Acute lymphoblastic leukemia in low and middle-income countries: disease characteristics and treatment results

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Purpose of review
Acute lymphoblastic leukemia is the most common pediatric cancer. The cure rate of this disease is over 80% in developed countries utilizing protocols with very tolerable toxicity. Several factors contributed to this success, including the implementation of large collaborative clinical trials and the better understanding of disease biology allowing for risk-stratified treatment. We will review the current state of the treatment of acute lymphoblastic leukemia in low-income and medium-income countries.

Recent findings
The picture differs from country to country, but recent advances have been made in many countries and the cure rates have improved significantly. Tackling problems such as access to care, abandonment of treatment and toxicity of protocols and the development of centers of excellence are critical for continued improvement. Twinning with programs in developed countries and the creation of regional collaborative groups will allow the implementation of risk-directed therapy and better supportive care.

Summary
The experience in low-income countries shows that a structured approach to the treatment of acute lymphoblastic leukemia results in improved survival.

Keywords
acute lymphoblastic leukemia, low-income and middle-income countries, risk stratification, twinning

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer in both high-income countries (HIC) and low-income countries (LIC). The successful treatment of this disease is one of the important medical advances of recent times, resulting in survival rates close to 90% in most developed countries, with low treatment-related mortality (TRM) [1]. This was achieved through a combination of widespread patient enrollment in large-scale clinical trials, improved understanding of the disease biology, the stratification of patients and their treatment according to risk groups and improvement in supportive care [1,2■■,3,4]. The situation, however, is different in resource-poor and middle-income countries (MIC) where 70% of all children live and where four out of five cases of ALL occur today. The outcome differences between HIC and low-to-middle income countries are a result of several factors, including inability to access cancer care facilities, the substantial delay from the onset of symptoms to the initiation of treatment, the high rate of abandonment of treatment and treatment-related toxicity leading to death [5–8,9■,10]. Differences between countries are striking as even in MIC that have enough resources to join a sophisticated intercontinental (iBFM) trial, the results remained worse than those observed in the HIC participating in the original BFM trial [11■]. Nonetheless, significant advances have been made in different countries and in some, the outcome is now similar to that observed in the developed countries [12–15].

Currently, we have a better understanding of the disease, more advanced diagnostic techniques and intensive supportive care protocols. Furthermore,

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KEY POINTS

- Outcome of ALL in LIC and MIC is still inferior to HIC.
- Factors affecting outcomes include late diagnosis, limited access to care, abandonment of treatment and toxicity of protocols.
- Public–private partnership leading to the creation of centers of excellence with dedicated oncology units results in a significant improvement in outcomes.
- Future progress will require availability of supportive care and wide international collaborations.

the work done in the developed countries has shown that the majority of children with ALL can be cured with relatively nonintensive treatment protocols, if their risk status can be accurately determined [1,2▪▪,3]. Concomitantly, studies have been published demonstrating improved survival in LIC and MIC using risk-adapted protocols, more sophisticated risk stratification techniques and protocols adapted to local conditions [12–15]. Studies have also demonstrated success in decreasing abandonment rates and toxic deaths during induction and maintenance [7,13,15,16]. These successes were in part also made possible by twinning and support of centers in LIC with programs in the developed countries such as the St. Jude International Outreach Program. Other important developments include the creation, staffing and equipping of national centers of excellence, often funded through mixed public and nongovernmental partnerships [11▪,12–15]. These centers and NGOs have played a critical role in improving outcomes and are the focal points for research and the establishment of national and regional collaborative groups.

DISEASE CHARACTERISTICS: EPIDEMIOLOGY

The epidemiology of childhood ALL varies between HIC, LIC and MIC [17▪▪,18] and marked regional differences may be observed within LIC and MIC [19,20]. The incidence of ALL varies from 1 to 40 per million in LIC, whereas this range is much narrower, 40–50 per million, in MIC and HIC [17▪▪,18]. Although there may be a real difference in incidence, these differences could also be explained by the fact that in LIC, many children with leukemia may die before a diagnosis can be made. This contention is supported by the fact that the incidence of non-leukemia cancers, mainly solid tumors, which are easier to recognize, does not seem to vary with gross national income [17▪▪,18]. This is most striking for some countries, which seem to have very low overall incidences of childhood leukemia, particularly countries in the southern and western parts of Africa.

