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

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## A B S T R A C T

**Purpose**

To develop an evidence-based guideline for the empiric management of pediatric fever and neutropenia (FN).

**Methods**

The International Pediatric Fever and Neutropenia Guideline Panel is a multidisciplinary and multinational group composed of experts in pediatric oncology and infectious disease as well as a patient advocate. The Panel was convened for the purpose of creating this guideline. We followed previously validated procedures for creating evidence-based guidelines. Working groups focused on initial presentation, ongoing management, and empiric antifungal therapy. Each working group developed key clinical questions, conducted systematic reviews of the published literature, and compiled evidence summaries. The Grades of Recommendation Assessment, Development, and Evaluation approach was used to generate summaries, and evidence was classified as high, moderate, low, or very low based on methodologic considerations.

**Results**

Recommendations were made related to initial presentation (risk stratification, initial evaluation, and treatment), ongoing management (modification and cessation of empiric antibiotics), and empiric antifungal treatment (risk stratification, evaluation, and treatment) of pediatric FN. For each recommendation, the strength of the recommendation and level of evidence are presented.

**Conclusion**

This guideline represents an evidence-based approach to FN specific to children with cancer. Although some recommendations are similar to adult-based guidelines, there are key distinctions in multiple areas. Implementation will require adaptation to the local context.

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## INTRODUCTION

Fever and neutropenia (FN) are common complications in children who receive chemotherapy for cancer. Although several guidelines for the management of FN have been developed,[1-7] none are dedicated to children. FN guidelines specifically focused on children with cancer are important.[8] To address this critical gap, we convened a panel of pediatric cancer and infectious disease experts, as well as a patient advocate, to develop an evidence-based guideline for the empiric management of pediatric FN.

## METHODS

The International Pediatric Fever and Neutropenia Guideline Panel included representatives from oncology, infectious disease, nursing, and pharmacy, as well as a patient advocate, from 10 different countries (Data Supplement 1). Participants (other than the patient advocate) were selected based on peer-reviewed publications in pediatric FN while considering balance by geography.

We followed previously validated procedures for creating evidence-based guidelines[9] and used the Appraisal of Guidelines for Research and Evaluation

II instrument as a framework.[10] Members were divided into working groups that addressed each of the three major sections (initial presentation, ongoing management, and empiric antifungal therapy). Each working group developed the key clinical questions to be addressed by the guideline and identified and rated the importance of outcomes relevant to the questions on a 9-point scale (Data Supplement 2). Ratings of 7 to 9 indicated that the outcome was critical for a decision or recommendation; 4 to 6, that it was important; and 1 to 3, that it was not important. The median ratings from working group members established the importance of the outcomes and guided recommendations.

For each question, systematic reviews of the published literature were conducted until March 2011 (available on request), and each working group compiled evidence summaries. Empiric treatments focused on pharmacologic interventions and did not include therapies such as growth factors. The Grades of Recommendation Assessment, Development, and Evaluation approach was used to generate summaries, and evidence was classified as high, moderate, low, or very low based on methodologic considerations.[11] Data Supplement 3 illustrates additional details of the guideline methodology.

## RECOMMENDATIONS AND EXPLANATIONS

The summary of recommendations is listed in Table 1, and the associated evidence profiles are illustrated in Data Supplements 4 to 10.

