Appendix 1. Outline of Sections, Clinical Questions and Median Importance Ratings for Outcomes

The following presents the specific clinical questions for guideline development. Italics illustrate how these clinical questions may be translated into practical questions relevant to clinical care.

SECTION 1: INITIAL PRESENTATION OF FEBRILE NEUTROPENIA (FN)

Initial presentation and evaluation of pediatric patients with FN

Specific Questions:

1. 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?

Can we select patient who need higher or lower degrees of observation and aggressiveness of antibiotic therapy?

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?

What tests should be routinely performed to identify the etiology of an episode? For example, should urine culture and chest radiography be conducted in children who do not have symptoms or signs localized to those sites?

Outcomes:

Outcomes	**Importance**
Death	Critical
Persistent fever / time to resolution of fever	Important
Sepsis syndrome	Critical
Intensive care unit admission	Critical
Serious medical complication	Critical
Microbiologically documented infection (e.g. bacterial, viral or fungal infection)	Critical
Clinically documented focal infection (included radiologically documented e.g. pneumonia)	Critical

Initial management of FN including drug choice, location of treatment, and route of administration

Specific Questions:

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

4. In children with low-risk FN, is initial or step-down outpatient management as effective and safe as inpatient management?

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

For those patients who are predicted to have a low risk of an adverse outcome to this episode of FN, can they be managed as out-patients, and can they be managed with oral antibiotics?

Outcomes:

Outcomes	Importance
Death	Critical
Sepsis syndrome	Critical
Intensive care unit admission	Critical
Serious medical complication	Critical
Persistent fever / time to resolution of fever	Important
Secondary infection including breakthrough bacteremia	Critical
Re-admission	Important
Recurrence of infection/fever	Important
Modification of initial empiric antibiotics	Important
Quality of life	Important

SECTION 2: ONGOING MANAGEMENT OF FN EXCLUDING EMPIRIC ANTIFUNGAL THERAPY

Treatments including modifications in therapy (excluding empiric antifungal therapy) and cessation of therapy in pediatric patients with FN who have been receiving antibiotic therapy

Specific Questions:

6. When and how should the initial empiric antibiotic therapy be modified during the pediatric FN episode?

How should the initial antibiotics be modified in those who are responding to initial treatment, those who remain persistently febrile and those who clinically deteriorate?

7. When can empiric antibiotics be discontinued in patients with low- and high-risk FN?

When can antibiotics be discontinued in those who become afebrile and are clinically stable in low and high risk FN?

Outcomes:

Outcomes	Importance
Death	Critical
Re-hospitalization	Critical
Resolution of FN without modification	Critical
Resolution of FN with modification	Important
Quality of Life	Important
Toxicity	Critical

SECTION 3: EMPIRIC ANTIFUNGAL TREATMENT

Risk stratification and evaluation of patients with persistent or recurrent FN despite broad-spectrum antibiotics

Specific Questions:

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

What clinical or laboratory features can indicate whether a child is at higher or lower risk of developing an IFD which could impact on whether a child receives more or less aggressive antifungal therapy?

9. What clinical features, laboratory tests, imaging studies and procedures (such as broncho-alveolar lavage and biopsy) are useful to identify a fungal etiology for persistent/recurrent FN despite broad-spectrum antibiotics?

What tests in which order should be performed to prove/exclude IFD? What is the appropriate timing of these tests?

Outcomes:

Outcomes	**Importance**
Death	Critical
Breakthrough fungal infection(proven/probable mold infection)	Critical
Breakthrough fungal infection (proven/probable yeast infection)	Critical
Development of pulmonary infiltrates	Critical
Fever unresponsive to antibiotic treatment	Important
Serious medical complication	Critical

Management of persistent or recurrent fever and neutropenic children despite broad-spectrum antibiotics: empiric antifungal therapy

Specific Questions:

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

What are the empiric antifungal regimens that have been evaluated in children and which ones have better efficacy and fewer toxicities?

Outcomes:

Outcomes	**Importance**
Death (overall)	Critical
Death attributable to invasive fungal infection	Critical
Breakthrough fungal infection (mould, yeast)	Critical
Clinical deterioration/intensive care unit admission	Critical
Development of pulmonary infiltrates	Critical
Resolution of FN with/without modification of empiric antifungal treatment	Important
Toxicity	Critical

Appendix 2. Details of Methodology Related to Working Groups, Formulation of Questions, Rating Importance of Outcomes, Development of Evidence Profiles, Panel Meetings and Development of Recommendations

Each member completed conflict of interest forms (http://www.icmje.org/coi_disclosure.pdf) and no conflicts precluded involvement in the Panel. The guideline was editorially independent from the funding body (Canadian Institutes of Health Research).

Formulating Questions, Rating Importance of Outcomes and Development of Evidence Profiles

A pragmatic, hierarchical approach was undertaken in the search. For all questions, systematic reviews of primary studies were sought and results in children were identified. In the event that there were little or no pediatric data to inform recommendations on a specific health question, evidence from adult studies and combined adult and pediatric studies was considered. Lack of pediatric data was accounted for in the quality description of evidence (i.e. indirect evidence). Where there were no studies of the highest quality or where they were few in number, for example, few randomized controlled trials, designs with a greater risk of bias such as observational studies were subsequently searched for and reviewed. Sample sizes were limited for some synthesized outcomes and thus, 95% confidence intervals were provided to facilitate interpretation. The Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach was used to generate summaries and evidence was classified as high, moderate, low or very low based upon methodologic considerations.[11] The key methodological elements are in study design, consistency of the body of evidence, directness of the studies to the question under consideration, and limitations in the conduct of the studies. Based upon the evidence summaries, each working group then developed recommendations which considered health benefits, side effects, risks and costs.

Panel Meeting and Development of Recommendations

The first meeting of the Panel was held on October 21st, 2010 (Boston, MA) to plan guideline development. A second meeting was held on September 18th, 2011 (Chicago, IL) to discuss the results of the evidence summaries and each working group's preliminary recommendations. Following several conference calls, revised documents were then circulated. Once the group had approved the final version, review by seven external expert reviewers was undertaken. A final revised version was created on February 17, 2012. A guideline update is planned in 3 years or sooner in the event of the publication of important new information.