

Approach to Non-Neutropenic Fever in Pediatric Oncology Patients—A Single Institution Study

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Background. Pediatric oncology patients with fever, even when not neutropenic, are known to be at an increased risk of bloodstream infections. However, there are no standard guidelines for management of fever in non-neutropenic patients, resulting in variability in practice across institutions. **Procedure.** We retrospectively analyzed the clinical characteristics, management, and outcome of all febrile non-neutropenic episodes in pediatric oncology patients at a single institution over the two-year period 2011–2012, to identify predictors of bloodstream infections. We assessed the efficacy of a uniform approach to outpatient management of a defined subset of patients at low risk of invasive infections. **Results.** A total of 254 episodes in 83 patients were identified. All patients had implanted central venous catheters (port). Sixty-two episodes (24%) were triaged as high-risk

and admitted for inpatient management; five (8%) had positive blood cultures. The remaining 192 episodes were triaged as low risk and managed with once daily outpatient intravenous ceftriaxone; three (1.6%) were associated with bacteremia, and 10% required eventual inpatient management. Of all the factors analyzed, only signs of sepsis (lethargy, chills, hypotension) were associated with positive bloodstream infection. **Conclusions.** Treatment of a defined subset of patients with outpatient intravenous ceftriaxone was safe and effective. Signs of sepsis were the only factor significantly associated with bloodstream infection. This study provides a baseline for future prospective studies assessing the safety of withholding antibiotics in this subset of patients. *Pediatr Blood Cancer* 2015;62:2167–2171. © 2015 Wiley Periodicals, Inc.

Key words: bacteremia; fever; non-neutropenic

INTRODUCTION

Bacterial infection is an important cause of morbidity and mortality in cancer patients.[1] Febrile illness is among the most commonly encountered complications occurring in patients with cancer during the course of their treatment. Such patients are at an increased risk of bloodstream and invasive infections, which is attributed primarily to the associated immunosuppression and the presence of indwelling central venous catheters (CVC). Although hospitalization and initial treatment with empiric broad-spectrum intravenous antibiotics remains the standard of care for management of febrile neutropenia,[2–4] several recent studies have suggested that outpatient management of patients with neutropenic fever who are at low risk for infections may also be feasible and safe.[2,5] For febrile episodes in non-neutropenic patients with an indwelling CVC, treatment in most cases includes empiric outpatient intravenous broad-spectrum antibiotic therapy, but varies considerably across different institutions. Prior studies have suggested a relatively high incidence of bacteremia and central line infections (6–24%) in such patients.[6–9] One study[7] found a higher incidence of bacteremia in febrile non-neutropenic pediatric cancer patients (23.6%) compared with neutropenic patients (9.4%), and this was mostly related to a higher incidence of CVC exit-site infections. Another study focusing on acute lymphoblastic leukemia showed that the incidence of bacteremia was 8% in febrile non-neutropenic patients, compared to 28% in febrile neutropenic patients.[8] In all studies, however, the incidence of bacteremia in non-neutropenic cancer patients with fever was not negligible. More recently, a few studies have suggested that it may be safe to observe a subset of patients with non-neutropenic fever and no evidence of sepsis or chills, without administration of antibiotics.[9–11] Although Gorelick et al.[7] suggested, based on the high incidence of bacteremia in their studied cohort, that empiric antibiotic therapy is warranted in all pediatric oncology patients with indwelling catheters who develop fever, Minotti et al.[12] found that single-agent oral antibacterial therapy may be as effective and safe as broad-spectrum parenteral

therapy in low-risk neutropenic and non-neutropenic cancer patients. Kelly et al.[6] showed an overall sensitivity of high-risk bacteremia to ceftriaxone in up to 94% of cases, providing justification for its empirical use in outpatient febrile non-neutropenic pediatric oncology patients. A recent study[9] evaluated possible risk factors for bacteremia in febrile non-neutropenic pediatric cancer patients at a single institution. Based on their findings, the authors suggest an elaborate risk-prediction model for identifying high-risk patients, to be further evaluated in future prospective studies. Notably, a survey of American Society of Pediatric Hematology/Oncology (ASPHO) members regarding their approach to the evaluation and treatment of febrile non-neutropenic children with cancer revealed that the majority of the respondents drew blood cultures from CVC if a CVC was present, and started empiric intravenous antibiotic therapy. If a CVC was not