| **Table 1.** Overall Summary of Recommendations* | | |
|---|---|---|
| Initial Presentation of FN | | |
| Risk Stratification | Evaluation | Treatment |
| Adopt a validated risk stratification strategy and incorporate it into routine clinical management (1C) | Obtain blood cultures at onset of FN from all lumens of central venous catheters (1C)<br>Consider peripheral-blood cultures concurrent with obtaining central venous catheter cultures (2C)<br>Consider urinalysis and urine culture in patients where clean-catch, midstream specimen is readily available (2C)<br>Obtain chest radiography only in symptomatic patients (1B) | High-risk FN: Use monotherapy with antipseudomonal β-lactam or carbapenem as empiric therapy in pediatric high-risk FN (1A)<br>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)<br>Low-risk FN: In children with low-risk FN, consider initial or step-down outpatient management if infrastructure is in place to ensure careful monitoring and follow-up (2B)<br>In children with low-risk FN, consider oral antibiotic administration if child is able to tolerate this route of administration reliably (2B) |
| Ongoing Management of FN: ≥ 24 to 72 Hours After Initiation of Empiric Antibacterial Treatment | | |
| | Modification of Treatment | Cessation 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)<br>Do not modify initial empiric antibacterial regimen based solely on persistent fever in children who are clinically stable (1C)<br>In children with persistent fever who become clinically unstable, escalate initial empiric antibacterial regimen to include coverage for resistant Gram-negative, Gram-positive, and anaerobic bacteria (1C) | 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)<br>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 Hours After Initiation of Empiric Antibacterial Treatment | | |
| Risk Stratification | Evaluation | Treatment |
| 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 prolonged (≥ 96 hours) broad-spectrum antibiotic therapy and expected prolonged neutropenia (> 10 days); all others should be categorized as IFD low risk (1B) | All patients: Consider galactomannan in bronchoalveolar lavage and cerebrospinal fluid to support diagnosis of pulmonary or CNS aspergillosis (2C)<br>In children, do not use β-D-glucan testing for clinical decisions until further pediatric evidence has accumulated (1C)<br>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)<br>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)<br>IFD low risk: In IFD low-risk patients, do not implement routine galactomannan screening (1C) | All patients: Use either caspofungin or liposomal amphotericin B for empiric antifungal therapy (1A)<br>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)<br>IFD low risk: In neutropenic IFD low-risk children, consider empiric antifungal therapy in setting of persistent FN (2C) |

Abbreviations: AML, acute myeloid leukemia; 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).

Identified research gaps and recommendations for future research are listed in Table 2.

## SECTION 1: INITIAL PRESENTATION OF FN

### Question

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?

### Recommendation

Adopt a validated risk stratification strategy (Table 3) and incorporate it into routine clinical management (1C; strong recommendation, low-quality evidence).

### Explanation

Studies of risk prediction in children include retrospective and prospective observational cohort studies that vary in inclusion criteria, specific definitions of FN, and exact outcomes measured.[12-17,20,21,23-33] Studies of risk assessment in adult FN populations were not included in recommendation formulation.[8]

Common elements informative for risk stratification included patient-specific factors (including age, malignancy type, and disease status), treatment-specific factors (type and timing of chemotherapy), and episode-specific factors (including height of fever, hypotension, mucositis, blood counts, and C-reactive protein [CRP]). The schemas uniformly exclude those with more severe myelosuppression and patients undergoing hematopoietic stem-cell transplantation (HSCT) from low-risk definitions. They are also consistent with the largely adult-focused Infectious Diseases Society of America guideline,[1] but in pediatric studies, the depth of thrombocytopenia or leukopenia has been examined rather than anticipation of prolonged neutropenia in predicting which patients are at higher risk of experiencing complications.

Six low-risk stratification schemas have been validated in different pediatric populations (Table 3). Evaluation of these studies does not allow the recommendation of a single low-risk prediction rule, because no single rule is clearly more effective or reliable than the others, nor does it allow us to convincingly recommend different rules for predicting specific outcomes.[34] It is important to recognize that the process of deriving prediction rules frequently overestimates their effectiveness in practice, so rules require validation. Furthermore, geographic and temporal validation are important, because differences in local practices, systems, and approaches may alter how the rules perform.[35]

The rule developed by Santolaya et al,[15] derived from Chile, was shown to be highly effective when used in the same population.[36] Similarly, the rule of Alexander et al[13] from Boston has been effectively used in England[19] and implemented in Canada. Consequently, clinicians in Chile would be justified in using the Santolaya et al rule, whereas those in England, Canada, and the United States could reasonably implement the rule of Alexander et al. The choice of strategy may also be influenced by the ability of an institution to implement more complex rules and the timeliness of receipt of test results such as CRP. Each institution should maintain records of which specific strategy is used and evaluate the performance of the chosen rule to ensure accuracy and safety within a specific clinical setting. Identification of a predominant risk stratification schema for use across clinical trials and in clinical practice (where appropriate) would optimize future research and patient care. It is important to note that there are no validated schemas for defining those patients at high risk of developing complications from FN.

