special articles

Guideline for the Management of Fever and Neutropenia in Pediatric Patients With Cancer and Hematopoietic Cell Transplantation Recipients: 2023 Update

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abstract

PURPOSE To update a clinical practice guideline (CPG) for the empiric management of fever and neutropenia (FN) in pediatric patients with cancer and hematopoietic cell transplantation recipients.

METHODS The International Pediatric Fever and Neutropenia Guideline Panel reconvened to conduct the second update of this CPG. We updated the previous systematic review to identify new randomized controlled trials (RCTs) evaluating any strategy for the management of FN in pediatric patients. Using the Grading of Recommendations Assessment, Development and Evaluation framework, evidence quality was classified as high, moderate, low, or very low. The panel updated recommendations related to initial management, ongoing management, and empiric antifungal therapy. Changes from the 2017 CPG were articulated, and good practice statements were considered.

RESULTS We identified 10 new RCTs in addition to the 69 RCTs identified in previous FN CPGs to inform the 2023 FN CPG. Changes from the 2017 CPG included two conditional recommendations regarding (1) discontinuation of empiric antibacterial therapy in clinically well and afebrile patients with low-risk FN if blood cultures remain negative at 48 hours despite no evidence of marrow recovery and (2) pre-emptive antifungal therapy for invasive fungal disease in high-risk patients not receiving antimold prophylaxis. The panel created a good practice statement to initiate FN CPG-consistent empiric antibacterial therapy as soon as possible in clinically unstable febrile patients.

CONCLUSION The updated FN CPG incorporates important modifications on the basis of recently published trials. Future work should focus on addressing knowledge gaps, improving CPG implementation, and measuring the impact of CPG-consistent care.

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INTRODUCTION

Fever and neutropenia (FN) is one of the most common complications of cancer treatments. The management of pediatric FN continues to be heterogeneous across and within centers[1-4]; this heterogeneity can be reduced through implementation of clinical practice guidelines (CPGs). CPGs are important to direct clinical care that is evidence-based, and CPG-consistent care can improve outcomes in FN.[5] Our original CPG on the management of FN in pediatric cancer and hematopoietic cell transplant (HCT) recipients was published in 2012[6] and updated in 2017.[7] The objective was to update this CPG for the empiric management of FN in pediatric patients with cancer and HCT recipients.

METHODS

Panel Constitution

The International Pediatric Fever and Neutropenia Guideline Panel continues to include representation from pediatric oncology, pediatric infectious disease, nursing, pharmacy, a patient advocate, and two CPG methodologists representing 10 different countries (Appendix Table A1, online only). Apart from the patient advocate, panel members were selected according to content or methodological expertise. Conflicts of interest were declared by each panel member; no panel member had conflicts that precluded panel participation (Appendix Table A2, online only).

General CPG Development Approach

We followed previously validated procedures for CPG creation.[8] The clinical questions addressed in the CPG update were discussed and remained unchanged from our previous CPG (Data Supplement, online only). The articulation and importance of outcomes of interest were refined by consensus and are presented in the Data Supplement. The target population consists of pediatric patients age 0-18 years receiving

ASSOCIATED CONTENT

Appendix

Data Supplement

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

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chemotherapy for cancer and recipients of HCT. The target users are health care professionals including physicians, nurse practitioners, physician assistants, microbiologists, antibiotic stewards, nurses, pharmacists, health care administrators, and other health care professionals who are concerned with infectious complications in pediatric patients receiving cancer treatments.

We used the Grading of Recommendations Assessment, Development and Evaluation approach to describe the level of evidence and to formulate recommendations.[9] Evidence quality was classified as high, moderate, low, or very low on the basis of certainty of effects as applied to our target population.[9,10] Recommendations may be strong or conditional.[9] A strong recommendation for a strategy reflects high certainty that its benefits outweigh its downsides, whereas a strong recommendation against a strategy reflects high certainty that its downsides outweigh its benefits. By contrast, a conditional recommendation is made when there is uncertainty regarding benefits and downsides of a strategy or when benefits and downsides are more closely matched.

The panel also judiciously considered making good practice statements.[11] Such statements can be made in situations where compelling indirect evidence from multiple comparisons strongly supports the benefit of the recommended action. The Grading of Recommendations Assessment, Development and Evaluation's suggested approach to recognizing a good practice statement is to ask whether the alternative action would be absurd or clearly not conform to ethical norms.[11]

Searching, Selecting, and Describing the Evidence

Although both the original 2012 CPG and 2017 CPG update used systematic reviews to inform the evidence base, the nature of those systematic reviews differed. The original CPG was based on systematic reviews and meta-analyses of nonrandomized comparisons because of the limited number of pediatric randomized controlled trials (RCTs) at that time. With the 2017 update, systematic reviews of both observational studies and RCTs were performed in acknowledgment of the increasing number of pediatric RCTs.

The approach taken in the 2023 update differed again. We hypothesized that direct, high-quality data would generally be required to substantially alter existing recommendations, and thus, we planned to restrict the systematic review to RCTs evaluating any strategy for the management of pediatric FN.

