

# Pediatric Leukemia: Advances in Diagnosis and Treatment Strategies

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## Abstract

Pediatric leukemia remains a significant challenge in oncology, despite advancements in diagnosis and treatment. The heterogeneity of the disease and disparities in outcomes across demographic and socioeconomic factors underscore the need for continued research and improved strategies. This review examines recent developments in diagnostic techniques and treatment approaches for pediatric leukemia, focusing on acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Diagnostic techniques have evolved to include minimal residual disease (MRD) detection using flow cytometry, qPCR, and next-generation sequencing (NGS), improving sensitivity and accuracy in detecting leukemic cells. Novel imaging technologies and spectroscopy techniques offer non-invasive alternatives for visualizing leukemic cells and detecting central nervous system (CNS) involvement. Genomic analysis has enhanced prognostic prediction and enabled risk-adjusted chemotherapy, reducing relapse rates. Treatment strategies have shifted towards more targeted and personalized approaches, with immunotherapy, particularly chimeric antigen receptor (CAR-T) cell therapy, showing promise for refractory or relapsed cases. Targeted therapies like tyrosine kinase inhibitors have been integrated into standard protocols for specific genetic subtypes. Novel agents such as venetoclax, menin inhibitors, and homoharringtonine are being explored, with the latter showing improved remission rates and survival when used in induction therapy. Future research should focus on addressing challenges such as data variability, model scalability, and unequal access to advanced technologies. Continued innovation is essential to expand the use of these diagnostic and treatment methods globally. Overcoming cost and infrastructure barriers, particularly in low- and middle-income countries (LMICs), will be crucial for the widespread application of these advancements in pediatric leukemia care.

**Keywords:** Diagnosis, Immunotherapy, Leukemia, Pediatric, Prognosis, Treatment

## Introduction

Leukemia, a heterogeneous group of hematological malignancies, represents a significant cause of morbidity and mortality in children worldwide [1-3]. While advancements in treatment have improved survival rates over the past four decades [4], disparities persist across various demographic and socioeconomic factors [5-7]. This section examines the current prevalence and mortality statistics of pediatric leukemia, highlighting these crucial differences and exploring associated risk factors.

The prevalence of leukemia varies significantly across geographical regions and populations. A cross-sectional study conducted in Yemen found a prevalence of leukemia among children treated at Al-Kuwait Hospital in Sana'a City, with a notable association between leukemia and younger age groups, particularly males [1]. Another study in Ethiopia reported a lower prevalence of childhood cancer overall, with leukemia being one of the identified cancer types, though the limited data emphasizes the need for better documentation in developing countries [8]. In contrast, a study in Saudi Arabia demonstrated a higher incidence of B-cell ALL (B-ALL) among pediatric hematological malignancies in Al-Madinah Al-Munawwarah [9]. This variation underscores the need for region-specific epidemiological studies to accurately assess prevalence. Studies employing open-source pediatric algorithms in Colorado, Massachusetts, and New Hampshire, while encompassing a broader range of childhood medical complexities, reveal a prevalence of children with medical complexity ranging from 0.67% - 11.44%, with children with medical complexity exhibiting significantly greater odds of mortality [10]. These differences in prevalence highlight the influence of access to healthcare and diagnostic capabilities. A study in Kazakhstan leveraged nationwide healthcare data to demonstrate an incidence rate of hematological malignancies of 6.8 per 100,000 in 2021, with ALL exhibiting a higher incidence than AML [11]. Further studies suggest that socioeconomic status may be correlated with higher prevalence rates although outcomes may be similar [12].

Pediatric cancer mortality, while decreasing overall [4], remains a concern. Leukemia and brain cancer consistently rank among the leading causes of death from pediatric cancer [4]. Studies reveal that mortality rates are associated with specific leukemia subtypes and age groups [1, 13]. For instance, AML shows higher mortality rates in younger children compared to older children [11], while neurological manifestations in acute leukemia patients are significantly linked to increased mortality [13]. In addition, septic shock and bloodstream infections due to multidrug-resistant

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organisms (MDROs) are identified as major risk factors for mortality in pediatric oncology patients, particularly those with febrile neutropenia [13]. A study analyzing ventriculostomy-related infections further highlights that infection can be a significant contributor to mortality in children requiring this procedure [14]. Data from a designated cancer center reveal that certain oncologic diagnoses (such as AML, neuroblastoma, and desmoplastic small round cell tumor) exhibit increased *Clostridioides difficile* infection (CDI) risk, resulting in higher mortality rates amongst severe CDI cases [15].

