Pediatric Acute Lymphoblastic Leukemia, Version 2.2025

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Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia (ALL) were developed as a result of meetings convened by a multidisciplinary panel of pediatric ALL experts, with the goal of providing recommendations on standard treatment approaches based on current evidence. The NCCN Guidelines for pediatric ALL focus on risk assessment and stratification of risk-adapted therapy; treatment strategies for *BCR::ABL1* (Philadelphia chromosome [Ph])-negative and *BCR::ABL1*-positive B-cell lineage, T-cell lineage, and infant ALL; and supportive care considerations. This selection from the NCCN Guidelines for pediatric ALL focuses on the diagnosis of and management of pediatric T-ALL.

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Overview

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. The age-adjusted incidence rate of ALL in the United States is 1.38 per 100,000 individuals per year,[1] with approximately 6,550 new cases and 1,330 deaths estimated in 2024.[2] It is also the most common pediatric malignancy, representing 75%–80% of acute leukemias among children. In contrast, ALL represents approximately 20% of all leukemias among adults.[3,4] The median age of diagnosis for ALL is 15 years,[5] with 55.4% of patients being diagnosed at <20 years of age.[6] In contrast, 28% of patients are diagnosed at ≥45 years and approximately 12.3% of patients are diagnosed at ≥65 years.[6] ALL is divided into 2 major subtypes, B-cell lineage (B-ALL) and T-cell lineage (T-ALL), with B-ALL accounting for approximately 80% of pediatric cases.[7–9]

The cure rates and survival outcomes for patients with ALL have improved dramatically over the past several decades, primarily among children.[10] Improvements are largely owed to advances in the understanding of the molecular genetics and pathogenesis of the disease, the incorporation of risk-adapted therapy, the advent of new targeted agents, the use of allogeneic hematopoietic cell transplantation (HCT), and improvements in supportive care. Analyses from the SEER database have shown improvements in survival for children and adolescent and young adult (AYA) patients with 5-year overall survival (OS) rates of 89% and 61%, respectively.[10,11] However, survival rates for adult patients remain low at approximately 20%–40%.[12–15] Although the exact OS percentage can vary based on how the age range is defined for pediatric, AYA, and adult patients, the trend is nonetheless clear that OS decreases substantially with increased age.[13,16] The exception is infants <1 year of age, which is an age group that has not seen any improvement in survival over the past 30 years, with a 6-year OS rate of 58.2%.[17] Nevertheless, recent data from the Interfant group incorporating immunotherapy into frontline cytotoxic chemotherapy treatment demonstrated very promising 2-year disease-free survival (DFS) rates (81.6%) in

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a small number of patients (n=30) treated on a pilot study, raising optimism that cure rates may improve in the modern era.[18] Historically, outcomes for children with T-ALL were worse than outcomes for children with B-ALL; however, with modern intensive T-ALL focused chemotherapy backbones, the prognoses for childhood T-ALL and B-ALL are nearly equivalent.[7–9]

Cure rates for AYA patients with ALL remain suboptimal compared with those for children, although substantial improvements have been seen with the adoption of pediatric treatment regimens.[19] AYA patients represent a unique population because they may receive treatment based on either a pediatric or an adult protocol, depending on local referral patterns and institutional practices. Given the complexity of ALL treatment regimens and the required supportive care measures, the NCCN Pediatric ALL Panel recommends that patients be treated at a specialized cancer center with expertise in the management of ALL.

The panel considers the term *pediatric* to include any patient aged ≤18 years and certain AYA patients >18 years of age. Across treatment centers, practice patterns vary with regard to AYA patients in terms of whether patients with ALL are treated primarily by pediatric or adult oncologists. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric ALL are intended to apply to AYA patients treated in a pediatric oncology setting and may include patients up to age 30 years. The NCCN Guidelines for ALL are intended to apply to AYA patients treated in an adult oncology setting.

Diagnosis

Clinical Presentation

Patients with ALL develop symptoms related to the infiltration of blasts in the bone marrow, lymphoid system (including thymus presenting as a mediastinal mass in T-ALL), and extramedullary sites (including the central nervous system [CNS] and testicles).[3,8] These symptoms may include fatigue or lethargy, constitutional symptoms (eg, fevers, night sweats, weight loss), dyspnea, dizziness, infections, and easy bruising or bleeding.[4,20] Among children, pain in the extremities or joints may be the only presenting symptom.[4] The presence of lymphadenopathy, splenomegaly, and/or hepatomegaly on physical examination may be found. Chin numbness or facial palsy may result from cranial nerve or CNS involvement.[21,22] Abdominal masses from gastrointestinal involvement are more suggestive of mature B-cell ALL (Burkitt lymphoma).[4]

Compared with patients with B-ALL, individuals with T-ALL generally present at older ages, are more likely to be male (3:1 male:female predominance), and are more likely to self-identify as Black or African American. Individuals with T-ALL are also more likely to present with a higher white blood cell count and are more likely to have extramedullary disease, including lymphadenopathy, mediastinal mass, and CNS involvement. Mediastinal mass is present in >50% of cases of T-ALL and can compress adjacent organs such as the trachea and blood vessels (eg, superior vena cava), causing dyspnea/airway obstruction and venous obstruction/facial edema/thrombosis (also known as superior vena cava syndrome), respectively. In addition to mediastinal mass, pleural and cardiac effusions can be seen.[7–9]

The diagnosis of ALL generally requires demonstration of ≥20% bone marrow lymphoblasts on hematopathology review of bone marrow aspirate and biopsy materials. A value of ≥25% marrow blasts is often used in treatment protocols to define leukemia.[23] Unlike with myeloid leukemia, there is no clear lower limit for the proportion of blasts required to establish an ALL diagnosis. In general, it is uncommon to observe presentations of ALL with low blast counts and the diagnosis of ALL should be avoided when there are <20% marrow blasts. In addition, there is no compelling evidence that not treating a patient when there are <20% marrow blasts has an adverse effect on outcome.[23] In clinical situations that preclude bone marrow aspirate and biopsy, such as hyperleukocytosis (eg, ≥100,000 leukocytes per microliter) and/or mediastinal mass, peripheral blood may be substituted for bone marrow provided there is a significant amount of circulating disease,[24,25] with the NCCN Pediatric ALL Panel suggesting a general guide of ≥1,000 circulating lymphoblasts per microliter or ≥20% lymphoblasts.

The 2022 WHO classification lists ALL and lymphoblastic lymphoma (LL) as the same entity, distinguished only by the primary location of the disease.[23] When the disease is restricted to a mass lesion primarily involving nodal (including thymus for T-ALL) or extranodal sites with no or minimal involvement in blood or bone marrow (generally defined as <20% lymphoblasts in the marrow), the case would be consistent with a

diagnosis of LL.[23] However, based on morphologic, genetic, and immunophenotypic features, LL is indistinguishable from ALL. Patients with LL generally benefit from treatment with ALL-like regimens versus traditional lymphoma therapy[26,27] and should be treated in a center that has experience with LL.

Hematopathology evaluations should include morphologic examination of malignant lymphocytes using Wright-Giemsa–stained slides and hematoxylin and eosin–stained core biopsy and clot sections; comprehensive immunophenotyping with flow cytometry and/or immunohistochemistry (see "Immunophenotyping"; next section); and baseline characterization of leukemic clone(s) by flow cytometry or molecular assay (eg, immunoglobulin [Ig] or T-cell receptor [TCR] gene rearrangements) to facilitate subsequent analysis of minimal residual disease (MRD).

Immunophenotyping

Immunophenotypic classification of ALL involves flow cytometry to determine the presence of cell surface or intracellular antigens on lymphocytes (Figures 1 and 2). ALL can be broadly classified into 2 groups based on immunophenotype, which include precursor B-cell ALL and T-cell ALL.[4,28] Among children, B-ALL constitutes approximately 80% of cases and T-ALL constitutes approximately 10%–15% of cases.[29–31] In adult patients, subtypes of B-ALL represent approximately 75% of cases, whereas the remaining 25% comprise T-ALL.[31,32]

T-ALL is typically associated with the presence of cytoplasmic CD3 (T-cell lineage blasts) or cell surface CD3 (mature T cells) in addition to variable expression of CD2/CD5/CD7, of variable expression of markers of T cell progenitors CD1a, CD99, CD117 (KIT), CD34 (in approximately 1/3 of cases), and expression of TdT.[23] CD4 and CD8 are frequently coexpressed (in approximately 46% of cases), and CD10 may be positive (in approximately 40% of cases). Previous classifications of T-ALL were based on intrathymic staging according to antigens expressed, and included these notations: pro-T/T-I, pre-T/T-II, cortical T/T-III, and medullary T/T-IV.[23,33] Most cases previously classified as pro-T or pre-T now meet the criteria for early T-cell precursor (ETP) ALL.[23] ETP ALL represents a distinct biologic subtype of T-ALL that accounts for 12% of pediatric T-ALLs (and about 2% of ALL) and is characterized by the absence of CD1a/CD8, weak expression of CD5 (<75% positive lymphoblasts), and the presence of ≥1 myeloid or stem cell markers (CD117, CD34, HLA-DR, CD13, CD33, CD11b, or CD65) on at least 25% of lymphoblasts.[23,34 23,34] When CD5 is expressed at higher level, it is called near-ETP ALL. Initial reports demonstrated that ETP ALL was associated with unfavorable outcomes[34–36]; however, with modern, more intensive therapies, multiple groups have reported similar outcomes among ETP ALL, near-ETP ALL, and non-ETP T-ALL.[37–39]

Genetic Abnormalities Associated With T-ALL

T-ALL is characterized by activating mutations of *NOTCH1*, and rearrangements of transcription factors *TLX1* (*HOX11*), *TLX3* (*HOX11L2*), *LYL1*, *TAL1*, and *KMT2A*.[40,41] Over 50% of T-ALL cases have activating *NOTCH1* mutations, and approximately 10%–15% of T-ALL cases have mutations in the *NOTCH1*-targeting E3 ligase *FBXW7*, which leads to prolonged *NOTCH1* activation.[42–44] In patients with T-ALL, *NOTCH1* and *FBXW7*

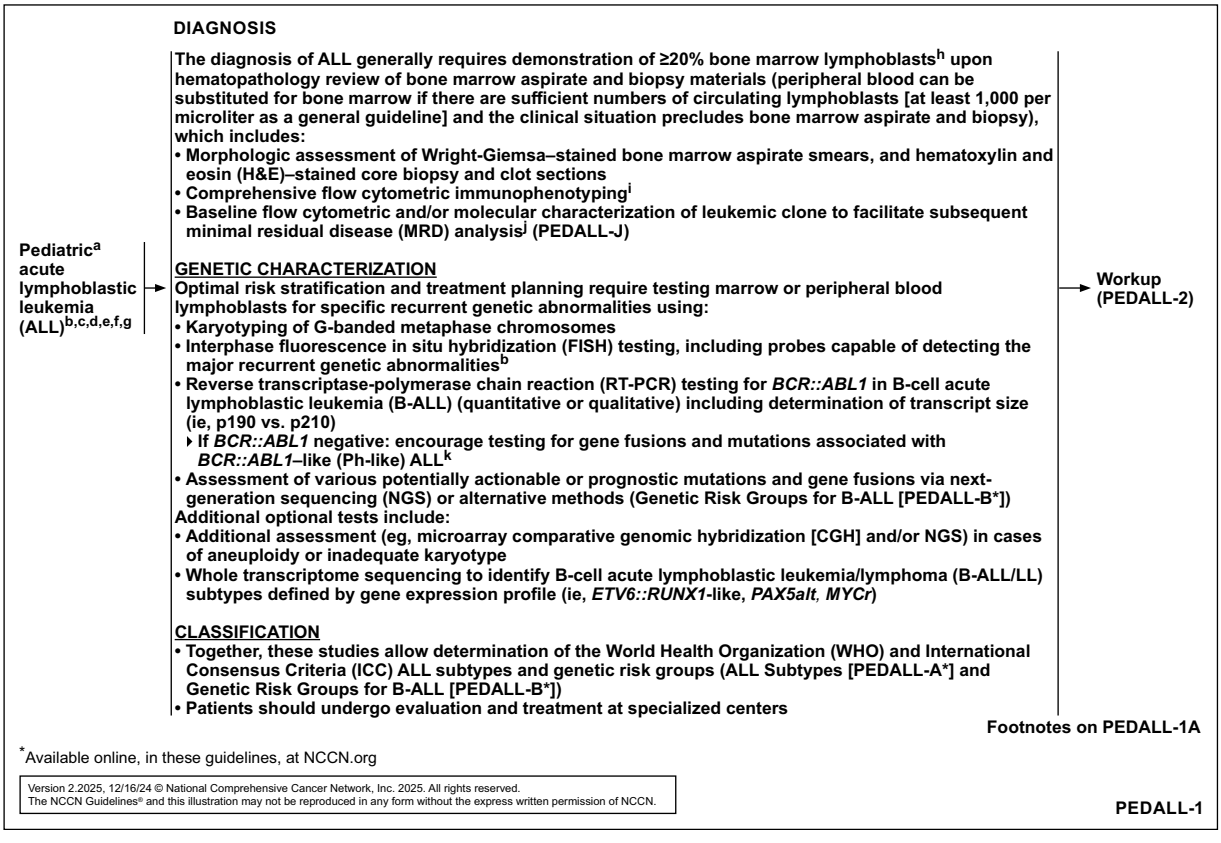

Figure 1. PEDALL-1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

FOOTNOTES

[a] The Pediatric ALL Panel considers "pediatric" to include any patient aged ≤18 years, and certain adolescent and young adult (AYA) patients >18 years of age. Practice patterns vary with regard to AYA patients from center to center in terms of whether patients with ALL are treated primarily by pediatric or adult oncologists. This guideline is intended to apply to AYA patients treated in a pediatric oncology setting, and this may include patients up to age 30 years. The NCCN Guidelines for Acute Lymphoblastic Leukemia are intended to apply to AYA patients treated in an adult oncology setting.

