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Diagnostic Advances and Management in Acute Lymphoblastic Leukemia: A Systematic Review

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is a malignancy of lymphoid progenitor cells characterized by proliferation of immature B- or T-cell blasts in the bone marrow, peripheral blood, and extramedullary sites. Over recent decades, survival rates in paediatric ALL has greatly improved, driven by diagnostic stratification, and the incorporation of targeted and immunological agents. However, adult and relapsed ALL still pose considerable challenges. ALL diagnosis requires integration of morphology, immunophenotyping, cytogenetics/molecular testing, CNS assessment, and MRD monitoring. Risk stratification using clinical cytogenetic, and MRD factors guides therapy [1-4]. Typical treatment is divided into induction, consolidation/intensification, CNS prophylaxis, and maintenance, with variations by age group. Use of paediatric inspired regimens in adolescent and young adult, and adult settings improves outcomes over classic adult regimens. Integration of targeted therapy and immunotherapies further enhances outcomes. Relapsed ALL management relies on salvage chemotherapy, immunotherapy, cellular therapies and transplantation[5,6].

Diagnostic precision and MRD guided risk adaptation are foundational in ALL management. While paediatric ALL is largely curable, adult disease still carries a high risk. Limitations in toxicity, access, and the need for better biomarkers remain. The incorporation of novel agents and immunotherapies, optimization of transplant strategies, and personalized approaches are the future directions of research [3-4].

Keywords: *Acute Lymphoblastic Leukemia, Diagnosis, Treatment Strategies, Paediatric*

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a clonal malignancy of lymphoid precursor cells that typically arises in bone marrow and may infiltrate peripheral blood, lymph nodes, spleen, central nervous system, and other sanctuaries. Though most common in children, it also occurs in adolescents, young adults, and older adults. Advances in diagnostics, supportive care, and treatment intensification (including targeted and immunologic therapies) over the past decades have significantly improved the outcome, particularly in paediatric populations [1,2]. Nevertheless, in adult ALL, relapse and toxicities remain major barriers to cure [3]. A rigorous, up to date synthesis of diagnostic and therapeutic strategies is therefore essential for clinicians and researchers.

This review comprehensively examines current practices in diagnosis, risk stratification, treatment regimens across age groups, incorporation of targeted and immunotherapies, salvage strategies, and outcomes. We also provide representative tables of treatment phases and chemotherapy dosing schedules to aid in planning and comparison.

METHODOLOGY

We conducted a literature search in PubMed, MEDLINE, and EMBASE using combinations of the following terms: “acute lymphoblastic leukemia”, “ALL diagnosis”, “treatment protocol”, “paediatric ALL therapy”, “adult ALL management” and “relapse ALL therapy”. The selection prioritized:

- International or national guideline documents
- Systematic reviews and meta-analyses
- Clinical trials

Data extraction included diagnostic criteria, immunophenotypic panels, cytogenetic/molecular testing, MRD methodology, therapeutic regimens (agents, dosages, schedules), outcomes (CR, event-free survival, overall survival, relapse rates), transplant outcomes, toxicity profiles, and salvage therapy results.

DIAGNOSTIC STRATEGIES

Clinical Presentation and Initial Workup

Patients with ALL typically present with symptoms of bone marrow failure, such as anemia (fatigue, pallor), thrombocytopenia (bleeding, petechiae), neutropenia (infections), as well as constitutional symptoms (fever, weight loss), lymphadenopathy, hepatosplenomegaly, bone pain, and sometimes CNS manifestations (headache, cranial nerve palsies) or testicular enlargement. CNS symptoms warrant urgent evaluation [1].

On initial evaluation, the following laboratory and imaging investigations are standard:

- Complete blood count with differential, peripheral smear
- Biochemistry (renal function, liver enzymes, uric acid, LDH)
- Coagulation profile
- Viral serologies (HIV, HBV, HCV)
- Baseline cardiac assessment (ECG, echocardiogram) because of anthracycline exposure risk
- Imaging: chest radiograph or chest CT to assess for mediastinal mass (especially in T-ALL), abdominal ultrasound or CT for organomegaly
- Testicular ultrasound in males, particularly if testicular involvement is suspected
- Lumbar puncture for cerebrospinal fluid (CSF) cytology and flow cytometry (for CNS evaluation)
- Bone marrow aspirate and biopsy for morphology, cytochemistry, flow cytometry, cytogenetics, and molecular studies

Morphology and Cytochemistry

Bone marrow aspirate and biopsy are mandatory for diagnosis. The presence of ≥ 20% blasts (or ≥ 25% in some protocols) in the marrow is typical for ALL diagnosis [4]. Morphologic assessment via Wright-Giemsa staining and H&E on biopsy sections allows classification of blast appearance, but morphology alone is insufficient. Cytochemical stains such as myeloperoxidase (MPO) and periodic acid–Schiff (PAS) may still be used in ambiguous cases, but immunophenotyping is the preferred method for lineage assignment.

