Chapter 7

Treating Childhood Cancer in Low- and Middle-Income Countries

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BURDEN OF CHILDHOOD CANCER IN LMICs

In high-income countries (HICs), the annual incidence of childhood cancer is approximately 140 per 1 million children younger than age 15 years, although estimates vary between and within countries (Parkin and others 1998). Incidence rates from low- and middle-income country (LMIC) registries are generally significantly lower, as annual rates per 1 million children of 45.6 in Namibia and 64.4 in India, respectively, illustrate (Parkin and others 1998). 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 (Howard and others 2008).

Incidence data from high-quality cancer registries with complete population coverage are rare in LMICs. In 2006, only 8 percent of people in Asia and 11 percent in Sub-Saharan Africa were covered by population-based cancer registries; when only high-quality registries are considered, these rates are 4 percent and 1 percent, respectively (Ferlay and others 2010).

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 third-level 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.

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 the symptoms are also associated with infections. Most non-leukemia cancers present with enlarging masses more easily recognizable as malignant. Accordingly, the magnitude of underdiagnosis 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 low-income countries (LICs) averaged 16.4 per million children, far lower than the incidence rate of 36.5 in middle-income countries (MICs) and 40.9 in HICs (figure 7.2) (Howard and others 2008). The non-leukemia cancer incidence was broadly similar in all income groups: 85 in LICs, 70 in MICs, and 89 in HICs (Howard and others 2008). The underdiagnosis of childhood brain tumors is likely even greater; many regions report few or no incident cases of pediatric central nervous system malignancies (Parkin and others 1998).

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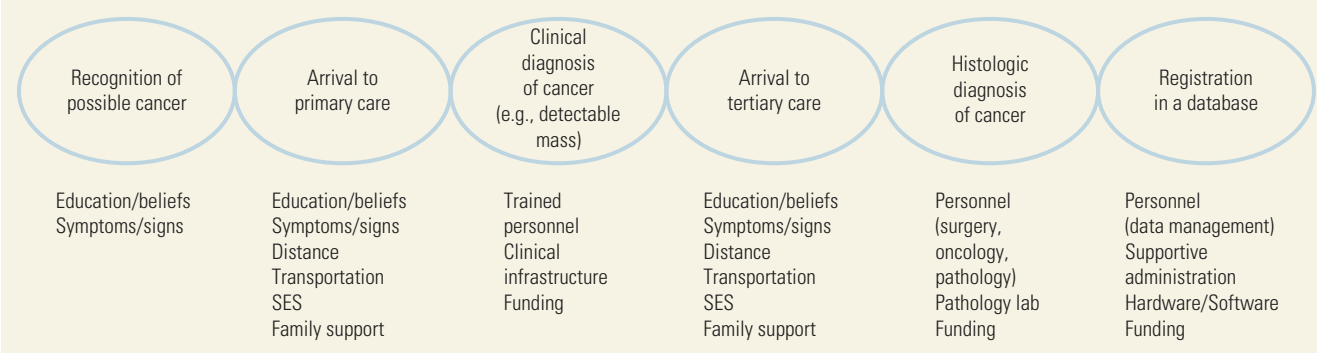
Figure 7.1 Links in the Chain of Childhood Cancer Diagnosis and Registration with Potential Barriers in Low- and Middle-Income Countries



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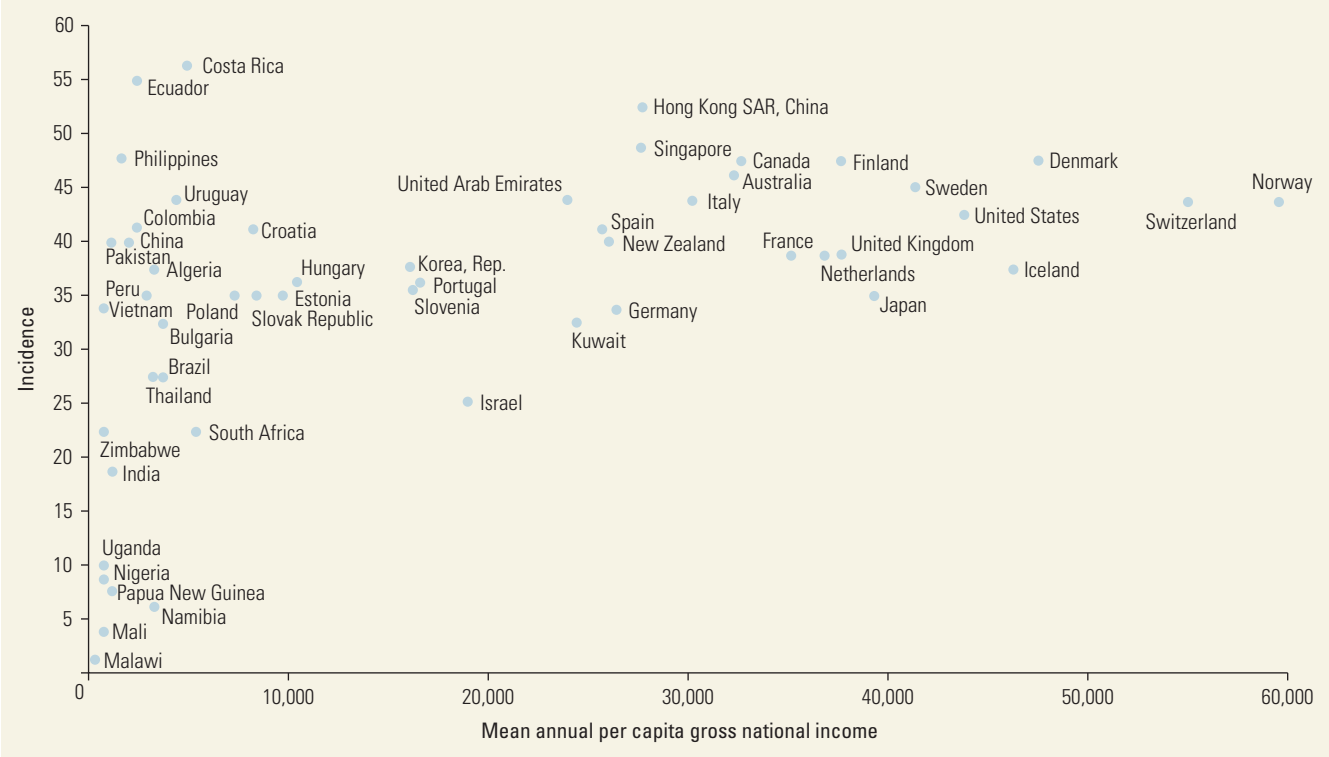
Note: SES = socioeconomic status.

