special articles

Guidance Statement for the Management of Febrile Neutropenia in Pediatric Patients Receiving Cancer-Directed Therapy in Central America and the Caribbean

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abstract

PURPOSE Our objective was to provide regionally appropriate, resource-conscious recommendations for the diagnosis and treatment of pediatric patients with febrile neutropenia.

METHODS A multinational panel of Central American and Caribbean clinicians who deliver pediatric oncology care prioritized clinically important questions and then used the Grading of Recommendations Assessment, Development and Evaluation methodology to provide recommendations on the selected topics.

RESULTS Twenty-two questions and 2 definitions were included in the guideline, which was intended to establish minimum care standards for pediatric patients treated in regional centers. Of all the included studies, 6.9% were conducted in low- and middle-income countries, and no studies were performed in countries represented on the panel.

CONCLUSION The panel made recommendations on the basis of existing evidence but identified important gaps in knowledge from the region and from resource-limited settings that may affect the clinical applicability of these recommendations. These deficiencies suggest a research agenda that will enable future guidelines to be more responsive to the local context.

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INTRODUCTION

Infections are the leading causes of morbidity and mortality in pediatric patients treated for cancer in low- and low-middle-income countries (LMICs).[1] A lack of process standardization contributes significantly to poor infectious outcomes. As part of the Prevencionistas e Infectólogos para Cáncer Infantil en América Latina (PRINCIPAL) network, infectious disease–associated health care providers in Central American and Caribbean countries identified the formation of a fever management guideline as a regional priority. A needs assessment survey of this network and related societies revealed management discrepancies and concern that international guidelines may not be regionally applicable because of differences in infectious etiologies and diagnostic and treatment resources (unpublished data). To address this issue, a multinational group conducted a formal guideline development process.

METHODS

Guideline development began with the establishment of a question-prioritization panel. A smaller panel was convened to make clinical practice recommendations.

Stage 1: Question Prioritization

A steering committee was formed, composed of 2 methodologists with expertise in systematic reviews/meta-analysis and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology, and 2 infectious disease content specialists.[2] Steering committee members did not vote but identified 25 questions for possible inclusion in the guideline. These were administered via Qualtrics survey software[3] to the question-prioritization panel, which was composed of 70 regional physicians providing pediatric oncology care in 8 countries. These oncologists, pediatricians, and infectious disease specialists were identified through snowball sampling. A 70% majority in favor was considered the threshold for guideline inclusion.

Stage 2: Recommendations

Search and study selection. After question prioritization, a systematic PubMed search without limits was performed to identify studies relating to each question. The content experts on the steering committee performed the final study selection.

ASSOCIATED CONTENT

Data Supplement

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

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Guideline methodology. The GRADE methodology was used.[2] A systematic review and meta-analysis was performed to synthesize evidence for each question. The findings were summarized as evidence profiles denoting the quantity and quality of evidence, along with the relative and absolute results for each outcome. Eleven clinicians specializing in infectious diseases in pediatric oncology and representing all participating countries served as panelists for guideline development. Before voting on recommendations, a formal session was conducted to refresh panel members' knowledge of GRADE methodology and the guideline development process. For each question, the panel members first voted for or against the recommendation and then the strength of the recommendation (strong *v* weak). No formal assessment of patient values/preferences or costs was conducted. However, it was assumed that the recommendations were feasible across regional practice settings and would not burden existing resources.

RESULTS

Question Prioritization

Forty of the 70 participants (57%) completed the prioritization survey. Forty-three percent were oncologists, 32% were infectious disease specialists, and 25% were general pediatricians. They represented Costa Rica, the Dominican Republic, El Salvador, Guatemala, Haiti, Honduras, Nicaragua, and Panama (Table 1). Twenty-two topics and 2 definitions were selected for inclusion in the guideline.

Systematic Review

Studies conducted in LMICs comprised 6.9% of studies included in the final evidence review. None of the included studies were performed in countries represented by panelists. Evidence reviews are provided in the Data Supplement, and Table 2 summarizes the panel recommendations.

