Clinical practice guideline for systemic antifungal prophylaxis in pediatric patients with cancer and hematopoietic stem-cell transplantation recipients.

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Pediatric Oncology Group of Ontario (POGO)

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. J Clin Oncol. 2020 Sep 20;38(27):3205-3216. [17 references] PubMed

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Overview

Guideline Objective

To develop a clinical practice guideline for systemic antifungal prophylaxis in pediatric patients with cancer and hematopoietic stem-cell transplantation (HSCT) recipients

Patient Population

Children and adolescents (age 0-18 years) receiving chemotherapy for cancer or undergoing HSCT

Recommendations

Recommendation Statements

Which pediatric patients with cancer and hematopoietic stem-cell transplantation (HSCT) recipients should routinely receive systemic antifungal prophylaxis?

Recommendation 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. (**Strong recommendation; High-quality evidence**)

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.

Recommendation 2. Consider administering systemic antifungal prophylaxis to children and adolescents with newly diagnosed and relapsed acute lymphoblastic leukemia at high risk for IFD. (**Weak recommendation; Low-quality evidence**)

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.

Recommendation 3. Do not routinely administer systemic antifungal prophylaxis to children and adolescents with acute lymphoblastic leukemia at low risk for IFD. (**Strong recommendation; Low-quality evidence**)

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. Other malignancies including most patients with lymphomas and solid tumors.

Recommendation 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. (**Strong recommendation; Moderate-quality evidence**)

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.

Recommendation 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-versushost disease. (**Strong recommendation; Moderate-quality evidence**)

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.

Recommendation 6. We suggest that systemic antifungal prophylaxis not be used routinely in children and adolescents undergoing autologous HSCT. (**Weak recommendation; Low-quality evidence**)

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.

If systemic antifungal prophylaxis is planned, which agents should be used?

Recommendation 7. If systemic antifungal prophylaxis is warranted, administer a mold-active agent. (**Strong recommendation; High-quality Evidence**)

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.

Recommendation 8. In choosing a mold-active agent, administer an echinocandin or a mold-active azole. (**Strong recommendation; Moderate-quality evidence**)

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.

Recommendation 9. Do not use amphotericin routinely as systemic antifungal prophylaxis. (**Strong recommendation; Low-quality evidence**)

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.

When should systemic antifungal prophylaxis be started and stopped?

Recommendation 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. (**Weak recommendation; Low-quality evidence**)

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.

Evidence Rating Scheme

To rate the level of evidence, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used. Evidence was rated as **high**, **moderate**, **low**, or **very low**.

Recommendation Rating Scheme

Strong recommendations were made where benefits clearly outweighed the risks or vice versa and, thus, patients should receive or not receive the intervention as a general policy.

Weak recommendations were made where the benefits and risks were closely matched or where there was uncertainty in their estimates.

Related Content

Supporting Documents

- Appendix 1 to 15.

Implementation Tools

No implementation tools available.

Patient Education

No patient education materials available.

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TRUST Scorecard

Composition of Guideline Development Group (GDG)

Multidisciplinary GDG Members	**Yes**
Methodologist Involvement	**Yes**
Incorporation of Patient and Public Perspective	

Systematic Review of Evidence

Literature Search	
Study Selection	
Evidence Synthesis	

Foundations for Recommendations

Strength of Evidence Grade	
Description of Benefits and Harms of Recommendations	
Summary of Evidence Supporting Recommendations	
Strength of Recommendations Rating	
Clear Articulation of Recommendations	

Funding Source

Yes

Disclosure and Management of Financial Conflicts of Interests



External Review



Updating



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