Abbreviations: ANC, absolute neutrophil count; ASPHO, American Society of Pediatric Hematology and Oncology; AUBMC, American University of Beirut Medical Center; C, celsius; CCCL, children's Cancer Center of Lebanon; CFU, colony-forming unit; CMV, cytomegalovirus; Cu.mm, cubic millimeter; CVC, central venous catheter; E. coli, Escherichia coli; spp., species; SPSS, statistical package for social sciences; UTI, urinary tract infection

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present, the majority drew peripheral cultures, and most did not admit these patients to the hospital. However, there was significant variability in the approach to the management of fever in this group of patients.[13]

The primary objective of this single-institution, retrospective study was to assess the incidence and the clinical characteristics associated with bacteremia in pediatric oncology patients with non-neutropenic febrile illness, and to evaluate the efficacy of uniform outpatient empirical antibiotic therapy in this category of patients. We investigated the clinical presentation of febrile episodes, laboratory studies performed, incidence of bacteremia, management, and outcome over the 2-year period 2011–2012.

PATIENTS AND METHODS

This study was approved by the Institutional Review Board at the American University of Beirut Medical Center (AUBMC). A retrospective review of medical records was conducted for all non-neutropenic febrile episodes in pediatric oncology patients presenting to the Children's Cancer Center of Lebanon (CCCL) at the AUBMC between January 2011 and December 2012.

At the CCCL, all patients undergoing active treatment for cancer have an implanted central venous catheter (CVC) inserted for chemotherapy administration. A unified approach to patients with non-neutropenic fever and implanted CVC has been used at the CCCL outpatient clinic, as follows: patients presenting with non-neutropenic fever are admitted for inpatient intravenous antibiotic therapy only if they are clinically ill-appearing, and/or have other abnormal vital signs (persistent tachycardia despite fever control, tachypnea, desaturation, and hypotension), and/or if they are complaining of chills or lethargy. Otherwise, well-appearing febrile patients without severe neutropenia (ANC >500 cu.mm) are assessed for focus of infection, central blood cultures are drawn, and patients receive ceftriaxone intravenously through the CVC. Depending on the presence of a focus of infection, further therapy is tailored. The patient is followed up the next day at the outpatient clinic, and another dose of ceftriaxone is administered, pending the blood culture results. This process is repeated until fever resolution or identification of a focus of infection.

Retrospective chart review was conducted to identify all episodes of febrile illness encountered in the outpatient setting and corresponding blood count results were checked to identify episodes without neutropenia. Febrile illness was defined as at least one documented episode of fever (defined as persistent temperature $\geq 38.0^{\circ}\text{C}$ orally for more than 30 min, or a single reading of $\geq 38.3^{\circ}\text{C}$), and non-neutropenia was defined as an absolute neutrophil count (ANC) of more than or equal to $500 \mu\text{l}$. For all the identified episodes, the following information was collected: patient age, tumor type, vital signs, associated symptoms, pertinent findings on physical examination, type and date of the most recent chemotherapy received, complete blood count results, ANC, culture results (blood, urine, and other cultures), other pertinent laboratory findings (abnormal electrolytes, abnormal renal, or liver function tests), choice and duration of antibiotics administered, clinical course of illness, disposition, and outcome. Recurring or persistent fever within a 7-day interval was counted as a single episode, and recurrence/persistence was included in the outcome description.