Several risk factors contribute to both the prevalence and mortality of pediatric leukemia. Younger age and male gender show a significant association with leukemia diagnosis [1]. Specific genetic predispositions, environmental exposures (like benzene) [16], and infections during treatment also play a role [17]. Access to quality healthcare, including timely diagnosis and treatment, influences outcomes significantly [4, 18]. Socioeconomic factors also impact both the prevalence [12] and potentially the mortality [4], highlighting existing health disparities. Other factors impacting mortality include neurological involvement [13], septic shock [19], and the development of infections including MDROs and CDI [15, 19].

Pediatric leukemia, particularly ALL and AML, remains a significant challenge in pediatric oncology (Table 1). Recent advances in diagnostic techniques and treatment strategies have improved outcomes for many children, yet challenges persist, particularly in high-risk populations. This article reviews the latest developments in the diagnosis and treatment of pediatric leukemia, focusing on ALL and AML.

## Advancements in Diagnostic Techniques

The diagnosis of pediatric leukemia has evolved significantly, with the integration of advanced genetic and molecular techniques [20, 21]. Advances in MRD detection using flow cytometry, quantitative polymerase chain reaction (qPCR), and NGS have improved the sensitivity and accuracy of detecting leukemic cells, enabling early relapse detection and personalized treatment adjustments [22, 23]. For instance, NGS has become a pivotal tool in characterizing childhood AML, allowing for the identification of recurrent mutations that can inform treatment strategies. A study demonstrated that NGS of over 150 cancer-related genes in pediatric AML patients revealed critical genetic alterations, which could serve as potential targets for therapy [24]. In the context of ALL, the immune microenvironment plays a crucial role in disease progression and treatment response. Research has shown that the remodeling of the bone marrow immune microenvironment is associated with the survival of B-ALL patients, highlighting the importance of immune profiling in diagnosis and treatment planning [25]. Furthermore, the identification of specific cytogenetic abnormalities, such as those found in mixed-phenotype acute leukemia, is essential for accurate diagnosis and treatment assignment [26].

Molecular techniques like reverse transcription PCR (RT-PCR) have demonstrated superior sensitivity and rapid turnaround times in diagnosing specific leukemia types, such as t(9;22)-positive leukemias, especially in low-resource settings. This allows for earlier treatment initiation, which is critical for managing aggressive leukemias [27]. The study evaluated three diagnostic methods: RT-PCR, fluorescence in situ hybridization, and karyotyping, among a sample of 23 patients. RT-PCR showed a remarkable sensitivity of 100%, making it the most effective diagnostic tool in this context. It also had the shortest turnaround time of just 7 days, which is crucial for timely treatment initiation. Both fluorescence in situ hybridization and karyotyping were found to have moderate performance levels. They were less accurate and had longer delays in providing results compared to RT-PCR. This indicates that while they can be useful, they are not as efficient in urgent clinical settings. The ability of RT-PCR to deliver rapid and reliable results allows for earlier treatment initiation. This is particularly important for managing aggressive leukemias, where time is a critical factor in improving patient outcomes. By adopting RT-PCR as the primary diagnostic tool in LMICs, healthcare systems can reduce overall treatment costs. This is achieved by minimizing diagnostic delays, which can lead to more timely and effective treatment decisions. Ultimately, the study suggests that implementing RT-PCR can significantly enhance survival rates for pediatric leukemia patients in resource-limited settings. The faster and more accurate diagnosis can lead to better management of the disease. In summary, the study highlights the superiority of RT-PCR in diagnosing t(9;22)-positive leukemias, emphasizing its role in improving treatment outcomes and survival rates in pediatric patients within LMICs [27].

Emerging imaging technologies, including positron emission tomography (PET) and magnetic resonance imaging, offer non-invasive methods to visualize leukemic cells in anatomical locations that traditional methods may not access. These techniques complement molecular and flow cytometry methods, although challenges such as sensitivity and cost remain [23]. Fourier transform infrared (FTIR) spectroscopy has shown

**Table 1:** Epidemiology and risk factors of pediatric leukemia.

Region/Country	Prevalence (per 100,000)	Common subtype	Key risk factors	Mortality rate	Notes/Findings
United States	4.7	ALL	Genetic predisposition, exposure to environmental toxins, and socioeconomic disparities	~15 - 20%	Higher survival rates due to access to advanced therapies
Saudi Arabia	Higher incidence in B-ALL	B-ALL	Male gender predominance, younger age groups, and limited access to specialized care	Varies by region	B-ALL accounts for majority of pediatric leukemia cases
Ethiopia	Lower childhood cancer prevalence	AML	Poor healthcare infrastructure, lack of diagnostic tools, and low socioeconomic status	Unknown	Limited epidemiological data available
Kazakhstan	6.8	ALL > AML	Socioeconomic factors, healthcare access, and environmental factors	Higher in AML cases	AML cases show higher mortality rates than ALL cases
Yemen	Increasing prevalence	ALL	Younger age groups, lack of early diagnosis, and poor healthcare access	High	Higher mortality due to limited treatment facilities

