

Prospective Evaluation of a Model of Prediction of Invasive Bacterial Infection Risk among Children with Cancer, Fever, and Neutropenia

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A risk prediction model for invasive bacterial infection (IBI) was prospectively evaluated among children presenting with cancer, fever, and neutropenia. The model incorporated assessment of 5 previously identified risk factors: serum level of C-reactive protein (CRP) ≥ 90 mg/L, hypotension, identification of relapse of leukemia as the cancer type, platelet count of $\leq 50,000$ platelets/mm³, and recent receipt of chemotherapy [16]. Children were uniformly evaluated at enrollment and were classified as having high or low risk for IBI according to a model that considers the number and type of variables present. Of the 263 febrile episodes evaluated during a 17-month period, 140 (53%) were in IBI-positive children. The sensitivity, specificity, and positive and negative predictive values of the model were 92%, 76%, 82%, and 90%, respectively. Identification of these 5 risk factors during the first 24 h of hospitalization was helpful in discriminating between children with a high or low risk for IBI.

During the past 2 decades, the standard approach to therapy for patients with cancer, fever, and neutropenia has involved admission of the patient to the hospital for intravenous administration of broad-spectrum antibiotics until resolution of fever and recovery of the absolute neutrophil count (ANC) are achieved [1, 2]. This approach has resulted in a reduction in the mortality rate associated with febrile neutropenia [3]. Different investigators worldwide, including our own group of investigators, agree that this aggressive management approach is suitable for children with fever and neutropenia who are at risk for invasive bacterial infection (IBI), but that it is not required and can be

detrimental for a significant number of children with low risk for IBI [4, 5].

Current knowledge indicates that these children do not all have the same risk for IBI and that nearly one-half of them could benefit from less aggressive management that includes early discharge from the hospital, a shortened course of antimicrobial therapy, use of orally administered antimicrobials, and outpatient management [6–14]. The key requirement for this management strategy is the identification of a predictive model that can safely identify children who have a low risk for IBI [15].

During 1996–1998, we developed a prospective, multicenter protocol for the assessment of IBI risk at the time of a patient’s first visit to the hospital [16]. Our evaluation of 447 episodes of febrile neutropenia led us to identify 5 variables independently associated with a risk of IBI at the time of enrollment. These variables, presented in order of significance, were a serum C-reactive protein (CRP) level of ≥ 90 mg/L (relative risk [RR], 4.2; 95% CI, 3.6–4.8), presence of hypotension

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(RR, 2.7; 95% CI, 2.3–3.2), identification of relapse of leukemia as the cancer type (RR, 1.8; 95% CI, 1.7–2.3), a platelet count of $\leq 50,000$ platelets/mm³ (RR, 1.7; 95% CI, 1.4–2.2), and recent receipt of chemotherapy (within 7 days of the hospital visit; RR, 1.3; 95% CI, 1.1–1.6). In the same protocol, we evaluated the risk for IBI according to the number of risk factors present at the time of enrollment. IBI occurred with 2%, 17%, 48%, 75%, and 100% of episodes of febrile neutropenia in patients presenting with 0, 1, 2, 3, or ≥ 4 risk factors, respectively. On the basis of the results of this study, we developed a risk prediction model that takes into account the number and type of risk factors for IBI that are present at the time of enrollment. In the government-sponsored, multicenter study presented here, our aim was to prospectively evaluate this model of prediction that incorporates our previously defined risk factors.

PATIENTS AND METHODS

Population selection. From 1 August 1999 through 31 December 2000, all children ≤ 18 years of age who were receiving chemotherapy for cancer and who were admitted to any of 6 hospitals for fever and severe neutropenia were enrolled in a prospective protocol study. The 6 participating hospitals were Hospitals Luis Calvo Mackenna, Exequiel González Cortés, Roberto del Río, San Juan de Dios, Sótero del Río, and San Borja Arriarán, all of which are located in Santiago, Chile, and are affiliated with the National Health Care System as well as the University of Chile. Together, these hospitals provide health care to 2 million children in the low-to-middle-income population. Physicians affiliated with the oncology services at each of these hospitals participate in the National Child Program of Antineoplastic Drugs (PINDA), which selects the treatment protocols to be used for different types of cancer countrywide. This protocol study was developed by physicians from the oncology and infectious disease services of each hospital, under the auspices of the PINDA Subcommittee of Infectious Diseases. Informed written consent was obtained from all patients, and the study was approved by the ethics committee of each hospital.

