Guideline for Primary Antifungal Prophylaxis for Pediatric Patients with Cancer or Hematopoietic Stem Cell Transplant Recipients

The C17 Primary Antifungal Prophylaxis for Pediatric Hematology / Oncology Patients Guideline Panel:

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C[17] supportive care guidelines are developed by Canadian health professional specialists using evidence-based or best practice references at the time of their creation. Format and content of the guidelines will change as they are reviewed and revised on a periodic basis. Care has been taken to ensure accuracy of the information. However, any physician or health professional using these guidelines will be responsible for administering care according to their own institutional policies and standards.

Glossary

Acute Graft versus Host Disease (GVHD) – graft versus host disease occurring within the first 100 days after HSCT. Graded I-IV based on severity, see Przepiorka et al.[1] for criteria.

Chronic GVHD – graft versus host disease occurring after the first 100 days following HSCT. New criteria for global scoring of chronic GVHD are presented by Filipovich et al. 2005.[2]

Chronic Extensive GVHD (old criteria) – chronic GVHD with either generalized skin involvement or localized skin involvement or liver dysfunction plus any one of: chronic aggressive hepatitis/bridging necrosis/cirrhosis, eye involvement, mucosalivary gland involvement, mucosal involvement or other target organ involvement.[3]

Engraftment – absolute neutrophil count (ANC) greater than or equal to 500 cells/μL after hematopoietic stem cell transplantation (HSCT).

Invasive Aspergillosis (IA) – Invasive fungal infection caused by *Aspergillus* sp. See definitions by De Pauw et al.[4]

Invasive Candidiasis (IC) – Invasive fungal infection caused by *Candida* sp. See definitions by De Pauw et al.[4]

Invasive Fungal Infection (IFI) – disease process caused by fungal infection. For definitions of proven, probable and possible IFI see definitions provided by the European Organization for Research and Treatment of Cancer/IFI Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) by De Pauw et al. 2008.[4]

Oncology (cancer) - inclusive of solid cancers and leukemia/ lymphoma as well as disorders such as myelodysplastic syndrome, myeloproliferative disorders and histiocytic disorders.

Primary Antifungal Prophylaxis – antifungal agent given to prevent fungal infection in the absence of previous fungal infection.

Secondary Antifungal Prophylaxis – antifungal agent given after treatment for fungal infection to prevent recurrence or new fungal infection.

Severe Neutropenia – ANC less than 500 cells/μL.

Abbreviations

ALL – Acute Lymphoblastic Leukemia
AML – Acute Myeloid Leukemia
ASBMT – American Society for Blood and Marrow Transplantation
CML – Chronic Myeloid Leukemia
GVHD – Graft versus Host Disease
HSCT – Hematopoietic Stem Cell Transplant
IA – Invasive Aspergillosis
IC – Invasive Candidiasis
IDSA – Infectious Disease Society of America
IFI – Invasive Fungal Infection
MDS – Myelodysplastic Syndrome
NCCN – National Comprehensive Cancer Network
NHL – Non-Hodgkin's Lymphoma
SD – Standard Deviation
WBC – White Blood Cell

Overview of Material

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Sources: Electronic copies available through www.c17.ca

Summary

The recommendations that follow (Table 1) are based on a critical evaluation of the available pediatric and adult evidence, expert clinical opinion and the deliberations of the Guideline for Primary Antifungal Prophylaxis for Pediatric Hematology/Oncology Patients Development Panel. The purpose of these recommendations are to provide clinical institutions and other organizations with a framework on which to build their own institutional protocols and to encourage standardization of protocols across regions to enhance consistency of care for patients and families.

The C[17] Guideline for Primary Antifungal Prophylaxis for Pediatric Hematology/Oncology Patients Development Panel recommends, based on the existence of significant research gaps, that C[17] and other institutions develop trials that can supply evidence to inform future decision-making on primary antifungal prophylaxis for children with hematologic malignancy or undergoing hematopoietic stem cell transplant (HSCT). Current open or registered trials are presented in Appendix A and research gaps are presented in Appendix B.

Table 1: Summary of Guideline Recommendations

Recommendation	Evidence*
1.1: Allogeneic HSCT	
For children one month to less than 19 years of age undergoing allogeneic HSCT, administer fluconazole 6 – 12 mg/kg/day (maximum 400 mg/day) intravenous (IV) or oral (PO) from the start of conditioning until engraftment.	Strong Recommendation, High quality evidence
For the above children where fluconazole is contraindicated, administer an echinocandin as an alternative to fluconazole.	Strong Recommendation, Moderate quality evidence
1.2: Allogeneic HSCT with Acute Grade II – IV GVHD or Chronic Extensive GVHD	
For children 13 years of age or older undergoing allogeneic HSCT with acute Grade II – IV or chronic extensive GVHD, prophylaxis with posaconazole 200 mg PO TID from GVHD diagnosis until resolution of acute grade II-IV GVHD or chronic extensive GVHD is suggested.	Weak Recommendation, Moderate quality evidence
For the above children where posaconazole is contraindicated, fluconazole 6 – 12 mg/kg/day (maximum 400 mg/day) IV/PO is suggested as an alternative to posaconazole.	Weak Recommendation, Low quality evidence
For children one month to less than 13 years of age undergoing allogeneic HSCT with acute Grade II – IV or chronic extensive GVHD, fluconazole 6 – 12 mg/kg/day (maximum 400 mg/day) IV/PO from GVHD diagnosis until resolution of acute grade II – IV GVHD or chronic extensive GVHD is suggested.	Weak Recommendation, Low quality evidence

2.1: Autologous HSCT with anticipated neutropenia greater than 7 days	
For children one month to less than 19 years of age undergoing autologous HSCT with anticipated neutropenia for more than 7 days, administer fluconazole 6 – 12 mg/kg/day (maximum 400 mg/day) IV/PO from the start of conditioning until engraftment.	Strong Recommendation, Moderate quality evidence
3.1: Children with AML / MDS	
For children one month to less than 19 years of age with AML or MDS, administer fluconazole 6 – 12 mg/kg/day (maximum 400 mg/day) IV/PO during chemotherapy-associated neutropenia.	Strong Recommendation, Moderate quality evidence
For children 13 years of age or older with AML or MDS, posaconazole 200 mg PO TID is suggested as an alternative to fluconazole in centers where there is a high local incidence of mold infections or if fluconazole is not available.	Weak Recommendation, Moderate quality evidence
4.1: Children with malignancy and anticipated neutropenia greater than 7 days other than those undergoing HSCT or with AML or MDS	Weak Recommendation, Moderate quality evidence
The panel suggests that antifungal prophylaxis not be given routinely to children with malignancy and neutropenia anticipated to persist for greater than 7 days, outside of patients undergoing HSCT or those with AML/MDS.	

HSCT: hematopoietic stem cell transplant; GVHD: graft-versus-host-disease; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome

*using American College of Chest Physicians "GRADE" criteria (Appendix C)[5]

Introduction

Invasive fungal infections (IFIs) are an important concern in immunocompromised patients. Once established, these infections are difficult to treat and are associated with significant morbidity and mortality.[6] In fact, for invasive *Aspergillosis* (IA), mortality may exceed 60%.[7] As a result, emphasis has been placed on preventing the development of IFI. Strategies include preventing exposure through environmental strategies (e.g. HEPA filters, avoidance of construction/renovation) and preventing disease with the use of antifungal prophylaxis. The focus of this guideline will be on the latter: the use of primary antifungal prophylaxis to prevent IFI with the ultimate goal of improving survival. Other considerations including the importance of early diagnosis, early empiric anti-fungal therapy, and pre-emptive therapy are beyond the scope of this guideline.

In deciding who should receive prophylaxis, targeting populations at highest risk for IFI would likely have the most favorable risk and cost benefit profile. Adult HSCT recipients are at high risk of IFI and risk factors for IFI in this group have been summarized by Bow et al. (2009)[8] as: transplant-recipient, transplant-procedure and transplant-complication related factors. One of the groups at highest risk of IFI are patients receiving allogeneic HSCT.[9] In adult patients, the following have been identified as additional risk factors of IFI: use of unrelated or mismatched donors,[10,11] presence of cytomegalovirus (CMV) disease as defined by CMV detected by direct fluorescence or cultured from bronchoalveolar

lavage or tissue,[10] a diagnosis of Grade II – IV graft-versus-host-disease (GVHD)[12] and administration of corticosteroids in doses greater than or equal to 2 mg/kg day.[10] Fewer studies have focused on identifying risk factors in adults with malignancy. However, diagnosis of acute myeloid leukemia (AML) and prolonged neutropenia have consistently been associated with a higher risk of IFI.[13,14]

Similar risk factors for IFI have been identified in pediatric studies. In pediatric allogeneic HSCT patients, prolonged neutropenia for more than 29 days, age greater than 10 years, administration of corticosteroids for greater than 10 days and an underlying diagnosis of severe aplastic anemia or Fanconi anemia have all been identified as risk factors.[15] Important risk factors in children with malignancy include a diagnosis of AML, age greater than 10 years, receipt of long term antibiotics and relapsed disease.[16]

Following a detailed review of these risk factors, a risk stratification system was developed by Prentice et al. in 2000[17] for use in adults and was subsequently validated by McLintock et al. in 2004.[18] However, no risk stratification tool has been developed for or validated in children.

The use of a risk stratification tool may be important to incorporate into prophylactic antifungal strategies. This is especially true as many of the antifungal prophylaxis trials have been conducted in heterogeneous patient populations (i.e. different malignancies and HSCT patients). However, for the purpose of this guideline, in the absence of a validated risk stratification tool in children, we have focused on the available literature to make recommendations. It may be that there are high risk groups other than those included in this guideline who may also benefit from primary antifungal prophylaxis.

In deciding what prophylactic agent to use in each patient population, the type of fungal infection the patient is most at risk for should be considered. IFIs include both invasive yeast infections (i.e. *Candida*) and invasive mold infections (i.e. *Aspergillus*). Antifungal agents vary in their spectrum from narrower agents covering predominantly yeasts (i.e. fluconazole) to broader agents that cover both yeasts and molds (i.e. posaconazole). Although the routine use of a broader agent may theoretically be appealing, other considerations including drug toxicities, drug interactions, resistance, administration issues and lack of pediatric experience may limit their use. Therefore, a narrower agent may be more appropriate in situations where the risk of *Candida* infection is high.

The risk for yeast and mold infections differ depending on several factors including patient-related (i.e. underlying malignancy), treatment-related (i.e. type of chemotherapy, timing post transplant), complication-related (i.e. GVHD) and institution-related (i.e. mold rates). In this guideline, we have attempted to outline what type of infection each patient population is considered to be at risk for, but we have focused on the evidence available from randomized trials to formulate our recommendations. We acknowledge that there may be other factors (i.e. institution specific mold rates) that may impact the implementation of these guidelines at various centers.

Scope and Purpose

The objective of this guideline is to provide healthcare professionals with evidence-based recommendations on the use of primary antifungal prophylaxis in children with cancer or undergoing HSCT. This guideline is intended to apply to all patients one month to less than 19 years of age with cancer or receiving HSCT in whom primary prophylaxis is a consideration. The scope of this guideline is

limited to the assessment of primary antifungal prophylaxis in the context of the patient's clinical status and underlying medical condition and does not address issues related to other medical diagnoses. Efficacy, cost, tolerability and toxicity of the medications were all considered when establishing these recommendations.

Although it is recognized they may impact on antifungal prophylaxis, this guideline does not consider other aspects of antifungal agent administration such as drug concentration monitoring and impact of previous fungal disease on antifungal choice. The scope of this guideline excludes secondary antifungal prophylaxis, or empiric, pre-emptive and therapeutic aspects of antifungal therapy. Specifically, pre-emptive therapy strategies based on surrogate markers (i.e. galactomannan) are not addressed because of a lack of pediatric data. However, further research in this area is needed and recommendations may change as more evidence becomes available. Although some consideration is given to the implications of using drugs that commonly interact with other medications, specific recommendations on what drugs to use in various circumstances are not given. This guideline is also focused only on systemic antifungal prophylaxis and does not address topical or aerosolized formulations or non-systemically absorbed oral medications (i.e. oral amphotericin).

This guideline has been developed within the context of pediatric oncology and HSCT. It is acknowledged that the recommendations presented here are based on the available evidence and that there are many gaps. Readers are reminded that implementation of these recommendations will require adaptation to the local context appreciating factors such as individual patient needs and preferences, clinician knowledge, skill and practice scope, available resources and organizational policies and standards. The choice of antifungal may also be affected by patient co-morbidities, the local incidence and prevalence of fungal disease, local epidemiology and environmental factors, antifungal resistance patterns, and potential drug-drug interactions.

The objectives of this guideline are:

1. To identify clinical circumstances in patients with cancer or undergoing HSCT where primary antifungal prophylaxis has been studied.

2. In the circumstances where primary antifungal prophylaxis has been studied, to provide recommendations on whether or not primary antifungal prophylaxis is indicated and the choice of antifungal agent to be given in different clinical circumstances.

3. To reduce the incidence of IFI in children with cancer or undergoing HSCT.

Target Audience of the Guideline

The intended users of this guideline are all health professionals within Canada caring for children and youth with cancer or undergoing HSCT. The guideline is primarily for use by physicians (oncologists and infectious disease physicians), pharmacists, nurse practitioners and nurses working in hospitals and satellite clinics where pediatric oncology patients and HSCT patients receive care.

The guideline will also be relevant to the administrators of health care institutions, laboratory services and insurance companies who must ensure sufficient resources are available to provide antifungal medications and laboratory services for monitoring purposes.

Health Questions

The following clinical questions guided the development of this guideline:

1. Should primary antifungal prophylaxis be used to prevent IFI in children undergoing allogeneic HSCT? If so, what medication (dose and duration) should be used?

2. Should primary antifungal prophylaxis be used to prevent IFI in children undergoing autologous HSCT? If so, what medication (dose and duration) should be used?

3. Should primary antifungal prophylaxis be used to prevent IFI in children with AML or MDS? If so, what medication (dose and duration) should be used?

4. Should primary antifungal prophylaxis be used to prevent IFI in children with malignancy and anticipated neutropenia greater than 7 days other than those undergoing HSCT or with AML or MDS?   If so, what medication (dose and duration) should be used?

Methods

Guideline Development Panel

The C[17] Guidelines Committee identified antifungal prophylaxis as a key supportive care initiative in 2009. The C[17] Antifungal Prophylaxis Working Group was formed in June 2009. Members were selected from C[17] sites across Canada with the aim to have an inter-disciplinary team including individuals with content expertise and guideline development experience.

Identification and Appraisal of Existing Guidelines

The initial stages of this project were informed by the guideline adaptation methodology developed by the ADAPTE Collaboration[19] and CAN-ADAPTE.[20] The ADAPTE process is a systematic approach to considering the use and/or modification of existing guidelines developed in one context for application in a different context, so as to enhance the efficient production and use of high-quality adapted guidelines. The strategies for searching for guidelines and guideline adaptation are outlined in Appendix D.

Guideline Search Strategy

In May and June of 2010, the Guideline for Primary Antifungal Prophylaxis for Pediatric Hematology/Oncology Patients Development Panel completed a comprehensive literature review with librarian support to identify guidelines on the use of antifungal prophylaxis in patients with malignancy or undergoing stem cell transplantation. The guideline search was conducted through to June 2010. The search details including search terms are provided in Appendix D.

To summarize in brief, literature searches of MEDLINE (OvidSP; 1966 to April Week 2 2011), Cumulative Index to Nursing & Allied Health Literature (CINAHL; OvidSP and EBSCO host; 1980 to April 2011) and PubMed were performed. Grey literature was searched by using the search engine Google. Individual panel members also reviewed their personal files, professional association documents and their own institutional documents for guidelines that were relevant for review.

Guideline Selection Criteria and Appraisal

The guideline inclusion / exclusion criteria are outlined in detail in Appendix D. Guidelines identified through the search were reviewed by the panel for relevance. Each guideline considered potentially relevant was independently reviewed and scored by 4 panel members, using the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument.[21]   The AGREE instrument provides a framework for the evaluation of guideline quality on the basis of 6 domains: scope and purpose; stakeholder involvement; rigour of involvement; clarity and presentation; applicability; and editorial independence. Domain scores and overall assessments from each reviewer were compiled for each guideline, and results were presented for discussion at an in-person panel meeting. Panel members were provided copies of all guidelines to facilitate discussion of the results and reach consensus on the suitability of each guideline for guideline adaptation via the ADAPTE process. Each guideline was discussed as to why they were or were not recommended. Particular attention was paid to rigor scores and guideline scope.

