Children presenting with fever and neutropenia (FN) pose unique diagnostic and management challenges. The absence of pediatric-specific guidelines has led physicians to rely on local expertise, interpretation of available data without benefit of national consensus, and extrapolation of adult guidelines for direction. However, the causes, treatment, and outcomes of children with FN differ in important ways from those of adults. Although individual studies have focused on different aspects of the management of FN in children, a universal approach has not been adopted. The literature review below provides a synopsis of a recently published international guideline on management of children with FN. The guideline reviewed represents the first evidence-based, consensus-driven approach to address management of FN in children.


The published guideline is the work of the International Pediatric Fever and Neutropenia Guideline Panel: a multidisciplinary team of pediatric infectious diseases and oncology experts, along with nursing and pharmacy specialists and a patient advocate. Working groups were created to focus on 3 major areas: management during the initial presentation of fever and neutropenia (FN), ongoing management of FN during the period ≥24–72 hours after initial workup, and the use of empiric antifungal therapy. Each group identified key areas for which consensus recommendations were needed. Systematic reviews of the published literature were conducted and evidence was evaluated. The Grades of Recommendation Assessment, Development, and Evaluation (GRADE) classification was used to characterize the strength of recommendations and quality of evidence. Table 1 contains a summary of the recommendations provided in the guideline. The synopsis that follows offers a brief description of the context for how each recommendation was derived, according to the guideline, as well as comments on the application of these recommendations in clinical practice.

Section 1. Initial Presentation of FN

The first section of the guideline focuses on management decisions at the time of initial presentation of a child with FN. In this critical time period, clinicians must identify sick patients, perform an appropriate diagnostic assessment, and start empiric antimicrobial therapy to cover the most likely pathogens.

The first recommendation in the guideline is for institutions to adopt a validated risk stratification scheme to identify children with FN at low-risk for poor outcomes. Six studies were recognized as offering validated strategies in different pediatric FN populations [1–6]. Each is based on a combination of different factors: underlying disease, chemotherapy being provided, degree of illness, laboratory findings, and others. The guideline does not identify a preferred strategy but instead emphasizes that centers implement a strategy that was derived from a patient population similar to those cared for at that institution. The performance of the chosen strategy should be prospectively assessed to assure effectiveness and safety.

There is controversy regarding the optimal diagnostic approach for identifying the source of fever in children with FN. Because the majority of children with cancer have an indwelling central venous catheter (CVC), it is imperative to adequately culture these potential sources of
Table 1. Summary of Recommendations from Pediatric FN Guidelinesa

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<thead>
<tr>
<th>Risk Stratification</th>
<th>Evaluation</th>
<th>Treatment</th>
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<tr>
<td><strong>Initial Presentation of FN</strong></td>
<td>Evaluate blood cultures at onset of FN from all lumens of central venous catheters (1C)</td>
<td>High-risk FN: Use monotherapy with anti-pseudomonal β-lactam or carbapenem as empiric therapy (1A) Reserve 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>
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<td>Adopt a validated risk stratification strategy and incorporate it into routine clinical management (1C)</td>
<td>Consider peripheral blood cultures concurrent with obtaining central venous catheter cultures (2C)</td>
<td>Low-risk FN: Consider initial or step-down outpatient management if infrastructure is in place to assure careful monitoring and follow-up (2B) In children with low-risk FN, consider oral antibiotics administration if child is able to tolerate this route of administration reliably (2B)</td>
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<tr>
<td>Obtain blood cultures at onset of FN from all lumens of central venous catheters (1C)</td>
<td>Consider urinalysis and urine culture in patients when clean-catch, midstream specimen in readily available (2C)</td>
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<tr>
<td>Evaluate risk stratification strategy (1C)</td>
<td>Obtain chest radiography only in symptomatic patients (1B)</td>
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<td><strong>Ongoing Management of FN: ≥24–72 Hours After Initiation of Empiric Antibacterial Treatment</strong></td>
<td>Cessation of Treatment</td>
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<td>Modify treatment</td>
<td>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)</td>
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<td>In patients who are responding to initial empiric antibiotic therapy, discontinue double coverage for Gram-negative infection or empiric glycopeptide (if initiated) after 24–72 hours if there is no specific microbiologic indication to continue combination therapy (1B)</td>
<td>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 or marrow recovery status, as long as careful follow-up is ensured (2B)</td>
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<td>Do not modify initial empiric antibiotic regimen based solely on persistent fever in children who are clinically stable (1C)</td>
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<td>In children with persistent fever who become clinically unstable, escalate initial empiric antibiotic regimen to include coverage for resistant Gram-negative, Gram-positive, and anaerobic bacteria (1C)</td>
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<td><strong>Empiric Antifungal Treatment: ≥96 Hours After Initiation of Empiric Antibacterial Treatment</strong></td>
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<tr>
<td>Risk Stratification</td>
<td>Evaluation</td>
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<td>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 (≥96 hours) broad-spectrum antibiotic therapy and expected prolonged neutropenia (≥10 days); all others should be categorized as IFD low risk (1B)</td>
<td>In children, do not use β-D-glucan testing for clinical decisions until further pediatric evidence has accumulated (1C)</td>
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<tr>
<td><strong>Evaluation</strong></td>
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<tr>
<td>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 (≥96 hours) broad-spectrum antibiotic therapy and expected prolonged neutropenia (≥10 days); all others should be categorized as IFD low risk (1B)</td>
<td>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 the lungs and targeted imaging of other clinically suspected areas of infection (1B); consider CT imaging of the sinuses in children ≥2 years of age (2C) IFD low risk: In IFD low-risk patients, do not implement routine galactomannan screening (1C)</td>
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Reprinted with permission. 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. J Clin Oncol 2012; 30:4428 ©2012 American Society of Clinical Oncology. All rights reserved. Abbreviations: AML, acute myeloid leukemia; CNS, central nervous system; CT, computed tomography; FN, fever and neutropenia; GRADE, Grades of recommendation Assessment, Development, and Evaluation; HSCT, hematopoietic stem-cell transplantation; IFD, invasive fungal disease. Parentheses indicate GRADE strength of recommendation (1, strong; 2, weak) and quality of evidence (A, high; B, moderate; C, low or very low).
infection. Although this is likely already standard of care at most institutions, the role of peripheral cultures in pediatric patients with CVCs is less clear. A balance must be struck between increasing the detection of bacteremia and the pain and potential introduction of contaminants associated with peripheral venipuncture. The guideline does not make a formal recommendation for routine peripheral blood cultures but instead presents the data and defers the decision to the discretion of the treating physician.

