Prospective Validation of a Risk Prediction Model for Severe Sepsis in Children With Cancer and High-risk Febrile Neutropenia

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Background: We previously created a risk prediction model for severe sepsis not clinically apparent during the first 24 hours of hospitalization in children with high-risk febrile neutropenia (HRFN), which identified 3 variables, age ≥12 years, serum C-reactive protein (CRP) ≥90 mg/L and interleukin-8 ≥300 pg/mL, evaluated at the time of admission and at 24 hours of hospitalization. The combination of these 3 variables identified a risk for severe sepsis ranging from 8% to 73% with a relative risk of 3.15 (95% confidence interval: 1.1–9.06). The aim of this study was to validate prospectively our risk prediction model for severe sepsis in a new cohort of children with cancer and HRFN.

Methods: Predictors of severe sepsis identified in our previous model (age, CRP and interleukin-8) were evaluated at admission and at 24 hours of hospitalization in a new cohort of children with HRFN between April 2009 and July 2011. Diagnosis of severe sepsis, not clinically apparent during the first 24 hours of hospitalization, was made after discharge by a blind evaluator.

Results: A total of 447 HRFN episodes were studied, of which 76 (17%) had a diagnosis of severe sepsis. The combination of age ≥12 years, CRP ≥90 mg/L and interleukin-8 ≥300 pg/mL at admission and/or at 24 hours in the new cohort identified a risk for severe sepsis ranging from 7% to 46% with an RR of 6.7 (95% CI: 2.3–19.5).

Conclusions: We validated a risk prediction model for severe sepsis applicable to children with HRFN episodes within the first 24 hours of admission. We propose to incorporate this model in the initial patient assessment to offer a more selective management for children at risk for severe sepsis.

Key Words: sepsis, high-risk febrile neutropenia

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Diagnosis and treatment of febrile neutropenic episodes occurring in children with cancer have improved significantly during the past 2 decades.[1,2] A key component of this improvement has been the development and validation of risk prediction models for early identification of an invasive bacterial infection (IBI).[3–6] These models have helped clinicians to identify children at low and high risks for IBI within 48 hours of enrollment.[3–6]

The current predictive models have been most useful for the early identification of one-third of children at low risk for IBI, allowing the implementation of selective less-aggressive management strategies including oral antimicrobials and partial or full ambulatory treatments with substantial benefit for the patients, families and health-care systems.[7–10]

For the remaining 70% of children categorized at the time of admission at high risk for IBI, current models do not allow to discriminate children who will develop a favorable clinical outcome from those who will develop severe sepsis. The latter group represents approximately 20% of children within this high-risk group and includes many children most likely to die if not aggressively treated.[11–15] In Chile, the current overall probability of a child dying as a result of a noncontrolled infection within a febrile neutropenic episode is 2.5%.[12] This probability rises to 6% if the child meets criteria for high IBI risk and to 15% if the child develops severe sepsis.[11,12] Thus, early identification of children at risk for severe sepsis could lead to prompt aggressive management strategies that could significantly improve prognosis.

In a previous multicenter study performed in 6 hospitals of Santiago, Chile, we developed a risk prediction model for severe sepsis, not clinically apparent during the first 24 hours of hospitalization, by studying several factors in 601 episodes of high-risk febrile neutropenia (HRFN) occurring in children with cancer. The model identified 3 independent variables that were detectable within 24 hours of admission and were associated with severe sepsis: age ≥12 years, serum C-reactive protein (CRP) ≥90 mg/L and interleukin-8 (IL-8) ≥300 pg/mL. The risk of severe sepsis increased with the number of risk factors reaching 73% in the subgroup of children with all factors present with a relative risk (RR) of 3.15 [95% confidence interval (CI): 1.1–9.06] compared with children with no risk factors.[16]

The aim of this study was to prospectively validate the risk prediction model for severe sepsis obtained from our primary series in a new cohort of children with cancer and HRFN.

