

Acute lymphoblastic leukaemia: tests, treatment by setting, options and problems during treatment

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A. Diagnosis and work-up tests and what they change

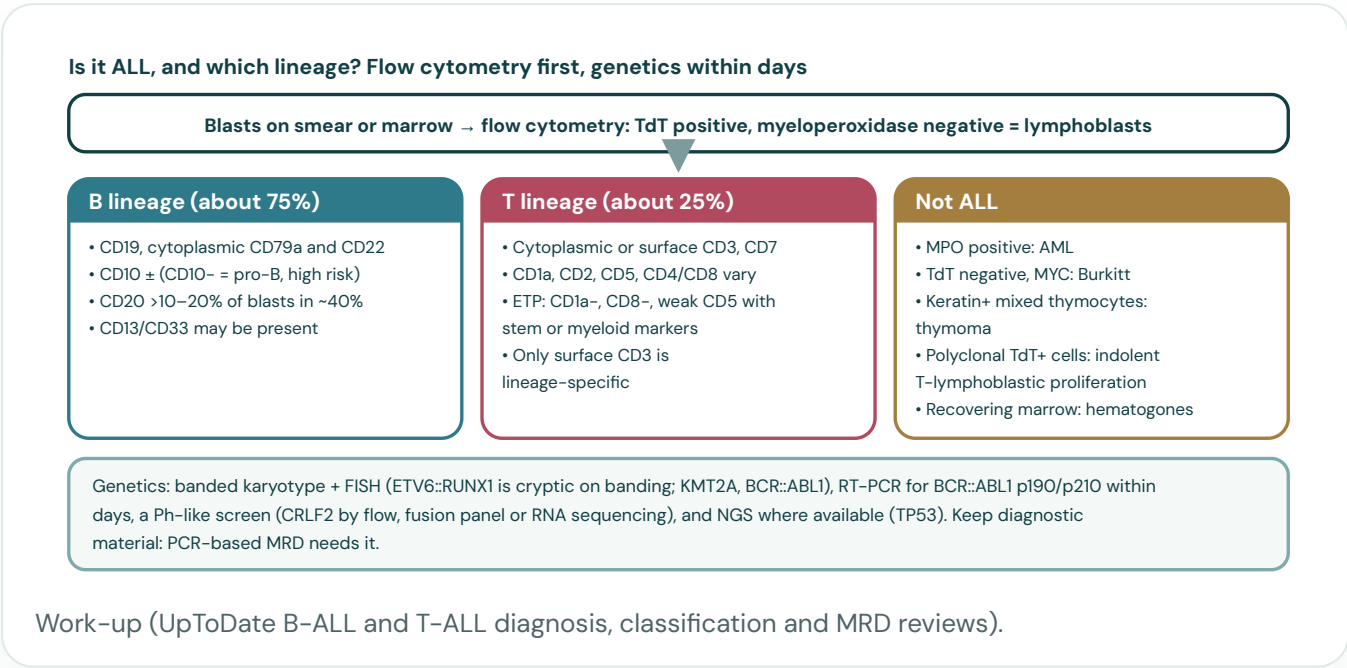


Table A. Diagnosis and work-up tests and what they change

Test	When	What it changes	Pitfalls
CBC + smear review	Every suspected case	Lymphoblasts; cytopenias	White count may be low, normal or very high
PT, aPTT, fibrinogen, D-dimer	At diagnosis; during asparaginase	Bleeding and clot risk	Asparaginase lowers fibrinogen and antithrombin
Potassium, phosphate, calcium, urate, creatinine, LDH	Before and during induction	TLS risk: high if WBC ≥100,000/μL or LDH ≥2× upper limit	ALL is never low risk for TLS
Flow cytometry (blood or marrow)	All	B vs T lineage; CD19, CD20, CD22 for antibody choice; MRD baseline	Only surface CD3 is T-lineage specific; MPO+ = AML

