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SPECIAL ARTICLE

Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2017 Update

Thomas Lehrnbecher, Paula Robinson, Brian Fisher, Sarah Alexander, Roland A. Ammann, Melissa Beauchemin, Fabianne Carlesse, Andreas H. Groll, Gabrielle M. Haeusler, Maria Santolaya, William J. Steinbach, Elio Castagnola, Bonnie L. Davis, L. Lee Dupuis, Aditya H. Gaur, Wim J.E. Tissing, Theo Zaoutis, Robert Phillips, and Lillian Sung

Author affiliations and support information (if applicable) appear at the end of this article.

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Corresponding author: Lillian Sung, MD, PhD, Division of Haematology/Oncology, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8; e-mail: lillian.sung@sickkids.ca.

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ABSTRACT

Purpose
To update a clinical practice guideline (CPG) for the empirical management of fever and neutropenia (FN) in children with cancer and hematopoietic stem-cell transplantation recipients.

Methods
The International Pediatric Fever and Neutropenia Guideline Panel is a multidisciplinary and multinational group of experts in pediatric oncology and infectious diseases that includes a patient advocate. For questions of risk stratification and evaluation, we updated systematic reviews of observational studies. For questions of therapy, we conducted a systematic review of randomized trials of any intervention applied for the empirical management of pediatric FN. The Grading of Recommendation Assessment, Development and Evaluation approach was used to make strong or weak recommendations and to classify levels of evidence as high, moderate, low, or very low.

Results
Recommendations related to initial presentation, ongoing management, and empirical antifungal therapy of pediatric FN were reviewed; the most substantial changes were related to empirical antifungal therapy. Key differences from our 2012 FN CPG included the listing of a fourth-generation cephalosporin for empirical therapy in high-risk FN, refinement of risk stratification to define patients with high-risk invasive fungal disease (IFD), changes in recommended biomarkers and radiologic investigations for the evaluation of IFD in prolonged FN, and a weak recommendation to withhold empirical antifungal therapy in IFD low-risk patients with prolonged FN.

Conclusion
Changes to the updated FN CPG recommendations will likely influence the care of pediatric patients with cancer and those undergoing hematopoietic stem-cell transplantation. Future work should focus on closing research gaps and on identifying ways to facilitate implementation and adaptation.

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INTRODUCTION

Fever and neutropenia (FN) is a common complication of cancer treatment. In 2012, we published a clinical practice guideline (CPG) focused on the management of FN in children with cancer and in recipients of hematopoietic stem-cell transplantation (HSCT).[1] Like all CPGs, it is important that the systematic reviews that inform the recommendations are timely, typically considered every 5 years in the absence of important new studies. Consequently, we updated the systematic reviews and present the 2017 pediatric FN CPG.

METHODS

The International Pediatric Fever and Neutropenia Guideline Panel includes representation from pediatric oncology, infectious diseases, nursing, and pharmacy, as well as a patient advocate and a guideline methodologist from 10 different countries (Data Supplement).

The methodology applied to our CPG update mirrored our 2012 FN CPG. We followed previously validated procedures for creating evidence-based

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guidelines[2] and used the Appraisal of Guidelines for Research & Evaluation II instrument as a framework.[3] Each member completed a conflict of interest form (Data Supplement). The funding agencies had no role to play in the recommendations or editing of the manuscript. The Grading of Recommendation Assessment, Development and Evaluation approach was used to generate recommendations. Details of methodology may be found in the Data Supplement.

Members were divided into working groups that focused on the three major sections addressed in the initial CPG: initial presentation, ongoing management, and empirical antifungal therapy. Given the paucity of pediatric data at the time of initial CPG development, none of the original systematic reviews were restricted to randomized controlled trials (RCTs). For the guideline update, we decided to focus on pediatric RCTs for questions related to therapy because we believed that clinical practice was unlikely to change on the basis of additional observational studies alone. For questions related to risk stratification and evaluation, the original systematic reviews were updated. The Data Supplement contains details of the search strategies, flow diagrams of study identification and selection, and eligibility criteria.

RECOMMENDATIONS AND EXPLANATIONS

Table 1 presents the 2017 recommendations, highlights changes from the 2012 FN CPG, and provides key remarks. The associated evidence profiles are illustrated in the Data Supplement when data were not published in separate manuscripts. Research gaps are presented in Table 2.

SECTION A: INITIAL PRESENTATION OF FN

Question

What clinical features and laboratory markers can be used to classify pediatric patients with FN as being at low risk or high risk of poor outcomes?

Recommendation

A1. Adopt a validated risk stratification strategy (Table 3) and incorporate it into routine clinical management (strong recommendation, low-quality evidence).