### Question

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?

### Recommendations

Obtain blood cultures at the onset of FN from all lumens of central venous catheters (CVCs; 1C; strong recommendation, low-quality evidence). Consider peripheral-blood cultures concurrent with obtaining CVC cultures (2C; weak recommendation, low-quality evidence). Consider urinalysis and urine culture in patients for whom a clean-catch, midstream specimen is readily available (2C; weak recommendation, low-quality evidence). Obtain chest radiography (CXR) only in symptomatic patients (1B; strong recommendation, moderate-quality evidence).

### Explanation

The etiology of initial fever may be noninfectious, bacterial, or viral, or less commonly, it may result from other pathogens. Viral pathogens are common, and evaluation should be directed at specific signs and symptoms.

*Blood culture.* Blood cultures obtained during the evaluation of FN are essential. A majority of children with cancer receiving chemotherapy have an indwelling CVC; for these children, obtaining a blood culture of adequate volume from all lumens of the CVC is important. However, the utility of peripheral-blood cultures in addition to CVC

| Table 2. Research Gaps in Pediatric FN |
|---|
| Identification of a validated high-risk stratification schema for pediatric fever and neutropenia |
| Determination of the incremental value of a peripheral-blood culture in addition to central venous catheter cultures of an adequate volume in children with FN |
| Identification of the optimal type and frequency of re-evaluation (for example, daily or every second day telephone contact or clinic visit) for pediatric outpatients with low-risk FN |
| Determination of the optimal treatment regimen for microbiologically documented sterile site infections during FN |
| Identification of the optimal frequency of blood culture sampling in persistently febrile pediatric patients with neutropenia who are either clinically stable or unstable |
| Determination of the optimal duration of antibiotic therapy for patients with high-risk FN without bone marrow recovery for prolonged periods |
| Determination of whether a strategy of routine galactomannan screening in IFD high-risk children is cost-effective and results in better clinical outcomes compared to a strategy without screening |
| Determination of the clinical utility and optimal cut-off of β-D-glucan testing in IFD high-risk children |
| Determination of the clinical utility of routine sinus imaging in children being evaluated for IFD |
| Determination of the safety and efficacy of a preemptive antifungal approach in IFD low-risk and IFD high-risk children |
| Identification of the optimal investigation and treatment for viral infections in children with FN |
| Abbreviations: FN, fever and neutropenia; IFD, invasive fungal disease. |

**Table 3.** Validated Pediatric Risk Stratification Strategies for Low-Risk Patients

| Strategy Factor | Rackoff et al[12] (1996) | Alexander et al[13] (2002) | Rondinelli et al[14] (2006) | Santolaya et al[15] (2001) | Ammann et al[16] (2003) | Ammann et al[17] (2010) |
|---|---|---|---|---|---|---|
| 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 | 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 | 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 | CRP ≥ 90 mg/L, hypotension, platelets ≤ 50 g/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 formulation | 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 | 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* | United States; Madsen et al[18] (2002) | United Kingdom; Dommett et al[19] (2009) | Brazil; Rondinelli et al[14] (2006) | South America; Santolaya et al[20] (2002) | Europe; Ammann et al[17] (2010); Macher et al[21] (2010) | Europe; Miedema et al[22] (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.

cultures is controversial. Seven studies evaluated concurrent peripheral and CVC cultures in adults and children with cancer and/or undergoing HSCT[37-43] (Data Supplement 4). Only two studies removed probable contaminants from the analysis. Overall, the proportion of bacteremia detected by peripheral-blood cultures alone (ie, CVC cultures were negative) was 13% (95% CI, 8% to 18%). The designation of this recommendation as weak arises from balancing increased yield of bacteremia against pain/inconvenience and contaminants associated with peripheral cultures. Peripheral cultures may also help to diagnose catheter-related infections, although the clinical utility of the diagnosis is unclear.[44]

Multiple variables can influence blood culture yield, including blood culture volume, choice of media type, number of culture bottles inoculated, and frequency of cultures.[45] Although an adequate volume of blood inoculated is important[46,47] and often not consistently collected,[48] minimum volumes have not been established in pediatric patients. Manufacturer volume recommendations and weight-based sliding scales[49] are two approaches to standardizing volume of blood collected.

