**Chapter 7. Treating Childhood Cancer in Low- and Middle-Income Countries**

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Stephen Hunger, Federico Antillon, Monika Metzger, Carlos Rodriguez-Galindo, Trijn Israels, Mhamed Harif

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Abstract
Of the 175,000 children who develop cancer annually, more than 150,000 live in low- and middle-income-countries (LMICs). Most of these children will not be treated at all, and will die as the result of their disease. If treated, most children would be cured and live for decades, as they do in high-income countries (HICs). This chapter discusses the rationale for and principles of LMIC childhood cancer treatments, as well as the platforms through which such treatment can feasibly be delivered.

The Burden of Childhood Cancer in LMIC
In high-income countries (HICs), the annual incidence of childhood cancer is approximately 140 per million children younger than 15 years of age, although estimates vary between and within countries. Incidence rates from low- and middle-income country (LMIC) registries are generally significantly lower, as annual rates per million children of 45.6 in Namibia and 64.4 in India, respectively, illustrate. Some of this variation may relate to differences in environmental exposures or to biologic susceptibility. However, deficiencies in diagnosis and registration likely contribute significantly to differences in the reported incidence of cancer, both overall and of particular subtypes, such as acute leukemias.

Incidence data from high-quality cancer registries with complete population coverage are rare in LMICs. In 2006, only 8 percent of Asians and 11 percent of Sub-Saharan Africans were covered by population-based cancer registries; when only high-quality registries are considered, these rates are 4 percent and 1 percent, respectively.

Multiple steps are required for children with cancer to be included in a registry (figure 7.1). Caregivers must seek medical attention for symptoms. Primary health care workers must appropriately refer patients to tertiary centers capable of recognizing and diagnosing pediatric malignancies and then entering data into cancer registries. Breaks in the chain of events may occur at any step.
In low-income countries, barriers occur at all steps. SES indicates socioeconomic status.

Links in the chain of childhood cancer diagnosis and registration with potential barriers in low- and middle-income countries.

Recognition of possible cancer
- Education/beliefs
- Symptoms/signs
- Distance
- Transportation
- SES
- Family support

Arrival to primary care
- Education/beliefs
- Symptoms/signs
- Distance
- Transportation
- SES
- Family support

Clinical diagnosis of cancer (e.g., detectable mass)
- Trained personnel
- Clinical infrastructure
- Funding
- Education/beliefs
- Symptoms/signs
- Distance
- Transportation
- SES
- Family support

Arrival to tertiary care
- Education/beliefs
- Symptoms/signs
- Distance
- Transportation
- SES
- Family support

Histologic diagnosis of cancer
- Personnel (surgery, oncology, pathology)
- Pathology lab
- Funding

Registration in a database
- Personnel (data management)
- Supportive administration
- Hardware/Software
- Funding

Source: Reprinted from Howard and others 2008.

Note: SES = socioeconomic status.

A comparison of leukemia and non-leukemia cancer incidence rates is instructive. Pediatric leukemia may present with a variety of nonspecific symptoms (such as fever, anemia, malaise, or hemorrhage), many of which are also associated with infections. Most non-leukemia cancers present with enlarging masses more easily recognizable as malignant. Accordingly, the magnitude of under-diagnosis would be expected to be greater in leukemia than in non-leukemia cancers; registry data bear this out. In the most recent global compilation of pediatric cancer data, leukemia incidence in LICs averaged 16.4 per million children, far lower than the incidence rate of 36.5 in MICs and 40.9 in HICs (figure 7.2). The non-leukemia cancer incidence was broadly similar in all income groups: 85 in LICs, 70 in MICs, and 89 in HICs.

* Annual per capita figures in US dollars. Gross national incomes were taken from the world development indicators database of the World Bank for 2005.
Figure 7.2. Reported Incidence Rate of Childhood Leukemia and its Association with 2005 Gross National Income, Selected Countries

Source: Reprinted with permission from Howard and others 2008.3

Note: In low-income countries, there is a wide range of recorded leukemia incidence.

Under-diagnosis and under-registration are not uniform across all segments of the population. In both Jordan and Honduras, higher leukemia incidence rates are reported in urban compared to rural districts.4,5 Comparing Indian cancer registries, the male-to-female ratio in acute lymphoblastic leukemia (ALL) incidence ranged from 1.7 per million in Mumbai to 2.6 in Delhi, compared to 1.3 in Canada during the same time period.1 At least in some cases, under-diagnosis may affect girls and rural children disproportionately.

Additionally, not only is childhood cancer severely underrepresented in LMIC cancer registration, but also only a proportion of the children who are registered receive appropriate treatment. From a survey of health care workers in 10 LMICs, including Bangladesh, the Philippines, Tanzania, and Vietnam, 15 percent to 37 percent of the expected patients were seen.6 Including children missed by registries would lower this percentage even further.

Thus, the approximately 175,000 children diagnosed with cancer globally every year are likely to represent a significant underrepresentation of the worldwide incidence. Expansion of current cancer registries, improvement in diagnosis and registration, and novel methodologies are needed to accurately establish the true pediatric cancer burden.2,7 Of note, the International Agency for Research on Cancer (IARC) is assembling...
an updated volume of the International Incidence of Childhood Cancer, drawn predominantly from registry data. Comparisons with previous editions will allow an assessment of progress.

Why Treat Childhood Cancer in LMICs?

The Epidemiologic Transition
In most HICs, cancer represents the leading cause of non-accidental death in children older than one year.\(^8,\)\(^9\) While infection accounted for 64 percent of global deaths in the first five years of life in 2010,\(^10\) major shifts in both the magnitude and causes of childhood mortality have occurred in many LMICs, especially in MICs. In Brazil, under-5 mortality decreased from 129 per 1,000 live births in 1970 to 59 per 1,000 in 1990, and 19 per 1,000 in 2010;\(^11\) cancer now leads the causes of non-accidental death in that country. Worldwide, 106 countries witnessed accelerated declines in childhood mortality from 1990 to 2011; about 80 percent of the decline was from infectious disease control.\(^12\) Consequently, non-communicable causes represent a greater proportion than before.\(^10,\)\(^13\) Indeed, while 3.2 percent of deaths among children ages five to 14 years in LICs are estimated to be due to cancer, the equivalent figures for low- and upper-middle-income countries are 6.0 percent and 18.6 percent, respectively.\(^7\)

Ineffectiveness of Prevention and Screening
Most pediatric malignancies are not caused by modifiable risk factors. Therefore, public health campaigns would have limited impact on decreasing the incidence of childhood cancer, although impact on delayed presentation is possible. Similarly, population-based screening programs have not been shown to affect cancer mortality in children.\(^14\) Decreasing childhood cancer mortality rates thus requires early and accurate diagnosis followed by effective treatment.

The Achievability of Cure
In HICs, over 80 percent of children with cancer are cured of their disease.\(^9,\)\(^15,\)\(^16\) Although cure rates in LMICs are much lower, there are many examples of successful treatment with less intensive regimens that can nonetheless cure a significant portion of patients in LMICs. Burkitt Lymphoma (BL), the most common childhood malignancy in many parts of Sub-Saharan Africa, is cured in 90 percent of cases in HICs, using intensive regimens and intense and costly supportive care.\(^17,\)\(^18\) However, up to 50% of Sub-Saharan African children with BL are curable with only three to six doses of single-agent cyclophosphamide and intrathecal therapy, demonstrating that cure is possible even in the most resource-limited settings.\(^19\)

The Spillover Effect from Pediatric to Adult Oncology
In societies in which cancer may be seen as a death sentence, pediatric oncology offers the opportunity to demonstrate high cure rates in a manageable number of patients through the establishment of a defined and feasible cancer infrastructure. Such success
can serve as powerful encouragement to both governments and policymakers to create and expand programs targeting adults with cancer.

Platforms for Childhood Cancer Treatment Delivery

Dedicated Centers
Childhood cancer treatment requires specialized diagnostic and therapeutic capabilities, as well as the ability to manage potential complications. Expensive, high-technology equipment is not however required. Although volume-outcome relationships have not been convincingly demonstrated in pediatric oncology, the dominant paradigm is to manage care through a limited number of treatment centers in which resources and expertise are concentrated. Satellite centers can, however, deliver some treatment, decreasing the burden on families, providing rapid management of complications and, in LMICs, decreasing abandonment of treatment (discussed in the section titled “Platforms for Childhood Cancer Delivery”).

Tables 7.1 and 7.2 list the personnel and infrastructural requirements for an ideal LMIC center delivering pediatric cancer care; however, many institutions in LMICs deliver curative treatment in the absence of many of these elements. Such treatment must be adapted to local capabilities. For example, centers without an intensive care unit or ventilators will not be able to deliver as intensive chemotherapy as ones with these resources, but they will nonetheless be able to cure a portion of children.

