Prospective, Multicenter Evaluation of Risk Factors Associated With Invasive Bacterial Infection in Children With Cancer, Neutropenia, and Fever

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Purpose: **To identify clinical and laboratory parameters present at the time of a first evaluation that could help predict which children with cancer, fever, and neutropenia were at high risk or low risk for an invasive bacterial infection.**

Patients and Methods: **Over a 17-month period, all children with cancer, fever, and neutropenia admitted to five hospitals in Santiago, Chile, were enrolled onto a prospective protocol. Associations between admission parameters and risk for invasive bacterial infection were assessed by univariate and logistic regression analyses.**

Results: **A total of 447 febrile neutropenic episodes occurred in 257 children. Five parameters were statistically independent risk factors for an invasive bacterial infection. Ranked by order of significance, they were as follows: C-reactive protein levels of 90 mg/L or higher (relative risk [RR], 4.2; 95% confidence interval [CI], 3.6 to 4.8); presence of hypotension (RR, 2.7; 95% CI, 2.3 to 3.2); relapse of leukemia as cancer type (RR, 1.8, 95% CI, 1.7 to 2.3); platelet count less than or equal to 50,000/mm^3 (RR, 1.7; 95% CI, 1.4 to 2.2); and recent (≤ 7 days) chemotherapy (RR, 1.3; 95% CI, 1.1 to 1.6). Other previously postulated risk factors (magnitude of fever, monocyte count) were not independent risk factors in this study population.**

Conclusion: **In a large population of children, common clinical and laboratory admission parameters were identified that can help predict the risk for an invasive bacterial infection. These results encourage the possibility of a more selective management strategy for these children.**

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FEVER AND NEUTROPENIA in cancer patients was considered a medical emergency during the past decade, requiring prompt in-hospital evaluation and administration of broad-spectrum intravenous antibiotics.[1] This aggressive approach was universally recommended because approximately 60% of febrile neutropenic episodes were caused by bacterial infections with or without bacteremia, a condition that was difficult to identify in many children at the time of their first evaluation.[2,3]

Although this aggressive approach reduces mortality,[3] patients may suffer adverse effects, such as antimicrobial toxicity, nosocomial infections, fungal superinfections, and the psychologic and financial impact of complex hospital treatment.[4] These drawbacks and the recent recognition that these patients form a heterogeneous group at different risks for infection-related morbidity and mortality[4] have led clinicians worldwide to consider a more selective management, including a shortened antimicrobial course, early hospital discharge, oral antimicrobial treatment, and management as an outpatient, that would significantly benefit these children and health care systems.[5-11] Recent studies have concluded that the critical issue is to find appropriate tools with which to identify those individuals who are at high risk or low risk for an invasive bacterial infection (IBI).[12-14]

For pediatric patients, studies on identification of risk factors for IBI[15-17] and studies on selective management are scarce.[18-21] Rackoff et al[15] identified two parameters, magnitude of fever and absolute monocyte count (AMC), that proved useful in identifying children at low risk, intermediate risk, or high risk for bacteremia. Other studies in pediatric populations have looked at risk factors associated with overall treatment failure and not with IBI specifically.[22] For selective management strategies, Aquino et al[18,19] reported that up to two thirds of children with cancer, fever, and neutropenia were at a low risk for bacteremia and could be managed safely with early hospital discharge. These authors estimated that this approach could save $5,000 per patient (United States dollars, here and throughout) and $23,000,000 per year for the United States.[20] In a pilot study of outpatient management, this same group successfully treated 19 children at low risk for bacteremia with ceftriax-

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one.[21] Other researchers have reported nonrandomized prospective experiences using intravenous antibiotics in outpatient settings.[23,24]

In Chile, a rapidly developing country, during the past 10 years, a team of physicians from our Subcommittee of Infectious Diseases of the National Child Program of Antineoplastic Drugs has worked, within an environment of limited resources, in a stepwise manner, to develop more selective strategies for pediatric patients with cancer, fever, and neutropenia. In two consecutive studies, we concluded that serial determination of serum C-reactive protein (CRP) can aid in identifying children at high risk for bacterial infections[25] and that for selected children at low-risk for bacteremia, antibiotic treatment can be safely stopped at day 3 of hospitalization.[26]

In this prospective, multicenter study, our aim was to advance a step further. We studied a significant number of clinical and laboratory variables at enrollment in children with cancer, fever, and neutropenia in order to determine which correlated with the presence of IBI. Our hypothesis was that independent variables significantly associated with a risk for IBI can be identified at enrollment.