[b] B-ALL/LL subtypes include those not otherwise specified (NOS), with high hyperdiploidy, hypodiploidy, and intrachromosomal amplification of chromosome 21 (iAMP21), with commonly recurring genetic abnormalities: t(9;22)(q34.1;q11.2)[*BCR::ABL1*]; *BCR::ABL1*–like B-ALL; t(v;11q23.3)[*KMT2A* rearrangement]; t(12;21)(p13.2;q22.1)[*ETV6::RUNX1*]; *ETV6::RUNX1*-like features, t(1;19)(q23;p13.3)[*TCF3::PBX1*]; t(5;14)(q31.1;q32.3)[*IGH::IL3*]; t(17;19)(q22;p13.3)[*TCF3::HLF*]; and t(17;18)(q22;q21.2)[*TCF4::HLF*] and with other defined genetic abnormalities that include rearrangements of *DUX4*, *MEF2D*, *ZNF384*, and *NUTM1*; *IG::MYC* fusion; and *PAX5alt*, *PAX5* p.P80R, *IKZF1* p.N159Y, and *CDX2/UBTF*. Of note, in cases of poor response to ALL therapy for ALL with *IG::MYC* rearrangement, therapy for mature B-cell lymphoma may be considered.

[c] T-cell ALL/lymphoma (T-ALL/LL) subtypes include T-ALL/LL, NOS and early T-cell precursor (ETP) lymphoblastic leukemia/lymphoma.

[d] FISH probes that may be useful include: centromeric probes for chromosomes 4, 10, and 17 to detect hyperdiploidy; dual-color probe set to detect cryptic t(12;21), which will also allow detection of iAMP21 (when ≥5 copies of the *RUNX1* gene are detected); probes to detect *BCR::ABL1* and *KMT2A* rearrangements; probes to detect *ABL1*, *ABL2*, and *PDGFRB* rearrangements; probes for *CDKN2A* at 9p21.3 to detect deletions; probes to detect cryptic t(X;14)(p22;q32)/t(Y;14)(p11;q32) *IGH::CRLF2* rearrangements; and probes to detect *JAK2* rearrangements.

[e] Criteria for classification of mixed phenotype acute leukemia (MPAL) should be based on the WHO 2022 and ICC 2022 criteria. Note that in ALL, myeloid-associated antigens such as CD13 and CD33 may be expressed, and the presence of these myeloid markers does not exclude the diagnosis of ALL, nor is it associated with adverse prognosis. ALL-directed therapy can be initiated for MPAL. Khoury JD, et al. Leukemia 2022;36:1703-1719; Arber DA, et al. Blood 2022;140:1200-1228; Alexander TB, et al. Nature 2018;562:373-379.

[f] For Burkitt leukemia/lymphoma; see the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas†.

[g] While these guidelines pertain primarily to patients with leukemia, patients with lymphoblastic lymphoma (LL) (B- or T-cell) would likely also benefit from ALL-like regimens. Such patients should be treated at a center that has experience with LL.

[h] In many treatment protocols, a value of >25% marrow blasts is used to define leukemia. Unlike with myeloid leukemias, there is no agreed-upon lower limit for the proportion of blasts required to establish a diagnosis of ALL. In general, the diagnosis should be avoided when there are <20% blasts. Presentations of ALL with low blast counts are uncommon; there is no compelling evidence that not treating a patient when there are <20% marrow lymphoblasts has an adverse effect on outcome. Alaggio R, et al. Leukemia 2022;36:1720-1748.

[i] The following immunophenotypic findings are particularly notable: CD10 negativity correlates with *KMT2A* rearrangement (*KMT2A*r); ETP T-ALL (ETP T-ALL typically lacks expression of CD5, CD8, and CD1a and has expression of one or more myeloid/stem cell markers); CD20 positivity: definition not clear, most studies have used >20% of blasts expressing CD20; and *CRLF2* overexpression as a surrogate for genomic alterations of the *CRLF2* gene including *P2RY8::CRLF2* and *IGH::CRLF2* (Harvey RC, et al. Blood 2012;120:2529). Flow cytometric DNA ploidy analysis could be considered for rapid identification of hyperdiploid and hypodiploid B-ALL.

[j] By either flow cytometric analysis or by identification of clonal immunoglobulin or T-cell receptor (*TCR*) gene rearrangements.

[k] The *BCR::ABL1*–like phenotype is associated with recurrent gene fusions and mutations that activate tyrosine kinase pathways and includes gene fusions involving *ABL1, ABL2, CRLF2, CSF1R, EPOR, JAK2,* or *PDGFRB* and mutations involving *CRLF2, FLT3, IL7R, SH2B3, JAK1, JAK3,* and *JAK2* (in combination with *CRLF2* gene fusions). Testing for these abnormalities at diagnosis may aid in risk stratification. Low-density array (LDA) (Harvey RC, et al. Blood 2013;122:21), NGS-based assays, FISH, and multiplex RT-PCR are used to detect a signature or cryptic rearrangements and mutations characteristic of *BCR::ABL1*–like ALL. The safety and efficacy of targeted agents in this population is an area of active research.

†To view the most recent version of these guidelines, visit NCCN.org.

PEDALL-1A

Figure 2. PEDALL-1A. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

mutations have generally been associated with favorable prognosis and lower MRD levels.[45–47] However, it is unclear if these mutations are independent predictors of outcome, or if there needs to be concurrent absence of *RAS* or *PTEN* mutations.[48–50]

Integrated analysis of whole genome, exome, and transcriptome sequencing of T-ALL were performed in samples from children and adolescents treated in AALL0434 study. The analysis identified 15 subtypes with distinct expression patterns, leukemic drivers, and outcomes as described in the "Prognostic Factors and Risk Stratification" section (page 45).[51]

Workup

The initial workup for ALL should include a thorough medical history and physical examination, along with laboratory and imaging studies, including chest X-ray, and, if LL is suspected, CT or PET/CT (Figures 3 and 4). Laboratory studies should include a complete blood count with platelets and differential, a blood chemistry profile, liver function tests, and disseminated intravascular coagulation panel (including measurements for D-dimer, fibrinogen, prothrombin time, and partial thromboplastin time). The blood chemistry panel should include a tumor lysis syndrome panel (including measurements for serum lactate dehydrogenase, uric acid, potassium, phosphates, and calcium), especially for those with hyperleukocytosis and large leukemia burden such as mediastinal mass. Patients of childbearing potential should undergo pregnancy testing, and patients with testes should be evaluated for testicular involvement of disease, including a scrotal ultrasound as indicated; testicular involvement is rare in ALL (1%–2% of males), but is slightly more common in T-ALL than B-ALL. For patients with T-LL and mediastinal mass, a multidisciplinary approach is necessary for obtaining biopsy specimen if peripheral blood and bone marrow are negative for blasts, and examination of pleural fluid, if present, by thoracentesis can be diagnostic which also can alleviate respiratory symptoms.

Pediatric and AYA patients treated with cytotoxic chemotherapy, radiation therapy, and/or HCT may be at increased risk for infertility. Fertility counseling and/or preservation options should be presented to all patients (see NCCN Guidelines for Adolescent and Young Adult [AYA] Oncology, available at NCCN.org). Fertility preservation techniques such as sperm cryopreservation, oocyte cryopreservation, harvesting of ovarian or testicular tissue for cryopreservation, or embryo cryopreservation are options for some patients. Referral to a fertility preservation/reproductive health program should be considered for eligible patients before starting chemotherapy.[52,53] Counseling on cessation of smoking, drugs/illicit substances, vaping, and alcohol is also encouraged for AYA patients (see NCCN Guidelines for Smoking Cessation, available at NCCN.org). Psychosocial assessment is also encouraged (see NCCN Guidelines for Adolescent and Young Adult [AYA] Oncology, available at NCCN.org).

Appropriate imaging studies should also be performed to detect meningeal disease, chloromas, or CNS bleeding for patients with major neurologic signs or symptoms at diagnosis. If neurologic symptoms are observed, a CT/MRI scan of the head with contrast is recommended. To rule out mediastinal masses and/or pleural effusion, a chest X-ray should be performed. If LL is suspected, a whole-body PET/CT scan is the recommended

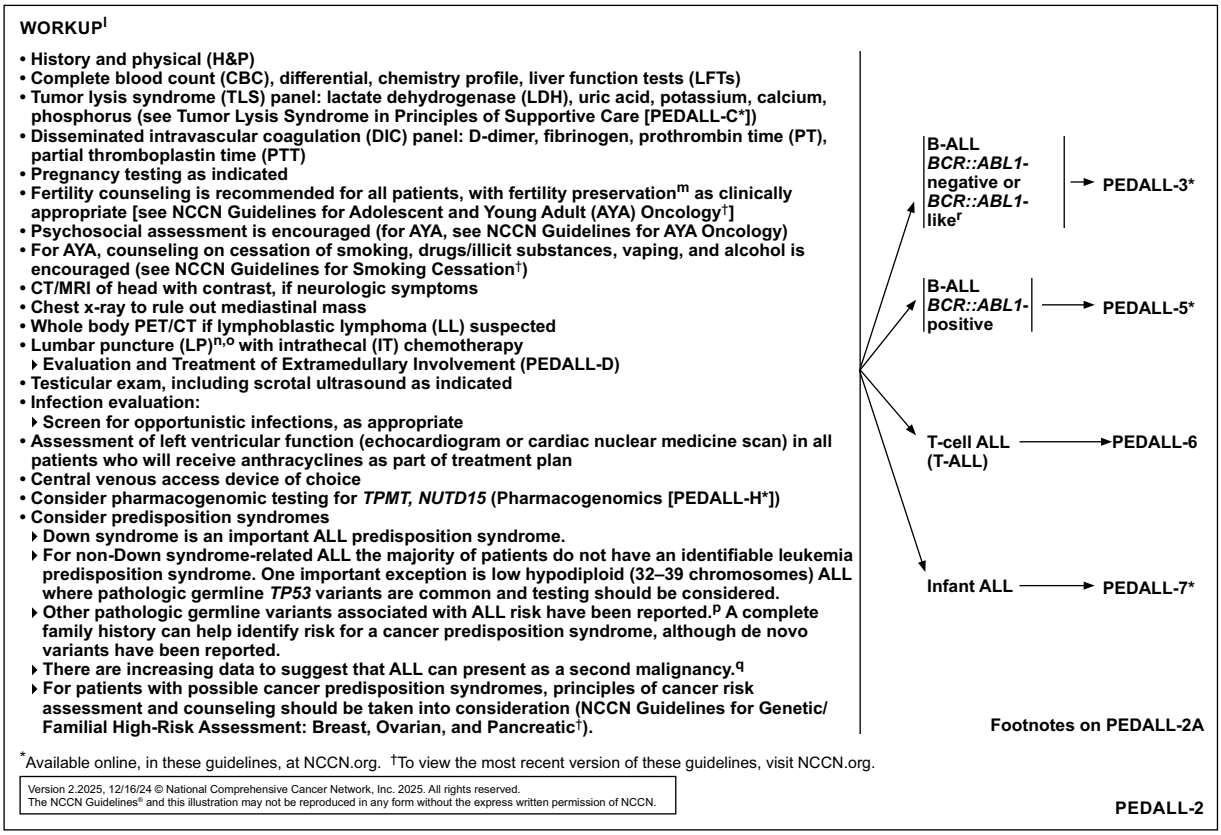

Figure 3. PEDALL-2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

imaging modality; however, PET/MRI scans are being used at more centers to reduce radiation exposure. For centers without access to PET imaging, a CT scan suffices to determinate areas of disease involvement. CNS involvement should be evaluated through lumbar puncture at timing that is consistent with the treatment protocol. Pediatric-inspired regimens typically include lumbar puncture and prophylactic intrathecal (IT) chemotherapy at the time of diagnostic workup. The NCCN Pediatric ALL Panel recommends that the first IT therapy be performed at the time of initially scheduled lumbar puncture unless directed by symptoms to perform earlier, although the procedure may be delayed in the presence of hyperleukocytosis and/or mediastinal mass.