Immunophenotyping (Flow Cytometry)

Multiparametric flow cytometry is the backbone of lineage classification (B- vs T-lineage) and maturation stage definition. Panels commonly include markers such as:

- B-lineage: CD19, CD10, CD20, CD22, CD34
- T-lineage: CD3 (surface and cytoplasmic), CD7, CD2, CD5, CD4, CD8
- Others: CD45, CD13, CD33 (to exclude mixed phenotypes), CD58, CD38

Flow cytometry also facilitates minimal residual disease (MRD) detection during therapy via leukemia-associated immunophenotypes. MRD is among the strongest prognostic markers in ALL [5].

Cytogenetic and Molecular Genetic Testing

Cytogenetic and molecular testing provide essential prognostic and therapeutic guidance:

- Conventional karyotyping on bone marrow cells (G-banding) to detect numerical and structural chromosomal aberration.
- Fluorescence in situ hybridization (FISH) for recurrent translocations
- Reverse transcription–PCR or quantitative PCR for fusion transcripts (e.g. BCR-ABL1)
- Next-generation sequencing panels or RNA-sequencing to detect gene mutations, copy-number variation, IKZF1 deletions, JAK/STAT pathway alterations
- Array-based comparative genomic hybridization or SNP arrays for copy-number changes
- Germline predisposition gene testing (e.g. PAX5, ETV6) in selected cases

Integration of cytogenetic and molecular findings with immunophenotype forms the basis of WHO classification and risk grouping.

CNS Assessment and Lumbar Puncture

At diagnosis (or immediately after stabilization), lumbar puncture is performed to evaluate CSF. CNS involvement is classified as:

- CNS-1: no blasts and <5 WBC/μL

- CNS-2: <5 WBC/μL but blasts present
- CNS-3: ≥5 WBC/μL with detectable blasts or cranial nerve palsy involvement

If CNS-3 disease is detected, treatment intensification (intrathecal therapy and/or cranial irradiation) is required [6].

Minimal Residual Disease (MRD) Monitoring

MRD monitoring is central to modern ALL management. Its detection during and after induction and during consolidation allows stratification of relapse risk and treatment intensification decisions. Sensitivities:

- Flow cytometry
- Allele-specific PCR (e.g. IG/TCR rearrangements, fusion transcripts)
- Next-generation sequencing–based MRD in research settings

MRD positivity after induction or consolidation is a strong predictor of relapse and is used by most contemporary protocols to guide therapy intensification or transplantation decisions [5].

Risk Stratification / Prognostic Factors

Common prognostic factors influencing risk stratification include:

- Age: in childhood, ages 1–9 years linked to favourable prognosis; <1 year or >10–15 years unfavourable
- Initial white blood cell (WBC) count (e.g. ≥ 50,000/μL as high-risk)
- Cytogenetic/molecular features: favorable (e.g. ETV6-RUNX1, high hyperdiploidy), adverse (e.g. BCR-ABL1, MLL rearrangements, hypodiploidy, complex karyotype)
- Early response to therapy (e.g. prednisone response on day 8, blast reduction by day 15/21)
- MRD levels at end-of-induction and later time points
- CNS disease at diagnosis
- Genetic high-risk lesions
- T- versus B-lineage (differences in certain subtypes)

Patients are often grouped into standard-risk, high-risk, or very high-risk categories, which guide intensity of therapy and transplant decisions.

Diagnostic and Risk Workflow Summary

1. Clinical presentation, labs, imaging
2. Peripheral smear → abnormal blasts
3. Bone marrow aspiration/biopsy
4. Flow cytometry lineage assignment + MRD baseline
5. Cytogenetics / FISH / molecular panel
6. Lumbar puncture for CSF cytology and flow
7. Risk stratification and assignment of therapeutic arm
8. MRD monitoring at defined timepoints to adjust therapy

MANAGEMENT OF ALL

Treatment of ALL is organized into successive phases:

1. Remission induction
2. Consolidation / Intensification
3. CNS prophylaxis
4. Maintenance / Continuation
5. Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

6. Relapsed / Refractory therapy

Paediatric ALL Treatment

Paediatric ALL is one of the greatest success stories in oncology, with current long-term cure rates of around 80–90% in many cooperative trial groups [5].

