Published in final edited form as:

Pediatr Blood Cancer. 2015 February ; 62(2): 262–268. doi:10.1002/pbc.25275.

Development and validation of a prediction model for diagnosing blood stream infections in febrile, non-neutropenic children with cancer

Adam J. Esbenshade, MD, MSCI^{1,4}, M. Cecilia Di Pentima, MD, MPH¹, Zhiguo Zhao, MS^{2,4}, Ayumi Shintani, PhD, MPH^{2,4}, Jennifer C. Esbenshade, MD, MPH¹, Monique E. Simpson, BS³, Kathleen C. Montgomery, BS, MPH³, Robert B. Lindell, MD³, Haerin Lee, BS³, Ato Wallace, BS³, Kelly L. Garcia, BA³, Karel G.M. Moons, PhD^{2,5}, and Friedman Debra L., MD, MS^{1,4}

¹Department of Pediatrics, Vanderbilt University School of Medicine and the Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville TN, USA ²Vanderbilt Department of Biostatistics, Nashville, TN, USA ³Vanderbilt School of Medicine, Nashville, TN, USA ⁴Vanderbilt-Ingram Cancer Center, Nashville, TN, USA ⁵Julius Center for Health Sciences and Primary Care, UMC Utrecht, The Netherlands

Abstract

Background—Pediatric oncology patients are at increased risk for blood stream infections (BSI). Risk in the absence of severe neutropenia (absolute neutrophil count (ANC) $< 500/\mu\text{l}$) is not well defined.

Procedure—In a retrospective cohort of febrile (temperature $\geq 38.0^\circ$ for > 1 hour or $\geq 38.3^\circ$) pediatric oncology patients with ANC $< 500/\mu\text{l}$, a diagnostic prediction model for BSI was constructed using logistic regression modeling and the following candidate predictors: age, ANC, absolute monocyte count, body temperature, inpatient/outpatient presentation, sex, central venous catheter type, hypotension, chills, cancer diagnosis, stem cell transplant, upper respiratory symptoms, and exposure to cytarabine, anti-thymocyte globulin, or anti-GD2 antibody. The model was internally validated with bootstrapping methods.

Results—Among 932 febrile episodes in 463 patients, we identified 91 cases of BSI. Independently significant predictors for BSI were higher body temperature (Odds ratio (OR) 2.36 $p < 0.001$), tunneled external catheter (OR 13.79 $p < 0.001$), peripherally inserted central catheter (PICC) (OR 3.95 $p = 0.005$), elevated ANC (OR 1.19 $p = 0.024$), chills (OR 2.09 $p = 0.031$) and hypotension (OR 3.08 $p = 0.004$). Acute lymphoblastic leukemia diagnosis (OR 0.34 $p = 0.026$), increased age (OR 0.70 $p = 0.049$) and drug exposure (OR 0.08 $p < 0.001$) were associated with decreased risk for BSI. The risk prediction model had a C-index of 0.898; after bootstrapping adjustment for optimism, corrected C-index 0.885.

Correspondence: Adam Esbenshade, MD, MSCI, 2220 Pierce Avenue 397 PRB, Nashville TN, 37232, USA. Phone: (615) 936-1762 Fax: (615) 936-1767, adam.esbenshade@vanderbilt.edu.

Conflict of Interest Statement

All authors have no conflicts of interest to disclose.

Conclusions—We developed a diagnostic prediction model for BSI in febrile pediatric oncology patients without severe neutropenia. External validation is warranted before use in clinical practice.

Keywords

Prediction modeling in cancer; Infections in immunocompromised hosts; Febrile Neutropenia; Pediatric Hematology/oncology; Support care

Introduction

Pediatric oncology patients are immunosuppressed and at increased risk for infection [1]. Presence of a central venous catheter (CVC) [Port-A-Cath, peripherally inserted central catheter (PICC), or tunneled indwelling catheter (Hickman or Broviac)] also increases infection risk [2]. Guidelines for hospital admission and use of empiric intravenous (IV) antibiotics exist for febrile patients who are severely neutropenic (absolute neutrophil count (ANC) $<500/\mu\text{l}$) or ill-appearing [3,4]. Management of pediatric oncology patients without severe neutropenia (ANC $\geq 500/\mu\text{l}$) is less clear [1,3,5]. At our institution, standard of care is a medical evaluation, complete blood count with differential (CBC), blood culture from the CVC and provision of a single dose of empiric ceftriaxone. However, administration of empiric antibiotics can select for resistant bacteria [6]. Therefore, if the diagnosis of bacterial blood stream infections (BSI) could be predicted with precision, an evidence-based algorithm could be established and incorporated into clinical care to guide judicious empiric antibiotic therapy. Diagnostic prediction models exist for oncologic patients with fever and severe neutropenia, but not for patients presenting with fever with an ANC $\geq 500/\mu\text{l}$ [4,7–26]. We, therefore, sought to construct and internally validate a diagnostic prediction model to estimate the likelihood of having a BSI in febrile pediatric oncology patients without severe neutropenia.