All patients should be evaluated for opportunistic infections as appropriate. In addition, an echocardiogram or cardiac scan should be considered for all patients due to the use of anthracyclines as the backbone of nearly all treatment regimens. Assessment of cardiac function is particularly important for patients with mediastinal mass, cardiomegaly, pleural effusion, prior cardiac history, prior anthracycline exposure, or clinical symptoms suggestive of cardiac dysfunction. To appropriately tailor doses of select components of chemotherapy including thiopurines and minimize adverse effects during treatment, pharmacogenomic testing for thiopurine methyltransferase (TPMT) and nucleoside diphosphate–linked moiety X-type motif (nudix hydrolase 15, *NUDT15*) should be considered. For dosing guidelines for thiopurines based on *TPMT* and *NUDT15* phenotype, see "Pharmacogenomics" in the algorithm.

During the workup, it is important to consider the potential influence of any ALL-predisposition syndromes. A growing number of pathologic germline variants associated with ALL risk have been reported.[54] Importantly, children with Down syndrome are at an increased risk for the development of ALL.[55] For non-Down syndrome–related ALL, most patients do not have an identifiable leukemia predisposition syndrome. An exception is low-hypodiploid (32–39 chromosomes) ALL where pathologic germline *TP53* variants are common and testing should be considered.[56] Other pathologic germline variants associated with ALL risk have been reported, particularly *PAX5, ETV6,* and *IKZF1*.[54] A complete family history can help identify risk for a cancer predisposition syndrome, although de novo mutations have been reported. There is increasing data to suggest that ALL can present as a second malignancy.[57] For patients with possible cancer predisposition syndromes, principles of cancer risk assessment and counseling should be considered (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate, available at NCCN.org).

It should be noted that the recommendations included in the guidelines represent a minimum set of workup considerations and that other evaluations or testing may be needed based on clinical symptoms. Procurement of cells should be considered for purposes of future research (in accordance with institutional practices or policies).

Prognostic Factors and Risk Stratification

Various disease-related and patient-specific factors may have prognostic significance in patients with ALL. In particular, patient age, white blood cell count, immunophenotypic/cytogenetic/genetic subtype, presence of CNS disease, and response to therapy

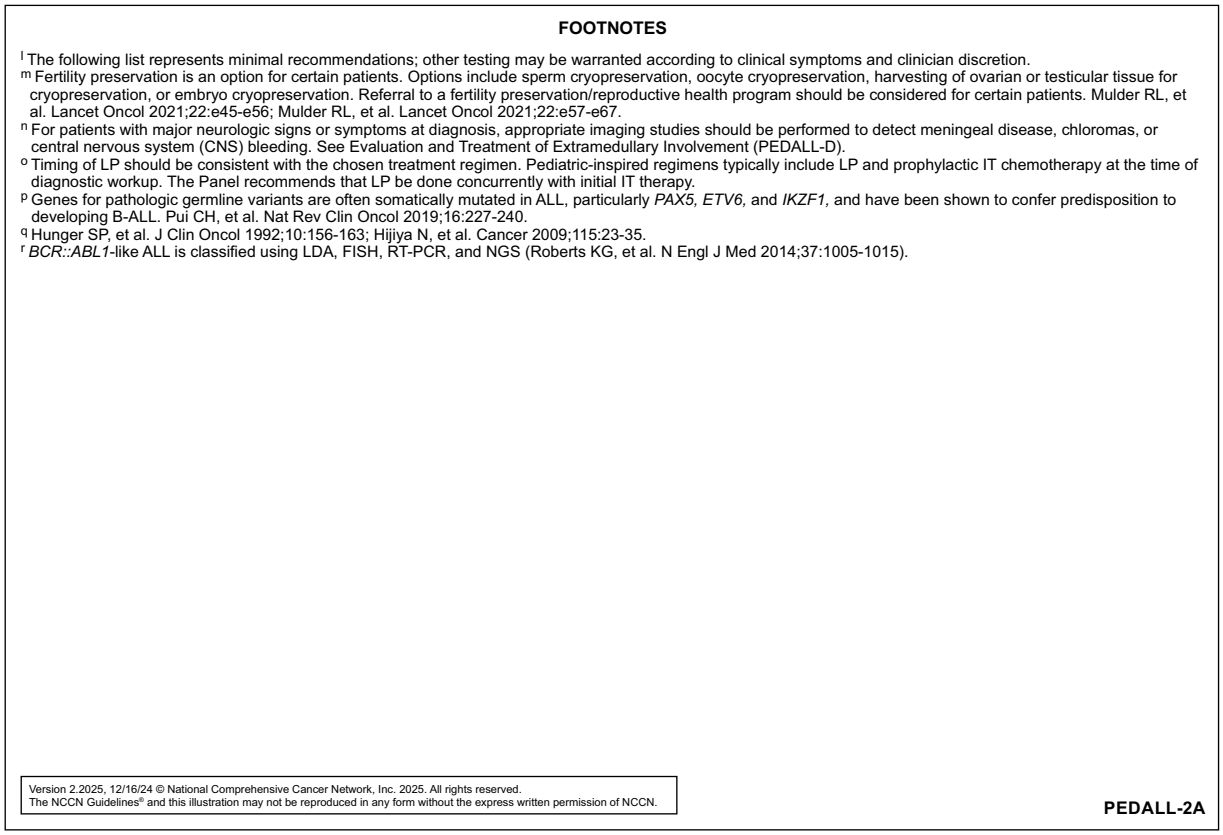

Figure 4. PEDALL-2A. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

have been identified as important factors in defining risk and assessing prognosis for both childhood and adult ALL.

Risk stratification of T-ALL has been challenging, because other than MRD measurements, the clinical variables used to classify risk in B-ALL, including age and white blood cell counts, are not independently prognostic in T-ALL.[38] Although T-ALL is often categorized as high risk depending on the institute, newer treatment options have resulted in improved survival outcomes for these patients.[37,38,58,59] Furthermore, the identification of genetic mutations and the use of targeted therapies may change the way T-ALL is treated and ultimately how these patients are assessed for risk. Through a comprehensive analysis of genome and transcriptome sequencing of both tumor and remission samples from children with T-ALL (n=1,300), genomic features associated with clinical outcome have been identified.[51] This comprehensive genomic analysis could divide T-ALL into 15 subtypes with distinct expression patterns, leukemic drivers, and outcomes. Notably, in approximately 60% of cases the primary leukemic driver was due to genetic alterations in noncoding regions, requiring whole genome sequencing in >25% of cases. A higher risk of MRD positivity (MRD ≥0.01%) was noted in the setting of alterations in JAK-STAT and RAS signaling pathways as well as in the setting of ETP-like drivers and colesions, including *ETV6*, *H2B3*, *NRAS*, and *WT1*. Conversely, alterations in NOTCH, ribosome, and PI3K pathways as well as *CCN3D*, *LEF1*, *PI3K*, and *USP7* lesions were associated with lower risk of MRD positivity. Subtypes associated with poor event-free survival (EFS), DFS, and OS outcomes included SPI1, MLLT10, HOXA1, NKX2-5, and LMO2γδ-like subtypes. Although the ETP-like KMT2A subtype was associated with poor outcomes, the non-ETP-like KMT2A subtype was associated with more favorable prognosis, despite higher MRD. Similarly, the ETP-like MLLT10 subtype was associated with worse prognosis than the non-ETP-like MLLT10 subtype, and the TLX3 immature subtype had worse prognosis than the TLX3 DP-like subtype. Similarly to the non-ETP like KMT2A subtype, the ZFP36L2 subtype was associated with favorable outcomes despite higher rates of MRD, suggesting that MRD status alone should not be the only factor in treatment decisions such as allogeneic HCT. Of note, these results should be validated in an independent cohort and require whole genome and/or whole transcriptome sequencing to identify many prognostic genomic features.

Minimal Residual Disease

MRD in ALL refers to the presence of leukemic cells below the threshold of detection using conventional morphologic methods (see Figure 5). Numerous studies in childhood ALL have shown the prognostic importance of postinduction and/or postconsolidation MRD measurements in predicting the likelihood of disease relapse.[60–69]

The most frequently used methods for MRD quantification include multiparameter flow cytometry (eg, 6-color or higher) to detect leukemia-associated immunophenotypes, PCR assays to detect fusion genes (eg, *BCR::ABL1*), and clonal rearrangements in Ig and/or TCR genes.[70–77] New multiplexed PCR and next-generation sequencing (NGS) for MRD are emerging methodologies. Of note, data on the accuracy of NGS MRD in T-ALL are limited, and NGS is not FDA approved for MRD detection in T-ALL.

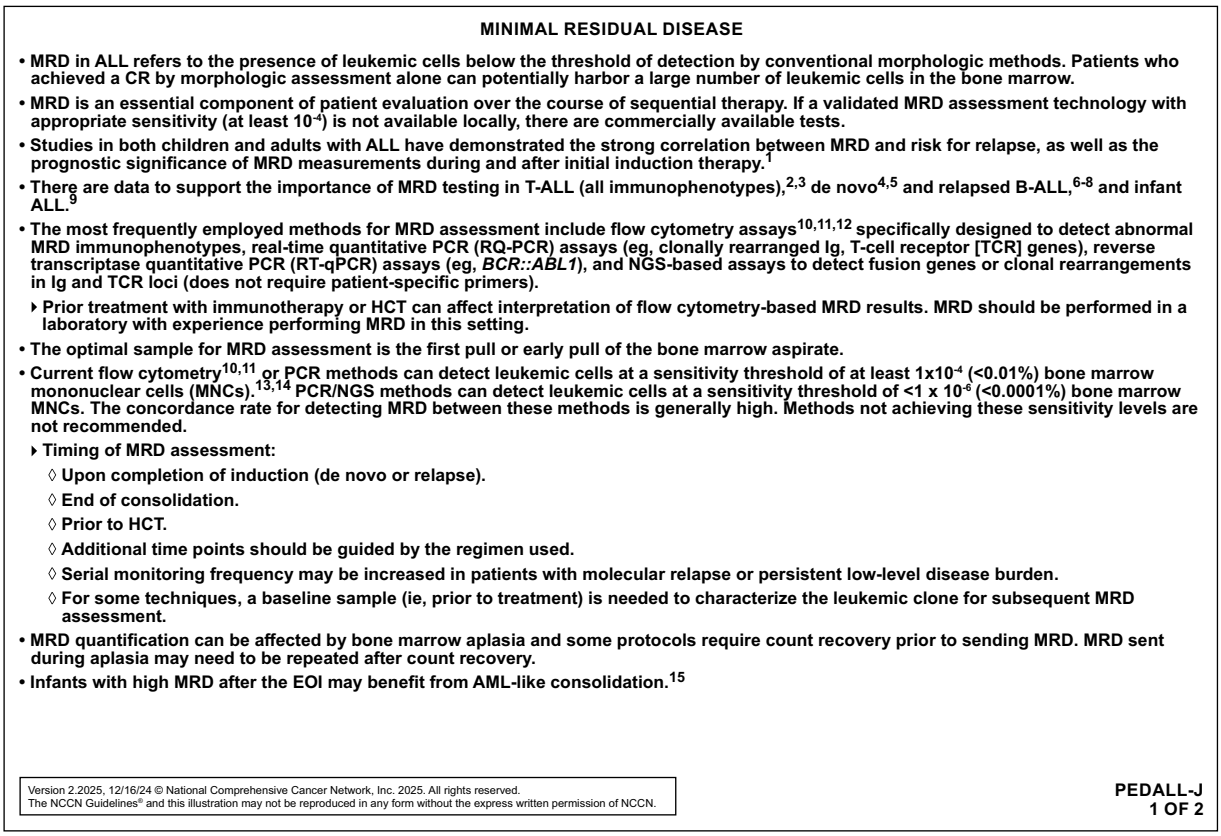

Figure 5. PEDALL-J 1 of 2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

Current multiparameter flow cytometry methods or PCR methods can detect leukemic cells at an optimal/maximal sensitivity threshold of at least 10^{-4} (<0.01%) bone marrow mononuclear cells (MNCs), and NGS methods can detect leukemic cells at an optimal/maximal sensitivity threshold of 10^{-6} (0.0001%) bone marrow MNCs, respectively.[71,73,75,76,78,79] The concordance rate for quantifying MRD between these methods is generally high at disease burdens 10^{-4} (>0.01%), but NGS is able to detect MRD at lower thresholds.[72,74,76,80–82] The combined or tandem use of both methods would allow for MRD monitoring in all patients, thereby avoiding potential false-negative results.[73,80,83] However, this practice could lead to an increase in cost without a clear directive in terms of modification of treatment.