It has been suggested that the lower incidence of ALL in LIC could be due to protective mechanisms, such as breast feeding, family aggregation and infections. Recent data from Brazil have shed important light into some of these issues. Studies utilizing data from population-based cancer registries (PBCR) showed that the incidence of ALL was observed to vary between different regions of the country [19]. In this population, with significant ethnic mixing, the age-adjusted incidence rate (AAIR) of ALL ranged from 12.8 to 69.0 per million for female children and 24.2 to 61.3 per million for male children. The highest rates of leukemia, and high AAIR of ALL (60.1 for males and 53.0 for females) were found in Manaus in the Amazon region, which is a relatively poor area of the country with lower development indices. Lower rates reported in other poor areas of the north-east may have been in part due to under reporting. In this study, the incidence of ALL was not correlated with the human development index, even though richer areas had a higher AAIR than poorer areas, with the exception of Manaus [19]. In a separate study, investigators looked at epidemiologic factors associated with ALL incidences in the Sao Paulo State [20]. In this region, PBCR data were more complete and showed that AAIR for ALL was significantly lower in areas of lower socioeconomic status and a higher percentage of households with more than seven persons [20]. These data point to the possible real impact of lower socioeconomic status on the incidence of the disease, but more importantly emphasize the importance of PBCR utilizing adequate capture–recapture methods. Data from such PBCR are critical for policy makers to allocate resources and plan treatment facilities. These data may also help identify risk factors for ALL and other cancers. Unfortunately, these PBCR are only available in a few LIC. Data from India, for example, had to be gathered from publications and abstracts [21]. Also of significant importance in Brazil was the devolvement of uniform guidelines for diagnosis of the disease and assignment of reference laboratories for diagnosis of pediatric cancer in impoverished areas of Brazil [19], allowing more rapid and accurate diagnosis of patients.

CLINICAL AND BIOLOGICAL FEATURES

The clinical and biological features of ALL have been reported from many MIC and LIC and two patterns emerge. First, despite some differences, to be detailed below, the biological features of the disease are essentially similar in most countries. This is important as it means that diagnostic tools and risk stratification criteria developed in HIC may be utilized in different settings. Second, treatment protocols used in collaborative or large institutional trials in HIC could also be successfully adapted for use in LIC and MIC [7,11▪,12,13].

IMMUNE PHENOTYPE

In the Middle East, where diagnostic facilities are available, a large study showed that among 1066 patients the majority of cases, 84.2%, were B-lineage ALL, 14.8% T-lineage and 1% mature B-lineage phenotype [22▪]. Similar data were reported from individual countries in the region [12,13]. Outside the Middle East, similar results were reported from Taiwan and Brazil [14,15].

GENETIC FEATURES

Genetic features have been studied by either cytogenetics or molecular methods in certain LIC and MIC like Brazil, India, China and countries in the Middle East. The main features that emerge are a small but significant decrease in the incidence of ETV6-RUNX 1 or t(12;21) [11▪,12,21] and an increase in t(9 : 22) BCR-ABL [13,22▪] compared to western countries. The increase in BCR-ABL was particularly seen in China and other Asian countries [23], but the lower incidence of ETV6-RUNX was observed across a large number of studies. Although technical factors may have contributed to this finding, the data raise questions about decreased risk of childhood ALL in children living in LIC due to earlier exposure to infections.

CLINICAL FEATURES AND TREATMENT PROTOCOLS

The last decade has seen the publication of numerous studies from LIC and MIC showing improvement in the survival for childhood ALL [23]. These results have invariably been the result of studied steps that involved the development of centers of excellence, implementation of well designed protocols adapted to local conditions, twinning or collaboration with centers or groups in developed countries, the adoption of measures to decrease abandonment of treatment and new supportive care guidelines.