*Urinalysis and urine culture.* Urinary tract infections (UTIs) are common in pediatric FN.[20] Routine urinalysis and culture at the initial evaluation of FN in children is controversial. Restricting urine culture to those with symptoms or abnormal urinalysis is probably not justified in children. Pyuria was found in only 4% of UTI episodes during neutropenia, compared with 68% in control patients with cancer without neutropenia ($P < .001$).[50] Nitrite testing in younger children (without cancer) is also known to be less effective than in older patients.[51]

Given the concerns regarding delay of therapy and possibly increased adverse events associated with invasive methods for urine collection, the Panel recommends that where a clean-catch or midstream urine sample can be collected, it should be obtained before commencing antibiotics. Urine collection should not delay treatment.

*CXR.* A CXR had been advocated as part of the routine, initial assessment of pediatric FN, because the neutropenic child was believed to be less likely to exhibit signs and symptoms of pneumonia than the immunocompetent child.[52] Four studies that included 540 episodes of FN[53-56] examined the value of routine CXR; each found that the frequency of pneumonia in an asymptomatic child was 5% or less.[57] Asymptomatic children who do not receive a CXR had no significant adverse clinical consequences,[56] and thus, routine CXRs are not recommended in asymptomatic children.

## Question

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

## Recommendations

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

## Explanation

Initial management of pediatric FN will be influenced by many factors, such as patient characteristics, clinical presentation, local infrastructure to support different models of care, drug availability and cost, and local epidemiology, including resistance patterns. In general, coverage should include Gram-negative organisms in all patients as well as viridans group streptococci and *Pseudomonas aeruginosa* in high-risk FN. The overall goal of empiric therapy is to provide coverage for virulent organisms while minimizing exposure to unnecessary antibiotics, because indiscriminant use of broad-spectrum antibiotics may accelerate antibiotic resistance rates.

Data Supplement 5 presents all published, English-language, prospective trials of pediatric FN evaluating a homogeneous initial empiric antibiotic strategy providing coverage appropriate for high-risk FN patients; combination regimens are included. Outcomes deemed clinically important by the Panel were synthesized by antibiotic type; no particular regimen was superior to another.

Two meta-analyses compared monotherapy versus an aminoglycoside-containing regimen in FN[58] and in immunocompromised patients with sepsis[59]; patients were primarily adults. The meta-analyses demonstrated noninferiority of monotherapy regimens and higher toxicity with combination regimens. The FN meta-analysis found fewer treatment failures with monotherapy (odds ratio [OR], 0.88; 95% CI, 0.78 to 0.99), but this analysis included only four trials that enrolled patients younger than 14 years of age.[58] A pediatric meta-analysis found that aminoglycoside-containing combination treatment did not improve clinical outcomes in comparison with antipseudomonal penicillin monotherapy.[60]

Specific monotherapy regimens evaluated in children and presented in Data Supplement 5 include antipseudomonal penicillins (such as piperacillin-tazobactam and ticarcillin-clavulinic acid), antipseudomonal cephalosporins (such as cefepime), and carbapenems (meropenem or imipenem). No difference in treatment failure, mortality, or adverse effects was seen when antipseudomonal penicillins were compared with antipseudomonal cephalosporins or carbapenems.[61,61] However, carbapenems may be associated with more pseudomembranous colitis in comparison with other β-lactam antibiotics.[62] In terms of antipseudomonal cephalosporins, a meta-analysis of randomized controlled trials (RCTs) found a statistically significant increase in all-cause mortality in cefepime-treated versus other β-lactam–treated patients.[62] However, this finding was refuted in a US Food and Drug Administration review,[63] and increased mortality was not observed in a pediatric meta-analysis.[56] Consequently, cefepime may be an appropriate initial empiric therapy for children with FN if local circumstances support its use. Ceftazidime monotherapy should not be used if there are concerns of Gram-positive or resistant Gram-negative infections.[64]

The role of empiric glycopeptides in FN was examined in a predominantly adult meta-analysis of 14 RCTs.[65] Inclusion of a glycopeptide led to less frequent treatment modification, but if addition of glycopeptides in the control arm was not considered failure, no difference in treatment success was seen (OR, 1.02; 95% CI, 0.68 to 1.52). However, adverse effects were more common in the empiric glycopeptide group.