MRD assessments at early time points in the course of treatment (eg, during or at the end of induction [EOI] and end of consolidation [EOC]) have been shown to be highly predictive of outcomes in children with ALL. In a study conducted by the COG for children with B-ALL (n=2,143), the prognostic impact of MRD was evaluated by flow cytometry in the peripheral blood at day 8, and in marrow at EOI (day 29) and EOC.[62] The presence of MRD in day 8 blood and day 29 marrow was associated with shorter EFS in all risk groups (NCI standard- and high-risk), and end-induction MRD predicted early relapses (within 3 years) and late relapses. The early relapse-free survival rates in the setting of MRD negativity versus MRD positivity (>0.01%) were 6.8% and 28%, respectively (P<.001). In addition, the late relapse-free survival rates in the setting of MRD negativity versus MRD positivity were 4.6% and 24%, respectively (P<.001).[62] In a study of pediatric patients with ALL enrolled in Total Therapy studies at the St. Jude Children's Research Hospital (n=158), patients with detectable MRD (flow cytometry optimal sensitivity level of 1×10^{-4}) at the EOI therapy had a significantly higher 3-year cumulative incidence of relapse than those who experienced MRD negativity (33% vs 7.5%; P<.001).[84] Subsequent studies confirmed these findings.[85] In another study of pediatric patients with ALL enrolled in Total Therapy studies, nearly 50% of patients experienced MRD clearance (MRD $<1 \times 10^{-4}$ by flow cytometry) before day 19 of induction therapy (about 2–3 weeks from initiation of induction); the 5-year cumulative incidence of relapse was significantly higher among patients with MRD at day 19 of treatment than those without detectable MRD (33% vs 6%; P<.001).[86]

The AIEOP-BFM ALL 2000 study investigated the prognostic value of MRD by PCR for Ig and TCR gene rearrangements in children with T-ALL (n=464).[66] The 7-year EFS rate was 91.1% for patients categorized as being at standard risk (n=75), 80.6% for intermediate risk (n=292), and 49.8% for high risk (n=97), resulting in a statistically significant difference among the groups (P<.001). MRD negativity at day 33 was the most favorable prognostic factor. Importantly, MRD ≥10%–3% on day 78 was the most important predictive factor for relapse and, if MRD on day 78 was negative (48% of all patients), early MRD levels on day 33 were irrelevant for outcomes, highlighting the significance of later MRD assessments (EOC) on outcomes in pediatric T-ALL.

In the COG AALL0434 trial, most children with T-ALL (n=1,256) were classified by flow cytometry as having ETP, near-ETP, or non-ETP.[39] MRD was assessed by flow cytometry in peripheral blood on day 8, in the bone marrow on day 15 and day 29 (EOI), and, for patients with high-risk disease (EOI M2 marrow or MRD≥1.0%) or lack of response to induction (EOI M3 marrow), in the bone marrow on approximately day 57 (EOC). The risk-stratification grouping included MRD assessment by flow cytometry using the following cutoffs: low risk, <0.1%; intermediate risk, <1%; and high risk, >1%. Patients with ETP and near-ETP ALL were more likely to have high end-induction MRD levels, with a 5 times higher rate of lack of response to induction than those with non-ETP ALL. Interestingly, no differences in EFS or OS were found among the 3 groups, suggesting that patients with ETP and near-ETP experienced response to postinduction and/or off-protocol treatment. There was no difference in EFS or OS between patients with a day 29 MRD <0.01% and 0.01%–0.1%. However, both near-ETP and non-ETP groups with day 29 MRD ≥0.1% had inferior EFS and OS, but this was not observed for those with ETP. A day 29 MRD ≥10% was a significant predictor of inferior outcomes in all patients, and for patients with non-ETP with day 29 MRD ≥1%, end-consolidation MRD ≥0.01% was an important predictor of inferior EFS.

To examine the impact of integrating the assessment of genetic abnormalities with MRD, samples from a pediatric ALL cohort treated in the UK ALL 2003 trial were analyzed (n=3,113).[87] MRD was measured at the EOI for 86% of the patients (n=2,678) by PCR analysis of Ig/TCR rearrangements. In tandem, patients were assigned to a genetic subtype based on immunophenotype, cytogenetics, and FISH.[87] Patients with disease with good-risk cytogenetics (*ETV6::RUNX1*, high hyperdiploidy [51–65 chromosomes]) demonstrated the fastest disease clearance, whereas patients with disease with high-risk genetics (*KMT2A* fusions, near haploidy, low hypodiploidy [<40 chromosomes], *iAMP21*, *TCF3::HLF*), and T-ALL demonstrated slower responses.[87]

For children and adolescents with T-LL who were treated on the COG A5971 trial (n=99), submicroscopic systemic disease (minimal disseminated disease) of T-LL cells was evaluated by flow cytometry.[88] In 71.7% (71 of 99) of the bone marrow samples obtained at initial diagnosis, T-LL cells made up 0.01%–31.6% (median, 0.22%) of mononuclear cells. Patients with stage II/III T-LL accounted for 57 of these 71 samples. Two-year EFS was significantly worse in patients with ≥1% and ≥5% of minimal disseminated disease than in those with <1% and <5%, respectively. The presence of T-LL cells in peripheral blood significantly correlated with that in the bone marrow. However, with more intensive therapy backbones in AALL0434 trial, minimal disseminated disease was no longer prognostic.[89] In patients with T-LL treated on the COG AALL1231 trial, 86 of the 209 patients (41%) underwent bone marrow MRD assessment at the end of induction.[90] MRD <0.1% (n=75) was associated with a significantly better 4-year EFS compared with MRD ≥0.1% (n=11) (89% ± 4.4% vs 63.6% ± 17.2%; P=.025), though MRD was not associated with a significant difference in OS.

Up to 20% of children treated with intensive therapies for ALL will experience disease relapse.[91] MRD assessment may play a prognostic role in the management of relapsed disease.[92–94]

EVALUATION AND TREATMENT OF EXTRAMEDULLARY INVOLVEMENT

- The aim of CNS prophylaxis and/or treatment is to clear leukemic cells within sites that cannot be readily accessed by systemic chemotherapy due to the blood-brain barrier, with the overall goal of preventing CNS disease or relapse or seeding of bone marrow.
- CNS involvement should be evaluated by LP at the appropriate timing:
  - Timing of LP should be consistent with the chosen treatment regimen.
  - Pediatric regimens typically include LP at the time of diagnostic workup.
  - The Panel recommends that LP be done concurrently with initial IT therapy.
- Classification of CNS status:
  - CNS-1: No lymphoblasts in CSF regardless of WBC count.
  - CNS-2: WBC count <5/µL in CSF with presence of lymphoblasts.
  - CNS-3: WBC count ≥5/µL in CSF with presence of lymphoblasts, or clinical symptoms (such as facial nerve palsy, brain/eye involvement, CNS hemorrhage, or hypothalamic syndrome).
  - If the patient has leukemic cells in the peripheral blood and the LP is traumatic and WBC count is ≥5/µL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least two-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.
- All patients with ALL should receive CNS prophylaxis. Although the presence of CNS-3 involvement at the time of diagnosis is uncommon (about 3%–7%), a substantial proportion of patients (>50%) will eventually develop CNS leukemia in the absence of CNS-directed therapy.
- CNS-directed therapy may include cranial irradiation, IT chemotherapy (eg, MTX, cytarabine, corticosteroids), and/or systemic chemotherapy (eg, high-dose MTX, cytarabine, pegaspargase/calaspargase). Cranial RT is often avoided in favor of IT chemotherapy and systemic therapy when possible due to concern for late effects.
- The use of cranial radiation for patients with ALL with CNS-3 disease at diagnosis varies based on protocol. Patients should be treated according to their protocol.
  - If cranial radiation is done, recommended dosing is 18 Gy at 1.5–1.8 Gy/fraction.
  - Timing of cranial radiation is less clear for patients with T-ALL. It is recommended that a specific treatment protocol be followed in its entirety.
- TBI is given for select patients with high-risk disease receiving HCT; in patients who require cranial irradiation and TBI, cranial RT should be given as a boost before or after TBI.
  - See Conditioning Regimen in the Principles of Hematopoietic Cell Transplant (PEDALL-K 3 of 5)
- The entire brain and posterior half of the globe should be included in the radiation field. The inferior border should include C2. Note that areas of the brain targeted by the radiation field in the management of ALL are different from areas targeted for brain metastases of solid tumors.
- Adequate systemic therapy should be given in the management of isolated CNS relapse. Cranial irradiation to 18 Gy is recommended, with timing depending on treatment protocol.
- Patients receiving cranial irradiation should be monitored for neurocognitive deficits and academic delays, neuroendocrine deficits, secondary malignancy, cataracts, and other late effects.
  - See COG Long-Term Follow-up Guidelines: http://www.survivorshipguidelines.org
- Patients with clinical evidence of testicular disease at diagnosis that is not fully resolved by the end of the induction therapy should be considered for radiation to the testes in the scrotal sac, with timing depending on the particular treatment protocol. Testicular total dose should be 24 Gy in 2.0 Gy/fraction.

PEDALL-D

Figure 6. PEDALL-D. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

Several studies suggest early assessment of MRD during induction treatment of initial relapse(eg, day 15 from initiation of treatment) may be highly predictive of subsequent relapse in children with ALL.[95,96] This raises the possibility of identifying patients with high-risk disease who may potentially benefit from earlier intensification or tailoring of treatment regimens, or for potentially allowing less-intensive treatments to be administered in patients at low risk for relapse based on early MRD measurements. Large trials are warranted to address these possibilities, although serial MRD measurements may likely be needed to monitor leukemic cell kinetics during the long course of treatment.

NCCN Recommendations for MRD Assessment

Collectively, studies show the high prognostic value of MRD in assessing risk for relapse in patients with ALL, and the role of MRD monitoring in identifying subgroups of patients who may benefit from further intensified therapies or alternative treatment strategies.[60,63–68,97] The optimal sample for MRD assessment is the first pull or early pull of the bone marrow aspirate (Figure 5). If a validated MRD assessment technology with appropriate sensitivity (at least 10^{-4}) is not available locally, there are commercially available tests. Current flow cytometry assays or PCR methods can detect leukemic cells at an optimal sensitivity threshold of at least 1×10^{-4} (<0.01%) bone marrow MNCs,[71,73,78,79] and NGS methods can detect leukemic cells at an optimal/maximal sensitivity threshold of 10^{-6} (<0.0001%) bone marrow MNCs, respectively.[71,73,75,76,78,79] As noted previously, NGS methods are FDA approved to detect MRD in B-ALL but not in T-ALL. A baseline sample to characterize the leukemic clone should be obtained to facilitate interpretation of future MRD assessments.

MRD quantification can be affected by bone marrow aplasia and some protocols require count recovery before sending MRD samples. Therefore, if an MRD sample is sent for analysis during aplasia, a subsequent MRD assessment may be needed after count recovery. In addition, prior treatment with immunotherapy or HCT can affect the interpretation of flow cytometry-based MRD results, and should be assessed by a laboratory with experience in this setting. Strong consideration should be made for NGS-based MRD testing after CAR T-cell therapy, as detectable bone marrow MRD by NGS has been shown to be highly predictive of relapse following tisagenlecleucel in patients with ALL.[98]

The timing of MRD assessment varies depending on the treatment protocol used and may occur during or after completion of initial induction therapy. Negative MRD at the end of induction is associated with excellent outcomes and could be used to identify patients at low risk of relapse. The kinetics of MRD response are different between B-ALL and T-ALL, and in T-ALL MRD after consolidation therapy has been shown to be an important prognostic factor regardless of MRD status at EOI.[39,66,87] Therefore, it is recommended that measurement be performed upon completion of induction therapy (during treatment of de novo or relapsed disease), EOC, and prior to HCT; additional time points for MRD evaluation should be guided by the treatment protocol or regimen used.[78,79] Serial monitoring frequency

PRINCIPLES OF HEMATOPOIETIC CELL TRANSPLANT

Indications for HCT (B-cell) in First Remission

- Unfavorable cytogenetics
  - Consider HCT if *MLL/KMT2A* mutation (<6 months in age) with high-risk features (PEDALL-7).[a,1]
- MRD
  - Consider HCT if MRD ≥0.01% post-consolidation (week 9–12 from diagnosis).[b,2]
- Other considerations
  - The role of HCT for patients with hypodiploid ALL in CR1 has not yet been established, even in patients who are MRD-positive at end-induction.[3-8]
    - ◊ HCT for hypodiploid ALL may be considered in the setting of a clinical trial.
  - HCT is not routinely indicated for *BCR::ABL1*+ ALL in CR1 (while on TKI plus systemic chemotherapy) provided that the patient has achieved MRD negativity (<0.01%) post-consolidation and is being treated on an intensive pediatric regimen plus TKI. Consider HCT (for *BCR::ABL1*+ ALL) if relapse (any time point), or MRD ≥0.01% (by week 9–12).[9,10]
  - For patients who are MRD positive (≥0.01%) at end-induction, there is insufficient evidence to suggest a survival advantage for HCT, even in patients with kinase activating mutations (ie, *IKZF1, CDKN2A/B, PDGFRB, ABL1, ABL2, CSF1R, JAK2, CRLF, EPOR*) or iAMP21.

Indications for HCT (B-cell) in Non-First Remission Settings

- Induction failure (M3 marrow): Recommend HCT after achieving MRD-negative status.
- CR2: Consider HCT based upon timing of relapse (or refractory disease) and leukemic phenotype; see PEDALL-K (2 of 5).
- CR3: Recommend HCT.
- For a patient with CNS involvement at the time of relapse (or refractory disease), consider a CNS boost at the time of administration of TBI. For those without CNS involvement at the time of relapse (or refractory disease), there is no clear evidence that CNS boost will prevent subsequent CNS relapse.[11,12]
- For relapsed/refractory disease, see PEDALL-K (2 of 5).

Indications for HCT (T-cell)

- HCT should be considered for:
  - Patients with MRD positivity (>0.1%) at completion of consolidation. Additional therapy should be given prior to HCT to achieve MRD negativity. See PEDALL-G (9 of 13).
  - Induction failure (M3 marrow).[13]
  - Patients with medullary or extramedullary relapse (any time point).[14] See PEDALL-K (2 of 5).
- For relapsed/refractory disease, see PEDALL-K (2 of 5).