The library scientist–assisted literature search was performed in the following databases: MEDLINE including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase, Cochrane Central Register of Controlled Trials, and PubMed. The Data Supplement shows the full search strategy and details specific eligibility criteria. Titles and abstracts of articles identified by the search strategy were independently screened by two reviewers (P.D.R. and H.H.), and articles potentially meeting eligibility criteria were evaluated at full text by the same two reviewers. In the event of disagreement, adjudication was performed by a third reviewer (L.S.). The Data Supplement shows the flow diagram of study identification, selection, and reasons for exclusion. We described agreement in study inclusion using the Kappa statistic.[12]

Study characteristics abstracted are as follows: year of publication, country of study conduct, age of participants, cancer diagnosis or HCT type, and number of randomized participants. We also collected information about the intervention and control groups and outcomes considered important (Data Supplement). We used the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[13]

Statistical Analysis

Data synthesis was planned when the same strategy was evaluated by at least three studies reporting the same outcome. If a trial had three or more arms, only arms with CPG-consistent therapy[7] were selected for data extraction. For binary outcomes, synthesis used the Mantel-Haenszel method and described intervention effects using the risk ratio with 95% CI. For continuous outcomes, synthesis used the inverse variance method and described intervention effects using the weighted mean difference. A random effect model was used for all analyses. The I^2 value was also calculated, which describes the percentage of total variation across studies because of heterogeneity rather than by chance.[13] Evaluation for publication bias was restricted to synthesis including at least 10 studies and was performed through visual inspection of funnel plots. Analysis was conducted using Review Manager 5.4.[14]

Formulating Recommendations

This process began with a description of newly identified RCTs published since the 2017 CPG update. Comparisons amenable to synthesis were then analyzed using all RCTs identified in the original and updated searches, with notation of whether newly added studies enabled or revised synthesis. In situations where synthesis was not possible, we also determined if findings of individual studies were likely to influence recommendation formulation. In this event, we retrieved all RCTs addressing a specific question and evaluated them together narratively.

Evidence was reviewed during two videoconference calls held in August 2022. Modified or new recommendations and good practice statements were drafted. Panel members voted; confirmation of 2017 recommendations or acceptance of new draft recommendations or statements were approved if at least 80% of panel members agreed with them. Draft versions of the recommendations and manuscript were circulated until approved by all authors.

The publication peer-review process was used as an efficient approach to external review. We plan to update this CPG in 5 years or sooner in the event of important new information.

RECOMMENDATIONS AND EXPLANATIONS

Table 1 presents the 2023 CPG update recommendations and highlights changes from the 2017 CPG. Table 2 shows the characteristics of RCTs included in the 2017 CPG (n = 69), new RCTs identified in the 2023 CPG update (n = 10), and all RCTs informing the 2023 CPG update (n = 79). Agreement in study inclusion was excellent (Kappa = 1.0). The Data Supplement provides detailed characteristics of all 79 RCTs. The Data Supplement describes the 10 new RCTs in the 2023 CPG update with a narrative summary of each study's main findings. Table 3 shows data synthesis results. No publication bias was observed (data not shown). Table 4 summarizes identified knowledge gaps.

SECTION A: INITIAL PRESENTATION OF FN

Initial Management: Risk Stratification

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

In the 2017 CPG, this recommendation was based on a systematic review of risk stratification schemas identifying multiple rules that had been validated in pediatric populations.[7] No new RCTs were identified that evaluated risk stratification, and thus, the 2017 recommendation was unchanged.

Initial Management: Evaluation

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 (conditional recommendation, moderate-quality evidence).

A4. Consider urinalysis and urine culture in patients where a clean-catch, mid-stream specimen is readily available (conditional recommendation, low-quality evidence).

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

The previous recommendations focused on central and peripheral cultures were derived from a systematic review evaluating the contribution of peripheral cultures to bacteremia detection.[7] The conditional recommendation to obtain peripheral cultures concurrent with central venous catheter cultures was made because peripheral cultures identified bacteremia missed by central venous catheter cultures. More specifically, the proportion of true bacteremia episodes detected by peripheral blood cultures alone, when central venous catheter cultures were negative, was 12% (95% CI, 8 to 17). It was a conditional rather than a strong recommendation because the impact of increased bacteremia detection is unknown and peripheral cultures are associated with pain and isolation of skin contaminants. More specifically, centers may choose to not perform a peripheral culture as it is uncertain how often it leads to different clinical actions or better outcomes.

The previous recommendation to consider urinalysis and urine culture where patients are old enough to provide a clean-catch mid-stream specimen readily was based on a systematic review identifying that urinary tract infections were often asymptomatic.[7] It was a conditional recommendation because failure to identify urinary tract infections may not affect outcomes since empiric regimens may provide sufficient therapy to treat unidentified infection. It is important to not delay empiric antibacterial therapy to obtain urine samples. Finally, the strong recommendation to not perform a chest radiograph in asymptomatic patients was based on a systematic review, demonstrating that pulmonary infection is very rare without respiratory signs or symptoms.[7] Omitting chest radiography in asymptomatic patients was not associated with adverse consequences related to undetected pneumonia.[7]

No new RCTs were identified that examined evaluation at the onset of pediatric FN, and thus, the 2017 recommendations were unchanged.

Initial Management: Treatment

A6. In high-risk FN

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

A6b. Reserve addition of a second anti-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).