In many LMICs, childhood cancer services are delivered through cancer hospitals serving primarily adult populations. In these instances, appropriately sized pediatric equipment and specific pediatric expertise are still required.

Table 7.1 Examples of Essential Personnel for Ideal Pediatric Cancer Care in Low- and Middle-Income Countries

<table>
<thead>
<tr>
<th>Personnel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical doctors</td>
<td>Individuals who have received training or have experience managing pediatric oncology patients are essential to lead the unit and coordinate all other personnel needed to achieve cure. In many centers, pediatricians, adult hematologists, adult oncologists, or surgeons with some degree of extra training or experience may fill this role. Training and fellowship programs now exist in several LMICs.</td>
</tr>
</tbody>
</table>
| Surgeons | Surgery is necessary for the diagnosis and treatment of many pediatric malignancies, such as Wilms tumor. However, some cancers are curable without surgical intervention (see the section titled “The
<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiation oncologists</strong></td>
<td>Radiation therapy is used for a variety of pediatric malignancies in HICs, such as Hodgkin lymphoma, Wilms tumor, and sarcomas. However, in some cases, substituting additional chemotherapy and/or surgery can result in cure (see the section titled “The Treatment of Specific Cancers”).[119,120]</td>
</tr>
<tr>
<td><strong>Pathologists</strong></td>
<td>Correct diagnosis is the foundation of cancer care, and a professional who has experience in the diagnosis of pediatric malignancies and who is connected with disease-specific pathology experts for difficult cases is ideal.</td>
</tr>
<tr>
<td><strong>Nursing</strong></td>
<td>Strong nursing support with additional training in safe chemotherapy administration is needed. Expertise in the recognition and management of complications related to either the malignancy or treatment is desirable. An open line of communication between nursing and medical colleagues is crucial. Models for training LMIC nurses in pediatric oncology have been described.[121,122]</td>
</tr>
<tr>
<td><strong>Pharmacists</strong></td>
<td>Dedicated pharmacists are needed to prepare chemotherapy, and to facilitate the safe preparation, handling, and disposal of chemotherapeutic medications.</td>
</tr>
<tr>
<td><strong>Social workers</strong></td>
<td>Addressing the emotional, social, financial, and spiritual needs of children and families facilitates adherence to treatment, improves quality of life, and reduces the risk of abandonment (see the section titled “Abandonment of Therapy”).</td>
</tr>
<tr>
<td><strong>Dieticians or nutritionists</strong></td>
<td>Nutritional support is particularly important in LMICs where malnutrition at diagnosis or during treatment is prevalent.[104,123,124]</td>
</tr>
</tbody>
</table>

**Source:** Authors.

**Note:** *This list is not meant to be exhaustive. Other personnel, including infectious disease specialists and intensive care physicians, play crucial roles but may not be available in many resource-constrained settings. While all the elements listed are desirable, a proportion of children will still be cured in their absence.*
Table 7.2. Infrastructure Needed To Deliver Ideal Pediatric Cancer care in Low- and Middle-Income Countries*#

<table>
<thead>
<tr>
<th>Infrastructure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inpatient and outpatient beds</strong></td>
<td>Sufficient inpatient and outpatient beds are required, preferably designated for pediatric oncology patients. A hand hygiene program, isolation capabilities, and other infection control methods are desirable.</td>
</tr>
<tr>
<td><strong>Laboratory and pathology services</strong></td>
<td>Basic hematologic, biochemical, microbiologic, and pathologic laboratory services capable of timely turnaround are desirable. While advanced diagnostic modalities such as flow cytometry and cytogenetics are available in HICs, their absence does not preclude the establishment of a pediatric oncology center.</td>
</tr>
<tr>
<td><strong>Diagnostic imaging</strong></td>
<td>Basic imaging capabilities are necessary. While advanced modalities such as computerized tomography and magnetic resonance imaging, are ideal, basic modalities such as plain radiographs and/or ultrasonography are sufficient to begin treating childhood cancer.</td>
</tr>
<tr>
<td><strong>Chemotherapy and supportive care medications</strong></td>
<td>Reliable supplies of selected chemotherapeutic agents and supportive care medications, such as antimicrobials, antiemetics, and analgesics are crucial. The World Health Organization Model List of Essential Medications for Children provides a starting point for specific medications.</td>
</tr>
<tr>
<td><strong>Blood product availability</strong></td>
<td>Treatment protocols may cause bone marrow suppression, necessitating the timely and reliable delivery of safe blood products. However, this is not the case for all chemotherapies; treatment for several malignancies requires minimal transfusion support.</td>
</tr>
<tr>
<td><strong>Psychosocial support</strong></td>
<td>Abandonment of therapy is a significant cause of treatment failure in many LMICs (see the section titled “Abandonment of Therapy”). The provision of financial support in case of inability to pay for medical care, and of transport and accommodation when necessary, decreases the risk of abandonment and must be considered an essential part of oncology care in LMICs.</td>
</tr>
<tr>
<td><strong>Surgical facilities</strong></td>
<td>Surgery is necessary for diagnosis and treatment of many pediatric malignancies, for example, Wilms tumor. Many cancers, however, are curable without surgical intervention (see the section titled “The Treatment of Specific Cancers”).</td>
</tr>
<tr>
<td><strong>Radiation facilities</strong></td>
<td>Radiation therapy is used for a variety of pediatric malignancies in HICs, for example, Hodgkin lymphoma, Wilms tumor, and sarcomas. However, in some cases, substituting additional chemotherapy</td>
</tr>
</tbody>
</table>
and/or surgery can result in cure (see the section titled “The Treatment of Specific Cancers”).

Source: Authors.

Note: *This list is not meant to be exhaustive. While all of the elements listed are desirable, a proportion of children can still be cured in their absence.

**Twinning Programs**

“Twinning” is the most effective model for sustained improvement in childhood cancer care in LMICs (although LMIC centers can be successful without a twinning partnership). Twinning programs foster interactions between hospitals in developing countries and established cancer treatment centers, with the goal of improving survival rates among children with cancer. Twinning allows a bidirectional exchange and combines disease-specific multidisciplinary expertise with local knowledge and capabilities. Twinning programs can also involve the flow of financial resources, although the presence of committed individuals on both sides predicts success better than the availability of funding. Interactive online tools such as Cure4Kids (www.Cure4Kids.org) facilitate communication between participating centers. In some cases, twinning programs have been associated with rapid increases in cure rates (map 7.1). The International Pediatric Oncology Society (SIOP) has created a forum for interested HIC and LMIC centers to build future twinning initiatives.

Despite the success of the twinning paradigm in improving individual pediatric cancer units, improvements must be translated into national childhood cancer strategies to have the greatest impact. Most LMICs lack policies to ensure good pediatric oncology care, and many have no national cancer plan, let alone one targeting the unique needs of children. Notable exceptions include Seguro Popular in Mexico, which includes an accreditation process for hospitals treating children with cancer, and reimbursement for care provided by qualifying institutions. Since this program began, abandonment of treatment has fallen from 52 percent to 5 percent, although access to care and the survival of treated patients varies widely among accredited pediatric cancer units. Current efforts in China to build comprehensive health insurance programs that also cover childhood cancer treatment hold great promise, but they are still in their infancy.
Map 7.1. Pediatric Oncology Twinning Partnerships, Selected Examples

Source: Authors.

Note:

1. Denver, United States, with Santo Domingo, Dominican Republic.
2. Memphis, United States, with multiple Central American centers, Recife, Brazil, and Mindanao, Philippines.
3. Boston, United States, with Bogota, Colombia.
4. Toronto, Canada, with Amman, Jordan.
5. Monza, Italy, with multiple Central American centers.
6. Madrid, Spain, with Asuncion, Paraguay
8. Multiple German and Austrian centers with multiple Russian and Belarussian centers.
9. Amsterdam, the Netherlands, with Universitas Gadjha Mada, Indonesia.
10. Tygerberg, South Africa, with multiple centers in Namibia and Malawi.
11. Auckland and Christchurch, New Zealand, with multiple South Pacific centers.
General Principles of Treatment

Importance of Locally Adapted Treatment Protocols

Although not true for all cancers, increasing the intensity of treatment has increased cure rates.28-30 Different childhood cancers require different treatment intensities for maximum cure rates; for example, the chemotherapy for Wilms tumor is far less intense than for acute myeloid leukemia (AML). One of the great achievements of pediatric oncology in recent decades is the refinement of risk stratification systems, allowing for an assessment of the aggressiveness of a particular child’s cancer and for treatment intensity to be matched to disease risk, thus reducing both under-treatment and overtreatment.31-34

Avoiding overtreatment is crucial in LMICs, since it carries with it an increased risk of treatment-related mortality (TRM), defined as death from complications of treatment (for example, infection, hemorrhage, and organ failure), as opposed to the disease itself.35-39 At some point, any benefit in disease control of intensifying treatment will be outweighed by an increase in TRM. Finding the balance point for each malignancy at each pediatric cancer center is key to optimizing therapy and curing the maximum number of children possible.