Statistical analysis was done using the Statistical Package for Social Sciences program (SPSS, version 20) for data management

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and analyses. Categorical variables were summarized by calculating the number and percent. Categorical data were analyzed using χ^2 test or Fisher's exact test (where sample size was small). On the other hand, continuous variables were analyzed using Student's *t*-test. Univariate logistic regression model was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for the effect of clinical variables on risk of bacteremia. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 254 febrile non-neutropenic episodes in the outpatient setting in 83 pediatric oncology patients were identified, over the two-year study period. All patients were receiving chemotherapy, with an implanted central venous catheter (port) in place. The patient characteristics including disease type, patient age, gender, temperature, and ANC at presentation, for all the episodes, are shown in Table I.

Sixty-two episodes (24%) were deemed high-risk for invasive infection at presentation necessitating inpatient management, and were directly hospitalized for broad-spectrum antibiotic therapy. The reasons for high-risk status are detailed in Table II and included a period of high-risk chemotherapy (acute leukemia induction or re-induction), clinical signs of sepsis, pyelonephritis, gastroenteritis with dehydration, associated cytopenias, influenza infection, lethargy, respiratory distress, varicella infection, severe pain, and localized severe infection. The remaining 192 episodes (76%) were triaged as low risk, and hence were managed with a plan of outpatient therapy with once daily intravenous ceftriaxone until fever resolution. Of these 192 "low-risk" episodes, 172 resolved successfully with outpatient management, and 20 (10%) were eventually admitted for inpatient management. Reasons for admission are detailed in Table III and included the development

TABLE I. Clinical Characteristics

Characteristics	Number (%), N = 254
Gender	
Male	115 (45)
Female	139 (55)
Age (years)	
<1	19 (7)
1–10	185 (73)
>10	50 (20)
Disease	
ALL	129 (51)
AML	3 (1)
Lymphoma	31 (12)
Solid tumor	69 (27)
LCH	22 (9)
ANC (cells/cu.mm)	
500–1,000	40 (16)
1,000–5,000	152 (60)
>5,000	62 (24)
Temperature ($^{\circ}\text{C}$)	
38.0–38.5	141 (55)
38.6–39.0	68 (27)
>39.0	45 (18)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; LCH, Langerhans cell histiocytosis; ANC, absolute neutrophil count.

TABLE II. Reasons for High-Risk Status and Admission Upon Presentation

Reason	Number of episodes (%), N = 62
Clinical signs of sepsis	12 (19)
High-risk chemotherapy (ALL induction or re-induction)	9 (14.5)
Pyelonephritis	9 (14.5)
Gastroenteritis with dehydration	8 (13)
Associated cytopenias	3 (5)
Influenza infection	3 (5)
Lethargy	2 (3)
Respiratory distress	2 (3)
Varicella infection	1 (2)
Severe pain	1 (2)
Localized severe infection:	12 (19)
Mucositis	4
Suppurative otitis media	2
Tooth abscess	1
Anal fissure/pain	1
Orbital cellulitis	1
Acute pericarditis	1
CMV colitis	1
Pneumonia	1

of febrile neutropenia, persistent fever, severe localized infection, urinary tract infection (UTI) with resistant organism, severe ileus, and CMV viremia. We analyzed whether development of neutropenic fever was associated with clinical factors such as time from previous chemotherapy, ANC at presentation, or tumor type (hematologic vs. solid tumor). We found that, of the three clinical variables, an ANC below 1,000 was significantly associated with a subsequent admission for febrile neutropenia (Table IV).

Invasive blood stream infection was diagnosed in eight of the total 254 episodes. In the high-risk group, five of 62 episodes (8%) were associated with a positive blood culture. Isolated organisms included *Staphylococcus epidermidis*, viridans group *Streptococcus*, extended-spectrum β -lactamase producing (ESBL) *E. coli*, ESBL *Klebsiella pneumoniae*, and *Candida albicans*. All patients recovered with no long-term sequelae. Of the 192 “low-risk” episodes, three (1.6%) were associated with positive blood cultures: one patient had positive *Streptococcus pneumoniae* bacteremia which was successfully treated with intravenous ceftriaxone, and