PATIENTS AND METHODS

Enrollment and Clinical Procedures

Patients aged ≤18 years with cancer experiencing an episode of HRFN[6,13] were approached between April 2009 and July 2011 in a prospective, collaborative and multicenter study. The 6 participating hospitals located in Santiago, Chile, and part of the National Child Program of Antineoplastic Drugs network were Luis Calvo Mackenna, Roberto del Río, Exequiel González Cortés, San Juan

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The study was approved by the ethical committee of each hospital. Patients with HRFN were invited to participate and enrolled after parental informed consent and assent if older than 11 years. A common protocol was used in the 6 hospitals based on the Chilean and Latin American consensus protocols for the management of patients with febrile neutropenia (FN).[17,18] These protocols include guidelines for clinical and laboratory evaluations, antimicrobial treatments and follow-up strategies.

The following variables were recorded at the time of study enrollment: (1) history: age, gender, cancer type, chemotherapy regimen, dates of onset and end of last cycle, use of granulocyte colony-stimulating factor, presence and type of central venous catheter and hours of fever before admission; (2) clinical examination: overall clinical assessment, axillary temperature, blood pressure and signs and symptoms indicative of any clinically identifiable infectious focus; (3) laboratory examination: absolute neutrophil count, absolute monocyte count, hemoglobin level, platelet count, quantitative serum CRP and IL-8. Automated central and peripheral blood cultures, urine analysis and culture were obtained in all patients; culture of any clinically suspicious location (respiratory, soft tissues and cerebrospinal fluid) was decided by the treating physicians.

All children were evaluated at admission and at 24 hours to determine their risk for severe sepsis according to the clinical and laboratory variables determined in our previous study (age, CRP and IL-8).[16] Children initiated empiric antimicrobial treatment at admission with an antipseudomonal third-generation cephalosporin with or without an aminoglycoside and a β-lactam or glycopeptide with anti–Gram-positive activity. This regimen was based on the microbiological distribution observed in our institutions represented by coagulase-negative *Staphylococcus* (25%), *Escherichia coli* (20%), viridans group streptococci (14%), *Staphylococcus aureus* (13%) and *Pseudomonas* spp. (9%).[19]

A clinical examination was performed every 8 hours during the first 48 hours followed by a daily examination until discharge; the following parameters were recorded: axillary temperature, overall clinical condition, level of consciousness (Glasgow scale), blood pressure, capillary refill time and detection of any clinically identifiable infectious focus. Urine output was measured during the first 48 hours and continued if the patient presented with oliguria (urine output <1 mL/kg/h) until resolution. Blood gases (PO_2) were measured at admission and at 24 hours and continued daily in patients with hypoxemia (PO_2 < 60 mm Hg) until resolution. A pulse oximetry measurement was obtained at least once daily in all patients irrespective of PO_2 status. Patient monitoring was performed until episode resolution, considered when all the following conditions were met: fever resolution (2 consecutive days with temperature <38°C), 2 CRP measurements <40 mg/L, absolute neutrophil count >500/mm^3, absolute monocyte count >100/mm^3 and platelet count >50,000/mm^3. After resolution, a study physician blind to the initial results of the biomarkers, assigned the severe sepsis status, according to an international definition, the same used in our original model of risk prediction for severe sepsis.[16,20,21]

Laboratory Procedures

Routine clinical laboratory and quantitative CRP determinations were performed at the local hospital laboratories using standardized methods certified by the Chilean Institute of Public Health. IL-8 was determined at the Central Laboratory of the Hospital Luis Calvo Mackenna by immunoassay according to the manufacturer instruction (Human IL-8/CXCL8 QuantiGlo ELISA Kit, 2nd Generation; R&D Systems, Minneapolis, MN).[22]