Figure 7.2 Reported Incidence Rate of Childhood Leukemia and Its Association with 2005 Gross National Income, Selected Economies



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Note: Incidence rates are per 1 million children per year.

Underdiagnosis and underregistration are not uniform across all segments of the population. In Jordan and Honduras, higher leukemia incidence rates are reported in urban compared with rural districts (Al Sheyyab and others 2003; Metzger and others 2003). 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 with 1.3 in Canada during the same time period (Parkin and others 1998). At least in some cases,

underdiagnosis may affect girls and rural children disproportionately.

In addition, not only is childhood cancer severely underrepresented in LMIC cancer registration; 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, 15–37 percent of the expected patients were seen (Ribeiro and others 2008). 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 establish the true pediatric cancer burden (Ferlay and others 2010; Magrath and others 2013). The International Agency for Research on Cancer 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?

Epidemiologic Transition

In most HICs, cancer represents the leading cause of non-accidental death in children older than age one year (Ellison, Pogany, and Mery 2007; Siegel, Naishadham, and Jemal 2013). Although infection accounted for 64 percent of global deaths in the first five years of life in 2010 (Liu and others 2012), major shifts in the magnitude and causes of childhood mortality have occurred in many LMICs, especially in MICs. In Brazil, mortality in children younger than age five years decreased from 129 per 1,000 live births in 1970 to 59 per 1,000 in 1990, and to 19 per 1,000 in 2010; 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 (Lozano and others 2011). Consequently, noncommunicable causes represent a greater proportion than before (Liu and others 2012; Patton and others 2012). Indeed, while 3.2 percent of deaths among children ages 5–14 years in LICs are estimated to be caused by cancer, the equivalent figures for LICs and upper-middle-income countries are 6.0 percent and 18.6 percent, respectively (Magrath and others 2013).

Ineffectiveness of Prevention and Screening

Most pediatric malignancies are not caused by modifiable risk factors, and public health campaigns would have limited impact on decreasing the incidence, although impact on delayed presentation is possible. Similarly, population-based screening programs have not been shown to affect cancer mortality in children (Schilling and others 2002). Decreasing childhood cancer mortality rates requires early and accurate diagnosis followed by effective treatment.

Achievability of Cure

In HICs, over 80 percent of children with cancer are cured of their disease (Ellison, Pogany, and Mery 2007; Pui and others 2012; Smith and others 2010). Although cure rates in LMICs are much lower, there are many examples of successful treatment with less intensive regimens that can nevertheless 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 (Patte and others 2007; Woessmann and others 2005). However, up to 50 percent of Sub-Saharan African children with BL are curable with only three to six doses of single-agent cyclophosphamide and intrathecal therapy (Harif and others 2008).

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 governments and policy makers to create and expand programs targeting adults with cancer, in addition to ensuring that children with cancer are not neglected in the face of far greater numbers of adult patients.

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 required, however. 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 deliver some treatment, decreasing the burden on families, providing rapid management of complications and, in LMICs, decreasing abandonment of treatment (Metzger and others 2003; Pediatric Oncology Group of Ontario 2012).

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 (Harif and others 2008; Madani and others 2006; Pedrosa and others 2000). 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.

It is worth highlighting the importance of stable drug supplies. Shortages of essential chemotherapy agents have been shown to impact pediatric survival, even in HICs (Metzger, Billett, and Link 2012). In LMICs, the impact of inconsistent chemotherapy availability is likely to be even greater.

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. Even when these requirements are met, the neglect of pediatric populations in the face of large volumes of adult patients may still adversely impact the quality of childhood cancer care.

Twinning Programs

"Twinning" is currently the most effective model for sustained improvement in childhood cancer care in LMICs. Twinning programs foster interactions between hospitals in LMICs and established cancer treatment centers,

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

Personnel	Requirements
Medical doctors	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.
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.
Radiation oncologists	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 or surgery can result in cure (Mauz-Korholz and others 2010; Nachman and others 2002).
Pathologists	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.
Nursing	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 nurses in pediatric oncology in LMICs have been described (Day and others 2011; Day and others 2012).
Pharmacists	Dedicated pharmacists are needed to prepare chemotherapy and to facilitate the safe preparation, handling, and disposal of chemotherapeutic medications.
Social workers	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.
Dieticians or nutritionists	Nutritional support is particularly important in LMICs where malnutrition at diagnosis or during treatment is prevalent (Israels and others 2009; Sala and others 2005; Viana and others 2001).