Irrespective of empiric choices, rigorous epidemiologic surveillance is critical, and empiric antibiotic regimens should be regularly

reviewed in light of evolving institutional microbial resistance patterns. Monotherapy may not be appropriate in institutions with a high rate of resistance.

## Question

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

## Recommendation

In children with low-risk FN, consider initial or step-down outpatient management if the infrastructure is in place to ensure careful monitoring and follow-up (2B; weak recommendation, moderate-quality evidence).

## Explanation

Outpatient management of children with FN is attractive, given the increased quality of life for children[66] and large reduction in costs[67] associated with an ambulatory approach. One meta-analysis of RCTs compared inpatient versus outpatient management of FN.[68] In six studies, outpatient management was not associated with significantly higher treatment failure (rate ratio [RR], 0.81; 95% CI, 0.55 to 1.28; $P = .28$), where RR < 1 favored inpatient care. There was no difference in mortality (RR, 1.11; 95% CI, 0.41 to 3.05; $P = .83$). In a stratified analysis of the two pediatric studies,[69,70] results were similar to the overall analysis.

Data from 16 prospective trials of pediatric low-risk FN based on site of care within the first 24 hours are presented in Data Supplement 6.[71] There was no increase in treatment failure (including modification) with outpatient relative to inpatient management (15% $v$ 27%; $P = .04$). Importantly, there were no infection-related deaths among the 953 outpatients.[71]

## Question

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

## Recommendation

In children with low-risk FN, consider oral antibiotic administration if the child is able to tolerate this route of administration reliably (2B; weak recommendation, moderate-quality evidence).

## Explanation

Oral antibiotics may be advantageous, because they facilitate outpatient management and are generally less costly compared with parenteral antibiotics. However, oral medication administration may present major challenges in children. Issues include drug availability as an oral liquid, palatability, cooperation of young children, mucositis, and impaired gastrointestinal absorption. Two meta-analyses of RCTs compared oral and parenteral antibiotics for FN; one included all settings (n = 2,770),[72] whereas the other was restricted to the outpatient setting (n = 1,595).[68] Both included all FN risk groups. They both showed no difference in treatment failure (including modification), overall mortality, or antibiotic adverse effects, either among all participants or when stratified among the pediatric subset. However, in the stratified analysis of five pediatric RCTs, oral outpatient management was associated with a higher rate of readmission compared

with parenteral outpatient management (RR, 0.52; 95% CI, 0.24 to 1.09; $P = .08$).[68]

Prospective pediatric trial data comparing parenteral and oral antibiotic therapy initiated within 24 hours of treatment initiation in low-risk FN are presented in Data Supplement 7.[71] Oral antibiotics used were fluoroquinolone monotherapy (seven studies; n = 581), fluoroquinolone and amoxicillin-clavulanate (three studies; n = 159), and cefixime (one study, n = 45). There were no differences in treatment failure (including modification) and no infection-related deaths among the 676 children administered oral antibiotics.[71]

## SECTION 2: ONGOING MANAGEMENT OF FN, EXCLUDING EMPIRIC ANTIFUNGAL THERAPY

## Question

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

## Recommendation

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; strong recommendation, moderate-quality evidence). Do not modify the initial empiric antibacterial regimen based solely on persistent fever in children who are clinically stable (1C; strong recommendation, low-quality evidence). In children with persistent fever who become clinically unstable, escalate the initial empiric antibacterial regimen to include coverage for resistant Gram-negative, Gram-positive, and anaerobic bacteria (1C; strong recommendation, very low-quality evidence).