Definitions

Neutropenia was defined as an absolute neutrophil count ≤500/mm^3; fever was defined as axillary temperature ≥38.5°C in 1 measurement or ≥38°C in 2 measurements separated by 1 hour; severe sepsis was defined as inflammatory response syndrome triggered by a microorganism, identified or not, plus one of the following: cardiovascular organ dysfunction or acute respiratory distress syndrome, or ≥2 other organ dysfunctions: neurologic, renal or hepatic.[20,21]

Sample Size Calculation, Severe Sepsis Status Assignment and Statistical Analysis

We estimated a potential enrollment capacity for the upcoming 2-year period of 440–460 HRFN episodes among the 6 participating hospitals, of which 15–20% would develop severe sepsis not apparent at admission. We calculated a minimum sample size requirement of 60 episodes with final diagnosis of severe sepsis.[22] This sample size would allow validating a ≥15% sepsis risk difference between the lowest risk and higher risk groups observed in the primary series with a 95% CI and power of 80%.

A study physician blind to CRP and IL-8 results assigned the severe sepsis status to all HRFN after discharge. Episodes with clinical diagnosis of severe sepsis made during the first 24 hours of hospitalization were excluded for the analysis of risk factors. All severe sepsis episodes were considered for the description of the population characteristics and microbiology results.

For children meeting criteria for HRFN, the 3 risk variables for severe sepsis age, serum CRP and IL-8 at admission and at 24 hours were prospectively evaluated. Odds ratio, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated in this new cohort using the same cutoff values identified in the primary series: age ≥12 years, CRP ≥90 mg/L and IL-8 ≥200 pg/mL at admission and CRP ≥100 mg/L and IL-8 ≥300 pg/mL at 24 hours of hospitalization. RR (95% CI) was used to compare the risk of developing severe sepsis not apparent at admission between the lowest risk group (absence of risk factors) and groups with increasing number of risk factors. As for our primary series and with the aim to simplify use of the model, for this analysis, we selected the same value of CRP and IL-8 at admission and at 24 hours of hospitalization (CRP ≥90 mg/L and IL-8 ≥300 pg/mL).

Categorical variables were compared by χ^2 test with Yates correction or Fisher exact test when appropriate. Continuous variables were compared by analysis of variance or Kruskal-Wallis test for 2 groups if variances were nonhomogeneous according to Bartlett's test for inequality of population variances. Statistical analysis was performed using the statistical package EpiInfo version 7.1.0.6, August 9, 2012 (Centers for Disease Control and Prevention, Atlanta, GA).

RESULTS

Population Characteristics

Between April 1, 2009, and July 31, 2011, a total of 403 children experiencing 447 HRFN episodes were enrolled in the 6 participating hospitals of which 76 episodes (17%) had a final diagnosis of severe sepsis. Children developing severe sepsis were significantly older, with an increased trend of acute myeloid leukemia cases. Severe sepsis was associated with a more prolonged duration of fever, neutropenia and monocytopenia and an increased rate of admission to intensive care unit (Table 1). All but one of the deaths occurred in the severe sepsis group.

TABLE 1. General Characteristics of 447 High-risk Febrile Neutropenic Episodes Occurring in 403 children According to Severe Sepsis Status

Characteristic	Severe Sepsis		*P* Value
	Yes (N = 76)	No (N = 371)	
At the time of admission			
Median age in years (IQR)	11.2 (6.2–13.7)	7.2 (3.6–12)	<0.001
% Male gender	48.6	54.1	0.4
% Cancer type			
ALL	29%	33%	0.59
AML	22%	14%	0.08
Leukemia relapse	21%	21%	0.95
Lymphoma	6%	6%	0.82
Solid tumor	22%	27%	0.49
Median hours of fever before admission (IQR)	3.5 (1.5–8.5)	2.5 (1–8.5)	0.6
% Use of G-CSF	44%	53%	0.2
% Use of CVC	92%	85%	0.1
% Glasgow coma score ≤13	4%	0	0.1
Median ANC cells/mm^3 (IQR)	0 (0–63)	11 (0–112)	0.3
After admission			
Median days of fever (IQR)	5.5 (2–9.5)	2.0 (1–4)	<0.001
Median days of ANC <500/mm^3 (IQR)	6.5 (4–12.5)	5.5 (3.5–8.5)	0.002
Median days of AMC <100/mm^3 (IQR)	7.5 (3.5–11.5)	4.5 (2.5–6)	<0.001
% ICU admission	75%	5%	<0.001
No. of deaths (%)	10 (13.1)	1 (0.3)	<0.001

ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; G-CSF, granulocyte colony stimulating factor; CVC, central venous catheter; ANC, absolute neutrophils count; AMC, absolute monocyte count; ICU, intensive care unit.