[a] The Interfant-99 study noted a potential benefit for HCT in children aged <6 months with *MLL* rearrangements plus either poor day 8 (induction) response to systemic corticosteroids, or WBC count at initial diagnosis >300 x 10^9/L.
[b] MRD based upon flow cytometry, PCR, or NGS.

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Figure 7. PEDALL-K 1 of 5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

may be increased in patients with molecular relapse or persistent low-level disease burden. In general, MRD positivity at the EOI in B-ALL and EOC in T-ALL, predicts high relapse rates and should prompt an evaluation for allogeneic HCT. When possible, therapy aimed at eliminating MRD before allogeneic HCT should be considered.

Treatment Considerations: Phases and Agents

The treatment approach to ALL represents one of the most complex and intensive programs in cancer therapy. Although the specific treatment regimens and selection of drugs, dose schedules, and treatment durations differ among pediatric, AYA, and adult patients, and among different subtypes of ALL, the basic treatment principles are similar. In general, the treatment phases can be largely grouped into induction, consolidation, and maintenance; however, these general treatment phases are further broken down into more detailed phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance I and II. All treatment regimens for ALL include CNS prophylaxis and/or treatment. Some treatment plans may involve targeted agents and HCT.

Induction

Remission induction is the first block of chemotherapy with the intent of reducing tumor burden by clearing as many leukemic cells as possible from the bone marrow.[29] Induction regimens are typically based on a backbone that includes a combination of vincristine, corticosteroids (eg, prednisone, dexamethasone), and asparaginase with or without anthracyclines (eg, daunorubicin, doxorubicin).[28,29,99,100]

The BFM/COG regimens are mainly based on a 4-drug induction regimen that includes a combination of vincristine, an anthracycline, a corticosteroid, and asparaginase.[101–105] In the COG, patients classified as having NCI standard-risk disease are treated with a 3-drug induction that does not include anthracyclines. Some studies from the Cancer and Leukemia Group B (CALGB) have used a 5-drug regimen in AYA and adult patients, which adds cyclophosphamide to the above 4-drug combination.[106] The majority of protocols for patients with T-ALL use a 4-drug regimen.

Randomized studies comparing the use of dexamethasone versus prednisone as part of induction therapy in children with ALL showed that dexamethasone significantly decreased the risk of isolated CNS relapse and improved EFS outcomes compared with prednisone.[107,108] The observed advantage in outcomes with dexamethasone may partly be attributed to improved penetration of dexamethasone into the CNS.[109] Although dexamethasone is reported to significantly reduce the risks for CNS relapse and improve EFS rates compared with prednisone, significant toxicities are associated with dexamethasone, especially used at high doses (eg, 10 mg/m^2 per day), including osteonecrosis and infection,[110,111] and an advantage for OS has yet to be conclusively shown, except in the subset of patients with T-ALL with prednisone good response in the AIEOP-BFM ALL 2000 study.[110]

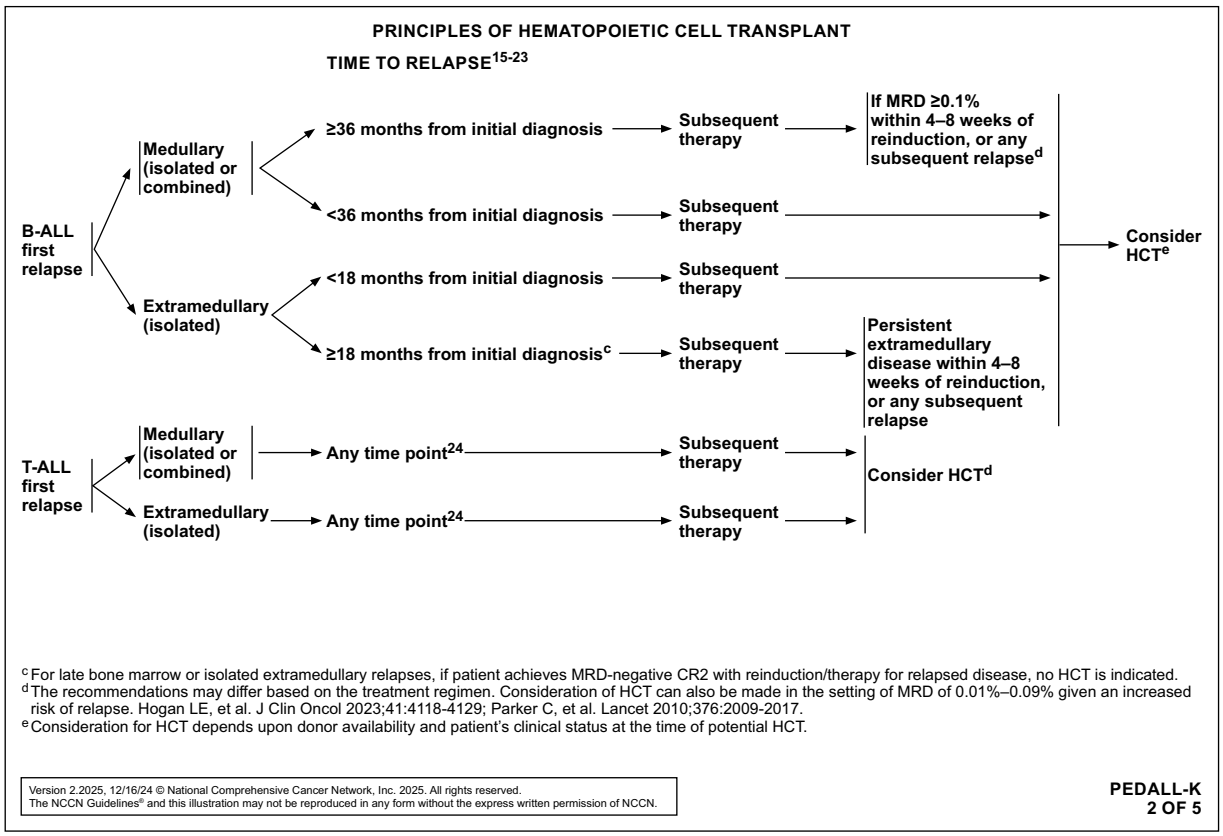


Figure 8. PEDALL-K 2 of 5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

COG uses a dexamethasone schedule of 6 mg/m^2 per day for 28 days (instead of 10 mg/m^2 per day for 21 days used in the AIEOP-BFM ALL 2000 study) that was derived from studies from the MRC/UK.

Several different agents exist for asparagine depletion, including calaspargase, pegaspargase, and asparaginase *Erwinia* chrysanthemi (recombinant)-rywn (ERW-rywn). Compared with native *Escherichia coli*-derived L-asparaginase, pegaspargase has a longer half-life and decreased immunogenicity.[29,112] Calaspargase is an asparaginase enzyme formulation with a different linker molecule that enhances its hydrolytic stability and increases its half-life relative to pegaspargase.[113] As of December 1, 2022, pegaspargase can only be ordered for patients <1 month (31 days) or ≥21.5 years in the United States,[114] limiting its use in the pediatric population; thus, calaspargase is the preferred formulation if available for patients >1 month through 21.5 years. Calaspargase is not available in many countries and pegaspargase is the most commonly used product. ERW-rywn is typically given to patients who have experienced an allergic reaction to calaspargase or pegaspargase, and it requires a more frequent administration schedule (see prescribing information for further details). The US FDA approved an intramuscular dosing schedule for ERW-rywn of 25 mg/m^2 Monday/Wednesday and 50 mg/m^2 Friday based on a positive risk:benefit ratio from a phase II/III study,[115] in addition to 25 mg/m^2 administered intramuscularly every 48 hours.[116] Moreover, *E. coli*-derived L-asparaginase is currently not available in the United States and has been discontinued by the manufacturer.

Post-Induction Therapy Including Consolidation

The intent of postinduction that includes consolidation is to eliminate any leukemic cells potentially remaining after induction therapy, further eradicating residual disease. This phase of treatment may involve four to six cycles of therapy, and in some settings may occur over a duration of up to 8 months.[99] The consolidation phase is the treatment phase most affected by risk stratification, such that patients with lower-risk disease receive less intensive consolidation and patients with higher-risk disease receive consolidation that is more intensive.

AIEOP/BFM protocols use consolidation regimens with cyclophosphamide, cytarabine, and 6-MP, and COG and others intensify therapy by adding vincristine and asparaginase (augmented BFM regimen) for patients with high-risk B-ALL and T-ALL For T-ALL, nelarabine can also be added.[29,99,100,104,105] Thereafter, patients receive interim maintenance therapy and delayed intensification therapy (also known as *reinduction therapy*). Methotrexate (MTX) is crucial for controlling systemic leukemia as well as CNS and testicular disease. Interim maintenance therapy includes high-dose MTX (HD-MTX) with leucovorin rescue plus 6-MP, Capizzi-MTX (escalating intermediate doses of MTX without leucovorin rescue plus vincristine and asparaginase) or escalating-MTX (escalating intermediate doses of MTX without leucovorin rescue plus vincristine) based on the treatment risk or leukemia cell lineage. The delayed intensification phase may vary among studies but can comprise combinations of drugs similar to those used during the induction and consolidation phases. In COG

PRINCIPLES OF HEMATOPOIETIC CELL TRANSPLANT

Donor Type

- **Unrelated vs. related donor**
  - **In children/young adults undergoing HCT for ALL, there is no survival advantage (event-free survival [EFS] or overall survival [OS]) by donor type when comparing use of matched unrelated donors to matched related donors.[25]**
- **Umbilical cord blood (UCB)[26-28]**
  - **Allows rapid procurement and more lenient human leukocyte antigen (HLA) matching.**
    - **No outcome differences are noted in HCT for childhood leukemia when comparing UCB versus matched related/matched unrelated donors.[26]**
    - **There are possible lower relapse rates using UCB versus matched unrelated donor if the patient achieves MRD positivity pre-HCT.[27]**
    - **There is no survival advantage for double (vs. single) UCB HCT in children/young adults, when a single cord unit with adequate cell dose is available.[28]**
- **The role of haploidentical transplants for childhood leukemia has been examined in several single and multicenter studies, with potential efficacy and favorable toxicity profiles. Haploidentical transplants (with post-transplant cyclophosphamide or αβ-depletion) may be considered as an alternative donor source, especially if no HLA-matched donor is available.[29,30,31,32]**

Donor Cell Source

- **When comparing bone marrow to peripheral blood stem cells (PBSCs) as the donor cell source, there is no survival advantage for use of PBSCs in matched unrelated donor transplantation. Higher graft-versus-host disease (GVHD) rates with equivalent survival are noted with PBSCs (vs. marrow) in recipients of matched unrelated donor transplants. The optimal donor cell source (marrow vs. PBSCs) has not been clearly defined with either matched related donor or haploidentical donor transplants. Due to increased risks of acute and chronic GVHD with PBSCs, the use of PBSCs should be considered with caution for HCT in children/young adults with ALL.[33,34]**

Conditioning Regimen

- **Both TBI and non-TBI–containing regimens have been used in HCT for children and young adults with ALL. Randomized controlled trials indicate that TBI is superior to non-TBI–containing regimens for children with ALL.[35,36,37] Non-TBI–containing regimens are under current investigation.**
- **The use of TBI in conditioning regimens for ALL demonstrated a disease-free survival advantage seen regardless of donor source (matched related vs. unrelated HCT).[37]**
- **For infants: If donor available, prefer non–TBI-based prep regimen and age ≥6 months at time of HCT.[38] See PEDALL-G, 2 of 13.**

Impact of Pre-HCT MRD Status

- **An increased risk of relapse has been noted in children with ≥0.1% MRD pre-HCT for ALL, suggesting the need to attain an MRD level <0.1% prior to HCT.[39,40] An increased risk of relapse has also been noted in children with an MRD of 0.01%–0.09%.[41,42]**
- **The absence of detectable MRD by NGS before and after HCT may be associated with favorable outcomes.[43]**

PEDALL-K 3 OF 5

Figure 9. PEDALL-K 3 of 5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

protocols, 6-TG is primarily incorporated into delayed intensification,[117–125] and is also part of reinduction I and II in COG AALL1122.[126]