Methods

Construction of the Cohort

With Institutional Review Board approval, using an institutional database, all patients diagnosed with any childhood cancer from 2007 – 2010, <23 years at the time of diagnosis and treated at the Monroe Carell Jr. Children's Hospital at Vanderbilt were identified, resulting in a cohort of 463 patients. Using the electronic medical record, a systematic review was conducted to identify febrile episodes among these patients occurring in 2007–2012, in the setting of a CVC and ANC of $\geq 500/\mu\text{l}$. Fever was defined as a temperature over 38.0° for > 1 hour or 38.3° for any duration, in accordance with the 2002 Infectious Diseases Society of America guidelines [1]. Fever used in the risk prediction model was the highest temperature within 24 hours prior to the initial blood culture being drawn. Excluded were fever events occurring within seven days of a previous febrile episode, during administration of antibiotics for previous fever or an infection, or within 30 days following a stem cell transplant. Subjects with falling ANC with a resultant value $< 500/\mu\text{l}$ within 24 hours of presentation were also excluded. Using a data collection instrument, demographics,

treatment-related variables, and symptoms at the time of fever, described below were abstracted to develop the diagnostic prediction model.

Outcome

The outcome of interest was diagnosis of BSI, defined as 1 positive blood culture obtained from a CVC for a recognized pathogen at the time of fever. For certain common pathogens (coagulase negative *staphylococci* [CoNS], viridians group streptococci, *diphtheroids*, *Micrococcus*, or *Bacillus* species), two or more positive blood cultures were required to meet criteria for BSI [2] [2,27]. Any of these bacterial isolates recovered from a single blood culture with a corresponding negative pre-antibiotic culture drawn were classified in the analysis as non-bacteremia (10 CoNS, 2 *Bacillus* species, 2 *diphtheroids*, and 2 alpha *Streptococcus* isolates) and those where there was only one pre-antibiotic culture drawn were excluded from the analysis [2]. High-risk bacteremias were defined as those with a high risk of associated severe sepsis (Gram-negative organism or *Staphylococcus aureus*).

Candidate predictors

To build the diagnostic prediction model, clinical predictors of BSI were selected *a priori*. These included demographic, disease, treatment and symptom-based risk factors that were 1) available within two hours of fever presentation, and 2) had biologic or clinical plausibility for association with presence or absence of bacteremia. Based on their magnitude of clinical importance to the outcome, we further classified these variables into Primary and Secondary Sets.

The Primary Set included demographic risk factors: age; disease and treatment risk factors: type of CVC, patient location (inpatient versus outpatient), cancer diagnosis, history of stem cell transplant (SCT), exposure to chemotherapy drugs known to commonly cause fever (cytarabine, anti-thymocyte globulin (ATG) or anti-GD2 antibody; and signs/symptoms at fever presentation: hypotension defined as a systolic or diastolic blood pressure (BP) less than the 5th percentile [28] within 2 hours of the initial blood culture, reported or observed chills and/or rigors occurring prior to or within an hour of the initial blood culture being drawn, upper respiratory symptoms (URI) defined as cough, nasal congestion or rhinorrhea, ANC, absolute monocyte count (AMC), and maximal body temperature within 24 hours prior to the initial blood culture.

The Secondary Set initially included demographic risk factors: sex; treatment-related risk factors: CVC line days, total parental nutrition (TPN) within the previous month, corticosteroid exposure within 24 hours, receipt of blood product transfusion within 2 hours prior to the initial fever, mental status change; and signs/symptoms at time of fever presentation: household sick contact, gastrointestinal symptoms, mucositis, decreased oral intake, decreased energy level, myalgias, skin and soft tissue infection (SSTI) at the CVC site, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), C-reactive protein (CRP), dysuria, hypoxia or crackles on lung auscultation, or an additional source of fever. These sources were *a priori* broken down into those increasing risk of BSI: SSTI, abscess, urinalysis with >10 white blood cells (WBC)/high powered field (HPF), appendicitis, ventriculoperitoneal shunt (VPS) infection, and those less likely associated

with BSI (positive rapid influenza or respiratory syncytial virus (RSV) tests, otitis media or externa, positive rapid Group A *Streptococcus* (GAS) test from a throat swab, and pneumonia. From this set, we then excluded those covariates reported on less than 10 occasions (mental status change, history of sick contact in the household, corticosteroid exposure within 24 hours, mucositis, SSTI at the CVC site, dysuria, hypoxia and/or crackles on exam, and blood product transfusion) and those not systematically collected on all patients (myalgias, AST, and ALT, CRP).