PATIENTS AND METHODS

Population Selection

From May 1,1996, to September 30, 1997, all children 18 years of age or younger receiving cancer chemotherapy who were admitted for fever and severe neutropenia to any of five hospitals were enrolled onto a prospective protocol. The five hospitals were Luis Calvo Mackenna, Exequiel González Cortés, Roberto del Río, San Juan de Dios, and Sótero del Río, all located in Santiago, Chile, and affiliated with the National Health Care System, as well as the University of Chile. Together these hospitals provide health care to two million children within the low-income to middle-income population. The oncology service of each hospital, which is responsible for the management of children with cancer, participates in the National Child Program of Antineoplastic Drugs (PINDA), which establishes standard protocols for treatment of different types of cancer. This study protocol was conducted by physicians from the oncology and infectious disease services of each hospital, under the auspices of the PINDA Subcommittee of Infectious Diseases. Informed consent was obtained for all patients. This study was approved by the ethical committee of each hospital.

Overall Study Design

A standard protocol for management of children with cancer, fever, and neutropenia was applied at each hospital. The protocol included guidelines for clinical and laboratory evaluation at admission and follow-up, as well as for antimicrobial management. Relevant clinical and laboratory parameters at the time of enrollment were predefined and recorded in a predesigned questionnaire. Children were monitored until fever resolved and the absolute neutrophil count (ANC) was greater than 500/mm^3. After resolution of each febrile episode, a blinded evaluator classified each episode as presenting or not with a demonstrated or probable IBI, according to our definitions.

Evaluation at Enrollment

All children were evaluated by one of our investigators and had the following laboratory tests performed: complete blood count, quantitative CRP, liver and renal function, chest radiograph**,** urine analysis and culture, blood cultures (including quantitative cultures if child had an indwelling central venous catheter), and cultures from other sites (skin lesions, CSF, stools) if focal signs and/or symptoms were present. CRP was determined by nephelometry with use of a Turbox nephelometer (Orion Diagnostica, Espoo, Finland), and results were available in 1 hour.[25]

The following entry variables were uniformly recorded: (1) demographic variables, ie, age, sex, and maternal educational level; (2) cancer-related variables, ie, cancer type, intensity of chemotherapy**,** use of granulocyte colony-stimulating factors since last administration of chemotherapy, and use of an indwelling catheter; (3) variables related to the febrile episode, ie, hours of fever before admission, days since last administration of chemotherapy, and use of prophylactic antimicrobial agents; (4) and admission clinical and laboratory variables, ie, axillary temperature, blood pressure, ANC, AMC, quantitative serum CRP level, hemoglobin level, and platelet count.

Patient Management and Monitoring

All children were placed on broad-spectrum intravenous antimicrobial therapy at admission. Antimicrobial agents were empirically selected based on data from previous studies that showed that, in Santiago, *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, *Escherichia coli*, and *Klebsiella pneumoniae* account for 75% of bacterial infections in children fitting our study profile (PINDA Subcommittee of Infectious Diseases, unpublished data). Children were monitored daily in the hospital until fever resolved and the ANC was greater than 500/mm^3. Monitoring included a physical examination and laboratory evaluation with daily determination of serum CRP levels and every-other-day measurement of ANC, AMC, hemoglobin level, and platelet count. Additional laboratory evaluations were based on individual clinical findings.

Definitions

Fever was defined as an axillary temperature of 38.5°C or higher in one measurement or 38°C or higher in two consecutive measurements separated by 1 hour. Severe neutropenia was defined as an ANC less than or equal to 500/mm^3. A child was considered to have a demonstrated IBI if one or both of the following criteria were met: (1) occurrence of bacteremia, defined as one or more blood cultures positive for a bacterial pathogen with the exception of coagulase-negative *Staphylococcus*, which required two or more positive blood cultures; and (2) a positive bacterial culture obtained from a usually sterile site (indwelling catheter, urine, CSF). A child was considered to have a probable IBI if in the absence of a positive culture one or both of the following criteria were met: (1) clinical and laboratory findings strongly suggestive of a sepsis syndrome; or (2) focal organ involvement in a child with hemodynamic instability and intense malaise. Sepsis syndrome was defined as a systemic response to a possible infection, accompanied by altered organ perfusion as manifested by hypoxemia, elevated plasma lactate levels, oliguria, and/or acute changes in mental status.[27] A child was considered to have hemodynamic instability if he or she had hypotension defined as blood pressure below the fifth percentile for age and/or a capillary refill of more than 3 seconds.[27] Maternal educational level was defined as low when a mother did not graduate from primary school. Chemotherapy was