promise in detecting CNS involvement in pediatric leukemia, offering a rapid, non-invasive, and accurate alternative to traditional diagnostic methods [28]. The results indicated that FTIR spectroscopy had a higher sensitivity in detecting biochemical markers associated with CNS involvement compared to conventional cytomorphology and automated cell counting. This suggests that FTIR can more effectively identify cases of CNS leukemia. FTIR spectroscopy was able to generate distinct spectral profiles that highlighted specific biochemical changes linked to CNS leukemia. This capability allows for a more precise identification of the disease's presence in the cerebrospinal fluid samples. When comparing FTIR to traditional methods, the study found that FTIR not only provided rapid results but also improved diagnostic accuracy. This is particularly important in clinical settings where timely diagnosis is crucial for effective treatment. The findings suggest that FTIR spectroscopy could serve as a promising alternative to conventional diagnostic methods. Its non-invasive nature and ability to deliver quick results could significantly enhance the management and treatment of pediatric leukemia patients with CNS involvement. In summary, the study supports the potential of FTIR spectroscopy as a valuable tool in the diagnosis of CNS involvement in pediatric leukemia, highlighting its advantages over traditional methods in terms of sensitivity, speed, and accuracy [28].

Genomic analysis techniques have improved the understanding of leukemic cell nature and prognostic prediction, allowing for risk-adjusted chemotherapy and reduced relapse rates. These analyses have also revealed the involvement of germline variations in leukemia treatment, further personalizing therapeutic strategies [29]. Novel biomarkers related to MRD have enabled the quantitative assessment of patient responses to treatment regimens, paving the way for personalized therapeutic strategies [30].

While these advancements have significantly improved diagnostic capabilities (Table 2), challenges such as data variability, model scalability, and unequal access to advanced technologies persist. Addressing these issues is crucial for the global application of these diagnostic techniques. Additionally, the integration of these technologies into routine clinical practice requires overcoming cost and infrastructure barriers, particularly in LMICs [31, 32]. Continued innovation and research are essential to expand the use of these methods, ensuring more effective and tailored approaches to pediatric leukemia diagnosis.

### Innovative Treatment Strategies

The treatment landscape for pediatric leukemia has shifted towards more targeted and personalized approaches (Figure 1) [33]. In ALL, the use of L-asparaginase has been a cornerstone of therapy, but its associated complications, such as pancreatitis, necessitate careful management of dosage and patient selection [34]. Recent findings indicate that the incidence of asparaginase-associated pancreatitis correlates more strongly with dose intensity than cumulative dosage, suggesting that optimizing treatment protocols could reduce complications [34]. Immunotherapy, particularly CAR-T cell therapy, has emerged as a promising option for refractory or relapsed leukemia [35]. In Mexico, efforts are underway to implement CAR-T cell therapy programs, addressing the high rates of relapsed disease in pediatric leukemia patients [36]. This approach has shown

Table 2: Advances in diagnostic techniques for pediatric leukemia.

Diagnostic method	Technique	Sensitivity	Specificity	Clinical application	Advantages	Limitations
Flow cytometry	Immunophenotyping of leukemic cells	High	High	Detects MRD	Rapid analysis, widely available	May miss rare abnormal cell populations
qPCR	DNA amplification	Very high	Very high	Early relapse detection	High sensitivity for specific mutations	Limited to known genetic targets
NGS	Genomic and transcriptomic profiling	Extremely high	Extremely high	Mutation profiling, risk stratification	Identifies rare mutations, personalized treatment	Expensive, complex bioinformatics required
FTIR spectroscopy	Spectral biomarker detection	High	Moderate	Non-invasive CNS leukemia detection	Rapid, non-invasive, lower cost	Lower specificity than genetic methods
PET	Functional imaging of leukemic cells	Moderate	High	Visualizes disease in hard-to-access sites	Identifies extramedullary involvement	Expensive, requires specialized equipment

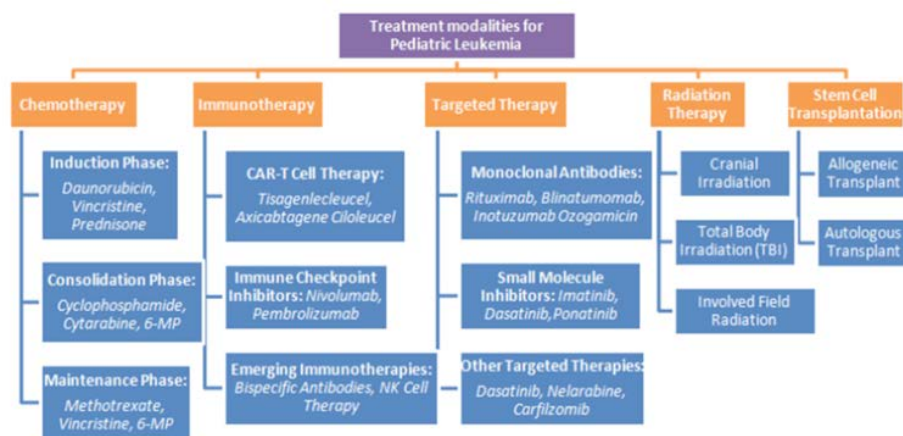


Figure 1: Overview of various treatments available for pediatric leukemia [33].