Local epidemiology and patient history of antimicrobial resistance should guide empiric antibacterial therapy choice. The updated systematic review comparing aminoglycoside-containing combination therapy versus monotherapy identified three new studies, resulting in 12 RCTs to inform this recommendation (Table 2). Table 3 shows that the revised synthesis failed to show a statistically significant difference in empiric antibacterial therapy failure, infection-related mortality, overall mortality, days of fever, or days of antibacterial therapy. Consequently, the 2017 recommendation to use monotherapy for empiric antibacterial therapy was confirmed.

In terms of specific monotherapy regimen choice, no additional studies contributed to the comparison between antipseudomonal penicillin monotherapy versus fourth-generation cephalosporin monotherapy. However, the updated systematic review was able to compare carbapenem monotherapy versus antipseudomonal penicillin monotherapy with the inclusion of two new RCTs (Table 2).

TABLE 1. Overall Summary of Recommendations and Changes From 2017 Recommendations

Recommendation	2023 Update Status
Initial management	
Risk stratification	
A1. Adopt a validated risk stratification strategy and incorporate it into routine clinical management (strong recommendation, low-quality evidence)	No new RCTs, 2017 recommendation not changed
Evaluation	
A2. Obtain blood cultures at the onset of FN from all lumens of central venous catheters (strong recommendation, low-quality evidence)	No new RCTs, 2017 recommendation not changed
A3. Consider obtaining peripheral blood cultures concurrent with central venous catheter cultures (conditional recommendation, moderate-quality evidence)	No new RCTs, 2017 recommendation not changed
A4. Consider urinalysis and urine culture in patients where a clean-catch, mid-stream specimen is readily available (conditional recommendation, low-quality evidence)	No new RCTs, 2017 recommendation not changed
A5. Obtain chest radiography only in patients with respiratory signs or symptoms (strong recommendation, moderate-quality evidence)	No new RCTs, 2017 recommendation not changed
Treatment	
A6. In high-risk FN	
A6a. Use monotherapy with an antipseudomonal β-lactam, a fourth-generation cephalosporin or a carbapenem as empiric antibacterial therapy in pediatric high-risk FN (strong recommendation, high-quality evidence)	New RCTs, 2017 recommendation confirmed
A6b. Reserve addition of a second anti-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)	New RCTs, 2017 recommendation confirmed
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 (conditional recommendation, moderate-quality evidence)	New RCTs, 2017 recommendation confirmed
A7b. Consider oral antibacterial therapy administration if the patient is able to tolerate this route of administration reliably (conditional recommendation, moderate-quality evidence)	No new RCTs, 2017 recommendation not changed
Ongoing management	
Modification of treatment	
B1. In patients who are responding to initial empiric antibacterial therapy, discontinue double coverage for Gram-negative infection or empiric glycopeptide (if initiated) after 24-72 hours if there is no specific microbiologic indication to continue combination therapy (strong recommendation, moderate-quality evidence)	No new RCTs, 2017 recommendation not changed
B2. Do not broaden the initial empiric antibacterial regimen based solely on persistent fever in patients who are clinically stable (strong recommendation, low-quality evidence)	No new RCTs, 2017 recommendation not changed
B3. In patients 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 (strong recommendation, very low-quality evidence)	No new RCTs, 2017 recommendation not changed
Cessation of treatment	
B4. In both high-risk and low-risk FN patients who have been clinically well and afebrile for at least 24 hours, discontinue empiric antibacterial therapy if blood cultures remain negative at 48 hours if there is evidence of marrow recovery (strong recommendation, low-quality evidence)	New RCTs, 2017 recommendation confirmed
B5. In patients with low-risk FN who have been clinically well and afebrile for at least 24 hours, consider discontinuation of empiric antibacterial therapy if blood cultures remain negative at 48 hours despite no evidence of marrow recovery (conditional recommendation, moderate-quality evidence) Remarks: In clinically well patients, the 48-hour blood culture evaluation refers to the initial blood culture obtained at presentation, even if a subsequent blood culture is obtained. Depending on institutional and laboratory procedures, 48-hour blood culture results may not be available until 48-72 hours or later, for example, if the sample was taken during the night and results are only reported during daytime hours	New RCTs, 2017 recommendation modified from discontinuing empiric antibacterial therapy at 72 hours to discontinuing empiric antibacterial therapy at 48 hours
Empiric antifungal therapy	
Risk stratification	

(continued on following page)

TABLE 1. Overall Summary of Recommendations and Changes From 2017 Recommendations (continued)