Note: HICs = high-income countries; LMICs = low- and middle-income countries.

a. 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. All the elements listed are desirable, but 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[a]

Infrastructure	Requirements
Inpatient and outpatient beds	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.
Laboratory and pathology services	Basic hematologic, biochemical, microbiologic, and pathologic laboratory services capable of timely turnaround are desirable. Although 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 (Hunger, Sung, and Howard 2009).
Diagnostic imaging	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 ultrasonography are sufficient to begin treating childhood cancer (Madani and others 2006; Marjerrison and others 2012).
Chemotherapy and supportive care medications	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 (WHO 2013).
Blood product availability	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.
Psychosocial support	Abandonment of therapy is a significant cause of treatment failure in many LMICs. 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.
Surgical facilities	Surgery is necessary for diagnosis and treatment of many pediatric malignancies, for example, Wilms tumor. Many cancers are curable without surgical intervention.
Radiation facilities	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 or surgery can result in cure (Mauz-Korholz and others 2010; Nachman and others 2002).

Note: HICs = high-income countries; LMICs = low- and middle-income countries.
a. 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.

with the goal of improving survival rates among children with cancer (Ribeiro and Pui 2005). Twinning allows a bidirectional exchange and combines disease-specific multidisciplinary expertise with local knowledge and capabilities.

Twinning programs can 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 (http://www.Cure4Kids.org) facilitate communication between participating centers (St. Jude Children's Research Hospital 2012). In some cases, twinning programs have been associated with rapid increases in cure rates (annex map 7A.1). The Pediatric Oncology in Developing Countries (PODC) committee of the International Society of Pediatric Oncology (SIOP) has created a forum for interested people from centers in HICs and LMICs to develop twinning programs. Indeed, the 12 working groups of PODC are exclusively dedicated to improving care for children with cancer in LMICs by fostering twinning programs, adapting treatment regimens, improving supportive care, and reducing treatment abandonment.

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 (Rivera-Luna and others 2012), although access to care and the survival of treated patients varies widely among accredited pediatric cancer units (Perez-Cuevas and others 2013). Current efforts in China to build comprehensive health insurance programs that cover childhood cancer treatment hold great promise but are in their infancy.

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 (Matthay and others 1999; Womer and others 2012; Woods and others 1996). 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, thereby reducing both undertreatment and overtreatment (Crawford, MacDonald, and Packer 2007; Maris 2010; Metzger and Dome 2005; Pui, Robison, and Look 2008).

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, as opposed to the disease itself (Creutzig and others 2004; Ethier and others 2011; Gupta and others 2009; Gupta and others 2011; Prucker and others 2009). 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 (Creutzig and others 2004; Lange and others 2008).

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 (Gupta and others 2009; Gupta and others 2011). 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 include the following:

- 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?

Box 7.1

Acute Promyelocytic Leukemia: Cost and Treatment Intensity

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia, with cure rates of about 80 percent in high-income countries. In Guangzhou, China, Luo and others (2009b) 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, of 16 children, six abandoned therapy and seven developed bacterial sepsis, one of whom died. With the less intensive protocol, none of the 14 children 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. Although 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: Ortega and others 2005; Testi and others 2005; Luo and others 2009b.

- Are basic radiographic, microbiologic, and hematologic diagnostic tests available?
- Is intensive care, including ventilator 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?

Further consequences stem from the principle that increased intensity and cost of treatment can do more harm than good. Many diagnostic modalities are utilized to 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 (Pui, Robison, and Look 2008). 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 (Howard and others 2005).

Abandonment of Therapy

Abandonment is defined as the "failure to start or complete [potentially] curative treatment" (Mostert and others 2011, 719). The phenomenon of abandonment, virtually unknown in HICs, is a significant problem in LMICs; in some contexts, it constitutes the most common cause of treatment failure (Arora, Eden, and Pizer 2007). The importance of this issue led SIOP to establish the Abandonment of Treatment Working Group (Mostert and others 2011). A systematic review of pediatric acute lymphoblastic leukemia in LMICs found that abandonment rates ranged from 3 percent to an astonishing 74 percent (Gupta and others 2013). None of 83 published reports of abandonment 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 (Bonilla and others 2009; Howard and others 2004; Kulkarni and Marwaha 2010; Luo and others 2009a; Mostert and others 2006). 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 (Bonilla and others 2009). 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 7.2) (Bonilla and others 2009; Howard and others 2004; Luo and others 2008; Mostert and others 2010).

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

Although 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

Box 7.2

Examples of Successful Efforts to Decrease the Abandonment of Therapy in Children with Cancer

- In Guatemala City, Guatemala, through the establishment of a psychosocial team including both social workers and psychologists whose aim is to support families throughout the cancer experience, abandonment has decreased from 42 to 2 percent (F. Antillon, personal communication).
- 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 acute lymphoblastic leukemia (ALL) decreased from 16 to 1 percent from 1980 to 2002 (Howard and others 2004).
- In Yogyakarta, Indonesia, after the introduction of a parental education program, upfront treatment refusal for children with ALL decreased from 14 to 2 percent among poor parents (Mostert and others 2010).