The selected guideline was to be updated by literature published since its development. However, after reviewing the available guidelines, it was determined that none of the guidelines considered pediatric specific literature. As a result, it was decided to undertake a comprehensive review of both pediatric and adult literature in order to develop a broader evidence base on which to make recommendations and allow for an emphasis to be placed on pediatric evidence.

Systematic Review of Primary Studies

Primary Literature Search Strategy

We ran searches using the OVID search platform in the following databases: MEDLINE, EMBASE, and Cochrane Central Register of controlled trials (CCTR). In addition, we searched conference proceedings of the American Society of Clinical Oncology and the American Society of Hematology (2004 – 2011). The tables and text presented in Appendix E record the search strategies and terms used. The initial search was conducted September 8, 2011 and updated August 29, 2012. The updated search yielded one additional study requiring inclusion after the content and stakeholder review. However, the results did not impact our recommendations.

Eligibility Criteria

Types of Studies
All randomized controlled trials comparing two antifungal agents, placebo or no prophylaxis were included. Trials were from any year and in any language.

Population
Trials conducted in patients of any age receiving chemotherapy for cancer or undergoing HSCT (regardless of source of stem cells) were included. Trials involving patients with previous fungal disease were excluded (i.e. secondary antifungal prophylaxis trials)

Intervention
Trials involving any of the following antifungal agents were included as long as they were administered systemically for prophylaxis: amphotericin B (conventional and lipid formulations), caspofungin, micafungin, anidulafungin, fluconazole, itraconazole, voriconazole or posaconazole. Trials with nonsystemic antifungals were excluded (i.e. oral or inhaled amphotericin). Studies of pre-emptive or empiric therapy or antifungal treatment were excluded.

Comparison

Trials comparing a systemic antifungal agent to either another systemic antifungal agent, placebo or no prophylaxis were included. Trials were excluded if more than one anti-fungal agent (systemic or nonsystemic) was given in the treatment or comparator arm (i.e. combined prophylaxis trials) were excluded.

Outcome

The outcomes of interest included: proven or probable IFI, fungal-related mortality, overall mortality and adverse events. Trials reporting on only suspected invasive fungal infection, empiric antifungal therapy use or fungal colonization were excluded.

Decision-Making Process for Formulation of Recommendations

Recommendations were developed for each of the *a priori* identified patient populations (allogeneic stem cell transplantation, autologous stem cell transplantation, AML/MDS and malignancy with anticipated neutropenia greater than 7 days). Included trials were considered in the evidence base for a specific patient population if the population accounted for more than 40% of the patients in the trial. This meant that some trials were considered for evidence in more than one patient population. Trials conducted in homogeneous patient populations were given higher weight as were pediatric specific trials and trials that included children.

For each patient population, the evidence base was reviewed by the committee members. Recommendations were established through panel discussions, whereby any differences of opinion were resolved by consensus. If consensus was unable to be reached, a vote was cast. The quality of evidence and strength of recommendations were assessed using the GRADE system developed by Guyatt et al.[22] by the lead author and confirmed through discussion by the remaining panel members. The panel purposely did not seek to include patient input because the primary outcomes of interest were development of IFI, fungal-related mortality and overall mortality. The panel felt that these decisions were made primarily by healthcare teams rather than patients. However, the impact of prophylaxis on patients was considered when making the recommendations, including ease/route of drug administration, tolerability and adverse effects. We also considered cultural issues, but did not identify any for this guideline.

External Review Process

The draft guideline was reviewed in a two stage process; content review and stakeholder review. Initally, the guideline was reviewed by a panel of experts in pediatric hematology/oncology and infectious disease. A total of 17 experts were contacted to review the document on December 4, 2011. Eleven of 17 experts responded. The experts were asked to complete a questionnaire; their responses and the panel's responses, including changes to the draft guideline, are summarized in Appendix F.

Secondly, the guideline was sent to all C[17] sites for stakeholder review on April 30, 2012. Similar to the content review process, the stakeholders were asked to complete a questionnaire; their responses and the panel's responses/guideline changes are summarized in Appendix F. A total of 42 responses were received. All cancer centers across Canada had at least one representative with the exception of one centre.

Conflicts of Interest

Conflicts of interest were determined for each panel member prior to beginning the guideline process; none were declared. Resources for guideline development were provided by the C[17] Council, an organization that represents the 16 pediatric cancer centers in Canada. Guideline development was editorially independent from the funder.

Plans for Scheduled Review and Update

The C[17] Guidelines Committee will review this guideline every 3 years and at any time if significant information becomes available.

Evidence Synthesis and Recommendations

Guideline Search Results

Five guidelines on antifungal prophylaxis were identified and assessed using the AGREE instrument.[23-27] All five guidelines were focused primarily on adult recommendations with a limited pediatric information. Based on the overall assessment of the guidelines and the number of recommendations received, it was a unanimous group decision to use the Infectious Disease Working Party (AGIHO) of the German Society of Haematology and Oncology Recommendations for "Primary prophylaxis of invasive fungal infections in patients with hematologic malignancies"[23] as the basis for guideline adaptation. The American Society for Blood and Marrow Transplantation (ASBMT) *Guidelines for preventing infectious complications among Hematopoietic Cell Transplantation Recipients*[27] as well as National Comprehensive Cancer Network (NCCN) *Guidelines on prevention and treatment of cancer-related infections*[25] were identified as having strengths that would be used to influence the development of the present guideline. A subsequent search also identified the Infectious Disease Society of America (IDSA) guideline that was also considered in this guideline development.[28]

Despite the number of guidelines to provide direction on the use of antifungal prophylaxis, there was a lack of evidence-based guidelines that were specifically within the scope of antifungal prophylaxis for pediatric patients. Both the ASBMT and NCCN guidelines are general guidelines based primarily on adult literature. The AGIHO guidelines were felt to be more rigorous and complete and formatted in a manner that would suit the purposes of this guideline. However, the AGIHO guidelines are also largely based on adult patient data. It is recognized that extrapolation of adult recommendations to the pediatric population is not always appropriate considering the differences in clinical disease, treatment protocols and the pharmacokinetics and pharmacodynamics of the medications. As a result, it was decided that a comprehensive search of both pediatric and adult literature was appropriate in order to expand the evidence base on which to make recommendations and allow for emphasis to be placed on pediatric literature.

Primary Literature Search Results

As of August 29, 2012, a total of **11,255** references were indentified from MEDLINE, EMBASE, CCTR and conference abstracts. All references were saved in an EndNote library used to identify the **3386** duplicates. The author (MS) reviewed the remaining **7869** unique references against our inclusion criteria. From those citations, a total of 46 full publications and 1 conference abstract met the eligibility criteria (Figure 1).

The remaining results and discussion have been divided into four sections: recommendations for allogeneic HSCT recipients, recommendations for autologous hematopoietic stem cell transplant recipients, recommendations for patients with AML or MDS and recommendations for patients with malignancy and anticipated neutropenia greater than 7 days. Each recommendation is accompanied by the evidence on which the recommendation was made as well as the assessment of quality and strength of the evidence.

Figure 1. Selection of studies investigating antifungal prophylaxis in patients with malignancy receiving chemotherapy and undergoing hematopoietic stem cell transplantation.
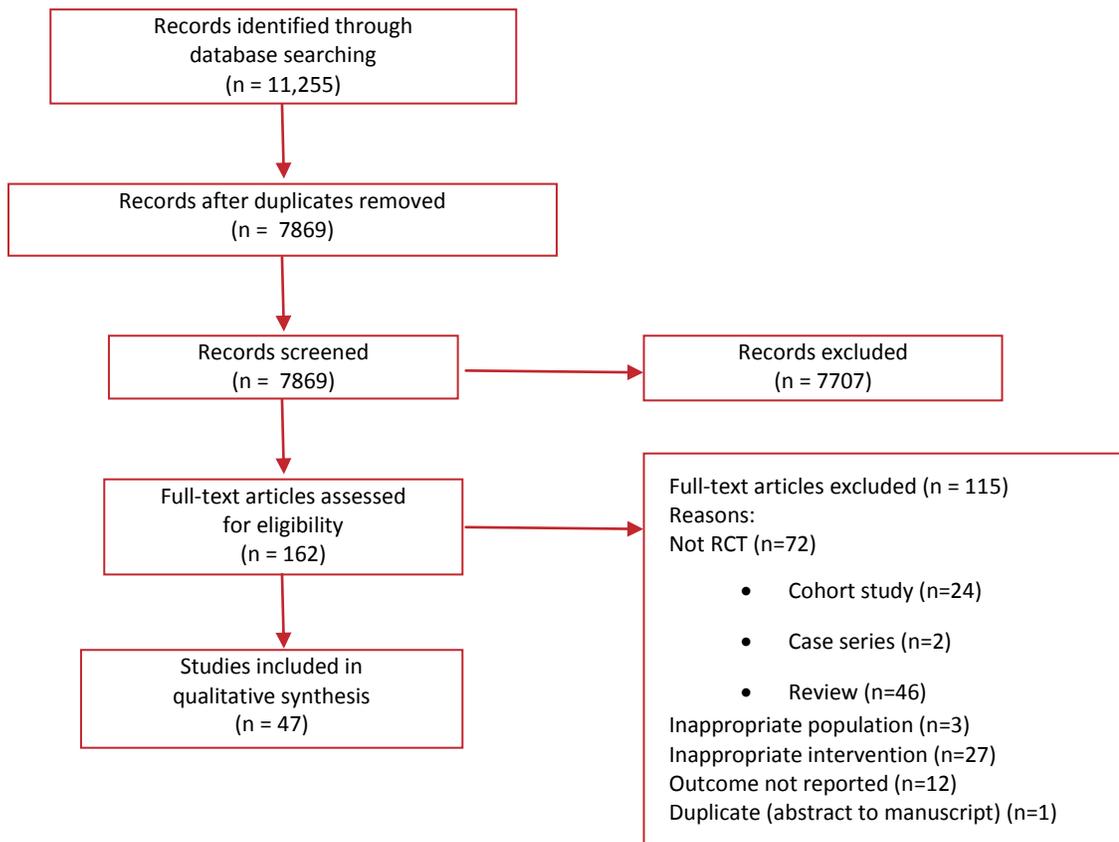
Health Question 1: Should primary antifungal prophylaxis be used to prevent IFI in children undergoing allogeneic HSCT? If so, what medication (dose and duration) should be used?

Recommendation 1.1: Allogeneic HSCT During and Immediately Following Conditioning

- *For children one month to less than 19 years of age undergoing allogeneic HSCT, administer fluconazole 6 – 12 mg/kg/day (maximum 400 mg/day) intravenous (IV) or oral (PO) from the start of conditioning until engraftment (strong recommendation, high quality evidence).*

- *For the above children where fluconazole is contraindicated, administer an echinocandin as an alternative to fluconazole (strong recommendation, moderate quality evidence).*

Note: Adjust fluconazole dose in children with renal impairment. Consideration may be given to initiating antifungal prophylaxis on the day of transplant for patients receiving conditioning agents known or suspected to interact with fluconazole.

Evidence Summary

Table 2: Summary of Studies Used to Inform Recommendation 1.1

COMPARISON Study and Results	Population *
FLUCONAZOLE High Dose vs. Low Dose	
MacMillan *et al* (2002)[29] • Randomized controlled trial (blinding unclear); two by two factorial design • 253 pediatric and adult HSCT patients (allogeneic 56%, autologous 44%) • Number of pediatric patients (≤ 19 years): 74 (29%) • Compared high dose fluconazole (400 mg/day; weight < 40 kg - 6 mg/kg/day) to low dose (200 mg/day; weight < 40 kg - 3 mg/kg/day) starting within 72 hours of conditioning until neutrophils ≥ 1000 cells/μL for 3 days and then second randomization to fluconazole 100 mg/day (weight < 40 kg - 1.5 mg/kg/day) or clotrimazole troches daily until Day +100 • Proven IFI by Day 50: 7.3% high dose fluconazole vs. 2.3% low dose (p = 0.06) • No difference in adverse events	PA
FLUCONAZOLE vs. PLACEBO	
Goodman *et al* (1992)[30] • Double blind randomized controlled trial • 356 HSCT patients (allogeneic 48%, autologous 52%); age ≥ 13 years • Number of pediatric patients (≤ 18 years): not available • Compared fluconazole 400 mg/day PO to placebo starting at conditioning until neutrophils > 1000 cells/μL for 7 days (max. 10 weeks) • Proven IFI: 2.8% fluconazole vs. 15.8% placebo (p < 0.001) • Fungal-related mortality: 0.6% fluconazole vs. 5.6% placebo (p < 0.001) • No difference in overall survival	PA
Slavin *et al* (1995)[31]	PA

Children's Cancer & Blood Disorders

- Double blind randomized controlled trial 300 HSCT patients (allogeneic 88%, autologous 12%); age >12 years and weight >34 kg - Number of pediatric patients (≤ 18 years): not available - Compared fluconazole 400 mg/day IV/PO to placebo starting within 24 hours of conditioning until Day + 75 - Proven IFI: 7% fluconazole vs. 18% placebo (p=0.004); predominantly *Candida albicans* resulting in difference - Fungal-related mortality: 12.5% fluconazole vs. 20.9% placebo (p=0.005) - Mortality (up to D+110): 20.4% fluconazole vs. 35.1% placebo (p=0.004)	
Chandrasekar et al (1994)[32] - Double blind randomized controlled trial 46 patients HSCT (allogeneic 41%, autologous 7%) or malignancy and anticipated neutropenia ≥ 7 days (52%); age ≥ 13 years - Number of pediatric patients (< 17 years): None - Compared fluconazole 400 mg/day IV/PO to placebo starting at conditioning (HSCT) or initiation of chemotherapy (malignancy) until resolution of neutropenia (≥ 1000 cells/μL) 7 days (max. 10 weeks) - Systemic fungal infection: 8.7% fluconazole vs. 4.3% placebo (p=NS) - Mortality: 17.4% fluconazole vs. 8.7% placebo (p=NS) - Fungal-related mortality: 8.7% fluconazole vs. 4.3% placebo (p=NS)	A
FLUCONAZOLE vs. ITRACONAZOLE	
Ota et al (2010) (Abstract)[33] - Randomized controlled trial (blinding unclear) 76 HSCT patients (63% allogeneic, 37% autologous); age not stated - Number of pediatric patients (≤ 18 years): not available - Compared fluconazole 400 mg/day IV/PO to itraconazole 200 mg/day IV/PO starting on day of HSCT until Day +28 (unclear whether itraconazole capsules vs. solution) - Proven or Probable IFI: No cases in either group - Severe hepatotoxicity: 13.5% fluconazole vs. 13.9% itraconazole	PA
Marr et al (2004)[34] - Open-label randomized controlled trial 304 allogeneic HSCT patients; age ≥ 13 years and weight > 40 kg - Number of pediatric patients (≤ 18 years): not available - Compared fluconazole 400 mg/day IV/PO to itraconazole 200 mg IV daily or solution 2.5 mg/kg PO TID starting at conditioning for a minimum of 120 days or 4 weeks after discontinuing GVHD therapy (max. 180 days) - Proven or probable IFI (intention to treat analysis): 16% fluconazole vs. 13% itraconazole (p=0.46) - Invasive mold infection (on treatment analysis): 12% fluconazole vs. 5% itraconazole (p=0.03) - Overall mortality (up to D+250): 31% fluconazole vs. 39% itraconazole (p=0.11) - Fungal-related mortality: 7% fluconazole vs. 8% itraconazole (p=NS) - Adverse events leading to discontinuation: 16% fluconazole vs. 36% itraconazole (p <0.001); predominantly gastrointestinal disturbance	PA
Winston et al (2003)[35] - Open-label randomized controlled trial 140 allogeneic HSCT patients; age range 14 – 63 years - Number of pediatric patients (≤ 18 years): not available - Compared fluconazole 400 mg/day IV/PO to itraconazole 200 mg IV BID on Day +1 and Day +2 then 200 mg IV daily or 200 mg solution PO BID until Day +100 - Proven IFI during first 180 days post stem cell transplant (per protocol analysis): 25% fluconazole vs. 9%	PA

itaconazole (p=0.01)
- High rates of *C. glabrata* and *C. krusei* contributing to higher rates IFI in fluconazole group
- Overall mortality: 42% fluconazole vs. 45% itraconazole (p=NS)
- Fungal-related mortality: 18% fluconazole vs. 9% itraconazole (p=0.13)
- Gastrointestinal side effects: 9% fluconazole vs. 24% itraconazole (p=0.02)