Microbiology Results

One or more microorganism were cultured from a sterile site (blood, urine, bronchoalveolar lavage, soft tissues and cerebrospinal fluid) in 34% of all HRFN episodes, including 66% and 29% of episodes with and without severe sepsis, respectively ($P < 0.001$). For severe sepsis, 88% of isolates were obtained from blood compared with 67% for the nonsepsis group. The description of microorganisms isolated by sepsis category is shown in Table 2. *E. coli* predominated in both groups with an increased trend in the sepsis compared with the nonsepsis episodes ($P = 0.08$). A similar trend was observed for *Pseudomonas* spp. ($P = 0.09$). Conversely, a trend toward a relative increase in proportion of coagulase-negative *Staphylococcus* ($P = 0.09$) was observed for the nonsepsis group.

Validation of the Severe Sepsis Prediction Model

The overall incidence of severe sepsis was 17% (76 cases), 19 of which were diagnosed during the first 24 hours of hospitalization and thus excluded from analysis of validation of prediction model. The 3 significant clinical and laboratory biomarkers independently associated with severe sepsis in our previous study, age ≥12 years, CRP ≥90 mg/L and IL-8 ≥200 pg/mL at admission and CRP ≥100 mg/L and IL-8 ≥300 pg/mL at 24 hours of hospitalization, maintained their significant association with severe sepsis in this new cohort. Table 3 shows the odds ratio, sensitivity, specificity, PPV and NPV for each variable.

The combination of the 3 variables identified a differential risk for severe sepsis ranging from 7% to 46% with an RR of 6.7

TABLE 2. Microorganisms Identified From Sterile Sites in 447 High-risk Febrile Neutropenic Episodes According to Severe Sepsis Status

	Severe Sepsis		*P* value
	Yes (N = 76)	No (N = 371)	
Positive episodes, N (%)	52 (66)	100 (29)	<0.001
Number of isolates*	57	106	
Microorganism			
Escherichia coli	21 (37%)	24 (23%)	0.08
Coagulase-negative *Staphylococcus*	4 (7%)	18 (17%)	0.09
Viridans group streptococci	3 (5%)	13 (12%)	0.24
Enterobacter spp.	3 (5%)	12 (11%)	0.32
Klebsiella spp.	3 (5%)	9 (8%)	0.66
Pseudomonas spp.	6 (11%)	4 (4%)	0.09
Staphylococcus aureus	3(5%)	6 (6%)	0.91
Enterococcus spp.	4 (7%)	4 (4%)	0.59
Candida spp.	1 (2%)	6 (6%)	0.44
Other†	9 (16%)	10 (9%)	0.34

*Sepsis group, 5/52 (10%) episodes had >1 microorganism; nonsepsis group, 6/100 (6%) episodes had >1 microorganism.

†Sepsis group (9): *Proteus* spp. (2), *Acinetobacter* spp. (2), *Citrobacter* spp. (2), *Salmonella* spp. (1), *Moraxella* spp. (1) and Group G *Streptococcus* (1); nonsepsis group (10): *Corynebacterium* spp. (2), *Acinetobacter* spp. (1), *Streptococcus pneumoniae* (1), *Citrobacter* spp. (1), *Capnocytophaga* spp. (1), *Bordetella pertussis* (1), *Neisseria* spp. (1), *Serratia* spp. (1) and *Moraxella* spp. (1).