Sources: F. Antillon, personal communication; Howard and others 2004; Mostert and others 2010.

monitoring of treatment outcomes. Collection of basic data on patient demographics, disease characteristics, and treatment outcomes, 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 (Hunger, Sung, and Howard 2009).

Health care workers in many LMICs lack the time to collect, review, and analyze outcome information. In most settings, a dedicated data manager with sufficient training, infrastructure, and support is needed to ensure accurate and timely data entry. 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 the 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.

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 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 achieved significant cure rates in these cancers could then address malignancies requiring more complex chemotherapy (for example, ALL) and multimodality treatment (for example, Wilms tumor) and could 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 because of their high potential cure rates with relatively low intensity treatment regimens. In addition, these five cancers 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.

Acute Lymphoblastic Leukemia

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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 (Ries and others 1999). 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 (Hunger and others 2012; Moricke and others 2010; Pui and others 2009; Silverman and others 2010). 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 (online annex table 7A.1). Thus, it is critical to consider how pediatric ALL can be cured in countries that have very different income

Table 7.3 Characteristics of Childhood Cancers to Consider When Determining Which Malignancies Are Appropriate for Treatment in a Particular Resource-Constrained Setting

Cancer	Approximate HIC cure rate[a] (percent)	Approximate treatment duration (months)	Supportive care level required	Chemotherapy necessary?	Surgery necessary?	Radiation necessary?	Late effects/ disability
ALL	90	24–40	++	Yes	No	No	+
AML	60	5–7	++++	Yes	No	No	++
Hodgkin lymphoma	90	2–8	++	Yes	No	No[b]	++
Burkitt lymphoma	90	6–8	+++[c]	Yes	No	No	+
Medulloblastoma	75	8–10	++	Yes	Yes	Yes	++++
Neuroblastoma	65	8–10	+++	Yes	Yes	Yes	+++
Wilms tumor	90	4–8	+	Yes	Yes	No[b]	++
Rhabdomyosarcoma	70	8–12	++	Yes	Yes	No[b]	++
Osteosarcoma	70	8–12	++	Yes	Yes	No	++
Ewing sarcoma	75	8–12	++	Yes	Yes	No[b]	++
Retinoblastoma	95[d]	0–3	+	No[e]	Yes[f]	No	++
Testicular cancer	90	0–3	+	No[e]	Yes	No	–
Hepatoblastoma	85[g]	4–6	+	Yes	Yes	No	+

Note: The scale is from not very significant (–) to very significant (++++). ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; HIC = high-income country.

a. Unless otherwise specified, HIC cure rates are taken from Surveillance, Epidemiology, and End Results Program registry data (Smith and others 2010).

b. Radiation is indicated in select cases.

c. While HIC regimens for Burkitt lymphoma require significant supportive care, lower intensity regimens requiring minimal supportive care can also be used.

d. Dimaras and others 2012.

e. Chemotherapy is required for advanced cases, although localized cases may be cured without it.

f . Local control methods, including cryotherapy and laser therapy, are often used instead of surgery in HICs, but these are unavailable in many low- and middle-income countries.

g. Perilongo and others 2009; Zsiros and others 2010.

structures and health care systems than those in North America and Western Europe.

Diagnosis of ALL

Children with ALL are commonly brought to medical attention for symptoms caused by ineffective production of normal blood cells because of 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 on 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 2.5–3 years, with six to eight months of relatively intensive therapy, followed by 1.5–2 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 (Masera and others 2004). 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 (Pui and Howard 2008).

Although 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 (Nguyen and others 2008).

Because most children with ALL live in LMICs, efforts have been made to improve treatment available in those countries through partnerships with centers in HICs (Masera and others 1998). This twinning has led to major improvements in ALL survival in LMICs, often through adoption of intact or modified HIC treatment regimens (Howard and others 2004; Veerman, Sutaryo, and Sumadiono 2005). Critical to these successes has been the transfer of knowledge regarding treatment regimens, supportive care, and emotional and psychosocial support. Abandonment of care is a major issue in LMICs because of economic and social pressures on parents and cultural beliefs that a child has been healed (Sitaresmi and others 2010; Wang and others 2011). Innovative programs have been developed to support patients and families and greatly reduce abandonment; a Guatemalan 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 (Ayoub and others 2007).

Specifics of Pediatric ALL Treatment

The development of large cooperative treatment groups that conduct clinical trials, which often include 70 percent or more of children with ALL in a given country (Hunger and others 2012), has been critical to improvements in survival for pediatric ALL in HICs. This development has resulted in near-universal access to effective treatments in most HICs (limited in some cases because of 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), 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 non-randomized clinical trials. In Guatemala, ALL survival rates now range from 50 percent (high-risk) to 90 percent (low-risk) for different patient subgroups (Antillon-Klussmann and others 2010). This strategy is possible in countries with reasonably well-developed health care systems, with infant mortality rates less than 40–50 per 1,000 live births serving as a good surrogate marker (online annex, table 7A.1).