This ideal balance point depends on the malignancy in question, as well as a particular center’s ability to provide supportive care to prevent and manage treatment complications. The same high intensity chemotherapy delivered at two centers, one with 24-hour availability of intensive care and the other without, will result in higher TRM rates in the latter. In HICs, advances in supportive care have allowed the delivery of ever higher intensity treatments. Even in this context, however, the ideal balance has at times been difficult to find; intensifying treatment for AML initially resulted in high TRM rates in Europe and North America, which later decreased as cancer units developed the new level of supportive care required.36,40

In many LMIC centers, supportive care capabilities lag behind those in HICs. Transposing treatment protocols designed for HIC levels of supportive care to LMIC centers is therefore almost certain to cause high levels of TRM.37,38 The possibility of doing more harm than good is significant. An important example is described in box 7.1, where decreasing treatment intensity actually led to higher cure rates. Questions to ask when trying to determine the supportive care capabilities of an individual institution are listed in box 7.2.

Box 7.1 Acute Promyelocytic Leukemia: Cost and Treatment Intensity

Acute promyelocytic leukemia (APL) is a subtype of AML, with cure rates of about 80 percent in HICs.9 In Guangzhou, China, Luo and others treated 30 children with APL between 1999 and 2008.1 In Guangzhou, China, Luo and others treated 30 children with APL between 1999 and 2008. Before September 2004, children were treated on an intensive protocol including high-dose cytarabine and high cumulative doses of anthracycline. After September 2004, children were treated with a far less intensive
protocol with fewer chemotherapy cycles, lower anthracycline doses, and no cytarabine. The total cost of therapy was lower, decreasing the financial burden on parents. With the first protocol, out of 16 children, six abandoned therapy and seven developed bacterial sepsis, one of whom died. With the less intensive protocol, no child out of the 14 studied abandoned therapy, and there was only one episode of sepsis, with no resultant infectious deaths. The three-year, event-free survival was 37.5 percent with the more intense protocol, and 79.6 percent with the less-intensive treatment. While the number of patients is small, this example illustrates an important principle: increased intensity and cost of treatment can do more harm than good.

Sources:
   b. Luo 2009.

Box 7.2 Sample Questions To Ask When Determining the Supportive Care Capacity of a Pediatric Cancer Unit

- Are 24-hour nursing and medical coverage available for inpatients?
- How quickly can antibiotics be ordered, received, and given to patients when urgent treatment is necessary?
- How quickly can a blood transfusion be ordered, received, and given to patients when urgent treatment is necessary?
- Are basic radiographic, microbiologic, and hematologic diagnostic tests available?
- Is intensive care, including ventilatory and inotropic support, available?
- What is the prevalence of malnutrition in the population? What programs are available in the pediatric cancer unit to address malnutrition?
- Are families able to reach medical attention quickly in case of a treatment complication?
- Where do outpatients go when emergencies develop after hours? Who treats them there? Are pediatric oncology professionals involved in their care after hours?

Source: Authors

Further consequences stem from the principle that increased intensity and cost of treatment can do more harm than good. Many diagnostic modalities are utilized in
order to better classify the extent of disease, including stage and risk group, of particular patients. For example, in ALL, the most common childhood cancer in many countries, flow cytometry and cytogenetics help to identify high-risk subgroups such as T-cell or hypodiploid ALL. Children with these high-risk subgroups are treated with higher intensity protocols. In a center in which higher intensity therapy leads to unacceptable TRM rates, spending limited resources on developing these diagnostic modalities is difficult to justify. However, making a correct diagnosis (such as distinguishing between myeloid and lymphoblastic leukemia) is often life-saving and cost-effective.

**Abandonment of Therapy**

Abandonment is defined as the “failure to start or complete [potentially] curative treatment.” While virtually unknown in HICs, the phenomenon of abandonment is a significant problem in LMICs; in some contexts, it constitutes the most common cause of treatment failure. The importance of this issue led SIOP to establish the Abandonment of Treatment Working Group. A recent systematic review of pediatric acute lymphoblastic leukemia in LMICs found that abandonment rates ranged from 3 percent to an astonishing 74 percent. It is worth noting that none of 83 published reports of abandonment in LMICs were from LICs, so the review likely underestimates the global incidence of abandonment.

Many reasons for abandonment have been cited, including a lack of financial resources, poor disease comprehension, cultural factors, belief in alternative medicines, fear of treatment toxicity, inadequate care on the part of health care workers, and decreased awareness of aid programs. Interestingly, even in the context of a treatment program in which chemotherapy, supportive care, lodging, and transport were provided at no cost to families, families of low socioeconomic status were still at higher risk of abandonment. Various efforts in LMICs have decreased abandonment rates, including providing financial support, adapting treatment protocols based on a family’s financial resources, providing parental education, and establishing a social work program (box 7.3).

**Box 7.3 Examples of Successful Efforts To Decrease the Abandonment of Therapy in Children with Cancer**

In Guatemala City, Guatemala, through the establishment of a pyscho-social team including both social workers and psychologists whose aim is to support families throughout the cancer experience, abandonment has decreased from 42 percent to 2 percent.

In Recife, Brazil, through the provision of lodging, social work, transportation and food subsidies, and the establishment of a parent group, a fundraising foundation, and a patient tracking system, abandonment among children with ALL decreased from 16 percent to 1.0 percent from 1980 to 2002.
In Yogyakarta, Indonesia, after the introduction of a parental education program, upfront treatment refusal for children with ALL decreased from 14 percent to 2 percent among poor parents.\(^{49c}\)

**Sources:**

a. F. Antillon, personal communication.


c. Mostert and others 2010.

<<end box 7.3>>

Thus, just as some level of basic supportive care capacity is necessary to treat children with cancer, basic educational and aid programs aimed at preventing abandonment are also imperative.

**Outcome Evaluation**

While it is possible to theorize as to what protocol modifications are best suited to a particular LMIC institution, there is no substitute for the actual monitoring of treatment outcomes. Collection of basic data on patient demographics, disease characteristics and treatment outcome (including cause of death) allows for evaluation of a specific treatment protocol, as well as the design of future interventions. For example, it is not enough to know that children with ALL in an individual center have a mortality rate of 50 percent, without evaluating the causes of death. If the predominant cause of death was TRM, then appropriate interventions would include the strengthening of supportive care, perhaps accompanied by de-intensification of treatment. However, if the predominant cause was relapse, increasing treatment intensity may be appropriate. Outcome monitoring allows for the gradual evolution of treatment strategies in a safe and efficient manner and cure of the maximum number of children possible at each stage.\(^{51}\)

Healthcare workers in many LMICs lack the time to collect, review, and analyze outcome information, so a dedicated data manager is needed to ensure the accurate and timely data entry. The Pediatric Oncology Networked Database (POND, www.POND4Kids.org) is a secure, multilingual, online database specifically designed for analysis of pediatric oncology data and provided at no cost by St. Jude Children’s Research Hospital.\(^{52}\) It is used by over 200 sites globally. POND can be adapted to the individual needs of a particular center. Data stored in the system are owned by the treating center; no individual or organization can access the data without express permission from local personnel. At the moment, a reliable Internet connection is required to use POND.

It is worth emphasizing that the collection and analysis of these data are neither academic research nor a luxury. Indeed, outcome monitoring is essential to improving care and outcomes at any pediatric cancer center, whether in LMICs or HICs. However,
quality improvement efforts in LMICs often mean the difference between life and death, whereas those in HICs affect more subtle outcomes.

**The Treatment of Specific Cancers**

The ideal malignancy targeted for treatment in LMICs would be one that accounts for a significant proportion of the local cancer burden and that is curable with either simple surgery or short-course chemotherapy alone. The treatment of this ideal target would involve minimal acute toxicity and few chronic late effects. (Survivorship issues specific to LMIC children are currently unstudied). Of course, no single malignancy perfectly fits this profile. Which malignancies should be treated in a particular LMIC center depends on the local incidence, the available treatment modalities, the institutional level of supportive care possible, and theoretically attainable cure rates.