## Explanation

Initial empiric antibiotics should be modified to include clinically or microbiologically documented infection. In patients who are responding to initial empiric antibiotic therapy in whom double Gram-negative coverage or empiric glycopeptide has been initiated (for example, because of clinical instability or concern about resistance), these additional antibiotics should be discontinued 24 to 72 hours after treatment initiation if there is no specific microbiologic indication to continue combination therapy. Early discontinuation is based on the rationale for initial monotherapy without the addition of aminoglycosides and empiric vancomycin as described earlier.

Empiric antibacterials should not be modified solely based on the persistence of fever in clinically stable patients; rather, modification should be based on clinical and microbiologic factors. For example, modification may occur on the basis of an evolving clinical site of infection, microbiology results including resistance profiles, or occurrence of hypotension or other signs of clinical instability. A double-blind RCT showed that the addition of vancomycin, compared with placebo, did not reduce the time to defervescence in neutropenic patients with cancer who had persistent fever 48 to 60 hours after the initiation of empiric piperacillin-tazobactam monotherapy.[73] However, only nine of 165 patients were children.

There are no trials evaluating the role of modifying initial empiric monotherapy in persistently febrile patients who become clinically unstable. The Panel recommends escalation of the initial

empiric antibiotic regimen to include coverage for resistant Gram-negative, Gram-positive, and anaerobic bacteria. In the clinically unstable child, nonbacterial etiologies such as fungi and viruses should also be considered.

## Question

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

## Recommendation

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; strong recommendation, low-quality evidence). 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; weak recommendation, moderate-quality evidence).

## Explanation

Appropriate cessation of antimicrobials is important to minimize exposure to unnecessary antibiotics. Data Supplement 8 summarizes the pediatric observational and randomized trials that describe outcomes with cessation of antibiotics.[74-93]

When pediatric studies were stratified by the status of bone marrow recovery at the time of antibiotic discontinuation, the pooled incidence of recurrent fever was 1% (95% CI, 0.1% to 5%) in children with definite marrow recovery, 5% (95% CI, 3% to 9%) where marrow recovery was not required, and 14% (95% CI, 5% to 36%) where there was no evidence of marrow recovery. Consequently, empiric antibiotics should be discontinued in patients who are clinically well with negative blood cultures who have been afebrile for at least 24 hours and who have evidence of bone marrow recovery. The pediatric studies did not set threshold criteria for evidence of marrow recovery,[75,80,83,85,86] but the Panel suggests that an absolute neutrophil count $\geq$ 100/uL postnadir is reasonable.

Pediatric patients in whom antibiotics were discontinued irrespective of bone marrow recovery were more likely to demonstrate recurrent fever and, less frequently, bacterial infection (incidence, 2%; 95% CI, 0.1% to 5%). No bacterial infectious deaths were identified among low-risk patients. One RCT[77] randomly assigned low-risk patients to either stopping or continuing antibiotics on day 3 irrespective of bone marrow status and found no difference in outcome and no infectious deaths. However, *Enterobacter aerogenes* bacteremia occurred in one child in the group who stopped antibiotics early. Thus, discontinuation of empiric antibiotics in low-risk patients at 72 hours irrespective of bone marrow status may be appropriate as long as careful follow-up is ensured.

The optimal duration of empiric antibiotics for high-risk patients with sustained bone marrow suppression is uncertain. In 1979, Pizzo et al[76] randomly assigned 33 high-risk patients age 1 to 30 years who were afebrile and neutropenic on day 7 to either continuing or stopping antibiotics. Of the 17 patients who discontinued antibiotics, seven developed infectious sequalae, and two died as a result of *Escherichia coli* bacteremia.[76] Because this single study was conducted more than 30 years ago, the optimal duration of antibiotic administration in high-risk patients represents a research gap.