TABLE 3. Clinical and Laboratory Biomarkers Associated With Severe Sepsis not Clinically Apparent at Admission in Children With HFRN

Variables	Severe Sepsis (N°/Total Episodes) Yes (%)	No (%)	OR (95% CI)	Sensitivity	Specificity	PPV	NPV
Age ≥12 years	23/57 (40%)	102/371 (27%)	1.7 (1.1–3.1)	40%	72%	18%	89%
Obtained at admission							
CRP ≥90 mg/L	28/54 (52%)	136/367 (37%)	1.8 (1.2–2.4)	51%	63%	15%	88%
IL-8 ≥200 pg/mL	37/56 (66%)	154/344 (45%)	2.4 (1.3–4.3)	53%	65%	20%	89%
Obtained at 24 hours							
CRP ≥100 mg/L	40/54 (74%)	180/346 (52%)	2.6 (1.3–5.0)	78%	44%	18%	93%
IL-8 ≥300 pg/mL	22/52 (42%)	74/338 (22%)	2.6 (1.4–4.8)	42%	78%	23%	90%

OR indicates odds ratio; IL-8, interleukin-8.

(95% CI 2.3–19.5) in 7% of children <12 years of age presenting with CRP and IL-8 below the cutoff values at admission and at 24 hours of hospitalization and in 46% of children ≥12 years of age presenting with CRP and IL-8 above the cutoff values at admission and at 24 hours of hospitalization. The presence of ≥1 of these variables at time 0 and/or 24 hours increased the risk to 14–26% in children <12 years of age and to 21–31% in children ≥12 years of age (Table 4). Importantly, children ≥12 years of age with at least 1 CRP value ≥90 mg/L or IL-8 value ≥300 pg/mL within 24 hours of admission had risk of severe sepsis over 20% (Fig. 1).

DISCUSSION

This study reproduced the significant incremental risk for severe sepsis associated with the progressive increase in risk factors at time 0 and 24 hours in children with cancer and HRFN. Our previous study showed a differential risk for severe sepsis ranging from 8% to 73% with an RR of 3.15 (95% CI: 1.1–9.06) in 601 episodes of HRFN in children with cancer. Compared with the primary series, we observed now a differential risk for severe sepsis ranging from 7% to 46% with an RR of 6.7 (95% CI: 2.3–19.5) in a new cohort of 447 HRFN episodes. With these 2 studies now completed, adding to >1000 HRFN episodes evaluated, we propose to incorporate a sepsis prediction model in the initial patient assessment including the 3 validated risk variables.

The validation cohort differed in several characteristics with the primary series. The overall risk of severe sepsis was lower as was the proportion of severe sepsis in each of the groups separated by number of risk factors. Mild variations in odds ratio, sensitivity, specificity, PPV and NPV among studies were observed. PPV was in general lower and NPV was higher in the validation group compared with the primary series group. This could mean that the absence of these factors more reliably predicts who will not develop severe sepsis than the opposite. The fact that the model provided significant RR in this changing scenario provides relative assurance that results could be reproduced in settings with diverse realities. However, local evaluation of the model is always needed before implementation.

Considering the significant impact of an opportune medical management in the outcome of children with FN,[23–25] the development of tools that can help clinician to predict risk for severe sepsis within 24 hours of admission, based on relatively simple parameters, is a step forward. The presence of biomarkers indicative of increased inflammation in a significant proportion of children despite such a short period of fever (3.5 and 2.5 hours in both child groups developing or not developing severe sepsis) is remarkable.

The validity of IL-8 in the early diagnosis of systemic infections occurring in children with FN has also been demonstrated by other groups.[27–30] Repeating the evaluation at 24 hours provides additional predictive value, especially in settings with early patient consultation,[29] as observed in our study.

