MANAGEMENT OF FEBRILE NEUTROPENIA IN CHILDREN WITH CANCER

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Febrile Neutropenia in Children With Cancer

- Neutropenic sepsis is a serious and potentially life-threatening complication of cancer chemotherapy
- Leading cause of infectious complications in patients receiving chemotherapy accounting for most chemotherapy-associated morbidity and mortality
- Compromises treatment outcomes by causing dose reductions and treatment delays

Febrile Neutropenia in Children With Cancer

- Frequent use of dose-intense and dose-dense chemotherapy has escalated the risk of neutropenic sepsis
- Prompt initiation of empirical antibiotic treatment in febrile neutropenia is the single most important advance in infectious disease supportive care leading to improved survival
- Before this approach in early 1970s, mortality form G- infections is about 80%; now declined to 10%-40%

Febrile Neutropenia in Children With Cancer

- Approximately 85%-90% of pathogens documented to be associated with new fevers in neutropenia patients are G+ and G- bacteria
- Several guidelines for the management of FN have been developed, mostly for adult cancer patients
- FN specifically focused on children with cancer important: The International Pediatric Fever and Neutropenia Guideline Panel (2012)

FN Guidelines

- Japan Febrile Neutropenia Study Group
- European Society of Medical Oncology (ESMO)
- Australian Consensus Panel
- National Comprehensive Cancer Network (NCCN)
- Infectious Disease Society of America (IDSA)
- Infectious Disease Working Party of the German Society of Hematology and Oncology
- American Society of Clinical Oncology (ASCO)

Febrile Neutropenia in Children With Cancer

- Initial presentation of febrile neutropenia
- On-going management: ≥ 24 – 72 hrs after initiation of empiric antibacterial treatment
- Empiric antifungal treatment: ≥ 96 hrs after initiation of empiric antibacterial treatment

Initial Management of Febrile Neutropenia: Risk Stratification

- Important implications in terms of management
- Treatment strategies for low-risk patients might be simplified (more convenient and less expensive) without compromising efficacy
- Stratification based on various variables, including response to treatment

Initial Management of Febrile Neutropenia: Risk Stratification

- The first prospectively validated risk assessment tool for FN patients was developed by Talcott *et al* (1992)
- Klatersky et al (2000) postulated a scoring system based on the logistic equation of the Multinational Association for Supportive Care in Cancer (MASCC) predictive model
- The need for hospital-based IV therapy can be challenged when stratified according to a validated scoring system

Initial Management of Febrile Neutropenia: Risk Stratification

- What clinical features and laboratory markers can be used to classify pediatric patients with FN as being low or high risk for poor outcomes?
- Adopt a validated risk stratification strategy and incorporate it into routine clinical management (1C)

Initial Management of Febrile Neutropenia: Risk Stratification

Common elements informative for risk stratification included:

- **Patient-specific factors: age, malignancy type, and disease status**
- **Treatment-specific factors: type and timing of chemotherapy**
- **Episode-specific factors: height of fever, hypotension, mucositis, blood counts, and CRP**

MASCC Scoring System to Identify Patients With Cancer and Febrile Neutropenia at Low Risk of Medical Complications*

Characteristics	Weight
Burden of febrile neutropenia with no or mild symptoms†	5
No hypotension (systolic blood pressure> 90 mmHg)	5
No chronic obstructive pulmonary disease‡	4
Solid tumor or hematologic malignancy with no previous fungal infection§	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms†	3
Outpatient status	3
Age <60 years	2

Abbreviation: MASCC, Multinational Association for Supportive Care in Cancer.

* Maximum score is 26; scores ≥ 21 Indicate a low risk for medical complications. Data adapted.[12.217]

†Burden of febrile neutropenia refers to the general clinical status of the patient as influenced by the febrile neutropenia episode. It should be evaluated on the following scale: no or mild symptoms (score of 5), moderate symptoms (score of 3), and severe symptoms or moribund (score of 0). Scores of 3 and 5 are not cumulative.