Definitions

Fever. The panel defined fever as an oral temperature of 38.3°C measured once or an oral temperature of ≥ 38°C measured twice at timepoints an hour or more apart. The panel members recognized the importance of specifying an axillary temperature because axillary measurements are commonly used in their practices. However, no consensus was reached on using the axillary temperature corresponding to the selected oral temperature (37.7°C if corrected by the usual parameters) or the axillary temperature of 38.5°C used by the Sociedad Latinoamericana de Infectología Pediátrica.[4]

Neutropenia. The panel defined neutropenia as an absolute neutrophil count (ANC) of < 500 cells/mm^3 or an ANC expected to fall below 500 cells/mm^3 within 48 hours.

RECOMMENDATIONS

1. The panel RECOMMENDS obtaining peripheral blood cultures in addition to blood cultures from central lines at the time of the episode of pediatric febrile neutropenia (Quality of evidence: moderate; Strength of recommendation: strong).

Nine studies (10,958 cultures), none of which were performed in an LMIC, addressed this issue.[5-14] The pooled proportion of additional positive patients identified on peripheral blood cultures was 14% (95% CI, 11% to 18%). The heterogeneity among the included studies was high (I^2, 65%; Data Supplement). Although some studies reported the number of patients testing positive with both peripheral and central line cultures, only 2 focused on concordance or the occurrence of false negatives, which is required for completeness of evidence.[8,11]

Panel deliberations. Obtaining both central and peripheral blood cultures may differentiate infection from contamination and primary bacteremia from catheter-related bloodstream infection through differential time to positivity between automated blood cultures. These distinctions affect treatment decisions, including antibiotic administration and catheter removal. The panel cannot recommend obtaining cultures from all lumens of all catheters based on available evidence because the studies reviewed did not specify the number of cultured lumens. Additionally, this practice may be prohibitively expensive in resource-limited settings.

2. The panel RECOMMENDS routinely obtaining urinalysis and urine cultures for pediatric patients with febrile neutropenia (Quality of evidence: low; Strength of recommendation: weak).

Eight studies addressed this issue[15,16]: 2 performed in 84 pediatric oncology patients with febrile neutropenia (112 specimens) and 6 performed in 2,506 pediatric patients (2,705 specimens).[16,17] Only 1 study was performed in an LMIC. The study that included asymptomatic patients with cancer reported the sensitivity, specificity, and negative predictive value of urinalysis as 40%, 94%, and 94%, respectively, and the corresponding values for urine culture as undefined, 100%, and 91%, respectively.[17] The 6 studies in pediatric patients focused on the diagnostic performance of leukocyte esterase and/or nitrite for diagnosing urinary tract infections (Data Supplement).[15]

Panel deliberations. Urinalysis should be combined with clinical presentation to determine the need for culture. Both urinalysis and culture are recommended for suspected urinary tract infection; however, the utility of urinalysis for pyuria is lower for neutropenic patients. Testing may not be indicated for asymptomatic older children.

3. The panel RECOMMENDS obtaining chest radiography for pediatric patients with febrile neutropenia only if they have respiratory symptoms (Quality of evidence: moderate; Strength of recommendation: strong).

Six studies addressed this issue (559 patients; 759 episodes)[18-20]; none was performed in an LMIC. The

TABLE 1. Characteristics of the Prioritization and Clinical Practice Recommendations Panel