# SECTION 3: EMPIRIC ANTIFUNGAL TREATMENT

## Question

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

## Recommendation

Patients at high risk for IFD are those with acute myeloid leukemia, relapsed acute leukemia, those receiving highly myelosuppressive chemotherapy for other malignancies, and allogeneic HSCT recipients with persistent fever despite prolonged ($\geq$ 96 hours) broad-spectrum antibiotic therapy and expected prolonged neutropenia ($>$ 10 days). All others should be categorized as being at low risk for IFD (1B; strong recommendation, moderate-quality evidence).

## Explanation

The risk stratification for IFD in children is based on underlying malignancy (higher risk in acute myeloid leukemia and relapsed acute leukemia) or type of HSCT (higher risk in unrelated cord blood and matched unrelated donor transplantation) as well as on certain clinical and laboratory factors (higher risk in patients with severe and prolonged neutropenia, mucositis, CVC, steroid exposure, and elevated CRP on day 4 of FN).[1,94-101] IFD low-risk patients include children with standard-risk acute lymphoblastic leukemia, lymphoma, and most solid tumors,[95,102,103] although IFDs have been described in these patients.[105] Importantly, environmental factors such as proximity to construction work also influence the risk for invasive aspergillosis.[105,106]

## Question

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

## Recommendation

Consider prospective monitoring of serum galactomannan (GM) twice per week in IFD high-risk hospitalized children for early diagnosis of invasive aspergillosis (2B; weak recommendation, moderate-quality evidence). In IFD low-risk patients, do not implement routine GM screening (1C; strong recommendation, low-quality evidence). Consider GM in BAL and cerebrospinal fluid to support the diagnosis of pulmonary or CNS aspergillosis (2C; weak recommendation, low-quality evidence). In children, do not use β-D-glucan (BG) testing for clinical decisions until further pediatric evidence has accumulated (1C; strong recommendation, low-quality evidence). In IFD high-risk children with persistent FN beyond 96 hours, perform evaluation for IFD. Evaluation should include computed tomography (CT) of the lungs and targeted imaging of other clinically suspected areas of infection (1B; strong recommendation, moderate-quality evidence). Consider CT of the sinuses in children 2 years of age or older (2C; weak recommendation, low-quality evidence).

## Explanation

*GM.* A total of 10 pediatric studies evaluated serum GM as a mycologic criterion[107] of IFD,[108-114] mostly in the setting of serial

screening in IFD high-risk patients (Data Supplement 9). The combined sensitivity and specificity of the five pediatric studies that included adequate information for individual patients and used European Organisation for Research and Treatment in Cancer/Mycoses Study Group IFD diagnostic criteria[109-112,115] were 0.76 (95% CI, 0.62 to 0.87) and 0.86 (95% CI, 0.68 to 0.95), respectively, favorably comparing with the results from a meta-analysis of GM testing in adults (0.73; 95% CI, 0.46 to 0.61 and 0.90; 95% CI, 0.88 to 0.92, respectively).[116] Although the diagnostic properties of GM testing are adequate in children, the overall effectiveness of routine GM screening in children to improve clinical outcomes is unclear, leading to a weak recommendation. It is important to note that some antibacterial compounds (such as piperacillin-tazobactam) may cause false-positive GM results in pediatric and adult patients.

In terms of GM testing in body fluids other than serum, a small pediatric study corroborated the results of a retrospective study of 99 adult IFD high-risk hematology patients[117] and suggested that BAL GM is a potentially valuable adjunctive diagnostic tool in addition to conventional microbiologic and radiologic studies.[118] Similarly, limited data suggest that detection of GM in cerebrospinal fluid can support the diagnosis of invasive aspergillosis in the CNS in both children and adults.[119,120]

*BG.* BG is included in the revised definitions of IFD by the European Organisation for Research and Treatment in Cancer/Mycoses Study Group.[107] In contrast to adults in whom BG testing has demonstrated good diagnostic accuracy for early diagnosis of IFD,[121] there are limited data in children.[122,123] Furthermore, the optimal threshold for positivity of BG testing in children is unknown. Mean BG levels are slightly higher in immunocompetent uninfected children than in adults.[124] BG should not currently be used to guide pediatric clinical decision making.

