

CLINICAL PRACTICE GUIDELINE OPEN ACCESS

Evidence-Based Clinical Practice Guidelines for the Management of Pediatric Febrile Neutropenia: Resource-Sensitive Recommendations for the Asian Continent

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ABSTRACT

Febrile neutropenia (FN) is a frequent and serious complication in children receiving cancer therapy. Standardizing FN management across Asia is challenging due to variable healthcare infrastructure, diagnostic capacity, and infection patterns; however, it could improve resource use and patient outcomes. A multidisciplinary panel, including patient advocates from 10 countries developed a clinical practice guideline (CPG) for FN using the Grading of Recommendations, Assessment, Development,

Abbreviations: ALSAC, American Lebanese Syrian Associated Charities; CPG, clinical practice guideline; CRP, C-reactive protein; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IL-6, interleukin-6; IL-8, interleukin-8; IV, intravenous; PCT, procalcitonin; TB, tuberculosis; UTI, urinary tract infection.

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and Evaluation (GRADE) methodology. The final CPG contains 25 recommendations addressing regional priorities in diagnosis, risk stratification, and management. This CPG creates a regional standard to be tailored and studied in local context.

1 | Introduction

Fever with Febrile neutropenia (FN) is common among children undergoing chemotherapy for cancer. Effective management requires prompt diagnosis and tailored interventions to mitigate the risks of severe infections and improve outcomes. Issuing recommendations at a regional level for FN is challenging due to varying institutional capabilities, healthcare infrastructure, pathogens, and resistance profiles across Asian continental centers. In addition, cost and access to both antimicrobial agents and testing practices vary both within and between countries [1, 2]. Therefore, creating a shared clinical practice guideline (CPG) may be advantageous to advocate for a standard of care that can be adapted according to local capacity. This model has precedent in region for adult oncology; however, it is new for pediatric oncology [3–7].

Recognizing this opportunity, clinicians and patient advocates identified from the regional members of the St. Jude Global Alliance (<https://global.stjude.org>) aimed to develop an evidence-based CPG for FN management. The objective was to balance the principles of evidence-based medicine with pragmatic considerations of resource availability while maintaining optimal standards of patient care, leading to the development of context-specific recommendations by a multidisciplinary panel.

2 | Methods

GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology was used in the development of this CPG [8]. The CPG development process comprised several steps, beginning with the formation of a CPG development panel. Individuals with content domain expertise were identified within the regional program of the St. Jude Global Alliance, which comprises over 400 institutions and foundations globally committed to improving outcomes for children with catastrophic disease. This was followed by question prioritization, training the CPG development panel on evidence interpretation and GRADE methodology, systematic search to identify all evidence, creation of evidence summaries for each question, panel deliberations, and voting on recommendations.

2.1 | Question Prioritization and Target Users

The guideline development panel formulated a list of 25 priority questions in FN management in children with cancer. The questions were then circulated to 79 clinicians from 40 institutions across 10 countries spanning all economies in the region for feedback. On the basis of the feedback, the questions were revised and refined by members of the steering committee and the CPG development panel. The target users of this CPG are clinicians providing care for pediatric patients with cancer and FN in

the Asia-Pacific region or similar settings. More broadly, these recommendations could be used by policymakers and guideline developers in the region to inform national policies.

2.2 | Search Methods and Evidence Summaries

We performed a systematic review for each prioritized question. We performed a broad search without any limits of language or region in MEDLINE (PubMed) until May 14, 2024, using a combination of MeSH and free text terms. Full search strategies are available in Supporting information 1. Each prioritized question was classified according to question type (diagnosis, prognosis, and treatment), and the appropriate study design was used for inclusion (randomized controlled trial for intervention questions, cross-sectional or case-control for diagnostic questions, and cohort for prognosis questions). Studies enrolling adults were excluded unless there were no pediatric studies that addressed a prioritized question. Additionally, any studies cited in relevant systematic reviews were included if they met the inclusion criteria.

Dual independent study selection was performed by members of the steering committee. Any conflicts in study selection were resolved by a clinician (S.M.) or methodologist (A.K.).