A center that is only beginning to treat childhood cancer could start with malignancies for which cure is possible with relatively simple and low-intensity chemotherapy, such as BL or Hodgkin lymphoma (HL). A center that has already achieved significant cure rates in these cancers could then address malignancies requiring more complex chemotherapy (for example, ALL), multimodality treatment (for example, Wilms tumor), and eventually advance to treatment of sarcomas, brain tumors, and diseases that require high levels of supportive care (for example, AML, high-risk neuroblastoma).

Table 7.3 lists characteristics of 13 of the most common childhood cancers; this information should be considered before deciding which malignancies to treat and which resources to develop in a specific setting. For each type of cancer, the elements required for successful treatment may differ based on stage and risk group. For example, while intensive chemotherapy, surgery, radiation, and autologous stem cell transplantation cure only a minority of advanced stage neuroblastoma in older children, surgery alone may cure localized and biologically favorable neuroblastoma in a younger child.

The subsequent sections discuss five childhood cancers often targeted by LMIC centers and that collectively account for a significant portion of pediatric malignancies: ALL, HL, Wilms tumor, BL, and retinoblastoma. Each section outlines aspects of diagnosis and treatment and how both may be adapted to local resource constraints.

<<insert table 7.3 about here>>
**Acute Lymphoblastic Leukemia**  
Stephen P. Hunger\(^1\) and Federico G. Antillon\(^2\)

\(^1\)Children’s Hospital Colorado and the Department of Pediatrics, University of Colorado School of Medicine, Aurora CO, USA; \(^2\)Unidad Nacional de Oncologia Pediatrica, Guatemala City, Guatemala

**Overview**

ALL, a cancer of white blood cells (WBC), is the most common childhood cancer, accounting for 25 percent of cancers among those younger than 15 years of age, and 20 percent of those that occur before 20 years of age.\(^{53}\) ALL is universally fatal without effective therapy. In North America and Western Europe, five-year survival rates have steadily improved, from below 10 percent in the 1960s to over 90 percent today.\(^{54-57}\)

However, most children who develop ALL do not reside in these countries. China and India are predicted to have four to five times as many pediatric ALL cases as the United States; Indonesia, Nigeria, and Pakistan are predicted to have about the same number of cases as the United States (U. S. Census 2010) (table 7.4). Thus, it is critical to consider how pediatric ALL can be cured in countries that have very different income structures and health care systems than those in North America and Western Europe.

**Table 7.4. Projected Cases of Acute Lymphoblastic Leukemia Occurring Before Age 20, and Infant Mortality Rates for the 10 Most Populous Countries**

<table>
<thead>
<tr>
<th>Country</th>
<th>2010 Population* (millions)</th>
<th>2010 Population, ages 0 to 19.99 years(^a) (millions)</th>
<th>Infant mortality rate (per 1000 live births)</th>
<th>Projected annual cases of ALL, ages 0 to 19.99 years(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>1,330</td>
<td>342</td>
<td>21</td>
<td>9,918</td>
</tr>
<tr>
<td>India</td>
<td>1,170</td>
<td>464</td>
<td>53</td>
<td>13,456</td>
</tr>
<tr>
<td>United States</td>
<td>309</td>
<td>83</td>
<td>6.4</td>
<td>2,407</td>
</tr>
<tr>
<td>Indonesia</td>
<td>243</td>
<td>89</td>
<td>30</td>
<td>2,581</td>
</tr>
<tr>
<td>Brazil</td>
<td>196</td>
<td>67</td>
<td>24</td>
<td>1,943</td>
</tr>
<tr>
<td>Pakistan</td>
<td>184</td>
<td>88</td>
<td>64</td>
<td>2,552</td>
</tr>
<tr>
<td>Nigeria</td>
<td>162</td>
<td>88</td>
<td>75</td>
<td>2,552</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>156</td>
<td>70</td>
<td>45</td>
<td>2,030</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>143</td>
<td>29</td>
<td>8.2</td>
<td>841</td>
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<td>----</td>
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<td>-----</td>
</tr>
<tr>
<td>Japan</td>
<td>128</td>
<td>24</td>
<td>2.6</td>
<td>696</td>
</tr>
</tbody>
</table>


**Diagnosis of ALL**

Children with ALL are commonly brought to medical attention for symptoms caused by ineffective production of normal blood cells due to replacement of the bone marrow by leukemia, including pallor, bleeding, fever, infections, and bone pain. They may also have leukemic involvement of other organs, including liver, spleen, mediastinum, central nervous system, and testicles.

ALL is diagnosed based upon review of peripheral blood cell counts and a bone marrow aspirate/biopsy, tests that can be performed at most medical facilities. Simple factors predictive of outcome include age (younger is better, except for infants less than one year), and initial WBC count (lower is better). More sophisticated and often very expensive diagnostic tests readily available in HICs include immunophenotyping to determine cell lineage, and cytogenetic or molecular genetic studies to define sentinel abnormalities, many of which have important prognostic implications. However, these tests are often not available in LMICs. A major prognostic factor is the rapidity of response to single agent or multiagent therapy, which can be measured in a simple and inexpensive manner by peripheral blood or bone marrow morphology, or in a complicated and expensive manner using advanced flow cytometry and/or molecular genetic techniques.

**General Concepts of Pediatric ALL Treatment**

Contemporary treatment for ALL consists of complex combination chemotherapy regimens that last 2.5 to 3 years, with 6 to 8 months of relatively intensive therapy, followed by 1.5 to 2 years of low-intensity maintenance therapy, during which most children can resume normal activities and attend school. Chemotherapy drugs included in these regimens have been widely available for decades; most are relatively inexpensive, with the exception of asparaginase preparations, which are extremely expensive (table 7.5). Radiation therapy to the brain was a critical component of early effective ALL regimens, but the use of cranial irradiation has been greatly reduced in most contemporary HIC regimens.
Table 7.5. Drugs Used in Treatment of Newly Diagnosed Pediatric Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Class</th>
<th>Specific drugs</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Prednisone, Dexamethasone</td>
<td>PO, IV</td>
</tr>
<tr>
<td></td>
<td>Vincristine</td>
<td>IV</td>
</tr>
<tr>
<td>Asparaginase preparations</td>
<td><em>e. coli</em>asparaginase, PEG-asparaginase, erwinia asparaginase</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Doxorubicin, Daunorubicin</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Cytarabine</td>
<td>IV, SC, IT</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>IV, IM, PO, IT</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>6-mercaptopurine, 6-thioguanine</td>
<td>PO</td>
</tr>
</tbody>
</table>

Source: Author

Note: IM = intramuscular; IT = intrathecal; IV = intravenous; PO = oral; SC = subcutaneous.

While treatment of pediatric ALL is associated with significant risk of short- and long-term side effects, most children cured of ALL will lead healthy and productive lives. Cure rates are much lower for children with ALL that relapses, with the chance of cure related to site of relapse, ALL genetic features, and time between initial diagnosis and relapse.60

Because most children with ALL live in LMICs, efforts have been made to improve treatment available in those countries through partnerships with HIC centers.61 This twinning has led to major improvements in ALL survival in LMICs, often through adoption of intact or modified HIC treatment regimens.47,62 Critical to these successes has been the transfer of knowledge regarding treatment regimens, supportive care, and emotional and psychosocial support. Abandonment of care, which occurs only rarely in HICs, is a major issue in LMICs due to economic and social pressures on parents and to cultural beliefs that a child has been healed.63,64 Innovative programs have been developed to support patients and families and greatly reduce abandonment; a Guatemala program reduced abandonment rates from 42 percent to less than 2 percent (unpublished observations; Rivas and Antillon). Successful implementation and improvement of therapies also requires close tracking of patient characteristics and outcomes, necessitating access to databases and data management personnel.65
Specifics of Pediatric ALL Treatment

The development of large cooperative treatment groups that conduct clinical trials, which often include 70 percent of more of children with ALL in a given country, has been critical to improvements in survival for pediatric ALL in HICs. This need has resulted in near-universal access to effective treatments in most HICs (limited in some cases due to country-specific differences in health care financing) and the widespread availability of knowledge about the specifics of effective treatment regimens.

Twinning has provided outstanding examples of very effective transfer of knowledge and adoption of contemporary treatment regimens in LMICs, such as the Central American Association of Pediatric Hematology Oncology (AHOPCA) in Central America, largely developed through collaborations with pediatric cancer programs in Monza and Milan, Italy, and St. Jude Children’s Research Hospital in the United States. AHOPCA now conducts its own clinical trials. In Guatemala, ALL survival rates now range from 50 percent (high-risk) to 90 percent (low-risk) for different patient subgroups. This strategy is possible in countries with reasonably well-developed health care systems, with infant mortality rates less than 40 to 50 per 1,000 live births serving as a good surrogate marker (table 7.4).