significant efficacy in clinical trials, offering hope for patients who do not respond to conventional therapies. Additionally, the role of exosomal microRNAs, such as miR-326, has been explored as potential biomarkers for drug resistance in pediatric ALL. Elevated levels of miR-326 in exosomes from patients have been associated with poor treatment response, suggesting that these molecules could serve as non-invasive diagnostic tools and therapeutic targets [37].

Immunotherapy has emerged as a promising approach, particularly for relapsed or refractory cases of pediatric leukemia. Monoclonal antibodies such as blinatumomab and inotuzumab ozogamicin, along with CAR-T cell therapies like tisagenlecleucel, have shown significant efficacy in treating B-ALL [33]. Targeted therapies, including tyrosine kinase inhibitors for Philadelphia chromosome-positive ALL, have been integrated into standard treatment protocols, improving outcomes for specific genetic subtypes [38]. Other targeted agents, such as aurora-kinase inhibitors and MEK-inhibitors, are under investigation in clinical trials [38]. Chemotherapy remains a cornerstone of pediatric leukemia treatment, with risk-adjusted regimens tailored to individual patient profiles. These regimens have been refined to reduce relapse rates and minimize complications [29]. Bone marrow transplantation, particularly allogeneic stem cell transplantation, offers a potential cure for high-risk or relapsed cases, although it carries risks such as graft-versus-host disease [33]. In pediatric AML, novel agents like venetoclax and menin inhibitors are being explored, alongside traditional chemotherapy agents in new combinations [39].

Homoharringtonine has shown promise in improving remission rates and survival in pediatric AML when used in induction therapy [40]. The study found that the complete remission (CR) rate was significantly higher in the Homoharringtonine-based induction group (H arm) compared to the etoposide-based group (E arm). Specifically, the CR rate was 79.9% in the H arm vs 73.9% in the E arm, with a p value of 0.014, indicating statistical significance. The 3 years overall survival rate was also better in the H arm, with 69.2% (95% confidence interval (CI): 65.1 - 72.9) compared to 62.8% (95% CI: 58.7 - 66.6) in the E arm. This difference was statistically significant with a p value of 0.025. The 3 years event-free survival rate was 61.1% (95% CI: 56.8 - 65.0) for the H arm and 53.4% (95% CI: 49.2 - 57.3) for the E arm, with a p value of 0.022, indicating a significant advantage for the H arm. The study highlighted that patients in the H arm, particularly those with intermediate cytogenetics, aged 1 - 10 years, or with a white blood cell count of  $\geq 50 \times 10^9/L$ , achieved improved CR rates compared to those in the E arm. Additionally, AML1-ETO-positive patients in the H arm showed enhanced survival. In the per-protocol population receiving maintenance therapy, the event-free survival did not show significant differences across the four arms (H 1 AT arm, H 1 AC arm, E 1 AC arm, and E 1 AT arm), with p values for overall survival and event-free survival being 0.0556 and 0.0872, respectively. The researchers noted limitations such as a shorter median follow-up duration in the H arm and variability in maintenance therapy choices among patients. Overall, the study concludes that the Homoharringtonine-based induction regimen may offer a better alternative for treating de novo pediatric AML, particularly for specific patient subgroups [40].

Despite these advancements, challenges such as treatment resistance, toxicity, and accessibility remain. The integration of novel therapies with existing treatment protocols continues to evolve, with ongoing research aimed at reducing adverse effects and improving long-term outcomes (Table 3) [33, 35]. Additionally, the development of nanotechnology for targeted drug delivery holds promise for enhancing treatment precision and efficacy [30]. While the advancements in pediatric leukemia treatment have been substantial, there is a continuous need for innovation to address the remaining challenges [41-43]. The integration of novel therapies and personalized treatment strategies are crucial for further enhancing survival rates and quality of life for pediatric leukemia patients [44-46]. Ongoing research and clinical trials will play a vital role in refining these approaches and overcoming current limitations.