*Imaging studies.* Prospective adult studies have demonstrated that CT detects pneumonia earlier than CXR, and systematic CT scans allow earlier diagnosis of invasive pulmonary aspergillosis with a resultant improvement in prognosis.[125,126] The limited data on imaging studies in children with underlying malignancy and persistent FN[127-130] demonstrate that radiographic findings in immunocompromised children with proven pulmonary IFD are often nonspecific.[127,128] In particular, in children younger than 5 years of age, typical signs of pulmonary IFD (halo sign, air crescent sign, and cavities) are not seen in the majority of patients.

The role of routine sinus imaging (such as by CT) during prolonged FN is uncertain, and data on the frequency of accompanying symptoms of sinonasal IFD in children are scarce.[131,132] Notably, children younger than 2 years of age have not had sufficient pneumatization of the sinus cavities, and thus, sinus imaging is rarely informative in this age range. Similarly, the role of routine abdominal imaging is uncertain, and imaging of abdominal lesions may be falsely negative in neutropenic children.[133]

*Diagnostic procedures in patients with positive laboratory studies and/or imaging.* In children with positive GM or imaging studies that suggest IFD, antifungal treatment with a mold-active agent should be initiated, and further diagnostic investigation should be considered whenever possible (such as BAL and *trans*-bronchial or *trans*-thoracic biopsy in the case of pulmonary lesions).[134] However, there are no published pediatric data to identify the diagnostic procedure with the greatest yield relative to procedure-related risks in this setting.

## Question

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

## Recommendation

In neutropenic IFD high-risk children, initiate empiric antifungal treatment for persistent or recurrent fever of unclear etiology that is unresponsive to prolonged ($\geq$ 96 hours) broad-spectrum antibacterial agents (1C; strong recommendation, low-quality evidence). In neutropenic IFD low-risk children, consider empiric antifungal therapy in the setting of persistent FN (2C; weak recommendation, very low-quality evidence). Use either caspofungin or liposomal amphotericin B (L-AmB) for empiric antifungal therapy (1A; strong recommendation, high-quality evidence).

## Explanation

Three prospective trials evaluated empiric antifungal therapy in children with persistent FN (Data Supplement 10).[135-137] Caspofungin was as effective as L-AmB,[136] L-AmB was slightly more effective than amphotericin B deoxycholate (AmB-D),[135] and the efficacy of AmB-D was similar to that of amphotericin B colloidal dispersion.[137] Caspofungin was better tolerated than L-AmB, and L-AmB was less nephrotoxic than AmB-D. Results were consistent with those of much larger trials in adults.[138-140] Thus, either caspofungin or L-AmB should be used for empiric antifungal therapy in children. However, AmB-D may be considered as an alternative in settings with limited resources.

Adult guidelines recommend empiric antifungal therapy be initiated in IFD high-risk neutropenic patients after 96 hours of fever in the setting of broad-spectrum antibiotics.[1] Because of the lack of pediatric-specific data, it is reasonable to recommend a similar approach in children. Although there are almost no data to guide cessation of antifungal therapy, the Panel agrees that empiric antifungal therapy should be continued until resolution of neutropenia (absolute neutrophil count $>$ 100-500/uL) in the absence of documented or suspected IFD.

Preemptive antifungal therapy has been accepted as an alternative to empiric antifungal therapy in a subset of IFD high-risk adult neutropenic patients.[1] There are no studies evaluating this approach in children. Although a preemptive approach may be feasible in centers with adequate experience and facilities, research describing the safety and effectiveness of this approach is needed.

## DISCUSSION

We have created an evidence-based guideline for the management of pediatric FN. Some recommendations are similar to those of adult guidelines, such as choice of empiric antibacterials and criteria for their modification. Some similar recommendations have benefitted from a pediatric-specific focus, such as consideration of outpatient management and oral antibacterial therapy. However, there are key distinctions. For example, the proposed risk stratification schemas are pediatric specific, and a number of diagnostic tools such as BG testing have pediatric-specific limitations. These factors have an important impact on the care of pediatric patients. Future iterations of this

guideline will need to incorporate evolving and emerging evidence as research is conducted in pediatric FN.

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