However, high rates of ALL TRM can be a major problem (Gupta and others 2011). Regimens that are delivered safely with TRM rates less than 5 percent in North America and Western Europe can be associated with TRM rates 5–10 times higher in LMICs; the problem is 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 the 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 (Hunger, Sung, and Howard 2009). 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, the Dominican Republic, shows the potential benefit of this strategy. In 2005–07, a relatively intensive HIC-type treatment regimen was followed for 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 to 70 percent, accompanied by a decrease in TRM from 29 of 91 cases in the early period to 8 of 101 in the later period (Hunger and others 2011).

Costs of Pediatric ALL Treatment

Pediatric ALL treatment in North America and Western Europe is widely recognized to be 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–US$163,350 per case, with highly favorable costs per life year saved of US$1,962–US$2,655 (van Litsenburg and others 2011). However, effective treatments can be implemented for much lower costs. Luo and others 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 (Luo and others 2008). More intensive regimens obtained slightly better results and could be implemented for US$9,900–US$12,500, similar to the average cost of US$11,000 per patient reported from Shanghai, China (Liu and others 2009).

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 40–50 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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In HICs, over 80 percent of children with HL survive long-term. In LMICs, survival has been lower because of 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. HL is curable, diagnosable without expensive technology, and constitutes an important portion of children with cancer.

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 age 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-positive and of mixed cellular histology (Siddiqui and others 2006). 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 of HL

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 (Hodgson, Hudson, and Constine 2007).

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 intra-abdominal 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 (Hines-Thomas and others 2010). 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 LMICs should also be broader, similar to early HIC chemotherapy-only trials. Table 7.4 provides examples of chemotherapy-only and combined modality treatment regimens used successfully in LMICs.

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 more than US$6,500 in a continent where the annual gross domestic product (GDP) per inhabitant is usually less than US$2,000 (Stefan and Stones 2009). However, these costs can be significantly reduced by carefully choosing the minimal necessary diagnostic imaging techniques

Table 7.4 Treatment Results of Pediatric Hodgkin Lymphoma Trials in Low- and Middle-Income Countries

Chemotherapy	Stage[a]	Number of patients	Outcome % (years)		
			Event-free survival	Disease-free survival	Overall survival
Chemotherapy-only regimens					
Grupo Argentino de Tratamiento de Leucemia Aguda[b]					
CVPP x 3	IA, IIA	10	86 (7)	—	—
CVPP x 6	IB, IIB	16	87 (7)	—	—
Nicaragua[c]					
COPP x 6	I, IIA	14	100 (3)	—	100 (3)
COPP-ABV x 8–10	IIB, III, IV	34	75 (3)	—	—
Chennai, India[d]					
COPP/ABV x 6	I–IIA	10	89 (5)	—	—
COPP/ABV x 6	IIB–IVB	43	90 (5)	—	—
New Delhi, India[e]					
COPP x 6	All stages	34	—	80 (5)	—
Uganda[f]					
MOPP x 6	I–IIIA	38	—	75 (5)	—
	IIIB–IV	10	—	60 (5)	—
Combined modality trials					
New Delhi, India[g]					
4 ABVD + 25–40 Gy IFRT	I–IIA	79	—	91 (5)	—
6–8 ABVD + 25–40 Gy to bulky disease sites	IIB, III, IV	183	—	73 (5)	—

Note: ABVD = doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; COPP = cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone; CVPP = cyclophosphamide, vincristine, procarbazine, prednisone; IFRT = involved-field radiation therapy; MOPP = mechlorethamine (Mustargen), vincristine (Oncovin), procarbazine, and prednisone; — = no information available.

a. Stage I represents involvement of a single lymph node region or extralymphatic site. Stage II represents involvement of two or more lymph nodes on the same side of the diaphragm. Stage III represents involvement of lymph node regions on both sides of the diaphragm. Stage IV represents involvement of extralymphatic organs (for example, lung). B represents the presence of B symptoms (fever, night sweats, weight loss), while A represents the absence of B symptoms.

b. Sackmann-Muriel and others 1997.

c. Baez and others 1997.

d. Sripada and others 1995.

e. Chandra and others 2008.

f. Olweny and others 1978.

g. Ganesan and others 2011.

required for staging and chemotherapy regimens that will permit the omission of radiotherapy. The most important cost to avoid is that of relapse.

Wilms Tumor

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Wilms tumor is relatively common, accounting for 5–7 percent of all childhood cancers (Stiller and Parkin 1996). 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 because of 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 (Graf, Tournade, and de Kraker 2000; Green 2004). Two treatment strategies have been used for Wilms tumor worldwide. The first operates on tumors upfront, as practiced by the Children's Oncology Group 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 (Graf, Tournade, and de Kraker 2000; Green 2004). 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 (Abuidris and others 2008; Israels 2012; Israels and others 2012; Moreira and others 2012; Wilde and others 2010). Known challenges are late presentation with advanced disease, malnutrition, abandonment of treatment, and poor facilities for specific cancer treatment and supportive care (Abuidris and others 2008; Harif and others 2005; Moreira and others 2012). Capacity building, earlier presentation, a multidisciplinary approach, social support, improved supportive care, and treatment adapted to local circumstances are key to improving results (Hadley 2010; Hadley, Rouma, and Saad-Eldin 2012; Israels and others 2012).

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 (table 7.5):

- *Setting 1* is one in which the minimal requirements for treatment with curative intent are available.