Literature update and analysis. The 2012 recommendation was derived from a systematic review[16] that demonstrated a number of schemas that varied by patients included, definitions of FN, and outcomes measured. Updating the systematic review (Data Supplement) demonstrated further validation of previously published schemas, and more small studies deriving new rules. Six clinically based low-risk stratification schemas that rely on a single assessment at presentation have been validated in different pediatric populations (Table 3). Even with further information, we remain unable to clearly recommend any single prediction rule. There remains evidence of geographical and temporal variation; thus, all schemas require local validation before use. The choice of strategy should be determined by an institution's ability to implement more complex rules and the timeliness of receipt of required components of the rule, such as C-reactive protein. Two additional risk stratification schemas including repeated measurement of biomarkers have been derived and successfully validated in their originating groups.[17,18] These use clinical assessment and IL-8 measurements for all pediatric patients[17] or IL8 and C-reactive protein for a high-risk group.[18]

Question

What clinical, laboratory, and imaging studies are useful at the initial presentation of FN to assess the cause of the episode and guide future treatment?

Recommendations

A2. Obtain blood cultures at the onset of FN from all lumens of central venous catheters (strong recommendation, low-quality evidence).

A3. Consider obtaining peripheral blood cultures concurrent with central venous catheter cultures (weak recommendation, moderate-quality evidence).

A4. Consider urinalysis and urine culture in patients in whom a clean-catch, midstream specimen is readily available (weak recommendation, low-quality evidence).

A5. Obtain chest radiography (CXR) only in patients with respiratory signs or symptoms (strong recommendation, moderate-quality evidence).

Literature update and analysis. The value of peripheral blood cultures has been addressed in nine studies,[19-27] two of which were published after 2011.[19,20] The updated estimate of the proportion of true bacteremia episodes detected by peripheral blood cultures alone, when central venous catheter cultures are negative, was 12% (95% CI, 8%–17%). Thus, peripheral cultures consistently increase the identification of true bacteremia compared with central cultures alone, which may be related to timing or volume. It is a weak recommendation because the impact of increased yield is unknown and it should be balanced against pain and isolation of contaminants.

In terms of urinalysis and urine culture to detect urinary tract infections in pediatric FN, in one study, all patients with positive urine cultures were asymptomatic,[28] strengthening the conclusion that restricting urine culture to those with symptoms is not adequate. The use of abnormal urinalysis to triage culture is also not recommended because pyuria was present in only 4% of urinary tract infection episodes during neutropenia[29] and nitrite testing in younger children (without cancer) is less discriminatory than in older patients.[30]

Two additional studies have been added to the initial systematic review[16] of the use of routine CXR during the initial assessment of pediatric FN. One was undertaken in a broad cohort of patients with FN[31] and one in children undergoing HSCT.[32] Both demonstrated rates of pneumonia of $< 3\%$ in an asymptomatic child. Asymptomatic children who did not undergo CXR had no significant adverse clinical consequences.[33] Thus, no change was made to the strong recommendation to obtain CXR only in patients with respiratory signs or symptoms.

Question

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

Recommendations

A6. In high-risk FN:

A6a. Use monotherapy with an antipseudomonal β-lactam, a fourth-generation cephalosporin, or a carbapenem as empirical therapy in pediatric high-risk FN (strong recommendation, high-quality evidence).

A6b. Reserve the 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).

Literature update and analysis. In the systematic review of RCTs of pediatric FN, we compared monotherapy with

aminoglycoside-containing combination therapy, and the results are presented in Table 4.[34] In this comparison, a rate ratio > 1 indicates that monotherapy is better than combination therapy. No significant differences in failure rates, infection-related mortality, or overall mortality were observed. Three studies were conducted solely in patients with high-risk FN,[35-37] and among these studies, no difference in treatment failure was observed (rate ratio, 1.14; 95% CI, 0.54 to 2.39; $P = .73$). However, it is important to note that these three RCTs did not evaluate monotherapy with a β-lactam against the same β-lactam plus an aminoglycoside, thus highlighting the importance of the specific monotherapy β-lactam antibiotic used. This analysis confirmed the efficacy and safety of monotherapy without the addition of aminoglycosides in treatment settings in which resistance rates were low enough to permit random assignment between monotherapy and combination therapy. Consequently, the updated CPG continues to have a strong recommendation to use empirical monotherapy in high-risk FN.