Data on patient and study characteristics, along with outcomes, were abstracted from included studies by members of the steering committee. The risk of bias in included studies was evaluated using Cochrane Risk of Bias tool for Randomized Controlled trials [9], Quality Assessment of Diagnostic Accuracy Studies tool for cross-sectional analytic and case-control diagnostic studies [10], and Newcastle Ottawa Scale for cohort studies [11].

When appropriate, data from similar studies with similar outcomes were pooled using the random effects model. Heterogeneity between studies was evaluated using the I^2 statistic [12]. All outcomes were summarized as summary of findings tables in GRADEpro [13]. When pooling was not possible, standardized tables were used to present narrative findings from each eligible study. A formal cost analysis was not performed; however, panelists were encouraged to consider local resource constraints, availability of interventions, and feasibility of implementation prior to voting on recommendations.

2.3 | Generating Recommendations and Voting

A 2-day in-person meeting was convened to review all evidence, deliberate, and vote on recommendations. All prioritized questions were presented as actionable recommendations in favor of intervention. Immediately before the vote, the panelists had the opportunity to make minor wording modifications. After deliberations, each panelist voted anonymously for the direction

(FOR vs. AGAINST) and strength (STRONG vs. WEAK) of the recommendation. A simple majority (>50%) was used to determine the final wording, direction (for or against) and strength (strong or weak) of each recommendation. When a majority of panelists voted strongly for or against a recommendation, the vote was translated to “the panel recommends” or “the panel recommends against,” respectively. When majority of panelists voted weakly for or against a recommendation, the vote was translated to “the panel suggests” or “the panel suggests against,” respectively.

2.4 | External Review

A draft of the recommendations and manuscript was shared with colleagues to ensure accuracy and clarity. An informal external review was performed by the faculty members of the participating institutions.

2.5 | Plan for Update

This CPG will be updated every 3 years.

2.6 | Source of Funding

This guideline development effort was supported by funds from the American Lebanese Syrian Associated Charities (ALSAC), which did not influence the content of the CPG.

3 | Results

3.1 | Characteristics of the CPG Panel Members

As illustrated in Table 1, 21 members representing 14 institutions across 10 countries in Asia served on the CPG panel. Most were pediatric hematology–oncology providers (57%, $n = 12$), followed by pediatric infectious diseases specialists (19%, $n = 4$), with one each (5%) from nursing, microbiology, and pharmacy. Two parent advocates (10%) also served on the CPG panel. Most members (86%; $n = 18$) of the CPG panel were female, worked in the public sector (52%, $n = 11$) tertiary or higher level of care (81%, $n = 17$).

3.2 | Definitions

3.2.1 | Fever

The threshold and method to measure fever varies between institutions. Panelists defined temperature for this guideline using two routes of measurement.

1. The panel defined fever as an oral temperature of 38.3°C (100.94°F) measured once or an oral temperature of $\geq 38^\circ\text{C}$ (100.4°F) measured twice at time points an hour or more apart.
2. The panel defined fever as an axillary temperature of 37.8°C (100.04°F) measured once or an axillary temperature of $\geq 37.4^\circ\text{C}$ (99.32°F) measured twice at time points an hour or more apart.

TABLE 1 | Characteristics of the clinical practice guideline (CPG) panel members.

Gender	Count (percent)
Female	18 (86)
Male	3 (14)
Professional background	
Infectious disease	4 (19)
Microbiologist	1 (5)
Nurse	1 (5)
Hematologist–oncologist/oncologist	12 (57)
Patient representative	2 (5)
Pharmacist	1 (5)
Practice setting	
Private sector	2 (10)
Public sector	11 (52)
Both private and public sectors	7 (33)
Other	1 (5)
Country of residence	
Philippines	8 (38)
Vietnam	3 (14)
Cambodia	2 (10)
Indonesia	2 (10)
India	1 (5)
Malaysia	1 (5)
Nepal	1 (5)
Sri Lanka	1 (5)
Singapore	1 (5)
Thailand	1 (5)
Level of care	
Primary level facility	3 (14)
Secondary level facility	1 (5)
Tertiary or quaternary academic center	17 (81)
Years of professional experience	
<5	5 (24)
5–10	6 (29)
11–15	5 (24)
16–20	3 (14)
>20	2 (10)

3.2.2 | Neutropenia

The panel defined neutropenia as an absolute neutrophil count (ANC) ≤ 500 cells/mm³ or an ANC ≤ 1000 cells/mm³ and expected to fall within 48 h.