‡Chronic obstructive pulmonary disease means active chronic bronchitis, emphysema, decrease in forced expiratory volumes, or need for oxygen therapy and/or steroids and/or bronchodilators requiring treatment at the presentation of the febrile neutropenic episode.

§Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection

Validated Pediatric Risk Stratification for Low Risk Patients

Strategy Factor	Rackoff et al (1996)	Alexander et al (2002)	Rondinelli et al (2006)
Patient- and disease-related factors	None	AML, Burkitt's lymphoma induction ALL, progressive disease, relapsed with marrow involvement	2 points for central venous catheter; 1 point for age ≤ 5 years
Episode-specific factors	Absolute monocyte count	Hypotension, tachypnea/hypoxia < 94%, new CXR changes, altered mental status, severe mucositis, vomiting or abdominal pain, focal infection, other clinical reason for inpatient treatment	4.5 points for clinical site of infection; 2.5 points for no URTI; 1 point each for fever > 38.5°C, hemoglobin ≤ 70 g/L
Rule information	Absolute monocyte count ≥ 100/uL, low risk of bacteremia; HSCT, high risk	Absence of any risk factor, low risk of serious medical complication, HSCT, high risk	Total score <6, low risk of serious infectious complication; HSCT, high risk
Demonstrated to be valid*	United States; Madsen et al (2002)	United Kingdom; Dommett et al (2009)	Brazil; Rondinelli et al (2006)

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CRP, C-reactive protein; CXR, chest radiograph; FN, fever and neutropenia; HSCT, hematopoietic stem-cell transplantation; URTI, upper respiratory tract infection.
* Valid refers to clinically adequate discrimination of a group at low risk of complications

Validate Pediatric Risk Stratification for Low Risk Patients

Strategy Factor	Santolaya et al (2001)	Ammann et al (2003)	Ammann et al (2010)
Patient- and disease-related factors	Relapsed leukemia, chemotherapy within 7 days of episode	Bone marrow involvement, central venous catheter, pre-B-cell leukemia	4 points for chemotherapy more intensive than ALL maintenance
Episode-specific factors	CRP ≥ 90 mg/L, hypotension platelets ≤ 50g/L	Absence of clinical signs of viral infection, CRP > 50 mg/L, WBC ≤ 500/uL, hemoglobin > 100 g/L	5 points for hemoglobin ≥ 90 g/L; 3 points each for WBC < 300/uL, platelets < 50 g/L
Rule information	Zero risk factors, only low platelets, or only < 7 days from chemotherapy, low risk of invasive bacterial infection	Three or fewer 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*	South America, Santolaya et al (2002)	Europe, Amman n et al (2010); Macher et al (2010)	Europe; Miedema et al (2011)

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CRP, C-reactive protein; CXR, chest radiograph; FN, fever and neutropenia; HSCT, hematopoietic stem-cell transplantation; URTI, upper respiratory tract infection.
* Valid refers to clinically adequate discrimination of a group at low risk of complications.

Initial Management of Febrile Neutropenia: Risk Stratification

- Consistent with largely adult-focused IDSA guideline
- Pediatric studies: depth of leukopenia or thrombocytopenia examined rather than anticipation of prolonged neutropenia in predicting which patients are not at higher complication risk
- No single rule is clearly effective or reliable than others, nor does it allow recommending different rules for predicting specific outcomes
- Geographic and temporal validation are important (local; practices, systems, approaches may alter how rules perform)

Initial Management of Febrile Neutropenia: Evaluation

What clinical, laboratory and imaging studies are useful to assess etiology and guide future treatment?