## Challenges in Treatment

The treatment of pediatric leukemia, particularly ALL and AML, presents numerous challenges despite advancements in therapeutic strategies. These challenges include treatment resistance, toxicity, accessibility, and the emergence of MDROs [47-50]. Additionally, the complexity of leukemia's molecular and clinical heterogeneity further complicates treatment [51, 52]. For example, the presence of double Philadelphia chromosomes in B-ALL is associated with a dismal prognosis, underscoring the need for tailored treatment strategies based on genetic findings [53]. Moreover, acute complications during intensive chemotherapy, such as infections and metabolic disturbances, continue to pose significant risks to pediatric patients. A recent study highlighted that nearly 81% of patients experienced acute complications during treatment, emphasizing the need for vigilant monitoring and a multidisciplinary approach to care [54].

- Chemotherapy and immunotherapy: While chemotherapy remains the cornerstone of leukemia treatment, resistance to drugs and severe side effects such as organ dysfunction and neurocognitive impacts are significant hurdles. Immunotherapy, including CAR-T cell therapy, offers promising results but is limited by issues like antigen escape and T-cell exhaustion, which can lead to treatment failure [33, 55].

**Table 3:** Emerging targeted therapies and immunotherapies in pediatric leukemia.

Therapy	Target/Mechanism	Indication	Clinical outcome	Advantages	Challenges/Limitations
CAR-T cell therapy	CD19-targeted T cells	Relapsed/refractory ALL	High response rates (~70 to 90%), durable remissions	Effective for refractory cases, long-lasting remission	Expensive, T-cell exhaustion may occur
Venetoclax	BCL-2 inhibitor	Pediatric AML	Improved remission and survival rates	Synergistic with chemotherapy	Resistance development with prolonged use
Homoharringtonine	Protein synthesis inhibitor	Pediatric AML	Higher CR rates (79.9%)	Enhances chemotherapy effectiveness	Myelosuppression and cardiac toxicity risk
Blinatumomab	CD19/CD3 bispecific antibody	B-ALL	Prolonged survival in relapsed cases	Lower toxicity than chemotherapy	Short half-life requires continuous infusion
Menin inhibitors	Epigenetic modulator	AML with MLL rearrangements	Promising response in early trials	Targets a high-risk genetic subgroup	Limited clinical data, ongoing trials
Tyrosine kinase inhibitors	Inhibits BCR-ABL fusion protein	Philadelphia chromosome-positive ALL	Improved survival in Ph+ cases	Precision targeting	Side effects: myelosuppression, hepatotoxicity

- **Bone marrow transplantation:** This is a potential cure for high-risk or relapsed cases but carries risks such as graft-versus-host disease and infections. The long-term side effects of these treatments can include secondary malignancies and chronic health issues [33].
- **MDROs:** Intensive chemotherapy in pediatric AML can lead to severe complications, including infections by MDROs like carbapenem-resistant *Pseudomonas aeruginosa*. These infections complicate treatment and require careful management of antibiotic therapies [56].
- **Septic shock and bone marrow failure:** These are common complications during chemotherapy, necessitating a multidisciplinary approach to manage infectious risks and support bone marrow recovery [56].
- **LMICs:** In LMICs, the management of pediatric chronic myeloid leukemia is hindered by limited access to diagnostic tools and essential medications like tyrosine kinase inhibitors. This disparity highlights the need for setting-adapted guidelines and improved healthcare infrastructure [57].
- **Novel therapies:** The development and approval of new targeted therapies and immunotherapies are slow, particularly for pediatric populations. International collaboration is crucial to improve access to these therapies and enhance treatment outcomes [58].
- **AML and Down syndrome:** Pediatric AML is highly heterogeneous, with varying responses to treatment. In children with Down syndrome, the disease mechanism differs, and while initial treatment responses are favorable, relapsed cases are challenging to treat due to resistance to conventional chemotherapy [59, 60].
- **Extramedullary involvement:** This complicates diagnosis and treatment, as it requires a combination of imaging and laboratory tools for accurate detection. The prognostic significance of extramedullary involvement remains unclear, complicating treatment decisions [61].

While significant progress has been made in the treatment of pediatric leukemia (Table 4), these challenges underscore the need for continued research and innovation. The development of personalized treatment strategies, improved diagnostic tools, and international collaboration are essential to overcome these obstacles and improve patient outcomes [62-64]. Additionally, addressing the socioeconomic disparities in treatment access is crucial for equitable healthcare delivery across different regions [65, 66].

## Clinical Studies

Recent clinical studies have made significant strides in the treatment of pediatric leukemia, particularly focusing on ALL and AML. These studies have explored various therapeutic approaches, including immunotherapy, chemotherapy, and hematopoietic stem cell transplantation, to improve remission rates and overall survival in children.