The CPG contains 25 recommendations on FN management, which were prioritized by the panel (Table 2). The evidence summaries for each recommendation are available in the [Supporting Information](#).

TABLE 2 | Summary of recommendations with certainty of evidence associated with each recommendation.

Recommendations	Certainty of evidence	Strength and the direction of the recommendation
Initial management		
<i>Blood cultures</i>		
The panel recommends obtaining blood cultures from peripheral blood in the absence of a central line or from both central line and peripheral blood if central line is present at the time of presentation of pediatric patients with febrile neutropenia	Moderate	Strong for
<i>Urinalysis</i>		
The panel suggests against routinely obtaining urinalysis and urine culture for pediatric patients with febrile neutropenia	Low to very low	Weak against
<i>Stool testing</i>		
The panel suggests against testing for stool pathogens using culture and <i>Clostridioides difficile</i> assays routinely in all pediatric patients with febrile neutropenia and diarrhea	Very low	Weak against
<i>Respiratory virus testing</i>		
The panel suggests routinely testing for respiratory viruses in all pediatric patients with febrile neutropenia and respiratory symptoms	Low to very low	Weak for
<i>Lower respiratory tract infection testing</i>		
The panel recommends routinely obtaining chest radiography in pediatric patients with febrile neutropenia presenting with respiratory symptoms suggestive of lower respiratory tract infection	Low	Strong for
<i>Risk stratification</i>		
The panel recommends incorporating a risk-stratification strategy into the routine management of pediatric patients with febrile neutropenia	Very low	Strong for
<i>Initial antibiotic therapy</i>		
The panel recommends monotherapy with an antipseudomonal beta-lactam, a fourth-generation cephalosporin, or an antipseudomonal carbapenem in pediatric patients with high-risk febrile neutropenia	Moderate to very low	Strong for
The panel recommends adding a second gram-negative agent at presentation for patients who are clinically unstable or when a resistant infection is suspected, or at centers with a high rate of resistant pathogens in pediatric patients with febrile neutropenia	Moderate to very low	Strong for
The panel recommends adding a glycopeptide for pediatric patients with febrile neutropenia only when a gram-positive infection is suspected or at centers with high rates of resistant pathogens	Low	Strong for
The panel recommends use of monotherapy with broad-spectrum antibiotic in pediatric patients with low-risk febrile neutropenia	Low to very low	Strong for
<i>Route of antibiotic administration</i>		
The panel recommends initial therapy with either oral or intravenous antibiotics as the route of administration in pediatric patients with low-risk febrile neutropenia	Low	Strong for
Modifications to initial antibiotic therapy		
The panel recommends de-escalation after 48–72 h for stable pediatric patients with neutropenia responding to initial antibiotic therapy in the absence of a clinical or microbiologic indication	Moderate to very low	Strong for
The panel suggests no change in the initial empirical antibacterial regimen in pediatric patients with febrile neutropenia who are clinically stable except for persistent fever	Moderate to very low	Weak for
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 febrile neutropenia patients who become clinically unstable	Moderate to very low	Strong for

(Continues)

TABLE 2 | (Continued)