Recommendation	2023 Update Status
C1. IFD high-risk patients are those with acute myeloid leukemia, high-risk acute lymphoblastic leukemia or relapsed acute leukemia; those with prolonged neutropenia; those receiving high-dose steroids; and those undergoing allogeneic HCT in the first year after HCT without evidence of T-cell reconstitution, or receiving steroids or multiple immune suppressive agents to prevent or treat graft-versus-host disease. Those not meeting these criteria are categorized as IFD low-risk patients (strong recommendation, low-quality evidence)	No new RCTs, 2017 recommendation not changed
Evaluation	
C2. In terms of biomarkers to guide empiric antifungal management for prolonged (≥ 96 hours) FN in IFD high-risk patients	
C2a. Consider not using serum galactomannan (conditional recommendation, moderate-quality evidence)	No new RCTs, 2017 recommendation not changed
C2b. Do not use β-D-glucan (strong recommendation, low-quality evidence)	No new RCTs, 2017 recommendation not changed
C2c. Do not use fungal polymerase chain reaction testing in blood (strong recommendation, moderate-quality evidence)	No new RCTs, 2017 recommendation not changed
C3. In terms of imaging for the evaluation of prolonged (≥ 96 hours) FN in IFD high-risk patients	
C3a. Perform CT of lungs (strong recommendation, low-quality evidence)	No new RCTs, 2017 recommendation not changed
C3b. Considering imaging of abdomen such as ultrasound (conditional recommendation, low-quality evidence)	No new RCTs, 2017 recommendation not changed
C3c. Consider not routinely performing CT of sinuses in patients without localizing signs or symptoms (conditional recommendation, low-quality evidence)	No new RCTs, 2017 recommendation not changed
Treatment	
C4. In IFD high-risk patients with prolonged (≥ 96 hours) FN unresponsive to broad-spectrum antibacterial therapy, initiate caspofungin or liposomal amphotericin B for empiric antifungal therapy unless a pre-emptive antifungal therapy approach is chosen (strong recommendation, high-quality evidence)	No new RCTs evaluating empiric antifungal choice, 2017 recommendation modified to reflect new C5 recommendation
C5. In non-HCT IFD high-risk patients not receiving antimold prophylaxis with prolonged (≥ 96 hours) FN unresponsive to broad-spectrum antibacterial therapy, consider a pre-emptive antifungal therapy approach by deferring empiric antifungal therapy and initiating antifungal therapy only if evaluation suggests or indicates IFD (conditional recommendation, moderate-quality evidence) Remarks: The one pediatric randomized trial evaluating a pre-emptive approach excluded HCT patients. Refer to Empiric Antifungal Therapy Evaluation (recommendations C2 and C3 above) for recommendations regarding IFD evaluation. Repeated IFD evaluation and empiric antifungal therapy administration should be re-considered in the event of ongoing prolonged FN	New RCT, new recommendation
C6. In IFD low-risk patients with prolonged (≥ 96 hours) FN, consider withholding empiric antifungal therapy (conditional recommendation, low-quality evidence)	No new RCTs, 2017 recommendation not changed
GPS	
GPS1. For febrile patients who are clinically unstable, initiate FN CPG-consistent empiric antibacterial therapy as soon as possible.	New good practice statement

Abbreviations: CPG, clinical practice guideline; CT, computed tomography; FN, fever and neutropenia; GPS, good practice statement; HCT, hematopoietic cell transplantation; IFD, invasive fungal disease; RCT, randomized controlled trial.

No statistically significant differences in empiric therapy failure or days of empiric antibacterial therapy were demonstrated (Table 3). Consequently, institutions can choose an antipseudomonal β-lactam, a fourth-generation cephalosporin, or an antipseudomonal carbapenem as empiric therapy on the basis of local susceptibility patterns, costs, and medication availability. If possible, carbapenems should be reserved for clinically unstable patients.

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 (conditional recommendation, moderate-quality evidence).

A7b. Consider oral antibacterial therapy administration if the patient is able to tolerate this route of administration reliably (conditional recommendation, moderate-quality evidence).

In considering alternative treatment approaches for patients with low-risk FN, the updated systematic review identified one additional study comparing inpatient versus outpatient management (Table 2). The revised synthesis included five RCTs and demonstrated no statistically significant differences in empiric therapy failure, infection-related mortality, overall mortality, days of fever, or days of empiric antibacterial therapy (Table 3). Not surprisingly, there were 3.85 fewer days of hospitalization associated

TABLE 2. Characteristics of Included RCTs

Characteristic and Strata	RCTs in 2017 CPG, No. (%)	New RCTs in 2023 Update, No. (%)	All RCTs in 2023 Update, No. (%)
No.	69	10	79
Study population setting			
Cancer	58 (84)	8 (80)	66 (84)
HCT	1 (1)	0 (0)	1 (1)
Both	10 (15)	2 (20)	12 (15)
Fever and neutropenia risk status			
Low	13 (19)	2 (20)	15 (19)
High	8 (12)	1 (10)	9 (11)
Unclear or mixed	48 (69)	7 (70)	55 (70)
Interventions included in synthesis[a]	33	6	39
Different antibacterial regimens			
Combination *v* monotherapy	9	3	12
Antipseudomonal penicillin *v* FGC	4	0	4
Carbapenem *v* antipseudomonal penicillin	1	2	3
Carbapenem *v* FGC	3	0	3
Different setting	4	1	5
Different route of administration	8	0	8
Therapeutic colony-stimulating factor	4	0	4
Risk of bias			
Adequate sequence generation	16 (23)	7 (70)	23 (29)
Adequate allocation concealment	7 (10)	7 (70)	14 (18)
Participants and personnel blinded	10 (14)	0 (0)	10 (13)
Outcome assessors blinded	12 (17)	2 (20)	14 (18)
Lack of attrition bias	64 (93)	10 (100)	74 (94)
Free of selective reporting	53 (77)	10 (100)	63 (80)

Abbreviations: CPG, clinical practice guideline; FGC, fourth-generation cephalosporin; HCT, hematopoietic cell transplant; RCTs, randomized controlled trials.

