SIOP PODC Supportive Care Education
Presentation Date: 13th March 2015
Recording Link at www.cure4kids.org:

CLINICAL PRACTICE GUIDELINES FOR THE MANAGEMENT OF PEDIATRIC FEVER AND NEUTROPENIA
Clinical Practice Guidelines for the Management of Pediatric Fever and Neutropenia

Full guidelines may be found at http://www.sickkids.ca/HaematologyOncology/IPFNG/

Citation: Lehrnbecher et al. JCO 2012;30(35):4427-38

Lillian Sung MD,
Associate Professor
Division of Haematology/Oncology
The Hospital for Sick Children
March 13, 2015
Overview

- Rationale for FN guideline development
- Methodology
- Areas for discussion
  - Risk Stratification and Evaluation at Initial Presentation of Pediatric Fever and Neutropenia
  - Initial Treatment of Pediatric Fever and Neutropenia
  - Approach to Empiric Antifungal Therapy
Overview

- Rationale for FN guideline development
- Methodology
- Areas for discussion
  - Risk Stratification and Evaluation at Initial Presentation of Pediatric Fever and Neutropenia
  - Initial Treatment of Pediatric Fever and Neutropenia
  - Approach to Empiric Antifungal Therapy
Rationale for FN Guidelines

Fever and neutropenia (FN) common
- Lack of guidelines focused on children
- Children have unique issues compared to adults

International Pediatric Fever and Neutropenia Guideline Panel
- Formed October 2010
- Oncology, infectious disease, nursing, pharmacy, patient advocate
- 10 different countries
<table>
<thead>
<tr>
<th>Name</th>
<th>Country</th>
<th>Profession</th>
<th>Discipline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarah Alexander</td>
<td>Canada</td>
<td>Physician</td>
<td>Oncology</td>
</tr>
<tr>
<td>Frank Alvaro</td>
<td>Australia</td>
<td>Physician</td>
<td>Oncology</td>
</tr>
<tr>
<td>Fabianne Carlesse</td>
<td>Brazil</td>
<td>Physician</td>
<td>Infectious disease</td>
</tr>
<tr>
<td>Elio Castagnola</td>
<td>Italy</td>
<td>Physician</td>
<td>Infectious disease</td>
</tr>
<tr>
<td>Bonnie Davis</td>
<td>Canada</td>
<td>Patient advocate</td>
<td></td>
</tr>
<tr>
<td>Lee Dupuis</td>
<td>Canada</td>
<td>Pharmacist</td>
<td>Oncology</td>
</tr>
<tr>
<td>Brian Fisher</td>
<td>US</td>
<td>Physician</td>
<td>Infectious disease</td>
</tr>
<tr>
<td>Faith Gibson</td>
<td>UK</td>
<td>Nurse</td>
<td>Oncology</td>
</tr>
<tr>
<td>Andreas Groll</td>
<td>Germany</td>
<td>Physician</td>
<td>Oncology, ID</td>
</tr>
<tr>
<td>Aditya Gaur</td>
<td>US</td>
<td>Physician</td>
<td>Infectious disease</td>
</tr>
<tr>
<td>Ajay Gupta</td>
<td>India</td>
<td>Physician</td>
<td>Oncology</td>
</tr>
<tr>
<td>Hana Hakim</td>
<td>US</td>
<td>Physician</td>
<td>Infectious disease</td>
</tr>
<tr>
<td>Rejin Kebudi</td>
<td>Turkey</td>
<td>Physician</td>
<td>Oncology</td>
</tr>
<tr>
<td>Thomas Lehrnbecher</td>
<td>Germany</td>
<td>Physician</td>
<td>Oncology</td>
</tr>
<tr>
<td>Sérgio Petrilli</td>
<td>Brazil</td>
<td>Physician</td>
<td>Oncology</td>
</tr>
<tr>
<td>Bob Phillips</td>
<td>UK</td>
<td>Physician</td>
<td>Oncology</td>
</tr>
<tr>
<td>Maria Santolaya</td>
<td>Chile</td>
<td>Physician</td>
<td>Infectious disease</td>
</tr>
<tr>
<td>William Steinbach</td>
<td>US</td>
<td>Physician</td>
<td>Infectious disease</td>
</tr>
<tr>
<td>Lillian Sung</td>
<td>Canada</td>
<td>Physician</td>
<td>Oncology, ID</td>
</tr>
<tr>
<td>Milena Villarroel</td>
<td>Chile</td>
<td>Physician</td>
<td>Oncology</td>
</tr>
<tr>
<td>Theo Zaoutis</td>
<td>US</td>
<td>Physician</td>
<td>Infectious disease</td>
</tr>
</tbody>
</table>
Overview