FLUCONAZOLE vs. VORICONAZOLE	
Wingard _et al_ (2010)[36] - Double blind randomized controlled trial - 600 allogeneic HSCT patients; age ≥ 2 years - Number of pediatric patients (< 18 years): 51 (8.5%) - Compared fluconazole 400 mg/day (children < 20 kg: 100 mg/day, > 20 kg: 200 mg/day) IV/PO to voriconazole 200 mg BID (children < 20 kg: 50 mg BID, > 20 kg: 100 mg BID) IV/PO from the start of conditioning until Day +100 or Day +180 (high risk patients) - Proven/probable IFI (up to D+180): 8.1% fluconazole vs. 4.6% voriconazole - Fungal free survival (alive and free from proven, probable and presumptive IFI) at 180 days: 75% fluconazole vs. 78% voriconazole (p=0.49) - Overall mortality (up to D+180): 20% fluconazole vs. 18.8% voriconazole (p=NS) - Trial conducted in environment with structured monitoring (galactomannan)	PA
FLUCONAZOLE vs. ECHINOCANDINS	
Van Burik _et al_ (2004)[37] - Double blind randomized controlled trial - 882 pediatric and adult HSCT patients (allogeneic 54%, autologous 46%) - Number of pediatric patients (< 16 years): 84 (9.5%) - Compared fluconazole 8 mg/kg/day (max 400 mg/day) IV to micafungin 1 mg/kg/day (max 50 mg/day) IV starting from conditioning until the earliest of 5 days after engraftment (ANC ≥ 500 cells/μL), Day +42, development of proven/probable/possible IFI, unacceptable drug toxicity, death, withdrawal or discontinuation of drug - Successful prophylaxis (absence of proven/probable/possible IFI) after 4 weeks therapy: 73.5% fluconazole vs. 80% micafungin (p=0.03) - Proven/Probable IFI: 2.4% fluconazole vs. 1.6% micafungin (p=0.481) - Possible IFI: 21.4% fluconazole vs. 15.1% micafungin (p=0.026) - No difference in rates of invasive candidiasis, but aspergillosis lower in the micafungin group - No difference in overall or fungal-related mortality - Adverse events leading to drug discontinuation: 7.2% fluconazole vs. 4.2% micafungin (p=0.058)	PA
Hiramatsu _et al_ (2008)[38] - Open label randomized controlled trial - 106 adult HSCT patients (allogeneic 52%, autologous 48%); age > 18 years - Compared fluconazole 400 mg/day IV to micafungin 150 mg/day IV starting within 48 hours of conditioning until the earliest of 5 days after engraftment, Day +42, proven/probable or possible IFI, drug toxicity, death, withdrawal or discontinuation - Treatment success (absence of proven/probable/suspected IFI): 88% fluconazole vs. 94% micafungin (p=0.295) - Proven IFI: 2% fluconazole vs. 2% micafungin (p = 1.0) - Probable IFI: 0 fluconazole vs. 0 micafungin (p = 1.0) - Overall mortality: 4% fluconazole vs. 8% micafungin (p=0.4) - Sample size determined based on number expected to enroll over 2 years; powered to detect 20% difference in treatment success between groups	A

AMPHOTERICIN vs. PLACEBO	
Riley *et al* (1994)[39] • Double blind randomized controlled trial • 35 pediatric and adult HSCT patients (69% allogeneic, 31% autologous) • Median age (range): amphotericin B 38 (10-51) years, placebo 38 (14-52) years • Number of pediatric patients (≤ 18 years): not available • Compared conventional amphotericin B 0.1 mg/kg/day to placebo starting at onset of neutropenia until neutrophils > 500 cells/μL • Proven IFI (positive culture from sterile site or histopathological evidence of fungus): 0% conventional amphotericin B vs. 28% placebo (p=0.045) • Fungal-related morality during hospitalization: 0% conventional amphotericin B vs. 11% placebo (no p value)	PA
Tollemar *et al* (1993)[40] • Double blind randomized controlled trial • 76 pediatric and adult HSCT patients (83% allogeneic, 17% autologous) • Median age (range): liposomal amphotericin B 33 years (1-53), placebo 30 years (1-52) • Number of pediatric patients (≤ 18 years): not available • Compared liposomal amphotericin B 1 mg/kg/day to placebo starting at onset of neutropenia until neutrophil recovery to > 500 cells/μL for 2 days • Proven IFI: 3% liposomal amphotericin B vs. 8% placebo • Overall mortality: 44% liposomal amphotericin B vs. 36% placebo	PA
Kelsey *et al* (1999)[41] • Double blind randomized controlled trial • 161 patients with malignancy or HSCT (chemotherapy 16%, allogeneic HSCT 53%, autologous HSCT 31%) • Mean age (SD): liposomal amphotericin B 39.6 years (11.0); placebo 40.2 (13.2) years • Compared liposomal amphotericin B 2 mg/kg three times/week to placebo starting at Day +1 after chemotherapy or HSCT until neutrophil recovery • Proven IFI: 0% liposomal amphotericin B vs. 3.4% placebo (p=NS) • Suspected IFI: 31% liposomal amphotericin B vs. 40% placebo (p=NS) • Overall mortality: 15% liposomal amphotericin B vs. 14% placebo (p=NS)	A
FLUCONAZOLE vs. AMPHOTERICIN	
Koh *et al* (2002)[42] • Open label randomized controlled trial • 186 pediatric and adult HSCT patients (allogeneic 75%, autologous 25%); • Median age (range): fluconazole 29.8 years (4 – 63), conventional amphotericin B 29.6 years (4 – 62) • Number of pediatric patients (≤ 18 years): not available • Compared fluconazole 200 mg/day (no pediatric dose specified) PO to conventional amphotericin B 0.2 mg/kg/day (max. 10 mg) IV starting from 1 day prior to conditioning until engraftment (ANC > 500 cells/μL x 3 days), drug toxicity, or proven/probable IFI • Proven IFI: 12% fluconazole vs. 12.8% conventional amphotericin B (p=0.09) • Suspected IFI: 4% fluconazole vs. 2.3% conventional amphotericin B (p=NS) • 100 day survival: 78% fluconazole vs. 70% conventional amphotericin B (p=0.25)	PA
ITRACONAZOLE vs. VORICONAZOLE	
Marks *et al* (2010)[43] • Open label randomized controlled trial • 503 pediatric and adult allogeneic HSCT patients; age ≥ 12 years	PA

- Mean age (range): voriconazole 43.3 years (11-70), itraconazole 42.3 (13-70)
- Number of pediatric patients (≤ 18 years): not available
- Compared voriconazole 6 mg/kg IV q12h loading dose on Day 1 then 200 mg PO BID (< 40 kg – doses halved) to itraconazole 200 mg IV q12h loading dose on Day 1 and 2 then 200 mg PO BID starting the day of HSCT until at least Day +100 and up to Day +180
- Successful prophylaxis at 180 days (alive and without proven or probable IFI and able to tolerate drug for at least 100 days with <= 14 days discontinuation): 48.7% voriconazole vs. 33.2% itraconazole (p<0.001)
- Proven or Probable IFI: 1.3% voriconazole vs. 2.1% itraconazole (p=0.54)
- Survival at one year: 73.5% voriconazole vs. 67.0% itraconazole (p=0.17)
- More hepatic (12.9% vs. 5.0%) and visual (5.4% vs. 0%) adverse events in voriconazole arm, more gastrointestinal side effects in itraconazole arm

RATIONALE:

FLUCONAZOLE

There have been two well designed randomized, controlled trials comparing fluconazole to placebo in adult patients.[30,31] Both studies showed that fluconazole prophylaxis at a dose of 400 mg/day reduced development of IFI largely secondary to the reduction in invasive candidal infections. Both pediatric patients 12 years and older and adults were included in these trials. Although children less than 12 years were excluded from these studies, it is reasonable to believe that this population would benefit similarly from fluconazole prophylaxis. Given that there is adequate safety data for fluconazole use in the pediatric age group, the recommendation has been extended to include all pediatric age groups. This is in keeping with the AGIHO[23], ASBMT[27], NCCN[25] and IDSA[28] guidelines.

One of the concerns with fluconazole prophylaxis in allogeneic HSCT patients is its lack of anti-mold coverage. Allogeneic HSCT patients are at risk for both invasive yeast infections such as *Candida sp*. and mold infections but fluconazole is active only against some yeasts. As a result, several trials have investigated broader spectrum agents. These trials are outlined in the following sections, but overall agents with broader spectra have failed to demonstrate a meaningful benefit over fluconazole. In addition, a recent meta-analysis that compared mold-active agents to fluconazole prophylaxis in adult and pediatric cancer patients receiving chemotherapy or HSCT, observed no difference in overall mortality (RR 1.0; 95% CI 0.88-1.13) between groups.[44] Prophylaxis with mold-active agents was associated with a significantly lower number of proven or probable IFI and IFI-related mortality. However, compared to patients receiving fluconazole, antifungal prophylaxis was modified or discontinued more often in patients receiving mold-active prophylaxis (RR 1.19; 95% CI 1.19-3.08). Thus, it is difficult to ascertain the contribution of anti-mold prophylaxis or the balance between risk and benefit under these circumstances. Given that mold-active agents did not influence overall mortality and have important limitations including drug interactions, toxicity, cost and, for some, limited experience in children, fluconazole remains the recommended agent. Recommendations may change as data becomes available in the future.

Among allogeneic HSCT recipients, some subgroups are considered to be at higher risk for mold infections and thus specifically targeted with anti-mold prophylaxis. The IDSA suggests that allogeneic HSCT patients with anticipated prolonged neutropenia of at least 2 weeks should receive anti-mold prophylaxis (C III, IDSA quality grading[45]) because of the high risk of *Aspergillus* infection. Given the lack of specific trials in children undergoing allogeneic HSCT, we have not made this recommendation at this time.

Another key consideration with fluconazole prophylaxis is its decreased effectiveness against certain *Candida* species including *C. glabrata* and *C. krusei*. Since the introduction of routine fluconazole prophylaxis in HSCT, the incidence of non-*albicans Candida* appears to be increasing,[36,37] but the exact burden is not clear. Health care providers should be aware of the gaps in coverage of fluconazole and the potential increasing incidence of these *Candida* species when treating patients with persistent fever on fluconazole prophylaxis. Similarly, for those patients known to be colonized with non-*albicans* fluconazole-resistant species, the potential for disease from these species should be considered early in patients with persistent fever or clinical signs of infection. Evidence-based recommendations for alternate prophylactic agents cannot be made at this time.

Dosing
The adult dosing recommendation of fluconazole 400 mg/day is extrapolated from the two placebo controlled trials.[30,31] This is the dose recommended by the AGIHO, ASBMT, NCCN and the IDSA Guideline on Management of Candidiasis. Doses less than 400 mg/day have not been used in placebo controlled trials. Only one trial has compared high dose (400 mg/day or 6 mg/kg/day) to low dose (200 mg/kg/day or 3 mg/kg/day) fluconazole prophylaxis.[46] This single center study was a two by two factorial design with patients randomized to low or high dose fluconazole until engraftment and then randomized to fluconazole 100 mg or clotrimazole trouches until 100 days after transplantation. At 50 days, there was no difference between rates of *Candida* infection or *Aspergillus* infection between groups. However, this outcome was measured at a time when majority of patients had crossed over to the second treatment course raising concerns about potential interaction or contamination. As a result, there is insufficient evidence to recommend the use of doses lower than 400 mg/day in adults at this time; this dose of fluconazole appears to be well tolerated.[47]

The optimal pediatric dose is less clear. There have been no randomized controlled trials with fluconazole conducted exclusively in children. The dosing recommendation we propose takes into consideration the current recommended adult dose, its equivalent pediatric dose based on pharmacokinetics and the fluconazole doses that have been used in pediatric trials. The pediatric fluconazole dose which is equivalent to the dose recommended for adults in the AGIHO guideline (400 mg/day) ranges from 6 - 12 mg/kg/day depending on patient age and weight.[48-52] This is based on pharmacokinetic studies in children showing that children less than 15 years of age have a higher volume of distribution and a faster elimination rate compared to adults.[48,49,51] However, in trials that have included children, fluconazole doses have ranged from 3 mg/kg/day[46] to 8 mg/kg/day.[37] The most recent trial involving children by Wingard et al.[36] used a fixed dose of 100 mg for children less than 20 kg and 200 mg for children greater than 20 kg resulting in a range of doses from approximately 3 to 10 mg/kg/day depending on the patient's weight.

From a safety standpoint, fluconazole is believed to be safe and well tolerated in doses up to 12 mg/kg/day.[50] These doses have been used for prolonged periods to treat certain candidal infections including meningitis, endophthalmitis and endocarditis. Furthermore, the IDSA recommends doses up to 12 mg/kg/day when using fluconazole for these clinical indications.[53] Although there is insufficient data on prolonged administration of prophylactic fluconazole at 12 mg/kg/day, doses up to 10 mg/kg/day have been used safely in HSCT prophylaxis.[36] Given the safety data from treatment studies and the doses used in the current trials, it is likely that doses up to 12 mg/kg/day can be administered safely for prophylaxis.

In summary, given the lack of trials conducted exclusively in children, an evidence-based recommendation regarding the optimal prophylactic dose of fluconazole in children undergoing

allogeneic HSCT cannot be made. However, considering the recommended adult dose, its pediatric equivalent and the available efficacy and safety data, we recommend a dose range of 6 – 12 mg/kg/day to a maximum of 400 mg/day. This dose range is higher than the ASBMT recommendation of 3 – 6 mg/kg/day (maximum 600 mg/day). However, we feel that the higher dose is justified given the available information outlined above and the adequate safety data. Further research specifically addressing the optimal dose of fluconazole in children would be useful.

Duration

The optimal duration of prophylaxis is also not clear. The trial by Goodman et al.[30] continued prophylaxis until the neutrophil count was greater than 1000 cells/µL for 7 days and Slavin et al.[31] continued prophylaxis until day +75 after HSCT. Both trials were associated with decreased rates of IFI in those who received fluconazole prophylaxis. However, in the trial by Slavin et al., there was an overall survival benefit in those treated with fluconazole that was not found in the trial by Goodman. This survival benefit was not entirely attributable to decreased fungal infection and not adequately explained. A post hoc long term follow-up of the trial by Marr et al. 2000[54] found that those on fluconazole had decreased rates of severe gut GVHD, lower mortality from severe gut GVHD and lower rates of disseminated candidal infections and *Candida*-associated death. Unfortunately, no such long term analysis was conducted for the Goodman trial.

Therefore, administration of fluconazole for 75 days after HSCT may be associated with a mortality benefit compared to administration of prophylaxis until engraftment. However, given the concerns with drug interactions, potential difficulties with prolonged administration of fluconazole and lack of clear evidence supporting the benefit of prolonged administration, we recommend continuing prophylaxis at least until engraftment. This is consistent with the ASBMT guideline. It is known that the risk of fungal disease may extend beyond this period but lack of study data limit an evidence-based recommendation to extend prophylaxis beyond this point. This recommendation may change as further data become available.

ECHINOCANDINS

There have been two randomized controlled trials comparing fluconazole to micafungin in allogeneic HSCT recipients. The initial study by Van Burik et al.[37] included both pediatric (n=84) and adult (n=798) patients. Micafungin had a higher proportion of patients with successful prophylaxis at 4 weeks following HSCT (80% vs. 73.5%) which reached statistical significance (p=0.03). However, the investigators' definition of IFI included proven, probable and possible IFI; thus, the comparability of these findings to other trials is limited. Also, when only proven or probable IFI were compared between treatment groups, there was no significant difference in infection rates and this is likely the more relevant outcome. Both agents were effective for the prevention of invasive candidiasis and although the rate of IA was lower in the micafungin group, this did not reach statistical significance. There was also no difference in all cause mortality or fungal-related mortality between groups. The second trial by Hiramatsu et al.,[38] did not detect a significant difference in treatment success between groups. However, the sample size was based on feasibility and the sample size was powered only to detect a large (20%) difference between groups.