Table 7.5 Classification of Different Settings Providing Care for Children with Wilms Tumor[a]

Setting	Medical facilities	Specialists	Drugs	Supportive care	Diagnostic facilities
0				Pain medication	Physical exam
1. Minimal requirements for curative intent	Pediatric ward	Surgeon (Pediatrician) Nurse	Vincristine Actinomycin (Doxorubicin)	Antibiotics Whole blood Morphine Social support	Full blood count Chest x-ray Ultrasonography
2. Intermediate	Pediatric oncology ward Radiotherapy Pathology Multidisciplinary care	Pathologist Pediatric surgeon Pediatric oncologist Radiation oncologist Oncology nurse	Doxorubicin Cyclophosphamide Etoposide Ifosfamide Carboplatin	All blood products Central venous access	CT scan
3. State of the art	Intensive care unit	Pediatric pathologist Pediatric radiation oncologist Pharmacist (oncology) Intensivist		Mechanical ventilation Hemodialysis Pressure support	Special stains Immunohistochemistry Cytogenetics

Note: CT = computed tomography.
a. Facilities and resources mentioned are in addition to those associated with lower settings. In setting 2, mentioned facilities may or may not be available.

- *Setting 3* is one where all state-of-the-art facilities are available.
- *Setting 2* is in between.

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 (Green 2004; Israels 2012). Ultrasonography of the abdomen is extremely useful to confirm the diagnosis (De Campo 1986; Hartman and Sanders 1982; Lowe and others 2000). 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 (Vujanic and others 2009). 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 (Vujanic and others 2003). Such biopsies may result in bleeding, infection, or tumor spillage with consequent upstaging.

Treatment of Wilms Tumor

Preoperative chemotherapy should be used for children with Wilms tumor in LMICs, even in cases of small, seemingly easily resectable tumors (Lemerle and others 1983). Preoperative chemotherapy reduces surgical complications, downstages the tumor, and allows for less intense postoperative chemotherapy and the potential avoidance of radiotherapy (Graf, Tournade, and de Kraker 2000). 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. The recent National Wilms Tumor Study 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 (Baez and others 2002; Madani and others 2006). Higher cure rates in these populations may, however, require radiotherapy.

Table 7.6 shows some elements of the therapy used and the results from selected countries with limited resources. More detailed treatment recommendations can be found in a recently published SIOP guideline developed for use in LMICs (Israels and others 2013).

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

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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 malaria-endemic regions of Sub-Saharan Africa (Burkitt 1958; Lewis and others 2012). 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, which is 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 (Patte and others 2007). In many LMICs with limited supportive care, delivery of such therapy causes excessive toxic death; adapted regimens are necessary to cure as many patients as possible (Hesseling, Israels, and others 2012).

Table 7.6 Reported Outcomes of Patients with Wilms Tumor Treated in Low- and Middle-Income Countries

Country or region	Setting[a]	Numbers of patients	Chemotherapy	Radiotherapy	Event-free survival % (years)	Overall survival % (years)
Sudan[b]	1	37	Generally postoperative, based on NWTS-5, 37 percent received preoperative chemotherapy based on specific indications	No	11[c]	—
Malawi[d]	1	84	Preoperative and postoperative, modified from SIOP protocols	No	46	—
Egypt, Arab Rep.[e]	2	62	Postoperative	Yes	58 (4)	70 (4)
Central America[f]	2	374	Postoperative, based on NWTS-4	Yes	59 (3)	74 (3)
Morocco[g]	2	86	Preoperative and postoperative, based on SIOP protocols	Yes	77 (5)	79 (5)
South Africa[h]	2 (–3)	188	Preoperative and postoperative, based on SIOP protocols	Yes	75 (5)	81 (5)
Turkey[i]	2 (–3)	327	Preoperative and postoperative, based on SIOP protocols	Yes	56 (10)	61 (10)

Note: NWTS = National Wilms Tumor Study; SIOP = International Society of Pediatric Oncology; — = not available.
a. *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.
b. Abuidris and others 2008.
c. 89 percent of children in this study abandoned therapy prior to the completion of therapy.
d. Israels and others 2012.
e. Abd El-Aal, Habib, and Mishrif 2005.
f. Ortiz and others 2012.
g. Madani and others 2006.
h. Davidson and others 2006.
i. Kutluk and others 2006.

Nevertheless, in even the most resource-constrained environment, a simplified protocol for patients with BL can cure 50 percent (Hesseling and others 2009). Indeed, treatment of BL is likely to be highly cost-effective in all settings (Bhakta and others 2012).

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.

Biopsy of the suspected tumor is recommended for diagnosis, but extensive surgery is contraindicated. The top priority must always be to make a diagnosis in the fastest, least invasive way possible and to initiate therapy rapidly. 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 (Razack and others 2011). 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; computed tomography imaging of the neck, chest, abdomen, and pelvis to define all sites of adenopathy; and the evaluation of cerebrospinal fluid, 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 the extent of disease (Murphy 1978). In LMICs, a physical examination, chest radiograph, abdominal ultrasound, bone marrow aspiration, and lumbar puncture may provide sufficient staging information (Marjerrison and others 2012).

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 chemotherapy 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 (Hesseling, Israels, and others 2012). 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, as well as 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 an 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 (Patte and others 2007). However, this treatment approach in settings with limited supportive care exposes patients to high rates of mortality and abandonment.

In LMICs and even in very poor settings, it has been shown that at least 50 percent of children with BL and up to 70 percent of children with localized stage I or stage II disease can be cured with intravenous or oral cyclophosphamide in combination with intrathecal methotrexate (Harif and others 2008; Hesseling and others 2009; Traore and others 2011). Treatment with simplified regimens is feasible everywhere and should always be attempted (table 7.7).