- Rationale for FN guideline development
- Methodology
- Areas for discussion
  - Risk Stratification and Evaluation at Initial Presentation of Pediatric Fever and Neutropenia
  - Initial Treatment of Pediatric Fever and Neutropenia
  - Approach to Empiric Antifungal Therapy
Methods

- Appraisal of Guidelines for Research & Evaluation II (AGREE II) framework

- Divided into working groups:
  - Developed the key clinical questions
  - Identified and rated the importance of outcomes
  - Conducted systematic reviews

- GRADE approach to:
  - Generate summaries
  - Classify evidence as high, moderate, low or very low
# Grading Recommendations

<table>
<thead>
<tr>
<th>Grade of Recommendation:</th>
<th>Benefit vs Risk and Burdens</th>
<th>Supporting Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A/strong recommendation, high-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>1B/strong recommendation, moderate quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>1C/strong recommendation, low-quality or very low-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>Observational studies or case series</td>
<td>Strong recommendation but may change when higher quality evidence becomes available</td>
</tr>
<tr>
<td>2A/weak recommendation, high quality evidence</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>2B/weak recommendation, moderate-quality evidence</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>2C/weak recommendation, low quality or very low-quality evidence</td>
<td>Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced</td>
<td>Observational studies or case series</td>
<td>Very weak recommendations; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>
Definitions

Fever

- Single oral temperature measurement of >38.3°C or a temperature of >38.0°C sustained over one hour

Neutropenia

- ANC of <500 cells/μL or an ANC that is expected to decrease to <500 cells/μL during next 48 hours

Freifeld CID 2010
Overview

- Rationale for FN guideline development
- Methodology
- Areas for discussion
  - Risk Stratification and Evaluation at Initial Presentation of Pediatric Fever and Neutropenia
  - Initial Treatment of Pediatric Fever and Neutropenia
  - Approach to Empiric Antifungal Therapy
Initial Risk Stratification and Evaluation Health Questions

What clinical features and laboratory markers can be used to classify pediatric patients with FN as being at low-risk 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?
Validated Risk Stratification Strategy

- 23 different risk strategies have been derived
  - Address variable outcomes using variable predictive elements
  - Common themes:
    - Broadly similar definitions of adverse outcome
    - Use of patient-specific and episode-specific clinical or laboratory features

- 6 subject to validation
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>AML, Burkitt lymphoma, induction ALL, progressive disease, relapsed with marrow involvement</td>
<td>2 points for central venous catheter, 1 point for age ≤5 years</td>
<td>Relapsed leukemia, chemotherapy within 7 days of episode</td>
<td>Bone marrow involvement, central venous catheter, pre-B-cell leukemia</td>
<td>4 points for chemotherapy more intensive than ALL maintenance</td>
<td></td>
</tr>
<tr>
<td>Episode specific factors</td>
<td>Absolute monocyte count</td>
<td>Hypotension, tachypnea/hypoxia &lt;94%, new CXR changes, altered mental status, severe mucositis, vomiting or abdominal pain, focal infection, clinical reason for in-patient treatment</td>
<td>4.5 points for clinical site of infection, 2.5 points for no URTI, 1 point each for fever &gt;38.5°C, hemoglobin ≤70g/L</td>
<td>CRP ≥90 mg/L, hypotension, platelets ≤50 g/L</td>
<td>Absence of clinical signs of viral infection, CRP &gt;50 mg/L, white blood cell count ≤500/uL, hemoglobin &gt;100 g/L</td>
<td>5 points for hemoglobin ≥90 g/L, 3 points each for white blood cell count &lt;300/uL, platelet &lt;50 g/L</td>
</tr>
<tr>
<td>Rule formulation</td>
<td>Absolute monocyte count ≥ 100/uL = low-risk of bacteremia</td>
<td>Absence of any risk factor = low-risk of serious medical complication</td>
<td>Total score &lt;6 = low-risk of serious infectious complication</td>
<td>Zero factors or only platelets or &lt;D7 from chemotherapy = low-risk of invasive bacterial infection</td>
<td>Three or fewer risk factors = low-risk of significant infection</td>
<td>Total score &lt;9 = low-risk of adverse FN outcome</td>
</tr>
</tbody>
</table>
Initial Risk Stratification Recommendation Summary

Risk Stratification
Adopt a validated risk stratification strategy and incorporate it into routine clinical management (Strong recommendation, low quality evidence).
Initial Evaluation

Peripheral blood cultures

Routine CXR
Peripheral Blood Cultures for FN

- Many/most children have a central line
- Routine to take only central cultures in some settings
  - Approach to peripheral blood culture varies widely
- Systematic review of studies examining contribution of peripheral and central samples
- 7 studies included – 1,933 episodes of bacteremia
- Examined proportion of bacteremia detected only by peripheral sample