Both studies included both allogeneic and autologous HSCT recipients with a high percentage of autologous recipients. Therefore, the results of these studies may be difficult to apply to the high risk allogeneic HSCT group. Further research focusing on the use of micafungin or other echinocandins in allogeneic HSCT patients would be helpful. In the meantime, it appears that micafungin is not inferior to fluconazole nor has micafungin been associated with more adverse effects. It therefore is reasonable to

consider micafungin as an alternate to prophylaxis in those patients where fluconazole is contraindicated.

Other echinocandins have not been studied in this population. However, it is reasonable to assume that they would be similarly effective. This is an important consideration as micafungin has not yet been approved in Canada for use in children and there is a black box warning in Europe based on increased number of liver tumors observed in rat models. As such, caspofungin is an attractive agent given it has been approved for use in children (for other indications) and there is significant experience with its use. This forms the basis for our recommendation that echinocandins can be considered as alternative prophylactic agents when fluconazole is contraindicated. In these scenarios, generally other azoles are contraindicated and given the lack of data for amphotericin products, echinocandins currently appear to be the best alternative. However, the high cost and need for intravenous administrations are important limitations to its use.

Dose

The adult dosing recommendation of micafungin 50 mg/day is based on pharmacokinetic-pharmacodynamic data[55] and it was the dose used in the Van Burik trial[37] showing that micafungin was not inferior to fluconazole. This is the adult dose recommended by the AGIHO guideline, ASBMT, NCCN and the IDSA Guideline on Management of Candidiasis[53]. Doses less than 50 mg/day have not been used in placebo controlled trials. Higher doses of 150 mg/day have been used safely,[38] but there have been no trials directly comparing higher and lower doses. As a result, there is no evidence to recommend doses higher than 50 mg/day.

The optimal pediatric dose is less clear given there are few studies of dosing in children. Current evidence is limited to pharmacokinetic / pharmacodynamic models, small clinical trials of short duration and case reports. The recommended treatment dose of 2 – 4 mg/kg/day is based on pharmacokinetic /pharmacodynamic data[56] and clinical trials.[57] This dose is equivalent to 100 – 200 mg/day in adults. Taking into consideration the recommended adult dose of 50 mg/day for prophylaxis, the pediatric dosing equivalent would be 1 mg/kg/day. However, pharmacokinetic modeling in children has shown that as weight decreases, higher doses of micafungin on a mg/kg basis are required to achieve equivalent adult dosing, especially for children less than 10 – 15 kg.[58] Therefore, the optimal dose of micafungin prophylaxis is not clear, especially for younger children.

Unfortunately, given the limited number of trials conducted exclusively in children, an evidence-based recommendation specific to HSCT regarding the optimal prophylactic dose of micafungin in children undergoing allogeneic HSCT cannot be made. However, considering the recommended adult dose, its pediatric equivalent, the available efficacy and safety data and the dose used in the one clinical trial that included children,[37] we recommend a dose of 1 mg/kg/day to a maximum of 50 mg/day. It is important to consider that children with lower weights may require a higher milligram per kilogram dose but evidence to make a specific recommendation are lacking. Further research specifically addressing the optimal dose of micafungin in children would be useful.

ITRACONAZOLE

Itraconazole is an alternative to fluconazole with a broader spectrum of activity. However, concerns regarding efficacy, tolerability, cost and drug interactions have curtailed its widespread use. From a practical standpoint, successful administration of itraconazole presents several challenges: very poor and variable bioavailability (capsule vs oral solution), poor palatability, drug-drug and drug-food interactions, and a relatively high incidence of adverse effects. There have been several trials comparing

itraconazole solution to fluconazole in allogeneic HSCT recipients. Winston et al.[35] found that itraconazole solution was associated with decreased rates of IFI but observed no impact on overall mortality. In the trial by Marr et al.,[59] itraconazole solution resulted in statistically significant fewer mold infections, but did not differ from fluconazole in terms of rates of proven or probable IFI. There was also no difference in overall mortality observed. Furthermore, prophylaxis was associated with a higher rate of toxicity leading to high withdrawal rates in the itraconazole arm (36%). Neither of these trials involved pediatric patients. A recent conference abstract by Ota et al.[33] also compared itraconazole to fluconazole and found no significant difference between groups in proven and probable IFI or severe hepatotoxicity. Given its equivocal efficacy relative to other agents, poor adverse effect profile and drug interactions associated with itraconazole, there is insufficient reason to recommend its use over fluconazole for the prevention of fungal infection in children undergoing allogeneic HSCT.

VORICONAZOLE

Voriconazole has recently been evaluated in a large randomized controlled trial comparing voriconazole to fluconazole in both adult and pediatric patients undergoing allogeneic HSCT.[36] This well designed trial did not find a difference between fluconazole and voriconazole with respect to fungal-free survival or overall survival at 180 days. This trial was conducted in a setting with intensive monitoring and surveillance for IFI and consequently its findings may not be applicable at other sites. Other considerations with voriconazole are the significant potential for drug interactions and the lack of data on the appropriate dose in children. The pharmacokinetic disposition of voriconazole in children is very different from that of adults. Young children are known to clear voriconazole faster as demonstrated by a 3-fold-lower plasma concentration in children given the standard adult dose of 4 mg/kg IV every 12 hours.[60] Furthermore, young children display linear pharmacokinetics following IV administration[60] whereas adults exhibit nonlinear pharmacokinetics[61,62] making extrapolations from adult dosing very difficult. Considering the lack of demonstrated efficacy for prophylaxis in patients undergoing allogeneic HSCT, lack of data on dosing in children, the potential for drug interactions and the high cost of voriconazole, there is insufficient evidence to recommend the use of voriconazole over fluconazole.

AMPHOTERICIN PRODUCTS

Several formulations of amphotericin have been studied in randomized controlled trials. Conventional amphotericin B infusion has been compared to placebo and fluconazole at doses of 0.1 and 0.2 mg/kg/day respectively. Compared to placebo, conventional amphotericin B was associated with significantly lower rates of IFI.[63] However, when compared to fluconazole there was no significant difference in rates of IFI between those receiving fluconazole and those receiving conventional amphotericin B.[42] Furthermore, conventional amphotericin B has been associated with higher infusion-related reactions and renal toxicity leading to higher rates of drug discontinuation.[64] Trials using conventional amphotericin B at doses higher than 0.2 mg/kg/day have not been conducted.

Three lipid formulations are available including liposomal amphotericin B (L-AmB, Ambisome®), amphotericin B lipid complex (ABLC, Abelcet®) and amphotericin B colloidal dispersion (ABCD, Amphotec®). Liposomal amphotericin B has been evaluated in this setting and remains an attractive alternative to conventional amphotericin because of its lower toxicity profile. There have been two randomized controlled trials comparing liposomal amphotericin B to placebo.[40,41] Both failed to demonstrate a reduction in proven IFI compared to placebo. However, both trials were underpowered to detect a significant difference.

Currently, there is insufficient evidence to recommend the use of amphotericin products for prophylaxis in allogeneic HSCT patients.

Recommendation 1.2: Allogeneic HSCT with Acute Grade II-IV GVHD or Chronic Extensive GVHD

- *For children 13 years of age or older undergoing allogeneic HSCT with acute Grade II – IV or chronic extensive GVHD, prophylaxis with posaconazole 200 mg PO TID from GVHD diagnosis until resolution of acute grade II-IV GVHD or chronic extensive GVHD is suggested (weak recommendation, moderate quality evidence).*

- *For the above children where posaconazole is contraindicated, fluconazole 6 – 12 mg/kg/day (maximum 400 mg/day) IV/PO is suggested as an alternative to posaconazole (weak recommendation, low quality evidence).*

- *For children one month to less than 13 years of age, fluconazole 6 – 12 mg/kg/day (maximum 400 mg/day) IV/PO from GVHD diagnosis until resolution of acute grade II – IV GVHD or chronic extensive GVHD is suggested (weak recommendation, low quality evidence).*

Evidence Summary

Table 3: Summary of Evidence Used to Inform Recommendation 1.2

COMPARISON Study and Results	Population *
Wingard *et al* (2010)[36] - Double blind randomized controlled trial - 600 allogeneic HSCT patients; age ≥ 2 years - Number of pediatric patients (< 18 years): 51 (8.5%) - Compared fluconazole 400 mg/day (children < 20 kg: 100 mg/day, > 20 kg: 200 mg/day) IV/PO to voriconazole 200 mg BID (children < 20 kg: 50 mg BID, > 20 kg: 100 mg BID) IV/PO from the start of conditioning until Day +100 or Day +180 (high risk patients) - Proven/probable IFI (up to D+180): 8.1% fluconazole vs. 4.6% voriconazole - Fungal free survival (alive and free from proven, probable and presumptive IFI) at 180 days: 75% fluconazole vs. 78% voriconazole (p=0.49) - Overall mortality (up to D+180): 20% fluconazole vs. 18.8% voriconazole (p=NS) - Trial conducted in environment with structured monitoring (galactomannan)	PA
Ullmann *et al* (2007)[65] - Double blind randomized controlled trial - 600 allogeneic HSCT patients with acute grade II - IV GVHD or chronic extensive GVHD; age ≥ 13 years and weight ≥ 34 kg - Number of pediatric patients (< 18 years): 12 (2%) - Compared fluconazole 400 mg/day PO to posaconazole 200 mg PO TID starting from randomization until 112 days of prophylaxis or development of outcome - Proven or probable IFI: 9% fluconazole and 5.3% posaconazole (p=0.07) - IA: 7% fluconazole and 2.3% posaconazole (p=0.006) - Fungal-related mortality: 4% fluconazole vs. 1% posaconazole (p=0.046) - Overall mortality: 28.1% fluconazole vs. 25.2% posaconazole (p=NS)	PA

Discussion

Patients with GVHD are considered to be at increased risk of IFI because of the associated impairment in cell mediated immunity, mucosal damage and immunosuppressive medications required for treatment.[66] Several trials in adults have confirmed this higher risk in patients with acute grade II – IV GVHD[10,12,67-69] and chronic extensive GVHD.[67,68] Trials specific to children have also found an increased risk of IFI in children with acute grade III-IV GVHD and chronic extensive GVHD.[70] There have been few prospective clinical trials conducted exclusively during this time period, however, in a retrospective review of HSCT for chronic myelogenous leukemia, over 75% of patients had acute grade II-IV GVHD and survival was improved in patients on fluconazole prophylaxis.[71] This study and the evidence suggesting that this is a high risk period for IFI, form the basis for recommending the use of anti-fungal prophylaxis for patients with acute Grade II-IV GVHD or chronic extensive GVHD.

In terms of the choice of prophylactic agent, there have been limited comparative clinical trials. The increased risk of IFI in this population appears to be attributable to an increased risk of invasive mold infections (predominantly *Aspergillus*) which suggests that anti-mold prophylaxis may be indicated. However, in the trial by Wingard et al.,[36] there was no difference in fungal free survival or overall survival in patients on fluconazole compared to voriconazole. Patients that were higher risk (i.e. developed grade II-IV GVHD) continued prophylaxis for 180 days and this occurred in 50% of patients in both trial arms. Although this group was not analyzed separately, this provides some evidence for the use of fluconazole in patients with GVHD despite its lack of anti-mold activity.

There has been only one clinical trial specifically conducted in patients with GVHD.[65] This double blind trial by Ullmann et al. compared fluconazole to posaconazole in patients 13 years and older who had acute grade II-IV or chronic extensive GVHD. Patients receiving posaconazole prophylaxis had lower rates of proven and probable IFI and a lower rate of fungal–related mortality. All cause mortality was similar between groups. Unfortunately, this trial included only 12 patients between the ages of 13 – 18 years (2%) thereby limiting its applicability to the pediatric population. Given that there is only one trial which included very few children and there has not yet been a recommended dose for children less than 13 years of age, there is insufficient information to routinely recommend posaconazole in pediatric patients. However, its use can be considered in patients 13 years and older with GVHD. The use of posaconazole in adolescents is therefore presented as a consideration. However, drug interactions, the exclusive oral administration and the need to administer each dose together with high fat food to ensure adequate absorption are important limitations of this agent.

For all children less than 13 years of age and for children 13 years and older where posaconazole is contraindicated, we recommend the use of fluconazole given the experience in the Wingard trial.[36] However, it is important to note that this trial was conducted in an intense monitoring environment with frequent galactomannan testing and structured use of empiric therapy which may have impacted on the rates of IFI, specifically invasive *Aspergillus*. Therefore, in centers with high rates of mold infections and without intense monitoring, a mold active agent may be a reasonable choice for prophylaxis in this patient population, although data is lacking. As more evidence becomes available, our fluconazole recommendation may change. Further research is recommended to evaluate the use of anti-mold agents for prophylaxis during this high risk period. For fluconazole dosing considerations see section 1.1.

The duration of antifungal prophylaxis in patients with GVHD has not been well studied. In the trial by Ullmann et al.,[65] prophylaxis was continued until 112 days of prophylaxis or development of the

outcome. However, a strict time period of prophylaxis may not be ideal given the varying resolution rates of GVHD. Given that patients with acute grade II-IV GVHD and chronic extensive GVHD have been shown to be at increased risk for invasive mold infection, it is reasonable to conclude that antifungal prophylaxis should continue until resolution of acute GVHD to Grade I or lower. This is consistent with the NCCN guideline[25] that suggests continuing prophylaxis until resolution of significant GVHD. Other guidelines including ASBMT[27] and IDSA[28], do not define a duration but imply a similar approach.

Health Question 2: Should antifungal prophylaxis be used to prevent IFI in children undergoing autologous HSCT? If so, what medication (dose and duration) should be used?

Recommendation 2.1: Autologous HSCT with anticipated neutropenia greater than 7 days

- *For children one month to less than 19 years of age undergoing autologous HSCT with anticipated neutropenia for more than 7 days, administer fluconazole 6 – 12 mg/kg/day (maximum 400 mg/day) IV/PO from the start of conditioning until engraftment (strong recommendation, moderate quality evidence).*

Evidence Summary

Table 4: Summary of Evidence Used to Inform Recommendation 2.1

COMPARISON Study and Results	Population *
FLUCONAZOLE vs. PLACEBO	
Goodman *et al* (1992)[30] • Double blind randomized controlled trial • 356 HSCT patients (allogeneic 48%, autologous 52%); age ≥ 13 years • Number of pediatric patients (≤ 18 years): not available • Compared fluconazole 400 mg/day PO to placebo starting at conditioning until neutrophils > 1000 cells/μL for 7 days (max. 10 weeks) • Proven IFI: 2.8% fluconazole vs. 15.8% placebo (p < 0.001) • Fungal-related mortality: 0.6% fluconazole vs. 5.6% placebo (p < 0.001) • No difference in overall survival	PA
Rotstein *et al* (1999)[72] • Double blind randomized controlled trial • 274 patients with malignancy or autologous HSCT (AML 47%, autologous HSCT 53%); age > 18 years • Compared fluconazole 400 mg/day PO to placebo starting within 72 hours of cytotoxic chemotherapy until neutrophils ≥ 500 cells/μL for 2 days • Proven IFI (per protocol analysis): 2.8% fluconazole vs. 16.5% placebo (p<0.001) • Probable IFI (per protocol analysis): 3.5% fluconazole vs. 7.5% placebo (p=0.04) • Fungal-related mortality: 0.7% fluconazole vs. 4.5% placebo (p=0.04) • Overall mortality: 11% fluconazole vs. 11% placebo • Patients with AML receiving cytarabine and anthracycline and autologous HSCT not receiving growth factors benefited most from antifungal prophylaxis	A
FLUCONAZOLE vs. ITRACONAZOLE	