Induction

Typical induction duration is approximately 4 weeks. Regimens differ by risk group (standard vs high), B- or T-lineage, and institutional protocol. The backbone generally consists of:

- Steroid (prednisone or dexamethasone)
- Vincristine
- Asparaginase (Peg-asparaginase or native E. coli asparaginase; Erwinia in hypersensitivity)
- ± Anthracycline (e.g. daunorubicin) in higher-risk subsets
- Intrathecal methotrexate (or methotrexate + cytarabine) for CNS prophylaxis

In standard-risk B-ALL, many protocols use three-drug induction (vincristine, steroid, asparaginase). In high-risk or T-ALL, a four-drug induction adding anthracycline is common [7]. According to the PDQ summary, children achieve CR rates of approximately 98% with induction [8].

Consolidation / Intensification

Consolidation usually involves multiple cycles using agents such as high-dose methotrexate, cytarabine, cyclophosphamide, asparaginase, mercaptopurine, and reinduction phases (sometimes called delayed intensification). For example, many protocols include high-dose methotrexate or intermediate-dose methotrexate with leucovorin rescue [7].

CNS Prophylaxis

Intrathecal therapy (methotrexate ± cytarabine ± corticosteroid) is given at fixed intervals during therapy. Some regimens incorporate systemic high-dose methotrexate and cytarabine for CNS penetration. Cranial irradiation is reserved for patients with initial CNS involvement or very high risk [6].

Maintenance / Continuation

Maintenance is a prolonged lower-intensity phase over 2–3 years, incorporating:

- Daily oral 6-mercaptopurine (6-MP)
- Weekly methotrexate (oral or intramuscular)
- Monthly pulses of vincristine + steroid
- Continued scheduled intrathecal therapy

Maintenance is essential: omission or reduction in intensity has been associated with worse survival [9].

Role of HSCT in Paediatric ALL

Allogeneic HSCT is generally reserved for very-high-risk patients in first remission (e.g. poor MRD response, adverse cytogenetics) or for those who relapse. The decision is balanced against long-term risks including growth, endocrine dysfunction, secondary malignancies, and graft-versus-host disease.

Adolescent / Young Adult (AYA) ALL

The AYA period (approx. age 15–39) has historically had worse outcomes than childhood ALL, likely due to the use of suboptimal adult regimens and biologic differences. However, multiple retrospective and prospective studies show that paediatric inspired regimens yield superior outcomes in AYA versus conventional adult regimens [10]. A systematic review by Zeckanovic et al. showed a trend toward improved outcomes and manageable toxicity when PIRs were used in AYAs compared to adult regimens [10].

In British Columbia, adult patients ≤40 years switched from adult to paediatric-derived protocols, achieving a 2-year event-free survival (EFS) of 79% vs 36% under adult treatment ($p = 0.011$) [2]. Thus, many centres now adopt paediatric-inspired or modified paediatric regimens for patients up to age 40, contingent upon fitness and comorbidity.

Treatment principles follow paediatric frameworks but adjusted for increased toxicity risk (e.g. hepatic, pancreatic, thrombotic) in older patients. Dose modifications, more aggressive supportive care, and vigilant monitoring are needed.

Adult ALL Treatment

Adult ALL has lagged behind paediatric outcomes, partly due to greater therapy intolerance, comorbidities, and more adverse biology. But in recent years, incorporation of paediatric-inspired regimens, targeted therapies, and immunotherapy has improved results.

Induction

Common adult regimens include:

- Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high-dose methotrexate + cytarabine)
- Hoeltzer protocol for patients under 65
- Modified regimens combining vincristine, steroids, anthracycline, cyclophosphamide, cytarabine, and sometimes asparaginase (in younger adults) [11]

These regimens aim for remission rates of around 80–90% in young adults. However, older adults (>60) often require reduced-intensity modifications.

Consolidation / Intensification

After induction, several cycles of consolidation are applied (e.g. high-dose methotrexate, cytarabine, cyclophosphamide, reinduction intensification). Maintenance may follow earlier cycles to prolong remission [11].

CNS Prophylaxis

Intrathecal therapy (methotrexate ± cytarabine) is given periodically. Some regimens use high-dose systemic methotrexate or cytarabine for CNS prophylaxis. Cranial irradiation is reserved for CNS disease.

Maintenance

Maintenance is also employed in adult regimens. According to 2024 ELN recommendations, maintenance is strongly recommended; omission leads to inferior OS [12]. Typical maintenance consists of 6-MP + methotrexate (± vincristine or steroid pulses), with intrathecal prophylaxis. Treatment duration is often 2 to 2.5 years inclusive of maintenance [12].