Test	When	What it changes	Pitfalls
Karyotype + FISH; RT-PCR BCR::ABL1	All, within days	Ph+ → TKI at once; KMT2A, hypodiploidy = high risk	ETV6::RUNX1 is cryptic on banding
Ph-like screen (CRLF2 flow, fusion panel, RNA sequencing); NGS for TP53	B-ALL, where available	High-risk group; trials of ABL/JAK inhibitors	Not standard everywhere
Lumbar puncture	When blasts clear from blood, with first intrathecal dose	CNS-1/2/3 → intensity of CNS therapy	Traumatic tap with blasts: compare WBC:RBC ratios
CT chest; biopsy of mass	Mediastinal mass or LBL	LBL if marrow blasts <20%; airway and SVC risk	Diagnose from blood, marrow or effusion if possible
ECG, echo; HBV, HCV, HSV, CMV; pregnancy test	Before induction	Anthracycline and TKI choice; antiviral prophylaxis	Dasatinib/ponatinib: QT, effusions, vascular risk
HLA typing (patient and siblings)	Transplant-eligible patients, at diagnosis	Donor search for high-risk or MRD-positive disease	Only about a quarter have a matched sibling

B. Treatment by setting

Ph-negative ALL: induction is chosen by age and fitness, not by lineage

Fit, ≤40 years

- Paediatric-inspired, asparaginase-rich (CALGB 10403, DFCI)
- CALGB 10403: 3-year OS 73%, treatment deaths 3%
- Cure 60–80%
- Obesity worsens results

Fit, 40–65 years

- Asparaginase regimen (E1910, GRAALL-2005) or hyper-CVAD
- GRAALL-2005: CR 92%, 5-year OS 59%
- Hyper-CVAD + rituximab: 3-year OS 50%
- Choose by toxicity and experience

Older or unfit B-ALL

- Inotuzumab + dexamethasone (>55 years): 3-year OS 73%
- Mini-hyper-CVD + inotuzumab: 3-year OS 56%; liver VOD 8%
- Mini-hyper-CVD + venetoclax (also T-ALL)
- Frail: vincristine + steroid, POMP

Everyone

- CD20+, under 65: add rituximab
- CNS prophylaxis from the first LP
- Steroid prephase if count very high
- Marrow and MRD at count recovery

Rituximab (GRAALL-2005/R, ≥8 doses): 4-year EFS 55% vs 43%, fewer relapses, no overall survival difference. Inotuzumab is not for T-ALL (no CD22). Nelarabine helped children and young adults with T-ALL (COG AALL0434: 5-year DFS 88% vs 82%) but has not improved outcomes in adults.

Induction (UpToDate Ph-negative induction review; Stock 2019; Huguet 2018; Thomas 2010; Stelljes 2024; Kantarjian 2018; Maury 2016; Dunsmore 2020). No doses.

Table B. Treatment by setting

Setting	Usual approach	Alternatives	Key points
Ph-, fit, ≤40 years	Paediatric-inspired asparaginase regimen (CALGB 10403, DFCI)	Hyper-CVAD	+ rituximab if CD20+; cure 60–80%
Ph-, fit, 40–65 years	Asparaginase regimen (E1910, GRAALL-2005) or hyper-CVAD	—	Choose by toxicity, comorbidity and experience
Ph-, older or unfit B-ALL	Inotuzumab-based or mini-hyper-CVD-based	Mini-hyper-CVD + venetoclax; vincristine + steroid; POMP	Watch liver VOD with inotuzumab
Ph-, older or unfit T-ALL	Mini-hyper-CVD + venetoclax	Vincristine + steroid	No inotuzumab (no CD22)
Ph-, CR, standard risk	Consolidation chemotherapy + blinatumomab, then maintenance ≥2 years	Allogeneic HCT (some experts, persistent MRD)	E1910: 3-year OS 85% vs 68%
Ph-, CR, high risk, MRD-negative	Chemo-immunotherapy + maintenance, or allogeneic HCT	—	Favour HCT for KMT2A, complex, low hypodiploid, TP53
Ph-, MRD-positive	Blinatumomab 1–2 cycles → allogeneic HCT	Chemo-immunotherapy + maintenance if not eligible	MRD cleared in about 78%