Table 1. Overall Summary of Recommendations, Changes, and Remarks

Recommendation	Change From Previous Guideline	Remarks
Initial management		
Risk stratification		
A1. Adopt a validated risk stratification strategy and incorporate it into routine clinical management (strong recommendation, low-quality evidence).	None	Strategy choice should be determined by validation in a similar context, and ability to implement based on complexity and availability of required components such as biomarkers.
Evaluation		
A2. Obtain blood cultures at the onset of FN from all lumens of central venous catheters (strong recommendation, low-quality evidence).	None	
A3. Consider obtaining peripheral blood cultures concurrent with central venous catheter cultures (weak recommendation, moderate-quality evidence).	Quality of evidence increased to moderate from low	Peripheral cultures consistently increase identification of true bacteremia compared with central cultures alone. It is a weak recommendation because the impact of increased yield is unknown and should be balanced against pain and isolation of contaminants.
A4. Consider urinalysis and urine culture in patients in whom a clean-catch, midstream specimen is readily available (weak recommendation, low-quality evidence).	None	Antibiotics should not be delayed to obtain urine specimen.
A5. Obtain chest radiography only in patients with respiratory signs or symptoms (strong recommendation, moderate-quality evidence).	None	
Treatment		
A6. In high-risk FN:		
A6a. Use monotherapy with an antipseudomonal β-lactam, a fourth-generation cephalosporin, or a carbapenem as empirical therapy in pediatric high-risk FN (strong recommendation, high-quality evidence).	Fourth-generation cephalosporin added	The Panel valued the consistency of data suggesting efficacy and safety of monotherapy in pediatric randomized trials. Monotherapy may not be appropriate for centers with a high rate of resistance, or for patients who present with hemodynamic instability.
A6b. 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).	None	Threshold for when rates of resistance are sufficiently high to support empirical combination or glycopeptide therapy has not been established and will vary by institution depending on preferences and available alternatives.
A7. In low-risk FN:		
A7a. Consider initial or step-down outpatient management if the infrastructure is in place to ensure careful monitoring and follow-up (weak recommendation, moderate-quality evidence).	None	It is a weak recommendation because institutions must have the infrastructure in place to safely implement outpatient management. Clinical outcomes were similar between strategies and thus, resources and preferences are important considerations.
A7b. Consider oral antibiotic administration if the child is able to tolerate this route of administration reliably (weak recommendation, moderate-quality evidence).	None	It is a weak recommendation because readmission may be higher among outpatients treated with oral *v* parenteral therapy, and other outcomes were similar. Thus, resources and preferences are important considerations.

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Table 1. Overall Summary of Recommendations, Changes, and Remarks (continued)

Recommendation	Change From Previous Guideline	Remarks
Ongoing management		
Modification of treatment		
B1. In patients who are responding to initial empirical antibiotic therapy, discontinue double coverage for gram-negative infection or empirical glycopeptide (if initiated) after 24 to 72 hours if there is no specific microbiologic indication to continue combination therapy (strong recommendation, moderate-quality evidence).	None	Rationale is same as that for the recommendation for initial empirical monotherapy. The Panel valued reducing unnecessary antibiotic administration to reduce toxicity, costs, and antibiotic resistance.
B2. Do not modify the initial empirical antibacterial regimen based solely on persistent fever in children who are clinically stable (strong recommendation, low-quality evidence).	None	
B3. In children with persistent fever who become clinically unstable, escalate the initial empirical antibacterial regimen to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria (strong recommendation, very low-quality evidence).	None	
Cessation of treatment		
B4. In all patients, discontinue empirical 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 (strong recommendation, low-quality evidence).	None	A specific threshold to define count recovery has not been established.
B5. In patients with low-risk FN, consider discontinuation of empirical antibiotics at 72 hours in 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 (weak recommendation, moderate-quality evidence).	None	Although safety of early discontinuation of empirical antibiotics in low-risk FN has been examined, the specific question of early discontinuation in the setting of no bone marrow recovery has not been directly addressed, thus leading to the weak recommendation.
Empirical antifungal therapy		
Risk stratification		
C1. Patients at high risk of IFD are those with AML, high-risk ALL, or relapsed acute leukemia, and children undergoing allogeneic HSCT. Children with prolonged neutropenia and children receiving high-dose corticosteroids are also at high risk of IFD. All others should be categorized as IFD low risk (strong recommendation, low-quality evidence).	Risk factors refined. Quality of evidence decreased to low from moderate	Risk stratification rules are not yet available for prediction of IFD. The Panel recognized that high-risk ALL is a heterogeneous group and this risk may be explained by prolonged neutropenia and corticosteroid administration. However, data to provide further specification around which patient with ALL is at particular risk of IFD and treatment periods of IFD risk are not available.
Evaluation		
C2. In terms of biomarkers to guide empirical antifungal management for prolonged (≥ 96 hours) FN in IFD high-risk patients:		
C2a. Consider not using serum GM (weak recommendation, moderate-quality evidence).	Previously had been weak recommendation for GM for surveillance and during FN. Now weak recommendation against GM and restricted recommendation to prolonged FN	The Panel deliberated over how GM results would be used clinically and the impact of poor positive predictive values in the setting of typical IFD rates. Poor positive predictive values mean that actions based on test results are often incorrect. High negative predictive values are less useful because GM does not rule out non-*Aspergillus* molds.
C2b. Do not use β-D-glucan. Strong recommendation, low-quality evidence	None	Poor positive predictive values and limited data in prolonged FN setting
C2c. Do not use fungal PCR testing in blood (strong recommendation, moderate-quality evidence).	New recommendation	Poor positive predictive values. Negative predictive values not sufficiently high to be clinically useful. PCR testing not yet standardized.

