FEBRILE NEUTROPENIA CURRENT GUIDELINES FOR CHILDREN

Alia Zaidi, MD.
St. Jude International Outreach Program

Supportive Care in Pediatric Oncology
4th Biennial ICON Meeting, January 23, 2016 Karachi, Pakistan

Presentation Overview

- Definitions

- Key points from basic knowledge about FN in children

- Challenges in establishing universal pediatric stratification criteria for low-vs high-risk for infectious complications

- Why the need for FN guidelines for children?

- Current evidence-based guidelines for management of febrile neutropenia in children.

Definitions

- Fever: a single oral temperature of $\geq$ 38.3°C (101°F) or a temperature of 38°C (100.4°F) sustained over at least hr.

- Neutropenia: absolute neutrophil count (ANC) of less than 0.5×10^9 (<500 cells/µL); or a count of 1.0×10^9 (<1000 cells/ µL)with a predicted decrease below 0.5×10^9 in next 48 hours.

  - Profound neutropenia: ANC less than 0.1×10^9 (<100 cells/µL)

  - Prolonged neutropenia: Neutropenia lasting more than 7 days

Definitions

- Central Venous Catheter (CVC) Infections:
  - Exit Site infection: redness, tenderness, induration or purulence within 2cm of CVC exit site.
  - CVC Tunnel/Portacath Pocket infection: infection of the subcutaneous tissue surrounding the CVC tunnel tract, or site of subcutaneous port.
- Hypotension: systolic blood pressure less than fifth percentile for age and sex, or need for vasopressor support
- Respiratory failure: an arterial oxygen pressure of less than 60mmHg in room air, or need for supplemental oxygen , or mechanical ventilation in a patient with no known respiratory compromise at baseline

Key Points-the easy part !

- Fever is frequently the <u>only</u> clinical manifestation of serious infection in a neutropenic cancer patient,

- Infection is the major cause of treatment related mortality for children with cancer

- Prompt initiation of empiric, broad-spectrum, intravenous antibiotic therapy is the single most important life-saving intervention in these patients. Treat as an emergency.

Key Point-the challenging part!

- ☐ Detailed history and physical examination with special attention to clues suggesting etiology or focus of infection, and also to try to identify any features that may help to risk stratify the patient !!

Risk Stratification Challenge

Validated Pediatric Risk Stratification Strategies for Low-Risk Patients

Strategy Factor	Rackoff et al (1996)	Alexander et al (2002)	Rondinelli et al (2008)	Santolaya et al (2001)	Ammann et al (2003)	Ammann et al (2010)
Patient & disease related factors	None	AML, Burkitt's lymphoma, ALL induction, progressive disease, relapsed with BM+	2 points for CVC; 1 point for age $\leq$ 5 years	Relapsed leukemia; chemotherapy within 7 days of episode	BM involvement, CVC, pre-B cell leukemia	4 points for chemotherapy more intensive than ALL maintenance
Episode-specific factors	Absolute monocyte count (AMC)	$\downarrow$BP, $\uparrow$RR, O2 < 94%, new CXR changes, altered mental status, severe mucositis, Vomiting or abd pain, focal infect, other clinical reason for inpatient treatment.	4.5 pts. for clinical site of infection; 2.5 pts. for no URTI; 1 pt. each for fever > 38.5, and Hemoglobin $\leq$ 70	CRP $\geq$ 90 mg/L; hypotension; platelets $\leq$ 50,000	No clinical signs of viral infection, CRP > 50 mg/L, WBC $\leq$ 500/μL, Hemoglobin >100 g/L	5 points for Hemoglobin $\geq$90 g/L , 3 pts. each for WBC < 300/μL, and platelets less than 50,000
Rule formulation	AMC $\geq$100/μL: low risk of bacteremia, HSCT, high risk	Absence of any risk factors, low risk for serious medical complication; HSCT, high risk	Total score < 6 low risk of serious infectious complication; HSCT, high risk	Zero risk factors, only low platelets, or only < 7 days from chemo, low risk for invasive bacterial infection	3 or less risk factors, low risk of significant infection; HSCT, high risk	Total score < 9, low risk of adverse FN outcome; HSCT, high risk
Demonstrated to be valid	USA	UK	Brazil	Chile	Europe	Europe

Lehrnbecher T et al. J Clin Oncol 30: 4427-4438

Risk Stratification Challenge

Systematic review and meta-analysis of the discriminatory performance of risk prediction rules in febrile neutropaenic episodes in children and young people

Bob Phillips [a,*], Ros Wade [a], Lesley A. Stewart [a], Alex J. Sutton [b]

Study conducted in accordance with the rules defined by the Center for Reviews and Dissemination, University of York, U.K.