Annaloro et al (1995)[73] • Open-label randomized controlled • 59 pediatric and adult HSCT patients (allogeneic 39%, autologous 61%); age ≥ 13 years • Number of pediatric patients (≤ 18 years): not available • Compared fluconazole 300 mg/day PO to itraconazole capsules 400 mg/day starting at conditioning until ANC > 500 cells/μL; both groups received nystatin • Proven IFI: 3.6% fluconazole vs. 12.9% itraconazole (p=NS) • No statistically significant differences in need to add amphotericin B, number of febrile episodes, infection mortality, or number of possible, proven or suspected fungal infection	PA
Oren et al (2006)[74] • Open-label randomized controlled trial • 195 patients with acute leukemia or HSCT (acute leukemia 22%, autologous HSCT 55%, allogeneic HSCT 23%); age ≥ 16 years • Number of pediatric patients (≤ 18 years): not available • Compared fluconazole 400 mg/day IV/PO to itraconazole solution 200 mg BID (or 200 mg IV daily) from start of chemotherapy until resolution of neutropenia (max. 8 weeks) • Proven IFI: 3% fluconazole vs. 3% itraconazole (p=NS) • Probable IFI: 6% fluconazole vs. 5.2% itraconazole (p=NS) • No significant difference in invasive candidiasis or invasive aspergillosis between groups • Fungal-related mortality: 9.1% fluconazole vs. 5.2% itraconazole (p=NS)	PA
Huijgens et al (1999)[38] • Double blind randomized controlled trial • 202 patients with malignancy and anticipated neutropenia ≥ 10 days (acute leukemia 39%, lymphoma 36%, autologous HSCT 57%); age > 18 years • Compared fluconazole 50 mg PO BID to itraconazole 100 mg PO BID from start of chemotherapy until neutrophils > 500 cells/μL • Proven IFI: 4% in each group (p=NS) • Fungal-related mortality: 3% fluconazole vs. 6% itraconazole • Overall mortality: 6.9% fluconazole vs. 10.1% itraconazole (p=NS)	A
FLUCONAZOLE vs. AMPHOTERICIN	
Timmers et al (2000)[75] • Open-label randomized controlled trial • 24 patients with malignancy or HSCT with anticipated neutropenia ≥ 10 days (autologous HSCT 63%, allogeneic HSCT 8%, malignancy 29%): age ≥ 18 years • Compared fluconazole 200 mg/day PO to amphotericin B colloidal dispersion (ABCD) 2 mg/kg/day IV from the start of chemotherapy until ANC > 500 cells/μL • Trial stopped early because of severe infusion-related toxicity in ABCD arm	A
Wolff et al (2000)[64] • Open-label randomized controlled trial • 355 adult HSCT patients (allogeneic 29%, autologous 71%); age ≥ 18 years • Compared fluconazole 400 mg/day IV/PO to conventional amphotericin B 0.2 mg/kg/day from Day -1 until neutrophils > 500 cells/μL • Proven IFI: 4.1% fluconazole vs. 7.5% conventional amphotericin B (p=NS) • Fungal-related morality: 2.6% fluconazole vs. 1.3% conventional amphotericin B • Overall mortality: 12.1% fluconazole vs. 11.9% conventional amphotericin B • Adverse events: 0.5% fluconazole vs. 19% conventional amphotericin B (p < 0.05); predominantly renal	A

toxicity and infusion related • Adverse events leading to discontinuation: 0.5% fluconazole vs. 12.6% conventional amphotericin B (p < 0.05)	
AMPHOTERICIN vs. PLACEBO	
Perfect *et al* (1992)[76] • Double-blind randomized controlled trial • 182 adult patients undergoing autologous HSCT • Compared conventional amphotericin B 0.1 mg/kg/day to placebo from start of leucopenia (white blood cell count < 1000 cells/µL) until neutrophils > 500 cells/µL • Sterile site fungal infection: 8.8% conventional amphotericin B vs. 14.3% placebo (p=0.35) • Fungal-related mortality: 0% conventional amphotericin B vs. 2.2% placebo (p=NS) • Overall survival (at 6 weeks): 3.3% conventional amphotericin B vs. 12.1% placebo (p < 0.03) • More infusion-related toxicity with conventional amphotericin B (p< 0.001)	A
FLUCONAZOLE vs. MICAFUNGIN	
Van Burik *et al* (2004)[37] • Double blind randomized controlled trial • 882 pediatric and adult HSCT patients (allogeneic 54%, autologous 46%) • Number of pediatric patients (< 16 years): 84 (9.5%) • Compared fluconazole 8 mg/kg/day (max 400 mg/day) IV to micafungin 1 mg/kg/day (max 50 mg/day) IV starting from conditioning until the earliest of 5 days after engraftment (ANC ≥ 500 cells/µL), Day +42, development of proven/probable/possible IFI, unacceptable drug toxicity, death, withdrawal or discontinuation of drug • Successful prophylaxis (absence of proven/probable/possible IFI) after 4 weeks therapy: 73.5% fluconazole vs. 80% micafungin (p=0.03) • Proven/Probable IFI: 2.4% fluconazole vs. 1.6% micafungin (p=0.481) • Possible IFI: 21.4% fluconazole vs. 15.1% micafungin (p=0.026) • No difference in rates of invasive candidiasis, but aspergillosis lower in the micafungin group • No difference in overall or fungal-related mortality • Adverse events leading to drug discontinuation: 7.2% fluconazole vs. 4.2% micafungin (p=0.058)	PA
Hiramatsu *et al* (2008)[38] • Open label randomized controlled trial • 106 adult HSCT patients (allogeneic 52%, autologous 48%); age > 18 years • Compared fluconazole 400 mg/day IV to micafungin 150 mg/day IV starting within 48 hours of conditioning until the earliest of 5 days after engraftment, Day +42, proven/probable or possible IFI, drug toxicity, death, withdrawal or discontinuation • Treatment success (absence of proven/probable/suspected IFI): 88% fluconazole vs. 94% micafungin (p=0.295) • Proven IFI: 2% fluconazole vs. 2% micafungin (p = 1.0) • Probable IFI: 0 fluconazole vs. 0 micafungin (p = 1.0) • Overall mortality: 4% fluconazole vs. 8% micafungin (p=0.4) • Sample size determined based on number expected to enroll over 2 years; powered to detect 20% difference in treatment success between groups	A

Discussion

There are two meta-analyses that suggest that antifungal prophylaxis should be used during autologous HSCT.[77,78] Robenshtok et al. found a trend toward lower rates of documented IFI in patients receiving

antifungal prophylaxis (RR 0.69, CI 0.13 to 1.01). Lower all-cause mortality was also observed in these patients; however, this finding was based on only one trial (RR 0.52, CI 0.0.08 to 0.95). Similarly, the meta-analysis by Bow et al. found that antifungal prophylaxis was associated with lower rates of IFI and fungal-related mortality. Overall mortality was reduced in the subgroups of patients who had prolonged neutropenia and in autologous or allogeneic HSCT recipients.

FLUCONAZOLE

Fluconazole has been compared to placebo in two well-designed clinical trials involving more than 50% of patients undergoing autologous HSCT.[30,72] Both trials found that there were fewer proven or probable IFIs and fewer deaths attributable to fungal infection in those receiving fluconazole. Based on these two trials and the meta-analyses suggesting antifungal prophylaxis should be used in this population, we recommend that patients undergoing autologous HSCT with anticipated neutropenia for more than 7 days receive prophylaxis from the start of conditioning until neutrophil recovery. This is a strong recommendation made on moderate quality of evidence because the patient populations in these trials were heterogeneous and included higher risk allogeneic HSCT patients. There have been no trials conducted exclusively in autologous HSCT patients.

Both NCCN[25] and ASBMT[27] guidelines also recommend the use of fluconazole prophylaxis in autologous HSCT but only in certain subpopulations. NCCN suggests that autologous HSCT patients with severe mucositis should receive fluconazole or micafungin prophylaxis because of the higher risk for candidemia in patients with mucosal breakdown. ASBMT recommends fluconazole prophylaxis in autologous HSCT patients who have underlying malignancies, who will have prolonged neutropenia and mucosal damage or who have received fludarabine or 2-chlorodeoxyadenosine (2-CDA) within 6 months prior to HSCT. These recommendations are based on expert opinion.

Issues with respect to pediatric fluconazole dosing have been addressed earlier (see recommendation 1.1). We recommend a dose of 6 – 12 mg/kg/day to a maximum of 400 mg/day.

ITRACONAZOLE

Randomized controlled trials comparing itraconazole to fluconazole have been conducted using itraconazole capsules[73,79] and, the more highly bioavailable itraconazole solution.[74] In each of these trials, greater than 50% patients were undergoing autologous HSCT. No statistically significant difference was found between groups with respect to rates of IFI or overall mortality in any of the trials. Therefore, there does not appear to be an advantage of itraconazole over fluconazole prophylaxis.

AMPHOTERICIN PRODUCTS

Conventional amphotericin B has been compared to placebo in a randomized controlled trial including only patients undergoing autologous HSCT.[76] This trial showed no difference in rates of IFI or fungal-related mortality between conventional amphotericin B and the control group. However, there was more infusion-related toxicity in the conventional amphotericin B arm (p < 0.001). Similar results were found in a trial comparing conventional amphotericin B to fluconazole.[64] There was no difference in rates of IFI, but there was significantly renal toxicity and infusion-related toxicity in the conventional amphotericin B arm. There have been no studies using lipid formulations of amphotericin B in this patient population.

ECHINOCANDINS

The trials by Hiramatsu et al.[38] and Van Burik et al.[37] both compared micafungin to fluconazole in a patient population with a high percentage of patients undergoing autologous HSCT; these results have

been previously discussed in the allogeneic HSCT section. To summarize, in the Van Burik trial, micafungin had a higher percentage of patients with successful prophylaxis at 4 weeks (80% vs. 73.5%) when the definition of successful prophylaxis included absence of proven, probable and possible IFI. When only proven or probable IFI were compared, there was no significant difference in infection rates. Hiramatsu et al.[38] did not detect a significant difference in treatment success but the sample size was not large enough to detect treatment differences less than 20%.

Both studies included both allogeneic and autologous HSCT recipients. Therefore, the results may be difficult to interpret when applying to the lower risk autologous HSCT. However, it appears that micafungin is not inferior to fluconazole and micafungin has not been associated with more adverse effects. However, given the lower risk of IFI in autologous HSCT patients and the moderate quality of evidence for fluconazole prophylaxis in this patient population, we have not recommended that micafungin be considered as an alternate to fluconazole prophylaxis. This recommendation may change as further data become available.

Health Question 3: Should antifungal prophylaxis be used to prevent IFI in children with AML or MDS? If so, what medication (dose and duration) should be used?

Recommendation 3.1: Children with AML or MDS

- *For children one month to less than 19 years of age with AML or MDS, administer fluconazole 6 – 12 mg/kg/day (maximum 400 mg/day) IV/PO during chemotherapy-associated neutropenia (strong recommendation, moderate quality evidence).*

- *For children 13 years of age or older with AML or MDS, posaconazole 200 mg PO TID is suggested as an alternative to fluconazole in centers where there is a high local incidence of mold infections or if fluconazole is not available (weak recommendation, moderate quality evidence).*

Evidence Summary

Table 5: Summary of Evidence Used to Inform Recommendation 3.1

COMPARISON Study and Results	Population *
FLUCONAZOLE 50 mg vs. 100 mg	
Huijgens *et al* (1993)[80] • Double blind randomized controlled trial • 60 patients with malignancy and anticipated granulocytopenia ≥ 15 days (AML 58%, ALL 17%, NHL/HD 25%); age ≥ 16 years • Compared fluconazole 50 mg/day PO to fluconazole 100 mg/day PO given during period of neutropenia (not defined) • Fungal related mortality: 7% fluconazole 50 mg vs. 3% fluconazole 100 mg (no p-value) • All deaths secondary to pulmonary aspergillosis, no documented invasive yeast infections	PA

FLUCONAZOLE vs. PLACEBO or No Prophylaxis	
Kern et al (1998)[81] • Open label randomized controlled trial • 68 high risk AML patients ≥ 18 years • Compared fluconazole 400 mg/day PO plus standard prophylaxis to standard prophylaxis alone (oral colistin sulfate, amphotericin B suspension and co-trimoxazole) from start of chemotherapy until leukocyte count > 1000 cells/µL • Proven IFI: 5.6% fluconazole vs. 6.3% standard prophylaxis alone (p=NS) • No difference in overall survival or fungal-related mortality between groups • Trial ended early because of perceived futility; intended sample size not achieved	A
Rotstein et al (1999)[72] • Double blind randomized controlled trial • 274 patients with malignancy or autologous HSCT (AML 47%, autologous HSCT 53%); age > 18 years • Compared fluconazole 400 mg/day PO to placebo starting within 72 hours of cytotoxic chemotherapy until neutrophils ≥ 500 cells/µL for 2 days • Proven IFI (per protocol analysis): 2.8% fluconazole vs. 16.5% placebo (p<0.001) • Probable IFI (per protocol analysis): 3.5% fluconazole vs. 7.5% placebo (p=0.04) • Fungal-related mortality: 0.7% fluconazole vs. 4.5% placebo (p=0.04) • Overall mortality: 11% fluconazole vs. 11% placebo • Patients with AML receiving cytarabine and anthracycline and autologous HSCT not receiving growth factors benefited most from antifungal prophylaxis	A
Schaffner et al (1995)[82] • Double blind randomized controlled trial • 151 patients with malignancy (AML 72%, NHL 28%); age ≥ 17 years • Compared fluconazole 400 mg/day IV/PO to placebo from the start of chemotherapy until stable neutrophil recovery > 500 cells/µL • Proven IFI: 8% fluconazole vs. 9.2% placebo • Proven/probable IFI: 10.6% fluconazole vs. 10.5% placebo (p=NS) • Invasive candidiasis: 0% fluconazole vs. 5.3% placebo (p=0.12) • Fungal-related mortality: 2.7% fluconazole vs. 2.6% placebo (p=NS) • Overall mortality: 5.3% fluconazole vs. 6.6% placebo • No significant difference in number of adverse events between group	A
Winston et al (1993)[83] • Double blind randomized controlled trial • 256 adults with malignancy and anticipated neutropenia ≥ 7 days (AML 71%, ALL 20%, other 9%); age ≥ 17 years • Compared fluconazole 400 mg/day PO/IV to placebo starting at the onset of chemotherapy until neutrophils > 1000 cells/µL for 7 days (max 10 weeks) • Proven IFI: 4% fluconazole vs. 8% placebo (p=0.3) • Overall mortality (while on study drug): 0.8% fluconazole vs. 3% placebo (p=NS)	A
FLUCONAZOLE vs. ITRACONAZOLE	
Ito et al (2007)[84] • Randomized controlled trial (blinding unclear) • 218 patients with malignancy (AML 87%, MDS 13%); age ≥ 16 years • Number of pediatric patients (≤ 18 years): not available	PA

• Compared fluconazole 200 mg/day PO to itraconazole capsules 200 mg/day at the start of chemotherapy until neutrophils > 1000 cells/μL • Proven IFI: None in either group • Probable IFI: 2.7% fluconazole vs. 0% itraconazole (p=0.25) • Possible IFI: 7.3% fluconazole vs. 3.7% itraconazole • Adverse events: 2% fluconazole vs. 4% itraconazole (p=0.65)	
Glasmacher _et al_ (2006)[85] • Open label randomized controlled trial • 494 patients with malignancy and anticipated neutropenia ≥ 10 days (AML 73%, ALL 12%, CML with blast crisis 4%); age ≥ 16 years • Number of pediatric patients (≤ 18 years): not available • Compared fluconazole 400 mg/day PO to itraconazole solution 2.5 mg/kg BID from the start of chemotherapy until neutrophils > 1000 cells/μL • Proven IFI: 2.0% fluconazole vs. 1.6% itraconazole (p=0.69) • Proven IA: 1.2% fluconazole vs. 0.9% itraconazole (p=0.58) • Fungal-related mortality: 1.2% fluconazole vs. 0.8% itraconazole (p=0.628) • Overall mortality: 11.4% fluconazole vs. 10.1% itraconazole (p=0.678) • Adverse events leading to discontinuation: 28% fluconazole vs. 36% itraconazole (p=0.006) • Study terminated early because of slow patient accrual	PA
Morgenstern _et al_ (1999)[86] • Open label randomized controlled trial • 445 patients with malignancy and HSCT with anticipated neutropenia ≥ 7 days (60% malignancy / chemotherapy, 31% autologous HSCT, 9% allogeneic HSCT); age ≥ 16 years • Number of pediatric patients (≤ 18 years): not available • 53% of neutropenic episodes were in patients had AML but the number receiving chemotherapy or HSCT was not stated • Compared fluconazole 100 mg/day PO to itraconazole solution 2.5 mg/kg BID starting before start of neutropenia until neutrophils > 1000 cells/μL for 7 days • Proven IFI: 2% fluconazole vs. 0.3% itraconazole (p = 0.06) • IA: 1.4% fluconazole vs. 0% itraconazole (no p-value) • IFI mortality: 1.4% fluconazole vs. 0% itraconazole (no p-value) • Adverse events leading to discontinuation: 4.4% fluconazole vs. 17.7% itraconazole (p< 0.001)	PA
FLUCONAZOLE vs. POSACONAZOLE	
Cornely _et al_ (2007)[87] • Open label randomized controlled trial • 602 patients with malignancy (AML 86%, MDS 14%) and anticipated neutropenia ≥ 7 days; age ≥ 13 years • Number of pediatric patients (≤ 18 years): 16 (2.7%) • Compared fluconazole 400 mg/day PO or itraconazole solution 200 mg/day to posaconazole 200 mg PO TID starting at the beginning of the chemotherapy cycle until remission and recovery of neutropenia • Proven/probable IFI: 8.4% fluconazole/itraconazole vs. 2.3% posaconazole (p < 0.001) • IA: 6.7% fluconazole/itraconazole vs. 0.7% posaconazole (p < 0.001) • Fungal-related mortality: 5.4% fluconazole/itraconazole vs. 1.6% posaconazole (p=0.01) • Overall mortality: 22.5% fluconazole/itraconazole vs. 16.1% posaconazole (p=0.048) • Treatment-related adverse events: 2.0% fluconazole/itraconazole vs. 6.3% posaconazole (p = 0.01), predominantly gastrointestinal	PA