Characteristic	Value
Characteristics of the prioritization panel members (n = 41)	
Clinical specialty	
Pediatric infectious diseases	32 (13)
Pediatric oncology	41 (17)
Pediatrics	27 (11)
Location of practice	
Panama	29 (12)
Dominican Republic	20 (8)
Costa Rica	10 (4)
El Salvador	10 (4)
Guatemala	10 (4)
Haiti	10 (4)
Honduras	7 (3)
Nicaragua	5 (2)
Characteristics of the members of the clinical practice recommendations panel (n = 11)	
Sex	
Male	45 (5)
Female	55 (6)
Mean years in practice (SD)	9 (7.8)
Clinical specialty	
Pediatric infectious diseases	64 (7)
Pediatric oncology	9 (1)
Pediatrics	27 (3)
Location of practice	
Panama	9 (1)
Dominican Republic	9 (1)
Costa Rica	9 (1)
El Salvador	18 (2)
Guatemala	18 (2)
Haiti	9 (1)
Honduras	18 (2)
Nicaragua	9 (1)

NOTE. Data are % (No.) unless otherwise specified.
Abbreviation: SD, standard deviation.

sensitivity of chest radiography ranged from 57% to 100%, and specificity ranged from 39% to 96%. Pneumonia prevalence in these studies varied from 1.9% to 7.5%, and the post-test probabilities ranged from 12% to 34% (Data Supplement).

Panel deliberations. Chest-x-rays may direct therapy in patients with respiratory symptoms; however, radiographic findings may be nonspecific. Additionally, pneumonia can be diagnosed clinically, and the panel emphasized the need to know the local pneumonia prevalence to best apply this recommendation.

4. The panel RECOMMENDS incorporating a risk-stratification strategy into the routine management of pediatric febrile neutropenia (Quality of evidence: low; Strength of recommendation: strong).

The search identified 15 rules for risk stratification. Ten were validated in a cohort other than the development cohort. The 12 total validation cohorts enrolled a total of 5,184 patients. Two of 12 validation studies (17%) were performed in LMICs, and the evidence from these studies was limited. The prevalence of low-risk febrile neutropenia ranged from 2.7% to 87% in the validation cohorts. Furthermore, several studies used the same cohort to validate multiple risk-stratification rules. In some instances, the validation outcomes differed from those used to develop the tool in the derivation cohort (Data Supplement).

Panel deliberations. There was significant heterogeneity in the clinical outcomes collected and the results from derivation and validation of the risk-stratification schema. No risk-stratification evaluations were performed in Central American or Caribbean nations. For this recommendation, the panel voted only on the perceived utility of a risk-stratification system to direct management. Given the inconsistent performance of tools across cohorts and uncertainty regarding the similarity of the tested to the target populations, each site is advised to select a rule based on the resources, particularly laboratory studies, available for stratification and the comparability of the populations used to derive the rules.

5. The panel RECOMMENDS monotherapy with an antipseudomonal beta-lactam, a fourth-generation cephalosporin, or a carbapenem for pediatric patients with high-risk febrile neutropenia (Quality of evidence: low; Strength of recommendation: strong).
6. The panel RECOMMENDS adding a second gram-negative agent only for patients who are clinically unstable, when a resistant infection is suspected, or at centers with a high rate of resistant pathogens (Quality of evidence: very low; Strength of recommendation: weak).
7. The panel RECOMMENDS adding a glycopeptide only for patients who are clinically unstable, when a resistant infection is suspected, or at centers with high rates of resistant pathogens (Quality of evidence: very low; Strength of recommendation: weak).

A total of 47 studies reported data from 5,525 episodes of febrile neutropenia in pediatric patients.[21-23] Five studies (485 episodes) were conducted exclusively in children with high-risk febrile neutropenia. Other studies had mixed risk groups of patients; therefore, conclusive evidence relating to other risk groups was unavailable. The recommendations for these groups are based on indirect inference from high-risk or mixed populations. Four studies (9%) were performed in LMICs. Pooled results involving high-risk groups showed no significant difference between monotherapy and combination therapy with regard to treatment success