However, high rates of ALL TRM can be a major problem. Regimens that are delivered safely with TRM rates less than 5 percent in North America and Western Europe can be associated with TRM rates 5 to 10 times higher in LMICs, with the problem being much worse in countries with less developed health care systems reflected by infant mortality rates more than 50 per 1,000 live births. High rates of TRM severely compromise cure rates and can be a major impediment to program development in LMICs. Treatment of relapsed ALL has a very low chance of success in LMICs.

One way to address these problems is through use of graduated intensity regimens, whereby centers first implement less intensive regimens similar to those used in North America and Western Europe in the 1970s and 1980s, and increase treatment intensity only when they establish these therapies to be safe and effective in their local settings. This strategy is attractive because it starts with regimens that are less costly, less toxic, and do not require sophisticated diagnostic tests, but that can cure about 50 percent of children with ALL if TRM can be kept low and abandonment can be minimized.

An example from the pediatric cancer program in Santo Domingo, Dominican Republic, shows the potential benefit of this strategy. From 2005-07 a relatively intensive HIC-type treatment regimen was used in 91 children with ALL; however, it was associated with excessive TRM. Following this experience, a less intensive regimen was used to treat 101 patients diagnosed in 2008-10. The less-intensive treatment improved 24-month overall survival from 40 percent to 70 percent, accompanied by a decrease in TRM from 29 out of 91 cases in the early period to 8 out of 101 in the later period.
Costs of Pediatric ALL treatment
Pediatric ALL treatment in North America and Western Europe is widely recognized to be both very expensive and highly cost effective. A report from the Dutch Childhood Oncology Group showed mean total costs for treating pediatric ALL to be US$115,858 to US$163,350 per case, with highly favorable costs per life year saved of US$1,962 to US$2,655. However, effective treatments can be implemented for much lower costs. Luo reported in 2008 that a reduced intensity, low-cost protocol that obtained a four-year event-free survival rate of 72.8 percent could be implemented in Guangzhou, China, for a total hospital cost of US$4,300 per case (the range is from US$3,100 to US$6,800). More intensive regimens obtained slightly better results and could be implemented for US$9,900 to US$12,500, similar to the average cost of US$11,000/patient reported from Shanghai.

Summary
ALL is the most common pediatric cancer. Five-year survival rates exceed 90 percent in HICs. Through twinning, centers in LMICs with infant mortality rates less than 40 to 50 per 1,000 live births have attained cure rates of about 70 percent. Outcomes for relapsed ALL are much worse, stressing the need for effective therapy at initial diagnosis. Graduated intensity regimens have the promise to decrease TRM and improve survival, and they may be particularly effective in LMICs with infant mortality rates greater than 50 per 1,000 live births.

Hodgkin Lymphoma
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Overview
In HICs, over 80 percent of children with HL survive long-term. In LMICs, survival has been lower due to lack of adequate staging, drug shortages, inadequate access to radiotherapy, delays in therapy, and social hardship leading to abandonment of therapy. Most children with HL in LMICs present to medical attention with advanced stage disease and a long history of symptoms. Despite these obstacles, many LMIC patients can still be cured with basic chemotherapy, with or without consolidative radiotherapy. Because HL is curable, easily diagnosed, and constitutes an important portion of children with cancer, every child presenting to medical attention with suspected diagnosis of HL should be given a chance of cure.
**Epidemiology and Prognostic Factors**

Childhood HL rarely presents before five years of age in HICs; however, in LMICs it can be seen in children as young as one year. In HICs, HL has a bimodal age distribution in early adulthood and after the age of 50 years. The age distribution is shifted toward younger ages in LICs, and it often occurs before adolescence. Furthermore, in LMICs, HL is most often Epstein-Barr virus (EBV) positive and of mixed cellular histology. Disease stage and bulk, as well as the presence of “B-symptoms” (fevers, drenching night sweats, or greater than 10 percent weight loss in the past six months) are established prognostic factors. Other potential prognostic factors include the erythrocyte sedimentation rate, and low hemoglobin and albumin levels, although these may be less reliable indicators in children suffering from chronic malnutrition or parasitic infections.

**Diagnosis**

An excisional lymph node biopsy is recommended, as fine-needle aspirates are often inadequate for diagnosis. This is, in fact, the only surgical procedure routinely required in the treatment of HL. Pathology is basic; the diagnosis can be confirmed with a simple hematoxylin and eosin stain without the need for immunohistochemistry.

**Staging and Treatment Options**

In HICs, the ideal initial evaluation of children for HL includes computed tomography of the neck, chest, abdomen, and pelvis, accompanied by FDG-positron emission tomography. Staging and the presence of B-symptoms allow risk stratification with therapy tailored according to risk of relapse and adapted based on disease response after two cycles of chemotherapy. Risk-stratified, response-adapted therapy offers the potential to maximize cure and minimize toxicity.

In LMICs with limited availability of diagnostic imaging, a thorough physical examination for determination of all pathologic peripheral adenopathy, chest radiograph for extent of mediastinal involvement, and ultrasonography for intrabdominal adenopathy can be sufficient for staging. Bone marrow biopsy is not recommended for most patients, since it is expensive, painful, and rarely affects risk classification or therapy. In some cases, a positive bone marrow biopsy may actually harm the patient by leading to the false perception that bone marrow involvement is incurable or that consolidative radiation therapy is not indicated.

In cases of limited staging evaluation, the treatment approach must account for incomplete ascertainment of affected areas. Accordingly, more weight must be placed on effective chemotherapy and less on local control with radiotherapy, which would not be applied to disease sites undetected by incomplete staging evaluations. Furthermore, radiation therapy is often unavailable, inconsistently available, or too toxic when given by radiation oncologists without pediatric expertise. Risk stratification in many LMIC should also be broader, similar to early HIC chemotherapy-only trials. Table 7.6 provides examples of chemotherapy-only and combined modality treatment regimens used successfully in LMICs.

<<insert table 7.6 about here>>
During HL treatment, the minimum necessary supportive care consists of antibiotics and antiemetics; blood products are rarely needed, and therapy can be administered in the outpatient setting without the need for growth factors.

**Costs of HL Treatment**

The bulk of the cost of HL therapy is due to pathologic evaluation, radiation therapy, and diagnostic imaging studies; chemotherapy and supportive care constitute a far smaller portion. In a study evaluating the cost of therapy in Sub-Saharan Africa for a child with stage II disease and followed for two years, the total cost was above US$6,500 in a continent where the annual gross domestic product (GDP) per inhabitant is usually less than US$2,000. However, these costs can be significantly reduced by carefully choosing both the minimal necessary diagnostic imaging techniques required for staging, and chemotherapy regimens that will permit the omission of radiotherapy. The most important cost to avoid is that of relapse.

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**Wilms Tumor**

Trijn Israels

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**Overview**

Wilms tumor is relatively common, accounting for 5 percent to 7 percent of all childhood cancers. In many settings, Wilms tumor is the most common malignant abdominal tumor. As treatment programs for pediatric oncology are developed, Wilms tumor should be one of the first tumors targeted, due to its frequency and curability. Treatment also requires the development of multidisciplinary capacities that may benefit other children and programs across the hospital.

Great progress has been made in the treatment of children with Wilms tumor in recent decades. The survival rates in HICs now exceed 85 percent. Multidisciplinary treatment combines surgery and chemotherapy, with radiotherapy in a selected group of patients. Two treatment strategies have been used for Wilms tumor worldwide. The first operates on tumors upfront as practiced by the Children’s Oncology Group (COG) in North America, followed by chemotherapy; the second starts with preoperative chemotherapy as practiced in Europe (SIOP). Both strategies result in similar long-term survival for HIC patients. Preoperative chemotherapy, however, reduces surgical complications such as tumor rupture and downstages the tumor at surgery, thereby allowing for lower intensity, postoperative chemotherapy and reducing the need for radiotherapy. This is a sensible strategy for many LMIC patients, who often present with...
large tumors, in settings where supportive care is limited and radiotherapy may not be available.

Survival rates in LMICs are lower than in HICs, ranging from 11 percent to 81 percent. Known challenges are late presentation with advanced disease, malnutrition, abandonment of treatment, and poor facilities both for specific cancer treatment and supportive care. Capacity building, earlier presentation, a multidisciplinary approach, social support, improved supportive care, and treatment adapted to local circumstances are key to improving results.

Treatment Settings
The facilities and resources available for the care of children with Wilms tumor vary among centers, but they can be defined using the following settings. Setting 1 is one in which the minimal requirements for treatment with curative intent are available. Setting 3 is one where all state-of-the-art facilities are available; Setting 2 is in between. Table 7.7 provides a detailed description of each setting.