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FLUCONAZOLE vs. AMPHOTERICIN	
Mattiuzzi _et al_ (2003)[88] • Open label randomized controlled trial • 137 patients with newly diagnosed malignancy undergoing induction chemotherapy (AML 70%, MDS 30%); age ≥ 15 years • Number of pediatric patients (≤ 18 years): not available • Compared fluconazole 200 mg/day PO BID combined with itraconazole 200 mg BID capsules to liposomal amphotericin B 3 mg/kg three times per week from the start of induction until the ANC > 500 cells/μL for 2 days • Proven IFI: 4.5% fluconazole/itraconazole vs. 4.3% liposomal amphotericin B (no p value) • Fungal-related mortality: 1.5% fluconazole/itraconazole vs. 1.4% liposomal amphotericin B (no p value) • Overall mortality: 11.9% fluconazole/itraconazole vs. 14.3% liposomal amphotericin B (p=0.45) • Adverse events leading to discontinuation: 8% fluconazole/itraconazole vs. 14% liposomal amphotericin B (p=0.28)	PA
Bodey _et al_ (1994)[89] • Open label randomized controlled trial • 77 patients with acute leukemia (94% AML, 6% ALL); age ≥ 16 years • Number of pediatric patients (≤ 18 years): not available • Compared conventional amphotericin B 0.5 mg/kg three times per week to fluconazole 400 mg/day PO from the start of chemotherapy until remission of leukemia and neutrophils > 1000 cells/μL (max. 8 weeks) • Proven IFI: 8.3% conventional amphotericin B vs. 4.9% fluconazole (p=0.66) • Probable IFI: 19.4% conventional amphotericin B vs. 7.3% fluconazole • Fungal-related morality: 2.8% conventional amphotericin B vs. 0% fluconazole (no p value) • Overall mortality: 11.1% conventional amphotericin B vs. 14.6% fluconazole (no p value) • Adverse events leading to discontinuation: 11.1% conventional amphotericin B vs. 2.4% fluconazole (no p value)	PA
ITRACONAZOLE vs. PLACEBO	
Nucci _et al_ (2000)[90] • Double blind randomized controlled trial • 210 pediatric and adult patients with malignancy or autologous HSCT (AML 60%, ALL 20%, autologous HSCT 15%) • Number of pediatric patients (≤ 18 years): not available; age < 12 years: 14 (7%) • Compared itraconazole capsules 100 mg PO BID to placebo from the start of chemotherapy until ANC > 1000 cells/μL for 3 days • Proven IFI: 4.8% itraconazole vs. 8.5% placebo (p=0.28) • Fungal-related mortality: 1.9% itraconazole vs. 0.9 % placebo (p=NS) • Overall mortality: 7.7% itraconazole vs. 6.6% placebo (p=0.76) • Adverse events related to medication: 5.8% itraconazole vs. 6.6% placebo (p=0.80)	PA
Vreugdenhil _et al_ (1993)[91] • Double blind randomized controlled trial • 92 patients with malignancy (AML 64%, ALL 24%, other 12%); age > 15 years • Number of pediatric patients (≤ 18 years): not available • Compared itraconazole capsules 400 mg/day to placebo started prior to chemotherapy and continued during cycles until the end of neutropenia following the last cycle of chemotherapy	PA

• Proven IFI: 10.9% itraconazole vs. 19.6% placebo (no p-value) • IA: 8.6% itraconazole vs. 6.5% placebo (no p-value) • Probable IFI: 4.3% itraconazole vs. 2.2% placebo (no p-value) • Fungal-related mortality: 15.2% itraconazole vs. 15.2% placebo (p=NS) • Overall mortality: 21.7% itraconazole vs. 30.4% placebo (p=NS)	
Kaptan *et al* (2003)[92] • Open label randomized controlled trial • 55 patients with malignancy and anticipated neutropenia ≥ 7 days (AML 56%, ALL 44%); age ≥ 20 years • Compared itraconazole capsules 200 mg BID to no prophylaxis from the start of chemotherapy until ANC > 1000 cells/μL for 3 days • Proven IFI: 3.7% itraconazole vs. 4.7% control (p=NS) • Probable IFI: 9.3% itraconazole vs. 4.7% control • Fungal-related mortality: None in either group • Overall mortality: 16.1% itraconazole vs. 8.3% control (p=NS) • Adverse events leading to discontinuation: 3.7% itraconazole	A
Menichetti *et al* (1999)[93] • Double blind randomized controlled trial • 405 adult patients with malignancy or autologous HSCT and anticipated neutropenia (leukemia 76%, autologous HSCT 18%); age ≥ 17 years • Compared itraconazole solution 2.5 mg/kg BID to placebo starting 1-3 days prior to start of chemotherapy until neutrophils ≥ 1000 cells/μL • Proven IFI: 2.5% itraconazole vs. 4.4% placebo (p=NS) • IA: 2.0% itraconazole vs. 0.5% placebo (p=NS) • IC: 0.5% itraconazole vs. 3.9% placebo (p=0.01) • Fungal-related mortality: 0.5% itraconazole vs. 2.5% placebo (p=0.11) • Overall mortality: 7.5% itraconazole vs. 8.8% placebo (p=NS)	A
ITRACONAZOLE vs. VORICONAZOLE	
Mattiuzzi *et al* (2011)[94] • Open label randomized controlled trial • 123 adult patients with malignancy undergoing induction chemotherapy or first salvage (AML 76%, high-risk MDS 24%); age ≥ 18 years • Compared voriconazole 400 mg IV q 12 h x 2 doses then 300 mg BID to itraconazole 200 mg IV BID x 2 days then 200 mg IV daily beginning at the start of chemotherapy until ANC > 500 cells/μL for 2 days • Proven/probable IFI: 0% voriconazole vs. 3.8% itraconazole arm (p=0.17) • IFI-related mortality: 0% voriconazole vs. 1.9% itraconazole (no p value) • Overall mortality: 8.4% voriconazole vs. 11.5% itraconazole (p=0.79) • Adverse events leading to discontinuation: 21.1% voriconazole vs. 11.5% itraconazole (p=0.23)	A
ITRACONAZOLE vs. CASPOFUNGIN	
Mattiuzzi *et al* (2006)[95] • Open label randomized controlled trial • 197 patients with malignancy (AML 75%, high risk MDS 25%); age ≥ 15 years • Number of pediatric patients (≤ 18 years): not available • Compared itraconazole 200 mg IV BID x 2 days then 200 mg/day IV to caspofungin 50 mg IV daily beginning at the start of chemotherapy until the ANC > 500 cells/μL for 2 days	PA

- Proven IFI: 5.8% itraconazole vs. 6.6% caspofungin - Successful prophylaxis (no proven/probable/possible IFI): 51.2% itraconazole vs. 51.9% caspofungin (p=0.92) - Fungal-related mortality: 2.3% itraconazole vs. 3.8% caspofungin (p=0.57) - Overall mortality: 8.1% itraconazole vs. 6.5% caspofungin (no p value) - Adverse events leading to discontinuation: 9.3% itraconazole vs. 3.8% caspofungin (p=0.12)	
Cattaneo et al (2011)[96] - Open label randomized controlled trial 175 patients with malignancy (AML 79%, ALL 21%); age ≥ 18 years - Compared standard prophylaxis (itraconazole 82%, fluconazole 12%, posaconazole 1%, none 5%) to caspofungin 70 mg/day and 50 mg/day IV from the start of chemotherapy until protocol endpoints reached (i.e. leukemia remission, invasive fungal infection, severe adverse event) or physician decision (for standard prophylaxis group) - Proven/probable IFI: 7.5% standard prophylaxis vs. 3.7% caspofungin (p=NS) - Possible IFI: 8.6% standard prophylaxis vs. 17.1% caspofungin (p=NS) - Fungal-related mortality: 0% standard prophylaxis vs. 1.1% caspofungin (no p-value) - Overall mortality: 7.3% standard prophylaxis vs. 9.7% caspofungin (no p-value)	A
VORICONAZOLE vs. PLACEBO	
Vehreschild et al (2007)[97] - Double blind randomized controlled trial 25 AML patients; age ≥ 18 years - Compared voriconazole 200 mg PO BID to placebo started 24-48 hours after the last anthracycline dose until ANC > 500 cells/µL (max. 21 days) - Incidence of lung infiltrate at Day +21 (primary outcome): 0% voriconazole vs. 33% placebo (p=0.06) - No significant difference in adverse events - Trial stopped early when Cornely et al (2007) published showing reduced mortality with posaconazole	A
AMPHOTERICIN vs. PLACEBO	
Penack et al (2006)[98] - Open label randomized controlled trial 132 patients with malignancy or autologous HSCT (AML 65%, NHL 20%, autologous HSCT 22%); age > 18 years - Compared liposomal amphotericin B 50 mg IV q 48 h to no prophylaxis from the start of neutropenia until neutrophil count > 500 cells/µL - Proven/probable IFI: 6.7% liposomal amphotericin B vs. 35.1% control (p=0.001) - IA less common in liposomal amphotericin B group (p = 0.0057) - Fungal-related mortality: 2.7% liposomal amphotericin B vs. 12.3% no prophylaxis (p=0.039) - Overall mortality: 5.3% liposomal amphotericin B arm vs. 14.0% no prophylaxis (p=0.13)	A

Discussion

The two previously discussed meta-analyses suggested that antifungal prophylaxis should probably be administered to high risk leukemia patients.[77,78] Although the Robenshtok et al. meta-analysis included trials with heterogeneous patient populations, several trials in the acute leukemia subgroup had a high proportion of AML patients. In this subgroup, the meta-analysis found that there was a significant reduction in fungal-related mortality and documented IFI. Five trials included children but there was no pediatric/adult subgroup analysis. The meta-analysis by Bow et al.[78] also found that antifungal

prophylaxis was associated with lower rates of IFI and fungal-related mortality. Overall mortality was reduced in the subgroups of patients who had prolonged neutropenia and in HSCT recipients. This evidence suggests that patients with AML should receive antifungal prophylaxis during their course of chemotherapy treatment when they often have prolonged neutropenia.

FLUCONAZOLE

Several antifungal agents have been evaluated for prevention of IFI in patients with AML and MDS. Randomized controlled trials have been conducted comparing fluconazole to no prophylaxis[81] and to placebo.[72,82,83] The trial by Kern et al.,[81] conducted in an exclusively AML population, did not find a difference in IFI incidence between patients receiving fluconazole compared to no prophylaxis. However, the trial was ended early secondary to perceived futility and did not achieve the required sample size to detect a significant difference. Three placebo controlled trials were conducted in mixed populations. The trials by Schaffner et al.[82] and Winston et al.[83] both had more than 70% patients with AML and found no significant difference in rates of IFI in the fluconazole group compared to placebo. In contrast, the study by Rotstein et al.[72] had fewer AML patients (47%) but found significantly fewer proven and probable IFIs in the fluconazole arm and lower fungal attributable mortality. On further subgroup analysis, patients with AML appeared to benefit most from antifungal prophylaxis with fluconazole.

Further support for the use of fluconazole in patients with AML comes from a meta-analysis of fluconazole to prevent fungal infection in neutropenic patients.[99] This meta-analysis found that fluconazole was effective at decreasing systemic fungal infection when the local incidence of IFI was greater than 15%. Consequently, on balance, the evidence supports the use of fluconazole prophylaxis in AML patients.

Although none of the above-mentioned trials included children, it is reasonable to assume that pediatric AML patients would benefit similarly from fluconazole prophylaxis. There is adequate safety data and significant experience with fluconazole use in this patient population and age group. Therefore, given that this is a high risk population, we recommend that children with AML/MDS receive prophylaxis with fluconazole throughout the course of chemotherapy while they are neutropenic. This is consistent with IDSA recommendations that prophylaxis against *Candida sp.* should be given in AML patients undergoing Intensive remission-induction or salvage induction chemotherapy.[28] However, this is in contrast to the NCCN guideline that recommends against the use of fluconazole prophylaxis in leukemia patients outside the HSCT period based on the two negative trials.[81,83] NCCN recommends posaconazole prophylaxis during induction or re-induction chemotherapy for adult patients with AML.

At centers with high rates of mold infections, mold active agents may be superior to fluconazole in this patient population. However, the panel recommended fluconazole because, apart from posaconazole, other agents have failed to show important benefits over fluconazole in RCTs and a recent meta-analysis[44] and other agents have important drawbacks. Based on the one RCT where posaconazole showed a benefit over fluconazole (see below), posaconazole was suggested as an alternative to fluconazole in older children.

ITRACONAZOLE

There have been several studies comparing itraconazole to placebo or other antifungal agents. Although these trials were often conducted in heterogeneous patient populations, most consisted of greater than 40% AML patients. Studies by Nucci et al.,[90] Kaptan et al.[92] and Vreugdenhil et al.[91] compared itraconazole capsules to placebo and failed to demonstrate a reduction in IFI incidence in the

itraconazole arm. These studies have been criticized for the use of capsules and their associated delay in reaching the plasma drug concentrations necessary for successful prophylaxis. Oral itraconazole suspension has better bioavailability and was used in the placebo-controlled trial by Menichetti et al.[93] In this study, 76% of patients had acute leukemia but the proportion of patients with AML was not stated. Patients in the itraconazole arm had lower rates of proven or suspected IFI (24% vs. 33% placebo, p = 0.035). This difference was largely attributable to decreased rates of fungemia due to *Candida sp.* and did not impact rates of IA. There was no significant difference between groups with respect to fungal-related mortality or overall mortality.

When compared to fluconazole, two trials found no difference in rates of IFI between patients receiving fluconazole compared to itraconazole.[84,85] Although Morgenstern et al.[86] found a trend toward more IFIs in participants on fluconazole compared to itraconazole (p=0.06), low doses of fluconazole were used as the comparator (100 mg/day). Therefore, there is insufficient evidence to support the use of itraconazole over fluconazole in pediatric AML despite its broader spectrum of coverage. Issues with drug interactions, palatability and toxicity are also limitations making the use of itraconazole less feasible.

VORICONAZOLE

Trials involving other azoles in AML have been limited. Itraconazole has recently been compared to voriconazole and no difference in rates of proven/probable IFI was observed.[94] Voriconazole has also been compared to placebo and a trend toward decreased incidence of lung infiltrate at Day +21 was found (0% voriconazole vs. 33% placebo, p = 0.06).[100] However, the trial was stopped early (n=25) secondary to ethical concerns when the study by Cornely et al. was published showing improved outcomes in AML/MDS patients receiving posaconazole prophylaxis.

