CHILDREN'S ONCOLOGY GROUP

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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 Children with Cancer and/or Undergoing Hematopoietic Stem-Cell Transplantation" was endorsed by the COG Supportive Care Guideline Committee in September 2017.

The source guideline is published in the Journal of Clinical Oncology 2017; 35: 2082-94: http://ascopubs.org/doi/abs/10.1200/JCO.2016.71.7017

The purpose of this guideline is to provide evidence-based recommendations for the empiric management of pediatric febrile neutropenia. The recommendations of the endorsed guideline are presented below.

Summary of Recommendations for the Empiric Management of Febrile Neutropenia

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
A. Initial Management of Febrile Neutropenia	
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 febrile 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	Weak recommendation Moderate quality evidence
A4. Consider urinalysis and urine culture in patients in whom a clean-catch, midstream specimen is readily available	Weak recommendation Low quality evidence
A5. Obtain chest radiography only in patients with respiratory signs or symptoms	Strong recommendation Moderate quality evidence
Treatment	
A6a. In high-risk febrile neutropenia: Use monotherapy with an antipseudomonal β-lactam, fourth generation cephalosporin, or a carbapenem as empirical therapy in pediatric high-risk febrile neutropenia	Strong recommendation High quality evidence
A6b. In high-risk febrile neutropenia: Reserve addition of second gram-negative agent or a glycopeptide for patients who are clinically unstable, when a resistant infection is suspected or for centers with a high rate of resistant pathogens.	Strong recommendation Moderate quality evidence
A7a. In low-risk febrile neutropenia: Consider initial or step-down outpatient management if infrastructure is in place to ensure careful monitoring and follow-up.	Weak recommendation Moderate quality evidence
A7b. In low-risk febrile neutropenia: Consider oral antibiotic administration if the child is able to tolerate this route of administration reliably.	Weak recommendation Moderate quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
B. Ongoing Management of Febrile Neutropenia	
Modification of Treatment	
B1. In patients who are responding to initial empiric antibiotic 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 modify initial empirical antibacterial regimen based solely on persistent fever in children who are clinically stable	Strong recommendation Low quality evidence
B3. In children with persistent fever who become clinically unstable, escalate the initial empirical antibacterial regimen to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria	Strong recommendation Very low quality evidence
Cessation of Treatment	
B4. In all patients, discontinue empirical antibiotics in patients who have negative blood cultures at 48 hours, who have been afebrile for at least 24 hours, and who have evidence of marrow recovery	Strong recommendation Low quality evidence
B5. In patients with low-risk febrile neutropenia, consider discontinuation of empirical antibiotics at 72 hours in patients who have negative blood cultures and who have been afebrile for at least 24 hours, irrespective of marrow recovery status, as long as careful follow-up is ensured	Weak recommendation Moderate quality evidence
C. Empiric Antifungal Treatment ≥96 Hours after Initiation of Empiric Antibacterial Treatment	
Risk Stratification	
C1. Patients at high risk of invasive fungal disease are those with AML, high-risk ALL, or relapsed acute leukemia and children undergoing allogeneic HSCT. Children with prolonged neutropenia and children receiving high-dose corticosteroids are also at high risk of invasive fungal disease. All others should be categorized as Invasive Fungal Disease low risk.	Strong recommendation Low quality evidence
Evaluation	
C2a. In terms of biomarkers to guide empirical antifungal management for prolonged (≥ 96 hours) febrile neutropenia in invasive fungal disease high-risk patients: Consider not using serum galactomannan	Weak recommendation Moderate quality evidence
C2b. In terms of biomarkers to guide empirical antifungal management for prolonged (≥ 96 hours) febrile neutropenia in invasive fungal disease high-risk patients: Do not use β-D-glucan.	Strong recommendation Low quality evidence
C2c. In terms of biomarkers to guide empirical antifungal management for prolonged (≥ 96 hours) febrile neutropenia in invasive fungal disease high-risk patients: Do not use fungal PCR testing in blood	Strong recommendation Moderate quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
C3a. In terms of imaging for the evaluation of prolonged (≥ 96 hours) febrile neutropenia in invasive fungal disease high-risk patients: Perform CT of the lungs.	Strong recommendation Low quality evidence
C3b. In terms of imaging for the evaluation of prolonged (≥ 96 hours) febrile neutropenia in invasive fungal disease high-risk patients: Consider imaging of abdomen in patients without localizing signs or symptoms.	Weak recommendation Low quality evidence
C3c. In terms of imaging for the evaluation of prolonged (≥ 96 hours) febrile neutropenia in invasive fungal disease high-risk patients: Consider not routinely performing CT of sinuses in patients without localizing signs or symptoms.	Weak recommendation Low quality evidence
Treatment	
C4. In invasive fungal disease patients with prolonged (≥ 96 hours) febrile neutropenia unresponsive to broad-spectrum antibacterial agents, initiate caspofungin or liposomal amphotericin B for empirical antifungal therapy.	Strong recommendation High quality evidence
C5. In invasive fungal disease low risk patients with prolonged (≥ 96 hours) febrile neutropenia, consider withholding empirical antifungal therapy.	Weak recommendation Low quality evidence

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.