Chemotherapy remains a cornerstone of treatment, with multiphase regimens tailored to individual risk profiles. High-dose cytarabine therapy has been effective in treating pediatric AML, achieving an 80% 5 years survival rate in some studies [67]. The study involved 15 pediatric patients diagnosed with AML who received high-dose chemotherapy with cytarabine. The patients were aged between 1.2 - 12 years, with a median age of 6.7 years. After treatment, the results showed an impressive 5 years overall survival rate of 80% and an event-free survival rate of 80% as well. This indicates that a significant number of patients were alive and free from disease progression 5 years after treatment. Among the 15 patients, there were two cases of disease recurrence, which accounts for 13.3% of the patients. Additionally, there was one case of death related to chemotherapy, representing 6.7% of the cohort. The study also noted that all patients experienced varying degrees of myelosuppression, which is a common side effect of chemotherapy. Symptoms included fever, myalgia (muscle pain), and bone pain, with some patients experiencing more severe reactions like chest pain and rash. The follow-up period for the patients was extensive, lasting up to 20 years, which allowed for a thorough assessment of the long-term efficacy of the treatment. The study highlighted that the majority of the patients were negative for the 43 fusion genes typically associated with leukemia, with only two cases testing positive for the AML1/ETO fusion protein. Overall, the findings suggest that high-dose chemotherapy with cytarabine is a clinically safe and effective treatment option for pediatric AML, achieving survival rates comparable to or better than those reported in other studies, despite the small sample size. The study propose that this treatment regimen could be a viable alternative, especially in settings with limited resources, due to its effectiveness and relatively low cost [67].

Enrollment in clinical trials has been associated with superior overall survival in pediatric AML patients, although disparities in trial enrollment based on sociodemographic factors have been noted [68]. The study included 342 pediatric patients diagnosed with AML, who were treated at 10 institutions in the United States between 2011 and 2018. The cohort represented three distinct frontline clinical trials: AAML1031, AML08, and

**Table 4:** Challenges and solutions in pediatric leukemia treatment.

Challenge	Description	Impact on patients	Proposed solution	Examples/Clinical insights
Treatment resistance	Relapsed/refractory cases	Poor prognosis, reduced survival rates	Combination of immunotherapy + targeted agents	CAR-T cells + tyrosine kinase inhibitors for resistance management
Chemotherapy-associated toxicity	Organ dysfunction, neurocognitive impairments	Long-term morbidity, reduced quality of life	Dose modification, supportive care	Reduced-intensity chemo regimens
Access in low-resource settings	Limited access to diagnostics and novel therapies	Higher mortality rates due to delayed treatment	International collaborations, affordable diagnostics	RT-PCR use in LMICs for faster diagnosis
Infection and septic shock	MDROs infections during chemotherapy	Increased mortality and morbidity	Improved infection control protocols, prophylaxis	Use of broad-spectrum antibiotics
Lack of clinical trial enrollment	Low participation in clinical trials	Fewer treatment options, poorer survival outcomes	Equity-focused enrollment strategies	Increased diversity in pediatric leukemia trials
Cost and accessibility of novel therapies	High cost of CAR-T and targeted agents	Limited access for LMIC patients	Financial assistance programs, local production	Expanded access to CAR-T in Mexico

AML16. The analysis revealed significant sociodemographic differences in trial enrollment. Notably, Black patients were underrepresented in the trial enrollment group (11% enrolled vs 24% not enrolled), Hispanic patients showed similar trends (24% enrolled vs 28% not enrolled), publicly insured patients also had lower enrollment rates (44% enrolled vs 55% not enrolled), and higher acuity patients (those requiring intensive care unit-level resources) were less likely to be enrolled in trials (3% enrolled vs 8% not enrolled). The study found that trial enrollment was significantly associated with improved overall survival. Unadjusted analysis showed a hazard ratio (HR) of 0.69 (95% CI: 0.47 - 0.99,  $p = 0.04$ ), indicating better survival for trial participants. However, there was no significant difference in event-free survival between the two groups (HR = 0.95, 95% CI: 0.69 - 1.31,  $p = 0.75$ ). When adjusting for various confounders using a propensity score model: The initial model accounted for 23% of the observed association between trial enrollment and overall survival. Acuity at diagnosis explained an additional 7% of the association. In fully adjusted analysis, the association between trial enrollment and overall survival was attenuated (HR = 0.93, 95% CI: 0.59 - 1.46,  $p = 0.76$ ), suggesting that other factors may also play a role in survival outcomes. The study concluded that significant sociodemographic and clinical differences exist in frontline trial enrollment for pediatric AML, which may contribute to worse overall survival outcomes for patients not enrolled in trials. The findings highlight the need for interventions to improve equity in healthcare access and to evaluate enrollment patterns in pediatric clinical trials [68].