Role of HSCT in Adult ALL

Allogeneic HSCT is more frequently used in adult ALL, particularly in high-risk subsets (e.g. Ph-positive, slow MRD clearance, adverse cytogenetics). Many retrospective and prospective trials and registry data support superior survival with transplant in first remission for those at high risk of relapse [3]. The decision must balance relapse risk with transplant-related mortality, especially in older or comorbid patients.

Below is a generic ALL treatment across phases.

Table 1. Generic ALL Treatment Phases

Phase	**Approximate Duration**	**Goal**
Induction	Approximately 4–6 weeks	Achieve complete remission (morphologic) and reduce leukemic clone burden
Consolidation / Intensification	Several cycles over weeks–months	Eliminate residual leukemic clones and deepen response
CNS Prophylaxis	Throughout therapy	Prevent CNS relapse
Maintenance / Continuation	2–3 years (children), around 2–3+ years (adults)	Suppress residual disease and prevent relapse
Allogeneic HSCT (selected)	After consolidation or in second remission	Provide graft-versus-leukemia effect in high-risk or relapsed disease
Relapse / Refractory Therapy	Variable	Salvage therapy aiming for second remission and transplant

Incorporation of Targeted and Immunologic Therapies

Philadelphia Chromosome–Positive ALL (Ph+ ALL)

In Ph-positive ALL, the integration of BCR-ABL targeted therapy (tyrosine kinase inhibitors) has revolutionized therapy. First-line approaches typically combine TKIs with multiagent chemotherapy or, in some newer protocols, with reduced-intensity chemotherapy or immunotherapy backbone [3].

Recent trials combining potent TKIs (e.g. ponatinib) with blinatumomab have demonstrated 4-year survival rates of 85–90% [3]. Some regimens may omit intensive chemotherapy in patients achieving deep molecular remission, potentially deferring HSCT in select patients.

Blinatumomab (Bispecific T-Cell Engager)

Blinatumomab (CD3 × CD19 bispecific) recruits T cells to CD19-positive B-ALL blasts and has demonstrated efficacy in relapsed/refractory settings and minimal residual disease clearance. It is increasingly used in early treatment phases. Combination regimens of blinatumomab plus chemotherapy or TKIs are under evaluation [3].

Inotuzumab Ozogamicin (Anti-CD22 ADC)

Inotuzumab ozogamicin, an anti-CD22 monoclonal antibody conjugated to calicheamicin, has shown substantial activity in relapsed/refractory B-ALL, achieving a high rate of complete remissions. It is being explored in frontline regimens as a substitute or addition to intensive chemotherapy [3].

CAR T-Cell Therapy (anti-CD19)

Chimeric antigen receptor (CAR) T-cell therapy targeting CD19 has become an established option in relapsed/refractory B-ALL. Tisagenlecleucel is approved in paediatric/young adult B-ALL, and brexucabtagene autoleucel (Tecartus) and other products (e.g. OBE-cel) are approved in adults [3]. Before CAR T infusion, lymphodepleting chemotherapy (commonly fludarabine + cyclophosphamide) is required. Major toxicities include cytokine release syndrome (CRS) and neurotoxicity (ICANS), requiring management in specialized centers.

Emerging Strategies

Other evolving approaches include:

- Bispecific antibodies targeting CD20, CD22, dual-antigen targeting
- Novel antibody–drug conjugates
- Small molecule inhibitors (e.g. JAK inhibitors in Ph-like ALL)
- Checkpoint inhibitors
- Multi-specific CARs, dual-target CARs to prevent antigen escape
- Combinations of immunotherapy and targeted therapy as chemo-sparing regimens

Relapsed / Refractory ALL Management

Relapse remains the major barrier to long-term survival in ALL. Commonly, relapse occurs within the first 2–3 years. Treatment strategies include:

- Reinduction salvage chemotherapy (e.g. fludarabine, cytarabine, etoposide, high-dose methotrexate, clofarabine)
- Blinatumomab (in patients with CD19 expression)
- Inotuzumab ozogamicin (for CD22-positive disease)
- CAR T-cell therapy
- Allogeneic HSCT (if not previously performed)
- Clinical trial enrollment for novel agents

The choice depends on prior therapy, fitness, antigen expression, and donor availability. Achieving MRD negativity prior to transplant is an important prognostic factor. CAR T therapy has substantially improved remission rates in relapsed B-ALL and may serve as a bridge to transplant [3].