TABLE 2. Summary of Recommendations

No.	Recommendation	Strength of Recommendation	Quality of Evidence	Studies in LMIC Setting (No.)
	Diagnosis			
1	The panel **recommends** obtaining peripheral blood cultures in addition to blood cultures from central lines at the time of the episode of pediatric febrile neutropenia.	Strong	Moderate	9 HIC
2	The panel **recommends** routinely obtaining urinalysis and urine culture for pediatric patients with febrile neutropenia.	Weak	Low	1 UMIC
				7 HIC
3	The panel **recommends** obtaining chest radiography for pediatric patients with febrile neutropenia only if they have respiratory symptoms.	Strong	Moderate	6 HIC
	Initial Management			
4	The panel **recommends** incorporating a risk-stratification strategy into the routine management of pediatric febrile neutropenia.	Strong	Low	2 LMIC
				3 UMIC
				19 HIC
5	The panel **recommends** monotherapy with an antipseudomonal beta-lactam, a fourth-generation cephalosporin, or a carbapenem in pediatric patients with high-risk febrile neutropenia.	Strong	Low	2 LMIC
				8 UMIC
				3 HIC
6	The panel **recommends** adding a second gram-negative agent only for patients who are clinically unstable, when a resistant infection is suspected, or at centers with a high rate of resistant pathogens.	Weak	Very low	1 LMIC
				7 UMIC
				1 HIC
7	The panel **recommends** adding a glycopeptide only for patients who are clinically unstable, when a resistant infection is suspected, or at centers with high rates of resistant pathogens.	Weak	Very low	1 LMIC
				7 UMIC
				2 HIC
8	The panel **recommends** using outpatient management for low-risk pediatric patients with febrile neutropenia if the infrastructure is in place for careful monitoring and follow-up.	Weak	Low	3 HIC
9	The panel **recommends** either oral or intravenous administration as the route of antibiotic therapy in patients with low-risk febrile neutropenia.	Strong	Moderate	1 LMIC
				2 UMIC
				5 HIC
	Modifications to Initial Therapy			
10	The panel **recommends** escalating the initial empirical antibacterial regimen in persistently febrile patients to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria in pediatric patients with febrile neutropenia who become clinically unstable.	Weak	Very low	Unclear
11	The panel **recommends** de-escalation to monotherapy after 48 to 72 hours for stable pediatric patients who are responding to initial antibiotic therapy in the absence of a clinical or microbiologic indication to continue a second agent.	Weak	Very low	Unclear

(Continued on following page)

TABLE 2 Summary of Recommendations (Continued)

No.	Recommendation	Strength of Recommendation	Quality of Evidence	Studies in LMIC Setting (No.)
12	The panel **recommends** no change in the initial empirical antibacterial regimen in pediatric patients with febrile neutropenia who are clinically stable except for persistent fever.	Weak	Very low	Unclear
13	The panel **recommends** stopping empirical antibiotics in high-risk pediatric patients with febrile neutropenia who have negative blood cultures at 48 hours, are afebrile for at least 24 hours, and have evidence of marrow recovery.	Strong	Low	3 HIC
14	The panel **recommends** stopping empirical antibiotics in low-risk pediatric patients with febrile neutropenia who have negative blood cultures at 72 hours, have assured follow-up, and are afebrile for at least 24 hours, regardless of marrow recovery status.	Strong	Moderate	3 HIC
15	The panel **recommends** early discharge (within 24-36 hours) for low-risk pediatric patients with febrile neutropenia who have negative blood cultures at 24-36 hours and have been afebrile for at least 24 hours, regardless of marrow recovery status, provided follow-up is reliable.	Strong	Low	2 HIC
16	The panel **recommends** early discharge (within 72 hours) for high-risk pediatric patients with febrile neutropenia who have negative blood cultures at 48 hours, have been afebrile for at least 24 hours, and have evidence of marrow recovery, provided that follow-up is reliable.	Weak	Low	1 LMIC
	Management of Prolonged Fever (≥ 96 hours)			
17	The panel **does not recommend** using galactomannan for diagnosis in pediatric patients with febrile neutropenia who are at high risk for invasive fungal disease.	Strong	Moderate	3 LMIC 5 HIC
18	The panel **does not recommend** routinely performing CT of the lungs of pediatric patients with febrile neutropenia, without localizing signs or symptoms, who are at high risk for invasive fungal infection.	Strong	Very low	2 UMIC 7 HIC
19	The panel **does not recommend** routinely performing imaging of the abdomen in pediatric patients with febrile neutropenia, without localizing signs or symptoms, who are at high risk for invasive fungal infection.	Strong	Very low	3 HIC
20	The panel **does not recommend** routinely performing CT of the sinuses in pediatric patients with febrile neutropenia, without localizing signs or symptoms, who are at high risk for invasive fungal infection.	Strong	Very low	4 HIC
21	The panel **recommends** caspofungin or liposomal amphotericin B as empirical antifungal therapy in pediatric patients at high risk for fungal disease.	Strong	Low	4 HIC
22	The panel **does not recommend** initiating antifungal therapy in pediatric patients with febrile neutropenia who are at low risk for invasive fungal infection.	Weak	Very low	4 HIC