Statistical considerations

Descriptive statistics on demographic and baseline clinical variables were presented as median with the 25th and 75th percentiles (interquartile range, IQR) for continuous variables, and frequency with percentages for categorical variables. To compare differences between the cases of bacteremia and non-cases (fever in absence of bacteremia), the Wilcoxon rank sum test was used for continuous variables, and Fisher's exact test was used for categorical variables. Multivariable logistic regression models with Penalized Maximum Likelihood Estimations (PMLE) were used to evaluate associations between these variables and the outcome, while controlling for model overfitting [29–31]. PMLE shrinks the effect of each variable in a model to reduce overfitting to improve model reproducibility. PMLE was performed using the Regression Modeling Strategies (*rms*) package in R (www.r-project.org). The robust covariance matrix estimates by the Huber-White method were used to account for the potential correlation among multiple episodes observed from same individual and the corresponding *p* values were reported [32,33]. A redundancy analysis was first conducted with all the variables in the Primary Set in order to prevent multicollinearity using criterion $R^2=0.8$ [29].

The usefulness of the Secondary Set variables in their predictive ability was tested by conducting a Likelihood-ratio (LR) test comparing the model including both the Primary and the Secondary Set variables and the model only including the Primary Set variables. The LR test was not statistically significant, thus the variables of Secondary Set were not further included in our model. With a model including only the Primary Set variables, we conducted the LR test which simultaneously compares non-linear effects of all continuous variables and a priori-determined interaction based on clinical relevance (interaction between the type of central line and number of days CVC was in place). The LR test did not indicate statistical significance, thus those non-linear terms and the interaction terms were excluded, which resulted in a regression model including only the main effects of the Primary Set variables as the final prediction model.

Bootstrap validation with cluster sampling was performed with 300 iterations to validate and calibrate the final prediction model which showed no evidence of over-optimism (optimism=3.7%). The bootstrap bias-corrected C-index was reported as the measure of the model prediction performance. We also evaluated the predicted risk of bacteremia among those who developed high-risk bacteremia. All statistical inferences were assessed using a two-sided 5% significance level and all summary statistics, graphics, and models were generated using R version 2.15 statistical software [34].

Results

There were 935 events of fever that met inclusion criteria however, three were excluded from the analysis, where CoNS was isolated with only a single pre-antibiotic culture (Consort diagram supplemental Figure 1), resulting in 932 febrile events in the final analysis. Blood cultures met criteria for BSI in 91/932 febrile episodes with a BSI rate of 9.7%.

Baseline characteristics for the febrile events are given in Table I. The median age of the subjects was five years and 64% were male. Central venous catheters included Port-A-Cath (71.4%), PICC (3.5%) and tunneled external catheter (25.1%). Forty-eight percent of the febrile episodes occurred in patients with acute lymphoblastic leukemia (ALL). Eighty percent of the episodes occurred in the outpatient setting. Ninety four patients (10.1%) had exposure to a drug with high febrile risk within 24 hours of a fever event: anti-GD2 antibody therapy (16), ATG (4), and cytarabine (67). Eighty nine patients had an identified infectious source of fever at presentation: positive RSV or influenza rapid test (10), otitis media or externa (29), SSTI(5), urinalysis demonstrating > 10 WBCs/HPF (4), GAS tonsillitis (3), pneumonia (35) abscess (1), appendicitis (1), and elevated WBC count on spinal fluid exam from a VPS (1).

Among those 750 febrile events presenting in the outpatient setting, 211 (28.4%) required admission to the hospital for broad spectrum antibiotics and the remaining 539 (71.9%) were discharged home. Of those subjects admitted, the BSI rate was 20.9%, compared to 5.5% in those discharged home. High-risk bacteremia was diagnosed in 3.0% of patients discharged. All were subsequently admitted to the hospital for appropriate treatment and none developed adverse outcomes. Among the 182 who developed a fever while hospitalized for chemotherapy administration or another reason, 16 developed BSI (8.8%). Ten patients were admitted to the intensive care unit directly from the outpatient or inpatient setting at the time of fever and of these, four (40%) had a BSI. There were no deaths related to bacterial pathogens isolated during febrile episodes.

Blood stream infections

Of the included initial 932 episodes of fever there were a total of 91 cases of BSI. This resulted in a total of 123 bacterial isolates, 59 Gram-negative and 64 Gram-positive isolates. Bacterial pathogens and their susceptibility pattern to ceftriaxone shown in Table II with more detailed information shown in Supplemental Table I. The median time to blood culture growth from BSI cultures (n=91) was 15 hours (*range* 1–45 hours): 29% < 12 hours, 86% 24 hours, and 100% by 48 hours. There were also two fungal isolates (*Candida parapsilosis* and *Trichosporin beigeli*) both occurring in one febrile episode at the same time as an *Enterobacter cloacae* infection.

Nineteen patients were also diagnosed with bacterial infections in the absence of a BSI. This included 8 urinary tract infections (6 with *E. coli*, 1 *Enterococcus*, and 1 *Pseudomonas*), 7 cases of *Clostridium difficile* colitis and one each, methicillin-susceptible *Staphylococcus aureus* (MSSA) VPS infection, MSSA and methicillin-resistant *Staphylococcus aureus* (MRSA) SSTI, and drainage from a Jackson-Pratt drain positive for *Escherichia coli* and

Klebsiella species. Thirty three subjects had pneumonia with one subject having bacteremia (*Escherichia hermannii*), 2 cases of confirmed enterovirus, and one tracheostomy culture growing *Haemophilus influenza*, with the other etiologies of pneumonia being unknown.