[a]Synthesis was not conducted if there were less than three studies reporting the same outcome.

with outpatient management ($P < .001$). Consequently, the 2017 conditional recommendation to consider outpatient management for centers that have an established ambulatory program for carefully selected low-risk patients was confirmed. In addition to low-risk features, social characteristics appropriate for outpatient management include history of adherence to treatment and ability to contact the clinical team reliably and return to hospital in the case of clinical deterioration. The ideal frequency and approach to monitor low-risk FN outpatients remain uncertain, but a combination of in-person and remote follow-up evaluations may be feasible and acceptable.

The previous conditional recommendation to consider oral empiric antibacterial therapy for patients who can tolerate this route of administration reliably was based on the lack of statistically significant differences in treatment failure and days of fever between oral and intravenous therapy and the absence of mortality among those randomly assigned to oral therapy.[7] It was a conditional recommendation because of the increased risk of readmission among outpatients treated with oral compared with intravenous therapy. The updated systematic review did not identify new RCTs comparing intravenous versus oral empiric antibacterial therapy, and thus, the 2017 recommendation was unchanged. When oral outpatient therapy is planned, it is important to ensure that patients can receive oral antibacterial therapy from pharmacies or health plans expeditiously, and if there is the possibility of treatment delay or concerns with oral therapy adherence, intravenous therapy should be administered.

SECTION B: ONGOING MANAGEMENT OF FN EXCLUDING EMPIRIC ANTIFUNGAL THERAPY

Ongoing Management: Modification of Treatment

B1. In patients who are responding to initial empiric antibacterial therapy, discontinue double coverage for Gram-negative infection or empiric glycopeptide

TABLE 3. Comparisons of Different Strategies and Whether Synthesis Revised in 2023 CPG Compared With 2017 CPG

Revised Synthesis	Comparison and Outcomes	No. of Studies	No. of Episodes	Effect[a]	95% CI	I^2	*P*
Aminoglycoside-containing combination *v* monotherapy[b]							
Yes	Failure with modification included[c]	11	836	RR 1.13	0.93 to 1.38	18	.200
Yes	Failure with modification excluded	5	453	RR 1.14	0.75 to 1.72	0	.550
Yes	Infection-related mortality	9	806	RR 2.06	0.65 to 6.53	0	.220
Yes	Overall mortality	5	551	RR 1.54	0.53 to 4.43	0	.430
Yes	Days of fever	7	592	MD -0.17	–0.85 to 0.52	76	.630
Yes	Days of antibacterial therapy	5	339	MD 0.75	–0.73 to 2.23	70	.320
Antipseudomonal penicillin monotherapy *v* fourth-generation cephalosporin monotherapy[b]							
No	Failure with modification included	4	430	RR 0.95	0.75 to 1.21	0	.700
No	Infection-related mortality	4	509	RR 2.52	0.49 to 12.90	0	.270
No	Days of fever	3	296	MD –0.03	–0.96 to 0.89	0	.940
No	Days of antibacterial therapy	3	382	MD 0.81	0.15 to 1.47	4	.020
Carbapenem monotherapy *v* antipseudomonal penicillin monotherapy[b]							
Yes	Failure with modification included	3	926	RR 1.12	0.84 to 1.50	49	.440
Yes	Days of antibacterial therapy	3	926	MD 0.00	–0.37 to 0.37	0	1.000
Inpatient *v* outpatient management							
Yes	Failure with modification included	3	327	RR 1.60	0.71 to 3.60	0	.260
Yes	Infection-related mortality	5	483	RR 1.60	0.37 to 6.88	0	.530
Yes	Overall mortality	4	456	RR 1.18	0.30 to 4.72	0	.810
No	Days of fever	3	228	MD –0.02	–0.81 to 0.78	45	.970
Yes	Days of antibacterial therapy	5	494	MD 0.25	–0.11 to 0.62	20	.180
No	Days of hospitalization	3	340	MD 3.85	3.01 to 4.69	63	< .001
Intravenous *v* oral empiric antibacterial therapy							
No	Failure with modification included	4	526	RR 0.95	0.72 to 1.24	0	.700
No	Failure with modification excluded	5	613	RR 0.65	0.28 to 1.52	0	.320
No	Infection-related mortality	7	932	No events			
No	Overall mortality	6	816	No events			
No	Readmission	5	578	RR 0.50	0.23 to 1.08	0	.080
No	Intensive care unit	4	462	No events			
No	Days of fever	6	758	RR 0.14	–0.27 to 0.56	75	.500

Abbreviations: CPG, clinical practice guideline; MD, mean difference; RR, risk ratio.

[a]MD > 0 and RR > 1 favor monotherapy (*v* combination), fourth-generation cephalosporin (*v* antipseudomonal penicillin), antipseudomonal penicillin (*v* carbapenem), outpatient (*v* inpatient), and oral (*v* intravenous) therapy.

[b]Only monotherapy regimens considered appropriate for high-risk fever and neutropenia included in analysis.

[c]Treatment failure in which modification of the antibiotic regimen was included as a criterion for failure.

(if initiated) after 24-72 hours if there is no specific microbiologic indication to continue combination therapy (strong recommendation, moderate-quality evidence).

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

B3. In patients 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 (strong recommendation, very-low-quality evidence).

In the 2017 CPG, the rationale for early discontinuation of combination therapy was based on data supporting the initial administration of monotherapy for empiric antibacterial therapy. Although indirect, these data also influenced the recommendation to not modify the initial empiric antibacterial regimen based solely on persistent fever in patients who are clinically stable. Escalation of coverage in a patient who becomes clinically unstable was recommended to maximize the probability of providing effective antimicrobial therapy in the setting of sepsis or impending

sepsis. No new RCTs were identified that examined therapy modification after initiation of empiric antibacterial therapy, and thus, the 2017 recommendations were unchanged.