Toxicities, Supportive Care, and Dose Intensity

Treatment-Related Toxicities

ALL therapy is severely myelosuppressive, leading to neutropenia, thrombocytopenia, and anemia, with risk of infections. Additional common toxicities include:

- Mucositis
- Hepatotoxicity (especially from asparaginase)
- Pancreatitis (asparaginase)
- Thrombosis (asparaginase)
- Hypersensitivity (asparaginase)
- Neurotoxicity (intrathecal therapy, high-dose methotrexate, cytarabine)
- Cardiotoxicity (anthracyclines)

- Secondary malignancies (especially with cranial irradiation)
- Tumor lysis syndrome (TLS)
- Late effects: growth retardation, endocrine dysfunction, infertility, neurocognitive deficits

Close monitoring, dose adjustments, prophylaxis (e.g. allopurinol or rasburicase, hydration for TLS; antimicrobials during neutropenia) and prompt management are critical. Supportive care measures such as transfusions, antibiotic prophylaxis, growth factors, and nutritional support are integral to success [13].

In chemotherapy prescribing, complexity can lead to errors: in one large analysis of 18,823 chemotherapy orders, 2% contained prescribing errors; complexity of protocols and repetitive orders increased error rates [6]. Rigorous checking protocols and double verification are essential.

Dose Intensity and Delivered Dose

Dose intensity (delivered dose/time) is a key parameter for curative potential. However, many protocols are not delivered at full planned doses due to toxicity or delays. A comprehensive analysis of delivered vs planned dose intensities of ALL drugs showed significant variance across paediatric and adult regimens, underscoring the challenge in comparing feasibility across settings [14]. As novel, less myelosuppressive agents are integrated, balancing dose intensity and tolerability becomes more complex.

Table 2. Common ALL Agents and Representative Dosages

Agent	**Paediatric Dose**	**Adult Dose**	**Key Adverse Effects**	**Special Considerations**
Vincristine	1.5 mg/m² IV weekly (cap at 2 mg)	2 mg IV weekly	Neurotoxicity (peripheral neuropathy), constipation, SIADH	Avoid intrathecal route; monitor for neuropathy
Prednisone / Dexamethasone	Prednisone 60 mg/m²/day × 28 days or Dexamethasone 6 mg/m²/day	Dexamethasone 20 mg/day for adults or pred equivalents	Hyperglycemia, immunosuppression, mood changes, myopathy	In T-ALL, dexamethasone preferred over prednisone
Daunorubicin / Doxorubicin	25–45 mg/m²/week × 1–3 doses	45–60 mg/m² weekly or per protocol	Cardiotoxicity, myelosuppression, mucositis	Monitor LVEF; lifetime anthracycline limits
Asparaginase (E. coli, PEG, Erwinia)	10,000 IU/m² IM/IV (or equivalent PEG dose)	~6,000 IU/m²	Pancreatitis, thrombosis, hepatotoxicity, hypersensitivity	Monitor coagulation, substitute Erwinia if hypersensitivity
Methotrexate (HD)	1–5 g/m² IV over 24 h with leucovorin rescue	2–5 g/m² IV	Mucositis, hepatotoxicity, renal injury, myelosuppression	Hydration, alkalinization, leucovorin rescue mandatory
Cytarabine (hi-dose)	3 g/m² IV q12h × 4 doses	1–3 g/m² IV q12h	Cerebellar toxicity, conjunctivitis, myelosuppression	Monitor neurotoxicity, use steroid eye drops
Cyclophosphamide	1,000–2,000 mg/m²	1,000–2,000 mg/m²	Hemorrhagic cystitis, bone marrow suppression, infertility	Mesna uroprotection, hydration
6-Mercaptopurine	75 mg/m² daily oral	50–75 mg/m² daily oral	Myelosuppression, hepatotoxicity, GI effects	TPMT/NUDT15 genotyping advisable
Cytarabine (intrathecal)	30–50 mg IT	30–50 mg IT	Neurotoxicity, arachnoiditis	Administer with appropriate CSF protocols

CONCLUSION

Accurate diagnosis integrating morphology, immunophenotyping, cytogenetic, and molecular testing, along with MRD monitoring, forms the cornerstone of risk-adapted therapy in ALL. Treatment is classically segmented into induction, consolidation, CNS prophylaxis, maintenance, and optionally transplant or salvage therapy. Paediatric ALL is now curable in approximately 80–90% of patients; adoption of paediatric-inspired regimens in AYA and adult settings improves outcomes relative to classic adult regimens. The integration of targeted therapy (TKIs) in Ph-positive ALL and immunotherapies (blinatumomab, inotuzumab, CAR T) is shifting the paradigm. Relapsed/refractory ALL remains a challenge, but novel agents and cellular therapies offer hope. Moving forward, better biomarkers, optimized sequencing of therapy, minimizing toxicity, and broader access are crucial.

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