Univariable analysis

Type of CVC (tunneled external catheter and PICC versus Port-A-Cath) was associated with increased risk of bacteremia ($p<0.001$) as was a history of SCT ($p=0.002$). Clinical features associated with increased probability of bacteremia included hypotension ($p<0.001$), reported chills or observed rigors ($p<0.001$), absence of URI symptoms ($p=0.04$), myalgia ($p<0.001$), visible infection at the line site ($p=0.002$), body temperature ($p<0.001$), increased line days for PICC and tunneled external catheter ($p<0.001$), and increasing ANC in those with $ANC>1000/\mu l$ ($p=0.02$). Features associated with a decreased probability of bacteremia were ALL diagnosis versus another cancer type ($p<0.001$), overall increased line days for all CVC types (driven by Port-A-Caths) ($p<0.001$), exposure to cytarabine, anti-GD2 antibody therapy, or ATG, and known source of fever other than URI or SSTI at the line site ($p<0.001$). Factors not associated with bacteremia included age, sex, inpatient versus outpatient presentation, sick contact exposure, corticosteroids or TPN in the preceding month, presence of gastrointestinal symptoms, mucositis, decreased oral intake, reported decreased energy level, and absolute monocyte count (AMC).

Diagnostic prediction model

Diagnostic prediction modeling was employed to predict the likelihood of BSI (Table III). The model performed very well with a raw C-index of 0.898 (Figure 1). When corrected for optimism using bootstrapping techniques, the model resulted in a C-index of 0.885. In a sensitivity analysis (Supplemental Table II), the 19 cases of bacterial infection in absence of BSI were eliminated from the analysis and the C-statistic was 0.899, with 300-iteration bootstrapping showing a bias-corrected C-index of 0.885. For prediction of high-risk bacteremia, the model performed with C-index of 0.919.

For the primary model, independent predictors increasing the odds of BSI included: height of temperature [Odds ratio (OR) 2.36 (95% CI 1.69, 3.29, $p<0.001$)], PICC line or tunneled external catheter versus Port-A-Cath [OR 3.95 (95% CI 1.53, 10.21, $p=0.005$)] and [OR 13.79 (95% CI 6.59, 28.86, $p<0.001$)], respectively, hypotension [OR 3.08 (95% CI 1.42, 6.7, $p=0.004$)], increased ANC [OR 1.19 (95% CI 1.02, 1.39, $p=0.024$)], and reported chills or observed rigors [OR 2.09 (95% CI 1.07, 4.09, $p=0.031$)]. Associated with a reduced probability of BSI were: ALL diagnosis [OR 0.34 (95% CI 0.13, 0.88, $p=0.026$)], increasing age [OR 0.70 (95% CI 0.49, 0.99, $p=0.049$)], location at presentation (outpatient) [OR 0.40 (95% CI 0.18, 0.90, $p=0.028$)], AMC [OR 0.79, 95% CI 0.65, 0.95, $p=0.012$] and exposure to cytarabine, anti-GD2 antibody therapy, or ATG [OR 0.08 (95% CI 0.03, 0.21, $p<0.001$)], respectively.

Figure 2 provides a nomogram from the model that can be used to generate a probability score, which is obtained by addition of points assigned by each clinical variable. A web based calculator for this model can be found at <http://www.vicc.org/biostatistics/ts/>

[Riskprediction.php](#). Figure 3 provides a distribution for the predicted probability from the model for each episode of non-BSI, non-high-risk BSI and high-risk bacteremia.

Discussion

This study was designed to evaluate risk factors for BSI in febrile pediatric oncology patients without severe neutropenia and to create and internally validate a diagnostic prediction model. A previous study evaluated risk factors for BSI in this patient population and examined 459 episodes of non-neutropenic fever, but no risk prediction modeling was performed. In this study, internal CVC type and a known source of fever were associated with lower occurrence of BSI [35].

Our model, which demonstrates accurate probability estimation for BSI in patients with CVCs, can contribute to the development of an evidence-based algorithm, which can be incorporated into clinical practice, whereby parameters can be set to guide antibiotic management. In such a model, one may consider no antibiotics for low-risk, outpatient antibiotic administration for intermediate-probability, with choices based on local antibiogram, and admission with broad-spectrum coverage for high-probability patients. As is true with any evidence-based model, it would serve to assist in patient management and not replace clinical judgment.