Ongoing Management: Cessation of Treatment

B4. In both high-risk and low-risk FN patients who have been clinically well and afebrile for at least 24 hours, discontinue empiric antibacterial therapy if blood cultures remain negative at 48 hours if there is evidence of marrow recovery (strong recommendation, low-quality evidence).

B5. In patients with low-risk FN who have been clinically well and afebrile for at least 24 hours, consider discontinuation of empiric antibacterial therapy if blood cultures remain negative at 48 hours despite no evidence of marrow recovery (conditional recommendation, moderate-quality evidence)

In the 2017 CPG, the strong recommendation to discontinue empiric antibacterial therapy with evidence of bone marrow recovery was based on a systematic review that described a very low risk of recurrent fever with this approach.[7] The updated systematic review identified two new studies evaluating discontinuation of empiric antibacterial therapy (Data Supplement). One study randomly assigned patients with low-risk FN without marrow recovery who had been afebrile for 24 hours to discontinue antibacterial therapy vs. continuing oral amoxicillin-clavulanic acid or levofloxacin.[15] Therapy cessation was noninferior to continuing oral antibacterial therapy in terms of treatment success. The second included patients with both high-risk and low-risk FN who had documented respiratory virus infection without evidence of bacterial infection and randomly assigned them to continue or discontinue antibacterial therapy after 48 hours if they had a favorable evolution. There was no significant difference in uneventful FN resolution.[16] Two patients in the group continuing antibacterial therapy experienced *Klebsiella pneumoniae* bacteremia, one of whom developed sepsis. These two studies, when considered together with the two previously identified RCTs,[17,18] suggest that empiric antibacterial therapy can be discontinued in clinically well patients with low-risk FN who have been afebrile for at least 24 hours if the initial blood culture remains negative at 48 hours, despite no evidence of marrow recovery (Data Supplement). The change from the 2017 recommendation was to consider discontinuation at 48 hours rather than 72 hours for patients with low-risk FN without evidence of marrow recovery. Defining evidence of marrow recovery remains elusive.

Although one study evaluated early antibacterial therapy discontinuation in patients with high-risk FN with a documented respiratory viral infection,[16] the panel decided against making a recommendation regarding early discontinuation in high-risk patients. This decision stemmed from a concern that such a recommendation may inadvertently promote ordering respiratory virus testing in asymptomatic patients and recognition that patients can remain positive for respiratory viruses after resolution of the acute infection. However, safety of early empiric antibacterial therapy discontinuation in patients with high-risk FN was raised as a knowledge gap (Table 4).

SECTION C: EMPIRIC ANTIFUNGAL THERAPY

Empiric Antifungal Therapy: Risk Stratification

C1. Invasive fungal disease (IFD) high-risk patients are those with acute myeloid leukemia, high-risk acute lymphoblastic leukemia or relapsed acute leukemia; those with prolonged neutropenia; those receiving high-dose steroids; and those undergoing allogeneic HCT in the first year after HCT without evidence of T-cell reconstitution, or receiving steroids or multiple immune suppressive agents to prevent or treat graft-versus-host disease. Those not meeting these criteria are categorized as IFD low-risk patients (strong recommendation, low-quality evidence).

The previous recommendation was based on a systematic review of risk factors for IFD.[19] No new RCTs were identified that evaluated risk stratification, and thus, the 2017 recommendation was unchanged.

Empiric Antifungal Therapy: Evaluation

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

C2a. Consider not using serum galactomannan (conditional recommendation, moderate-quality evidence).

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

C2c. Do not use fungal polymerase chain reaction 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 lungs (strong recommendation, low-quality evidence).

C3b. Consider imaging of abdomen such as ultrasound (conditional recommendation, low-quality evidence).

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

The 2017 recommendations focused on biomarkers for evaluation of prolonged FN were derived from a systematic review of diagnostic tests for IFD.[20] The conditional recommendation against the routine use of serum galactomannan was based on its poor positive predictive value and the limited utility of a high negative predictive value for diagnosing IFD. It is important to stress that these recommendations are applicable to patients at onset of prolonged FN before they have undergone radiologic evaluation. In patients with pulmonary infiltrates characteristic of IFD such