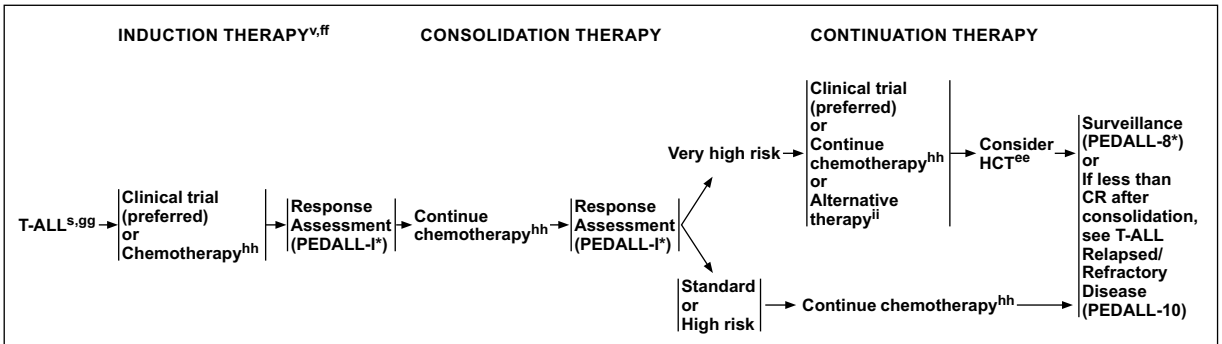
Maintenance

The goal of extended maintenance or continuation therapy is to prevent disease relapse after postinduction therapy. Most maintenance regimens are based on a backbone of daily 6-MP and weekly MTX (typically with the addition of periodic vincristine and corticosteroids) for 2 to 3 years.[29,99,100] Factors that affect the bioavailability of 6-MP can significantly impact patient care. Oral 6-MP can have highly variable drug and metabolite concentrations among patients.[127,128] Furthermore, age, gender, and genetic polymorphisms can affect bioavailability.[129–131] The efficacy of maintenance therapy is determined by the metabolism of 6-MP to the antimetabolite chemotherapeutic agent 6-TG; however, other pathways compete for 6-MP, thereby reducing the amount of active metabolite produced. The four enzymes that metabolize 6-MP are xanthine oxidase (XO), hypoxanthine-guanine phosphoribosyltransferase (HPRT), TPMT, and NUDT15. Heterozygosity at the *TPMT* gene locus occurs in 5%–10% of the population and has been shown to have intermediate enzyme activity.[132–134] NUDT15 deficiency, which is more prevalent in patients of East Asian descent and patients of Hispanic ethnicity, is also associated with 6-MP intolerance.[135] Therefore, determining a patient's *TPMT* and *NUDT15* genotype is recommended to optimize 6-MP dosing, especially in patients who experience myelosuppression at standard doses.[135] For dosing guidelines for thiopurines based on *TPMT* and *NUDT15* phenotype, see "Pharmacogenomics" in the algorithm.

Nonadherence also results in undertreatment, particularly in the AYA population. Adherence issues should be addressed for patients without cytopenia. If increasing doses of 6-MP are given during maintenance but no drop in the counts is observed, this may be indicative of nonadherence.[136] Quantification of 6-MP metabolites can be very useful in determining whether the lack of myelosuppression is due to nonadherence or hypermetabolism. Clinicians can also take a detailed history and perform pill counts to confirm adherence.

Extramedullary Disease Prophylaxis and Treatment

The goal of CNS prophylaxis and/or treatment is to prevent CNS disease or relapse by clearing leukemic cells within sites that cannot be readily accessed with systemic chemotherapy because of the blood-brain barrier (Figure 6). CNS3 disease is associated with worse outcomes compared with CNS1 or CNS2 disease.[137] Patients with CNS2 also have worse outcome than those with CNS1 in B-ALL.[138] CNS-directed therapy may include IT therapy (eg, IT MTX with or without cytarabine and corticosteroid), cranial irradiation, and/or systemic chemotherapy (eg, dexamethasone, HD-MTX, intermediate-/high-dose cytarabine, asparaginase).[29,99,100,109,139] Cranial irradiation is often avoided in favor of IT therapy and systemic chemotherapy when possible due to concern for late adverse effects, particularly in patients with CNS1 or CNS2 status. CNS prophylaxis is typically given to all patients throughout the entire course of ALL therapy, from induction, to consolidation, to the maintenance phases of



T-ALL Post-Induction Risk Group Definitions:

Risk Group	Features[y]
Very High	End consolidation MRD >0.1%
High	Absence of standard- and very-high-risk features
Standard	Day 29 MRD <0.01% and CNS-1 and absence of testicular disease and no steroid pretreatment[jj]

[s] For patients with Down syndrome, see Special Considerations for Patients with Down Syndrome and Infants (PEDALL-E*).
[v] Principles of Supportive Care (PEDALL-C*).
[y] The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information, see Minimal Residual Disease (PEDALL-J).
[ee] Principles of Hematopoietic Cell Transplant (PEDALL-K).
[ff] MRD and morphologic marrow response should be assessed after induction, and if not MRD negative, repeat assessment after consolidation therapy. Assess MRD at additional time points based on chemotherapy regimen and response as indicated. See Minimal Residual Disease (PEDALL-J).
[gg] The Panel believes it is reasonable to use bortezomib with Berlin-Frankfurt-Münster (BFM) backbone chemotherapy in patients with pediatric T-cell LL (T-LL), because it was shown to improve event-free survival (EFS)/overall survival (OS) in T-LL but not leukemia (Teachey DT, et al. J Clin Oncol 2022;40:2106-2118).
[hh] See regimens for T-ALL on Principles of Systemic Therapy (PEDALL-G, 2 of 13).
[ii] See regimens for T-ALL on Principles of Systemic Therapy (PEDALL-G, 9 of 13).
[jj] The specific definition of steroid pretreatment differs by protocol. Refer to regimen-specific definition of steroid pretreatment.

*Available online, in these guidelines, at NCCN.org.

PEDALL-6

Figure 10. PEDALL-6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

treatment. Patients with testicular disease at diagnosis that is not resolved by the EOI therapy may receive radiation to the testes.

Hematopoietic Cell Transplantation

Allogeneic HCT has demonstrated improved clinical outcomes in pediatric patients with ALL with evidence of certain high-risk features and/or persistent disease.[99,140,141] In addition, survival rates appear to be comparable regardless of the stem cell source (matched related, matched unrelated, umbilical cord blood, or haploidentical donor).[141–143] Both total body irradiation (TBI) and non-TBI–containing regimens have been used in HCT for children and young adults with ALL. Randomized controlled trials indicate that TBI is superior to non-TBI–containing regimens for children with ALL.[143–145] Non-TBI–containing regimens are currently under investigation. Based on the data, it is reasonable to consider HCT in first remission (CR1) for certain patients as described in the HCT sections throughout the discussion (Figure 7, Figure 8, and Figure 9).

Targeted Agents

The emergence of targeted therapies for hematologic malignancies, including the purine nucleoside analog nelarabine, which has been approved for the treatment of relapsed or refractory (R/R) T-ALL or LL, represents an important advancement in ALL therapy.[146]

Management of T-ALL

T-ALL is biologically distinct from B-ALL, but similar to B-ALL, MRD is a key prognostic determinant.[38] A major theme in current T-ALL treatment approaches is early intensification with multiagent chemotherapy followed by intensive consolidation therapy. Based on trials referenced in the algorithm, the management of de novo T-ALL is summarized subsequently.

Front-Line Management of T-ALL

Cog Aall0434

Nelarabine is a nucleoside metabolic inhibitor and a prodrug of ara-G, approved for the treatment of patients with T-ALL with disease that has not responded to or that has relapsed after at least 2 chemotherapy regimens. The randomized phase III COG study (AALL0434) evaluated the safety of nelarabine as part of frontline therapy, using the augmented BFM chemotherapy regimen, with or without nelarabine, and showed that the toxicity profiles were similar between patients with high-risk T-ALL who received nelarabine (n=47) and those who did not (n=47).[123] No significant differences were observed in the occurrence of neurologic adverse events between these groups, including peripheral motor neuropathy, peripheral sensory neuropathy, or CNS neurotoxicity. The incidence of adverse events such as febrile neutropenia and elevation of liver enzymes was also similar between treatment groups. These initial safety data suggest that nelarabine may be better tolerated in frontline regimens than in the R/R setting.[123]

Results from the efficacy phase of this study evaluated data from 1,562 patients with newly diagnosed T-ALL.[147] Patients were randomized to receive Capizzi-MTX or HD-MTX with leucovorin rescue. Patients with intermediate- and high-risk T-ALL

PRINCIPLES OF SYSTEMIC THERAPY[a,b]

Regimens for T-ALL[f,g,h,i]

Regimen Components and Risk Stratification Applications on PEDALL-G (6 of 13)

Preferred	Other Recommended Regimens
• Clinical trial	• COG AALL1231 regimen[b,d,j,13] • COG AALL0434 regimen[b,d,j,14] • DFCI-ALL Protocol 16-001[e] (based on DFCI ALL protocol 11-001[5,6]) • SJCRH regimen based on Total Therapy XVII Regimen[e]

Regimens for Infant ALL[c]

Regimen Components and Risk Stratification Applications on PEDALL-G (6 of 13)

Preferred	Other Recommended Regimens
• Clinical trial	• Interfant regimens ± blinatumomab[15-19]

[a] All regimens include CNS prophylaxis with systemic therapy (MTX, cytarabine) and/or IT therapy (IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).
[b] See Pharmacogenomics (PEDALL-H*) for recommended dosing alterations for 6-MP and 6-TG.
[c] Blinatumomab may be incorporated into frontline therapy as a postremission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673; Topp MS, et al. J Clin Oncol 2011;29:2493-2498; Litzow MR, et al. Blood 2022;140(Suppl):Abstract LBA-1. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557Orig1s028Correctedlbl.pdf.
[d] This regimen contains 6-TG as a part of delayed intensification. For full details on other systemic agents incorporated into all phases of therapy, such as induction/induction IA, consolidation/induction IB, interim maintenance phases, intensification phases, delayed intensification, continuation phases, and maintenance, see References.
[e] Ongoing clinical trials from multi-institutional or cooperative group studies.
[f] Incorporation of nelarabine is reasonable post-induction for all patients with T-ALL, especially those who are MRD+ or have CNS disease at diagnosis. Strongly consider including nelarabine in post-induction therapy for patients who do not achieve CR after induction therapy.
[g] CNS-directed therapy with IT chemotherapy is recommended during all phases of therapy in all patients.
[h] Cranial radiation should be strongly considered for CNS-3 patients and is reasonable for other patients with high-risk T-ALL.
[i] The Panel believes it is reasonable to use bortezomib with BFM backbone chemotherapy in patients with pediatric T-LL, because it was shown to improve EFS/OS in T-LL but not leukemia (Teachey DT, et al. J Clin Oncol 2022;40:2106-2118).
[j] It is reasonable to transition patients treated with AALL1231 induction to the AALL0434 backbone with nelarabine post-induction.

*Available online, in these guidelines, at NCCN.org.

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Figure 11. PEDALL-G 2 of 13. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

received prophylactic or therapeutic cranial irradiation and were also randomized into arms with or without nelarabine (650 mg/m^2/day). The 4-year DFS rate for patients with T-ALL in the nelarabine arm (n=323) versus those who did not receive nelarabine (n=336) was 88.2% ± 2.4% and 82.1% ± 2.7%, respectively (*P*=.029). Patients treated with Capizzi-MTX plus nelarabine had the most superior 5-year DFS of 91%. The addition of nelarabine led to significantly fewer isolated and combined CNS relapses (1.3% ± 0.63% vs 6.9% ± 1.4%, respectively, *P*=.0001).

Another report from the COG AALL0434 study investigated the impact of 2 different approaches to MTX intensification on pediatric T-ALL outcomes.[59] All patients without CNS3 disease or testicular leukemia were randomized to receive an augmented BFM chemotherapy regimen with either Capizzi-MTX (n=519) or HD-MTX (n=512) during the 8-week interim maintenance phase.[59] The estimated 5-year DFS and OS rates in the Capizzi-MTX group were significantly higher than observed in the HD-MTX group, at 91.5% versus 85.3%, respectively (*P*=.005) and 93.7% versus 89.4%, respectively (*P*=.04).[59] These data demonstrate that the Capizzi-MTX is superior to the HD-MTX regimen in patients with T-ALL.[59]

COG AALL *1231*

The randomized phase III COG AALL1231 trial evaluated the efficacy of the proteasome inhibitor bortezomib in children and young adults with newly diagnosed T-ALL/LL.[122] Patients were randomized to receive a modified BFM backbone with or without bortezomib during induction and DI. The BFM backbone was modified to intensify CNS-directed systemic therapy, as the trial also aimed to reduce the use of prophylactic cranial irradiation. For patients with T-ALL, the 4-year EFS and OS rates were similar for those who received bortezomib versus those who did not (EFS, 82.9% ± 2.4% vs 81.5% ± 2.5%; *P*=.396; OS, 87.9% ± 2.1% vs 88.3% ± 2.1%; *P*=.469). For T-LL, however, EFS and OS rates were significantly improved with the addition of bortezomib (EFS, 86.4% ± 4.0% vs 76.5% ± 5.1%; *P*=.041; OS, 89.5% ± 3.6% vs 78.3% ± 4.9%; *P*=.009). Rates of peripheral neuropathy and grade 4+ pulmonary toxicity did not differ significantly between the 2 arms. Comparison of patients treated on COG AALL0434 who received cranial irradiation and patients treated on COG AALL1232 who did not receive cranial irradiation revealed similar EFS and OS rates (*P*=.412 and .600, respectively).

DFCI ALL Consortium Protocols 05-001 and 11-001

In the DFCI ALL Consortium Protocol 05-001, pediatric patients (aged 1–18 years) with newly diagnosed T-ALL were treated as high risk regardless of other presenting features (n=69).[58] The 5-year EFS and OS rates were 87% and 91%, respectively.