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Table 1. Overall Summary of Recommendations, Changes, and Remarks (continued)

Recommendation	Change From Previous Guideline	Remarks
C3. In terms of imaging for the evaluation of prolonged (≥ 96 hours) FN in IFD high-risk patients:		
C3a. Perform CT of the lungs (strong recommendation, low-quality evidence).	Quality of evidence decreased to low from moderate	Lungs consistently the most commonly affected site. Optimal timing of initial and repeated imaging not known.
C3b. Consider imaging of abdomen in patients without localizing signs or symptoms (weak recommendation, low-quality evidence).	New recommendation	Ideal imaging modality not known, but ultrasound is readily available, is not associated with radiation exposure, usually does not require sedation, and thus is likely preferable over CT or MRI.
C3c. Consider not routinely performing CT of sinuses in patients without localizing signs or symptoms (weak recommendation, low-quality evidence).	Previously had been weak recommendation for CT sinuses. Now weak recommendation against CT sinuses	Sinus imaging is frequently abnormal in prolonged FN, and abnormalities do not seem to distinguish between those with and without sinus IFD. It is a weak recommendation because studies directly addressing the usefulness of routine sinus CTs are limited.
Treatment		
C4. In IFD high-risk patients with prolonged (≥ 96 hours) FN unresponsive to broad-spectrum antibacterial agents, initiate caspofungin or liposomal amphotericin B for empirical antifungal therapy (strong recommendation, high-quality evidence).	None	
C5. In IFD low-risk patients with prolonged (≥ 96 hours) FN, consider withholding empirical antifungal therapy (weak recommendation, low-quality evidence).	Previously had been weak recommendation for empirical therapy for IFD low-risk patients. Now weak recommendation against empirical therapy for IFD low-risk patients	Single randomized trial showed similar outcomes with providing *v* withholding empirical antifungal therapy for IFD low-risk patients. However, the study was small and thus considerable imprecision exists, resulting in a weak recommendation.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CT, computed tomography; FN, fever and neutropenia; GM, galactomannan; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.

However, local epidemiology and resistance patterns should be evaluated regularly.

Table 4 also demonstrates the comparison between antipseudomonal penicillin monotherapy and fourth-generation cephalosporin monotherapy.[38-42] Five studies were included; one study[42] was identified in the updated search after publication of the FN systematic review.[34] No differences in treatment failure, infection-related mortality, or duration of fever were observed, and the point estimate for mortality was in favor of the fourth-generation cephalosporin, thus arguing for its inclusion in the empirical antibiotic recommendation. The 0.81 day increase in duration of antibiotics associated with cephalosporin therapy was not considered clinically meaningful.

Question

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?

Recommendations

A7. In low-risk FN:

A7a. Consider initial or step-down outpatient management if the infrastructure is in place to ensure careful monitoring and follow-up (weak recommendation, moderate-quality evidence).

A7b. Consider oral antibiotic administration if the child is able to tolerate this route of administration reliably (weak recommendation, moderate-quality evidence).

Literature update and analysis. In the systematic review of pediatric FN RCTs, treatment setting and route of antibiotic administration were examined[34] (Table 4). Four studies randomized patients to inpatient versus outpatient therapy[43-46]; no differences in outcomes were observed. The point estimates favored outpatient management in the mortality analyses, and no infection-related deaths were reported for the 124 randomly assigned low-risk patients treated as outpatients. It is a weak recommendation because institutions must have the infrastructure in place to safely implement outpatient management. Because clinical outcomes were similar among strategies, resources and preferences are important considerations in strategy choice.

Table 4 also lists the comparison between intravenous and oral therapy among patients treated in the same setting (n = eight studies).[47-54] There was no significant difference in treatment failure, and no infection-related mortality was reported among the 470 patients randomly assigned to receive oral empirical therapy. It is a weak recommendation because readmission may be higher among outpatients treated with oral versus parenteral therapy, and other outcomes were similar. Thus, resources and preferences are important considerations.

SECTION B: ONGOING MANAGEMENT OF FN EXCLUDING EMPIRICAL THERAPY

Question

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

Table 2. Research Gaps

Initial presentation
Optimal temperature threshold to define fever
New serum biomarkers as diagnostic and monitoring aids
Impact of viral diagnosis and the role of systemic viruses on management of FN
Appropriate monitoring and follow-up for outpatient therapy
Optimal choice of empirical antibiotics in low-risk FN
Ongoing management
Timing and necessity of repeated blood cultures for persistent fever
Duration of empirical antibiotics for low- and high-risk FN
Role of providing targeted antibiotics only *v* continuing broad-spectrum coverage in patients with positive cultures who remain neutropenic
Determining whether the diagnostic and therapeutic approach should differ between patients with prolonged continuous fever *v* recurrent fever during FN
Empirical antifungal management
Role of combination biomarkers for IFD evaluation and ongoing management
Identifying novel biomarkers for IFD detection
Role and timing of standard imaging on patient outcomes
Efficacy and safety of pre-emptive antifungal therapy*
Appropriate duration of empirical antifungal therapy
Determining appropriate pediatric dosing for currently available antifungal agents, and identifying novel antifungal agents for empirical therapy
Overall
Cost effectiveness of different approaches to manage pediatric FN

Abbreviations: FN, fever and neutropenia; IFD, invasive fungal disease.
*Defined as initiating systemic antifungal therapy initiation only on clinical, radiologic, or biomarker evidence of IFD.

Recommendations

B1. In patients who are responding to initial empirical antibiotic therapy, discontinue double coverage for gram-negative infection or empirical glycopeptide (if initiated) after 24 to 72 hours if there is no specific microbiologic indication to continue combination therapy (strong recommendation, moderate-quality evidence).