The development of centers of excellence has been proven to impact pediatric oncology care. This was evident in case studies from Brazil, Lebanon and central America. In Recife, Brazil, the 5-year event-free survival for ALL in children improved from 32 to 63% after the establishment of a dedicated pediatric oncology unit [7]. This unit ensured proper training of and coverage by nurses and physicians, support for families through a nongovernmental organization and the implementation of a uniform treatment protocol. Funding was provided equally by governmental and nongovernmental sources and significant funding went to support families. This program worked in close collaboration with the St. Jude International outreach program. In Lebanon, despite a protracted civil war, the overall survival rates were 75% for low-risk patients and 57% for high-risk patients treated at a university medical center prior to the establishment of a dedicated pediatric oncology program [24]. After the establishment of a specialized pediatric oncology center within the same medical center, these results improved to 92.3 and 82.3%, respectively [12]. This center is funded through a public–private partnership and affiliated to St. Jude Children's Research Hospital.

Despite the different settings, similar elements were responsible for success in Recife, Brazil, as well as in other countries [25▪,26▪▪,27]. The first and the most important step is the establishment of a dedicated pediatric cancer center and the other steps include the following:

(1) The development of a protocol document that outlines the diagnostic evaluation, risk stratification, inclusion and exclusion criteria and a road map of therapy.
(2) Training and education of physician and nursing staff.
(3) Data gathering and management.
(4) Case by case review internally and the availability of prompt consultation for problem cases.
(5) Availability of support care facilities and programs for the management of complications of chemotherapy.
(6) The development of strategies to prevent abandonment of care.
(7) A public–private partnership to support the program and families such that no financial burdens are incurred by the parents.

The importance of training of medical staff and education of parents cannot be overemphasized. In Indonesia, poor compliance of physicians with treatment guidelines was demonstrated to lead to worse outcomes in children with ALL [28]. In the same setting, education of parents was found to influence patient outcomes. Education about the disease and the development of simple tools like treatment diaries positively impacted access to care and treatment compliance [29▪,30,31].

TREATMENT-RELATED TOXICITY AND MORTALITY

With increasing intensity of protocols, survival rates improve but the rates of TRM and toxicity also increase, mandating that attention to supportive care and adjustment of treatment protocols become a priority. This is a particular problem with utilization of intensive protocols adapted from HIC where TRM is less than 1%. A recent study evaluated TRM among 1670 children in three countries in central America over an 8-year period [16]. TRM in this study was 9.3%, which is significantly higher than the 1–2% reported in HIC. More importantly, there was a significant TRM during maintenance that is a very rare occurrence in HIC. This trend improved over time but TRM during induction remained around 5%. Infections were the main cause of death during maintenance whereas bleeding and other toxicities were more common during induction. In the central American setting, nutritional and socioeconomic status did not have an impact on TRM, but these are important variables in other parts of the world, such as India and Indonesia [21,32]. The protocols utilized in the central American countries were intensive, based on St. Jude total XIII and XV protocols. Factors associated with TRM were travel time to clinic, lower initial platelet count and high-risk ALL. The authors attributed the improvement in TRM over time to more prompt dealing with infections and weekly online meeting with the St. Jude Children's Research Hospital investigators [17▪▪].

A similar picture was observed in Recife, Brazil, where implementation of a treatment protocol based on St. Jude total XIII led to improved survival rates, but at the same time there was a significant increase in deaths from infectious and noninfectious toxicities [7]. In Lebanon and Jordan, adoption of the St. Jude total XV and XIII protocols led to a significant improvement in survival with low death rates of 1% during induction and 2% during maintenance [12,13]. The analysis of complications, however, revealed a large number of nonfatal complications attributable to intensive therapy. These included septic shock during reinduction, varicella infection, cytomegalovirus retinitis and pneumonia. These complications were associated with significant morbidity and their treatment required expertise and resources [12,32].

The findings described above suggest that a double-pronged approach should be taken into consideration to improve outcomes and decrease treatment-associated morbidity and TRM. The most obvious is the improvement in supportive care and the inclusion of clear supportive care guidelines in the treatment protocols [17▪▪,33▪▪]. This is clear from the case of a center in China that saw improvement after including *Pneumocystis* prevention in the ALL protocol [5] and from the experience of central America described in detail above. Twinning with centers of excellence and the development of a multidisciplinary approach to patient management are of critical importance. The learning curve for preventing TRM of intensive treatment protocols can be steep even in HIC and requires concerted effort [34].