TABLE III. Reasons for Admission in Initially Low-Risk Triaged Episodes

Reason	Number (%), N = 20
Febrile neutropenia	9 (45)
Persistent fever for more than 3 days	4 (20)
Appearance of severe localized infection:	3 (15)
Pneumonia	1
Cellulitis	1
Oral ulcerative lesions	1
Urinary tract infection with resistant organism	2 (10)
Functional intestinal obstruction	1 (5)
Cytomegalovirus viremia	1 (5)

the other two had CVC infections (*Staphylococcus spp.*, coagulase negative) and were hospitalized for persistent fever and neutropenic fever, respectively. Logistic regression analysis showed that there was no association of bacteremia with patient age, tumor type, ANC, or temperature at presentation. However, patients with clinical signs of sepsis (chills, hypotension, and lethargy) were more likely to have invasive blood stream infection (Table V).

Of note, there was a documented focus of infection via symptom review or on physical examination in 155 (61%) of all 254 episodes: 54 (87%) of “high-risk” and 101 (40%) of “low-risk” episodes. Suspected foci of infection are detailed in Table VI. Absence of a focus of infection more commonly occurred in the low-risk group, whereas UTI and gastroenteritis more commonly occurred in the high-risk group, as shown in Table VI. Importantly, a focus of infection was identified in four of the eight patients who had bacteremia. This focus was an upper respiratory tract infection in three cases and bilateral acute suppurative otitis media in one case, and did not correlate causally with the organism identified on blood culture. In addition, six patients (2.4%) had a single positive central blood culture for skin flora, judged to be skin contaminants and did not receive further therapy.

DISCUSSION

Our study shows that, in a cohort of pediatric oncology patients with implanted CVC (port) undergoing a uniform approach to risk-stratified management of non-neutropenic fever in the outpatient setting, patients with absence of “high-risk” clinical features may be successfully and safely treated with outpatient administration of intravenous ceftriaxone, with daily follow-up and re-assessment. Our study reveals a lower incidence of bacteremia compared to other studies, with a rate of 3.1% of febrile non-neutropenic episodes in our patients. This is likely due to the fact that all our patients had internal CVCs (port), rather than external CVCs (Broviac or Hickman lines), as bacteremia has been shown to occur more often in association with external CVC as compared to ports.[9,14] Indeed, a single institution study by Kelly et al.[6] showed bacteremia in 6.3% of pediatric oncology patients presenting with non-neutropenic fever, with 4.4% incidence in patients with ports and 16.2% incidence in patients with external catheters. The study by Esbenshade et al.[9] similarly showed an incidence of 2.7 versus 27.3%, respectively. Notably, the definition of fever differed slightly among those studies. For instance, our study and that of Esbenshade et al.[9] defined fever as a single temperature above 38.3°C, or a temperature of $\geq 38.0^\circ\text{C}$ for at least 30 min (our study) to 1 hr (Esbenshade et al.), whereas other studies defined fever as a single temperature $\geq 38.5^\circ\text{C}$, or two measured temperatures, $\geq 38.0^\circ\text{C}$ within a 24 hr period[10] a single temperature $\geq 38.0^\circ\text{C}$ [6] or an oral temperature of 38°C measured twice 4 hr apart or $\geq 38.5^\circ\text{C}$ documented once. [14] Although these differences are unlikely to have greatly influenced the reported outcomes, they do need to be taken into consideration when comparing and analyzing results.

Our results also showed that in the high-risk group (patients presenting with clinical signs of sepsis or during high-risk periods of chemotherapy), five episodes (8%) were associated with invasive bloodstream infections, and four of those patients were clinically ill appearing. None of the identified organisms were sensitive to ceftriaxone, in concordance with findings reported in febrile neutropenic patients presenting with abnormal vital signs.[15–22]

TABLE IV. Clinical Factors Associated With Febrile Neutropenia in Initially “Low-Risk” Patients