Setting	Usual approach	Alternatives	Key points
Ph+, any fitness	TKI + steroid or TKI + low-intensity chemotherapy	TKI + blinatumomab (chemotherapy-free)	TKI in every phase; avoid high-intensity chemotherapy
Ph+, in CR	MRD-guided: allogeneic HCT if fit and MRD falling	Consolidation if MRD-negative	TKI ≥1 year after HCT; 24–30 months if no HCT
Relapsed B-ALL, CD19+/CD22+	Blinatumomab, inotuzumab or CAR-T	Chemotherapy	Then allogeneic HCT if eligible
Relapsed KMT2A-r; relapsed T-ALL	Revumenib; nelarabine-based chemotherapy	Trial	Then allogeneic HCT
Lymphoblastic lymphoma	Same protocol as ALL of that lineage	—	CNS prophylaxis; marrow and LP at staging

C. Treatment options: evidence and best fit

Relapsed or refractory ALL: choose by antigen, genetics and lineage, then transplant

B-ALL, CD19+ or CD22+

- Blinatumomab: median OS 7.7 vs 4.0 months (TOWER)
- Inotuzumab: CR 81% vs 29%, MRD-negative 78% (INO-VATE); VOD 9%
- CAR-T: see next figure

CD19- and CD22-

- KMT2A-rearranged: revumenib (response 63%, CR 23%)
- Watch differentiation syndrome (16%) and QT
- Others: chemotherapy by fitness
- Relapse ≥3 years: repeat first regimen

Ph+

- Kinase-domain mutation test
- Second-generation TKI, asciminib, or ponatinib (T315l)
- Plus immunotherapy or chemotherapy

T-ALL

- Nelarabine-based: CR 36%, 1-year OS 37% (CAMPUS ALL)
- Neurotoxicity: stop for grade ≥2
- Bridge to allogeneic HCT

Everyone: lumbar puncture and CNS prophylaxis; examine the testes; HLA typing and donor search at once. Allogeneic HCT in second remission is the usual cure, best when MRD-negative. Isolated CNS relapse: intrathecal therapy + cranial RT 24 Gy. Residual testicular disease: RT 24 Gy to both testes.

Relapse (UpToDate adult relapsed/refractory review; Kantarjian 2017; Kantarjian 2016; Issa 2025; Candoni 2020).

Table C. Treatment options: evidence and best fit

Option	Best fit	Evidence	Watch for
Asparaginase-rich paediatric-inspired regimen	Fit adults, especially ≤40	CALGB 10403: 3-year OS 73%	Liver, pancreatitis, thrombosis, allergy
Hyper-CVAD ± rituximab	Fit adults 40–65	Thomas 2010: 3-year OS 50%	Neutropenia, infections, admissions
Rituximab	CD20+ (>10–20% of blasts), under 65	GRAALL-2005/R: 4-year EFS 55% vs 43%	Infusion reactions; HBV reactivation
Blinatumomab (CD19×CD3)	Consolidation; MRD-positive; relapse	E1910; BLAST; TOWER	CRS, neurotoxicity; continuous infusion
Inotuzumab ozogamicin (CD22)	Relapse; older adults in first line	INO-VATE: CR 81% vs 29%	Liver VOD (9%), especially before HCT
Dasatinib / imatinib / ponatinib	Ph+ ALL, all phases	PhALLCON; D-ALBA	Effusions, QT, bleeding; ponatinib: arterial events
Nelarabine	Relapsed T-ALL; children/young adults first line	Candoni 2020; AALLO434	Neuropathy, Guillain-Barré-like weakness
CD19 CAR-T	Relapsed/refractory B-ALL	ELIANA; ZUMA-3; FELIX	CRS, ICANS, cytopenias, low IgG
Revumenib (menin inhibitor)	Relapsed KMT2A-rearranged ALL	AUGMENT-101: response 63%	Differentiation syndrome, QT
Allogeneic HCT	High risk/MRD-positive CR1; Ph+; second remission	UKALL XII/ECOG 2993; Dhédin 2015	Non-relapse mortality 15–35%; GVHD