Recommendations	Certainty of evidence	Strength and the direction of the recommendation
<i>G-CSF use</i>		
The panel suggests use of G-CSF as a secondary therapy in pediatric patients with febrile neutropenia	Low to very low	Weak for
<i>Endemic disease testing</i>		
The panel suggests routinely testing for applicable endemic diseases in pediatric patients with febrile neutropenia	Very low	Weak for
<i>Bacterial biomarkers</i>		
The panel suggests use of bacterial biomarkers (CRP, PCT, IL-6, and/or IL-8) to guide decisions around modifications to therapy for the management of pediatric patients with febrile neutropenia	Very low	Weak for
Management of prolonged febrile neutropenia		
<i>Imaging for fungal infections</i>		
The panel recommends routinely performing imaging of the lungs, abdomen, and/or sinuses of pediatric patients with prolonged febrile neutropenia without localizing signs or symptoms, who are at high risk for invasive fungal infection	Very low	Strong for
<i>Tuberculosis testing</i>		
The panel suggests testing for tuberculosis in all pediatric patients presenting with febrile neutropenia who have tuberculosis exposure and/or clinical features suggestive of tuberculosis	Very low	Weak for
<i>Galactomannan for diagnosing fungal disease</i>		
The panel does not recommend using galactomannan or β -D-glucan for the diagnosis of invasive fungal disease in pediatric patients with febrile neutropenia who are at high risk for invasive fungal disease	Very low	Strong against
<i>Fungal disease management</i>		
The panel recommends administering empirical antifungal therapy in pediatric patients with febrile neutropenia who have a prolonged fever and are at high risk for fungal disease	Moderate to low	Strong for
Resolution of episode		
<i>Antibiotic discontinuation</i>		
The panel recommends stopping empirical antibiotics in clinically stable high-risk pediatric patients with febrile neutropenia who are afebrile for at least 24 h and have negative blood cultures at a minimum of 48 h	Low to very low	Strong for
The panel recommends stopping empirical antibiotics in clinically stable low-risk pediatric patients with febrile neutropenia who are afebrile for at least 24 h and have negative blood cultures at a minimum of 48 h	Moderate to very low	Strong for
<i>Early discharge</i>		
The panel recommends early discharge for clinically stable high-risk pediatric patients with febrile neutropenia who have been afebrile for at least 24 h and have negative blood cultures at a minimum of 48 h, provided follow-up is reliable	Low	Strong for
The panel recommends early discharge for clinically stable low-risk pediatric patients with febrile neutropenia who have been afebrile for at least 24 h and have negative blood cultures at a minimum of 48 h, provided follow-up is reliable	Low	Strong for

Abbreviations: CRP, C-reactive protein; G-CSF, granulocyte colony-stimulating factor; IL-6, interleukin-6; IL-8, interleukin-8; PCT, procalcitonin.

3.3 | Recommendations

Recommendation 1: The panel **recommends** obtaining blood cultures from peripheral blood in the absence of a central line or from both central line and peripheral blood if central line is present at the time of presentation of pediatric patients with febrile neutropenia (certainty of evidence: moderate; strength of recommendation—strong).

Panel deliberations:

Central lines are not routinely used at centers across the region. When present, paired cultures from the central line and periphery can help distinguish catheter colonization from true bloodstream infections and increase yield. Nevertheless, the financial resources associated with obtaining additional blood cultures may limit the feasibility of routine paired sampling in some settings. Furthermore, parent advocates highlighted the importance of minimizing patient discomfort by avoiding peripheral blood sampling if a central line is present.

Recommendation 2: The panel **suggests against** routinely obtaining urinalysis and urine culture for pediatric patients with febrile neutropenia (certainty of evidence: low to very low; strength of recommendation—weak).

Panel deliberations:

Acknowledging the low certainty of evidence, panelists suggested that urine testing be reserved for patients with symptoms that suggest urinary tract infection (UTI), citing costs and confusion caused by false positive results. There was a concern that neutropenic patients might be asymptomatic so that culture could be indicated in specific circumstances; these may include cases of unexplained fever or a clinical history of UTI.

Recommendation 3: The panel **suggests against** testing for stool pathogens using culture and *Clostridioides difficile* assays routinely in all pediatric patients with febrile neutropenia and diarrhea (certainty of evidence: very low; strength of recommendation—weak).

Panel deliberations:

Panelists discussed that the different prevalence of stool pathogens in different centers complicates the establishment of standardized protocols for stool testing. The diagnostic utility of testing every patient with loose stool is uncertain due to a lack of robust evidence, increased resource utilization related to unnecessary diagnostic workups, and potential overuse of antimicrobial agents without clear clinical benefit. Most participating institutions reserve stool testing for those with severe or persistent diarrhea.

Recommendation 4: The panel **suggests** routinely testing for respiratory viruses in all pediatric patients with febrile neutropenia and respiratory symptoms (certainty of evidence: low to very low; strength of recommendation—weak).