Characteristics	Admitted for febrile neutropenia N = 9, number (%)	Admitted for other reasons N = 11, number (%)	Not admitted N = 172, number (%)	P-value
Time to last chemotherapy				
≤7 days	3 (33)	9 (82)	111 (64)	0.07
>7 days	6 (67)	2 (18)	61 (36)	
ANC				
<1,000	5 (56)	2 (18)	20 (12)	0.001
≥1,000	4 (44)	9 (82)	152 (88)	
Disease type				
Hematological	7 (78)	10 (91)	107 (62)	0.11
Solid tumor	2 (22)	1 (9)	65 (38)	

On the other hand, we found that in the low-risk group, only three episodes (1.6%) were associated with invasive bloodstream infections, all of which occurred in well-appearing patients. In this group, ceftriaxone was appropriate treatment for one patient (*Streptococcus pneumoniae* bacteremia), whereas the remaining two patients required modification of treatment for gram-positive central line infection (*Staphylococcus spp.*, coagulase negative). Our findings show a low incidence of gram-negative bacteremia in this ‘low-risk’ group of patients (zero cases in our cohort), suggesting that a prospective study assessing the safety of monitoring such low-risk patients without antibiotic treatment may be warranted, to reduce the use of broad-spectrum antibiotics without compromising patient safety. This is especially important in view of the rising prevalence of antibiotic resistance,[23] necessitating judicious use of broad-spectrum antibiotics when safe and feasible.

The low number of bacteremic episodes in our patients limits comparisons with rates of bacteremia found in other reports. One recent study suggested that for non-neutropenic patients, it may be safe to withhold antibiotics and treat only those with signs of sepsis or chills.[10] On the other hand, another recent single-institution study reported that almost 50% of bacteremic episodes in non-

neutropenic febrile patients were due to gram-negative organisms. [9] That study differed from ours in the mix of patients having different types of central catheters (internal, external, and peripherally inserted central catheters). In addition, it is unclear whether these patients with gram-negative bacteremia would have fit the “high-risk” criteria defined in our retrospective study, as we found a higher rate of gram-negative bacteremia in the high-risk group (two out of five episodes, 40%). However, as mentioned above, our relatively small number of patients with bacteremia limits this comparison.

Our study identified clinical features of “ill-appearance,” comprising chills, hypotension, or lethargy, as significantly correlating with bacteremia, with a significant odds ratio of 9.696. In fact, 4 of 14 patients (28.6%) who presented with signs of sepsis, lethargy, or were ill-appearing at initial presentation, had bacteremia. This is in concordance with the recent study by Esbenshade et al.[9] which also identified chills and hypotension as predictors of bacteremia in such patients. However, our study found no correlation between bacteremia and presenting temperature, ANC, primary tumor diagnosis, or age. In the series by Esbenshade et al.,[9] on the other hand, it was found that patients with bacteremia were also more likely to have higher temperature,

TABLE V. Univariate Analysis of Risk Factors for Bacteremia

Characteristics	Bloodstream infection (%) N = 8	No bloodstream infection (%) N = 246	Odds ratio	Confidence interval	P-value
Age					
<10 years	5 (62)	201 (82)	2.68	Reference group 0.62–11.63	0.18
≥10 years	3 (38)	45 (18)			
Disease type					
Hematologic	6 (75)	157 (64)	1.70	Reference group 0.34–8.61	0.72
Solid	2 (25)	89 (36)			
Temperature (°C)					
<38.5	4 (50)	138 (56)	1.06	Reference group 0.19–5.95	1
38.5–39	2 (25)	65 (26)			
>39	2 (25)	43 (18)			
ANC					
<1,000	2 (25)	38 (16)	0.51	Reference group 0.09–2.91	0.606
1,000–5,000	4 (50)	148 (60)			
>5,000	2 (25)	60 (24)			
Ill-appearing					
No	4 (50)	223 (91)	9.70	Reference group 2.27–41.37	0.005
Yes	4 (50)	23 (9)			