Blood Culture:

- Utility of peripheral blood cultures in addition to CVC cultures is controversial
- Proportion of bacteremia detected by peripheral blood cultures alone (i.e., CVC cultures were negative) was 13% (95% CI, 8%-18%)

Scheinemann K et al (2010) Utility of peripheral blood cultures in bacteremic pediatric cancer patients with a central line. Support Care Cancer 18: 913-919

Initial Management of Febrile Neutropenia: Evaluation

Blood Culture:

- Multiple variables influence blood culture yield: volume, choice of media type, number of bottles inoculated, frequency of cultures
- Although an adequate volume of blood inoculated is important and often not consistently collected, minimum volumes have not been established in pediatric patients

Connel TG et al (2007) How reliable is a negative blood culture result? Volume of blood submitted for culture in routine practice in a children's hospital. Pediatrics 119: 891-896

Initial Management of Febrile Neutropenia: Evaluation

Urinalysis and Urine Culture:

- UTIs are common in pediatric FN

  Santolaya ME et al (2002) Prospective evaluation of a model of prediction of invasive bacterial infection risk among children with cancer, fever and neutropenia. Lin Infect Dis 35: 678-683

- Restricting urine culture to those with symptoms or abnormal urinalysis is probably not justified: pyuria in only 4% with UTI episode and N+ vs 68% in N- ($p<.001$)

  Klaassen IL et al (2011) Pyuria is absent during urinary tract infections in neutropenic patients. Pediatr Blood cancer 56: 868-870

Initial Management of Febrile Neutropenia: Evaluation

Urinalysis and Urine Culture:

- Where a clean-catch or mid-stream urine sample can be collected, obtain sample before starting antibiotics
- Urine collection should not delay treatment

Lehrnbecher T et al (2012) Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. Journal of Clinical Oncology 30(35): 4427-4438

Initial Management of Febrile Neutropenia: Evaluation

Chest Xrays:

- Value of routine CXR: frequency of pneumonia in an asymptomatic child was 5% or less

  Phillips R et al (2011) Systematic review and meta-analysis of the value of clinical features to exclude radiographic pneumonia in FN episodes in children and young people. J Paediatric Child Health

- Asymptomatic children who do not receive a CXR had no significant adverse clinical consequences

  Renoult E et al (2004) Is routine chest radiography necessary for the initial evaluation of FN in children with cancer. Pediatr Blood Cancer 43: 224-228

- Routine CXRs are not recommended in asymptomatic children

  Lehrnbecher T et al (2012) Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. Journal of Clinical Oncology 30(35): 4427-4438

Initial Management of Febrile Neutropenia: Evaluation

- Obtain blood cultures at onset of FN from all lumens of central venous catheters (1C)
- Consider peripheral blood cultures concurrent with obtaining central venous catheter cultures (2C)
- Consider urinalysis and urine culture in patients where clean-catch, midstream specimen is readily available (2C)
- Obtain chest radiography only in symptomatic patients (1B)

Initial Management of Febrile Neutropenia: Treatment

High-Risk Pediatric FN:

- No particular regimen superior to another
- Non-inferiority of monotherapy regimens and higher toxicity with combination regimens

Furno P et al (2002) Monotherapy or aminoglycoside-containing combinations for empirical antibiotic treatment of FN patients: A meta-analysis. Lancet Infect Dis 2: 231-242

Paul M et al (2003) B-lactam monotherapy vs B-lactam-aminoglycoside combination therapy for FN: A systematic review and meta-analysis. BMJ 326: 1111

- Aminoglycoside-containing combination treatment did not improve clinical outcomes in comparison with antipseudomonal penicillin monotherapy

Manji A et al (2011) A systematic review and meta-analysis of antipseudomonal penicillins and carbapenems in pediatric FN. Support Care Cancer (eprint)

Initial Management of Febrile Neutropenia: Treatment

High-Risk Pediatric FN:

- Antipseudomonal penicillins (e.g., piperacillin-tazobactam, ticarcillin-clavulanic acid)
- Antipseudomonal cephalosporins (e.g., cefepime)
- Carbapenems
- No difference in treatment failure, mortality, or adverse effects

Manji A et al (2011) A systematic review and meta-analysis of antipseudomonal penicillins and carbapenems in pediatric FN. Support Care Cancer (eprint)

Manji A et al (2012) A meta-analysis of antipseudomonal penicillins and cephalosporins in pediatric patients with FN. Pediatr Infect Dis J 31: 353-358