This study had limitations. Although all risk factors identified in the previous cohort remained significant independent predictors of severe sepsis in the current study, there was a wide difference in the level of risk identified in both cohorts (73% versus

TABLE 4. Risk for Severe Sepsis not Clinically Apparent at Admission in Children With HRFN, According to the Absence or Presence of ≥1 Risk Factors at Admission and/or 24 Hours

Predictor Variables Obtained at: Admission				24 h			Severe Sepsis		
CRP		IL-8		CRP		IL-8	N*	%	RR(95% CI)†
Episodes in children <12 years of age (N = 303)									
↓	and	↓	and	↓	and	↓	74	7%	–
↑	and/or	↑	or	↑	and/or	↑	213/230‡	14%/18%	2.6 (1.1–6.4)
↑	and	↑	or	↑	and	↑	49/54‡	14%/26%	3.8 (1.4–10.0)
↑	and	↑	and	↑	and	↑	25	16%	2.4 (0.7–8.1)
Episodes in children ≥12 years of age (N = 125)									
↓	and	↓	and	↓	and	↓	26	11%	1.7 (0.4–6.6)
↑	and/or	↑	or	↑	and/or	↑	96/109‡	26%/21%	3.8 (1.5–9.5)
↑	and	↑	or	↑	and	↑	29/20‡	31%/30%	4.5 (1.6–12.5)
↑	and	↑	and	↑	and	↑	11	46%	6.7 (2.3–19.5)

*Episodes meeting criteria; episodes may be included in more than one category.

†Relative risk compared with the lowest risk category for each age group.

‡N and % severe sepsis for combination of variables occurring at admission or at 24 hours; the highest of the 2 RR is shown for simplicity.

↓, CRP or IL-8 < cutoff value; ↑, CRP or IL-8 ≥ cutoff value; IL-8, interleukin-8, RR, relative risk; CI, confidence interval.

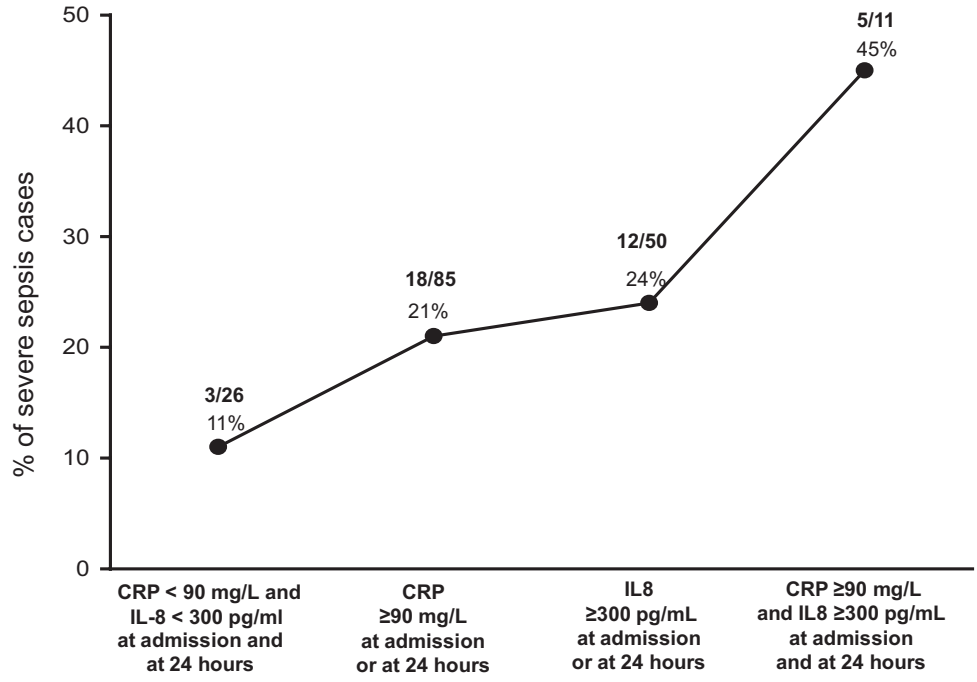

FIGURE 1. Proportion of severe sepsis cases not clinically apparent at admission according to the presence of CRP ≥90 mg/L and/or IL-8 ≥300 pg/mL at admission and/or at 24 hours of hospitalization in children ≥12 years of age.