- Both prospective and retrospective cohorts were included (ages 0-18 years)
- 20 studies
- 8388 episodes of febrile neutropenia
- 16 different clinical decision rules (CDR) for risk stratification

Conclusion: This review cannot conclude that any system is more effective or reliable than any other

Risk Stratification Challenge

Predicting infectious complications in
neutropenic children and young people with
cancer (IPD protocol)

The PICNICC Collaboration Study (Predicting Infectious Complications of Neutropenic sepsis In Children with Cancer)

- Builds on the findings of the previous meta-analysis
- Aims to undertake a collaborative meta-analysis using individual participant data (IPD) from existing data sets for the studies with defined clinical decision rules (CDRs) for risk stratification in FN children.
- This data will be pooled and reanalyzed applying individual CDRs across studies with the primary aim of finding the most validated criteria that could be used to define a more accurate and unanimous predictive rule.
- Study currently ongoing.

Risk Stratification at St. Jude
(Phase 1 of a 3-Phase ongoing study)

Risk Prediction in Pediatric Cancer Patients With Fever and Neutropenia

Hakim H., Flynn P.M., Srivastava D.K., et al. Pediatr Infect Dis J 2010; 29: 53-59

Phase 1: Retrospective review. Initial predictive factors identified

- underlying diagnosis,
- severity of fever,
- patient's clinical appearance,
- Absolute neutrophil count

Phase 2: Prospective cohort study to validate these predictive factors, plus assess predictive role of inflammatory markers like CRP, procalcitonin

Phase 3: Will be a randomized clinical trial to evaluate risk stratified management of FN

Assessing severity of FN

Patient and disease related factors

- Type of malignancy: AML; Pre-B ALL; Burkitt's lymphoma; progressive malignancy; relapse with BM involvement.

- Type of chemotherapy: HSCT; ALL induction; chemotherapy any chemo more intensive than ALL maintenance therapy.

- Timing of chemotherapy: Given within 7 days prior to onset of FN episode

- Other factors: presence of central venous catheter (CVC); age ≤ 5 years

Episode specific factors

- Vital signs: Fever $\geq$ 38.5; hypotension; tachypnea; hypoxia < 94%

- Other Signs and Symptoms: altered mental status; severe mucositis; vomiting or abdominal pain; focal infection; upper respiratory tract infect; any other specific clinical reason for inpatient admission.

- Laboratory: Hemoglobin: ≤ 70 g/L; Platelets: < 50,000/μL; WBC: <300 /< 500; AMC: ≥ 100/μL (low risk);

- Imaging: New chest X-ray changes

Lehrnbecher T et al. J Clin Oncol 2012

AML=Acute myeloid leukemia; Pre-B ALL= Precursor B-cell acute lymphoblastic leukemia; BM= Bone marrow; HCST=hemotopoietic stem cell transplantation; WBC= White blood count; CRP= C-reactive protein; AMC= Absolute monocyte count

Why the need for FN guidelines?

- Fever with neutropenia is the most common complication of cancer chemotherapy

- High risk of serious complications, but only a minority of patients have invasive infections

- Treatment involves hospitalization of all patients

- Risk-adapted guidelines are well established for adults.

- For children there is lack of consensus on safe reduction of standard therapy in patients at low risk of complications

Adult Guidelines for FN Management

☐ Developed by organizations like ASCO (American Society of Clinical Oncology), Joint European groups guidelines, IDSA (Infectious Diseases Society of America), and NCCN (National Comprehensive Cancer Network).