Panel deliberations:

The panel acknowledged that routine viral testing when respiratory symptoms are present could reduce unnecessary inves-

tigations (blood tests, chest radiographs, etc.) and antibiotic escalation, which is valuable in resource-limited settings. Nevertheless, limited access may preclude testing, and limited access to antiviral agents and isolation rooms may decrease its utility. Panelists also suggested that the benefit-to-cost ratio may be greater in a pandemic.

Recommendation 5: The panel **recommends** routinely obtaining chest radiography in pediatric patients with febrile neutropenia presenting with respiratory symptoms suggestive of lower respiratory tract infection (certainty of evidence: low; strength of recommendation—strong).

Panel deliberations:

Although guidelines from other areas and high-income countries do not support routine chest radiography, the panel recognized that regional factors may justify its use, even in patients without respiratory symptoms [14–17]. Panelists cited higher rates of tuberculosis, preexisting lung infections in undernourished children, and recurrent respiratory infections possibly warranting screening using chest x-rays in symptomatic patients. The panel emphasized the need for further regional studies to validate this practice.

Recommendation 6: The panel **recommends** incorporating a risk-stratification strategy into the routine management of pediatric patients with febrile neutropenia (certainty of evidence: very low; strength of recommendation—strong).

Panel deliberations:

The panelists discussed that risk-adapted management is desirable, but more evidence is needed to decide which risk-stratification factors can be consistently identified and are applicable locally. Furthermore, additional resources and infrastructure are necessary to maximize the impact of risk stratification.

The panel members highlighted the potential that outpatient management of low-risk patients has to improve resource use, however, emphasized that context-specific validation of risk factors and protocols to ensure safe outpatient care is critical. Key areas for future research, which could support risk-based management, include defining reliable clinical predictors of risk, establishing follow-up systems, and strengthening caregiver training on symptom recognition and medication adherence.

Recommendation 7: The panel **recommends** monotherapy with an antipseudomonal beta-lactam, a fourth-generation cephalosporin, or an antipseudomonal carbapenem in pediatric patients with high-risk febrile neutropenia (certainty of evidence: moderate to very low; strength of recommendation—strong).

Panel deliberations:

The panel recognized the need to always include antipseudomonal coverage (e.g., piperacillin-tazobactam, cefepime, and meropenem). Nevertheless, antibiotic selection will vary by institution based on availability, resistance patterns, and tolerance for adverse events.

Recommendation 8: The panel **recommends** adding a second gram-negative agent at presentation for patients who are

clinically unstable or when a resistant infection is suspected, or at centers with a high rate of resistant pathogens in pediatric patients with febrile neutropenia (certainty of evidence: moderate to very low; strength of recommendation—strong).

Panel deliberations:

Use of a different antibiotic class versus addition of a second agent is impacted by the variation in initial antibiotic regimens employed and local resistance patterns. The panel also highlighted that the term “clinically unstable,” one of the critical criteria for the recommendation, lacks a standardized definition, prompting the need for clear and measurable indicators such as specific cut-offs for vital signs or clinical markers like altered mental status or delayed capillary refill. As such, further refinement and adaptation are necessary to ensure its practicality and effectiveness across diverse settings.

Recommendation 9: The panel **recommends** adding a glycopeptide for pediatric patients with febrile neutropenia only when a gram-positive infection is suspected or at centers with high rates of resistant pathogens (certainty of evidence: low; strength of recommendation—strong).

Panel deliberations:

The panel members commented that most patients do not have central lines or catheters, which affects risk of gram-positive infections. The panel discussed potential nephrotoxicity of glycopeptides and the preference to use positive culture results in guiding the use of glycopeptides. Furthermore, the institution's antibiogram, including prevalence of methicillin-resistant *Staphylococcus aureus*, determines whether agents like oxacillin or cefepime are sufficient for gram-positive coverage.

Recommendation 10: The panel **recommends** use of monotherapy with a broad-spectrum antibiotic in pediatric patients with low-risk febrile neutropenia (certainty of evidence: low to very low; strength of recommendation—strong).

Panel deliberations:

Although broader agents like antipseudomonal beta-lactams or carbapenems are effective, their overuse may contribute to resistance. Panelists noted that oral therapy may be necessary after careful evaluation of the diagnosis and clinical condition of the patient to reduce delays for patients residing far from treatment centers. Local epidemiology and institutional protocols should guide the antibiotic selection as resistance levels and cost may affect use of various oral agents (e.g., levofloxacin, ciprofloxacin, cefixime, and amoxicillin/clavulanic acid).