TABLE 4. Identified Knowledge Gaps

General
Conduct RCTs in pediatric FN addressing identified knowledge gaps
Conduct RCTs in pediatric HCT patients to better define risk groups and practices
Evaluate cost-effectiveness of different approaches to manage pediatric FN
Examine approaches to facilitate CPG implementation and increase CPG-consistent care
Evaluate the role of sequence-based testing in identifying pathogens at onset of FN and throughout the episode including during prolonged FN
Initial presentation
Evaluate the benefits and downsides of obtaining peripheral blood cultures at onset of FN
Evaluate the benefits and downsides of obtaining urine cultures at onset of FN
Evaluate the clinical impact of novel serum biomarkers for diagnosis and monitoring
In clinically well patients presenting with fever, determine whether the ideal strategy is to await neutrophil results before empiric antibacterial therapy administration
Ongoing management
Evaluate necessity and timing of repeated blood cultures for persistent fever
Determine safety of providing targeted antibacterial therapy only *v* continuing broad-spectrum coverage in patients with positive bacterial cultures and no evidence of marrow recovery
Determine safety of stopping empiric antibacterial therapy in patients with positive viral tests (such as respiratory viruses), negative blood cultures, and no evidence of marrow recovery
Determine safety of stopping empiric antibacterial therapy in patients with high-risk FN and no evidence of marrow recovery, with or without antibacterial prophylaxis
Determine whether any evidence of marrow recovery is sufficient or whether a target absolute neutrophil recovery threshold is required to stop empiric antibacterial therapy
Empiric antifungal management
Evaluate the role of combination biomarkers in IFD evaluation and ongoing management
Determine the role and timing of repeated IFD evaluation in the absence of fever resolution when empiric or pre-emptive strategies are chosen
Confirm safety of the pre-emptive approach in IFD-high risk patients
In patients receiving antimold prophylaxis with prolonged FN despite empiric antibacterial therapy, determine whether the same antifungal agent should be continued or whether antifungal coverage should be modified
Identify appropriate duration of empiric antifungal therapy

Abbreviations: CPG, clinical practice guideline; FN, fever and neutropenia; HCT, hematopoietic cell transplant; IFD, invasive fungal disease; RCT, randomized controlled trial.

as dense, well-circumscribed lesions, halo sign, air crescent sign, and cavity or wedge-shaped segmental or lobar consolidation,[21] the high pretest probability of invasive aspergillosis may enhance the clinical utility of serum galactomannan testing. The strong recommendations against routine β-D-glucan and fungal polymerase chain testing in blood were based on these tests' very poor positive predictive values (49% and 17%, respectively) and negative predictive values that were not high enough to support clinical utility (96% and 95%, respectively).

The 2017 recommendations focused on imaging for the evaluation of prolonged FN were based on a systematic review of imaging studies.[7] The strong recommendation to perform CT of lungs was made because lungs were the most frequent site of IFD and characteristic radiologic signs were often observed. The systematic review also identified that abdominal IFD may not be associated with signs or symptoms, leading to the conditional recommendation to consider imaging of the abdomen. Ultrasound is likely the preferred approach since it does not require sedation and is not associated with radiation exposure. The conditional recommendation against routine sinus CT was based on the common occurrence of abnormal sinus imaging and that abnormalities often did not distinguish between fungal and nonfungal sinusitis.

No new RCTs were identified that examined evaluations such as biomarkers or imaging at the onset of prolonged FN, and thus, the 2017 recommendations were unchanged.

Empiric Antifungal Therapy: Treatment

C4. In IFD high-risk patients with prolonged (≥ 96 hours) FN unresponsive to broad-spectrum antibacterial

therapy, initiate caspofungin or liposomal amphotericin B for empiric antifungal therapy unless a pre-emptive antifungal therapy approach is chosen (strong recommendation, high-quality evidence).

C5. In non-HCT IFD high-risk patients not receiving antimold prophylaxis with prolonged (≥ 96 hours) FN unresponsive to broad-spectrum antibacterial therapy, consider a pre-emptive antifungal therapy approach by deferring empiric antifungal therapy and initiating antifungal therapy only if evaluation suggests or indicates IFD (conditional recommendation, moderate-quality evidence).

C6. In IFD low-risk patients with prolonged (≥ 96 hours) FN, consider withholding empiric antifungal therapy (conditional recommendation, low-quality evidence).

The previous strong recommendation to initiate caspofungin or liposomal amphotericin B for empiric antifungal therapy was based on three RCTs showing that caspofungin and liposomal amphotericin B had similar efficacy[22,23] and that liposomal amphotericin B was less nephrotoxic than conventional amphotericin B.[24] Although caspofungin was the agent tested in the RCTs, other echinocandins such as micafungin are also likely appropriate. The conditional recommendation to withhold empiric antifungal therapy in IFD low-risk patients was based on a study that randomly assigned patients with persistent fever to empiric antifungal therapy versus no empiric antifungal therapy. No benefit relative to fever resolution or IFD was detected with empiric antifungal therapy administration.[22]

One new RCT randomly assigned patients with high-risk and prolonged FN to pre-emptive antifungal therapy versus empiric antifungal therapy (Data Supplement).[25] For those randomly assigned to pre-emptive therapy, evaluation included repeat blood cultures, serum galactomannan, chest and sinus CT, and abdominal ultrasound. Antifungal therapy was administered only in those with evidence of IFD. Pre-emptive therapy reduced the median duration of antifungal therapy (6 days *v* 11 days; $P < .001$) with no significant difference in the prevalence of IFD (9 of 76 *v* 9 of 73; $P = .92$). This RCT was designed before the publication of the 2017 CPG, and its IFD evaluation strategy differed from IFD evaluation recommendations C2 and C3. Given that those recommendations were derived from a large and systematically evaluated evidence base, IFD evaluation should follow recommendations C2 and C3, even when a pre-emptive strategy is chosen.

The panel believed that a pre-emptive approach was reasonable although it acknowledged that the trial might have limited generalizability as it excluded patients undergoing HCT and patients receiving voriconazole or posaconazole prophylaxis. Many IFD high-risk patients currently receive antimold prophylaxis.[26] If patients receiving antimold prophylaxis develop prolonged FN unresponsive to broad-spectrum antibacterial therapy, it is uncertain whether antifungal coverage should be modified or whether continuing the same antimold agent should be considered pre-emptive or empiric therapy. If a pre-emptive approach is used in the absence of antimold prophylaxis, antimold therapy should be started in the presence of suggestive clinical or radiologic findings (such as pulmonary nodules) without waiting for microbiologic confirmation.