Overall study design. We designed a prospective, multicenter, blinded study. All patients were uniformly evaluated at the time of enrollment. Study physicians recorded the absence or presence of risk factors at the time of admission of each patient. The variables recorded included type of cancer, number of days since most recent receipt of chemotherapy, blood pressure, serum level of CRP, and platelet count. All children who were admitted to the hospital were given antimicrobial agents against both gram-positive and gram-negative bacteria, on the basis of data from previous studies that showed that, in Santiago, *Staphylococcus aureus*, coagulase-

negative *Staphylococcus* species, *Escherichia coli*, and *Klebsiella pneumoniae* account for 75% of bacterial infections in children with febrile neutropenia [17].

A prediction of risk for IBI was made within the first 24 h after admission. A child was considered to have a high risk for IBI if ≥ 2 risk factors were identified or if a serum CRP level of ≥ 90 mg/L, hypotension, or relapse of leukemia was identified as the sole risk factor. A child was considered to have a low risk for IBI if no risk factors were identified or if a platelet count of $\leq 50,000$ platelets/mm³ or recent receipt of chemotherapy was identified as the sole risk factor [16].

Children were monitored daily until their fever resolved and their ANC increased to >500 neutrophils/mm³. Monitoring involved daily physical examination, daily laboratory evaluations of the serum level of CRP, and every-other-day measurements of the ANC, absolute monocyte count (AMC), hemoglobin level, and platelet count. Additional laboratory evaluations were performed on the basis of individual clinical findings. After resolution of fever in each patient, an independent evaluator, who was unaware of the risk category assigned at enrollment, classified the IBI status with each episode as positive or negative, according to predefined criteria.

Definitions. “Fever” was defined as an axillary temperature of either $\geq 38.5^\circ\text{C}$ (on the basis of 1 measurement) or $\geq 38^\circ\text{C}$ (on the basis of 2 consecutive measurements taken at a 1-h interval). “Severe neutropenia” was defined as an ANC of ≤ 500 neutrophils/mm³. A child was considered to have a demonstrated IBI if 1 or both of the following criteria were met: (1) occurrence of bacteremia (1 or more blood cultures positive for a bacterial pathogen, with the exception of a coagulase-negative *Staphylococcus* species, for which ≥ 2 positive blood culture results were required) and/or (2) a positive result of bacterial culture of a specimen obtained from a usually sterile site (e.g., indwelling catheter, urine, CSF). A child was considered to have “probable IBI” if, in the absence of a positive culture result, 1 or both of the following criteria were met: (1) clinical and laboratory findings strongly suggestive of a sepsis syndrome and/or (2) focal organ involvement in a child with hemodynamic instability and severe 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 [18]. A child was considered to have hemodynamic instability if he/she had hypotension (defined as a blood pressure in the fifth percentile or lower for age and/or a capillary refill time of >3 s) [18].

Statistical analysis. Patient characteristics at baseline were summarized using descriptive statistics: mean \pm SD was used for the expression of continuous variables, and percentages were used for the expression of categorical variables. The Mann-Whitney *U* test was used to compare the variables of IBI-

positive children with those of IBI-negative children, and $P < .05$ was required for statistical significance.

Univariate analysis and logistic regression analysis were applied to assess the association between IBI and both the AMC and the presence of fever at enrollment. The OR was calculated with the corresponding 95% CI. The sensitivity, specificity, and positive and negative predictive values of the IBI risk prediction model were evaluated for all episodes and for the first episodes only.

The cutoff points for the CRP level and the platelet count were determined by constructing a receiver operator characteristic curve. All statistical analyses were performed with the STATA 6.0 statistical package (Stata).

