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ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN: GLOBAL, SOUTH ASIAN, AND CENTRAL ASIAN PERSPECTIVES

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Abstract

Acute lymphoblastic leukemia (ALL) is the leading childhood cancer worldwide. Over recent decades, survival from pediatric ALL has risen dramatically in high- income countries due to risk- adapted combination chemotherapy, robust supportive care, and coordinated clinical trial networks. However, striking disparities persist between and within regions, particularly in South Asia and Central Asia, where late presentation, treatment abandonment, and limited diagnostic and therapeutic capacity remain major obstacles. This review summarizes the global epidemiology and biology of childhood ALL, outlines treatment outcomes and health- system constraints, and examines specific challenges and opportunities in South Asia and Central Asia.

Key words: Childhood acute lymphoblastic leukemia (ALL); Pediatric leukemia; epidemiology; South Asia; Central Asia; Survival outcomes; Supportive care; Pediatric oncology; Low- and middle-income countries (LMICs).

Introduction

Acute lymphoblastic leukemia represents about three- quarters of all childhood leukemias and roughly one quarter to one third of all pediatric malignancies.[1] It arises from uncontrolled proliferation of immature lymphoid precursors in the bone marrow, blood, and other organs. Dramatic improvements in therapy have transformed childhood ALL from a largely fatal disease into one with cure rates above 85–90% in many high- income settings.[2,3] In low- and middle- income countries (LMICs), however, these outcomes are not yet routinely achieved.[4]

Global efforts, including the WHO Global Initiative for Childhood Cancer, the St. Jude Global Alliance, and regional pediatric oncology collaborations, aim to narrow these gaps by strengthening health systems and harmonizing treatment approaches.[5] This review summarizes the global burden of pediatric ALL and then focuses on South and Central Asia, where a substantial proportion of cases occur.

Global burden and incidence

Worldwide, childhood ALL has an estimated annual incidence of about **1–4 per 100,000 children**, varying by age, sex, and population group.[1,6]

- The incidence peaks between 2 and 5 years of age.
- Boys are affected slightly more often than girls.
- Certain ethnic groups (for example, Hispanic/Latino children and some Asian populations in high- income countries) appear to have higher incidence, suggesting both genetic and environmental contributions.[6,7]

B- cell precursor ALL (B- ALL) accounts for most cases, while T- cell ALL (T- ALL) constitutes around 10–15%.[1] The prevalence of specific immunophenotypic and genetic subtypes differs between populations.

Table 1. Approximate epidemiology of childhood ALL by region

Region / setting	Approx. annual incidence of	Proportion of all childhood cancers	Notes

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	childhood ALL*		
Global[1,5,6]	~1–4 per 100,000 children; tens of thousands of new cases/year	~25–30% of all pediatric cancers; ~75–80% of childhood leukemias	Incidence peak at 2–5 years; B-ALL predominant, T-ALL ~10–15%
High-income countries (North America, W. Europe, parts of East Asia)[1–3,5]	Typically ~3–4 per 100,000 children	ALL often ~25–30% of childhood cancers	Well-established cancer registries; ethnic variation (e.g. higher incidence in Hispanic/Latino children)
LMICs overall (incl. much of South & Central Asia)[4,10,15]	Reported ~1–3 per 100,000, but likely underestimated	ALL commonly 25–40% of childhood cancers	Under-diagnosis and under-registration; fewer population-based registries
South Asia (India, Pakistan, Bangladesh, Nepal, Sri Lanka, Bhutan, Maldives)[12–15]	Crude incidence estimates often ~2–4 per 100,000 where registries exist	ALL ~25–40% of childhood cancers in hospital/registry series	Large child population → very high absolute case numbers; true incidence likely higher than reported
Central Asia (Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan)[10,15]	Incidence broadly similar to global averages (~1–3 per 100,000), but data sparse	ALL the predominant childhood leukemia	Estimates largely from hospital-based or partial registries; under-ascertainment likely

*Approximate ranges from global and regional registry/modelling studies; figures are illustrative rather than precise country-level estimates.

Etiology and risk factors

The causes of childhood ALL are complex and not fully elucidated. Factors that have been implicated include:

• **Host genetic susceptibility:** Germline variants (e.g. in IKZF1, ARID5B, PAX5), familial clustering, and cancer predisposition syndromes (Down syndrome, Li–Fraumeni syndrome, ataxia–telangiectasia).