The risk prediction models designed for febrile oncology patients with severe neutropenia are not applicable to the setting of fever with an ANC ≥ 500 as they were designed as a prognostic rather than diagnostic model to primarily predict the probability of developing complications in order to inform discharge decisions [4,7–26]. However, as patients with an ANC ≥ 500 are at lower probability of BSI, a model for predicting BSI in patients with an ANC ≥ 500 should focus on risk stratification for delivery of empiric antibiotics and initial admission to the hospital. The novel diagnostic prediction model developed in this study was specifically designed to address these gaps in knowledge and the unique features of the febrile pediatric oncology patient without severe neutropenia.

Our study identified important independent predictors for BSI, the strongest of which is the type of central line, consistent with the known increased probability of infection with CVCs such as Hickman and PICC lines, due in part to environmental exposure and frequent manipulation [21,35,36]. Other predictors, degree of fever, hypotension, reported chills or observed rigor, have also been shown to predict probability of BSI in neutropenic hosts [7,8,12,24,25].

Equally important, our model identified factors associated with decreased risk of BSI, such as ALL diagnosis, increasing age, higher monocyte count, and exposure to cytarabine, ATG, and anti-GD2 antibody therapy. With a small number of non-BSI bacterial infections in our cohort, we did not find that presence of such infections increased risk for BSI. However, this model is being designed to predict BSI in those without another identifiable bacterial infection, for use and selection of empiric antibiotics. Therefore, other infections should be assessed and treated independent of the BSI risk.

Our study provides a very strong prediction model for BSI in the febrile pediatric oncology patient without severe neutropenia. However, limitations must be acknowledged. The model was developed using retrospective medical chart review, limiting factors to those available in the electronic medical record. There may be additional presenting features or laboratory data that could have further improved this model had they been systematically collected. Similarly, with retrospective review, it was not possible to truly categorize severity of symptoms. For example, while we found chills or rigors to be mild independent risk factor for bacteremia, presentation was variable ranging from reported “coldness” to observed rigors. There were 50 episodes of reported chills or observed rigors in patients with a predicted risk of bacteremia less than 10% by the model and only one (2%) had BSI. Moving forward, the model is designed to be incorporated in the care of clinically stable pediatric oncology patients, and patients with observed rigors would not fall into this category and all ill appearing immunocompromised patients would receive antibiotic therapy.

This diagnostic model requires external validation before it can be widely used as a clinical decision tool for clinically stable febrile pediatric oncology patients with CVCs in the absence of severe neutropenia [4]. Once validated and incorporated into an evidence-based clinical algorithm, its implementation can result in improved antibiotic stewardship and clinical care for this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by National Center for Research Resources at the National Institutes of Health [KL2TR000446] and the National Cancer Institute at the National Institutes of Health [CA090625].

References

1. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2002; 34(6):730–751. [PubMed: 11850858]
2. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2009; 49(1):1–45. [PubMed: 19489710]
3. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013; 31(6):794–810. [PubMed: 23319691]
4. Lehnbecher T, Phillips R, Alexander S, et al. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012; 30(35):4427–4438. [PubMed: 22987086]
5. Sung L, Manji A, Beyene J, et al. Fluoroquinolones in children with fever and neutropenia: a systematic review of prospective trials. *The Pediatric infectious disease journal*. 2012; 31(5):431–435. [PubMed: 22189521]