46%). Other limitations include the decrease in severe sepsis cases in the previous versus the current cohort (25–17%), which limited the statistical power for comparing some of the variables. We did not identify differences in baseline characteristics between 2 groups. Cancer types, chemotherapy and antimicrobial regimens were similar between both studies. Evaluation of sepsis cases for both studies was performed by the same blind evaluator using the same criteria,[20,21] and no change in techniques for serum CRP or IL-8 determination occurred between the primary series and this study.

In summary, we validated a risk prediction model for severe sepsis applicable within the first 24 hours of hospital admission in children with HRFN. Children with HRFN without risk factors for severe sepsis (<12 years of age; CRP <90 mg/L and IL-8 <300 pg/mL at time 0 and 24 hours) could be monitored in a standard hospitalization setting, while children with incremental risk for severe sepsis should be considered for more aggressive management including early intensive care unit transfer in children with all risk factors for severe sepsis. This advancement could positively impact in the overall goal of reducing mortality, largely concentrated in the severe sepsis group while avoiding excessive intervention in children at low risk for severe sepsis, despite an increased risk for IBI.

REFERENCES

1. Anaissie EJ, Vadhan-Raj S. Is it time to redefine the management of febrile neutropenia in cancer patients? *Am J Med*. 1995;98:221–223.
2. Klastersky J, Awada A, Paesmans M, et al. Febrile neutropenia: a critical review of the initial management. *Crit Rev Oncol Hematol*. 2011;78:185–194.
3. Rackoff WR, Gonin R, Robinson C, et al. Predicting the risk of bacteremia in childen with fever and neutropenia. *J Clin Oncol*. 1996;14:919–924.
4. Klaassen RJ, Goodman TR, Pham B, et al. "Low-risk" prediction rule for pediatric oncology patients presenting with fever and neutropenia. *J Clin Oncol*. 2000;18:1012–1019.
5. Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol*. 2000;18:3038–3051.
6. Santolaya ME, Alvarez AM, Becker A, et al. Prospective, multicenter evaluation of risk factors associated with invasive bacterial infection in children with cancer, neutropenia, and fever. *J Clin Oncol*. 2001;19:3415–3421.
7. Paganini H, Gómez S, Ruvinsky S, et al. Outpatient, sequential, parenteral-oral antibiotic therapy for lower risk febrile neutropenia in children with malignant disease: a single-center, randomized, controlled trial in Argentina. *Cancer*. 2003;97:1775–1780.
8. Santolaya ME, Alvarez AM, Avilés CL, et al. Early hospital discharge followed by outpatient management versus continued hospitalization of children with cancer, fever, and neutropenia at low risk for invasive bacterial infection. *J Clin Oncol*. 2004;22:3784–3789.
9. Oude Nijhuis C, Kamps WA, Daenen SM, et al. Feasibility of withholding antibiotics in selected febrile neutropenic cancer patients. *J Clin Oncol*. 2005;23:7437–7444.
10. Kern WV, Heiss M, Steinbach G. Prediction of gram-negative bacteremia in patients with cancer and febrile neutropenia by means of interleukin-8 levels in serum: targeting empirical monotherapy versus combination therapy. *Clin Infect Dis*. 2001;32:832–835.
11. Basu SK, Fernandez ID, Fisher SG, et al. Length of stay and mortality associated with febrile neutropenia among children with cancer. *J Clin Oncol*. 2005;23:7958–7966.
12. Santolaya ME, Alvarez AM, Avilés CL, et al. Admission clinical and laboratory factors associated with death in children with cancer during a febrile neutropenic episode. *Pediatr Infect Dis J*. 2007;26:794–798.
13. Santolaya ME, Alvarez AM, Avilés CL, et al. Prospective evaluation of a model of prediction of invasive bacterial infection risk among children with cancer, fever, and neutropenia. *Clin Infect Dis*. 2002;35:678–683.
14. Rondinelli PI, Ribeiro Kde C, de Camargo B. A proposed score for predicting severe infection complications in children with chemotherapy-induced febrile neutropenia. *J Pediatr Hematol Oncol*. 2006;28:665–670.
15. Amman R, Bodmer N, Hirt A, et al. Predicting adverse events in children with fever and chemotherapy-induced neutropenia: the prospective multicenter SPOG 2003 FN study. *J Clin Oncol* 2010;28:2008–2014.
16. Santolaya ME, Alvarez AM, Aviles CL, et al. Predictors of severe sepsis not clinically apparent during the first twenty-four hours of hospitalization in children with cancer, neutropenia, and fever: a prospective, multicenter trial. *Pediatr Infect Dis J*. 2008;27:538–543.

