CHILDREN'S ONCOLOGY GROUP

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

COG Supportive Care Endorsed Guidelines

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The "Guideline for the Management of Fever and Neutropenia in Pediatric Patients with Cancer and Hematopoietic Cell Transplantation Recipients: 2023 Update" was endorsed by the COG Supportive Care Guideline Committee in May 2023.

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The purpose of this guideline is to provide evidence-based recommendations for the empiric management of fever and neutropenia in pediatric patients with cancer and hematopoietic cell transplant patients. The recommendations of the endorsed guideline are presented below.

Summary of Recommendations for the Empiric Management of Fever and Neutropenia

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
A. Initial Management	
Risk Stratification	
A1. Adopt a validated risk stratification strategy and incorporate it into routine clinical management	Strong recommendation Low quality evidence
Evaluation	
A2. Obtain blood cultures at onset of fever and neutropenia 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
Treatment	
A6. In high-risk fever and neutropenia:	
A6a. Use monotherapy with an antipseudomonal β-lactam, a fourth generation cephalosporin or a carbapenem as empiric antibacterial therapy in pediatric high-risk fever and neutropenia	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
A7. In low-risk fever and neutropenia:	
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

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
B. 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 to 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
Cessation of Treatment	
B4. In both high-risk and low-risk fever and neutropenia 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 fever and neutropenia 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
C. Empiric Antifungal Treatment	
Risk Stratification	
C1. Invasive fungal disease high-risk patients are those with AML, 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 invasive fungal disease low-risk patients.	Strong recommendation Low quality evidence
Evaluation	
C2. In terms of biomarkers to guide empiric antifungal management for prolonged (≥ 96 hours) fever with neutropenia in invasive fungal disease 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

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
C3. In terms of imaging for the evaluation of prolonged (≥ 96 hours) fever with neutropenia in invasive fungal disease high-risk patients:	
C3a. Perform CT of the 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
Treatment	
C4. In invasive fungal disease high-risk patients with prolonged (≥ 96 hours) fever with neutropenia unresponsive to broad-spectrum antibacterial therapy, initiate caspofungin or liposomal amphotericin B for empirical antifungal therapy unless a pre-emptive antifungal therapy approach is chosen	Strong recommendation High quality evidence
C5. In non-HCT invasive fungal disease high-risk patients not receiving antimold prophylaxis with prolonged (≥ 96 hours) fever with neutropenia, consider a pre-emptive antifungal therapy approach by deferring empiric antifungal therapy and initiating antifungal therapy only if evaluation suggests of indicates invasive fungal disease	Conditional recommendation Moderate quality evidence
C6. In invasive fungal disease low-risk patients with prolonged (≥ 96 hours) fever with neutropenia, consider withholding empiric antifungal therapy	Conditional recommendation Low quality evidence

HCT, hematopoietic cell transplant

Appendix 1: GRADE

Strength of Recommendations:

Strong Recommendation	When using GRADE, panels make strong recommendations when they are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
Weak Recommendation	Weak recommendations indicate that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident.

Strength of Recommendations Determinants:

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted

Quality of Evidence

High Quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate Quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low Quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low Quality	Any estimate of effect is very uncertain

Guyatt, G.H., et al., *GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.* BMJ, 2008; 336: 924-926.
Guyatt, G.H., et al., *GRADE: going from evidence to recommendations.* BMJ, 2008; 336: 1049-1051.