Initial Management of Febrile Neutropenia: Treatment

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

- Use monotherapy with an antipseudomonal B-lactam or a carbapenem as an empiric therapy in pediatric high-risk FN (1A)
- Reserve addition of second G- agent or glycopeptide for patients who are clinically unstable, when resistant infection is suspected, or for centers with high rate of resistant pathogens (1B)

Lehrnbecher T et al (2012) Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. Journal of Clinical Oncology 30(35): 4427-4438

Initial Management of Febrile Neutropenia: Treatment

Low-Risk Pediatric FN:

- Outpatient management attractive given increased quality of life for children

Speyer E et al (2009) Agreement between children with cancer and their parents in reporting the child's health-related QOL during stay at the hospital and at home. Child Care Health Dev 35: 489-495

- Large reduction in costs associated with ambulatory approach

Teuffel O et al (2011) Cost-effectiveness of outpatient management for FN in children with cancer. Pediatrics 127: e279-e286

Initial Management of Febrile Neutropenia: Treatment

Low-Risk Pediatric FN:

- Outpatient management was not associated with significantly higher treatment failure; no difference in mortality

Teuffel O et al (2011) Outpatient management of cancer patients with FN: A systematic review and meta-analysis. Ann Oncol 22: 2358-2365

- No increase in treatment failure (including modification) with outpatient relative to inpatient management (15% vs 27%; p=.04); no infection-related deaths among 953 outpatients

Manji A et al (2012) Outpatient and oral antibiotic management of low-risk FN are effective in children: A systematic review of prospective trials. Support Care Cancer 20: 1135-1145

Initial Management of Febrile Neutropenia: Treatment

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

- Issues: drug availability as oral liquid, palatability, cooperation of young children, mucositis, impaired GIT absorption
- No difference in treatment failure (including modifications), overall mortality, or antibiotic adverse effects
- Stratified analysis (pediatric sub-set): oral outpatient management associated with higher rate of readmission vs parenteral outpatient management

Teuffel O et al (2011) Outpatient management of cancer patients with FN: A systematic review and meta-analysis. Ann Oncol 22: 2358-2365

Psychosocial and Logistics Criteria for OPD Management (ASCO)

- Residence ≤ 1hr or ≤ 30 miles (48 km) from the clinic or hospital
- Patient's primary care physician or oncologist agrees to OPD management
- Able to comply with logistics requirement, including frequent clinic visits
- Family member or caregiver at home 24hrs a day
- Access to a telephone and transportation 24hrs a day
- No history of non-compliance with treatment protocols

Initial Management of Febrile Neutropenia: Treatment

Low-Risk Pediatric FN:

Oral antibiotics used:

- Fluoroquinolone monotherapy (7 studies; n=581)
- Fluoroquinolone and amoxicillin-clavulanate (3 studies; n=159)
- Cefixime (1 study; n=45)
- No difference in treatment failure (including modification) and no infection-related deaths among 676 children administered oral antibiotics

Manji A et al (2012) Outpatient and oral antibiotic management of low-risk FN are effective in children: A systematic review of prospective trials. Support Care Cancer 20: 1135-1145

Initial Management of Febrile Neutropenia: Treatment

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

Lehrnbecher T et al (2012) Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. Journal of Clinical Oncology 30(35): 4427-4438

Additional Requirements for OPD Management (ASCO)

- Frequent evaluation for at least 3 days in clinic or at home
- Daily or frequent telephone contact to verify resolution of fever
- Monitoring of ANC and platelet counts for myeloid reconstitution
- Frequent visits to clinic

For Hospital Admission (ASCO)

- PNF syndrome; fever recurrence
- New signs or symptoms of infection
- PO route no longer possible or tolerable
- Change or addition of antibiotic is necessary
- Culture results revealed organism not susceptible to initial regimen

Ongoing Management of FN: ≥24-72 Hrs After Initiation treatment

Modification of Treatment

- In patients who are responding to initial empiric antibiotic therapy, discontinue double coverage for Gram-negative infection or empiric glycopeptide (if initiated) after 24 to 72 hours if there is no specific microbiologic indication to continue combination therapy (1B)
- Do not modify initial empiric antibacterial regimen based solely on persistent fever in children who are clinically stable (1C)
- In children with persistent fever who become clinically unstable, escalate initial empiric antibacterial regimen to include coverage for resistant Gram-negative, Grampositive, and anaerobic bacteria (1C)