Recommendation 11: The panel **recommends** initial therapy with either oral or intravenous (IV) antibiotics as the route of administration in pediatric patients with low-risk febrile neutropenia (certainty of evidence: low; strength of recommendation—strong).

Panel deliberations:

The panel emphasized that the choice between oral and IV antibiotics is impacted by oral tolerance (e.g., mucositis), care-

giver education, geographic access to care, and local monitoring capacity. In settings with limited infrastructure or high infection risk, inpatient IV therapy is suggested to ensure safe and effective treatment.

Recommendation 12: The panel **recommends** de-escalation after 48–72 h for stable pediatric patients with neutropenia responding to initial antibiotic therapy in the absence of a clinical or microbiologic indication (certainty of evidence: moderate to very low; strength of recommendation—strong).

Panel deliberations:

The panel discussed the need to clearly define the timing and meaning of antibiotic “de-escalation” and determine whether specific agents should be recommended. During deliberations, panelists noted that patients should remain afebrile for at least 48 h before considering de-escalation but that defervescence should be part of the overall assessment of clinical stability. In some instances, microbiologic results are not available for up to 96 h, so de-escalation may not be possible before 72–96 h. De-escalation practices should consider local resistance patterns, available resources, and patient-specific factors, prioritizing safety while reducing unnecessary antibiotic use to decrease the toxicity and limit development of antibiotic resistance.

Recommendation 13: The panel **suggests** no change in the initial empirical antibacterial regimen in pediatric patients with febrile neutropenia who are clinically stable except for persistent fever (certainty of evidence: moderate to very low; strength of recommendation—weak).

Panel deliberations:

The panel discussed the importance of clearly defining terms such as persistent fever, temperature thresholds, and clinical stability. The panel generally considered 72 h of persistent fever as an appropriate time point for reassessment and agreed that if the patient remains clinically stable, and no microbiologically documented infection is identified, continuing the initial empirical therapy is acceptable. That said, the panelists stated that whether patients have leukemia, solid tumors, or are posttransplant might impact the threshold for reevaluation and antimicrobial changes.

Recommendation 14: 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 febrile neutropenia patients who become clinically unstable (certainty of evidence: low to very low; strength of recommendation—strong).

Panel deliberations:

The panel agreed that clinical instability warrants prompt reassessment and escalation of the initial empirical regimen. The panel highlighted the importance of defining clear clinical indicators of instability, such as hemodynamic changes (e.g., hypotension and tachycardia), altered mental status, or signs of organ dysfunction. There was consensus that escalation should not be routine but guided by the clinical condition of the patient.

Recommendation 15: The panel suggests use of granulocyte colony-stimulating factor (G-CSF) as a secondary therapy in pediatric patients with febrile neutropenia (certainty of evidence: low to very low; strength of recommendation—weak).

Panel deliberations:

Given the limited evidence, cost, and potential side effects highlighted by parent advocates, the panel does not recommend G-CSF be used routinely in FN. The panel supports its selective use in high-risk or clinically complex cases, with decisions tailored to individual patient needs and resource availability.

Recommendation 16: The panel **suggests** routinely testing for applicable endemic diseases in pediatric patients with febrile neutropenia (certainty of evidence: very low; strength of recommendation—weak).

Panel deliberations:

The panel discussed the need to maintain a high index of suspicion for endemic diseases, including dengue, chikungunya, malaria, schistosomiasis, and leishmaniasis, given their high prevalence in some settings. The panel emphasized an individualized approach to testing, considering local disease patterns, laboratory limitations, potential exposures, and suggestive symptoms.

Recommendation 17: The panel **suggests** use of bacterial biomarkers (C-reactive protein [CRP], procalcitonin [PCT], interleukin-6 [IL-6], and/or interleukin-8 [IL-8]) to guide decisions around modifications to therapy for the management of pediatric patients with febrile neutropenia (certainty of evidence: very low; strength of recommendation—weak).