TABLE VI. Foci of Infection in Low- and High-Risk Episodes

Suspected focus of infection	Low-risk number (%), N = 192	High-risk number (%), N = 62	P-value
Upper respiratory tract infection	54 (28)	24 (39)	0.12
Acute otitis media	12 (6)	2 (3)	0.29
Urinary tract infection	3 (1.5)	7 (11)	0.0006
Pneumonia/bronchitis	7 (4)	1 (2)	0.37
Tonsillitis	7 (4)	0 (0)	0.13
Gastroenteritis	6 (3)	8 (13)	0.007
Mucositis	3 (2)	4 (6)	0.062
Other*	1 (1)	6 (10)	0.001
No focus of infection	99 (51.5)	10 (16)	<0.0001

*One episode of scarlet fever in low-risk group. In high-risk group, one episode each of: tooth abscess, anal pain, orbital cellulitis, acute pericarditis, CMV colitis, and varicella zoster.

tunneled or peripherally inserted external catheter, and elevated ANC, while they reported a decreased incidence of bacteremia in patients with a diagnosis of acute lymphoblastic leukemia, increased line days, known source of fever other than UTI, and certain chemotherapeutic medication exposure within 24 hr of presentation. These differences may be explained by the difference in patient population; e.g., in addition to some differences in patient inclusion criteria between the two studies, our patient population was different in that all had internal central venous catheters, making evaluation of risk factors in our study specific to this group of patients.

Notably, 61% of all episodes in our study were associated with an identifiable focus of infection. Interestingly, a focus was present in four of eight (50%) cases that had invasive bloodstream infections; but the identified focus (three upper respiratory tract infections and one suppurative otitis media) did not correlate causally with the organism identified on blood culture. This finding underscores the importance of obtaining blood cultures in all febrile patients on chemotherapy who have CVC, irrespective of the presence of an identifiable possible source of infection.

In conclusion, our study shows that, for febrile non-neutropenic patients with implanted CVC (port), clinical signs of sepsis were significantly associated with risk of bloodstream infection. Treatment of clinically well appearing patients who fit the criteria of low risk for invasive infections with outpatient administration of intravenous ceftriaxone was safe and effective. Only 1.6% of these patients had bacteremia and/or CVC infection, and all were due to gram-positive organisms; however there were no identifiable clinical predictors for this group of patients. Finally, the presence of a focus of infection such as upper respiratory tract infection did not preclude bloodstream infection, underscoring the fact that patients should have central blood cultures even when a superficial focus of infection is identified. Based on our results, it may be useful

to conduct prospective studies evaluating the safety of a non-antibiotic approach, pending blood culture results, in this defined “low-risk” group of pediatric oncology patients presenting with non-neutropenic fever.