17. Santolaya ME, Rabagliati R, Bidart T, et al.; Sociedad Chilena de Infectología; Sociedad Chilena de Hematología. Consenso manejo racional del paciente con cáncer, neutropenia y fiebre. *Rev Chil Infectol*. 2005;22(suppl 2):S79–S113.
18. Paganini H, Santolaya ME. Diagnóstico y tratamiento de la neutropenia febril en niños con cáncer. Consenso de la Sociedad Latinoamericana de Infectología Pediátrica. *Rev Chil Infectol*. 2010;28(suppl 1):S38.
19. Solís Y, Alvarez AM, Fuentes D, et al. Agentes causantes de bacteriemia en niños con cáncer y neutropenia febril de alto riesgo en seis hospitales de Santiago, Chile, período 2004–2009. *Rev Chil Infectol*. 2012;29:156–162.
20. Goldstein B, Giroir A, Randolph A; An international consensus conference on Pediatric sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6:2–8.
21. Brilli RJ, Goldstein B. Pediatric sepsis definitions: past, present, and future. *Pediatr Crit Care Med*. 2005;6(3 suppl):S6–S8.
22. Kern WV, Heiss M, Steinbach G. Prediction of gram-negative bacteremia in patients with cancer and febrile neutropenia by means of interleukin-8 levels in serum: targeting empirical monotherapy versus combination therapy. *Clin Infect Dis*. 2001;32:832–835.
23. Casagrande JT, Pike MC. An improved approximate formula for calculating sample sizes for comparing two binomial distributions. *Biometrics*. 1978;34:483–486.
24. Lehrnbecher T, Phillips R, Alexander S, et al.; International Pediatric Fever and Neutropenia Guideline Panel. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. *J Clin Oncol*. 2012;30:4427–4438.
25. Cull LF, Nolan MB. Treating neutropenic fever in the emergency department: delays may be deadly! *J Emerg Nurs*. 2009;35:36–39.
26. Klastersky J. Why empirical therapy? *J Antimicrob Chemother*. 2009;63(suppl 1):i14–i15.
27. Lehrnbecher T, Venzon D, de Haas M, et al. Assessment of measuring circulating levels of interleukin-6, interleukin-8, C-reactive protein, soluble Fc gamma receptor type III, and mannose-binding protein in febrile children with cancer and neutropenia. *Clin Infect Dis*. 1999;29:414–419.
28. Kaplan JM, Wong HR. Biomarker discovery and development in pediatric critical care medicine. *Pediatr Crit Care Med*. 2011;12:165–173.
29. Wong HR, Cvijanovich N, Wheeler DS, et al. Interleukin-8 as a stratification tool for interventional trials involving pediatric septic shock. *Am J Respir Crit Care Med*. 2008;178:276–282.
30. Urbonas V, Eidukaitė A, Tamulienė I. The diagnostic value of interleukin-6 and interleukin-8 for early prediction of bacteremia and sepsis in children with febrile neutropenia and cancer. *J Pediatr Hematol Oncol*. 2012;34:122–127.