The other approach is to develop protocols that are effective with less toxicity. This requires a significant investment in techniques that will allow for better risk stratification and training of nursing and medical staff. This approach entails the gathering and analysis of data on large numbers of patients. This was successfully done in the iBFM trial and in the national Brazilian trial, both of which showed that decreasing treatment intensity for certain risk groups was not associated with worse outcomes. In the Brazilian trial, the utilization of intermittent doses of 6-mercaptopurine and methotrexate led to less toxicity with similar DFS [15]. The issue of research and collaborative groups will be discussed below.

COST OF CARE

Cost of care for childhood ALL is divided into two parts as follows: cost to families and cost of treatment in different facilities. Diagnosis of pediatric cancer in general and ALL in particular often leads to significant financial hardship for families [35–37]. Furthermore, disparities in treatment results for ALL have been shown in both HIC and LIC with patients in lower socioeconomic groups faring worse [37,38]. These results were improved by providing care at no expense to families [39]. On another level, the positive correlation between annual government spending on healthcare and childhood cancer survival is well known and highly significant [40▪▪]. ALL treatment is prolonged, lasting from 2.5 to 3 years, and requires close monitoring and follow-up. The induction and consolidation phases are the most intensive and expensive, often requiring inpatient admission, whereas the maintenance phase is outpatient and does not demand frequent clinic visits or complicated laboratory testing. Although treatment schemes may be complex, the drugs used are relatively inexpensive and not complicated to prepare. Costs of treatment for pediatric cancer vary, but seem to be related to general income in particular countries. The costs of running and operating a pediatric oncology service are significant and the time that the family spends in procuring care can be very expensive. It was estimated that in 2003 in central America, the cost of running a pediatric oncology service for 150 new cases a year would be 3 million dollars [4]. The treatment of a child with ALL in Recife, Brazil was calculated to be 17 500 dollars in 2004 [7,40■■]. The economic burden in a country like India, where 10 000 new cases of ALL are expected a year, is significant. At 20 000 dollars per year, the yearly cost of care for these patients would be 200 million dollars. The cost would be even higher, if cost of care for relapsed patients and bone marrow transplants were included. Given these costs, it has often been assumed that treatment of pediatric cancers in LIC and MIC is not cost-effective. Calculations have, however, shown that the costs of treating ALL in Brazil, as well as Burkitt's lymphoma in Malawi, were well within the threshold for cost-effective care [41].

COLLABORATIVE GROUPS AND RESEARCH

The advances made in the treatment of ALL in developed countries were in large part due to the implementation of successive large-scale clinical trials, with very high enrollment, involving many institutions within national groups. These studies now involve children in many countries. In HIC, the vast majority of children are enrolled and treated on protocols that aim at addressing different questions but also ensure the uniformity of treatment delivery and supportive care [1,2■■,3]. In the resource-poor countries, such collaboration would be important in improving children's care and allowing the development of protocols better adapted to local conditions [42■]. The experiences of collaborative groups in Morocco, central America, Brazil and the iBFM [11■,15,16,43,44] are examples that such groups can be successful and that regional and national collaboration contribute greatly to improve the survival and outcome of childhood cancers. This experience is, however, far from universal in the developing world and there are many barriers to collaboration and research [45–47].

CONCLUSION

The outlook for children with ALL is still dependent to a large extent on the country in which a child is born. Recently, however, significant advances have been made in LIC and MIC leading to early diagnosis and treatment and lower rates of abandonment [46,47]. Protocols have been adapted from developed countries and treatment-related toxicities have been addressed. Public–private partnerships and twinning with centers in the developed world were critical for these advances. It is hoped that these models can be more widely implemented in the future.

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Conflicts of interest

The authors declare that they have no conflict of interest pertaining to this publication.

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All research and speaking is related to sickle cell disease.

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