B2. Do not modify the initial empirical antibacterial regimen based solely on persistent fever in children who are clinically stable (strong recommendation, low-quality evidence).

B3. In children with persistent fever who become clinically unstable, escalate the initial empirical antibacterial regimen to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria (strong recommendation, very low-quality evidence).

Literature update and analysis. In the 2012 FN CPG, early discontinuation of combination therapy was based on the rationale for initial monotherapy without the addition of an aminoglycoside or empirical glycopeptide. As described previously, the recent systematic review confirmed the efficacy and safety of monotherapy without the addition of an aminoglycoside.[34] The evidence remains indirect because the RCTs were in the setting of initial therapy and not ongoing therapy and consequently, this reduces the evidence quality to moderate.

There were no pediatric RCTs that evaluated the role of continuing empirical glycopeptides or the appropriate course of action in patients with persistent fever who remain clinically stable or who deteriorate. Thus, there were no changes to the 2012 recommendations.

Question

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

Recommendations

B4. In all patients, discontinue empirical 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 (strong recommendation, low-quality evidence).

B5. In patients with low-risk FN, consider discontinuation of empirical antibiotics at 72 hours in 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 (weak recommendation, moderate-quality evidence).

Literature update and analysis. The 2012 CPG recommendation to discontinue antibiotics in patients with negative blood cultures who have been afebrile for at least 24 hours and who have evidence of count recovery was based on a summary of both randomized and observational trials.[55-74] In that analysis, the risk of recurrent fever was low in patients with definitive marrow recovery.

No new RCTs of antibiotic cessation were identified in our recent systematic review,[34] and thus, the recommendations have not changed. Two RCTs included in the 2012 CPG compared early cessation with continuation of empirical antibiotics.[58,75] Both studies were small and showed no differences in outcomes. However, it is notable that the two patients with bacteremia (viridans group streptococci and *Enterobacter aerogenes*) were both in the cessation arm. Importantly, a large proportion of patients in one study[75] had evidence of marrow recovery at the time of random assignment, whereas this proportion was not stated in the second study.[58] Thus, it remains a weak recommendation to discontinue antibiotics in low-risk patients who have been afebrile for at least 24 hours but who have no evidence of count recovery on Day 3, because the specific question of safety of antibiotic discontinuation without marrow recovery has not been directly addressed.

The optimal duration of empirical antibiotics for high-risk patients with sustained bone marrow suppression was not addressed in the systematic review[34] and continues to be an important research gap.

SECTION C: EMPIRICAL ANTIFUNGAL TREATMENT

Question

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

Recommendation

C1. Patients at high risk of IFD are those with acute myeloid leukemia, high-risk acute lymphoblastic leukemia (ALL), or relapsed acute leukemia, and children undergoing allogeneic HSCT. Children with prolonged neutropenia and children receiving high-dose corticosteroids are also at high risk of IFD. All others should be categorized as IFD low risk (strong recommendation, low quality evidence).

Literature update and analysis. The updated CPG was modified based on a systematic review of risk factors for IFD specifically in pediatric oncology and HSCT recipients.[75a] This review included 22 studies[76-97] and confirmed most risk factors for IFD previously described in the 2012 CPG. However, additional factors now

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

Schema-Related Factors	Rackoff[4]	Alexander[5]	Rondinelli[6]	Santolaya[7]	Ammann[8]	Ammann[9]
Patient- and disease-related factors	None	AML, Burkitt 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 or 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 ≤ 70g/L	CRP ≥ 90 mg/L, hypotension, platelets ≤ 50 g/L	Absence of clinical signs of viral infection, CRP > 50 mg/L, white blood cell count ≤ 500/μL, hemoglobin > 100 g/L	5 points for hemoglobin ≥ 90 g/L, 3 points each for white blood cell count < 300/μL, platelet < 50 g/L
Rule formulation	Absolute monocyte count ≥ 100/μL = 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 or 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*	USA, Madsen[10]	United Kingdom, Dommett[11], Arif[12]	Brazil, Rondinelli[6]	South America, Santolaya[13]	Europe, Ammann,[9] Macher,[14] Arif[12]	Europe, Miedema[15]

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CRP, C-reactive protein; CXR, chest radiography; HSCT, hematopoietic stem-cell transplantation; URTI, upper respiratory tract infection.
*Valid refers to clinically adequate discrimination of a group at low risk of complications.