Ongoing Management of FN: ≥24-72 Hrs After Initiation treatment

Cessation of Treatment

- All patients: Discontinue empiric antibiotics in patients who have negative blood cultures at 48 hours, who have been afebrile for at least 24 hours, and who have evidence of marrow recovery (1C)

- Low-risk FN: Consider discontinuation of empiric antibiotics at 72 hours in low-risk patients who have negative blood cultures and who have been afebrile for at least 24 hours, irrespective of marrow recovery status, as long as careful follow-up is ensured (2B)

Empiric Antifungal Treatment: ≥ 96 Hrs After Initiation of treatment

Risk Stratification:

Patients at high risk of IFD: AML or relapsed acute leukemia, 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)

IFD Evaluation

- All patients: Consider galactomannan in bronchoalveolar lavage and cerebrospinal fluid to support diagnosis of pulmonary or CNS aspergillosis (2C)
- In children, do not use ß-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)

Empiric Antifungal Treatment

- 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)

Neutropenic Patients But Not Yet Febrile (ASCO)

- Consider antibacterial prophylaxis only if profound neutropenia is expected (<100/uL) likely to last for ≥ 7 days

  - systemically absorbed fluoroquinolone (less effective when >20% G- resistance)

- Antifungal prophylaxis:

  - Triazole PO; Echinocandin IV in outpatient setting

  - For environment with substantial risk for IFI: >10% ICI, >6% for IA

Neutropenic Patients But Not Yet Febrile (ASCO)

- Trimethoprim-sulfa prophylaxis only if >3.5% pneumonia risk for P. jirovecii (e.g., ≥ 20mg prednisone equivalent daily ≥ 1 month)
- Lamivudine prophylaxis if substantial risk for HBV infection reactivation
- Nucleoside analog for HSV or VZV seropositive patients in hematologic patients
- Seasonal influenza immunization (trivalent inactive vaccine) for all patients

Other Preventive Precautions

- Hand hygiene; respiratory hygiene/cough etiquette
- Avoid areas of possible high concentration of airborne fungal spores (e.g., construction and demolition sites)
- Not necessary:
  - HEPA filters ± laminar air flow
  - Respiratory or surgical masks
  - Footwear exchange at entry and exit
  - Neutropenic diets
  - Gloving and gowning (use only in certain situations)

Key Distinctions of FN in Children With Cancer

- Some recommendations similar to adult guidelines such as choice of empiric antibacterials and criteria for their modifications
- Some similar recommendations have benefitted from pediatric-specific focus such as consideration of outpatient management and oral antibiotic therapy
- Risk stratification schemas are pediatric specific
- Diagnostic tools such as BG testing have pediatric-specific limitations

Research Gaps in Pediatric Febrile Neutropenia

- Validated high-risk stratification schema for pediatric fever and neutropenia
- Incremental value of peripheral-blood culture in addition to CVC cultures of an adequate volume
- Optimal type and frequency of re-evaluation (e.g., daily or every second day telephone contact or clinic visit) for outpatients with low-risk FN
- Optimal treatment regimen for microbiologically documented sterile site infections during FN
- Optimal frequency of blood culture sampling in persistently febrile pediatric patients with neutropenia who are either clinically stable or unstable

Research Gaps in Pediatric Febrile Neutropenia

- Optimal duration of antibiotic therapy for patients with high-risk FN without bone marrow recovery for prolonged periods
- Whether routine galactomannan screening in IFD high-risk children is cost–effective and results in better clinical outcomes compared to a strategy without screening
- Clinical utility and optimal cut-off of β-*D*-glucan testing in IFD high-risk children
- Clinical utility of routine sinus imaging in children being evaluated for IFD
- Safety and efficacy of a pre-emptive antifungal approach in IFD low-risk and IFD high-risk children
- Optimal investigation and treatment for viral infections in children with FN

THANK YOU