POSACONAZOLE

Cornely et al.[87] compared posaconazole to fluconazole or itraconazole in an open label randomized controlled trial. Patients in the posaconazole arm had significantly lower rates of proven/probable IFI, mainly attributable to a reduction in IA. Overall and fungal-related mortalities were also reduced in the posaconazole arm. However, there were significantly more adverse events possibly or probably related to treatment in the posaconazole arm (6%) compared to the other treatment arms (2%). This trial forms the basis for the current recommendation in our guideline to consider posaconazole prophylaxis during chemotherapy cycles for AML/MDS patients 13 years of age or older. Unfortunately, this trial included only 16 patients between the ages of 13 – 18 years (2%) thereby limiting its applicability to the pediatric population. Given that there is only one trial which included very few children and there has not yet been a recommended dose for children less than 13 years of age, there is insufficient information to routinely recommend posaconazole in pediatric patients although its use can be considered in patients 13 years and older. The use of posaconazole in adolescents is therefore presented as a consideration.

There are several other important considerations with respect to posaconazole use in children receiving chemotherapy for AML or MDS. Currently, it is only available orally and needs to be given with high fat food to optimize absorption. Therefore, it may not be tolerated in patients with mucositis or nausea/vomiting. In addition, in the Cornely trial[87], several patients received additional chemotherapy and the indication was not clear. It should be cautioned that further studies are needed to determine if posaconazole interactions with chemotherapy agents may have a negative impact on the malignancy treatment. Finally, posaconazole is more expensive than the standard fluconazole prophylaxis. Although an economic evaluation of posaconazole compared to fluconazole or itraconazole prophylaxis in the Netherlands suggested that posaconazole is cost-effective,[101] it was based on data from only one

randomized controlled trial [87] and may have limited applicability in Canada where costs and care are different.

Therefore, the current recommendation is that fluconazole should be used for antifungal prophylaxis in AML patients during chemotherapy. For those patients 13 years and older, posaconazole can be considered as an alternative, especially for those considered at higher risk for IA. This is consistent with the IDSA guideline.[28]

AMPHOTERICIN PRODUCTS

There has been one open label randomized controlled trial in a predominantly AML population (65%) comparing liposomal amphotericin B to placebo by Penack et al.[102] Liposomal amphotericin B administered every other day was associated with lower rates of proven or probable IFI and IA. However, when either conventional or liposomal amphotericin B products have been compared to fluconazole in similar populations, no differences in rates of IFI or mortality have been found.[88,89] In the trial using conventional amphotericin B, more toxicity was observed in the conventional amphotericin B arm and the risk of discontinuing prophylaxis due to fungal infection or toxicity was greater (p=0.02). Consequently, based on lack of benefit in comparison to fluconazole and substantial issues with toxicity at least with conventional amphotericin B, we have not recommended amphotericin B products for prophylaxis in patients with AML or MDS.

ECHINOCANDINS

There have been no trials comparing fluconazole to echinocandins in the AML population. Mattiuzzi et al.[95] compared itraconazole to caspofungin and found no significant difference in rates of successful prophylaxis or documented IFI. Given the potential higher risk for invasive mold infection in this patient population, further research into the benefit of mold active agents, including echinocandins, is needed.

Health Question 4: Should antifungal prophylaxis be used to prevent IFI in children with malignancy and anticipated neutropenia greater than 7 days? If so, what medication (dose and duration) should be used?

Recommendation 4.1: Children with malignancy and anticipated neutropenia greater than 7 days other than those undergoing HSCT or with AML or MDS

- *The panel suggests that antifungal prophylaxis not be given routinely to children with malignancy and neutropenia anticipated to persist for greater than 7 days, outside of patients undergoing HSCT or those with AML/MDS (weak recommendation, moderate quality evidence).*

Evidence Summary

Table 6: Summary of Evidence Used to Inform Recommendation 4.1

COMPARISON Study and Results	Population *
FLUCONAZOLE vs. PLACEBO	
Yamac _et al_ (1995)[103] • Open label randomized controlled trial • 70 patients with malignancy (acute leukemia 33%, NHL 33%, other 34%); age ≥ 16 years • Number of pediatric patients (≤ 18 years): not available • Compared fluconazole 400 mg/day PO to no prophylaxis started at the onset of neutropenia until neutrophil count ≥ 2000 cells/μL • Systemic fungal infection: 9.8% fluconazole vs. 31.0% no prophylaxis (p < 0.05) • Heterogeneous population of high risk (AML) and low risk (lymphoma)	PA
Chandrasekar _et al_ (1994)[32] • Double blind randomized controlled trial • 46 patients HSCT (allogeneic 41%, autologous 7%) or malignancy and anticipated neutropenia ≥ 7 days (52%); age ≥ 13 years • Number of pediatric patients (< 17 years): None • Compared fluconazole 400 mg/day IV/PO to placebo starting at conditioning (HSCT) or initiation of chemotherapy (malignancy) until resolution of neutropenia (≥ 1000 cells/μL) 7 days (max. 10 weeks) • Systemic fungal infection: 8.7% fluconazole vs. 4.3% placebo (p=NS) • Mortality: 17.4% fluconazole vs. 8.7% placebo (p=NS) • Fungal-related mortality: 8.7% fluconazole vs. 4.3% placebo (p=NS)	A
ITRACONAZOLE vs. PLACEBO	
Menichetti _et al_ (1999)[93] • Double blind randomized controlled trial • 405 adult patients with malignancy or autologous HSCT and anticipated neutropenia (leukemia 76%, autologous HSCT 18%); age ≥ 17 years • Compared itraconazole solution 2.5 mg/kg BID to placebo starting 1-3 days prior to start of chemotherapy until neutrophils ≥ 1000 cells/μL • Proven IFI: 2.5% itraconazole vs. 4.4% placebo (p=NS) • IA: 2.0% itraconazole vs. 0.5% placebo (p=NS) • IC: 0.5% itraconazole vs. 3.9% placebo (p=0.01) • Fungal-related mortality: 0.5% itraconazole vs. 2.5% placebo (p=0.11) • Overall mortality: 7.5% itraconazole vs. 8.8% placebo (p=NS)	A
Kaptan _et al_ (2003)[92] • Open label randomized controlled trial • 55 patients with malignancy and anticipated neutropenia ≥ 7 days (AML 56%, ALL 44%); age ≥ 20 years • Compared itraconazole capsules 200 mg BID to no prophylaxis from the start of chemotherapy until ANC > 1000 cells/μL for 3 days • Proven IFI: 3.7% itraconazole vs. 4.7% control (p=NS) • Probable IFI: 9.3% itraconazole vs. 4.7% control • Fungal-related mortality: None in either group • Overall mortality: 16.1% itraconazole vs. 8.3% control (p=NS) • Adverse events leading to discontinuation: 3.7% itraconazole	A

ITRACONAZOLE vs. FLUCONAZOLE	
Morgenstern *et al* (1999)[86] • Open label randomized controlled trial • 445 patients with malignancy and HSCT with anticipated neutropenia ≥ 7 days (60% malignancy / chemotherapy, 31% autologous HSCT, 9% allogeneic HSCT); age ≥ 16 years • Number of pediatric patients (≤ 18 years): not available • 53% of neutropenic episodes were in patients had AML but the number receiving chemotherapy or HSCT was not stated • Compared fluconazole 100 mg/day PO to itraconazole solution 2.5 mg/kg BID starting before start of neutropenia until neutrophils > 1000 cells/μL for 7 days • Proven IFI: 2% fluconazole vs. 0.3% itraconazole (p = 0.06) • IA: 1.4% fluconazole vs. 0% itraconazole (no p-value) • IFI mortality: 1.4% fluconazole vs. 0% itraconazole (no p-value) • Adverse events leading to discontinuation: 4.4% fluconazole vs. 17.7% itraconazole (p< 0.001)	PA
FLUCONAZOLE vs. MICAFUNGIN	
Sawada *et al* (2009)[104] • Open label randomized controlled trial • 107 pediatric patients with malignancy or HSCT (AML 14%, ALL 27%, NHL 36%, allogeneic HSCT 14%, autologous HSCT 9%) • Median age (range): micafungin 7 years (0-14), fosfluconazole 5 years (0-14) • Compared micafungin 2 mg/kg/day (max. 100 mg/day) to fosfluconazole 10 mg/kg/day (max. 400 mg/day) • Event free ratio of IFI: 94.4% micafungin vs. 94.3% fosfluconazole (p=NS)	P
AMPHOTERICIN vs. PLACEBO	
Uhlenbrock *et al* (2002)[105] • Open label trial; 24 patients randomized; 57 patients according to choice • 81 patients with malignancy or HSCT (AML 20%, ALL 33%, HSCT 34%, NHL 9%, aplastic anemia 4%) • Patient age (median, range): 5 years (0 - 23 years) • Number of pediatric patients (≤ 18 years): not available • Compared liposomal amphotericin B 1 mg/kg three times per week to placebo starting 3 days prior to the anticipated white blood cell count nadir until WBC > 1000 cells/μL and ANC > 500 cells/μL • Proven IFI: 5.8% liposomal amphotericin B vs. 3.4% placebo • Proven/probable IFI: 23.1% liposomal amphotericin B vs. 27.6% placebo	PA
AMPHOTERICIN vs. VORICONAZOLE	
Mandhaniya *et al* (2011)[106] • Open label randomized controlled trial • 100 children with acute leukemia (68% ALL, 30% AML, 2% biphenotypic) • Patient age ≤ 15 years (range 1.5-15) • Compared amphotericin B 0.5 mg/kg/day three times per week to voriconazole 6 mg/kg/dose for 2 doses then 4 mg/kg/dose PO BID starting at initiation of induction chemotherapy until ANC > 1000 cells/mm^3 for 3 consecutive days or completion of induction therapy • Proven IFI: 0% amphotericin vs. 2.0% voriconazole • Probable IFI: 0% both arms (p=NS) • Overall mortality: 2.0% amphotericin vs. 2.0% voriconazole (p=NS) • Adverse events related to drug: 100% amphotericin vs. 70% voriconazole (p<0.001) • Adverse events leading to discontinuation: 2.0% amphotericin vs. 2.0% voriconazole (p=NS)	P

Discussion

The populations in the trials considered for this recommendation were heterogeneous (leukemia, lymphoma and solid tumors); the ability to assess the risks and benefits in each individual population was therefore limited. Based on the lack of benefit observed, the panel suggested that prophylaxis not be used routinely in patients with malignancy and anticipated neutropenia greater than 7 days outside of patients with AML/MDS or undergoing HSCT. However, uncertainty remains as to whether there are certain subpopulations that may benefit from antifungal prophylaxis, specifically those considered at highest risk for prolonged neutropenia based on treatment intensity (e.g. Burkitt lymphoma, high risk ALL).

Given its frequency in pediatrics, a specific subgroup of interest is patients with acute lymphoblastic leukemia (ALL). Unfortunately, there have been no randomized controlled trials conducted exclusively in this population and these patients have been included in trials of malignancy and anticipated neutropenia or combined with AML patients in acute leukemia trials. As such, a separate analysis is not possible. There has been one recent pediatric study in acute leukemia in which 68% of children had ALL.[106] This trial compared intravenous amphotericin B to oral voriconazole and found no difference between proven or probable IFI between groups. However, the event rates were low with only one participant having a proven IFI and no patients having a probable IFI. This study was also conducted in India, a country where the epidemiology and risks for fungal infection may be different than in Canada.[107] The use of antifungal prophylaxis has not been compared to placebo and therefore its use in this lower risk group remains controversial. Although it is acknowledged that certain populations with ALL may be at higher risk for IFI (high dose steroids, relapsed ALL, infant ALL), there is currently insufficient evidence to make recommendations at this time. Further research in this area is necessary.

FLUCONAZOLE

Fluconazole has been studied in patients with malignancy and anticipated neutropenia in one open label trial by Yamac et al.[96] that compared fluconazole to no prophylaxis. A significant difference in IFI in patients receiving fluconazole compared to no prophylaxis (10% vs. 31%) was observed. However, the definition of IFI used in this trial included proven, probable and possible fungal infections and no breakdown was given for proven or probable infection, which are the more clinically relevant outcomes. Given the open-label design of this trial and the inclusion of possible fungal infection in the IFI definition, it is difficult to make a recommendation based on this one trial. The study was also conducted in heterogeneous patient groups with different underlying diseases and different risk groups for IFI.

ITRACONAZOLE

Itraconazole has been compared to placebo in two trials in malignancy and HSCT patients.[92,93] Kaptan et al.[92] compared itraconazole capsules to no prophylaxis and found no difference in proven IFI between the groups. However, as previously discussed, itraconazole capsules are associated with suboptimal bioavailability. The trial by Menichetti et al.[93] included 76% patients with leukemia and used the oral solution. In this study, patients in the itraconazole arm had lower rates of proven or suspected IFI (24% vs. 33% placebo, p = 0.035). This difference was largely attributable to decreased rates of candidemia. There was no difference in rates of IA and no significant difference in death due to fungal disease. Unfortunately, the proportion of acute leukemia patients with AML was not stated. It is therefore difficult to know whether this benefit was seen because patients were predominantly higher risk AML patients or whether this can be generalized to all patients with leukemia with prolonged anticipated neutropenia.

Itraconazole has also been compared to fluconazole. Morgenstern et al.[86] found that there was a trend toward more proven fungal infections in patients receiving fluconazole compared to itraconazole (p=0.06). This difference reached statistical significance when only the first study episodes were considered (p=0.03). However, low doses of fluconazole were used (100 mg/day) and, as a result, it is difficult to draw conclusions from this comparison.

There have been no trials in this patient population studying other azole antifungal agents including posaconazole and voriconazole.

ECHINOCANDINS

One trial by Sawada et al.[97] conducted in children with malignancy or undergoing HSCT compared micafungin to fosfluconazole. Fosfluconazole is a phosphate prodrug of fluconazole that is highly water soluble and can be administered in smaller volumes, but requires higher doses compared to fluconazole.[108] This open-label trial was conducted in a heterogeneous group of patients consisting of patients with AML, ALL, lymphoma, and HSCT. This study found that there was no difference in event free survival between children receiving fosfluconazole compared to micafungin. Adverse events were similar between groups.

AMPHOTERICIN

There have been a limited number of trials evaluating amphotericin for the prevention of IFI in patients with malignancy and anticipated neutropenia. There was one small interim analysis of 35 pediatric patients that showed no difference in rates of IFI between patients receiving liposomal amphotericin B compared to placebo.[109] After completion of the trial, there was still no statistically significant difference between groups with respect to rates of proven or probable IFI.[105] Unfortunately, this was not a randomized controlled trial as over half of the patients received the drug of their choice. Given the need to administer amphotericin intravenously, toxicity and lack of benefit over placebo, we have not recommended amphotericin prophylaxis in this population at lower risk of IFI.

Plan for Scheduled Review and Update

The C[17] Guidelines Committee will review this guideline every 3 years and at any time if significant information becomes available.

Implementation Considerations

The guideline will be circulated to the seventeen Canadian centres providing tertiary pediatric hematology/oncology care for feedback prior to finalization of the guideline. This is an essential step to identify and address concerns and build consensus. This will also allow us to identify center specific barriers to guideline implementation and develop multi-faceted implementation strategies targeting these barriers to change. The aspect most likely to cause difficulty in implementation is the site availability and financial burden of some of the recommended antifungal agents (i.e. posaconazole). To deal with this, we plan to specifically target administrators of health care institutions, insurance companies and pharmacies with educational interventions. Alternative antifungal agents are also presented in the guideline for those instances where a medication is contraindicated or not available.

A second aspect that may affect implementation is the geographical differences in fungal species, including higher rates of mold infections at certain centers. This may result in some centers recommending the use of broader agents to include mold coverage when our recommendation is for a narrower agent.

It will also be essential to communicate the recommendations to physicians, nurses and pharmacists at the various C[17] sites. To accomplish this knowledge transfer, we will employ multiple strategies including educational interventions, monitoring and feedback and collaborative care with pharmacists. We will identify key stakeholders at the various C[17] hospital sites to conduct small group sessions to disseminate the information to other physicians, nurses and pharmacists with the goal of incorporating these antifungal prophylaxis recommendations into protocols. A key component of this knowledge transfer will be to educate health care providers about the use of prophylaxis and considerations if a patient develops an IFI having received antifungal prophylaxis. In general, the use of a chemoprophylaxis strategy based on one antifungal class, precludes use of members of that class for therapy. Finally, computerized real-time alerts could provide reminders to physicians to order antifungal prophylaxis when patients are admitted for chemotherapy or stem cell transplantation.