Abbreviations: CT, computed tomography; HIC, high-income country; LMIC, low-middle-income country; UMIC, upper-middle-income country.

with and without regimen modification, overall mortality, and overall adverse events. Furthermore, 5 studies compared piperacillin/tazobactam with second-generation cephalosporin monotherapy, and the pooled results showed no difference in treatment success, infection-related mortality, or mean days of fever. In a direct comparison, cefepime treatment was favored for the outcome of mean duration of antibiotic treatment because the duration of piperacillin/tazobactam treatment was 0.9 days longer (95% CI, 0.3 to 1.49 days longer). Five studies compared meropenem with other empirical monotherapy in pediatric patients with febrile neutropenia, and the pooled results showed no difference with regard to treatment success, infection-related mortality, mean days of fever, or mean days of antibiotic therapy (Data Supplement).

Panel deliberations. The panel recommends reviewing institutional antibiograms to determine the most appropriate monotherapy. Evidence to establish the proportion of circulating strains that should be susceptible to the monotherapy agent is currently insufficient. The development of resistance was considered a critical outcome, but was not evaluated in these studies. Based on the biologic plausibility of resistance development, the panelists recommend that carbapenems be used only in patients at high risk for infection with cephalosporin/beta-lactam–resistant bacteria or in patients presenting with severe clinical illness.

The lack of evidence defining a "high rate" of resistant pathogens and unclear clinical definitions of stability versus instability limit the usefulness of these recommendations. Gram-negative bacteria resistant to monotherapy options may have high prevalence in guideline countries. Additional coverage may be warranted in patients developing infection while on broad-spectrum antibiotics or with past infection/colonization with resistant bacteria. In practice, a glycopeptide is often added in a patient with skin/soft tissue infection or recent chemotherapy with potential for mucosal damage. Clinical discretion is therefore advised when choosing the initial regimen and subsequent modifications.

8. The panel RECOMMENDS using outpatient management for low-risk pediatric patients with febrile neutropenia if the infrastructure is in place for careful monitoring and follow-up (Quality of evidence: low; Strength of recommendation: weak).

Three studies addressed this issue (186 patients; 248 episodes of febrile neutropenia),[21,24-26] but none was performed in an LMIC. Pooled results showed no significant difference between outpatient and inpatient management with regard to treatment success, overall mortality, and treatment duration (Data Supplement).

Panel deliberations. Recommendation implementation is dependent on the infrastructure available to support outpatient antibiotic administration and follow-up, along with individual and social characteristics. This recommendation may decrease hospitalizations, but requires staffing and resources to support close follow-up. The clinician must select patients for outpatient management cautiously.

9. The panel RECOMMENDS either oral or intravenous administration as the route of antibiotic therapy in patients with low-risk febrile neutropenia (Quality of evidence: moderate; Strength of recommendation: strong).