SickKids
Synthesis

- 13% of positive blood cultures are detected by only the peripheral blood samples
- Will not detect these if omit peripheral blood cultures
Routine CXR

- Concern that neutropenia may reduce signs of pneumonia
- Systematic review of signs/symptoms
- 2057 articles screened to include 4 studies
- Probability of abnormal CXR very low if no signs or symptoms
Initial Evaluation

Recommendation Summary

**Evaluation**

Obtain blood cultures at the onset of FN from all lumens of central venous catheters (Strong recommendation, low evidence).

Consider peripheral blood culture concurrent with obtaining central venous catheter cultures (Weak recommendation, low quality evidence).

Obtain chest radiography only in symptomatic patients (Strong recommendation, moderate evidence).
Overview

- Rationale for FN guideline development
- Methodology
- Areas for discussion
  - Risk Stratification and Evaluation at Initial Presentation of Pediatric Fever and Neutropenia
  - Initial Treatment of Pediatric Fever and Neutropenia
  - Approach to Empiric Antifungal Therapy
Initial Treatment Health Questions

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

- Influenced by patient characteristics, clinical presentation, local infrastructure, drug availability and costs and local resistance patterns

- Coverage - Gram-negative organisms in all patients and viridans group streptococci and *Pseudomonas aeruginosa* in high-risk FN

- Overall goal to provide coverage for virulent organisms while minimizing exposure to unnecessary antibiotics
Monotherapy vs Combination Therapy

- Original regimens combination therapy
- Two meta-analyses RCTs compared monotherapy versus aminoglycoside-containing regimens
- Non-inferiority of monotherapy regimens and higher toxicity with combination regimens
- Primarily adult trials

Furno Lancet Inf 2002
Paul BMJ 2003
Empiric Anti-pseudomonal Penicillin with an Aminoglycoside versus Anti-pseudomonal Penicillin Monotherapy (N=19)

<table>
<thead>
<tr>
<th></th>
<th>APP with Aminoglycoside</th>
<th>APP Monotherapy</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. regimens</td>
<td>No. patients/episodes</td>
<td>Percentage with Outcome (95% CI)</td>
</tr>
<tr>
<td>Treatment failure including modification</td>
<td>12</td>
<td>1039</td>
<td>41 (32, 50)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>9</td>
<td>699</td>
<td>4.2 (1.8, 6.6)</td>
</tr>
<tr>
<td>Infection-related mortality</td>
<td>13</td>
<td>1092</td>
<td>1.3 (0.42, 2.3)</td>
</tr>
<tr>
<td>Adverse events causing antibiotic discontinuation</td>
<td>3</td>
<td>201</td>
<td>0.40 (0.0, 1.3)</td>
</tr>
</tbody>
</table>
Role of Empiric Vancomycin

- RCTs studying glycopeptides as part of the initial empirical treatment of febrile neutropenic patients with a beta-lactam with or without an aminoglycoside

- 14 RCTs with 2,413 patients

Vardakas Lancet Infect 2005
When addition of any antibiotic classified as failure, addition of glycopeptides associated with more success
OR 1.63; 95% CI (1.17, 2.28)

Figure 1: Odds ratios of treatment success (without modification of the empirical regimens) with the inclusion, or not, of a glycopeptide as part of the empirical regimen of febrile neutropenic patients

Vertical line—“no difference” point between the compared groups. Square—odds ratio; the size of each square denotes the proportion of information given by each trial. Diamond—pooled odds ratio for all randomised controlled trials. Horizontal lines—95% CI.
Glycopeptide Meta-analysis

Addition of glycopeptide:

- If delayed addition of vancomycin not considered failure (i.e. for Gram positive blood culture)
  - No difference in success
  - OR 1.02 (95% CI 0.71, 1.46)

- More adverse effects
  - OR 4.98 (95% CI 2.91, 8.55)

- More nephrotoxicity
  - OR 2.10 (95% CI 1.12, 3.95)
### Initial Treatment

**Recommendation Summary**

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-Risk FN</strong></td>
</tr>
<tr>
<td>Use monotherapy with an anti-pseudomonal $\beta$-lactam or a carbapenem as empiric therapy in pediatric high-risk FN (Strong recommendation, high quality evidence).</td>
</tr>
</tbody>
</table>

Reserve addition of a second Gram-negative agent or a glycopeptide for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high rate of resistant pathogens (Strong recommendation, moderate quality evidence).
Monotherapy Regimens Studied in Children