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 (Howard, Jones, and Pui 2011). 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

Table 7.7 Selected Cohorts and Outcomes of Children with Burkitt Lymphoma Treated in Low- and Middle-Income Countries with Locally Adapted Protocols of Lower Intensity

Study	Countries	Subgroups	Number of patients	Outcome (percent)
Hesseling, Njume, and others 2012	Cameroon	Stages I and II	18	EFS 94
		Stage III, clinical remission, or residual abdominal < 30 mL	58	EFS 76
		Stage IV, no clinical remission, or residual abdominal mass > 30 mL	45	EFS 40
Ngoma and others 2012	Tanzania, Kenya, Nigeria	All stages	326	EFS 52; OS 62[a]
Traore and others 2011	Burkina Faso, Cameroon, Côte d'Ivoire, Madagascar, Mali, Senegal	Stage I	19	EFS 44
		Stage II	23	EFS 49
		Stage III	128	EFS 30
		Stage IV	6	EFS 17

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

produce remarkable results, even in LMICs (Gavidia and others 2012; Israels and others 2009).

Relapses are usually seen during the first six months and are rare after one year. Follow-up after one 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.

More detailed treatment recommendations can be found in a published SIOP guideline developed for use in LMICs (Hesseling, Israels, and others 2012).

Costs 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 cyclophosphomide, a relatively inexpensive drug, can cure a significant portion of children, the treatment of BL is likely to be highly cost-effective. A 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 (Bhakta and others 2012). Actual estimated costs of treatment per case, at US$50, were far lower, although this figure only accounted for the costs of chemotherapy and is likely an underestimate.

Retinoblastoma

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Retinoblastoma is the most frequent neoplasm of the eye in childhood, representing 2.5–4 percent of all pediatric cancers and 11 percent of cancers in the first year of life. Retinoblastoma presents in two distinct clinical forms.

- *Bilateral or multifocal* (25 percent of cases) is hereditary, characterized by the presence of germline mutations of the *RB1* gene. Multifocal retinoblastoma may be inherited from an affected survivor or be the result of a new germline mutation.
- *Unilateral* retinoblastoma (75 percent) is almost always nonhereditary. Retinoblastoma is a cancer of the very young; two-thirds of the cases are diagnosed before age two years, and 90 percent of the cases are diagnosed before age five years (Ries and others 1999).

Epidemiology

The incidence of retinoblastoma in the United States and Europe is 2–5 per million children (approximately one in 14,000–18,000 live births). However, the incidence is not consistent around the world, appearing higher (6–10 per million) in India, Sub-Saharan Africa, and among children of Native American descent in North America (Stiller and Parkin 1996). Whether this variation is because of ethnic or socioeconomic factors is unknown, although an environmental role has been suggested (de Camargo and others 2011; Fajardo-Gutierrez and others 2007). 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 (Chantada and others 2011).

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 relatives.

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, 60–90 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 underdiagnosis 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 (Leander and others 2007; Rodriguez-Galindo and others 2008). 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 health care providers (Leal-Leal and others 2011).

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 required to examine the entire retina. Additional imaging studies, including bi-dimensional ultrasound, computerized tomography, and magnetic resonance imaging, are desirable but not necessary 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 (Chantada and others 2006).

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 subretinal 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 (Rodriguez-Galindo and others 2007a).

Treatment

The treatment goal is to save life and preserve vision; accordingly, treatment is 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. Although 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 (Gobin and others 2011; Rodriguez-Galindo and others 2007b).

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 20–25 percent of cases (Rodriguez-Galindo and others 2007b). 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; patients without central nervous system spread may benefit from intensive chemotherapy and consolidation with high-dose chemotherapy and autologous stem cell rescue (Dunkel and others 2010; Rodriguez-Galindo and others 2007b). In children in LMICs presenting with advanced extraocular retinoblastoma, measures to decrease suffering and improve quality of life may be most appropriate. Low-dose oral chemotherapy and radiation therapy may result in temporary symptom control.

More detailed treatment recommendations can be found in a published SIOP guideline developed for use in LMICs (Chantada and others 2013).

Costs of Retinoblastoma Treatment

Little is known about the cost-effectiveness of retinoblastoma treatment, but measures targeting early diagnosis are likely key. Failures in public awareness and deficiencies in education among frontline health care providers represent major barriers in early diagnosis and result in the high incidence of metastatic disease and mortality rates in LMICs (Chantada and others 2011). In LMICs, 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. Delayed diagnosis remains an issue in 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 (Rodriguez-Galindo 2011).

COST-EFFECTIVENESS OF TREATING CHILDHOOD CANCER

Financial objections are often raised to the treatment of childhood cancer in resource-constrained settings; policy makers and lay persons may assume that any such treatment is prohibitively expensive. However, 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 to the annual per capita GDP of the area (WHO 2003). 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 BL in Malawi (Bhakta and others 2012). Although treatments costing these theoretical thresholds may still be unachievable for many LMICs, Bhakta and others also found that these cancers could be treated for a fraction of the threshold values: US$16,400 and less than US$50, respectively. Table 7.8 and figure 7.3 illustrate cost-effective thresholds for several malignancies in various countries and compare them with actual costs, when available. These figures, however, do not account for the initial expenditures associated with developing new pediatric oncology treatment centers, such as the initial training of personnel or acquisition of infrastructure. Further data on theoretical cost-effectiveness thresholds and real costs are needed to aid LMIC policy makers.