Eight studies addressed this issue (763 patients; 1,049 episodes of febrile neutropenia)[21]; only 1 was performed in an LMIC. Pooled results showed no significant difference between oral and intravenous therapy with regard to treatment failure, mean days of fever, and neutropenia (Data Supplement).

Panel deliberations. The evidence indicates no significant difference in clinical outcomes with oral versus intravenous therapy. The route should be selected by considering patient and family preferences, along with the feasibility of oral antibiotic administration.

10. The panel RECOMMENDS escalating the initial empirical antibacterial regimen in persistently febrile patients to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria in pediatric patients with febrile neutropenia who become clinically unstable (Quality of evidence: very low; Strength of recommendation: weak).

For evidence and panel deliberations, please refer to recommendations 5-7.

11. The panel RECOMMENDS de-escalation to monotherapy after 48 to 72 hours for stable pediatric patients who are responding to initial empirical antibiotic therapy in the absence of a clinical or microbiologic indication to continue a second agent (Quality of evidence: very low; Strength of recommendation: weak).

A literature review found no randomized controlled trials to inform this recommendation.

Panel deliberations. The panel prioritized the prevention of antibiotic-associated toxicities and the development of resistance and therefore recommends stopping glycopeptides or the second of 2 gram-negative–directed agents (usually an aminoglycoside) without a clear indication to continue therapy. The panel could not determine the optimal duration of combination therapy and recommends following institutional practices.

12. The panel RECOMMENDS no change to the initial empirical antibacterial regimen in pediatric patients with febrile neutropenia who are clinically stable except for persistent fever (Quality of evidence: very low; Strength of recommendation: weak).

A literature review found no randomized controlled trials to inform this recommendation.

Panel deliberations. The panelists considered the potential for antibiotic-associated adverse effects and development

of antibiotic resistance, and agreed that the persistence of fever alone is insufficient justification for antimicrobial changes.

13. The panel RECOMMENDS stopping empirical antibiotics in high-risk pediatric patients with febrile neutropenia who have negative blood cultures at 48 hours, are afebrile for at least 24 hours, and have evidence of marrow recovery (Quality of evidence: low; Strength of recommendation: strong).
14. The panel RECOMMENDS stopping empiric antibiotics in low-risk pediatric patients with febrile neutropenia who have negative blood cultures at 72 hours, have assured follow-up, and are afebrile for at least 24 hours, regardless of marrow recovery status (Quality of evidence: moderate; Strength of recommendation: strong).

Three studies, none performed in an LMIC, addressed this issue in the low-risk population (139 patients).[21,27-29] The recommendation for the high-risk population is based on indirect inference from the low-risk population. Pooled results showed no significant difference between early discontinuation and continuation of treatment with regard to overall mortality, hospital readmission, favorable clinical outcome, or any adverse events (Data Supplement).

Panel deliberations. The panel valued the avoidance of antibiotic-associated adverse effects and the development of antibiotic resistance. The definition of bone marrow recovery was not consistent across studies; therefore, the panel recommends that clinicians follow institutional definitions. A shorter duration of empirical therapy may be possible under favorable clinical circumstances.

15. The panel RECOMMENDS early discharge (within 24-36 hours) for low-risk pediatric patients with febrile neutropenia who have negative blood cultures at 24-36 hours and have been afebrile for at least 24 hours, regardless of marrow recovery status, provided follow-up is reliable (Quality of evidence: low; Strength of recommendation: strong).

Two studies addressed this issue in a low-risk population (159 patients; 211 episodes).[25,30,31] Neither was performed in an LMIC. Pooled results showed no significant difference between early discharge and continued hospitalization with regard to overall mortality, treatment success, and treatment duration (Data Supplement).

Panel deliberations. The panel considered all patients, regardless of risk category, because few studies were performed in pediatric patients and different stratification scales were used. Furthermore, recommendations for oral therapy and antibiotic discontinuation are not synonymous with patient discharge. Outpatient therapy presents significant risks for some patients because of unhygienic living conditions and geographic inaccessibility. Patient and family preferences must also be considered.