Table 4. Synthesized Outcomes for Comparisons of Different Antibiotic Strategies

Comparison and Outcome	Number of Studies	Number of Episodes	Effect	95% CI	*P*
Aminoglycoside-containing combination *v* monotherapy*†					
Failure with modification included	9	672	RR 1.13	0.92 to 1.38	.23
Failure with modification excluded	4	289	RR 1.65	0.61 to 4.51	.33
Infection-related mortality	7	524	RR 1.99	0.58 to 6.85	.28
Overall mortality	3	269	RR 1.44	0.47 to 4.43	.52
Days of fever	6	546	MD -0.10	−0.88 to 0.67	.80
Days of antibiotics	4	293	MD 0.71	−1.20 to 2.61	.47
Adverse events	5	437	RR 0.93	0.54 to 1.60	.79
Antipseudomonal penicillin monotherapy *v* fourth-generation cephalosporin monotherapy†					
Failure with modification included	4	430	RR 0.95	0.75 to 1.21	.70
Infection-related mortality	4	509	RR 2.52	0.49 to 12.90	.27
Days of fever	3	296	MD -0.03	−0.96 to 0.89	.94
Days of antibiotics	3	382	MD 0.81	0.15 to 1.47	.02
Inpatient *v* outpatient management†					
Infection-related mortality	4	366	RR 1.60	0.37 to 6.88	.53
Overall mortality	3	339	RR 1.18	0.30 to 4.72	.81
Days of fever	3	228	MD -0.02	−0.81 to 0.78	.97
Days of antibiotics	4	377	MD 0.17	−0.47 to 0.82	.60
Days of hospitalization	3	340	MD 3.85	3.01 to 4.69	< .0001
Intravenous *v* oral empirical antibiotics†					
Failure with modification included	4	526	RR 0.95	0.72 to 1.24	.70
Failure with modification excluded	5	613	RR 0.65	0.28 to 1.52	.32
Infection-related mortality	7	932	No events		
Overall mortality	6	816	No events		
Readmission	5	578	RR 0.50	0.23 to 1.08	.08
Intensive care unit	4	462	No events		
Days of fever	6	758	RR 0.14	−0.27 to 0.56	.50
Adverse events	4	459	RR 0.46	0.11 to 1.92	.29

Abbreviations: MD, mean difference; RR, risk ratio.
*Only monotherapy regimens considered appropriate for high-risk fever and neutropenia included in analysis.
†MD > 0 and RR > 1 favor monotherapy (*v* combination), fourth-generation cephalosporin (*v* antipseudomonal penicillin), outpatient (*v* inpatient) and oral (*v* intravenous) therapy.

specified include high-risk ALL and high-dose corticosteroids. The Panel recognized that high-risk ALL is a heterogeneous group and that the risk of IFD may be explained by prolonged neutropenia and corticosteroid administration. However, data to provide further specification around which patient with ALL is at particular risk of IFD and the treatment phases of elevated risk are not available.

Question

What clinical features, laboratory tests, and imaging studies are useful to identify a fungal cause for persistent or recurrent FN despite broad-spectrum antibiotics?

Recommendations

C2. In terms of biomarkers to guide empirical antifungal management for prolonged (≥ 96 hours) FN in IFD high-risk patients:

C2a. Consider not using serum galactomannan (GM; weak recommendation, moderate-quality evidence).

C2b. Do not use β-D-glucan (BG; strong recommendation, low-quality evidence).

C2c. Do not use fungal polymerase chain reaction (PCR) testing in blood (strong recommendation, moderate-quality evidence).

C3. In terms of imaging for the evaluation of prolonged (≥ 96 hours) FN in IFD high-risk patients:

C3a. Perform computed tomography (CT) of the lungs (strong recommendation, low-quality evidence).

C3b. Consider imaging of abdomen in patients without localizing signs or symptoms (weak recommendation, low-quality evidence).

C3c. Consider not routinely performing CT of sinuses in patients without localizing signs or symptoms (weak recommendation, low-quality evidence).

Literature update and analysis. In the 2012 CPG, we included recommendations related to surveillance and further investigation of identified foci of infection such as lung nodules. In this CPG update, we realized that these areas were outside of the scope of the FN CPG and thus, those recommendations have been removed.

The 2017 FN CPG altered the recommendation related to GM testing based on a recently conducted systematic review of fungal biomarkers in pediatric cancer and HSCT.[98] Eight studies assessed GM as a diagnostic tool in children with symptoms potentially suggestive of IFD, such as prolonged FN.[99-106] Among these studies, seven showed positive predictive values (PPV) ≤ 75%, and four studies showed PPV < 50%. Table 5 illustrates a clinical vignette of GM testing in a population with a 10% risk of invasive aspergillosis (IA) during FN and illustrates that using the pooled sensitivity and specificity of 89% and 85% from the systematic review, PPV would be 41% and negative predictive value (NPV)

would be 97%. Among 100 patients at high risk of IA evaluated, testing would miss one patient with true infection and would erroneously conclude IA in 14 patients without infection. Of the 23 children with a positive test, only nine would actually have IA; in other words, most patients with a positive test in this clinical setting will not have IA. The basis for the weak recommendation against use of GM during FN was the poor PPV, and the limited usefulness of high NPV because GM does not rule out non-*Aspergillus* molds.

The recommendation related to BG testing remains unchanged. In the systematic review of biomarkers for IFD,[98] only one study evaluated BG in an applicable setting,[107] and it showed PPV of 49% (95% CI, 32 to 66) and NPV of 96% (95% CI, 89 to 99), precluding clinical usefulness.