Panel deliberations:

The panel acknowledged the limitations of the current evidence, particularly difficulty in interpreting thresholds, timing of measurement, and study populations. Nevertheless, the panel recognized that these biomarkers, in selected clinical circumstances, may support decisions about treatment adjustment in some situations where clinical signs are unclear or evolving. However, the panel discussed using biomarkers with caution, considering the availability of resources.

Recommendation 18: The panel **recommends** routinely performing imaging of the lungs, abdomen, and/or sinuses of pediatric patients with prolonged febrile neutropenia without localizing signs or symptoms, who are at high risk for invasive fungal infection (certainty of evidence: very low; strength of recommendation—strong).

Panel deliberations:

The panel noted variability in defining “prolonged” (typically >3–7 days) FN. A risk-adapted approach was endorsed, with early imaging recommended for patients whose diagnosis and treatment create a high risk of fungal infection, including those with acute myeloid leukemia and after hematopoietic stem cell transplant. Abdominal ultrasound was favored as an initial

modality due to its safety and accessibility; lung CT was advised. Sinus imaging was not routinely recommended but may be appropriate for persistent fever with sinus symptoms, including facial pain. In high-risk cases, antifungal therapy should begin without delay, with imaging used later to guide continuation. Local fungal prevalence and multidisciplinary input should inform imaging decisions.

Recommendation 19: The panel **suggests** testing for tuberculosis in all pediatric patients presenting with febrile neutropenia who have tuberculosis exposure and/or clinical features suggestive of tuberculosis (certainty of evidence: very low; strength of recommendation—weak).

Panel deliberations:

As tuberculosis is prevalent across much of the continent, and the patients are immunocompromised and susceptible to the infection, it should be considered as a possible cause of fever. The panel discussed extensively whether screening should be guided by history of TB exposure, clinical symptoms, or both. Ultimately, the group aligned with existing TB recommendations, while recognizing the need for continued discussion about the most appropriate tests and the most specific clinical features [18]. The panel also emphasized that clinicians should consider extrapulmonary tuberculosis that may not present with typical respiratory symptoms.

Recommendation 20: The panel **does not recommend** using galactomannan or β -D-glucan for the diagnosis of invasive fungal disease in pediatric patients with febrile neutropenia who are at high risk for invasive fungal disease (certainty of evidence: very low; strength of recommendation—weak).

Panel deliberations:

The panel raised practical concerns, including high cost, variable sample-collection methods, and inconsistent test interpretation. Additionally, there was concern that due to variable predictive value, false positive results in low-prevalence settings could trigger unnecessary interventions and consume resources.

Recommendation 21: The panel **recommends** administering empirical antifungal therapy in pediatric patients with febrile neutropenia who have a prolonged fever and are at high risk for fungal disease (certainty of evidence: moderate—low; strength of recommendation—strong).

Panel deliberations:

The panel recognized the need to start antifungals within 5–7 days of FN in high-risk patients. Decisions regarding the timing and choice of empiric antifungal therapy should be guided by local protocols, drug availability, and patient-specific risk factors.

Recommendation 22: The panel **recommends** stopping empirical antibiotics in clinically stable high-risk pediatric patients with febrile neutropenia who are afebrile for at least 24 h and have negative blood cultures at a minimum of 48 h (certainty of evidence: low to very low; strength of recommendation—strong).

Panel deliberations:

The panel decided against including a requirement for bone marrow recovery before stopping antibiotics, stating that many centers lack resources to perform the testing. Some panelists expressed concerns about stopping antibiotics too early due to the high risk of gram-negative infections in this patient subgroup; however, the panelists also noted that most organisms of significance are recovered within 48 h of incubation. Implementation of this recommendation requires laboratories to notify clinicians with positive culture results in a timely fashion. Panelists underscored the importance of stipulating a minimum number of hours of antibiotic therapy but also recognized that most centers in the region do not have the laboratory support to stop antibiotics in a high-risk patient at 48 h.

Recommendation 23: The panel **recommends** stopping empirical antibiotics in clinically stable low-risk pediatric patients with febrile neutropenia who are afebrile for at least 24 h and have negative blood cultures at a minimum of 48 h (certainty of evidence: moderate to very low; strength of recommendation—strong).