16. The panel RECOMMENDS early discharge (within 72 hours) for high-risk pediatric patients with febrile neutropenia who have negative blood cultures at 48 hours, have been afebrile for at least 24 hours, and have evidence of marrow recovery, provided that follow-up is reliable (Quality of evidence: low; Strength of recommendation: weak).

One study addressed this issue in a high-risk population (129 episodes of febrile neutropenia) and was performed in an LMIC.[30,32] The results showed no significant difference between early discharge and continued hospitalization with regard to overall mortality, treatment success, and treatment duration (Data Supplement).

Panel deliberations. Considerations for the high-risk population were similar to those for the low-risk population, except that the discharge criteria were modified based on clinical judgment. The panelists recommend a longer inpatient observational period to assure clinical improvement.

17. The panel DOES NOT RECOMMEND using galactomannan for diagnosis in pediatric patients with febrile neutropenia who are at high risk for invasive fungal disease (Quality of evidence: moderate; Strength of recommendation: strong).

Eight studies addressed this issue (733 patients).[33] Three of these studies (38%) were performed in an LMIC. The sensitivities ranged from 35% to 100%, and specificities ranged from 14% to 100%. The results were associated with wide 95% CIs (0% to 31%), indicating a lack of precision (Data Supplement).

Panel deliberations. Panelists were concerned about the high risk of bias in the included studies. The clinical question was whether the test should be performed in patients with prolonged fever as the sole manifestation of illness. This population of interest was not represented in the validation cohorts.

The sparse literature on fungal infections in LMICs is a key limitation of all antifungal diagnosis and management recommendations. Whether the high-risk criteria for fungal infection described in the literature from high-income countries are extrapolatable to the settings served by the guideline audience remains unclear. Differences in immunosuppressive regimens, fungal prophylaxis, and fungal epidemiology may affect the applicability of these criteria. For these recommendations, the panel assumed published high-risk criteria (acute myeloid leukemia, high-risk acute lymphoblastic leukemia, relapsed leukemia, and receipt of an allogenic hematopoietic stem cell transplantation [HSCT]), while noting that HSCT is not routinely performed in their practice settings.[34]

18. The panel DOES NOT RECOMMEND routinely performing computed tomography (CT) of the lungs of pediatric patients with febrile neutropenia, without

localizing signs or symptoms, who are at high risk for invasive fungal infection (Quality of evidence: very low; Strength of recommendation: strong).

Nine studies addressed this issue (687 patients),[33] but none was performed in an LMIC. All were nonrandomized, without extractable data, and provided very limited evidence relating to the utility of CT of the lungs (Data Supplement).

Panel deliberations. Nonresponsiveness to antibacterial therapy is a prerequisite to recommending imaging. Based on the adult literature, the panel specified that fungal work-up would be initiated only after 96 hours of failure to respond to antibacterial agents; however, the lack of pediatric data for the timepoint is a major limitation.

19. The panel DOES NOT RECOMMEND routinely performing imaging of the abdomen in pediatric patients with febrile neutropenia, without localizing signs or symptoms, who are at high risk for invasive fungal infection (Quality of evidence: very low; Strength of recommendation: strong).

Three studies, none performed in an LMIC, addressed this issue (408 patients).[33] All were nonrandomized without extractable data, resulting in limited evidence to inform a recommendation regarding the utility of imaging the abdomen (Data Supplement).

Panel deliberations. Panelists stated a preference for abdominal ultrasound rather than CT scans for fungal work-up because of the lower cost, ease of access, and reduced radiation exposure; however, the paucity of evidence comparing these modalities prevented a recommendation of this modality.

20. The panel DOES NOT RECOMMEND routinely performing CT of the sinuses in pediatric patients with febrile neutropenia, without localizing signs or symptoms, who are at high risk for invasive fungal infection (Quality of evidence: very low; Strength of recommendation: strong).