defined as intensive or not intensive based on the severity of medullar depression expected for the specific chemotherapy regimen.[28] We considered as intensive all induction and consolidation chemotherapy used for acute lymphocytic leukemia or acute nonlymphocytic leukemia, relapse of leukemia, chemotherapy for lymphomas, and induction chemotherapy for solid tumors. Chemotherapy considered as not intensive were maintenance therapies for any type of leukemia and maintenance therapy for solid tumors.

Statistical Analysis

Univariate analysis was used to screen for admission parameters potentially associated with high risk for IBI. Parameters significantly associated with a high risk for IBI ($P < .05$ by univariate analysis) were selected for logistic regression analysis. For each variable significantly associated with a high risk for IBI by logistic regression analysis, the risk ratio was calculated with the corresponding 95% confidence interval (CI). An independent analysis was performed for all cases of IBI, for demonstrated cases, and for probable cases as previously defined.

The cutoff points for CRP level and platelet count were determined by constructing a receiver operator characteristic curve.[29] All statistical analyses were performed with the BMDP Solo statistical package (SPSS, Inc, Chicago, IL). Results for continuous variables were expressed as mean ± SD.

RESULTS

Overall Description of Febrile Neutropenic Episodes

During the 17-month study period, a total of 447 febrile neutropenic episodes occurred in 257 children. Of these children, 148 (58%) had one episode, 63 (25%) had two, 27 (10%) had three, and 19 (7%) had four episodes during the study. Age of children at the time of fever onset ranged from 6 months to 18 years (mean age, 7 ± 4.2 years), sex was male for 50%, and maternal educational level was low for 55%.

The characteristics of cancer-related variables at the time of admission for 257 children with 447 febrile neutropenic episodes are listed in Table 1. The predominant cancer type was acute lymphocytic leukemia, and all episodes of fever and neutropenia occurred in children who were receiving chemotherapy. Intensive chemotherapy was being used in 257 episodes (57%). None of the children had received a bone marrow transplant.

IBI Status of Febrile Neutropenic Episodes

An IBI based on our definition occurred in 178 (40%) of the 447 episodes. Diagnoses and frequency of microbial confirmation for these 178 episodes are listed in Table 2. According to our definitions, 87 episodes had a demonstrated IBI and 91 had a probable IBI. Bacterial species recovered from 87 episodes of demonstrated IBI are shown in Table 3. Clinical diagnoses in the 91 episodes of probable IBI were based on the following criteria: for bacterial bronchopneumonia, clinical findings and chest radiographs; for sepsis syndrome, see above; for enterocolitis, clinical findings and the presence of blood and/or leukocytes in stools; for typhlitis, clinical findings, abdominal radiographs, and ultrasound; for cellulitis, mucositis, and perianal abscess, clinical findings; and for endocarditis, clinical findings and the presence of vegetations by echocardiography.

Table 1. Cancer-Related Characteristics at Time of Admission for 257 Children With 447 Febrile Neutropenic Episodes

Characteristic at Admission	Children or Episodes With Indicated Characteristic (%)
Cancer type, n = 257 children	
Acute lymphocytic leukemia	40
Sarcoma	17
Other solid tumor	15
Relapse of any leukemia	14
Acute nonlymphocytic leukemia	8
Lymphoma	6
Cancer-related therapy, n = 447 episodes	
Intensive chemotherapy use*	57
G-CSF since last chemotherapy	19
Indwelling catheter in place	55

*See text for definition.