6. Courcol RJ, Pinkas M, Martin GR. A seven year survey of antibiotic susceptibility and its relationship with usage. *The Journal of antimicrobial chemotherapy*. 1989; 23(3):441–451. [PubMed: 2732126]
7. Agyeman P, Aebi C, Hirt A, et al. Predicting bacteremia in children with cancer and fever in chemotherapy-induced neutropenia: results of the prospective multicenter SPOG 2003 FN study. *The Pediatric infectious disease journal*. 2011; 30(7):e114–e119. [PubMed: 21394050]
8. Alexander SW, Wade KC, Hibberd PL, et al. Evaluation of risk prediction criteria for episodes of febrile neutropenia in children with cancer. *Journal of pediatric hematology/oncology*. 2002; 24(1): 38–42. [PubMed: 11902738]
9. Ammann RA, Hirt A, Luthy AR, et al. Predicting bacteremia in children with fever and chemotherapy-induced neutropenia. *The Pediatric infectious disease journal*. 2004; 23(1):61–67. [PubMed: 14743049]
10. Baorto EP, Aquino VM, Mullen CA, et al. Clinical parameters associated with low bacteremia risk in 1100 pediatric oncology patients with fever and neutropenia. *Cancer*. 2001; 92(4):909–913. [PubMed: 11550165]
11. Dommett R, Geary J, Freeman S, et al. Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting. *Eur J Cancer*. 2009; 45(16):2843–2849. [PubMed: 19616427]
12. Hakim H, Flynn PM, Srivastava DK, et al. Risk prediction in pediatric cancer patients with fever and neutropenia. *The Pediatric infectious disease journal*. 2010; 29(1):53–59. [PubMed: 19996816]
13. Hann I, Viscoli C, Paesmans M, et al. A comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. *International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC)*. *British journal of haematology*. 1997; 99(3):580–588. [PubMed: 9401070]
14. Jones GR, Konsler GK, Dunaway RP, et al. Infection risk factors in febrile, neutropenic children and adolescents. *Pediatric hematology and oncology*. 1996; 13(3):217–229. [PubMed: 8735337]
15. Klaassen RJ, Goodman TR, Pham B, et al. "Low-risk" prediction rule for pediatric oncology patients presenting with fever and neutropenia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2000; 18(5):1012–1019. [PubMed: 10694551]
16. Lucas KG, Brown AE, Armstrong D, et al. The identification of febrile, neutropenic children with neoplastic disease at low risk for bacteremia and complications of sepsis. *Cancer*. 1996; 77(4): 791–798. [PubMed: 8616774]
17. Lucking V, Rosthoj S. Prediction of bacteremia in children with febrile episodes during chemotherapy for acute lymphoblastic leukemia. *Pediatric hematology and oncology*. 2013; 30(2): 131–140. [PubMed: 23281776]
18. Macher E, Dubos F, Garnier N, et al. Predicting the risk of severe bacterial infection in children with chemotherapy-induced febrile neutropenia. *Pediatric blood & cancer*. 2010; 55(4):662–667. [PubMed: 20806364]
19. Madsen K, Rosenman M, Hui S, et al. Value of electronic data for model validation and refinement: bacteremia risk in children with fever and neutropenia. *Journal of pediatric hematology/oncology*. 2002; 24(4):256–262. [PubMed: 11972092]
20. Miedema KG, de Bont ES, Oude Nijhuis CS, et al. Validation of a new risk assessment model for predicting adverse events in children with fever and chemotherapy-induced neutropenia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011; 29(7):e182–e184. author reply e185. [PubMed: 21245423]
21. Mueller BU, Skelton J, Callender DP, et al. A prospective randomized trial comparing the infectious and noninfectious complications of an externalized catheter versus a subcutaneously implanted device in cancer patients. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1992; 10(12):1943–1948. [PubMed: 1453208]
22. Paganini HR, Aguirre C, Puppa G, et al. A prospective, multicentric scoring system to predict mortality in febrile neutropenic children with cancer. *Cancer*. 2007; 109(12):2572–2579. [PubMed: 17492687]

23. Rackoff W, Breitfeld P. Risk factors in children with fever and neutropenia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2001; 19(22):4270–4271. [PubMed: 11709573]
24. Rondinelli PI, Ribeiro Kde C, de Camargo B. A proposed score for predicting severe infection complications in children with chemotherapy-induced febrile neutropenia. *Journal of pediatric hematology/oncology*. 2006; 28(10):665–670. [PubMed: 17023827]
25. Santolaya ME, Alvarez AM, Aviles CL, et al. Prospective evaluation of a model of prediction of invasive bacterial infection risk among children with cancer, fever, and neutropenia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2002; 35(6):678–683. [PubMed: 12203164]
26. Santolaya ME, Alvarez AM, Aviles CL, et al. Prospective Validation of a Risk Prediction Model for Severe Sepsis in Children with Cancer and High Risk Fever and Neutropenia. *The Pediatric infectious disease journal*. 2013
27. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control*. 2002; 51(RR-10):1–29.
28. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004; 114:555–576. (2 Suppl 4th Report). [PubMed: 15286277]
29. Harrell, FE. *Regression modeling strategies : with applications to linear models, logistic regression, and survival analysis*. New York: Springer; 2001. p. xxii-568.
30. Moons KG, Donders AR, Steyerberg EW, et al. Penalized maximum likelihood estimation to directly adjust diagnostic and prognostic prediction models for overoptimism: a clinical example. *Journal of clinical epidemiology*. 2004; 57(12):1262–1270. [PubMed: 15617952]
31. van JCH. Shrinkage and penalized likelihood methods to improve diagnostic accuracy. *Stat Neerl*. 2001; 55:17–34.
32. Huber, PJ. *The behavior of maximum likelihood estimates under nonstandard conditions*. Berkeley, CA: University of California Press; 1967.
33. White H. A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. *Econometrica : journal of the Econometric Society*. 1980; 48:817–830.
34. Team RDC. *A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2012.
35. Kelly MJ, Vivier PM, Panken TM, et al. Bacteremia in febrile nonneutropenic pediatric oncology patients. *Pediatric blood & cancer*. 2010; 54(1):83–87. [PubMed: 19774640]
36. McLean TW, Fisher CJ, Snively BM, et al. Central venous lines in children with lesser risk acute lymphoblastic leukemia: optimal type and timing of placement. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2005; 23(13):3024–3029. [PubMed: 15860859]

Figure 1. Receiver operating curve (ROC) for the Primary Diagnostic Model to estimate the probability of having a blood stream infection in 932 episodes of fever without severe neutropenia.

Figure 2. Nomogram for the Primary Diagnostic Model to estimate the probability of having blood stream infection from available data. Points for each variable are added together and the estimated probability of a blood stream infection is given at the bottom of the nomogram.