Four studies, none performed in an LMIC, addressed this issue (219 patients).[33] The data were not extractable (Data Supplement).

Panel deliberations. In the study populations, sinus radiographs were frequently abnormal, and CT findings correlated poorly with the diagnosis of invasive fungal infection. It was not possible to make informed conclusions as to whether CT reveals occult fungal rhinosinusitis in patients without facial or nasal symptoms. The value of endoscopy versus CT was not directly evaluated in the target population.

21. The panel RECOMMENDS caspofungin or liposomal amphotericin B (L-AmB) as empirical antifungal therapy in pediatric patients at high risk for fungal disease (Quality of evidence: low; Strength of recommendation: strong).

Four studies, none performed in an LMIC, addressed this issue in the high-risk or mixed population (389 patients).[35-38] Pooled results comparing caspofungin and L-AmB showed no significant difference in the outcomes of response to treatment, any serious adverse events, and renal toxicity (Data Supplement).

Panel deliberations. The available evidence supports the use of an echinocandin or L-AmB; however, these options are costly. The biologic mechanism supports the use of amphotericin B deoxycholate as an alternative to L-AmB; however, there has been no direct efficacy trial of L-AmB versus amphotericin B deoxycholate in analogous clinical scenarios. The toxicity profile of amphotericin B deoxycholate exceeds that of L-AmB and would be unacceptable in a setting with access to the latter formulation, but the panel agreed that treatment with amphotericin B deoxycholate is preferable to no treatment if less-toxic broad-spectrum antifungals are unavailable. The optimal timing for empirical antifungal therapy in pediatric patients is unclear. Without a clinical syndrome suggestive of fungus, panelists recommend initiating antifungal therapy if patients are at high risk for fungal infection and remain febrile despite 96 hours of broad-spectrum antibacterial therapy.

22. The panel DOES NOT RECOMMEND initiating antifungal therapy in pediatric patients with febrile neutropenia who are at low risk for invasive fungal infection (Quality of evidence: very low; Strength of recommendation: weak).

Literature review yielded no studies directly addressing this question (Data Supplement).

Panel deliberations. Indirect evidence from studies in patients at high risk for fungal infection, along with clinical judgment, informed this recommendation. The panel considered the toxicity of antifungal therapies and the likelihood of fungal infection in a low-risk population. Limitations include the lack of validated criteria for categorizing patients as being at low risk for fungal infection within a comparable population.

DISCUSSION

A Central American and Caribbean clinician panel generated an evidence-based guideline for managing febrile neutropenia in children receiving cancer-directed therapy. The represented countries spanned World Bank categories (1 high-income country, 3 upper-middle-income countries, 3 LMICs, and 1 low-income country), but panelists were mindful of regional resource constraints. This guideline was intended to establish minimum standards of care that some centers may exceed. The systematic review yielded a paucity of evidence within LMICs and no evidence generated within the region. This highlights the need to build systems for standardized data collection to generate LMIC-specific evidence that can inform decision making.

Panel recommendations are concordant with other guidelines, which illustrates the reproducibility of GRADE methodology.[4,34,39,40] The few differences, including stronger recommendations against fungal diagnostics and imaging,

may reflect greater awareness of cost/resource use by LMIC providers. Panelists expressed the view that recommendations should be used to advocate for interventions if these are strongly supported by evidence, even if cost and access barriers prohibit implementation. It will be important to study guideline adherence and identify reasons for nonadherence to inform future efforts and revisions.

In summary, there are several conclusions from this guideline development process. First, GRADE methodology can be used to develop evidence-based guidelines regardless of the geographic or economic setting. Second, when presented with similar evidence, informed clinicians will make similar recommendations. These recommendations should be used for shared decision making, with consideration for patient values and preferences. Finally, the process demonstrated that a systematic evaluation of evidence is important for decision making, but its clinical utility is limited by the available evidence. A key outcome of this process was the identification of research priorities to enable decision making to respond to regional and resource needs.

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