Urinary tract infections are a frequent cause of fever in neutropenic children with and without symptoms, and the guideline states that urine culture should be considered in the initial diagnostic evaluation. A urinalysis may not reliably demonstrate signs of urinary tract infection in neutropenic patients and should not be relied upon to prompt collection of a urine culture in these patients. Meanwhile, the frequency of pneumonia in children with FN who lack signs and symptoms of respiratory illness is low. Findings on chest radiography rarely influence care in these patients, and thus the guideline discourages routine chest radiography in asymptomatic patients.

Antibiotic decision-making is critical in the initial management of FN patients, and there is significant variability across centers in the empiric antibiotic regimens that are used. The goal of empiric antibiotic therapy is to cover the most likely pathogens such as Gram-negative bacilli, including *Pseudomonas aeruginosa*, and viridans group streptococi in high-risk FN patients. Citing high-quality evidence, the guideline strongly recommends that monotherapy with an anti-pseudomonal β-lactam or a carbapenem should be used for empiric therapy in children with high-risk FN; the empiric addition of a second Gram-negative agent or a glycopeptide should be limited to unstable patients, those with an increased risk of resistant organisms, or in centers with high rates of resistant pathogens. Numerous prospective trials have evaluated the efficacy of various empiric antibiotic regimens in children with FN, and no one regimen has demonstrated superiority. Notably, the use of combination antimicrobial therapy does not provide clear benefit in FN patients, whereas the risk of toxicity is increased. The choice of antibiotic(s) revolves largely around individual patient histories, the clinical status of the patient, local resistance patterns, and the anticipated side-effect profile. It should be noted that the guideline discourages the empiric use of ceftazidime monotherapy if Gram-positive or resistant Gram-negative infections are suspected.

Not all children with FN require hospital admission, and some may be candidates for oral rather than parenteral antibiotics. Studies have shown similar efficacy and safety in low-risk FN patients managed as outpatients compared to inpatients [7]. When close follow-up is possible, outpatient management may be reasonable in low-risk patients. Similarly, studies cited by the guideline comparing oral and parenteral antibiotics in low-risk patients have shown no differences in treatment failure or mortality [7, 8]. When oral antibiotics can be tolerated (swallowed, absorbed, and are bioavailable), they should be considered a viable option.

### Section 2. Ongoing Management of FN

The second section of the guideline concentrates on the use of antibacterial therapy beyond the initial evaluation. After empiric antibiotics have been selected and the preliminary diagnostic tests have been performed, clinicians need to frequently reevaluate the treatment plan. This section provides guidance on how to modify antibiotics after the initial 24–72 hours.

If the patient is responding to empiric antibiotics, the guideline strongly recommends the discontinuation of a glycopeptide or second Gram-negative agent after 24–72 hours, if they have been started at presentation. So long as there is no documented indication for these antibiotics, negative culture results may allow practitioners to narrow the spectrum of antimicrobial activity. The rationale for de-escalation of therapy stems from the goal to address the most likely pathogen(s) and minimize unnecessary antibiotic exposure. In addition, in stable patients, persistence of fever alone should not prompt the addition of antibiotics or modification of ongoing therapy. For some practitioners, persistence of fever in vulnerable patients can be disconcerting. However, there is no evidence that escalation of antibiotics due to fever alone improves clinical outcomes. Instead, the impetus for adjustment of antibacterial therapy should be the identification of a source on examination (to target therapy at most likely organisms), positive microbiological testing (to focus antibiotics on known pathogens), or clinical instability (which should prompt escalation or broadening of therapy).