Figure 3.
Distribution of predicted risk from the Primary Diagnostic Model assigned to each case of non-high-risk blood stream infection and high-risk bacteremia.

Table I

Demographic and clinical characteristics of non-neutropenic febrile oncology patients with and without blood stream infection

<u>Characteristics</u>	<u>Blood Stream Infection</u> (N=91)	<u>No blood stream infection</u> (N=841)	<u>Groups Combined</u> (N=932)	<u>P-value</u>
Age in years ¹	3.0; 5.0; 12.5	3.0; 5.0; 10.0	3.0; 5.0; 10.0	0.37 ³
Location at time of event				0.68 ²
Inpatient	18% (16)	20% (166)	20% (182)	
Outpatient	82% (75)	80% (675)	80% (750)	
Sex				0.25 ²
Male	58% (53)	64% (551)	64% (594)	
Female	42% (38)	36% (300)	36% (338)	
Type of Central Venous Catheter (CVC)				<0.001 ²
Port-a-cath	19.8% (18)	76.9% (647)	71.4% (665)	
PICC line ⁵	5.5% (5)	3.3% (28)	3.5% (33)	
External tunneled catheter	74.7% (68)	19.7% (166)	25.1% (234)	
Hypotension	8.8% (8)	1.0% (8)	1.7% (16)	<0.001 ²
Reported/observed chills or shaking rigors	35.2% (32)	9.3% (78)	11.8% (110)	<0.001 ²
Diagnosis				<0.001 ^{2,4}
Acute lymphoblastic leukemia	8.8% (8)	52.1% (438)	47.9% (446)	
Acute myeloblastic leukemia	9.9% (9)	4.4% (37)	4.9% (46)	
Lymphoma	9.9% (9)	8.8% (74)	8.9% (83)	
Sarcoma	31.9% (29)	9.9% (83)	12.0% (112)	
Central nervous system tumor	9.9% (9)	7.3% (61)	7.5% (70)	
Neuroblastoma	22.0% (20)	5.5% (46)	7.1% (66)	
Wilms' tumor	2.2% (2)	3.3% (28)	3.2% (30)	
Langerhans cell histiocytosis	0% (0)	3.9% (33)	3.5% (33)	
Other	5.5% (5)	4.9% (41)	4.9% (46)	
History of stem cell transplant				0.001 ¹
Allogeneic transplant	4.4% (4)	2.4% (20)	2.6% (24)	
Auto-transplant	12.1% (11)	3.7% (31)	4.5% (42)	
No transplant history	83.5% (76)	93.9% (788)	92.9% (864)	
Upper respiratory infections symptoms ⁶	12% (11)	21% (180)	20% (191)	0.04 ²
Other source of fever				<0.001 ²
No	94.5% (86)	78.8% (663)	80.4% (749)	
Drug Exposure ⁷	1.1% (1)	11.1% (85)	10.1% (94)	
High risk source ⁸	1.1% (1)	1.3% (11)	1.3% (12)	
Low risk source ⁹	3.3% (3)	8.8% (74)	8.3% (77)	
Number of days CVC in place ¹	41, 83, 130	62; 193; 533	59; 170; 490	<0.001 ³

Characteristics	Blood Stream Infection (N=91)	No blood stream infection (N=841)	Groups Combined (N=932)	P-value
Absolute neutrophil count ¹	2210; 4250; 7660	1830; 3290; 5580	1858; 3360; 5735	0.02 ³
Absolute neutrophil count <1000	8.8% (8)	8.3% (70)	8.4% (78)	0.84 ²
Absolute monocyte count ¹	120; 440; 842	230; 460; 820	220; 460; 820	0.29 ³
Height of temperature at presentation ^{1,10}	38.5; 39.1; 39.4	38.3; 38.6; 39.0	38.3; 38.7; 39.1	<0.001 ³
TPN ¹¹	11.0% (10)	7.4% (62)	7.7% (72)	0.22 ²
Sick contact reported in household	8.8% (8)	13.0% (109)	12.6% (117)	0.32 ²
Corticosteroid exposure ¹²	6.6% (6)	9.5% (80)	9.2% (86)	0.45 ²
Gastrointestinal symptoms ¹³	29% (26)	29% (242)	29% (268)	1.0 ²
Mucositis	4.4% (4)	3.1% (26)	3.2% (30)	0.52 ²
Reported decreased oral intake	20% (18)	22% (189)	22% (207)	0.60 ²
Reported decreased energy level	19% (17)	22% (186)	22% (203)	0.51 ²
Reported arthralgias	15.4% (14)	4.9% (41)	5.9% (55)	<0.001 ²
Skin and soft tissue infection at CVC site	4.4% (4)	0.4% (3)	0.8% (7)	0.002 ²

¹ a; b; c represent the 25th quartile a, the median b, and the 75th quartile c for continuous variables. Numbers after percents are frequencies.