RESULTS

Overall description of episodes of febrile neutropenia and IBI status. A total of 263 episodes of febrile neutropenia in 170 children were evaluated during the study period. Of these 170 children, 104 (61%) had 1 episode, 47 (28%) had 2 episodes, 14 (8%) had 3 episodes, and 5 (3%) had ≥ 4 episodes of febrile neutropenia during the study period. The mean age (\pm SD) of the children at the time of enrollment was 7 ± 4.2 years (range, 7 months to 17 years), and 56% were male. The mean ANC (\pm SD) at enrollment was 190 ± 171 neutrophils/mm³ (range, 0–498 neutrophils/mm³), and the mean temperature (\pm SD) was $38.7^\circ\text{C} \pm 0.5^\circ\text{C}$ (range, 38°C – 40.5°C). The number and percentage of children with specific cancer types were as follows: 92 (54%) had acute lymphocytic leukemia, 14 (8%) had acute nonlymphocytic leukemia, 54 (32%) had a solid tumor, and 10 (6%) had lymphoma. All episodes of fever and neutropenia occurred among children who were receiving chemotherapy; 47% of these children had an indwelling catheter. None of the children had received a bone marrow transplant.

The infectious disease–related diagnoses for the 263 febrile episodes are shown in table 1. IBI occurred with 140 (53%) of 263 episodes of febrile neutropenia that were diagnosed as bronchopneumonia, sepsis syndrome, bacteremia, urinary tract infection, catheter infection, typhlitis, and/or cellulitis. Of the 123 children without IBI, a majority had either upper respiratory infection or fever of unknown origin diagnosed. For 140 episodes in children who were IBI positive, a total of 61 bacteria (44%) were recovered; the most common organisms recovered were *E. coli*, *S. aureus*, coagulase-negative *Staphylococcus* species, and *Klebsiella* species (table 2). Mean duration of fever (\pm SD) was 5.6 ± 4.3 days (range, 1–27 days) for children with IBI and 3 ± 2.5 days (range, 1–14 days) for children without IBI ($P = .0001$, by the Mann-Whitney *U* test). Mean duration of severe neutropenia (\pm SD) was 5.7 ± 3.9 days (range, 1–20 days) for children with IBI and 4.3 ± 2.9 days (range, 1–18 days) for children without IBI

($P = .003$, by the Mann-Whitney *U* test). Four children who had an IBI died during the study period.

Validation of the IBI risk prediction model. We analyzed the risk for IBI according to the number and type of risk factors present at admission (table 3). IBI occurred with 3 (8%) of 40 episodes of febrile neutropenia in children who did not have any risk factors at enrollment, and it also occurred with 20 (25%) of 80 episodes in children who had 1 risk factor at enrollment. In the latter group of children, occurrence of IBI differed according to which risk factor was present; 3 of 30 children who had a low platelet count and 5 of 35 children who had recently received chemotherapy had IBI develop. In total, our predefined group of children with low risk for IBI had an overall IBI risk of 11% (11 of 105 children). IBI occurred in the 1 child who had hypotension, in 9 of 11 children who had a serum level of CRP ≥ 90 mg/L, and in 2 of 3 children who had relapse of leukemia as sole risk factors, conditions that were predefined as indicating a high risk for IBI. IBI occurred with 78%, 83%, and 100% of episodes in children presenting with 2, 3, or ≥ 4 risk factors, respectively.

When matching the risk assessment determined at admission with the blinded evaluation obtained after resolution of the episode, we observed that 129 (82%) of 158 episodes among children initially classified as having a high risk for IBI ultimately were associated with an IBI-positive status (table 4). On the other hand, 94 (90%) of 105 episodes in children who were initially classified as having a low risk for IBI were associated with an IBI-negative status. Sensitivity, specificity, and positive and negative predictive values for the occurrence of IBI were 92%, 76%, 82%, and 90%, respectively. We performed the same

Table 1. Diagnoses associated with 263 episodes of febrile neutropenia, according to whether invasive bacterial infection (IBI) was subsequently identified.

Diagnosis	No. of episodes	
	For which IBI was identified (n = 140)	For which IBI was not identified (n = 123)
Fever of unknown origin	—	47
Upper respiratory tract infection	—	39
Bronchopneumonia	36	—
Sepsis syndrome	36	—
Viral bronchopneumonia	—	21
Bacteremia	17	—
Urinary tract infection	12	—
Catheter infection	11	—
Diarrhea/typhlitis	13	—
Cellulitis/ecthyma	9	—
Superficial skin infection	—	5
Dental abscess	—	3
Other	6	8

Table 2. Bacterial species recovered for 140 episodes of febrile neutropenia among children with invasive bacterial infection, according to the site of the isolate.