Flowers et al. JCO 2013 Feb 20;31(6):794-810
Averbuch et al. Haematologica. 2013 Dec;98(12):1826-35
Freifeld et al. Clin Infect Dis. 2011 Feb 15;52(4):e56-93.
J Natl Compr Canc Netw. 2012 Nov 1;10(11):1412-45

☐ Created for adult patient population with limitations in direct applicability to children and adolescents.

Evidence based approach to febrile neutropenia management in children

St. Jude Children's Research Hospital
ALSAC · Danny Thomas, Founder
Finding cures. Saving children.

Guideline for the Management of Fever and Neutropenia in Children With Cancer and/or Undergoing Hematopoietic Stem-Cell Transplantation

Thomas Lehrnbecher, Robert Phillips, Sarah Alexander, Frank Alvaro, Fabianne Carlesse, Brian Fisher, Hana Hakim, Maria Santolaya, Elio Castagnola, Bonnie L. Davis, L. Lee Dupuis, Faith Gibson, Andreas H. Groll, Aditya Gaur, Ajay Gupta, Rejin Kebudi, Sérgio Petrilli, William J. Steinbach, Milena Villarroel, Theoklis Zaoutis, and Lillian Sung

Evidence based guidelines: Methodology

- Multidisciplinary panel of 20 professional experts (oncology, infectious diseases, nursing, pharmacy) and a patient advocate, from 10 different countries.

- Panel split into working groups for 3 areas of focus for systematic reviews of the published literature to develop evidence based guidelines for:
  - **Initial presentation**
  - **Ongoing management** (24-72 hours after initial empiric antimicrobials)
  - **Empiric antifungal therapy** ($\geq$ 96 hours after initial empiric antimicrobials)

- Each working group developed a set of specific questions for their systematic review.

Lehrnbecher T et al. J Clin Oncol 2012

Grading and Evaluation of Significance of Evidence (GRADE Approach)

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Grades of Recommendation © 2014 Centre for Evidence-Based Medicine

A	consistent level 1 studies
B	consistent level 2 or 3 studies *or* extrapolations from level 1 studies
C	level 4 studies *or* extrapolations from level 2 or 3 studies
D	level 5 evidence *or* troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation that has potentially clinically important differences than the

Levels of Evidence for Therapeutic Studies*

Level	Type of evidence
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	"Outcomes" research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case-control study)
5	Expert opinion without explicit critical appraisal or based on physiology bench research

*From the Centre for Evidence-Based Medicine, http://www.cebm.net.

Table 2.
H. Balshem et al. / Journal of Clinical Epidemiology 64 (2011) 401–406
Significance of the four levels of evidence

Strength of recommendation:

1=Strong;

2=Weak

Quality of evidence:

A= High

B= Moderate

C= low, or very low

	Previous definition
t lies	Further research is very unlikely to change our confidence in the estimate of effect
ose to	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
imited: erent	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
ect	Any estimate of effect is very uncertain
of	

Specific clinical questions were put together for guidelines development:

☐ What clinical features and laboratory markers can be used to classify pediatric patients with FN as being at low or high risk for poor outcomes?

☐ What clinical, laboratory, and imaging studies are useful at the initial presentation of FN to assess the etiology of the episode and guide future treatment?

☐ What empiric antibiotics are appropriate for children with high-risk FN?

☐ In children with low-risk FN:

  ◻ is initial or step-down outpatient management as effective and safe as inpatient management?

  ◻ is initial or step-down oral antibiotic management as effective and safe as management with parenteral antibiotics?