² Fisher's exact test

³ Wilcoxon rank sum test

⁴ Comparison ALL versus all other diagnosis

⁵ Peripherally inserted central catheter

⁶ Cough, rhinorrhea, and/or congestion

⁷ Exposure to cytarabine, neuroblastoma antibody therapy (Anti- GD2) , or ATG within 24 hours of presentation.

⁸ A priori sources thought to have an increased risk of bacteremia (cellulitis, abscess, >10 white blood cells in urine, appendicitis, and elevated white blood cell count on VP shunt tap)

⁹ A priori sources of fever thought to have a decreased risk of bacteremia (pneumonia, rapid RSV or influenza positive, otitis media/externa, positive rapid Streptococcus throat swab).

¹⁰ Celsius

¹¹ Received Total Parental Nutrition within the month prior to presentation

¹² Exposure within the 24 hours prior to presentation

¹³ Vomiting, diarrhea, or abdominal pain

Table II

Gram-negative and Gram-positive Isolates with Sensitivity Pattern to Third generation Cephalosporin

Bacteria isolated (% sensitive)	Number of isolates	Number sensitive to third generation Cephalosporin
Gram-negative isolates¹		
<i>Acinetobacter species</i>	7	0 (0%)
<i>Alcaligenes xylosoxidans</i>	1	0 (0%)
<i>Escherichia species</i>	5	5 (100%)
<i>Enterobacter cloacae</i>	7	7 (100%)
<i>Pantoea species</i>	7	7 (100%)
<i>Pseudomonas aeruginosa</i>	4	0 (0%)
<i>Citrobacter youngae</i>	1	1 (100%)
<i>Klebsiella oxytoca</i>	3	3 (100%)
<i>Serratia marcescens</i>	3	3 (100%)
<i>Pseudomonas fluorescens/putida</i>	2	0 (0%)
<i>Klebsiella pneumonia</i>	8	8 (100%)
<i>Citrobacter freundii</i>	1	0 (0%)
<i>Sphingomonas paucimobilis</i>	1	1 (100%)
<i>Stenotrophomonas maltophilia</i>	1	0 (0%)
Gram-positive isolates³		
<i>Coagulase negative Staphylococcus</i>	19	2 (11%) (Test for Cefazolin)
<i>Staphylococcus aureus</i>	7	6 (86%) (Test for Cefazolin)
<i>Enterococcus faecium</i>	6	0 (0%)
<i>Enterococcus faecalis</i>	11	0 (0%)
<i>Enterococcus casseliflavus</i>	2	0 (0%)
<i>Enterococcus gallinarum</i>	1	0 (0%)
<i>Gamma-hemolytic Streptococcus</i>	2	1 (50%) (Test for Penicillin)
<i>Streptococcus pneumoniae</i>	3	3 (100%)
<i>Bacillus Species</i>	2	0 (0%)
Total (with sensitivities data available)	104	47 (45%)

¹ Also isolated gram negatives but no sensitivities: *Aeromonas hydrophila* (1), *Wautersiella falsenii* (1), *Alcaligenes faecalis* (1), *Flavobacterium species* (1), *Pseudomonas fluorescens* (1).

² Piperacillin-Tazobactam

³ Also isolated but no sensitivity data (N) isolates: *Diphtheroids* (2), *Bacillus species* (5), *Rhodococcus* (1), *Lactobacillus species* (1), *Corynebacterium urealyticum* (1), *Staphylococcus aureus* (1).

Table III

Risk Prediction Model for Blood Stream Infection in Non-neutropenic Fever (n=932)

Characteristics	Odds Ratio	95% CI	P-value
Age in years at time of episode (10 vs. 3) ¹	0.7	(0.489, 0.998)	0.049
Absolute Neutrophil Count (3360 vs. 750) ¹	1.19	(1.023, 1.385)	0.024
Absolute Monocyte Count (820 vs. 220) ¹	0.79	(0.652, 0.949)	0.012
Height of temperature (Celsius) (39.1 vs. 38.3) ¹	2.36	(1.693, 3.293)	<0.001
Location at presentation (Inpatient vs. Outpatient)	0.4	(0.178, 0.904)	0.028
Type of CVC% (PICC vs. Port)	3.95	(1.529, 10.21)	0.005
Type of CVC% (Hickman line vs. Port)	13.79	(6.587, 28.862)	<0.001
Hypotension	3.08	(1.421, 6.7)	0.004
Chills or shaking rigors	2.09	(1.068, 4.094)	0.031
Diagnosis (Acute Lymphoblastic leukemia vs. other)	0.34	(0.131, 0.879)	0.026
History of stem cell transplant	1.06	(0.464, 2.365)	0.896
Upper respiratory symptoms present	0.6	(0.335, 1.068)	0.082
Drug exposure ²	0.08	(0.029, 0.211)	<0.001

¹Odds ratio for the 75th vs. 25th quartile %Central venous catheter,²Exposure to cytarabine, neuroblastoma antibody therapy (anti-GD2) or ATG in 24 hours previous to episode.