Enrollment Variables Associated With Presence of an IBI

Presence or absence of an enrollment variable was compared for the episodes associated (all, demonstrated, and probable) and not associated with an IBI (Table 4). Low maternal educational level, presence of a leukemia relapse, use of intensive chemotherapy, presence of an indwelling catheter, an interval of less than or equal to 7 days since last chemotherapy, a temperature of 39°C or higher, presence of

Table 2. Diagnoses and Frequency of Microbial Confirmation for 178 Episodes of IBI

		Microbiologic Confirmation		
		Yes		No
Clinical Diagnosis	No. of Episodes	No.	%	No.
Bronchopneumonia	59	20	34	39
Sepsis syndrome	26	12	46	14
Catheter infection	19	19	100	0
Enterocolitis	18	4	22	14
Urinary tract infection	16	16	100	0
Typhlitis	10	3	30	7
Bacteremia	8	8	100	0
Cellulitis	8	3	38	5
Mucositis	8	0	0	8
Perianal abscess	3	1	33	2
Endocarditis	2	0	0	2
Meningitis	1	1	100	0
Total	178	87	49	91

Table 3. Bacterial Species Recovered From 87 Episodes of Demonstrated IBI in Patients With Febrile Neutropenia, by Site

Bacterial Species	No. of Isolates by Site					Total*	
	Blood	Catheter	Urine	Stool	Other	No.	%
Escherichia coli	12	2	10			24	26
Staphylococcus aureus	11	2	1		4	18	20
Coagulase-negative *Staphylococcus*	9	7				16	18
Klebsiella sp.	6	3				9	10
Streptococcus pneumoniae	3				1	4	4
Pseudomonas aeruginosa	1	2	1			4	4
Enterococcus sp.	1	1	1			3	3
Proteus sp.			3			3	3
Haemophilus influenzae b	2					2	2
Viridans streptococci		2				2	2
Shigella sp.				2		2	2
Streptococcus pyogenes	1					1	1
Enterobacter aerogenes	1					1	1
Salmonella sp.				1		1	1
Yersinia sp.				1		1	1
Total							
No.	47	19	16	4	5	91†	
%	52	21	18	4	6		

Abbreviation: sp., species.

*Percentages do not add up to 100% because values were approximated to the unit.

†Four episodes were polymicrobial, for 91 species recovered from 87 episodes.

Table 4. Univariate Analysis of Episode Characteristics by Presence or Absence of an IBI

Variable	Percent of Indicated Variable for			
	All IBI Episodes (n = 178)	Demonstrated Episodes Only* (n = 87)	Probable Episodes Only* (n = 91)	Absence of IBI (n = 269)
Male sex	52	53	55	47
Low maternal educational level	62	55	68	51†
Cancer type				
ALL	33	22	27	45
AnLL	11	8	13	6
Relapse of any acute leukemia	23	24	22	8†
Sarcomas	16	8	23	18
Lymphomas	4	5	4	6
Other solid tumors	13	7	12	17
Intensive chemotherapy use	70	76	65	49†
Use of G-CSF	23	23	23	16
Use of indwelling catheter	53	67	39‡	39†
Duration of fever before admission ≤ 24 hours	85	82	88	85
Interval ≤ 7 days since last chemotherapy	72	78	66‡	62†
TMP/SMX prophylaxis	54	52	57	47
Temperature ≥ 39°C	19	23	15‡	12†
Presence of hypotension	26	31	22	2†
ANC ≤ 100/mm^3	73	71	75	55†
AMC ≤ 100/mm^3	82	84	80	66†
Serum CRP level ≥ 90 mg/L	75	66	83	20†
Serum hemoglobin level < 7 g/dL	24	23	25	21
Platelet count ≤ 50,000/mm^3	63	61	65	40†

Abbreviations: ALL, acute lymphocytic leukemia; AnLL, acute nonlymphocytic leukemia; G-CSF, granulocyte colony-stimulating factor; TMP/SMX, trimethoprin-sulfamethoxazole.

*See text for definitions.

†Absence of IBI differs from all of the other three categories; $P < .05$, with the exception of a category marked with a double dagger (‡).

hypotension, an ANC of less than or equal to 100/mm^3, an AMC of less than or equal to 100/mm^3, serum CRP level of 90 mg/L or higher, and platelet count of less than or equal to 50,000/mm^3 were all significantly associated with a risk of an IBI by univariate analysis. These variables were included in the logistic regression model.