Lehrnbecher T et al. J Clin Oncol 2012

Initial presentation: Recommendations

Lehrnbecher T et al. J Clin Oncol 2012

Initial Presentation of FN

Risk Stratification	Evaluation	Treatment
Adopt a validated risk stratification strategy and incorporate it into routine clinical management (1C)	Obtain blood cultures at onset of FN from all lumens of central venous catheters (1C) Consider periph... concurrent with ... venous catheter ... Consider urinalysis and urine culture in patients where clean-catch midstream specimen is readily available (2C) Obtain chest radiography only in symptomatic patients (1C)	High-risk FN: use monotherapy with antipeudomonal β-lactam or carbapenem as empiric therapy (1A) Reserve the addition of second gram-negative agent or ... ients who are clinically unstable, ... on is suspected, or for centers with ... pathogens (1B) Low-risk FN: (i)consider initial or step-down outpatient management if infrastructure is in place to ensure careful monitoring and follow-up (2B) (ii) Consider oral antibiotics if child is able to tolerate this route of administration reliably (2B)

KEY POINT
Adaptation to the local context

WG-1 Recommendation: Risk Stratification

Qs.1:

What clinical features and laboratory markers can be used to classify pediatric patients with FN as being at low or high risk for poor outcomes?

☐ Adopt a validated risk stratification strategy and incorporate it into routine clinical management (1C)

Key message

Each treating center must choose a strategy and incorporate it into routine clinical practice

Lehrnbecher T et al. J Clin Oncol 2012

WG-1 Recommendation: Evaluation

Qs.2:

What clinical, laboratory, and imaging studies are useful at the initial presentation of FN to assess the etiology of the episode and guide future treatment?

☐ Obtain blood cultures at onset of FN from all lumens of central venous catheter (CVC) (1C)

☐ Consider peripheral blood cultures concurrent with obtaining CVC cultures (controversial) (2C)

☐ Consider urinalysis and urine culture in patients where clean catch midstream specimen is readily available (2C)

☐ Obtain chest X-ray only in symptomatic patients (1B)

Key messages

➢ Upfront blood cultures <u>essential in all</u> patients with FN

➢ Other evaluations are recommended in the clinical context but should not delay initiation of antibiotics.

WG-1 Recommendation: Treatment

High-risk FN

- Use monotherapy with antipseudomonal B-lactam (penicillins/cephalosporins), or carbapenem as empiric therapy (1A)

- Reserve the addition of second gram negative agent (aminoglycoside), or glycopeptide for clinically unstable patients; patients with suspicion of resistant infection; or in centers with high rate of resistant pathogens (1B)

Lehrnbecher T et al. J Clin Oncol 2012

Key Messages

(Evidence-based)

High-risk FN

➢ Specific choice of antibiotics should be based on institutional resistance patterns, and should be reviewed periodically.

➢ Antipsuedomonal penicillin monotherapy is _non-inferior_ to aminoglycoside containing regimens for initial management, and has less toxicity.

➢ No significant difference in efficacy, toxicity, or mortality found between antipseudomonal penicillins(piperacillin-tazobactam; ticarcillin-clavulanic acid) vs cefipime vs carbapenems

➢ Ceftazidime monotherapy should not be used if there are concerns of Gram-positive or resistant Gram-negative infections.

Lehrnbecher T et al. J Clin Oncol 2012

WG-1 Recommendation: Treatment

Qs.4 (a):

In children with low-risk FN: Is initial or step-down outpatient management as effective and safe as inpatient management?

Low-risk FN

☐ Consider initial or step down outpatient management if infrastructure is in place to ensure careful monitoring and follow-up (2B)

Key Message:

The infrastructure for close monitoring and reliable evaluation with ready access to appropriate medical care must be in place.

Lehrnbecher T et al. J Clin Oncol 2012

Qs.4 (b):

In children with low-risk FN: Is initial or step-down oral antibiotic management as effective and safe as management with parenteral antibiotics?

Low-risk FN

☐ Consider this route of administration if child is able to reliably tolerate oral antibiotics (2B)

Key Message:

➢ Oral route presents the challenges of palatability of formulations for children, and reliable achievement of therapeutic drug levels especially in the presence of mucositis and/or impaired gastrointestinal absorption

➢ Oral antibiotics used successfully in children with low risk FN are fluoroquinolones alone; or in combination with amoxicillin-clavulanate

Lehrnbecher T et al. J Clin Oncol 2012

TIMING:

24-72 hours after initiation of empiric antibacterial treatment

Specific clinical questions put together for guidelines development:

☐ <u>Modification of treatment</u>: when and how should the initial antibiotic therapy be modified during the pediatric FN episode?