The Associazione Italiana Ematologia/Oncologia Pediatrica (AIEOP) AML 2013 trial reported a 3 years overall survival of 83.9% and event-free survival of 68.5%, with significant improvements over previous protocols [69]. The study included 371 patients aged 0 to 18 years diagnosed with de novo AML, excluding acute promyelocytic leukemia. Patients were enrolled from June 2015 to June 2022 across 33 centers affiliated with the AIEOP group. Patients were stratified into three risk groups based on molecular/cytogenetic characteristics and MRD levels: (i) Standard risk: 19% (72 patients), (ii) Intermediate risk: 23% (81 patients), and (iii) High risk: 58% (218 patients). A remarkable 92% of patients achieved morphological CR after the two induction courses, which is an improvement compared to the previous AIEOP AML 2002 study (87%). Only 7% (25 patients) experienced primary induction failure, and there were only 3 deaths during or after the induction courses. The cumulative incidence of 3 years non-relapse mortality in continuous CR was 6.8%. Leukemia recurrence was observed in 63 patients, leading to a 3 years cumulative incidence of relapse of 18.9%. With a median follow-up of 4.5 years, the 3 years probabilities of overall survival and event-free survival were 83.9% and 68.5%, respectively. Both rates showed significant improvement compared to the AIEOP AML 2002 study ( $p < 0.01$ ). The 3 years overall survival rates were: Standard risk: 99.2%, Intermediate risk: 84.2%, and High risk: 79.4% ( $p = 0.01$ ). The 3 years estimate of disease-free survival was 74.3%, with no significant differences among the three risk groups. MRD levels after the second induction course significantly influenced event-free survival, with rates of 76% for MRD  $< 0.1\%$  and 48% for MRD  $> 0.1\%$  ( $p < 0.01$ ). Among the 160 patients who underwent allogeneic hematopoietic stem cell transplantation, the 3 years probabilities of overall survival and disease-free survival were 87.7% and 85.1%, respectively (Figure 2). These results indicate a successful approach in treating childhood AML, with improved survival rates and effective risk stratification leading to tailored therapies [69].

Decitabine combined with low-dose chemotherapy has been effective in high-risk, refractory, and relapsed AML, achieving a 3 years overall survival of 79% [70]. The study analyzed clinical data from 19 children diagnosed with AML, consisting of 10 males and 9 females. Among these, 5 cases were classified as high-risk AML, 7 as refractory AML, and 7 as relapsed AML. After one course of treatment with decitabine and low-dose chemotherapy: 15 out of 19 patients achieved CR, 3 patients experienced partial remission, and only 1 patient did not achieve any form of remission. All patients underwent allogeneic hematopoietic stem cell transplantation as a consolidation therapy following the initial treatment. The follow-up period for all cases averaged 46 months (ranging from 37 - 58 months). Cumulative 3 years overall survival rate:  $79\% \pm 9\%$ , event-free survival rate:  $68\% \pm 11\%$ , and recurrence-free survival rate:  $81\% \pm 10\%$ . The most common adverse effects observed during the treatment included: Cytopenia, which affected all 19 patients, and Infections, which were reported in 16 patients. Importantly, there were no treatment-related deaths during the therapy. The study concluded that decitabine combined with low-dose chemotherapy is a safe and effective treatment option for children with high-risk, refractory, and relapsed AML, providing a viable pathway for subsequent hematopoietic stem cell transplantation [70].

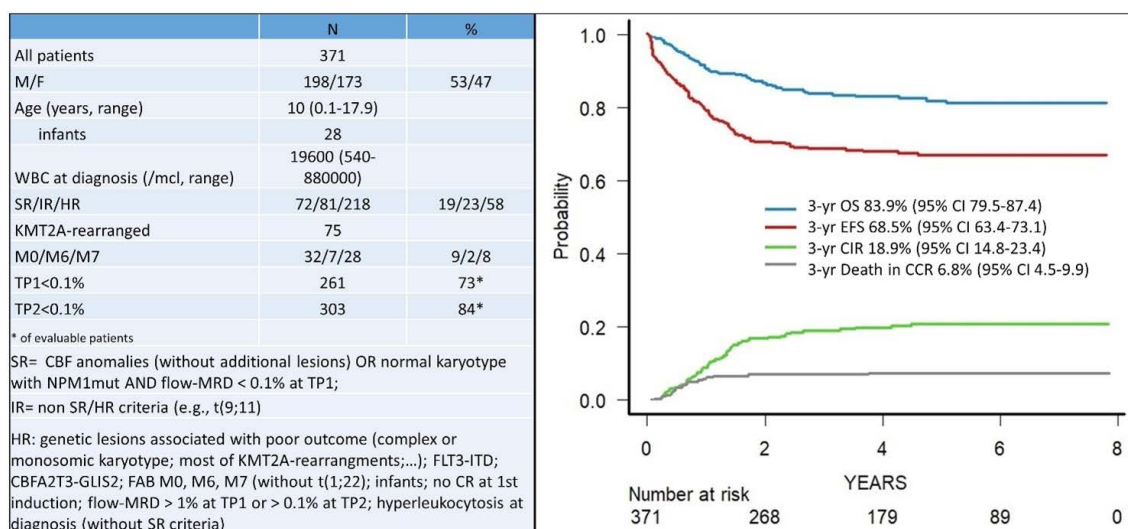


Figure 2: Treatment of children with newly diagnosed AML is based on induction therapy [69].