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 to 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

Table 7.8 Comparison of Cost-Effectiveness Thresholds among Common Childhood Cancers, Selected Countries

Threshold	Brazil	Malawi	El Salvador	El Salvador	China	Brazil	United States	Brazil	Morocco
Type of pediatric cancer	ALL	BL	SR-ALL	HR-ALL	ALL	ALL	ALL	BL	Wilms
Source	Howard and others 2004	Hesseling and others 2009	Bonilla and others 2010	Bonilla and others 2010	Tang and others 2008	Brandalise and others 2010	Pui and others 2009	Sandlund and others 1997	Madani and others 2006
Event-free survival definition	5-year	1-year	5-year	5-year	5-year	5-year	5-year	5-year	5-year
Percentage abandoning treatment[a]	1	—	—	—	48.3	—	—	—	—
Percentage event-free survival[b]	63	48	56.3	48.6	38.5	83.6	85.6	39	56.0
Gross domestic product per capita	$11,900	$900	$7,600	$7,600	$8,500	$11,900	$49,000	$11,900	$5,100
Life expectancy	72.79	52.31	73.69	73.69	74.84	72.79	78.49	72.79	76.11
Age at diagnosis	5.4	6.9	4.6	7.1	4.7	5.3	5.3	5.5	3
Upper limit of very cost-effective (US$ per patient)	257,075	14,243	147,756	129,037	58,620	344,385	1,454,695	167,146	100,285
Upper limit of cost-effective (US$ per patient)	771,225	42,729	443,268	387,112	175,859	1,033,156	4,364,086	501,438	300,855

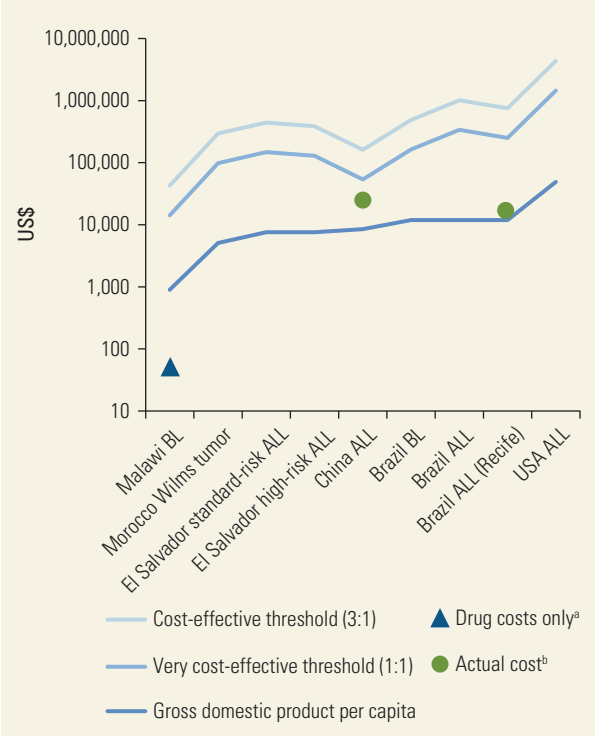
Source: Bhakta and others 2012.

Note: ALL = acute lymphoblastic leukemia; BL = Burkitt lymphoma; HR-ALL = high-risk ALL; SR-ALL = standard-risk acute lymphoblastic leukemia; — = not available.

a. When no abandonment percentage is listed, the authors included abandonment as an event when calculating event-free survival.

b. In all studies cited, relapse and abandonment were included as events when calculating event-free survival.

Figure 7.3 Cost-Effective Thresholds Compared with Actual Costs in Selected Pediatric Malignancies



Source: © BMJ Publishing Group Ltd. Reproduced, with permission, from Bhakta and others 2012; further permission required for reuse.
Note: ALL = acute lymphoblastic leukemia; BL = Burkitt lymphoma; US$= U.S. dollars.
a. Costs only include chemotherapy and supportive care medications, such as antibiotics and antipyretics.
b. 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.

health system have instead been allocated to pediatric oncology centers. The success of Unidad Nacional de Oncología Pediátrica (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 government and private donors. The creation of an independent fundraising organization (Fundación Ayúdame a Vivir, http://ayuvi.org.gt) was essential to this outcome. Figure 7A.1 in the online annex 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 non-monetary value of children to society may well hold resonance for governments, policy makers, health care workers, and the general public.

CONCLUSIONS AND 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 clinicians and parent groups is required, as are strengthening links between childhood cancer advocates in HICs and LMICs.
- 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 continually to 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 how to effectively treat various different childhood malignancies in settings 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 protocol evaluation and advocacy; AHOPCA, the French-African Pediatric Oncology Group, and the Brazilian Childhood Cooperative Group for ALL Treatment 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 more than 150,000 children in LMICs who develop cancer every year; it will also have long-lasting benefits for the societies to which they belong.

NOTE

World Bank income classifications as of July 2014 are as follows, based on estimates of gross national income per capita for 2013:

- Low-income countries: US$1,045 or less
- Middle-income countries:
  - Lower-middle-income: US$1,046–US$4,125
  - Upper-middle-income: US$4,126–US$12,745
- High-income countries: US$12,746 or more

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