Panel deliberations:

The panel commented that patients identified to be at low risk for infections and bad outcomes should have discharge criteria no more restrictive than that for high-risk patients. Panel members would be more comfortable discharging this subgroup of patients even earlier than the minimum of 48 h stipulated for culture results.

Recommendation 24: The panel **recommends** early discharge for clinically stable high-risk pediatric patients with febrile neutropenia who have been afebrile for at least 24 h and have negative blood cultures at a minimum of 48 h, provided follow-up is reliable (certainty of evidence: low; strength of recommendation—strong).

Recommendation 25: The panel **recommends** early discharge for clinically stable low-risk pediatric patients with febrile neutropenia who have been afebrile for at least 24 h and have negative blood cultures at a minimum of 48 h, provided follow-up is reliable (certainty of evidence: low; strength of recommendation—strong).

Panel deliberations:

The panel recognized that differing risk profiles and implementation challenges might affect recommendations for discharge; however, it could improve resource use in carefully selected patients whose vital signs remained stable after fever. Although caution was advised for early discharge in high-risk cases, panelists discussed that a critical feature was a minimum of 48 h of clinical stability. This timeframe aligns with the usual availability of culture results. Discharge decisions should be individualized, factoring in family education, preferences, socioeconomic conditions, follow-up access, and system responsiveness. Ensuring safe and reliable follow-up after discharge was strongly emphasized. Families must be able to recognize signs and symptoms of clinical deterioration and be able to return promptly to the hospital if indicated.

4 | Discussion

The 25 recommendations and two definitions developed by a collaborative group of clinicians and patient representatives reflect an ambitious attempt to optimize FN management across diverse healthcare settings on the Asian continent. The CPG addresses key aspects of care in children with cancer, including resource-conscious approaches to diagnosis and treatment. It attempts to reconcile best evidence, when available, with disparate practice settings to promote children receiving timely, appropriate, and equitable treatment wherever they are managed.

Developing a CPG to encompass this wide range of practice settings means that the CPG may require tailoring for use. To ensure broad applicability, the panel did not specify medications and testing that would be inappropriate or prohibitively expensive in many settings. For example, although the panel discussed mitigating antibiotic resistance through antibiotic stewardship and use of diagnostic testing, it prioritized immediate outcomes of patient safety and resistance during the current episode. Although other international CPGs recommend avoiding carbapenems as initial treatment, the high rates of resistance in gram-negative bacteria in many regional centers made it impossible for this panel to recommend a frontline carbapenem-sparing approach [15, 16, 19]. Meanwhile, there is a strong recommendation for a risk-stratified approach without endorsing a specific schema. Although risk-adapted approaches improve resource utilization, their success depends on emergency transport, timely laboratory and antimicrobial access, infrastructure for follow-up, and caregiver education that are unreliable in many settings. These recommendations underscore the need for local validation of risk-stratification tools and context-specific discharge criteria.

Beyond this, strong recommendations in the CPG should push decision makers to invest at multiple levels. Strengthening data systems and microbiology capacity is essential to operationalize risk stratification, early discharge, or modification of treatment. Additionally, consistent access to broad-spectrum antibiotics and antifungals is essential. Beyond the hospital environment, risk-based management necessitates robust follow-up systems and safe outpatient environments for early discharge.

Each of these implementation challenges poses an opportunity for research, shared learning, and capacity-building across the region. The CPG is a foundation for training, quality audits, and policy development and encourages sharing of data among institutions. These efforts will strengthen the regional evidence base, promote accountability, and support alignment with global standards while preserving flexibility for local adaptation. Together, they represent a regionally driven model of care that promotes both scientific rigor and regional solidarity. Future collaboration will focus on harmonizing implementation strategies and establishing outcome registries to sustain progress in FN care.

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Ethics Statement

This CPG required use of publicly available literature. There was no interaction with patients or use of patient data.

Consent

The authors have nothing to report.

Conflicts of Interest

Sally Jane G. Velasco-Aro reports receiving honoraria for lectures and being on a speaker's bureau and an advisory board for GlaxoSmith Kline as well as serving on an advisory board for Zuellig Pharma and being a speaker for MSD. All other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information 1. List of prioritized questions and search strategies. **Supporting Information 2.** Evidence summaries for recommendations.