<<insert table 7.7 about here>>

Diagnosis
The diagnosis of Wilms tumor can be made with reasonable certainty based on history, physical examination, and ultrasonography of the abdomen. The typical presentation of a child with Wilms tumor in low-income settings is that of a malnourished young child with a large abdominal or flank mass, who is relatively well without acute pain or severe general malaise, but with hematuria and hypertension. Ultrasonography of the abdomen is extremely useful to confirm the diagnosis. An x-ray should be done to detect chest metastases.

In HICs, pathology is useful to confirm the diagnosis and, in addition to stage, to help risk-stratify children and determine postoperative chemotherapy. In many LMICs, however, the availability of pathologists with pediatric expertise is limited, and pathology results often are available too late to effect clinical decision making. Other challenges include the appropriate processing of specimens and the availability of special stains and immunohistochemistry, although central pathology review or telepathology may be helpful. Fortunately, a diagnosis can often be made with some certainty based on clinical findings and ultrasonography. Postoperative chemotherapy can be based on surgical staging, only if needed.

A diagnostic biopsy before preoperative chemotherapy is not standard practice in current SIOP Wilms protocols; it is only recommended in LMICs when there is serious doubt about the diagnosis. Such biopsies may result in bleeding, infection, or tumor spillage with consequent upstaging.
Treatment
Preoperative chemotherapy should be used for children with Wilms tumor in LMICs, even in cases of small, seemingly easily resectable tumors. Preoperative chemotherapy reduces surgical complications, downstages the tumor, and allows for less intense postoperative chemotherapy and the potential avoidance of radiotherapy. Reliable and continuous access to the chemotherapeutic drugs such as vincristine, actinomycin D, and doxorubicin is essential.

Radiotherapy is used in patients with advanced stage or unfavorable histology disease in centers with advanced capabilities. Unfortunately, safe radiotherapy for children is often unavailable in developing countries. Recent National Wilms Tumor Study (NWTS) and SIOP studies have shown that omitting or decreasing radiation therapy may not compromise cure rates, but these studies have not been done in children with very advanced disease or large tumors. Studies from Morocco and Nicaragua have demonstrated that cure can be achieved in some patients with advanced disease without radiotherapy. Higher cure rates in these populations may, however, require radiotherapy.

Table 7.8 shows some elements of the therapy used and the results from a selected number of countries with limited resources.

<<insert table 7.8 about here>>

Cost of Wilms Treatment
To date, cost analyses related to the treatment of children with Wilms tumor in LMICs have not been reported. Although of relatively long duration (six months to two years), treatment is of relatively low-intensity and does not involve expensive chemotherapeutic agents. The costs of surgery are likely to be high. Social support enabling parents to complete treatment is very likely to be cost-effective in LMICs.

Burkitt Lymphoma
Mhamed Harif

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Overview
BL is a mature B-cell neoplasm that arises in lymphoid tissue, commonly in the jaw or abdomen. Described first in 1957 by Denis Burkitt in Uganda, it remains the most common pediatric cancer in endemic regions of Sub-Saharan Africa. BL invariably arises from chromosomal translocations in which an oncogene (c-myc) is juxtaposed
with genes encoding immunoglobulins. These translocations lead to an overexpression of monoclonal surface immunoglobulins in malignant cells, important for diagnosing and distinguishing it from other lymphoid cancers.

Although more than 90 percent of children with BL in HICs can be cured, doing so requires timely, accurate, diagnosis and risk-directed treatment with high-intensity chemotherapy and well-developed supportive care.\footnote{In many LMICs with limited supportive care, delivery of such therapy causes excessive toxic death; adapted regimens are necessary in order to cure as many patients as possible.} Nevertheless, in even the most resource-constrained environment, a simplified protocol for patients with BL can cure 50 percent of patients.\footnote{Indeed, treatment of BL is highly cost-effective in all settings; an attempt at treatment is always warranted.}

**Diagnosis**

Suspected BL is a medical emergency. BL is the fastest growing human malignancy, in some cases doubling its volume every 24 hours. The risks of tumor lysis syndrome (TLS)—a collection of metabolic derangements caused by the rapid turnover of malignant cells, disease progression, nutritional deterioration, and concomitant infection—make diagnosis and therapy critical. Indeed, any child from an endemic region presenting with massive facial swelling or an abdominal mass requires immediate physical and laboratory evaluation for any of these complications.

While biopsy of the suspected tumor is recommended for diagnosis, extensive surgery is contraindicated. The top priority must always be to make a diagnosis in the fastest, least invasive way possible and to rapidly initiate therapy. In rare cases, BL cells may be seen in the peripheral blood (as in Burkitt leukemia), obviating the need for a biopsy. A fine-needle aspiration may be sufficient in patients whose clinical features are consistent with BL.\footnote{When possible, the presence of mature B-cell markers (for example, CD20, immunoglobulin) and proliferative markers such as Ki67 should be verified to differentiate BL from other small, round, blue cell tumors.}

In cases in which the diagnosis is very likely and pathologic confirmation will be delayed, chemotherapy with cyclophosphamide, vincristine, and prednisone (COP) may be initiated empirically in potentially life-threatening situations. These agents have low toxicity and are active for most lymphomas. The benefits of prompt therapy initiation greatly outweigh the risks, as delayed therapy can lead to metabolic complications such as TLS that can be rapidly fatal.

**Staging Evaluations and Risk Stratification**

Staging evaluations in HICs includes a detailed physical examination to document peripheral adenopathy and testicular involvement; CT imagining of the neck, chest, abdomen, and pelvis to define all sites of adenopathy; and the evaluation of CSF, bone marrow aspirates, and biopsies. Ideally, lumbar punctures are delayed until a diagnosis is made, so that intrathecal therapy can be administered at the time of the diagnostic puncture. The Murphy (St. Jude) staging system is most commonly used to classify extent of disease (table 7.9).\footnote{In LMICs, a physical examination, CXR, abdominal}
ultrasound, bone marrow aspiration, and lumbar puncture may provide sufficient staging information.\(^\text{100}\)

Table 7.9. Staging of Non-Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>• Single tumor in a node or extralymphatic site, excluding the mediastinum or abdomen</td>
</tr>
<tr>
<td>Stage II</td>
<td>• Single extranodal tumor with regional node positive</td>
</tr>
<tr>
<td></td>
<td>• Two or more nodal areas on the same side of the diaphragm</td>
</tr>
<tr>
<td></td>
<td>• Two extranodal tumors on the same side of the diaphragm regardless of nodal involvement</td>
</tr>
<tr>
<td></td>
<td>• Primary gastrointestinal tract tumor with or without associated mesenteric nodes, grossly completely excised</td>
</tr>
<tr>
<td>Stage III</td>
<td>• Two single extranodal tumors on opposite sides of the diaphragm</td>
</tr>
<tr>
<td></td>
<td>• Two or more nodal areas above and below the diaphragm</td>
</tr>
<tr>
<td></td>
<td>• All tumors originating in mediastinum, pleura, or thymus</td>
</tr>
<tr>
<td></td>
<td>• All extensive primary intra-abdominal disease (usually many implants, not totally resectable); often ascites</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any of the preceding stages with initial central nervous system, bone marrow, or both central nervous system and bone marrow involvement</td>
</tr>
</tbody>
</table>

Source: Author

Disease risk assignment, and thus treatment intensity, is determined mainly by disease stage. Lactate dehydrogenase level indicates disease activity and affects risk group assignment in some, but not all, HIC protocols. Inadequate response to treatment, defined in HICs as less than 20 percent reduction in tumor size after the initial COP cycle or residual cancer after the first intense blocks of therapy, require intensification of therapy. Different definitions of inadequate response have been used in resource-constrained settings.\(^\text{95}\) In either case, the dimensions of all masses must be documented at presentation.

**Treatment**
The optimal treatment regimen for a particular patient depends on disease stage but also on the environment of care. Families with high socioeconomic status, good transportation, and proximity to a pediatric cancer unit with excellent infrastructure and supportive care can be treated on a HIC regimen, including intensive- and short-duration
therapy with vincristine, cyclophosphamide, doxorubicin, cytarabine, high-dose methotrexate, and intrathecal agents. Duration and intensity vary according to risk group, but overall the therapy produces a 90 percent cure rate.\textsuperscript{18} However, this treatment approach in settings with limited supportive care exposes patients to high rates of mortality and abandonment.