D. Managing problems during treatment

Asparaginase: the drug that makes paediatric-style regimens work, and how to keep it safe

Allergy and silent inactivation

- Give only where anaphylaxis can be treated
- Pegylated form: less immunogenic
- Check activity: day 7 <0.1 IU/mL or nil at day 14 = inactivation
- Switch to an Erwinia product

Liver, pancreas, metabolism

- Raised transaminases common (two-thirds on some regimens)
- Pancreatitis
- High glucose and triglycerides
- Worse with BMI >30 or fatty liver
- Avoid other liver toxins while active

Clots and bleeding

- Low antithrombin, protein C/S, fibrinogen
- Thrombosis in 14% of adults (half catheter-related)
- Cerebral sinus thrombosis
- Fibrinogen often <100 mg/dL

ISTH guidance: consider prophylactic LMW heparin while platelets are $\geq 30,000/\mu\text{L}$ (data are retrospective and mixed: 14% vs 27% VTE in one study, no difference in another); weekly antithrombin with replacement below 50–60%. Treat VTE with LMW heparin (anti-Xa monitoring) for ≥ 6 months; hold asparaginase for cerebral sinus thrombosis, large PE, proximal DVT or arterial clots, and consider resuming after about 4 weeks.

India: pegylated asparaginase from Indian manufacturers has lowered cost but remains dearer than native asparaginase; JIPMER limits asparaginase above 50–60 years (Ganesan 2021).

Asparaginase (UpToDate Ph-negative induction and antithrombin deficiency reviews; Zwicker 2020; Sibai 2020; Mort 2025; Wetzler 2007; Ganesan 2021). No doses.

Table D. Managing problems during treatment

Problem	Clues	First steps	Then
Tumour lysis	K, phosphate, urate up; calcium down; creatinine rising	Fluids; rasburicase if high risk (check G6PD)	Do not give calcium for asymptomatic low calcium while phosphate is high
Neutropenic fever	Fever $\geq 38^\circ\text{C}$, neutrophils low	Cultures; broad antibiotics within the hour	See the AML module, emergencies section
Asparaginase thrombosis	Swollen limb; headache, seizure (sinus thrombosis)	Imaging; LMW heparin (anti-Xa); antithrombin if high-risk clot	Hold asparaginase; resume after about 4 weeks if judged safe
Asparaginase pancreatitis or allergy	Abdominal pain, lipase; rash, wheeze	Stop the dose; treat anaphylaxis	Allergy or silent inactivation → Erwinia product
Delayed methotrexate clearance	Rising creatinine, high level	More fluids, alkalinise, more leucovorin; stop interacting drugs	Glucarpidase within 48–60 hours
Vincristine neuropathy, ileus	Tingling, constipation, cramps	Avoid azoles near doses; bowel care	Dose changes per protocol

Problem	Clues	First steps	Then
Blinatumomab or CAR-T reactions	Fever, low BP; confusion, tremor, speech change	Grade CRS and ICANS; tocilizumab, steroids	See the Aggressive B-cell Lymphomas module
Liver VOD/SOS (inotuzumab, HCT)	Weight gain, ascites, tender liver, bilirubin	EBMT criteria; fluid balance; avoid liver toxins	Defibrotide if severe
Myelosuppression on maintenance	Low counts on standard 6-mercaptopurine	Check TPMT and NUDT15	Adjust per protocol
Steroid effects	Hip or shoulder pain; high glucose; mood change	Look for osteonecrosis; control glucose	Discuss steroid schedule with the protocol team