodes; steroids blur the picture
IHC: CD20, CD10, BCL6, MUM1, Ki-67, MYC, BCL2, CD5, CD30; EBER	Every biopsy	Cell of origin (Hans); double-expressor; EBV-positive DLBCL; mimics	IHC agrees with gene-expression profiling in about 80%
FISH for MYC (then BCL2, BCL6)	All large B-cell lymphomas, at least when MYC protein is high	High-grade B-cell lymphoma with MYC and BCL2 rearrangements; Burkitt	MYC IHC can be falsely low; MYC partner gene matters

Test	When	What it changes	Pitfalls
PET-CT	Staging and end of treatment (4–8 weeks after chemotherapy)	Lugano stage, marrow and extranodal disease; complete metabolic response	Interim PET does not guide escalation; inflammation and infection take up FDG
CBC, chemistry, uric acid, LDH, calcium	Baseline and before cycle 1	IPI; tumour lysis risk	High LDH or uric acid: start lysis prophylaxis before treatment
HBsAg, anti-HBc (HBV DNA if either positive), HCV, HIV	Before rituximab	Antiviral prophylaxis; HIV changes regimen choice and supportive care	Anti-HBc alone still carries reactivation risk with rituximab
Echocardiogram or MUGA	Before anthracycline	LVEF below 40%: replace doxorubicin	Baseline for survivorship
CNS-IPI; MRI and lumbar puncture with flow cytometry if risk or symptoms	Baseline	CNS-directed therapy; Burkitt and HIV-Burkitt always have an LP	Cytology misses cases that flow cytometry finds
Bone marrow biopsy	Optional if PET shows marrow disease; consider for cytopenias	Stage; discordant small-cell involvement	PET may miss diffuse low-volume marrow disease
Pregnancy test; fertility counselling; sperm banking	Before treatment	Timing and options	Fertility is usually preserved after R-CHOP; transplant and repeated lines lower it

B. Treatment by setting and entity

Prognosis at diagnosis: the IPI still works in the rituximab era



Prognostic indices. Survival from Ziepert 2010 (1063 patients, R-CHOP or CHOP-like) and Zhou 2014 (NCCN-IPI validation cohort), as quoted in the UpToDate prognosis review.

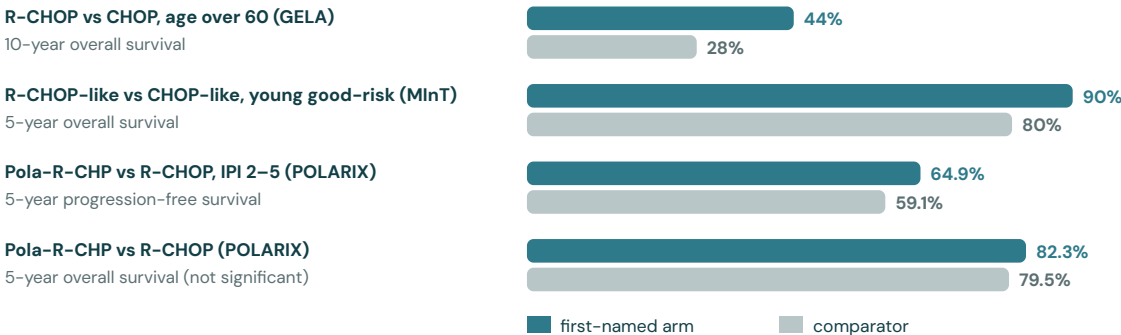
Table B. Treatment by setting and entity

Setting	Standard choice	Key evidence	Notes
DLBCL stage I-II, no bulk (under 10 cm)	R-CHOP × 3 → PET3: Deauville 1-3 → one more cycle (4 in total)	S1001, FLYER	Deauville 4 → 3 more cycles or ISRT; 5 → biopsy. Alternatives: R-CHOP × 6, or × 3 + ISRT
DLBCL stage I-II, bulky (10 cm or more)	R-CHOP × 6 → PET6: Deauville 4 → ISRT 30 Gy	UNFOLDER, RICOVER-noRTH (no routine RT)	Some use Pola-R-CHP for IPI ≥2
Primary testicular DLBCL	Orchiectomy + R-CHOP × 6 + CNS prophylaxis + scrotal RT	IELSG-10	Orchiectomy alone is never enough
DLBCL stage III-IV	R-CHOP × 6 or Pola-R-CHP × 6	POLARIX, RICOVER-60, MinT	Pola-R-CHP favoured for non-GCB and IPI 2-5 when affordable
Age over 80 or frail	R-mini-CHOP × 6 after a steroid pre-phase	Peyrade 2011	Geriatric assessment; G-CSF
LVEF below 40%	R-CEOP or R-GCVP	Moccia 2021, Fields 2014	Cardio-oncology input