• **Somatic genetic changes:** Chromosomal translocations (ETV6-RUNX1, BCR-ABL1), high hyperdiploidy, and a range of lesions revealed by genomic studies.

• **Environmental exposures:** Ionizing radiation, prior high-dose chemotherapy, and probable contributions from certain chemicals and pesticides.

• **Perinatal and early-life factors:** High birth weight, mode of delivery, and infection patterns in early childhood. The "delayed infection" hypothesis proposes that immune dysregulation in genetically predisposed children may follow an abnormal pattern of infection exposure in infancy.[8]

Despite these associations, most children with ALL have no clearly identifiable risk factor.

Biology and Classification

Diagnosis and classification of ALL combine morphology, immunophenotyping, cytogenetics, and molecular profiling.[1,9] Major B-ALL categories include:

• High-hyperdiploid ALL

• ETV6-RUNX1–rearranged ALL

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• TCF3- PBX1 and BCR- ABL1 fusions, KMT2A (MLL) rearrangements
• BCR- ABL1–like (Philadelphia- like) ALL
• Hypodiploid ALL

T- ALL is further classified based on stage of T- cell maturation and recurrent genetic abnormalities (e.g. NOTCH1 mutations, CDKN2A/B deletions).[9] These features are central to modern risk stratification and guide the intensity of therapy, particularly in cooperative group protocols in high- income countries.

In many LMICs, including much of South and Central Asia, access to full cytogenetic and molecular testing is restricted, making comprehensive biological risk assessment difficult.[4],[10]

Treatment and Outcomes: Global Overview

Standard care for childhood ALL is prolonged multi- agent chemotherapy delivered in distinct phases—induction, consolidation/intensification, and maintenance—combined with CNS- directed therapy (primarily intrathecal chemotherapy, with cranial irradiation now used sparingly).[2],[3],[9] Early treatment response, particularly minimal residual disease (MRD), is a key determinant of risk group assignment.

• In North America and Western Europe, 5- year event- free survival frequently exceeds **85–90%**, and death from treatment toxicity is generally below **3–4%**.[2],[3],[11]
• These outcomes are achieved within cooperative study groups (COG, BFM, UKALL, St. Jude and others) that provide protocolized therapy and high- quality supportive care.

South Asia Perspective

South Asia (India, Pakistan, Bangladesh, Nepal, Sri Lanka, Bhutan, and Maldives) contains a large share of the world's child population and correspondingly a substantial portion of the global childhood cancer burden. ALL is the most common pediatric cancer in most countries of this region.[12],[13]

Incidence and clinical features

While comprehensive population- based incidence data are incomplete, registry studies suggest that ALL constitutes roughly **25–40%** of all childhood malignancies in South Asia.[12],[13] Common clinical observations include:

• Presentation at an advanced stage, often with high leukocyte counts.
• Frequent hepatosplenomegaly and lymphadenopathy.
• A relatively high proportion of patients with adverse clinical risk features.

These patterns reflect both biological heterogeneity and system- level delays in diagnosis and referral.[12]

Table 2. Selected epidemiologic indicators for childhood ALL in South Asia (illustrative)

Country / setting	Approx. childhood ALL incidence*	ALL as % of childhood cancers[12]–[14]	Notable features
India	Often ~2–4 per 100,000 children where registries exist	~25–40% in population- based and hospital- based registries	Very large absolute case load; significant urban–rural and public–private disparities
Pakistan	Similar order of magnitude; detailed population- based data limited	ALL usually 30–40% of pediatric cancers in tertiary centres	Many children present late with high- risk features; abandonment remains a challenge

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Bangladesh, Nepal, Sri Lanka	Incidence likely in range of 1–3 per 100,000, but data sparse	ALL commonly the most frequent pediatric cancer in referral hospitals	Under-ascertainment likely due to diagnostic gaps and referral patterns

*Where population-based cancer registry data are available; otherwise extrapolated from regional patterns.

Outcomes and health-system barriers

Centres that have implemented adapted BFM- or COG-inspired protocols, together with improved supportive care, have reported encouraging outcomes:

• Tertiary centres in India and Pakistan now describe 5-year event-free survival approaching **70–80%** for standard-risk groups.[12–14]

• Nevertheless, at the national level, outcomes are uneven, and in some institutions, treatment abandonment exceeds **10–20%**.[12]

Key obstacles include:

• Insufficient awareness and delayed recognition of leukemia in primary and secondary care.