The DFCI ALL Consortium Protocol 11-001, as previously discussed in "Front-Line Management of BCR::ABL1-Negative or BCR::ABL1-Like ALL," also included pediatric patients with newly diagnosed T-ALL.[113] A total of 123 patients with T-ALL were enrolled in the DFCI ALL Consortium Protocols 05-001 and 11-001 combined and the 5-year EFS and OS rates for patients with T-ALL in both studies combined were 81% (95% CI, 73%–87%) and 90% (95% CI, 83%–94%), respectively.[148]

PRINCIPLES OF SYSTEMIC THERAPY

Regimen Components[a,i,k]

T-ALL	Induction	Consolidation
COG AALL1231 regimen[b,d,n,13]	Dexamethasone, vincristine, pegaspargase/calaspargase,[l] daunorubicin[n]; IT therapy: cytarabine and MTX	Cyclophosphamide, cytarabine, mercaptopurine,[b] pegaspargase/calaspargase,[l] vincristine[n]; IT therapy: MTX
COG AALL0434 regimen[b,d,14]	Prednisone, vincristine, pegaspargase/calaspargase,[l] daunorubicin; IT therapy: cytarabine and MTX	Cyclophosphamide, cytarabine, mercaptopurine,[b] pegaspargase/calaspargase,[l] vincristine, nelarabine; IT therapy: MTX
DFCI ALL 16-001[e] **based on DFCI-ALL Protocol 11-001**	Dexamethasone, vincristine, pegaspargase/calaspargase,[l] doxorubicin; IT therapy: cytarabine then ITT[a]	Cyclophosphamide, cytarabine, mercaptopurine,[b] IT therapy: MTX or ITT[a]
SJCRH regimen based on Total Therapy XVII regimen[e]	Prednisone, vincristine, pegaspargase/calaspargase,[l] cyclophosphamide, daunorubicin, mercaptopurine,[b] cytarabine[o]; ITT[a]	High-dose MTX, mercaptopurine,[b] pegaspargase/calaspargase[l]; ITT[a]

Infant ALL	Induction	Consolidation[p,q]
Interfant regimens[c,15-17]	Prednisone, dexamethasone, vincristine, cytarabine, daunorubicin, pegaspargase/calaspargase,[l] MTX; IT therapy: cytarabine, prednisone (if initial CNS involvement, MTX, prednisone) ± blinatumomab (*KMT2A* rearranged)	Intermediate-risk and HR arms: Chemotherapy consolidation: cyclophosphamide, mercaptopurine,[b] cytarabine, MTX, prednisone, pegaspargase/calaspargase[l,15] Post-consolidation, and HR arm not undergoing HCT: Dexamethasone, 6-TG,[b] vincristine, cytarabine, daunorubicin, pegaspargase/calaspargase,[l] cytarabine, prednisone, cyclophosphamide, MTX, mercaptopurine[b,15]
		LR arm: Identical approach as pediatric ALL risk-stratified chemotherapy based on genetics and MRD response (see PEDALL-J) or interfant consolidation (see above)

Risk groups: low risk (LR), high risk (HR).

Footnotes on PEDALL-G 6A

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Figure 12. PEDALL-G 6 of 13. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

Low MRD ($<10^{-4}$) at end of induction, assessed by PCR, correlated to superior DFS. Compared with non-ETP phenotype, ETP phenotype was associated with inability to achieve CR, but not with inferior OS.

Hematopoietic Cell Transplant

In a retrospective analysis of the ALL BFM 90 and 95 trials evaluating the impact of chemotherapy alone versus allogeneic HCT in pediatric patients with T-ALL, Schrauder et al[149] reported a significant improvement in 5-year DFS and OS with allogeneic HCT versus chemotherapy alone in CR1. However, HCT in CR1 is not indicated in the contemporary protocols, except for certain patients as described in the HCT sections (see Figure 7 through Figure 9).

Management of R/R T-ALL

Most T-ALL disease recurs within 2 years of diagnosis, and successful remission induction is a significant challenge in R/R T-ALL.[38] Based on trials referenced in the algorithm, the management of R/R T-ALL is summarized below.

Nelarabine-Based Regimens

Nelarabine is a nucleoside analog that is currently approved for the treatment of patients with T-ALL who have unresponsive or relapsed disease after at least two chemotherapy regimens. A phase II study of nelarabine monotherapy in children and adolescents with R/R T-ALL or T-cell non-Hodgkin lymphoma (n=121) showed a 55% response rate among the subgroup with T-ALL with first bone marrow relapse (n=34) and a 27% response rate in the subgroup with a second or greater bone marrow relapse (n=36).[146] Major toxicities included grade 3 or higher neurologic (both peripheral and CNS) adverse events in 18% of patients. Nelarabine as single-agent therapy was also evaluated in AYAs and adults (≥16 years of age) with R/R T-ALL or T-LL in a phase II study (n=39; median age, 34 years; range, 16–66 years; median 2 prior regimens; T-ALL, n=26).[150] The CR rate (including CRi) was 31%; an additional 10% of patients experienced a partial remission. The median DFS and OS were both 20 weeks and the 1-year OS rate was 28%. Grade 3 or 4 myelosuppression was common, but only one case of grade 4 CNS toxicity (reversible) was observed.[150]

In a phase I trial, NECTAR, the efficacy and safety of nelarabine in combination with etoposide and cyclophosphamide was evaluated in children with R/R T-ALL or T-LL (n=23).[151] Of evaluable patients with R/R T-ALL (n=12), a 33% response rate was observed.

Bortezomib-Based Regimens

The COG AALL07P1 phase II study tested the hypothesis that adding bortezomib to reinduction chemotherapy in pediatric patients experiencing first relapse would increase CR2 rates.[152] Of the evaluable patients treated with bortezomib and chemotherapy (n=135; B-ALL, n=103; T-ALL, n=22; T-LL, n=10), overall CR2 rates were 68% ± 5% for patients with precursor B-ALL (<21 years of age), 63% ± 7% for very early relapse (<18 months from diagnosis), and 72% ± 6% for early relapse (18–36 months from diagnosis). The CR2 rate for patients with relapsed T-ALL

FOOTNOTES

[a] All regimens include CNS prophylaxis with systemic therapy (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).
[b] See Pharmacogenomics (PEDALL-H*) for recommended dosing alterations for 6-MP and 6-TG.
[c] Blinatumomab may be incorporated into frontline therapy as a postremission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673; Topp MS, et al. J Clin Oncol 2011;29:2493-2498; Litzow MR, et al. Blood 2022;140(Suppl):Abstract LBA-1. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557Orig1s028Correctedlbl.pdf.
[d] This regimen contains 6-TG as a part of delayed intensification. For full details on other systemic agents incorporated into all phases of therapy, such as induction/induction IA, consolidation/induction IB, interim maintenance phases, intensification phases, delayed intensification, continuation phases, and maintenance, see References.
[e] Ongoing clinical trials from multi-institutional or cooperative group studies.
[i] The Panel believes it is reasonable to use bortezomib with BFM backbone chemotherapy in patients with pediatric T-LL, because it was shown to improve EFS/OS in T-LL but not leukemia (Teachey DT, et al. J Clin Oncol 2022;40:2106-2118).
[k] For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; IM I; and interim maintenance I and II, see References.
[l] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multiagent chemotherapeutic regimen to complete the full treatment course.
[n] It is reasonable to transition patients treated with AALL1231 induction to the AALL0434 backbone with nelarabine post-induction.
[o] Patients treated on the high-risk arm of St. Jude Children's Research Hospital (SJCRH) TXVII receive an intensification phase after induction prior to consolidation.
[p] IT therapy: cytarabine, prednisone (if initial CNS involvement, MTX, prednisone).
[q] For patients with MRD ≥$5x10^{-4}$ at the EOI, myeloid type consolidation therapy (eg, ADE/MAE) can be considered (Stutterheim J, et al. J Clin Oncol 2021;39:652-662).

*Available online, in these guidelines, at NCCN.org.

PEDALL-G 6A OF 13

Figure 13. PEDALL-G 6A of 13. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

was 68% ± 10%. COG considers any T-ALL relapse as high-risk, regardless of site or timing.[87]

UK ALLR3

The UK ALLR3 trial investigated the outcomes of pediatric patients with relapsed ALL aged 1 to 18 years (n=212 total patients randomized, 24 of which had relapsed T-ALL).[153] Patients were stratified into standard-, intermediate-, or high-risk groups based on the duration of CR1, site of relapse, and immunophenotype. All patients with T-ALL with isolated bone marrow and combined relapses were considered high-risk. For patients with isolated extramedullary relapse, very early (<18 months from first diagnosis), early (≥18 months from diagnosis and <6 months from completing therapy), and late (≥6 months from completing therapy) relapses were considered high-risk, intermediate-risk, and standard-risk, respectively. In addition, patients were randomized to receive mitoxantrone or idarubicin on days 1 and 2 of induction. After three blocks of therapy, all patients in the high-risk group and patients in the intermediate-risk group with postinduction high MRD ($\geq 10^{-4}$ cells) received HCT. The estimated 3-year PFS and OS rates in the mitoxantrone versus idarubicin groups in the whole cohort were 64.6% versus 35.9% (P=.0004) and 69% versus 45.2% (P=.004), respectively.

ALL-REZ BFM 90

ALL-REZ BFM 90 (ALL-REZ BFM 90) trial was designed to improve prognosis for pediatric patients with relapsed ALL (<19 years of age; n=525) through additional multichemotherapy blocks.[154] The patients were stratified into 3 risk groups: A (early bone marrow relapses; n=126); B (late bone marrow relapses; n=183); and C (isolated extramedullary relapses; n=64). Patients with early bone marrow or T-ALL relapse (poor prognosis group/PPG; n=152) were eligible for experimental regimens. After treatment with this regimen, 440 patients (84%) experienced CR2, 25 patients died during induction, and 60 patients (11%) did not experience a response. A majority of patients in groups A, B, and C experienced CR2 (Group A: 83%; Group B: 94%; and Group C: 100%), compared with 65% in group PPG. In addition, 117 patients received HCT in CR2. Significant differences existed between strategic groups: probability of EFS (pEFS)(A) = 0.17±0.03; pEFS(B) = 0.43±0.04; pEFS(C) = 0.54±0.06; pEFS(PPG) = 0.15±0.03; log-rank P<.001.[154] Significant predictors of EFS in multivariate analyses included time point, site of relapse, immunophenotype, and HCT.

Venetoclax-Based Regimens

As mentioned previously, in a phase I open-label study, venetoclax combined with dexamethasone, vincristine, and pegaspargase revealed an ORR of 56% in patients <25 years of age with R/R ALL.[155] For a summary, refer to "Management of Relapsed or Refractory BCR::ABL1-Negative or BCR::ABL1-Like ALL" (available in these guidelines at NCCN.org).

Another study retrospectively evaluated the efficacy and safety of venetoclax combined with various chemotherapy regimens in adult patients with R/R T-ALL, including patients with ETP ALL.[156] Of evaluable patients (n=10), 6 (60%) experienced a remission with <5% bone marrow blasts.

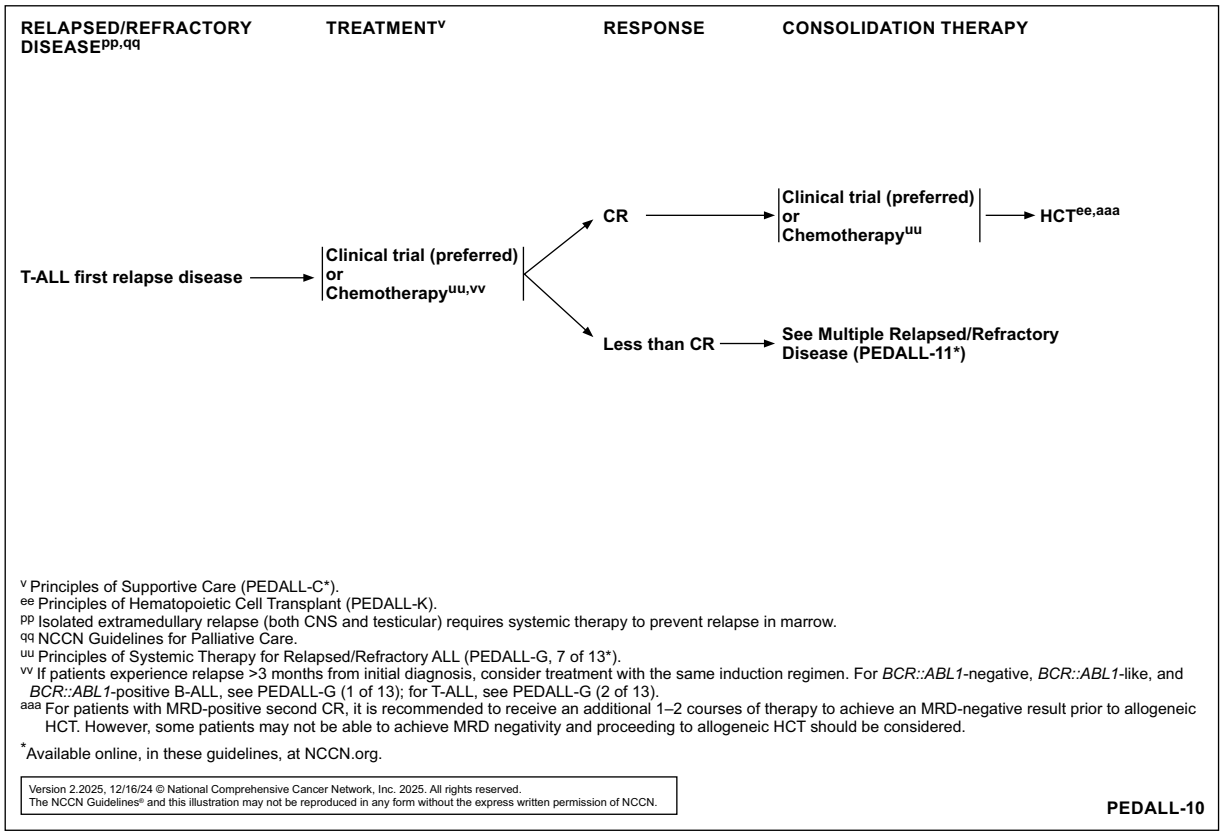

Figure 14. PEDALL-10. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

Daratumumab-Based Regimens

The phase II, open-label DELPHINUS study evaluated the anti-CD38 monoclonal antibody daratumumab combined with vincristine, prednisone, pegaspargase, and doxorubicin in patients with R/R T-ALL/LL.[157] Among 24 pediatric patients with T-ALL who were 1 to17 years of age, ORR (CR + CRi) was 83.3%, with 41.7% experiencing MRD negativity.