Five variables proved to be independent risk factors for an IBI (Table 5). These factors, ranked by order of significance, were CRP levels greater than or equal to 90 mg/L, presence of hypotension, relapse of leukemia as a type of cancer, presence of platelet count less than or equal to 50,000/mm^3, and an interval of less than or equal to 7 days since last chemotherapy. When analyzed separately for demonstrated and probable IBI groups, CRP, hypotension, and relapse of leukemia remain significant. Variables with lower relative risk (RR), such as low platelet count for the demonstrated IBI group and recent chemotherapy for the probable IBI group, lost significance (Table 5).

Ten children died during the febrile episode, all of them with an IBI (eight were blood culture–positive), for an overall lethality of 10 (3.9%) of 257 patients, or 10 (2.2%) of 447 episodes. All 10 children had two or more risk factors at enrollment, and nine of them had CRP levels of 90 mg/L or higher, eight had hypotension, seven had relapse of leukemia, nine had platelet counts less than or equal to 50,000/mm^3, and 10 had an interval of 7 days or less since last chemotherapy.

Predictive Model for the Risk of IBI

The risk of IBI increased according to the number of risk factors present at the time of enrollment (Table 6). Absence of risk factors was associated with IBI in 2%. Two or more risk factors at enrollment were associated with a risk greater than 48%. Episodes presenting with one risk factor had an overall risk for IBI of 22%. Elevated CRP as the sole variable had a 38% risk of IBI, compared with 17% for low platelets and 21% for recent chemotherapy. None of these differences reached significance. Hypotension (one case)

Table 5. Enrollment Variables Independently Associated With a Risk of IBI Ranked by Order of Significance

Variable	All IBI		Demonstrated IBI*		Probable IBI*	
	RR	95% CI	RR	95% CI	RR	95% CI
Serum CRP level ≥ 90 mg/L	4.2	3.6-4.8	2.9	2.3-3.5	7.2	6.6-7.7
Presence of hypotension	2.7	2.3-3.2	4.0	3.5-4.6	3.7	3.3-4.1
Relapse of leukemia	1.8	1.7-2.3	2.2	1.6-2.7	1.9	1.3-2.4
Platelet count ≤ 50,000/mm^3	1.7	1.4-2.2	1.7	1.0-2.7	2.1	1.4-2.7
Interval of ≤ 7 days since last chemotherapy	1.3	1.1-1.6	2.0	1.4-2.5	1.2	0.6-1.8

*See text for definitions.

and relapse of leukemia (four cases) as sole factors were too few for us to obtain a meaningful value. The overall risk for IBI according to the number of risk factors did not differ between children with demonstrated and probable IBI (data not shown).

Because a second or third febrile neutropenic episode in a same child could eventually influence the model, we also performed the above analysis for the first episode only. For the 257 first febrile episodes, analysis was not statistically different from that for all 447 episodes: CRP levels greater than or equal to 90 mg/L, (RR, 4.0; 95% CI, 3.4 to 4.9), presence of hypotension (RR, 2.5; 95% CI, 2.0 to 3.2), relapse of leukemia as cancer type (RR, 1.8; 95% CI, 1.6 to 2.5), platelet count less than or equal to 50,000/mm^3 (RR, 1.5; 95% CI, 1.2 to 2.1), and recent (≤ 7 days) chemotherapy (RR, 1.4; 95% CI, 1.1 to 1.6).

DISCUSSION

Children with cancer, fever, and neutropenia differ in their risk for IBI, a potentially fatal complication of bone marrow depletion. Previous studies have concluded that children can be separated into different risk categories for IBI according to clinical and laboratory parameters present at the time of admission.[15-17] In one study, an AMC less than 100/mm^3 and a temperature of 39°C or higher were significantly associated with a higher risk for bacteremia. The 95% CI for the odds ratio comparing high- versus intermediate-risk groups in that study was wide (1.6 to 12.9).[15] Two other studies concluded that risk factors were presence of leukemia as the cancer type,[16,17] induction chemotherapy treatment, ANC less than or equal to 200/mm^3,[16] occurrence of chills, hypotension, and need for resuscitation.[17] Other studies have been performed in adult populations.[30,31] The characteristics of febrile episodes among adults with cancer and neutropenia differ from those that occur in children, mainly in the high proportion of adult patients with comorbidity; therefore, conclusions obtained from these patients cannot be reliably extrapolated to children. In adults with fever, cancer, and neutropenia, serious concurrent comorbidity, such as inadequate fluid intake, inadequate pain control, uncontrolled bleeding, and so on, occurred in 36% of cases.[31]

