FEBRILE NEUTROPENIA
CURRENT GUIDELINES FOR CHILDREN

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St. Jude International Outreach Program
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?
Definitions

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

- **Neutropenia**: absolute neutrophil count (ANC) of less than $0.5 \times 10^9$ ($<500$ cells/$\mu L$); or a count of $1.0 \times 10^9$ ($<1000$ cells/$\mu L$) with a predicted decrease below $0.5 \times 10^9$ in next 48 hours.
  - Profound neutropenia: ANC less than $0.1 \times 10^9$ ($<100$ cells/$\mu L$)
  - 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 **only** 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

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</thead>
<tbody>
<tr>
<td>Patient &amp; disease related factors</td>
<td>None</td>
<td>AML, Burkitt’s lymphoma, ALL induction, progressive disease, relapsed with BM+</td>
<td>2 points for CVC; 1 point for age ≤ 5 years</td>
<td>Relapsed leukemia; chemotherapy within 7 days of episode</td>
<td>BM involvement, CVC, pre-B cell leukemia</td>
<td>4 points for chemotherapy more intensive than ALL maintenance</td>
</tr>
<tr>
<td>Episode-specific factors</td>
<td>Absolute monocyte count (AMC)</td>
<td>↓BP, ↑RR, O2 &lt; 94%, new CXR changes, altered mental status, severe mucositis, Vomiting or abd pain, focal infect, other clinical reason for inpatient treatment.</td>
<td>4.5 pts. for clinical site of infection; 2.5 pts. for no URTI; 1 pt. each for fever &gt; 38.5, and Hemoglobin ≤ 70</td>
<td>CRP ≥ 90 mg/L; hypotension; platelets ≤ 50,000</td>
<td>No clinical signs of viral infection, CRP &gt; 50 mg/L, WBC ≤ 500/μL, Hemoglobin &gt;100 g/L</td>
<td>5 points for Hemoglobin ≥90 g/L, 3 pts. each for WBC &lt; 300/μL, and platelets less than 50,000</td>
</tr>
<tr>
<td>Rule formulation</td>
<td>AMC ≥100/μL: low risk of bacteremia, HSCT, high risk</td>
<td>Absence of any risk factors, low risk for serious medical complication; HSCT, high risk</td>
<td>Total score &lt; 6 low risk of serious infectious complication; HSCT, high risk</td>
<td>Zero risk factors, only low platelets, or only &lt; 7 days from chemo, low risk for invasive bacterial infection</td>
<td>3 or less risk factors, low risk of significant infection; HSCT, high risk</td>
<td>Total score &lt; 9, low risk of adverse FN outcome; HSCT, high risk</td>
</tr>
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</table>

**Demonstrated to be valid**
- USA
- UK
- Brazil
- Chile
- 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 PICNIC 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

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 ≥ 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


AML=Acute myeloid leukemia; Pre-B ALL= Precursor B-cell acute lymphoblastic leukemia; BM= Bone marrow; HCST=hematopoietic 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).

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

Flowers et al. JCO 2013 Feb 20;31(6):794-810
Evidence based approach to febrile neutropenia management in children

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

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 (≥ 96 hours after initial empiric antimicrobials)

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

Grading and Evaluation of Significance of Evidence (GRADE Approach)

Grades of Recommendation © 2014 Centre for Evidence-Based Medicine

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Consistent level 1 studies</td>
</tr>
<tr>
<td>B</td>
<td>Consistent level 2 or 3 studies or extrapolations from level 1 studies</td>
</tr>
<tr>
<td>C</td>
<td>Level 4 studies or extrapolations from level 2 or 3 studies</td>
</tr>
<tr>
<td>D</td>
<td>Level 5 evidence or troublingly inconsistent or inconclusive studies of any level</td>
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*Extrapolations* are where data is used in a situation that has potentially clinically important differences than the original data.

Levels of Evidence for Therapeutic Studies

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
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<tbody>
<tr>
<td>1A</td>
<td>Systematic review (with homogeneity) of RCTs</td>
</tr>
<tr>
<td>1B</td>
<td>Individual RCT (with narrow confidence intervals)</td>
</tr>
<tr>
<td>1C</td>
<td>All or none study</td>
</tr>
<tr>
<td>2A</td>
<td>Systematic review (with homogeneity) of cohort studies</td>
</tr>
<tr>
<td>2B</td>
<td>Individual cohort study (including low quality RCT, e.g., &lt;50% follow-up)</td>
</tr>
<tr>
<td>2C</td>
<td>“Outcomes” research; Ecological studies</td>
</tr>
<tr>
<td>3A</td>
<td>Systematic review (with homogeneity) of case-control studies</td>
</tr>
<tr>
<td>3B</td>
<td>Individual case-control study</td>
</tr>
<tr>
<td>4</td>
<td>Case series (and poor quality cohort and case-control study)</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal or based on physiology bench research</td>
</tr>
</tbody>
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Strength of recommendation:

1=Strong; 2=Weak

Quality of evidence:

A= High  B= Moderate  C= low, or very low

Table 2. Significance of the four levels of evidence

<table>
<thead>
<tr>
<th>Previous definition</th>
<th>New definition</th>
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<tbody>
<tr>
<td>Further research is very unlikely to change our confidence in the estimate of effect</td>
<td>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</td>
</tr>
<tr>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
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<tr>
<td>Further research is unlikely to have an important impact on our confidence in the estimate of effect</td>
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<tr>
<td>Any estimate of effect is very uncertain</td>
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*From the Centre for Evidence-Based Medicine, http://www.cebm.net.*
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?
**Initial presentation: Recommendations**

**Initial Presentation of FN**

<table>
<thead>
<tr>
<th>Risk Stratification</th>
<th>Evaluation</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Adopt a validated risk stratification strategy and incorporate it into routine clinical management (1C)</td>
<td>Obtain blood cultures at onset of FN from all lumens of central venous catheters (1C)</td>
<td>High-risk FN: use monotherapy with antipseudomonal β-lactam or carbapenem as empiric therapy (1A)</td>
</tr>
<tr>
<td>Consider peripheral blood cultures concurrent with obtaining central venous catheter cultures (2C)</td>
<td>Consider urinalysis and urine culture in patients where clean-catch midstream specimen is readily available (2C)</td>
<td>Reserve the addition of second gram-negative agent or glycopeptide for patients who are clinically unstable, when resistant infection is suspected, or for centers with high rate of resistant pathogens (1B)</td>
</tr>
<tr>
<td>Obtain chest radiography only in symptomatic patients (1C)</td>
<td>Obtain chest radiography only in symptomatic patients (1C)</td>
<td>Low-risk FN: (i) consider initial or step-down outpatient management if infrastructure is in place to ensure careful monitoring and follow-up (2B)</td>
</tr>
<tr>
<td>(ii) Consider oral antibiotics if child is able to tolerate this route of administration reliably (2B)</td>
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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.
**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 essential in all patients with FN
- Other evaluations are recommended in the clinical context but should not delay initiation of antibiotics.
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)

Qs.3: What empiric antibiotics are appropriate for children with high-risk FN?
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.
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.

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

Specific clinical questions put together for guidelines development:

- **Modification of treatment**: when and how should the initial antibiotic therapy be modified during the pediatric FN episode?

- **Cessation of treatment**: when can empiric antibiotics be discontinued in patients with low- and high-risk FN?

TIMING:

24-72 hours after initiation of empiric antibacterial treatment
WG-2 Recommendations Treatment Modification
(24-72 hours after start of empiric treatment)

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)

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)

Working Group 3: Empiric Antifungal Treatment
(96 hours or more after start of empiric treatment)

**TIMING:**
96 hours or more after initiation of empiric antibacterial treatment

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<thead>
<tr>
<th>Risk Stratification</th>
<th>Evaluation</th>
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</thead>
<tbody>
<tr>
<td>Patients at high risk of IFD...</td>
<td>All patients: Consider galactomannan in bronchoalveolar lavage and cerebrospinal fluid to support diagnosis of pulmonary or CNS aspergillosis (2C)</td>
<td>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)</td>
</tr>
<tr>
<td>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)</td>
<td>In children, do not use β-D-glucan testing for clinical decisions until further pediatric evidence has accumulated (1C)</td>
<td>IFD low risk: In neutropenic IFD low-risk children, consider empiric antifungal therapy in setting of persistent FN (2C)</td>
</tr>
<tr>
<td>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)</td>
<td>In children, those receiving highly myelosuppressive chemotherapy for other malignancies, and those undergoing allogeneic H SCT with persistent fever despite prolonged (≥ 96 hours) broad-spectrum antibiotic therapy and expected prolonged neutropenia (&gt; 10 days); all others should be categorized as IFD low risk (1B)</td>
<td>All patients: Use either caspofungin or liposomal amphotericin B for empiric antifungal therapy (1A)</td>
</tr>
</tbody>
</table>

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)
WG-3 Recommendation: IFD Evaluation

- **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?

- **IFD high risk:**
  - 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)

- **IFD low risk:** Do not implement routine GN screening. (1C)
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.

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 to 100-500/μL, and no 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.
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