☐ <u>Cessation of treatment</u>: when can empiric antibiotics be discontinued in patients with low- and high-risk FN?

Lehrnbecher T et al. J Clin Oncol 2012

WG-2 Recommendations Treatment <u>Modification</u>

(24-72 hours after start of empiric treatment)

If responding to empiric therapy	**If NOT responding to empiric therapy**

If responding to empiric therapy

☐ Do not modify initial coverage based solely on persistence of fever, if child is otherwise clinically stable (1C)

☐ Discontinue double gram-negative, or empiric glycopeptides coverage (if initiated) after 24-72 hours UNLESS this combination is justified by specific microbiologic indication (1B)

If NOT responding to empiric therapy

☐ If persistent fever and clinically unstable:

  ☐ escalate initial empiric antibacterial regimen to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria (1C)

Lehrnbecher T et al. J Clin Oncol 2012

WG-2 Recommendations: Treatment Cessation
(24-72 hours after start of empiric treatment)

For all patients

☐ Discontinue empiric antibiotics if:

- ☐ blood culture negative at 48 hours,
- ☐ afebrile for at least 24 hours, and
- ☐ there is evidence of bone marrow recovery

(1C)

For low-risk FN

☐ Consider discontinuation of empiric antibiotics in low-risk patients at 72 hours irrespective of marrow recovery status, if:

- ☐ blood culture negative,
- ☐ afebrile for at least 24 hours, as long as
- ☐ careful follow-up is ensured

(2B)

Lehrnbecher T et al. J Clin Oncol 2012

TIMING:

96 hours or more after initiation of empiric antibacterial treatment

Empiric Antifungal Treatment: ≥ 96 Hours After Initiation of Empiric Antibacterial Treatment		
Risk Stratification	Evaluation	Treatment
Patients at high risk of IFD are those with AML or relapsed acute leukemia, those receiving highly myelosuppressive chemotherapy for other malignancies, and those undergoing allogeneic HSCT with persistent fever despite prolonged (≥ 96 hours) broad-spectrum antibiotic therapy and expected prolonged neutropenia (> 10 days); all others should be categorized as IFD low risk (1B)	All patients: Consider galactomannan in bronchoalveolar lavage and cerebrospinal fluid to support diagnosis of pulmonary or CNS aspergillosis (2C) In children, do not use β-D-glucan testing for clinical decisions until further pediatric evidence has accumulated (1C) IFD high risk: Consider prospective monitoring of serum galactomannan twice per week in IFD high-risk hospitalized children for early diagnosis of invasive aspergillosis (2B) In IFD high-risk children with persistent FN beyond 96 hours, perform evaluation for IFD; evaluation should include CT of lungs and targeted imaging of other clinically suspected areas of infection (1B); consider CT imaging of sinuses in children ≥ 2 years of age (2C) IFD low risk: In IFD low-risk patients, do not implement routine galactomannan screening (1C)	All patients: Use either caspofungin or liposomal amphotericin B for empiric antifungal therapy (1A) IFD high risk: In neutropenic IFD high-risk children, initiate empiric antifungal treatment for persistent or recurrent fever of unclear etiology that is unresponsive to prolonged (≥ 96 hours) broad-spectrum antibacterial agents (1C) IFD low risk: In neutropenic IFD low-risk children, consider empiric antifungal therapy in setting of persistent FN (2C)

Lehrnbecher T et al. J Clin Oncol 2012

Qs.1:

What clinical parameters can classify pediatric patients with persistent FN as high risk or low risk for invasive fungal disease (IFD)?

Patients with persistent fever despite 96 hours or more of broad-spectrum antibiotics can be stratified into:

- **High-risk of IFD**, if:
  - Have AML, or relapsed leukemia
  - Receiving HSCT, or on other highly immunosuppressive chemotherapy for any malignancy
  - Expected prolonged neutropenia (>10 days).
- **Low-risk of IFD**, if do not fulfil the above three criteria

(1B)

Lehrnbecher T et al. J Clin Oncol 2012

St. Jude Children's Research Hospital
ALSAC · Danny Thomas, Founder
Finding cures. Saving children.

