CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Clinical Practice Guideline for Systemic Antifungal Prophylaxis in Pediatric Patients with Cancer and Hematopoietic Stem-Cell Transplantation Recipients

COG Supportive Care Endorsed Guidelines

Click **here** to see all the COG Supportive Care Endorsed Guidelines.

DISCLAIMER

For Informational Purposes Only: The information and contents offered in or in connection with the *Children's Oncology Group Supportive Care Endorsed Guidelines* (the "Guidelines") is provided only for informational purposes to children affected by cancer, their families and their health care providers. The Guidelines are not intended to substitute for medical advice, medical care, diagnosis or treatment obtained from doctors or other healthcare providers.

While the Children's Oncology Group tries to provide accurate and up-to-date information, the information in the Guidelines may be or may become out of date or incomplete. The information and guidelines may not conform to current standard of care, state-of-the art, or best practices for a particular disease, condition, or treatment. Some information in the Guidelines may be intended to be used by clinical researchers in special clinical settings or situations that may not apply to you, your child or your patient.

Special Notice to cancer patients and their parents and legal guardians: The Children's Oncology Group is a research organization and does not provide individualized medical care or treatment.

The Guidelines are not intended to replace the independent clinical judgment, medical advice, screening, health counseling, or other intervention performed by your or your child's doctor or other healthcare provider. Please do not rely on this information exclusively and seek the care of a doctor or other medical professional if you have any questions regarding the Guidelines or a specific medical condition, disease, diagnosis or symptom.

*Please contact "911" or your emergency services for any health emergency***!**

Special Notice to physicians and other healthcare providers*:* This document is aimed specifically at members of the Children's Oncology Group or Member affiliates who have agreed to collaborate with the Children's Oncology Group in accordance with the relevant procedures and policies for study conduct and membership participation. Requirements and restrictions applicable to recipients of U.S. governmental funds or restrictions governing certain private donations may apply to the use and distribution of the Guidelines and the information contained herein.

The Guidelines are not intended to replace your independent clinical judgment, medical advice, or to exclude other legitimate criteria for screening, health counseling, or intervention for specific complications of childhood cancer treatment. The Guidelines provided are not intended as a sole source of guidance in the evaluation of childhood cancer patients. Nor are the Guidelines intended to exclude other reasonable alternative care. Specific patient care decisions are the prerogative of the patient, family and healthcare provider.

Warranty or Liability Assumed by Children's Oncology Group and Related Parties: While the Children's Oncology Group has tried to assure that the Guidelines are accurate and complete as of the date of publication, no warranty or representation, express or implied, is intended to be made in or with the Guidelines. No liability is assumed by the Children's Oncology Group or any affiliated party or member thereof for damage resulting from the use, review, or access of the Guidelines.

The "Clinical Practice Guideline for Systemic Antifungal Prophylaxis in Pediatric Patients with Cancer and Hematopoietic Stem-Cell Transplantation Recipients" developed by the Pediatric Oncology Group of Ontario was endorsed by the COG Supportive Care Guideline Committee in August 2020.

The source clinical practice guideline is published (Lehrnbecher T, Fisher BT, Phillips B, et al. Clinical practice guideline for systemic antifungal prophylaxis in pediatric patients with cancer and hematopoietic stem-cell transplantation recipients. JCO 2020; [ePub May 27, 2020]) and is available at: https://ascopubs.org/doi/full/10.1200/JCO.20.00158

The purpose of the source clinical practice guideline is to provide recommendations for systemic antifungal prophylaxis administration in pediatric patients with cancer and hematopoietic stem cell transplant recipients. These recommendations are presented in the table below.

Summary of Recommendations for Systemic Antifungal Prophylaxis in Pediatric Patients with Cancer and Hematopoietic Stem-Cell Transplantation Recipients