Anti-pseudomonal penicillins
  ▪ Piperacillin-tazobactam, ticarcillin-clavulanic acid

Anti-pseudomonal cephalosporins
  ▪ Cefepime

Carbapenems
  ▪ Meropenem, imipenem
Overview

- Rationale for FN guideline development
- Methodology
- Areas for discussion
  - Risk Stratification and Evaluation at Initial Presentation of Pediatric Fever and Neutropenia
  - Initial Treatment of Pediatric Fever and Neutropenia
  - Approach to Empiric Antifungal Therapy
Empiric Antifungal Treatment

Health Question

When should empiric antifungal therapy be initiated, what antifungal agents are appropriate, and when is it appropriate to discontinue empiric therapy?
Empiric Antifungal Therapy for FN

- Adult guidelines recommend empiric antifungal therapy be initiated in neutropenic patients after 96 hours of fever in the setting of broad-spectrum antibiotics.

- Data specific to children are lacking and in the absence of additional data, reasonable to recommend a similar approach in children.
Empiric Antifungal Therapy Trials in Children

Three RCTs in children:

- **Prentice et al (1997)**
  - AmB-D (1 mg/kg) vs L-AmB (1mg/kg) vs L-AmB (3 mg/kg)
  - N=204, > 60% children with leukemia

  - AmB-D (0.8 mg/kg) vs ABCD (4mg/kg)
  - N=49, > 60% children with leukemia/HSCT

- **Maertens et al (2010)**
  - L-AmB (3 mg/kg) vs Caspo (50 mg/m² after loading day 1)
  - N=82, > 70% children with leukemia/HSCT
Empiric Antifungal Therapy in Children: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>AmB-D</th>
<th>L-AmB 1</th>
<th>L-AmB 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prentice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy*</td>
<td>51%</td>
<td>64%</td>
<td>63%</td>
</tr>
<tr>
<td>Breakthrough IFD</td>
<td>1 (C.alb)</td>
<td>3 (2 C.alb,1 IA)</td>
<td>1 (IA)</td>
</tr>
<tr>
<td>Sanders</td>
<td></td>
<td>ABCD</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>41%</td>
<td>69%</td>
<td>(NS)</td>
</tr>
<tr>
<td>Breakthrough IFD</td>
<td>2 (IA, yeast)</td>
<td>1 (Fusarium)</td>
<td></td>
</tr>
<tr>
<td>Maertens</td>
<td>L-AmB</td>
<td>Caspo</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>32%</td>
<td>46%</td>
<td>(NS)</td>
</tr>
<tr>
<td>Breakthrough IFD</td>
<td>1 (IA)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*All studies used composite endpoints for efficacy

**Conclusion:**
- L-AmB = Caspo; L-AmB slightly better than AmB-D
- Similar to adult trials
**Empiric Antifungal Therapy in Children: Safety**

<table>
<thead>
<tr>
<th></th>
<th>Prentice</th>
<th>Sanders</th>
<th>Maertens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AmB-D</td>
<td>L-AmB1</td>
<td>L-AmB 3</td>
</tr>
<tr>
<td>Nephrotoxicity (creatinine)</td>
<td>21%</td>
<td>8 %</td>
<td>11 %</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>26%</td>
<td>10 %</td>
<td>11 %</td>
</tr>
<tr>
<td></td>
<td>AmB-D</td>
<td>ABCD</td>
<td></td>
</tr>
<tr>
<td>Nephrotoxicity (creatinine)</td>
<td>9%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>55%</td>
<td>52 %</td>
<td></td>
</tr>
<tr>
<td>Infusion related (e.g, chills)</td>
<td>50%</td>
<td>78 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L-AmB</td>
<td>Caspo</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>11.5%</td>
<td>1.8 %</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>11.5 %</td>
<td>3.6 %</td>
<td></td>
</tr>
<tr>
<td>Discontinued due to AEs</td>
<td>11.5 %</td>
<td>3.6 %</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:**
- Caspo better tolerated than L-Am-B
- L-AmB better tolerated than AmB-D
**Empiric Antifungal Treatment Recommendation Summary**

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
</table>

Use either caspofungin or liposomal amphotericin B for empiric antifungal therapy  
(Strong recommendation, high quality evidence).
Conclusions

• Clinical practice guidelines optimally developed by international panel

• Provided recommendations for risk stratification, initial therapy and empiric antifungal treatment

• Guideline will be updated early 2016
Acknowledgements

International Pediatric Fever and Neutropenia Guideline
Panel members
Bob Phillips (Leeds, UK)
Thomas Lehrnbecher (Frankfurt, Germany)
Tanya Hesser

CIHR meeting grant
CIHR New Investigator Award
Thank you!