Isolate	No. of isolates, by site of recovery					Total
	Blood	Catheter	Urine	Bronchi	Other	
<i>Escherichia coli</i>	9	—	7	—	—	16
<i>Staphylococcus aureus</i>	6	—	—	1	3	10
Coagulase-negative <i>Staphylococcus</i> species	4	5	—	—	—	9
<i>Klebsiella</i> species	2	1	3	—	—	6
<i>Enterobacter aerogenes</i>	1	2	1	—	—	4
<i>Streptococcus</i> species	4	—	—	—	—	4
<i>Pseudomonas aeruginosa</i>	2	1	—	1	—	4
<i>Stenotrophomonas maltophilia</i>	2	1	—	—	—	3
<i>Enterococcus</i> species	1	2	—	—	—	3
<i>Proteus</i> species	—	—	1	—	—	1
<i>Eikenella corrodens</i>	1	—	—	—	—	1
Total	32	12	12	2	3	61

analysis for the first episode of IBI in each patient. In this case, sensitivity, specificity, and positive and negative predictive values were 92%, 66%, 73%, and 89%, respectively.

Finally, we analyzed variables (an AMC of <100 monocytes/mm³ and temperature $\geq 39^\circ\text{C}$) that, in other studies, have been significantly associated with a higher risk for IBI but that were not independent risk factors for IBI in our previous study [16]. An AMC of <100 monocytes/mm³ was again associated with a higher risk of IBI by univariate analysis ($P = .04$) but not by logistic regression analysis (OR, 1.35; 95% CI, 0.8–2.2; $P = .236$). Temperature $\geq 39^\circ\text{C}$ was not associated with IBI by use of univariate analysis ($P = .19$).

Twenty-nine episodes were in children who were classified as having a high risk for IBI despite not actually having IBI. On the other hand, 11 episodes occurred among children who were initially classified as having a low risk for IBI but who were ultimately found to be IBI positive. The diagnoses for these 11 episodes were urinary tract infection (3 episodes), pneumonia (3), catheter infection due to coagulase-negative *Staphylococcus* species (3), sepsis syndrome (1), and *S. aureus* bacteremia (1). The final outcomes for these 11 children were favorable, as all episodes resolved without sequelae after patients completed a full course of broad-spectrum antimicrobial therapy.

We retrospectively reanalyzed the risk classification of the children with these 11 “misclassified episodes” after the children were hospitalized for 24 h. Risk classification for children with 7 of the 11 episodes was switched to high-risk classification on day 2 of hospitalization because of an increase in the serum level of CRP to ≥ 90 mg/L. Recalculation of model prediction values after the inclusion of variables from day 2 (obtained 24 h after enrollment) resulted in increases in sensitivity and neg-

ative predictive value (to 97% and 96%, respectively) without affecting specificity or the positive predictive value.

DISCUSSION

The prospective evaluation of our IBI risk prediction model demonstrated that 5 simple clinical and laboratory parameters assessed at admission, which were rigorously identified in our previous study [16], maintained high predictive values when combined appropriately. In the present prospective study, we obtained sensitivity, specificity, and positive and negative pre-

Table 3. Risk of invasive bacterial infection (IBI), according to the type of risk and the number of risk factors present at the time of patient enrollment in the study.

Risk group, no. of risk factors at enrollment	Risk
Low risk	
0	3/40 (8)
1 ^a	8/65 (12)
High risk	
1 ^b	12/15 (80)
2	66/85 (78)
3	34/41 (83)
4 or 5	17/17 (100)

NOTE. Data are no. of cases of IBI among children with febrile neutropenia/no. of children with febrile neutropenia with indicated no. of risk factors (%).

^a The sole risk factor was either a period of ≤ 7 days since receipt of chemotherapy treatment or a platelet count of $\leq 50,000$ platelets/mm³.

^b The sole risk factor was either hypotension, a C-reactive protein level of ≥ 90 mg/L, or relapse of leukemia.

Table 4. Correlation between classification of risk for invasive bacterial infection (IBI) at enrollment and classification of risk for IBI after final assessment.

IBI risk classification at enrollment	IBI status after final assessment		
	Positive	Negative	Total
High	129	29	158
Low	11	94	105
Total	140	123	263

NOTE. Data are no. of episodes of febrile neutropenia.

dictive values that were similar to those previously calculated during development of the model [16], with 40 (15%) of 263 episodes in patients for whom risk status was misclassified. The cumulative experience from both the present prospective study, which included 263 episodes of febrile neutropenia, and our initial study [16], which included 447 episodes (total number of episodes, 710), provides a strong base for proposing that this model be used for the identification of children with low risk for IBI. These children are candidates for selective treatment strategies.