Setting	Standard choice	Key evidence	Notes
HGBL with MYC and BCL2 rearrangements	No randomised standard: DA-EPOCH-R or Pola-R-CHP commonly used; trial preferred	Retrospective series	High CNS risk; consider CNS-directed therapy
Primary mediastinal LBCL	R-CHOP × 6 + RT, or DA-EPOCH-R × 6–8 without RT	Dunleavy 2013; IELSG-26	Avoid RT to breast tissue in young women where possible
Burkitt lymphoma	R-CODOX-M/R-IVAC (fit); DA-EPOCH-R (older or less fit)	Ribrag 2016, HOVON/SAKK	Rituximab from cycle 2; CNS prophylaxis always
Primary CNS lymphoma	High-dose methotrexate combination + rituximab → autologous transplant if fit	IELSG32, PRECIS	Kidney function and fitness, not age, decide
Synchronous systemic + CNS DLBCL	High-dose methotrexate with R-CHOP or Pola-R-CHP, or MATRix-RICE	MARIETTA	Transplant consolidation in responders
Relapse within 12 months or refractory, fit	CD19 CAR-T: axi-cel or liso-cel	ZUMA-7, TRANSFORM ; not tisa-cel (BELINDA)	India: NexCAR19, Qartemi
Later first relapse, fit	Intensive salvage → autologous transplant if complete or near-complete response	CORAL	No rituximab maintenance after transplant
Second relapse, or not fit for transplant/CAR-T	GemOx + glofitamab, epcoritamab or polatuzumab; bispecific after CAR-T	STARGLO, EPCORE	Others: Pola-BR, tafasitamab–lenalidomide, loncastuximab; frail: palliation

C. Regimens: evidence and best fit

First-line DLBCL: rituximab made the difference; polatuzumab adds a little



Six 21-day cycles, full doses (dose cuts lower cure). R-CHOP-14 and DA-EPOCH-R were not better and were more toxic. Interim PET does not guide escalation (PETAL). No consolidation transplant or maintenance in complete response.
POLARIX benefit was in non-GCB disease; grade ≥ 2 neuropathy 14–17% with either regimen.

First-line evidence (Coiffier 2010; Pfreundschuh 2006; POLARIX five-year report, Morschhauser 2025), as quoted in the UpToDate advanced-stage review. Compare arms within a trial, not across trials.

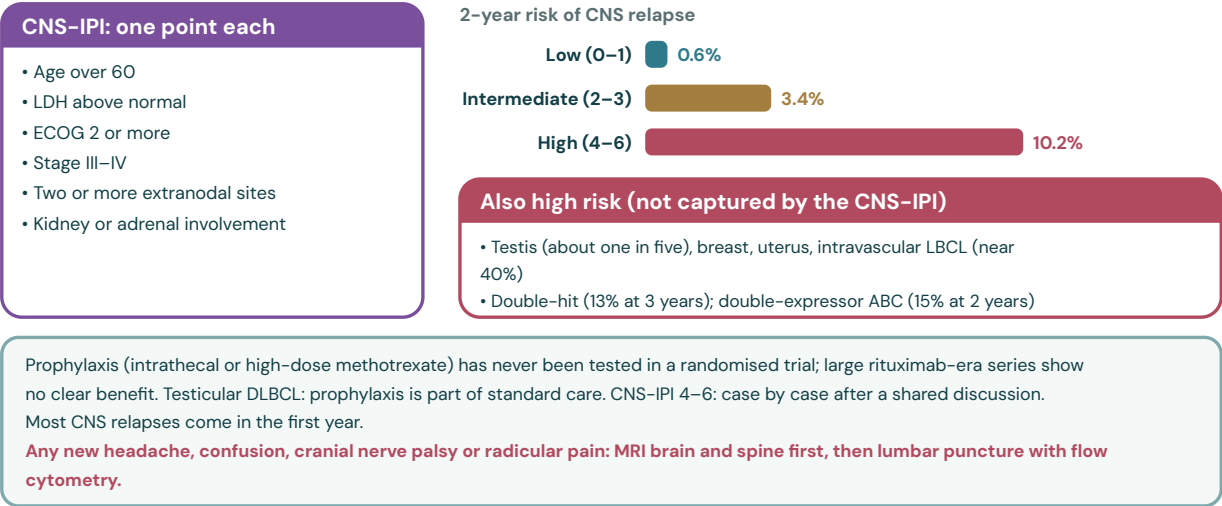
Table C. Regimens and drugs: evidence and best fit