In developing countries and even in very poor settings, it has been shown that at least 50 percent of children with BL and up to 70 percent children with localized stage I or stage II disease can be cured with intravenous or oral cyclophosphamide in combination with intrathecal methotrexate (table 7.10).\textsuperscript{19,96,101} Treatment with simplified regimens is feasible everywhere and should always be attempted (table 7.11).

**Table 7.10. Chemotherapy Regimen in Use by the French-African Pediatric Oncology Group**

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Days of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide 1.2 g/m2 IV</td>
<td>Stage 1 and 2</td>
</tr>
<tr>
<td>MTX 15 mg + HCT 15 mg IT</td>
<td>Days 1 and 2, 8, and 15</td>
</tr>
<tr>
<td><strong>Stage 3 and 4</strong></td>
<td></td>
</tr>
<tr>
<td>Days 28, 43, and 57</td>
<td></td>
</tr>
<tr>
<td><strong>Second-line chemotherapy (refractory/relapsed patients)</strong></td>
<td></td>
</tr>
<tr>
<td>COMP (course 1 and 2)</td>
<td>Days 2 to 4, with IV hydration</td>
</tr>
<tr>
<td>Cyclophosphamide 500 mg/m2/day IV</td>
<td>Day 1</td>
</tr>
<tr>
<td>Vincristine 2 mg/m2 IV (maximum of 2 mg)</td>
<td>Day 1 with folinic acid rescue/alkalinization</td>
</tr>
<tr>
<td>MTX 3 g/m2 IV over 2 hours,</td>
<td>Days 1 to 5, and then over 3 days</td>
</tr>
<tr>
<td>Prednisone 60 mg/m2 PO or IV</td>
<td>Days 2 and 6</td>
</tr>
<tr>
<td>MTX 15 mg + HCT 15 mg IT</td>
<td>Days 2 to 6 divided in two injections</td>
</tr>
<tr>
<td>CYM (course 3 and 4)</td>
<td></td>
</tr>
<tr>
<td>Cytarabine 100 mg/m2/day SC</td>
<td></td>
</tr>
<tr>
<td>MTX 3 g/m2 IV over 2 hours</td>
<td></td>
</tr>
<tr>
<td>MTX 15 mg + HCT 15 mg IT</td>
<td></td>
</tr>
<tr>
<td>Cytarabine 30 mg + HCT 15 mg IT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Traore and others 2011 (to confirm)

Note: HCT = hydrocortisone; IT= intrathecal; IV = intravenous; MTX = methotrexate.
Table 7.11. Selected Cohorts and Outcomes of Children with Burkitt Lymphoma Treated in Low- and Middle-Income Countries with Locally Adapted Protocols of Lower Intensity

<table>
<thead>
<tr>
<th>Countries</th>
<th>Subgroups</th>
<th>Number of Patients</th>
<th>Outcome (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hesseling et al. (^{139})</td>
<td>Cameroon Stages I and II</td>
<td>18</td>
<td>EFS 94</td>
</tr>
<tr>
<td></td>
<td>Stage III, clinical remission, or residual abdominal &lt;30 mL</td>
<td>58</td>
<td>EFS 76</td>
</tr>
<tr>
<td></td>
<td>Stage IV, no clinical remission, or residual abdominal mass &gt;30 mL</td>
<td>45</td>
<td>EFS 40</td>
</tr>
<tr>
<td>Ngoma et al. (^{140})</td>
<td>Tanzania, Kenya, Nigeria -</td>
<td>326</td>
<td>EFS 52; OS 62*</td>
</tr>
<tr>
<td>Traore et al. (^{101})</td>
<td>Madagascar, Cote d’Ivoire, Mali, Senegal, Burkina-Faso, Cameroon Stage I</td>
<td>19</td>
<td>EFS 44</td>
</tr>
<tr>
<td></td>
<td>Stage II</td>
<td>23</td>
<td>EFS 49</td>
</tr>
<tr>
<td></td>
<td>Stage III</td>
<td>128</td>
<td>EFS 30</td>
</tr>
<tr>
<td></td>
<td>Stage IV</td>
<td>6</td>
<td>EFS 17</td>
</tr>
</tbody>
</table>

Source: Hesseling et al. \(^{139}\), Ngoma et al. \(^{140}\), Traore et al. \(^{101}\)

Note: EFS = event free survival; OS = overall survival.*No significant differences according to stage.

In all cases, optimizing supportive care includes the prevention and treatment of TLS, infection, and vomiting. TLS is the most common cause of early death in patients with BL. \(^{102}\) Aggressively hydrating (three liters/m\(^2\)/day), frequently monitoring urine output and serum chemistry values, and controlling uric acid with rasburicase (where available) or allopurinol can prevent acute kidney injury in most cases. Nutritional support and the
prompt diagnosis and treatment of febrile neutropenia and mucositis are the mainstays of supportive care after the first week. Family education, written care pathways, and creative nutritional supplements can produce remarkable results, even in LMICs.\textsuperscript{103,104}

Relapses are usually seen during the first six months and are rare after one year. Follow-up after a year focuses on identifying late toxicities and assisting with reintegration into society. In LMICs, recruiting survivors to improve community awareness of pediatric cancer care and the possibility of cure is essential.

**Cost of BL Treatment**
As in other pediatric malignancies, data on the cost-effectiveness of treatment are rare. Given that a small number of doses of cyclophosphamide, a relatively inexpensive drug, can cure a significant portion of children, the treatment of BL is likely to be highly cost-effective. A recent paper using data from Malawi demonstrated that using the World Health Organization (WHO) definition, treatment costs under US$14,243 per case would be considered very cost-effective.\textsuperscript{97} Actual estimated costs of treatment per case, at US$50, were far lower, though this figure only accounted for the costs of chemotherapy.

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**Retinoblastoma**
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**Overview**
Retinoblastoma is the most frequent neoplasm of the eye in childhood, representing 2.5 percent to 4 percent of all pediatric cancers and 11 percent of cancers in the first year of life. Retinoblastoma presents in two distinct clinical forms.\textit{Bilateral or multifocal} (25 percent of cases) is hereditary, characterized by the presence of germline mutations of the \textit{RB1} gene. Multifocal retinoblastoma may be inherited from an affected survivor or be the result of a new germline mutation. \textit{Unilateral} retinoblastoma (75 percent) is almost always nonhereditary. Retinoblastoma is a cancer of the very young; two-thirds of the cases are diagnosed before 2 years of age, and 90 percent of the cases are diagnosed before 5 years of age.\textsuperscript{53}

**Epidemiology**
The incidence of retinoblastoma in the United States and Europe is 2 to 5 per million children (approximately one in 14,000 to18,000 live births). However, the incidence is not consistent around the world, appearing higher (six to 10 per million) in India, Sub-
Saharan Africa, and among children of Native American descent in North America.\textsuperscript{75} Whether this variation is due to ethnic or socioeconomic factors is unknown, although an environmental role has been suggested.\textsuperscript{105,106} Therefore, an estimated 8,000 children develop retinoblastoma each year worldwide. This burden is unequally distributed, with the majority of children living in LMICs; these settings witness 90 percent of metastatic cases and virtually all cases of abandonment.\textsuperscript{107}

**Prevention and Early Detection**
As with virtually all childhood cancers, retinoblastoma is not amenable to primary prevention. However, identification of the hereditary forms and proper counseling of these patients and their families is key to limiting the incidence and burden of retinoblastoma in those kindred.

The successful management of retinoblastoma depends on the ability to detect the disease while it is still intraocular. Disease stage correlates with delay in diagnosis; growth and invasion occur in sequence, with extension beyond the retina occurring only once the tumor has reached large intraocular dimensions. In HICs, retinoblastoma typically presents while still intraocular; in LMICs, 60 percent to 90 percent of children present with extraocular tumor. Poverty, limited health care access, poor education, and other aspects of low socioeconomic status are factors in delayed diagnosis and under-diagnosis in LMICs. The true magnitude of the problem is difficult to ascertain, given the paucity of population-based cancer registries.

Conversely, retinoblastoma educational and public awareness campaigns have been shown to increase referrals, decrease rates of advanced disease, and improve outcomes in LMICs.\textsuperscript{108,109} Also critical is the ability of the first health care contact to identify the problem and make the appropriate referrals. A lack of knowledge on the part of frontline health care workers has been shown to be a significant barrier, highlighting the importance of targeting educational initiatives to primary healthcare providers.\textsuperscript{110}

**Diagnosis and Staging**
The diagnosis of intraocular retinoblastoma does not require pathologic confirmation. An examination under anesthesia with a maximally dilated pupil and scleral indentation is, however, required to examine the entire retina. Additional imaging studies including bi-dimensional ultrasound, computerized tomography, and magnetic resonance imaging are desirable but not necessary in order to evaluate extraocular extension and to differentiate retinoblastoma from other causes of leukocoria.