The therapeutic advances in childhood leukemia and lymphoma (TACL) consortium's phase 1 study on decitabine, vorinostat, and FLAG therapy showed a 65% overall response rate (ORR) in relapsed/refractory pediatric AML, particularly effective in cases with epigenetic alterations [71]. The study focused on the treatment of pediatric patients with relapsed/refractory myeloid malignancies using a combination of decitabine, vorinostat, and FLAG therapy. The ORR among 26 evaluable patients was 65%. This includes complete responses and complete responses with incomplete count recovery. Among 13 patients with relapsed AML who had epigenetic alterations, the ORR was 69%. This is comparable to the TACL study, which reported an ORR of 68% in a similar group. For 8 patients with refractory AML, the ORR was 38%, slightly lower than the 41% reported in the TACL study. The ORR for five patients with therapy related AML was notably high at 80%, compared to 75% in the TACL study. The mean number of grade 3/4 toxicities experienced by the T2016-003-eligible real-world data population (22 patients) was one per patient-cycle. This was not significantly different from the 6 patients who were TACL study-ineligible due to comorbidities, who experienced two per patient-cycle. The combination therapy was found to be well tolerated and effective, particularly in pediatric patients with specific conditions such as epigenetic alterations, therapy related AML, and refractory disease. These results highlight the potential of this treatment regimen in improving outcomes for pediatric patients facing challenging myeloid malignancies [71].

The need for personalized treatment approaches based on genetic and molecular profiling is evident, as is the importance of addressing disparities in clinical trial enrollment to ensure equitable outcomes (Table 5). Further research is essential to refine these therapies, enhance their efficacy, and reduce adverse effects, ultimately improving survival and quality of life for young patients [33, 68]. While significant progress has been made in the treatment of pediatric leukemia, the complexity of the disease and variability in patient response necessitate ongoing research and innovation [72-74]. The integration of novel therapies and personalized medicine approaches holds promise for further improving outcomes in this challenging field.

**Table 5:** Summarizing recent clinical trials and their outcomes in pediatric leukemia.

Trial name	Therapy tested	Patient group	Clinical outcome	Key findings
AIEOP AML 2013	Chemotherapy with risk stratification	Pediatric AML	3 years overall survival: 83.9%, Event free survival: 68.5%	Improved survival with stratified treatment
TACL phase 1 study	Decitabine + vorinostat + FLAG	Relapsed/refractory pediatric AML	65% ORR	Effective in epigenetically altered AML
Decitabine + low-dose chemotherapy	Decitabine + chemotherapy	High-risk, relapsed AML	3 years overall survival: 79%, Event free survival: 68%	Safe and effective in relapsed AML
CAR-T cell therapy trials	CAR-T targeting CD19	Relapsed/refractory B-ALL	70 to 90% CR rates	Durable responses, reduced relapse rates

## Conclusions and Future Directions

In conclusion, the landscape of pediatric leukemia treatment has evolved dramatically, with genomic insights and novel therapies playing crucial roles in improving outcomes. However, challenges such as treatment resistance and long-term side effects continue to necessitate further research and innovation. The integration of precision medicine and continued advancements in immunotherapy and targeted treatments hold promise for achieving even better outcomes in the future.

The future of pediatric leukemia treatment lies in the continued integration of precision medicine, where therapies are tailored to the individual genetic and molecular characteristics of each patient's disease. Ongoing research into the genetic underpinnings of leukemia will likely yield new therapeutic targets and improve risk stratification, ultimately enhancing patient outcomes. Overall, while significant strides have been made in the diagnosis and treatment of pediatric leukemia, ongoing research and clinical innovation are essential to address the remaining challenges. The integration of advanced diagnostic techniques, targeted therapies, and a focus on the immune microenvironment will be crucial in improving the prognosis for children with leukemia.

While significant progress has been made, challenges such as treatment resistance, toxicity, and accessibility persist. Long-term side effects, including secondary malignancies and organ dysfunction, remain concerns for survivors. Ongoing research is focused on refining existing therapies and developing new ones to enhance efficacy and reduce adverse effects. The goal is to achieve 100% survival rates while maintaining a high quality of life for survivors.

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## Conflict of Interest

None.

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