The updated CPG includes a new strong recommendation against the use of fungal PCR in blood for evaluation of IFD during prolonged FN based on eight studies[99,108-114] that applied PCR in a similar setting.[109] Table 5 illustrates a clinical vignette of PCR testing in a population with a 10% risk of IFD during FN and illustrates that using the pooled sensitivity and specificity of 76% and 58% from the systematic review, PPV would be 17% and NPV would be 95%. Among 100 IFD high-risk patients evaluated, testing would miss two patients with true infection and would erroneously conclude IFD in 38 patients without infection. Of the 46 patients with a positive test, only eight would truly have IFD. The basis for the strong recommendation against use of PCR is the poor PPV and NPV, which were not sufficiently high to be clinically useful. The Panel also noted the current lack of standardization for PCR testing, which also makes clinical use challenging.

A limitation of the recommendations related to fungal biomarkers is how we approached them as diagnostic tests and evaluated their usefulness in detecting true disease. Randomized trials comparing utilization with nonutilization of these biomarkers to detect IFD would be a better approach to evaluation, but such trials are unlikely to be feasible. In fact, our current standard to recommend empirical antifungal therapy for IFD high-risk patients with prolonged fever is based on the assumption that prolonged fever is a good predictor of IFD when this factor has never been evaluated as a diagnostic test. Comparative effectiveness studies of fungal biomarker use may be the best way to bridge this knowledge gap.

Table 5. Clinical Implications of Fungal Biomarkers in the Diagnostic Setting

GM	Fungal PCR
Pooled sensitivity = 0.89	Pooled sensitivity = 0.76
Pooled specificity = 0.85	Pooled specificity = 0.58
Positive predictive value: 0.41	Positive predictive value: 0.17
Negative predictive value: 0.97	Negative predictive value: 0.95
23 children will have a positive test	46 children will have a positive test
Nine will have IA (true positives)	Eight will have IFD (true positives)
14 will not have IA (false positives)	38 will not have IFD (false positives)
77 will have a negative test	54 will have a negative test
76 will not have IA (true negatives)	52 will not have IFD (true negatives)
One will have IA (missed one of 10 with true infection)	Two will have IFD (missed two of 10 children with true infection)

NOTE. The table assumes that serum GM and fungal PCR are performed in 100 consecutive IFD high-risk patients with prolonged FN. The pretest probability (prevalence) of IFD in this high-risk population is estimated at 10% (10 patients will truly have IFD). Pooled sensitivity and specificity were obtained from a systematic review of biomarkers.[78] Predictive values were directly calculated assuming 10% prevalence of disease and using pooled sensitivity and specificity. Beta-D-glucan was not included because synthesis in FN setting was not possible, given the number of available studies.

Abbreviations: FN, fever and neutropenia; GM, galactomannan; IA, invasive aspergillosis; IFD, invasive fungal disease; PCR, polymerase chain reaction.

The data supporting recommendations related to imaging for the evaluation of IFD during prolonged FN are shown in the Data Supplement. A strong recommendation to perform lung CTs remained unchanged in the updated CPG. Of the nine studies evaluating lung CT[115-123] for the evaluation of IFD, lungs were usually the most frequent site of infection, and characteristic radiographic signs were often observed. A new weak recommendation for abdominal imaging even in the absence of localizing signs or symptoms was made with this CPG update, based on the systematic review (Data Supplement). Among the four studies included,[118,122-124] findings on imaging consistent with IFD were observed in many patients without localizing signs or symptoms. The Panel noted that the ideal imaging modality is not known, but ultrasound is readily available, is not associated with radiation exposure, and usually does not require sedation and thus, is likely preferable over CT or magnetic resonance imaging for abdominal assessment.

In the updated CPG, a revised weak recommendation against routine sinus imaging was made in the absence of localizing signs or symptoms based on the systematic review (Data Supplement). Among the five studies that described sinus findings,[118,122,123,125,126] sinus imaging was frequently abnormal in prolonged FN, and abnormalities did not distinguish between those with and without sinus IFD. It is a weak recommendation because studies directly addressing the usefulness of routine sinus CTs were limited.

Question

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

Recommendations

C4. In IFD high-risk patients with prolonged (≥ 96 hours) FN unresponsive to broad-spectrum antibacterial agents, initiate caspofungin or liposomal amphotericin B (L-AmB) for empirical antifungal therapy (strong recommendation, high-quality evidence).

C5. In IFD low-risk patients with prolonged (≥ 96 hours) FN, consider withholding empirical antifungal therapy (weak recommendation, low-quality evidence).

Literature update and analysis. Recommendations regarding the choice of empirical antifungal agents in IFD high-risk patients remain unchanged from the 2012 FN CPG, but they are changed in IFD low-risk patients. Recommendations in IFD high-risk patients were originally based on three RCTs[127-129] demonstrating that caspofungin was as effective as L-AmB,[127,128] and that L-AmB was less nephrotoxic than amphotericin B deoxycholate.[129] Either caspofungin or L-AmB was strongly recommended as empirical

antifungal therapy. One recent study prospectively compared administration of empirical antifungal therapy versus withholding empirical antifungal therapy in neutropenic children with persistent fever who were IFD low-risk. No benefit relative to fever resolution or IFD was detected from empirical antifungal therapy.[127]

No RCTs addressed empirical antifungal therapy cessation or a pre-emptive antifungal therapy approach and thus, original recommendations were unchanged. Both of these areas remain important knowledge gaps in pediatric FN.