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
Which pediatric patients with cancer and HSCT recipients should routinely receive systemic antifungal prophylaxis?	
Acute myeloid leukemia	
1. Administer systemic antifungal prophylaxis to children and adolescents receiving treatment of acute myeloid leukemia that is expected to result in profound and prolonged neutropenia. *Remarks*: This strong recommendation is based on the increasing benefit of systemic antifungal prophylaxis versus no prophylaxis to reduce proven or probable invasive fungal disease (IFD) as the risk for IFD increases. Although this recommendation advocates for a universal prophylaxis approach, future research should identify patient and treatment factors that may allow tailoring of prophylaxis to those at the highest risk for IFD.	Strong recommendation High-quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
Acute lymphoblastic leukemia	
2. Consider administering systemic antifungal prophylaxis to children and adolescents with newly diagnosed and relapsed acute lymphoblastic leukemia at high risk for IFD. *Remarks:* Children and adolescents with acute lymphoblastic leukemia encompass a group with wide variability in IFD risk that is not solely accounted for by relapse status. Those with relapsed acute lymphoblastic leukemia receiving intensive myelosuppressive chemotherapy are most likely to warrant systemic antifungal prophylaxis, whereas greater uncertainty is present for those with newly diagnosed acute lymphoblastic leukemia. Given the heterogeneity in IFD risk across protocols overall and by phase of treatment, adaptation will be required for each protocol to recommend whether and when systemic antifungal prophylaxis should be administered.	Weak recommendation Low-quality evidence
3. Do not routinely administer systemic antifungal prophylaxis to children and adolescents with acute lymphoblastic leukemia at low risk for IFD. *Remarks*: A low risk for IFD can be inferred based on absence of risk factors such as prolonged neutropenia and corticosteroid administration and observed IFD rates across different protocols. This group includes, for example, pediatric patients receiving maintenance chemotherapy for acute lymphoblastic leukemia.	Strong recommendation Low-quality evidence
Other malignancies including most patients with lymphomas and solid tumors	
4. Do not routinely administer systemic antifungal prophylaxis to children and adolescents with cancer at low risk for IFD, such as most pediatric patients with lymphomas and solid tumors. *Remarks:* In pediatric patients at low risk for IFD, the benefit of systemic antifungal prophylaxis is likely to be small and outweighed by the risk for adverse effects, costs, and inconvenience. Thus, systemic antifungal prophylaxis should not routinely be administered in this setting.	Strong recommendation Moderate-quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
HSCT	
5. Administer systemic antifungal prophylaxis to children and adolescents undergoing allogeneic HSCT pre-engraftment and to those receiving systemic immunosuppression for the treatment of graft-versus host disease. *Remarks*: The panel recognized that these two phases of therapy are associated with different epidemiology of IFD. However, the nature of the trials included in the systematic review precluded the ability to make separate recommendations for them. This strong recommendation was influenced by the finding in the systemic prophylaxis versus no systemic prophylaxis stratified analysis that HSCT recipients experienced greater benefit in IFD reduction compared with chemotherapy recipients. In addition, the subgroup analysis showed that among the HSCT stratum, prophylaxis significantly reduced fungal infection–related mortality.	Strong recommendation Moderate-quality evidence
6. We suggest that systemic antifungal prophylaxis not be used routinely in children and adolescents undergoing autologous HSCT. *Remarks*: This weak recommendation was based on the lower risk for IFD associated with autologous HSCT. There is less certainty in the setting of tandem transplantations where the cumulative duration of neutropenia may be longer.	Weak recommendation Low-quality evidence
If systemic antifungal prophylaxis is planned, which agents should be used?	
7. If systemic antifungal prophylaxis is warranted, administer a mold-active agent. *Remarks:* This strong recommendation was based on the comparison of different systemic antifungal prophylaxis agents where mold-active agent versus fluconazole significantly reduced proven or probable IFD, mold infection, and invasive aspergillosis (IA), and reduced fungal infection–related mortality. Direct pediatric data were available, increasing quality of the evidence.	Strong recommendation High-quality evidence
8. In choosing a mold-active agent, administer an echinocandin or a mold-active azole. *Remarks*: The choice of specific mold-active agent is influenced by multiple factors including local epidemiology, adverse effect profile, potential for drug interactions, costs, and jurisdictional availability. For children younger than 13 years of age, an echinocandin, voriconazole, or itraconazole is suggested based on efficacy and adverse effects. In those 13 years of age and older, posaconazole also is an option.	Strong recommendation Moderate-quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
9. Do not use amphotericin routinely as systemic antifungal prophylaxis. *Remarks*: This strong recommendation was based on the finding that both conventional and lipid formulations of amphotericin were not more effective than fluconazole in reducing IFD. It is important to note that liposomal amphotericin was not included in studies comparing amphotericin versus fluconazole and, thus, there is less certainty about the benefits and risks of this formulation.	Strong recommendation Low-quality evidence
When should systemic antifungal prophylaxis be started and stopped?	
10. If systemic antifungal prophylaxis is warranted, consider administration during periods of observed or expected severe neutropenia. For allogeneic HSCT recipients, consider administration during systemic immunosuppression for graft-versus-host disease treatment. *Remarks*: There are limited data that inform the decision of when to initiate and discontinue systemic antifungal prophylaxis. This recommendation was based on the criteria used in the included randomized trials and the anticipated highest risk period.	Weak recommendation Low-quality evidence

*see Appendix 1

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 or Conditional Recommendation	Weak or conditional recommendations indicate that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident.

Strength of Recommendation 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
Certainty in 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

Certainty in Evidence or Quality of Evidence

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