Table 6. Risk for IBI According to Number and Type of Risk Factor(s) Present at Enrollment

No. of Risk Factors at Enrollment	Episodes (%)	Episodes Presenting With an IBI (%)
0	11	2
1*	33	22
Platelet count ≤ 50,000/mm^3	7	17
≤ 7 days since last chemotherapy	21	21
Relapse of leukemia	0.7	67
Hypotension	0.3	50
CRP ≥ 90 mg/L	4	38
2	32	48
3	19	75
4 or 5	5	100

*Type of risk factor was analyzed only for children presenting with one risk factor at enrollment (see text).

In this prospective, multicenter study, we identified five clinical and laboratory parameters that at a time of a first evaluation were independently associated with a higher risk for an IBI. The two variables with strongest association, CRP level 90 mg/L or higher and presence of hypotension, were indicators of significant systemic bacterial infection. In previous studies, we validated the usefulness of serial determinations of serum CRP for the diagnosis and follow-up of bacterial infections (cutoff value of 40 mg/L) in children with cancer, fever, and neutropenia.[25,26] This study confirmed that a cutoff value of 90 mg/L is a useful predictor of IBI. The other three variables, relapse of leukemia as cancer type, interval of 7 days or less since last chemotherapy treatment, and platelet count less than or equal to 50,000/mm^3, albeit less intensely associated, can be considered patient-related risk factors for an IBI. A more strict analysis by IBI groups defined bacteriologically (demonstrated IBI) and clinically (probable IBI) showed that the variables with higher RR (CRP ≥ 90 mg/L, hypotension, and relapse of leukemia) remained significant despite separate analysis. Variables with lower RR maintained the

trend (although low platelet count for demonstrated IBI and recent chemotherapy for probable IBI lost significance). This may have been more a problem of sample size after splitting of the analysis than a true loss of significance, an issue that will require further evaluation.

An analytic strength of our study was the simultaneous assessment of potential risk factors within a large study population allowing for the identification of independent factors predictive of an IBI, as well as for factors that do not add predictive value to an evaluation. In this study, high fever and low AMC, factors that had previously resulted in significant risk factors for IBI,[15] reached significance in the univariate but not multivariate analysis. It is possible that a similar situation would have occurred in the study by Rackoff et al if more children had been included.

A limitation of our study was the relatively low yield in bacterial detection. A bacterial pathogen was isolated in 20% of all febrile episodes and in 49% of episodes classified as IBI. The relatively low culture yield does not differ from that reported in other publications and reflects our current diagnostic capacity.[12,13,15]

Our principal aim was to identify independent factors that predict risk of IBI in pediatric cancer patients with fever and neutropenia, a requirement for establishing a model that can be safely adopted to manage these children. The variables have been identified; children that present with absence of risk factors are at a low risk (2%) of having an IBI. These children are evident candidates for outpatient management. On the other hand, children with two or more risk factors have a risk of IBI that surpasses 48%; these children will require a more aggressive approach. The group that is more complex includes 33% of children who have only one risk factor. With these results, we can propose a model of risk prediction that takes into account the number and type of risk factors present at enrollment. A child with a febrile neutropenic episode can be considered at high risk for IBI if he or she has two or more risk factors or a serum CRP level of 90 mg/L or higher, hypotension, or relapse of leukemia as sole factors; the child can be considered at low risk if he or she has an absence of risk factors, a platelet count less than or equal to 50,000/mm^3, or recent chemotherapy as sole factors. In this study, this model would have a sensitivity of 90%, specificity of 65%, and positive and negative predictive values of 75% and 87%, respectively. A prospective validation of this model is required before we can propose that it be used for the adoption of a selective management strategy. We are currently validating the predictive value of this model in a prospective, government-sponsored, multicenter study. A strategy that considers a selective approach for febrile neutropenic children will be of significant benefit to the increasing population of children with cancer and also to the health care systems of industrialized and developing countries worldwide.

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