Risk assessment models have been proposed by other investigators, although the 2 most relevant models have been applied in adult populations [19, 20]. The model of the Multinational Association for Supportive Care in Cancer (MASCC) [20] was based on a large multicenter study of nearly 1000 episodes of febrile neutropenia. Compared with the model presented by Talcott et al. [19], the MASCC model showed a lower misclassification rate (30% vs. 59%), higher sensitivity (71% vs. 30%), and comparable positive predictive values (91% vs. 93%).

Investigators worldwide agree that the management approach for febrile neutropenia in children and adults differs, mainly because death, significant infection, and comorbidity occur more frequently among adults [3, 19]. Models validated in adult populations thus may not be applicable to children. The MASCC scoring system considers the following variables for prediction of low risk: mild, moderate, or no symptomatology; absence of hypotension; absence of chronic obstructive pulmonary disease; either identification of a solid tumor as the cancer type or absence of previous history of fungal infections; absence of dehydration; outpatient status; and age <60 years. In an attempt to determine the usefulness of this model, we applied these criteria to our population. Burden of illness is difficult to measure (especially in younger children), chronic obstructive pulmonary disease is seldom present in children with cancer, and age <60 years obviously is not applicable.

In 1996, Rackoff et al. [21] published a model for pediatric populations in which an AMC of <100 monocytes/mm³ and a temperature of $\geq 39^{\circ}\text{C}$ were significantly associated with an

increased risk of bacteremia, although, to our knowledge, this model has not been validated. Klaassen et al. [22] recently reported a model for prediction of low risk that is based on a primary set of 227 episodes of febrile neutropenia and a validated group of 136 episodes. They concluded that an AMC of ≤ 100 monocytes/mm³ was the sole factor associated with high risk for “significant bacterial infection.” Fever was significant in the primary group but lost significance in the validation group.

In our original group of 447 episodes of febrile neutropenia, AMC and fever were significantly associated with a higher risk of IBI by univariate analysis but not by logistic regression analysis [16]. In our current evaluation set, we confirmed our previous results: an AMC of <100 monocytes/mm³ and a temperature $\geq 39^{\circ}\text{C}$ were not independently associated with IBI. As an admission variable, an AMC of <100 monocytes/mm³ seems to be a predictor for risk of bacteremia and significant bacterial infection, as defined by Rackoff et al. [21] and Klaassen et al. [22], respectively, but not for IBI, as defined by our group of investigators for our study population. Temperature $\geq 39^{\circ}\text{C}$ appears to be less strongly associated with the risk for significant and invasive bacterial infection, as defined by Klaassen et al. [22] and the present study, but it may be associated with an increased risk for bacteremia, the end point specified by Rackoff et al. [21].

The risk prediction model that we are proposing is comparable to the model proposed by Klaassen et al. [22], considering that our outcome is “invasive bacterial infection” and theirs is “significant bacterial infection.” Both models include bacteriologically demonstrated bacterial infections as well as nondemonstrated, albeit probable bacterial infections. We would like to propose the prospective validation of both models by other pediatric groups to identify a representative worldwide model that could best predict, by use of readily identifiable clinical and laboratory parameters, the risk of invasive or significant bacterial infection among children with febrile neutropenia.

The proposed models have a capacity for prediction that is more significantly negative than positive, and, as such, they better predict the low-risk episodes. This supports our final aim of selective management, which is based on the reliable identification of children with low risk for IBI. In concordance with the results of the present study, we are currently working on a prospective protocol of less aggressive management that includes a 24-h period of hospitalization to confirm low risk, followed by outpatient management. In addition, and in an attempt to improve our classification of the high-risk group, we are working on a means of identifying the subset of children who develop IBI that has a more severe clinical evolution and a higher associated mortality rate, to determine who should receive more-aggressive management at the time of enrollment.

We strongly believe that this selective management approach for children with episodes of febrile neutropenia who have low or high risk for IBI will benefit the increasing population of children with cancer, as well as the health care systems of industrialized and developing countries worldwide.

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