• Concentration of pediatric oncology expertise in large urban centres, leaving rural regions underserved.

• Heavy out-of-pocket costs, despite emerging government-sponsored schemes.

• Constraints in supportive care—limited blood products, antimicrobials, nutritional support, and infection-control measures.

• Restricted access to MRD testing and advanced cytogenetics, hampering precise risk stratification.[12–14]

On a more positive note, numerous national and regional initiatives—such as standardized protocols, collaborative networks, and expanded public financing—are gradually improving access and outcomes.

Central Asia Perspective

Central Asia (Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan) has a smaller pediatric population than South Asia but faces its own post-Soviet health-system legacy. High-quality epidemiologic data for childhood ALL are relatively scarce, and many reports are institution-based.[10,15]

Table 3. Childhood ALL in Central Asia – indicative epidemiology and service context

Country/ subregion	Approx. childhood ALL incidence*	Service organization	Key issues[10,15]
Kazakhstan	Likely ~1–3 per 100,000 children (similar to global averages)	National/regional oncology centres with increasing adoption of BFM-based protocols	Partial access to immunophenotyping/cytogenetics; urban–rural disparities in care
Kyrgyzstan, Tajikistan	Limited registry-based data; incidence presumed similar order	Care concentrated in a few national centres	Resource constraints; inconsistent protocol implementation; data gaps
Turkmenistan, Uzbekistan	Sparse published paediatric incidence data	Care in former Soviet oncology facilities, some modernization underway	Stock-outs, variable drug quality,incomplet

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			e diagnostic work- up

*Based on global incidence ranges and limited national reports; precise country- level estimates generally unavailable.

In the past decade, several countries have:

• Adopted or adapted international protocols (often BFM- based).

• Begun strengthening childhood cancer registries.

• Improved availability of essential chemotherapeutic agents and supportive- care resources, though stock- outs and variability in drug quality may still be problematic.

Outcomes and ongoing challenges

Published survival estimates indicate that long- term outcomes, while better than in the most resource- limited settings, still lag behind Western Europe and North America, placing many Central Asian programmes in an "intermediate resource" category.[10],[15] Important challenges remain:

• Limited availability of immunophenotyping, cytogenetics, and MRD assessment in many centres.

• Inconsistent adherence to treatment and supportive- care protocols, particularly outside major urban hospitals.

• Financial, geographic, and logistical barriers that make prolonged therapy difficult for families.

• Need for formal training pathways in pediatric hematology- oncology and nursing.

Regional partnerships with international organizations and neighbouring high- income countries are increasingly seen as a route to standardize practice and improve outcomes.

Supportive Care, Treatment Toxicity, and Late Effects

The ability to deliver intensive chemotherapy safely depends heavily on supportive care capacity.[2],[3],[11] In high- income settings, access to broad- spectrum antibiotics and antifungals, intensive care, standardized transfusion support, nutritional services, and infection- control infrastructure has markedly reduced treatment- related mortality.

In South and Central Asia, supportive care is often the weakest link:

• Higher rates of severe infections, including sepsis and invasive fungal disease, are reported.[12–15]

• Many children start therapy with pre- existing nutritional deficits, increasing vulnerability to toxicity.

• Infection- prevention measures (isolation facilities, hand hygiene, environmental controls) are variably available.

As survival improves, attention must also turn to long- term sequelae, such as endocrine and growth disturbances, neurocognitive impairment, cardiotoxicity, and secondary malignancies.[3],[11] Dedicated survivorship programmes remain uncommon in many South and Central Asian settings.

Emerging Therapies and Access Inequities

However, in South and Central Asia, access to these modalities is extremely limited because of cost, regulatory barriers, and the need for specialized infrastructure. Most children continue to receive conventional chemotherapy, and only a subset can access hematopoietic stem cell transplantation for high- risk or relapsed disease.

Conclusion

Childhood ALL is a highly curable disease, yet survival remains strongly determined by geography and resource level. While high- income countries routinely achieve survival rates above 85–90%, many children in South Asia, Central Asia, and other LMICs do not yet benefit from these advances. Achieving more equitable outcomes will require sustained investments in diagnostics, standardized risk- adapted chemotherapy, robust supportive care, financial

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protection for families, and long- term survivorship services. Strengthened regional and global collaborations offer a pathway to gradually replicate the success seen in high- income settings, so that a diagnosis of ALL confers a realistic chance of cure for children everywhere.

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