The staging of retinoblastoma reflects the sequential nature of its progression, beginning with extension into the ocular coats (choroids and sclera) and optic nerve. Loco-regional dissemination occurs by direct extension into the orbital contents and pre-auricular lymph nodes. Extraorbital disease manifests as both intracranial dissemination and hematogenous metastases to bones, bone marrow, and liver. Patients are accordingly staged as having intraocular, orbital, or extraorbital disease.\textsuperscript{111}

For patients with intraocular retinoblastoma, dedicated staging of the eye is performed to guide treatment modalities. This classification system is based on tumor size and
location within the eye, as well as the extent of tumor seeding within the vitreous cavity and sub-retinal space, all of which must be documented on the initial exam under anesthesia. An evaluation for the presence of metastatic disease (bone scintigraphy, bone marrow aspirates and biopsies, lumbar puncture) should be considered in patients presenting with intraocular retinoblastoma with specific high risk features.\textsuperscript{112}

**Treatment**
The treatment goal is to save life and preserve vision; treatment is therefore individualized according to the unilaterality or bilaterality of the disease, potential for vision, and disease stage. In HICs, more than 90 percent of children present with intraocular disease; clinical and research programs aim to improve ocular salvage and preserve vision. While surgical removal of the eye (enucleation) is commonly performed for patients with advanced intraocular unilateral disease, more conservative approaches are followed for children with bilateral and early unilateral disease. Modalities include systemic or intra-arterial chemotherapy as well as intensive focal treatments, such as laser thermotherapy and cryotherapy.\textsuperscript{113,114} Orbital radiation therapy is used when the preceding methods fail. For patients undergoing upfront enucleation, chemotherapy is only used in the presence of high-risk features, which in HICs occurs in 20 percent to 25 percent of cases.\textsuperscript{113} In general, the outcome for children with retinoblastoma in HICs is excellent, with survival rates in excess of 95 percent. Many of the modalities discussed require state-of-the-art equipment and expertise that are unavailable in most LMIC settings. Thus, for LMIC patients presenting with orbital disease, the use of chemotherapy, enucleation, and radiation therapy may offer the best chances of cure.

Patients presenting with metastatic disease are not curable with standard therapies in any setting, though patients without central nervous system spread may benefit from intensive chemotherapy and consolidation with high-dose chemotherapy and autologous stem cell rescue.\textsuperscript{113,115} In LMIC children presenting with advanced extraocular retinoblastoma, measures decreasing suffering and improving quality of life may be most appropriate. Low-dose oral chemotherapy and radiation therapy may result in temporary symptom control.

**Costs of Retinoblastoma Treatment**
While little is known about the cost-effectiveness of retinoblastoma treatment, measures targeting early diagnosis are likely key. Failures in public awareness and deficiencies in education among frontline healthcare providers represent major barriers in early diagnosis and result in the high incidence of metastatic disease and mortality rates in LMICs.\textsuperscript{116} In HICs, children with retinoblastoma are usually diagnosed with advanced intraocular disease; by the time leukocoria is obvious, the tumor may fill more than 50 percent of the globe, complicating ocular salvage. Thus, delayed diagnosis remains an issue in both HICs and LMICs, although with consequences on a different scale. As retinoblastoma is a cancer of the infant and young child, initiatives targeting early recognition during standard health supervision visits and immunizations should facilitate diagnosis, decrease disease and treatment burdens and costs, and increase survival.\textsuperscript{117}
The Cost-Effectiveness of Treating Childhood Cancer

Financial objections are often raised to the treatment of childhood cancer in resource-constrained settings; policymakers and laypersons may assume that any such treatment is prohibitively expensive. This assumption is often unsupported.

Indeed, preliminary evidence suggests that treating childhood cancer may be highly cost-effective. Standard WHO methodology defines cost-effectiveness as the ratio of the cost required to avert one disability-adjusted life year (DALY) to the annual per capita GDP of the area\(^\text{118}\). Ratios of 3:1 are considered cost-effective, while ratios of 1:1 are considered very cost-effective. Bhakta and others found that the amount that could be spent on a single case and still remain under the very cost-effective threshold was US$257,000 for ALL in Brazil and US$14,243 for Burkitt lymphoma in Malawi\(^\text{97}\). In reality, these cancers can be treated for a fraction of these threshold values: US$16,400 and less than US$50, respectively. Table 7.12 and figure 7.3 illustrate cost-effective thresholds for several malignancies in various countries and compare them to actual costs, when available. These figures, however, do not account for initial expenditures associated with developing new pediatric oncology treatment centers, such as the initial training of personnel or acquisition of infrastructure.

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Figure 7.3. Cost-Effective Thresholds Compared to Actual Costs in Select Pediatric Malignancies

Source: Bhatka and others 2012.

Note: *Costs only include chemotherapy and supportive care medications, such as antibiotics and antipyretics.

**Includes total costs for the entire treatment. Not included are the costs of lost economic productivity, associated infrastructure and personnel costs, or indirect costs to parents, such as transportation, accommodation, and food.

ALL = acute lymphoblastic leukemia; BL = Burkitt lymphoma; US$= U. S. dollars.

See text for definitions of cost-effective and very cost-effective. See references in Table 7.12 for details about the data presented in this figure. Taken from Bhakta et al. 97
Discussions of cost and cost-effectiveness in pediatric oncology should consider three additional factors.

- First, adapted treatment regimens of lower intensity can cure a significant proportion of children, with further increases in intensity delivering real, but diminishing, gains. This observation suggests that in most LMICs, an initial modest commitment of funds toward childhood cancer will result in a dramatic increase in survival, although further improvements will require significant additional resources.

- Second, traditional cost-effective models assume a finite resource pool; funding one intervention requires cutting another. This zero-sum assumption may not be applicable to childhood cancer. In multiple LMICs, largely through the efforts of nongovernmental organizations, private funds that otherwise may have remained outside the health system have instead been allocated to pediatric oncology centers. The success of the Unidad Nacional de Oncologia Pediatrica (UNOP) in Guatemala provides an example of how multiple sectors can be mobilized, creating a positive-sum scenario. An initial outlay of funds to UNOP through a twinning program was leveraged into additional resources from both government and private donors. The creation of an independent fundraising organization (Fundacion Ayudame a Vivir, http://ayuvi.org.gt) was essential to this outcome. Figure 7.4 illustrates the results of this process.

- Finally, determining whether resources should be allocated to the treatment of childhood cancer may be more complex than simple analyses of cost and cost-effectiveness. Arguments pertaining to justice, equity, and the nonmonetary value of children to society may well hold resonance for governments, policymakers, health care workers, and members of the general public.
Figure 7.4. Budget of the Unidad Nacional de Oncologia Pediatria of Guatemala

Source: Personal communication F. Antillon, Director Unidad Nacional de Oncologia Pediatria

Note: The red area indicates funding from St. Jude Children’s Research Hospital and the blue area funding from all other sources.

Future Directions
Although the advances in pediatric oncology in HICs have not been fully realized in most LMICs, significant progress has been achieved in some pediatric cancer units. The challenge remains to extend this progress to all cancer centers in LMICs and to close the survival gap. The following steps are key prerequisites:

- The development of national childhood cancer strategies is needed to move beyond the twinning paradigm and to increase cure rates for entire populations. Lobbying of governments by both clinicians and parental groups is required, as are links between and among HICs and LMIC childhood cancer advocates.

- To better inform governments and health officials, further research into the cost and cost-effectiveness of treatment is necessary. Without such data, the misconception of childhood cancer treatment as unaffordable will persist.
• The outcomes of children with cancer should be monitored by individual treatment centers using data entry systems. These data should be used to continually evaluate and modify the local implementation of therapeutic interventions. Governments can encourage this process through national childhood cancer strategies that include high-quality pediatric registries.

• Further research is needed into to how to most effectively treat various different childhood malignancies in the setting of different resource constraints. Studies identifying how to prevent common causes of treatment failure in LMICs should be conducted.

• The formation of cooperative groups of LMIC centers should be encouraged as forums for both protocol evaluation and advocacy; AHOPCA, the French-African Pediatric Oncology Group (GFAOP), and the Brazilian Childhood Cooperative Group for ALL Treatment (GBTLI) are three excellent examples. Collaborations with HIC cooperative groups may aid this process.

Pediatric oncology treatment can create a cohort of cancer survivors in LMICs while building cancer management capacity and galvanizing cancer advocacy efforts more generally. Closing the pediatric oncology survival gap will help not only the 150,000 children in LMICs who develop cancer every year; it will also have long-lasting benefits for the societies to which they belong.
References