Revumenib

In the ongoing phase II AUGMENT-101 study, the safety and efficacy of the oral menin inhibitor revumenib was evaluated in adult and pediatric patients ≥30 days old (n=94; 57 with efficacy-evaluable data; age range, 1.3–75 years) with primary refractory or relapsed *KMT2Ar* acute leukemia, including 14 patients with ALL.[158] Many patients (43.6%) had received ≥3 prior lines of therapy and 50% of patients had undergone prior allogeneic HCT. Patients received revumenib 163 mg (or 95 mg/m^2 for those weighing <40 kg) every 12 hours in 28-day continuous cycles. Dose of revumenib could be increased to 276 mg (or 160 mg/m^2 if weight <40 kg) if no concomitant strong CYP3A4 inhibitor was being utilized; however, this did not occur on study and is rare in R/R acute leukemia, as most patients require fungal prophylaxis with azoles. Among patients with evaluable data, the CR/CRh rate was 22.8%. ORR was 63.2% with 68.2% of patients with available data achieving MRD negativity. Among those who experienced response, 38.9% were able to proceed to allogeneic HCT and half of these patients receive revumenib maintenance therapy following HCT. The most common adverse effects were nausea/vomiting/diarrhea, febrile neutropenia (grade ≥3 febrile in 37.2% of patients, and edema. Grade ≥3 differentiation syndrome occurred in 16% of patients and grade ≥3 QTc prolongation occurred in 13.8% of patients.

Based on thse data, the FDA approved revumenib for R/R acute leukemia with a *KMT2A* translocation in adult and pediatric patients ≥1 year.

Hematopoietic Cell Transplant

HCT is the only curative treatment of R/R T-ALL, but this requires successful remission induction and the data are limited.[38] In the COG AALL01P2 study, most patients with T-ALL (n=5 of 7) did not experience CR2.[159] In the combined cohort of patients with high-risk relapsed ALL who were enrolled in ALLR3 or ALL-REZ BFM 2002, 10-year EFS for those with B-ALL and T-ALL were 22.6% and 26.2%, respectively.[160] Ten-year OS was 32.6% and 28.2%, respectively. Achievement of "MRD good response" (10^{-4} at EOI or 10^{-3} at EOI with MRD $<10^{-4}$ during consolidation or pretransplant) was associated with superior DFS (57.4% vs 22.6%; $P<.0001$) and OS (57.8% vs 32.0%; $P=.0004$). For B-ALL and T-ALL, post-HCT DFS and OS were 42.1% and 56.8% and 51.6% and 55.4%, respectively. The cumulative incidences of post-HCT relapse for B-ALL and T-ALL were 36.9% and 17.8% ($P=.012$), respectively, while the cumulative incidences of death were 10.7% and 25.5% ($P=.013$), respectively.

PRINCIPLES OF SYSTEMIC THERAPY

Regimens for Relapsed/Refractory ALL[r,s]
T-ALL[a]

Preferred	Other Recommended Regimens
• Clinical trial	• Nelarabine-containing regimen: eg, nelarabine, cyclophosphamide, and etoposide[43] • Bortezomib-containing regimen: eg, bortezomib, vincristine, doxorubicin, pegaspargase/calaspargase,[l] and prednisone or dexamethasone[27] • UKALL R3 Block 1: dexamethasone, mitoxantrone, pegaspargase/calaspargase,[l] and vincristine[24] • BFM Intensification Block 1: high-dose MTX, high-dose cytarabine, dexamethasone, vincristine, pegaspargase/calaspargase,[l] and cyclophosphamide[26] • Venetoclax-containing regimen: eg, venetoclax, vincristine, pegaspargase/calaspargase,[l] and prednisone or dexamethasone[41,44] • Daratumumab-containing regimen: eg, daratumumab, vincristine, pegaspargase/calaspargase,[l] doxorubicin, and prednisone or dexamethasone[y] • Consider TKI-based regimen if *ABL*-class translocation

[a] All regimens include CNS prophylaxis with systemic therapy (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).
[l] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multiagent chemotherapeutic regimen to complete the full treatment course.
[r] Principles of Hematopoietic Cell Transplant (PEDALL-K).
[s] Guidelines for managing specific sites of extramedullary relapse (ie, testicular) are included in the protocols listed.
[y] Clinical trial recently completed and full manuscript is pending publication [Hogan LE, et al. J Clin Oncol 2022;40(Suppl):Abstract 10001].

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Figure 15. PEDALL-G 9 of 13. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

NCCN Recommendations for T-ALL

Front-Line Management

The panel recommends that pediatric and AYA patients with T-ALL be treated in a clinical trial when possible. In the absence of an appropriate clinical trial, patients are treated with chemotherapy (see Figure 10). Recommended chemotherapy regimen options include the COG AALL1231 regimen[122], the COG AALL0434 regimen[123], DFCI-ALL protocol 16-001 (NCT03020030; based on DFCI ALL protocol 11-001[113]), or the SJRCH Total Therapy XVII regimen (NCT03117751; based on the Total Therapy XVI regimen[161]). It is reasonable to transition patients treated with COG AALL1231 induction to the COG AALL0434 backbone with nelarabine postinduction. The panel believes it is reasonable to use bortezomib with BFM backbone chemotherapy in patients with pediatric T-LL, because it was shown to improve EFS/OS in T-LL but not leukemia (see Figures 11, 12, and 13).[122] After a response assessment, patients at standard or high risk continue consolidation chemotherapy (see Figure 10). The features that define standard risk in this context are day 29 MRD <0.01%, CNS-1, absence of testicular disease, and no steroid pretreatment. Patients at very high risk have end consolidation MRD >0.1%. Patients at high risk in this context do not exhibit any standard- or very-high-risk factors. Patients who have very-high-risk features may continue chemotherapy or pursue alternative therapy and consider HCT as part of consolidation therapy. However, it is recommended that additional therapy be given to achieve MRD negativity prior to HCT.

R/R Management

For pediatric and AYA patients with T-ALL experiencing first relapse, the panel recommends initial treatment with clinical trial or systemic therapy (see Figure 14). Recommended systemic therapy regimen options include nelarabine-containing regimens (eg, nelarabine, cyclophosphamide, and etoposide)[151], bortezomib-containing regimens (eg, bortezomib, vincristine, doxorubicin, pegaspargase/calaspargase, and prednisone or dexamethasone)[152], the UK ALLR3 Block 1 (dexamethasone, mitoxantrone, pegaspargase/calaspargase, and vincristine)[153], the BFM Intensification Block 1 (high-dose MTX, high-dose cytarabine, dexamethasone, vincristine, pegaspargase/calaspargase, and cyclophosphamide)[154], venetoclax-containing regimens (eg, venetoclax, vincristine, pegaspargase/calaspargase, and prednisone or dexamethasone)[155,156], or daratumumab-containing regimens (eg, daratumumab, vincristine, pegaspargase/calaspargase, doxorubicin, and prednisone or dexamethasone) (see Figure 15).[162] TKI-based regimens can be considered in the setting of an *ABL*-class translocation. Revumenib can be considered for R/R *KMT2Ar* T-ALL.[159]

If patients experience CR2, consolidation therapy with systemic therapy should be continued with HCT (see Figure 11). If patients experience less than CR (ie, multiple relapse), treatment options include systemic therapy, and patients may receive HCT as consolidation therapy if their disease subsequently responds to therapy (see Figure 16). If the disease does not respond to therapy, alternative treatment options may be considered with best supportive and palliative care.

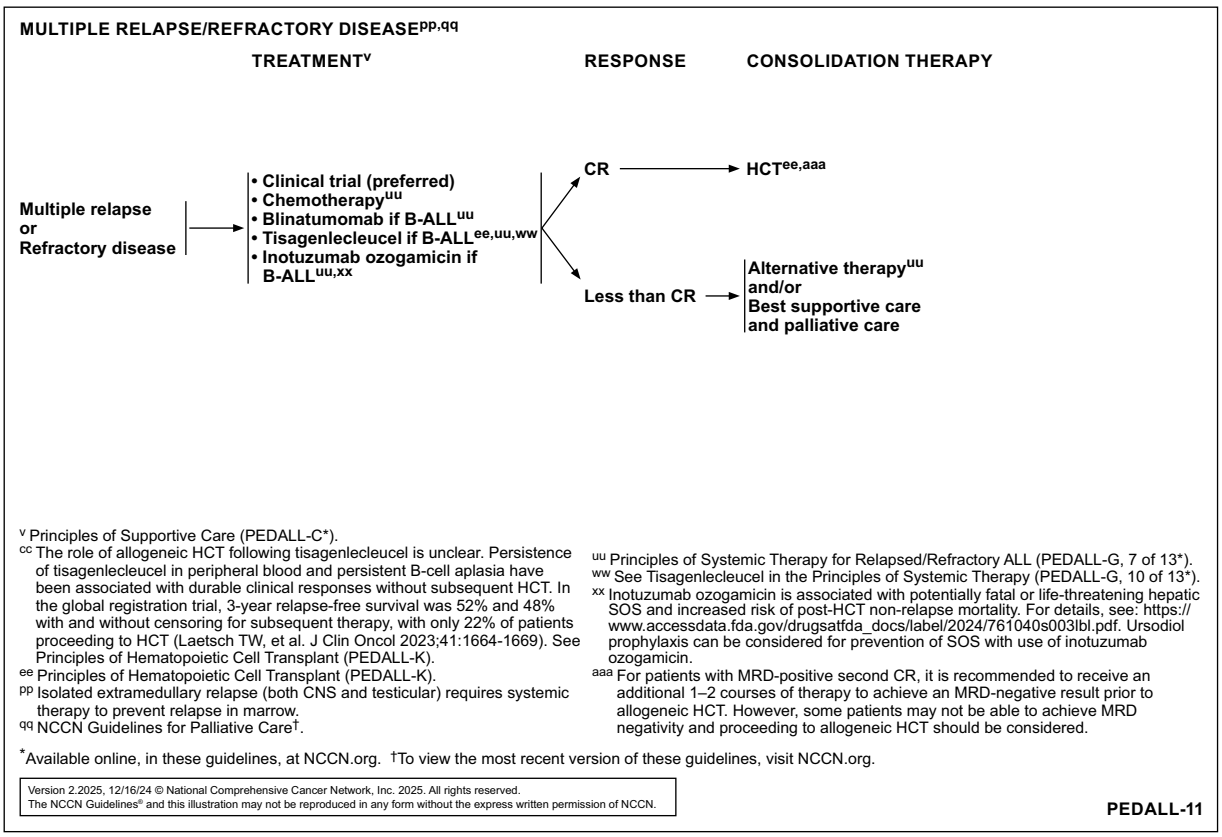

Figure 16. PEDALL-11. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025.

Summary

The management of pediatric T-ALL includes intensive and complex multiagent chemotherapy regimens. Regimens are largely broken down into 3 treatment phases: (1) induction, with regimens typically comprised of a backbone that includes vincristine, corticosteroids, and asparaginase, with or without an anthracycline; (2) consolidation, the MRD response to which is the important prognostic factor, and this phase is followed by interim maintenance and delayed intensification (reinduction) therapy, and (3) maintenance therapy, which aims to prevent disease relapse. The NCCN Pediatric ALL Panel recommends that patients with T-ALL be treated at a specialized cancer center with expertise in the management of ALL given the complexity of therapy.

Over the past several decades, the cure rates and survival outcomes for patients with T-ALL have improved dramatically, primarily among children, largely due to greater understanding of the genetics and pathogenesis of the disease, utilization of risk-adapted therapy, incorporation of allogeneic HCT, improved supportive care, and the advent of targeted therapy, such as nelarabine for T-ALL.

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