Qs.2:

What clinical features, lab tests, imaging studies, and procedures are useful to identify a fungal etiology for persistent/recurrent FN despite broad spectrum antibiotics?

- <u>IFD high risk</u>:

  - Perform imaging to evaluate IFD. Should include CT of lungs and targeted imaging of other clinically suspected areas of infection (1B)

  - Consider CT imaging of sinuses in children > 2 years of age. (2C)

  - Consider prospective monitoring of serum galactomannan (GM) twice per week in hospitalized children for early diagnosis of invasive aspergillosis. (2B)

  - Consider galactomannan in BAL and CSF to support diagnosis of pulmonary of CNS aspergillosis (2C)

- <u>IFD low risk</u>: Do not implement routine GN screening. (1C)

Lehrnbecher T et al. J Clin Oncol 2012

WG-3 Recommendation: IFD Empiric Treatment

Qs.3:

When should empiric antifungal therapy be initiated, what antifungal agents are appropriate, and when is it appropriate to discontinue empiric therapy?

- Start of therapy:
  - For IFD high risk: *start* empiric antifungal therapy if persistent or recurrent fever of unclear etiology at or beyond 96 hours of broad-spectrum antibacterial treatment. (1C)
  - For IFD low risk: *consider* empiric antifungal therapy if persistent or recurrent fever of unclear etiology at or beyond 96 hours of broad-spectrum antibacterial treatment. (2C)
- Choice of antifungal:
  - Caspofungin, or liposomal amphotericin b recommended for empiric treatment, where resources allow (1A).
  - Amphotericin-B in places with limited resources
- Prophylactic antifungal therapy in children with IFD high risk
  - No studies evaluating the safety of this approach in pediatric patients found. Research needed to evaluate its safety and effectiveness in children.

Lehrnbecher T et al. J Clin Oncol 2012

WG-3 Recommendation: IFD Empiric Treatment

OTHER ISSUES

Cessation of antifungal therapy, and

anti-fungal prophylaxis

- ☐ Cessation of antifungal therapy:
  - ☐ No data exists to guide this decision
  - ☐ International pediatric FN guideline panel agrees that empiric therapy should be continued until absolute neutrophil count rises to100-500/µL, <u>and no </u>documented or suspected IFD.
- ☐ Prophylactic antifungal therapy in children with IFD high risk
  - ☐ No studies evaluating the safety of this approach in pediatric patients found.
  - ☐ Research needed to evaluate its safety and effectiveness in children.

Lehrnbecher T et al. J Clin Oncol 2012

Summary

- ☐ Pediatric FN management guidelines by the international pediatric FN panel, are the only evidence based guidelines created specifically for children.

- ☐ Research gaps in pediatric FN knowledge remain, and have been identified by this panel.

- ☐ Each institution must develop a plan of care, based on local epidemiology and resistance pattern of infections.

- ☐ Until a universally applicable model for initial stratification of FN children into low- or high- risk for complications has been identified, one of the six published models validated in various countries should be adopted by treating institutions according to their local capabilities of implementing the chosen model.

Key References

1. Lehrnbecher 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):4427-38.

2. Miedema KG, Tissing WJ, Abbink FC, et al. Risk-adapted approach for fever and neutropenia in paediatric cancer patients - A national multicentre study. European journal of cancer. 2015;53:16-24.

3. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases. 2011;52(4):427-31.

4. 2.   Phillips B, Wade R, Stewart LA, Sutton AJ. Systematic review and meta-analysis of the discriminatory performance of risk prediction rules in febrile neutropaenic episodes in children and young people. European journal of cancer. 2010;46(16):2950-64.

5. 3.   Hakim HMD, Flynn PMMD, Srivastava DKP, et al. Risk Prediction in Pediatric Cancer Patients With Fever and Neutropenia. . Pediatric Infectious Disease Journal. 2010;29(1):53-9.

6. Hakim H, Flynn PM, Knapp KM, et al. Etiology and clinical course of febrile neutropenia in children with cancer. Journal of pediatric hematology/oncology. 2009;31(9):623-9.