Regimen or drug	Best fit	Evidence	Main toxicity
R-CHOP (21-day)	Default first line for most DLBCL	Cures about 60% of advanced disease; 10-year OS 44% vs 28% over CHOP in older adults	Neutropenia, neuropathy, cardiomyopathy, hyperglycaemia
Pola-R-CHP	IPI 2–5, especially non-GCB	POLARIX: 5-year PFS 64.9% vs 59.1%; OS difference not significant	Similar to R-CHOP; neuropathy 14–17% grade ≥ 2
R-mini-CHOP	Over 80, or frail	2-year OS 59%, PFS 47%	Febrile neutropenia 7%; treatment-related death 8%
DA-EPOCH-R	PMBL; Burkitt in older or less fit; HIV-DLBCL; double-hit (debated)	No better than R-CHOP in DLBCL (CALGB 50303); excellent PMBL series	More neutropenia, mucositis, neuropathy; needs infusion pump or admission
R-CODOX-M/R-IVAC	Fit adults with Burkitt	Rituximab: 3-year EFS 75% vs 62%; OS 83% vs 70%	Severe myelosuppression, mucositis; prolonged admission
CD19 CAR-T	Early relapse or refractory; third line	ZUMA-7: 4-year OS 54.6% vs 46.0%	Cytokine release syndrome, ICANS, prolonged cytopenias, infections

Regimen or drug	Best fit	Evidence	Main toxicity
Bispecific antibodies (glofitamab, epcoritamab)	Transplant-ineligible relapse; after CAR-T	STARGLO: median OS 25.5 vs 12.9 months with GemOx	Cytokine release syndrome (step-up dosing), infections
Rituximab (any combination)	Every CD20-positive aggressive lymphoma	Survival gain in DLBCL, Burkitt and children	Infusion reactions, HBV reactivation, PML (rare), low immunoglobulins

D. Managing problems during treatment

Who is at risk of CNS relapse? (3.4% of DLBCL in a Danish national cohort)



CNS relapse risk (Schmitz 2016; UpToDate secondary CNS lymphoma and advanced-stage DLBCL reviews; Lewis 2023 for high-dose methotrexate).

Table D. Managing problems during treatment

Problem	Prevent	Recognise	Act
Tumour lysis	High risk (Burkitt, bulky, high LDH or uric acid, kidney impairment): IV fluids + rasburicase; intermediate: fluids + allopurinol	K, phosphate, uric acid up; calcium down; creatinine rising; arrhythmia	Monitor closely for the first 72 hours; kidney team; check G6PD before rasburicase where possible
Hepatitis B reactivation	Screen HBsAg and anti-HBc; tenofovir or entecavir from before rituximab until at least 12 months after the last dose	Rising ALT, HBV DNA	Hold rituximab; hepatology; entecavir or tenofovir rather than lamivudine
Febrile neutropenia	G-CSF for age 65+ on curative chemotherapy, and for R-CHOP-14 or intensive regimens	Fever 38 °C or more	Same-day assessment; empirical antibiotics within an hour
Infections	Co-trimoxazole for HIV, R-CHOP-14 and intensive regimens; aciclovir as indicated	Cough, breathlessness (PJP), shingles	Low immunoglobulins with repeated infections: replace
Cardiotoxicity	Baseline echo; control risk factors; dexrazoxane or liposomal doxorubicin in selected patients	Breathlessness, oedema, falling LVEF	Cardio-oncology; switch regimen if LVEF below 40%

Problem	Prevent	Recognise	Act
Neuropathy (vincristine, polatuzumab)	Ask at every cycle	Numb or weak hands and feet, constipation	Reduce or omit vincristine; never omit the curative backbone casually
CAR-T and bispecific toxicity	Step-up dosing for bispecifics; experienced centre with ICU	Fever $\geq 38^{\circ}\text{C}$, low BP, hypoxia (CRS); confusion, word-finding or writing change (ICANS)	Severe CRS: tocilizumab + steroid; ICANS grade ≥ 2 : steroids, levetiracetam