GOOD PRACTICE STATEMENT

Good practice statement 1. For febrile patients who are clinically unstable, initiate FN CPG-consistent empiric antibacterial therapy as soon as possible.

With this new good practice statement, the panel recognized the urgent need for early recognition of sepsis and expeditious administration of empiric antibacterial therapy to improve survival for patients with invasive infection. Antibacterial therapy should be administered as soon as possible, while other measures to stabilize the patient are taken and should ideally occur much sooner than 1 hour after presentation. Administration of CPG-consistent empiric antibacterial therapy is important to ensure appropriate microbial coverage against potential pathogens.

The panel also deliberated making good practice statements focused on time to antibacterial therapy. For clinically well, patients with low-risk FN, some panel members preferred to err on the side of antibacterial therapy administration pending neutrophil count results. Others emphasized that administration of antibacterial therapy is associated with resistance, costs, and toxicity and thus preferred to defer antibacterial therapy administration until neutrophil count results were available. Regardless, institutions should be encouraged to expedite neutrophil count results to avoid unnecessary antibacterial therapy administration where feasible. More research is required in this area.

DISCUSSION

In this 2023 FN CPG update, changes from the 2017 CPG included two conditional recommendations regarding earlier discontinuation of empiric antibacterial therapy in clinically well and afebrile patients with low-risk FN if blood cultures remain negative at 48 hours despite no evidence of marrow recovery and pre-emptive antifungal therapy for IFD high-risk patients not receiving antimold prophylaxis. The panel also created a good practice statement to initiate FN CPG-consistent empiric antibacterial therapy as soon as possible in clinically unstable febrile patients.

This CPG is founded on direct pediatric cancer[27] or HCT data as we believed that pediatric patients could be different from adult patients in terms of their presentation, medication availability and tolerability, and risk-benefit profile when comparing different strategies. More high-

quality RCTs are required to better inform pediatric FN clinical care. CPG implementation and uptake continue to be challenging. Implementation may be improved through creation and adaptation of institution-specific care pathways[28-31] on the basis of CPGs.[32,33]

In conclusion, this updated CPG includes important modifications on the basis of recently published trials. Future work should focus on addressing knowledge gaps, improving FN CPG implementation, and measuring the outcomes of CPG-consistent care.

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Final approval of manuscript: All authors
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Guideline for the Management of Fever and Neutropenia in Pediatric Patients with Cancer and Hematopoietic Cell Transplantation Recipients: 2023 Update

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APPENDIX

TABLE A1. Guideline Panel Membership

Name	Country	Profession	Discipline
Sarah Alexander	Canada	Physician	Oncology
Rolland Ammann	Switzerland	Physician	Oncology
Melissa Beauchemin	United States	Nurse practitioner	Oncology
Fabianne Carlesse	Brazil	Physician	Infectious disease
Elio Castagnola	Italy	Physician	Infectious disease
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Priya Patel	Canada	Pharmacist	Oncology, guideline methodology
Bob Phillips	United Kingdom	Physician	Oncology
Paula Robinson	Canada	Physician	Guideline methodology
Maria Santolaya	Chile	Physician	Infectious disease
Lillian Sung	Canada	Physician	Oncology, infectious disease
Wim Tissing	The Netherlands	Physician	Oncology
Joshua Wolf	United States	Physician	Infectious disease, antibiotic stewardship

APPENDIX

TABLE A2. Guideline Panel Conflict of Interest Disclosures

Name	Conflict Declared	Details
Sarah Alexander	None	
Rolland Ammann	None	
Melissa Beauchemin	None	
Fabianne Carlesse	None	
Elio Castagnola	Yes	Received grants from Pfizer, F2G, Astellas, Gilead
Bonnie Davis	None	
Lee Dupuis	None	
Caitlin Elgarten	None	
Brian Fisher	Yes	Serves as the Chair of the Data Safety Monitoring Board for Astellas Pharmaceuticals for a phase II trial of isavuconazole Institution receives funding for research that team performs from Merck and Pfizer. Neither of these relationships are associated with the work that would be related to this guideline
Andreas Groll	Yes	Received grants from Gilead, Merck, Sharp & Dohme, and Pfizer Has served as consultant in antifungal drug development to Amplyx, Astellas, Basilea, F2G, Gilead, Merck, Sharp & Dohme, Pfizer, Scynexis, and Mundipharma
Gabrielle Haeusler	None	
Christa Koenig	None	
Thomas Lehrnbecher	Yes	Gilead Sciences, financially supported a study on pulmonary imaging in children with suspected fungal disease of the lungs Has served as consultant in antifungal drug development to Basilea, Gilead, Merck, Sharp & Dohme, Pfizer, Roche, and Mundipharma
Priya Patel	None	
Bob Phillips	None	
Paula Robinson	None	
Maria Santolaya	None	
Lillian Sung	None	
Wim Tissing	None	
Joshua Wolf	Yes	In kind research support from Karius Inc; Merck Inc Participation in industry-sponsored research; Pfizer Inc: Grant to St Jude