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REFERENCES

- Pizzo P. Empirical therapy and prevention of infection in the immunocompromised host. In: Mandell 5th edition. Elsevier: Philadelphia, 2000;3103–3111.
- te Poele EM, Tissing WJ, Kamps WA, de Bont ES. Risk assessment in fever and neutropenia in children with cancer: What did we learn? *Crit Rev Oncol Hematol* 2009;72:45–55.
- Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, Feld R, Pizzo PA, Rolston KV, Shenep JL, Young LS. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;34:730–751.
- Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2011;52:e56–e93.
- Teuffel O, Sung L. Advances in management of low-risk febrile neutropenia. *Curr Opin Pediatr* 2012;4:40–45.
- Kelly MJ, Vivier PM, Panken TM, Schwartz CL. Bacteremia in febrile nonneutropenic pediatric oncology patients. *Pediatr Blood Cancer* 2010;54:83–87.
- Gorelick MH, Owen WC, Seibel NL, Reaman GH. Lack of association between neutropenia and the incidence of bacteremia associated with indwelling central venous catheters in febrile pediatric cancer patients. *Pediatr Infect Dis J* 1991;10:506–510.
- Rahiala J, Perkkio M, Riikonen P. Infections occurring during the courses of anticancer chemotherapy in children with ALL: a retrospective analysis of 59 patients. *Pediatr Hematol Oncol* 1998;15:165–174.
- Esbenshade AJ, Cecilia Di Pentima M, Zhao Z, Shintani A, Esbenshade JC, Simpson ME, Montgomery KC, Lindell RB, Lee H, Wallace A, Garcia KL, Moons KGM, Friedman DL. Development and validation of a prediction model for diagnosing blood stream infections in febrile, non-neutropenic children with cancer. *Pediatr Blood Cancer* 2015;62:262–268.
- Bartholomew F, Aftandilian C, Andrews J, Gutierrez K, Luna-Fineman S, Jeng M. Evaluation of febrile, nonneutropenic pediatric oncology patients with central venous catheters who are not given empiric antibiotics. *J Pediatr* 2015;166:157–162.
- Nijhuis CO, Kamps WA, Daenen SM, Gietema JA, van der Graaf WT, Groen HJ, Vellenga E, Ten Vergert EM, Vermeulen KM, de Vries-Hospers HG, de Bont ES. Feasibility of withholding antibiotics in selected febrile neutropenic cancer patients. *J Clin Oncol* 2005;23:7437–7444.
- Minotti V, Gentile G, Bucaneve G, Iori AP, Micozzi A, Cavicchi F, Barbabietola G, Landonio G, Menichetti F, Martino P, Del Favero A. Domiciliary treatment of febrile episodes in cancer patients: a prospective randomized trial comparing oral versus parenteral empirical antibiotic treatment. *Support Care Cancer* 1999;7:134–139.
- Salzer W, Steinberg SM, Liewehr DJ, Freifeld A, Balis FM, Widemann BC. Evaluation and treatment of fever in the non-neutropenic child with cancer. *J Pediatr Hematol Oncol* 2003;25:606–612.
- Averbuch D, Makhoul R, Rotshild V, Weintraub M, Engelhard D. Empiric treatment with once-daily cefonicid and gentamicin for febrile non-neutropenic pediatric cancer patients with indwelling central venous catheters. *J Pediatr Hematol Oncol* 2008;30:527–532.
- Rackoff WR, Gonin R, Robinson C, Kreissman SG, Breitfeld PB. Predicting the risk of bacteremia in children with fever and neutropenia. *J Clin Oncol* 1996;14:919–924.
- Klaassen RJ, Goodman TR, Pham B, Doyle JJ. “Low-risk” prediction rule for pediatric oncology patients presenting with fever and neutropenia. *J Clin Oncol* 2000;18:1012–1019.
- Agyeman P, Aebi C, Hirt A, Niggli FK, Nadal D, Simon A, Ozsahin H, Kontny U, Kühne T, Beck Popovic M, Leibundgut K, Bodmer N, Ammann RA. Predicting bacteremia in children with cancer and fever in chemotherapy-induced neutropenia: results of the prospective multicenter SPOG 2003 FN study. *Pediatr Infect Dis J* 2011;30:e114.
- Alexander SW, Wade KC, Hibberd PL, Parsons SK. Evaluation of risk prediction criteria for episodes of febrile neutropenia in children with cancer. *J Pediatr Hematol Oncol* 2002;24:38–42.
- Hakim H, Flynn PM, Srivastava DK, Knapp KM, Li C, Okuma J, Gaur AH. Risk prediction in pediatric cancer patients with fever and neutropenia. *Pediatr Infect Dis J* 2010;29:53–59.
- 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.
- Santolaya ME, Alvarez AM, Avilés S, Becker A, Cofré J, Enríquez N, O’Ryan M, Payá E, Salgado C, Silva P, Tordecilla J, Varas M, Villarreal M, Viviani T, Zubieta M. 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.
- Santolaya ME, Alvarez AM, Avilés S, Becker A, King A, Mosso C, O’Ryan M, Payá E, Salgado C, Silva P, Topelberg S, Tordecilla J, Varas M, Villarreal M, Viviani T, Zubieta M. 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.
- Trecarichi EM, Tumbarello M. Antimicrobial-resistant gram-negative bacteria in febrile neutropenic patients with cancer: current epidemiology and clinical impact. *Curr Opin Infect Dis* 2014;27:200–210.