DISCUSSION

We updated the 2012 FN CPG for children with cancer and HSCT recipients. Although most recommendations remained unchanged, some key differences emerged. Changes included the listing of a fourth-generation cephalosporin for empirical therapy, refinement of IFD risk stratification, changes in recommended biomarkers and radiologic investigations for the evaluation of IFD, and a weak recommendation to withhold empirical antifungal therapy in IFD low-risk patients.

Implementation is an important issue, and national and international guidance will be important to effect change. Adaptation will be required at the institutional level to delineate specific rather than generic antibiotic choices and to decide whether to implement or not implement weak recommendations. Decision making for weak recommendations could also be made at the specific provider or patient level. Cost-effectiveness studies may be relevant when deciding whether to implement weak recommendations.

Changes to the updated FN CPG recommendations will likely influence the care of children with cancer and pediatric patients undergoing HSCT. Future work should focus on closing research gaps and identifying ways to facilitate implementation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Thomas Lehrnbecher, Paula Robinson, Robert Phillips, Brian Fisher, Lillian Sung
Financial support: Lillian Sung
Administrative support: Paula Robinson, Lillian Sung
Collection and assembly of data: Thomas Lehrnbecher, Paula Robinson, Robert Phillips, Brian Fisher, Lillian Sung
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Affiliations

Thomas Lehrnbecher, Hospital for Children and Adolescents, Johann Wolfgang Goethe University, Frankfurt; **Andreas H. Groll**, University Children's Hospital, Muenster, Germany; **Paula Robinson**, Pediatric Oncology Group of Ontario; **Sarah Alexander**, **L. Lee Dupuis**, and **Lillian Sung**, The Hospital for Sick Children, Toronto, Ontario, Canada; **Brian Fisher** and **Theo Zaoutis**, Children's Hospital of Philadelphia, Philadelphia, PA; **Roland A. Ammann**, Bern University Hospital, University of Bern, Switzerland; **Melissa Beauchemin**, Columbia University/Herbert Irving Cancer Center, New York, NY; **Fabianne Carlesse**, Pediatric Oncology Institute, GRAACC/Federal University of Sao Paulo, Sao Paulo, Brazil; **Gabrielle M. Haeusler**, Peter MacCallum Cancer Centre, Melbourne; Monash Children's Hospital, Clayton, Victoria, Australia; **Maria Santolaya**, Hospital Luis Calvo Mackenna, Universidad de Chile, Santiago, Chile; **William J. Steinbach**, Duke University Medical Center, Durham, NC; **Elio Castagnola**, Istituto Giannina Gaslini, Genova, Italy; **Bonnie L. Davis**, High Tor Limited, Nassau, Bahamas; **Aditya H. Gaur**, St Jude Children's Research Hospital, Memphis, TN; **Wim J.E. Tissing**, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; and **Robert Phillips**, Leeds Teaching Hospital, NHS Trust, Leeds; University of York, York, United Kingdom.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Thomas Lehrnbecher
Consulting or Advisory Role: Gilead Sciences, Merck/Merck Sharp & Dohme, Astellas Pharma
Speakers' Bureau: Astellas Pharma, Gilead Sciences
Research Funding: Gilead Sciences
Travel, Accommodations, Expenses: Astellas Pharma

Paula Robinson
No relationship to disclose

Brian Fisher
Research Funding: Pfizer (Inst), Merck (Inst), Ansun BioPharma (Inst)

Sarah Alexander
No relationship to disclose

Roland A. Ammann
Travel, Accommodations, Expenses: EUSA Pharma

Melissa Beauchemin
No relationship to disclose

Fabianne Carlesse
Speakers' Bureau: Astellas, United Medical, Pfizer

Andreas H. Groll
Consulting or Advisory Role: Astellas Pharma, Basilea, Gilead Sciences, Merck Sharp & Dohme, Schering-Plough, Zeneus/Cephalon
Speakers' Bureau: Astellas Pharma, Basilea, Gilead Sciences, Merck Sharp & Dohme, Schering-Plough, Zeneus/Cephalon, Pfizer
Research Funding: Gilead Sciences, Merck Sharp & Dohme, Pfizer, Schering-Plough

Gabrielle M. Haeusler
No relationship to disclose

Maria Santolaya
No relationship to disclose

William J. Steinbach
Consulting or Advisory Role: Gilead Sciences, Merck
Research Funding: Astellas Pharma

Elio Castagnola
Consulting or Advisory Role: Basilea, Astellas Pharma, Pharmaceutica, Gilead Sciences, Pfizer
Travel, Accommodations, Expenses: Pfizer

Bonnie L. Davis
No relationship to disclose

L. Lee Dupuis
Consulting or Advisory Role: Jazz Pharmaceuticals
Research Funding: Jazz Pharmaceuticals

Aditya H. Gaur
Research Funding: Gilead Sciences (Inst)

Wim J.E. Tissing
No relationship to disclose

Theo Zaoutis
Consulting or Advisory Role: Napriva
Research Funding: Merck (Inst)

Robert Phillips
No relationship to disclose

Lillian Sung
No relationship to disclose

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