The guideline also provides advice regarding the discontinuation of antibiotics when no source of infection has been found. Antibiotics should be stopped after 48 hours of negative blood cultures in all FN patients who have been afebrile for at least 24 hours and have signs of marrow recovery. There is no established definition for marrow recovery, but the authors suggest an absolute neutrophil count ≥100/µL after the neutrophil nadir. According to the referenced studies, the risk of recurrent fever among children with definite marrow recovery, negative blood cultures at 48–72 hours, and absence of fever for ≥24 hours is very low (incidence = 1%; 95%
Section 3. Empiric Antifungal Therapy

The final section of the guideline focuses on recommendations regarding the use of empiric antifungal therapy and diagnostic tests to identify fungal infection in FN patients. The risk for invasive fungal disease (IFD) is based largely on a patient’s underlying malignancy, degree of immunosuppression, or type of hematopoietic cell transplant. In addition, factors that may signify a higher risk of IFD include prolonged neutropenia, mucositis, steroid exposure, presence of a central line, and others. Patients who do not meet criteria described in the guideline can be considered at low-risk for IFD.

It is encouraged that patients at high-risk for IFD with persistent FN (≥96 hours) despite antibiotics undergo evaluation for fungal disease, according to the guideline. Imaging may aid in diagnosis and should include a chest computed tomography (CT) and imaging of any clinically suspicious areas. A CT of the sinuses in children older than 2 years of age can also be considered, although evidence is limited. The role of fungal biomarkers (galactomannan [GM] and β-D-glucan) has not been established in pediatric FN patients. Galactomannan from bronchoalveolar lavage fluid or cerebrospinal fluid may aid in detection of pulmonary or central nervous system aspergillosis, respectively. Meanwhile, the guideline suggests that twice weekly monitoring of serum GM in hospitalized patients at high risk for IFD could aid in early detection of invasive aspergillosis. The sensitivity and specificity of GM screening for detection of IFD in high-risk pediatric patients were 0.76 (95% confidence interval, 0.62–0.87) and 0.86 (95% confidence interval 0.68–0.95), respectively, according to combined data from 5 pediatric studies [9–13]. Routine GM screening in low-risk patients is not advised, however, and the guideline also recommends against the use of β-D-glucan testing because of insufficient data in pediatric patients.

The guideline strongly recommends starting either caspofungin or liposomal amphotericin B empirically in children with FN at high-risk for IFD after 96 hours of fever despite use of broad-spectrum antibiotics. Consideration could also be given to starting empiric antifungal therapy in low-risk patients with persistent fever, although the evidence for this recommendation is less compelling. The guideline encourages continuation of antifungals until neutropenia resolves, so long as IFD has not been established or suspected. Most of the evidence supporting these recommendations stems from extrapolation of adult literature because few pediatric trials have been conducted.

Discussion

The consensus guideline from Lehrnbecher et al provides the first pediatric-specific, evidence-based approach for the management of FN in children with cancer. It offers practical guidance on a number of topics that have been controversial within the pediatric infectious diseases and oncology communities. Although not all recommendations will be universally accepted, the evidence is synthesized clearly and easily accessible within the document. Most importantly, the guideline provides straightforward justifications for each recommendation and openly states when supporting data is lacking.

Although the guideline addresses many important issues in the management of FN in children, several areas remain unaddressed primarily due to a paucity of data in pediatric FN patients. For instance, there are no validated risk stratification rules for high-risk FN patients. In addition, what constitutes a sufficiently high rate of resistant pathogens in a center to justify the use of a particular empiric antibiotic regimen has not been established. It also remains unclear how often blood cultures should be obtained in patients with persistent fevers. In addition, although twice weekly GM screening is recommended for high-risk patients, whether serial GM screening leads to improved outcomes or is cost-effective requires further investigation. The areas where more pediatric-specific research is needed are highlighted throughout the guideline. And, as additional evidence become available, future versions of the guideline will likely address the existing gaps and refine the current recommendations.

Overall, the guideline provides an important and timely contribution to the pediatric infectious diseases literature. It offers a consensus approach to the management of children with FN based on a synthesis of available data by international experts in the field. These recommendations should be able to translate into clinical practice and allow for standardization of care across institutions. The justifications set forth by the guideline balances the safety and outcomes of individual patients with the responsibility of antimicrobial stewardship owed to all. Practitioners who provide care for children with FN should familiarize themselves with this guideline and the rationale contained within. Hopefully, this document will lead to more consistent practice and better outcomes for children with FN.
References