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Panel Members

The Guideline Development Panel included:
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- Rod Rassekh, pediatric hematologist/oncologist
- Tamara MacDonald, clinical pharmacy specialist
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Appendix A: Open / Registered Trials

Trial Name	Age	Contact / Study Chair	Current Status
Caspofungin Acetate or Fluconazole in Preventing Invasive Fungal Infections in Patients With Acute Myeloid Leukemia Who Are Undergoing Chemotherapy (NCT01307579)	< 30 years	Theoklis Zaoutis	Recruiting participants
Antifungal Prophylaxis in Pediatric Acute Leukemia (NCT00624143)	Up to 15 years	Sameer Bakhshi	Recruiting participants
Pharmacokinetic, Safety and Efficacy of Intermittent Application of Caspofungin for Antifungal Prophylaxis (CASPHYLAX) (NCT01318148)	≥ 18 years	Werner J Heinz	Recruiting participants
Posaconazole versus Micafungin for Prophylaxis against invasive fungal infections during neutropenia in Patients undergoing chemotherapy for Acute Myelogenous Leukemia or Myelodysplastic Syndrome (NCT01200355)	≥ 18 years	Genovefa Papanicolaou	Recruiting participants
Pharmacokinetics of Anidulafungin (Ecalta ®) Intravenous Given to Patients at High Risk for Developing Invasive Fungal Disease (ANIDULAPK) (NCT01249820)	18 – 64 years	R. Brüggemann	Recruiting participants
PROPHESSOR: AmBisome in Antifungal Primary Prophylaxis Treatment of High Risk Patients Undergoing Allogeneic Stem Cell Transplant (NCT00326157)	≥ 18 years	Luigi Picaro	Completed. Results pending
A Study of Safety and Pharmacokinetics of Repeated Doses of Micafungin as Antifungal Prophylaxis in Children and Adolescents who undergo Hematopoietic Stem Cell Transplant (NCT00606268)	4 months to 16 years	Astella Pharma Global Development (Phase 1 trial)	Completed. Results pending

Appendix B: Research Gap Summary

1. General

   - What is the optimal dose of fluconazole for prophylaxis in children?

   - When is anti-mold coverage important in those who benefit from anti-fungal prophylaxis?

   - What are the benefits and disadvantages, including patient preferences and costs, regarding the use of mold-active agents compared to the use of fluconazole for prophylaxis?

2. Allogeneic stem cell transplantation:

   - What is the optimal duration of antifungal prophylaxis for patients undergoing allogeneic HSCT?

- What is the efficacy of fluconazole compared to echinocandins for pre-engraftment prophylaxis?
- Is antifungal prophylaxis needed in children with GVHD and, if so, what agent should be used?

3. Autologous Stem cell transplantation:
   - Are there subgroups of patients undergoing autologous HSCT who require prophylaxis and others who do not need prophylaxis?

4. Patients with AML / MDS:
   - What is the optimal antifungal agent to use for prophylaxis in children with AML/MDS (fluconazole vs. mold active agent)?

5. Patients with malignancy and anticipated neutropenia greater than 7 days:
   - Are there other high risk malignancy groups who would benefit from antifungal prophylaxis?
   - Are there subgroups of patients with ALL (i.e. high-risk ALL) who require prophylaxis?

Appendix C: Classification of Levels and Quality of Evidence and Strength of Recommendation

Current Guideline Classification

Grades for Recommendations[6]

Grade for Recommendation	Benefit vs. Risk and Burdens	Methodology	Implications
1A Strong recommendation, high-quality evidence	Desirable effects clearly outweigh undesirable effects or *vice versa*	Evidence from well done RCTs or Exceptional observational studies	Apply to most patients in most circumstances Further research unlikely to change recommendation
1B Strong recommendation, moderate quality evidence	Desirable effects clearly outweigh undesirable effects or *vice versa*	Evidence from RCTs with some flaws in study or Very strong evidence from observational studies	Apply to most patients in most circumstances Further research might be helpful
1C Strong recommendation, poor quality evidence	Desirable effects clearly outweigh undesirable effects or *vice versa*	Evidence of at least one critical outcome from observational studies, case series or RCTs with flaws	Apply to most patients in many circumstances Further research would be helpful
2A	Desirable effects closely	Consistent evidence from	Best action may depend

Weak recommendation, high quality evidence	balanced with undesirable effects	RCTs without important flaws or Exceptionally strong evidence from observational studies	on circumstances or patient or society values Further research unlikely to change recommendation
2B Weak recommendation, moderate quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important flaws or Very strong evidence from observational studies	Best action dependent on patient circumstances or patient or society values Further research may change recommendation
2C Weak recommendation with poor quality evidence	Desirable effects closely balanced with undesirable effects	Evidence of at least one critical outcome from observational studies, case series or RCTs with serious flaws	Other alternatives may be equally reasonable Further research very likely to change recommendation

(American College of Chest Physicians [ACCP] criteria)*

Appendix D: Guideline Strategy Search

Search Strategy

In May and June 2010, the C[17] Guidelines Committee conducted a comprehensive literature review and environmental scan to identify Guidelines and Standards specific to antifungal prophylactic strategies for children and youth with cancer or undergoing HSCT. To ensure the currency of this list, a Librarian Research Consultant used the following search strategy to identify guidelines and standards:

1. <u>Review of scientific literature sources using empirical databases</u> - PubMed, Medline, CINAHL were systematically searched by a Research Consultant using the following search terms:

   PubMed Search terms: antifungal prophylaxis combined with terms of neoplasms, guideline or practice guideline, recommendations, consensus statements, systematic reviews and meta-analyses.

   Medline Search Terms: antifungal prophylaxis combined with terms of neoplasms, guideline or practice guideline, recommendations, consensus statements, systematic reviews and meta-analyses.

   CINAHL Search Terms: antifungal prophylaxis combined with terms of neoplasms, guideline or practice guideline, recommendations, consensus statements, systematic reviews and meta-analyses.

2. <u>Review of grey literature sources such as annual reports or publications of organizations as identified on the world-wide web</u> - The internet search engine utilized was Google Scholar. Search terms included: antifungal prophylaxis paired with terms of cancer, guidelines and standards, recommendations, consensus statements, systematic reviews and meta-analyses.

3. Review of local, provincial, national and international databases -

    a. All oncology professional associations and organizations for antifungal prophylaxis guidelines.

    b. All Canadian Provincial Cancer Care Organizations within provinces websites were searched (except Quebec: no provincial source found) including the *"site map"* to reveal any guideline or standard embedded under another topic inclusive of provincial cancer organizations, regional and local cancer organizations within provinces and specific guideline development organizations in cancer care at the provincial level.

    c. International organizations or agencies or associations whose mandate is focused on systematic reviews or guideline development.

The organizations and agency's sites that were searched are included in Appendix G.

Inclusion/Exclusion Criteria

Inclusion:

1. Guidelines focused on clinical practice of practitioners relevant to **antifungal prophylaxis** for pediatric hematology/ oncology patients and their families**.**

    a. Clinical practice guidelines: those specific to situations in which clinicians are making decisions about direct patient care.

    b. Best practice guidelines: those that identify the best choice from a range of appropriate health care options, as defined by a consensus of experts following review of relevant literature using systematic review methods.

2. Published between 2000-2010.

Exclusion:*

1. Guidelines for which it was not clear that the guideline statements or recommendations were based on a review of evidence from the literature and/or were not based on a source that used evidence to support the guideline development process (included as topic areas in appendices only).

2. Guidelines focused strictly on assessment.

Excluded guidelines may have still been considered by the panel during the guideline development process, but were not considered for the basis of guideline adaptation.

Note: Preference was given to guidelines and guides to practice that based the development of substantive statements/recommendations on a review of evidence from the literature and/or were based on a source that used evidence to support the guideline development process.

Guidelines Reviewed

Clinical guideline on antibiotic prophylaxis for patients at risk. Pediatr Dent. 2004;26(7 Suppl):142-3.
Not applicable, advice on antibiotic prophylaxis, not antifungal prophylaxis.

Considerations re: Antibiotic prophylaxis for dental patients at risk. Canadian Dental Association. J Can Dent Assoc. 2000 Jan;66(1):19-20.
Not applicable, not a guideline, no advice on antifungal prophylaxis.

[Consensus conference: Preventing the risk of Aspergillus infection in immunocompromised patients]. Bull Cancer. 2001 Jun;88(6):589-600.
Not applicable, not a guideline.

[Guideline for perioperative prevention in interventions on the urinary tract and male genitalia. German Society of Urology]]. Urologe A. 2001 Jan;40(1):73-80.
Not applicable, no advice on antifungal prophylaxis, wrong patients population.

Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep. 2000 Oct;49(RR-10):1-125, CE1-7.
Applicable.

Therapy of deep fungal infection in haematological malignancy. Working Party of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother. 1997 Dec;40(6):779-88.
Not applicable, for use in fungal treatment review.

Alfandari S, Leroy O, de Botton S, Yakoub-Agha I, Durand-Joly I, Leroy-Cotteau A, et al. [Management of aspergillosis in immunocompromised patients. Recommendations of Lille University Hospital--4th version--November 2004]. Med Mal Infect. 2005 Mar;35(3):121-34.
Not applicable, for use in fungal treatment review.

Barberan J, Mensa J, Farinas C, Llinares P, Serrano R, Menendez R, et al. [Recommendations of antifungal treatment in patients with low grade immunosuppression]. Rev Esp Quimioter. 2008 Jun;21(2):127-42.
Not applicable, for use in fungal treatment review.

Bohme A, Ruhnke M, Buchheidt D, Cornely OA, Einsele H, Enzensberger R, et al. Treatment of invasive fungal infections in cancer patients - Recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol. 2009;88(2):97-110.
Not applicable, for use in fungal treatment review.

Bow EJ, Laverdiere M, Lussier N, Rotstein C, Cheang MS, Ioannou S. Antifungal prophylaxis for severely neutropenic chemotherapy recipients: a meta analysis of randomized-controlled clinical trials. Cancer. 2002 Jun 15;94(12):3230-46.
Not applicable, not a guideline, systematic review of literature.

Colomba C, Antinori S. [Fungal infections in transplantation patients]. Recenti Prog Med. 2003 Nov;94(11):516-28.
Not applicable, not a guideline, review article.

Cornely OA, Bohme A, Buchheidt D, Einsele H, Heinz WJ, Karthaus M, et al. Primary prophylaxis of invasive fungal infections in patients with hematologic malignancies. Recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. Haematologica. 2009 January;94(1):113-22.
> **Applicable.**

Cruciani M, Mengoli C, Malena M, Bosco O, Serpelloni G, Grossi P. Antifungal prophylaxis in liver transplant patients: a systematic review and meta-analysis. Liver Transpl. 2006 May;12(5):850-8.
> **Not applicable, not a guideline, wrong patient population.**

de Pauw B. Preventative use of antifungal drugs in patients treated for cancer. Journal of Antimicrobial Chemotherapy. 2004 Feb;53(2):130-2.
> **Not applicable, not a guideline, review article.**

Dini G, Castagnola E, Comoli P, van Tol MJ, Vossen JM. Infections after stem cell transplantation in children: state of the art and recommendations. Bone Marrow Transplant. 2001 Aug;28 Suppl 1:S18-21.
> **Not applicable, not a guideline, review article.**

Engelhard D, Akova M, Boeckh MJ, Freifeld A, Sepkowitz K, Viscoli C, et al. Bacterial infection prevention after hematopoietic cell transplantation. Bone Marrow Transplant. 2009 Oct;44(8):467-70.
> **Not applicable, no advice on antifungal prophylaxis.**

Fernandez Alonso R, Gonzalez Garcia ME, Fernandez Garcia J, Cepeda Piorno FJ. Anti-fungal drugs. Current status and guidelines for their administration. [Spanish]
> **Not applicable, no advice on antifungal prophylaxis.**

Farmacos antifungicos. Situacion actual y pautas para su administracion. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2005 Oct;7(9):377-88.
> **Not applicable, not a guideline, no advice on antifungal prophylaxis.**

Freifeld AG, Baden LR, Brown AE, Elting LS, Gelfand M, Greene JN, et al. Fever and neutropenia clinical practice guidelines. *J Natl Compr Canc Netw*. 2004 Sep;2(5):390-432.
> **Not applicable, no advice on antifungal prophylaxis.**

Gea-Banacloche J, Masur H, Arns da Cunha C, Chiller T, Kirchhoff LV, Shaw P, et al. Regionally limited or rare infections: prevention after hematopoietic cell transplantation. Bone Marrow Transplant. 2009 Oct;44(8):489-94.
> **Not applicable, not a guideline, no advice on antifungal prophylaxis.**

Goldberg E, Gafter-Gvili A, Robenshtok E, Leibovici L, Paul M. Empirical antifungal therapy for patients with neutropenia and persistent fever: Systematic review and meta-analysis. Eur J Cancer. 2008 Oct;44(15):2192-203.
> **Not applicable, not a guideline, no advice on antifungal prophylaxis.**

Groll AH, Ritter J. [Diagnosis and management of fungal infections and pneumocystis pneumonitis in pediatric cancer patients]. Klinische Padiatrie. 2005 Nov;217 Suppl 1:S37-66.
> **Not applicable, not a guideline, no advice on antifungal prophylaxis.**

Groll AH, Ritter J, Muller FM. [Guidelines for Prevention of Pneumocystis carinii Pneumonitis in Children and Adolescents with Cancer]. Klin Padiatr. 2001 Sep;213 Suppl 1:A38-49.
>   **Not applicable, not a guideline, no advice on antifungal prophylaxis.**

Ho KM, Rochford SA, John G. The use of topical nonabsorbable gastrointestinal antifungal prophylaxis to prevent fungal infections in critically ill immunocompetent patients: a meta-analysis. Crit Care Med. 2005 Oct;33(10):2383-92.
>   **Not applicable, not a guideline.**

Imataki O, Kami M, Kim SW, Gotoh M, Komaba S, Kasai M, et al. A nationwide survey of deep fungal infections and fungal prophylaxis after hematopoietic stem cell transplantation in Japan. Bone Marrow Transplant. 2004 Jun;33(12):1173-9.
>   **Not applicable, not a guideline, survey of current practice.**

Kern WV, Beyer J, Bohme A, Buchheidt D, Cornely O, Einsele H, et al. [Prophylaxis of infection in neutropenic patients. Guidelines of the Working Party on Infections in Hematology and Oncology]. Dtsch Med Wochenschr. 2000 Dec 22;125(51-52):1582-8.
>   **Applicable, but updated guideline available (Cornely 2009).**

Liberati A, D'Amico R, Pifferi S, Telaro E. Antibiotic prophylaxis in intensive care units: meta-analyses versus clinical practice. Intensive Care Med. 2000;26 Suppl 1:S38-44.
>   **Not applicable, not a guideline, no advice on antifungal prophylaxis.**

Lindsey H. Preventing infection in immunocompromised cancer patients: latest recommendations. *Oncology Times*. 2008;30(18):25
>   **Not applicable, review article.**

Mahi L. [Comments about "Management of aspergillosis in immunocompromised patients. Recommendations of Lille University Hospital--4th version--November 2004"]. Med Mal Infect. 2005 Jun;35(6):376-7; author reply 7.
>   **Not applicable, for use in fungal treatment review.**

Marr K, Bow E, Chiller T, Maschmeyer G, Ribaud P, Segal B, et al. Fungal infection prevention after hematopoietic cell transplantation. Bone Marrow Transplant. 2009 Oct;44(8):483-7.
>   **Applicable, ASBMT guideline.**

Mensa J, De La Camara R, Carreras E, Cuenca Estrella M, Garcia Rodriguez JA, Gobernado M, et al. [Treatment of fungal infections in patients with hematologic neoplasia]. Med Clin (Barc). 2009 Apr 11;132(13):507-21.
>   **Not applicable, for use in fungal treatment review.**

Michallet M, Ito JI. Approaches to the management of invasive fungal infections in hematologic malignancy and hematopoietic cell transplantation. Journal of Clinical Oncology. 2009 10 Jul;27(20):3398-409.
>   **Not applicable, for use in fungal treatment review**.

Morrissey CO, Bardy PG, Slavin MA, Ananda-Rajah MR, Chen SC, Kirsa SW, et al. Diagnostic and therapeutic approach to persistent or recurrent fevers of unknown origin in adult stem cell transplantation and haematological malignancy. *Intern Med J*. 2008 Jun;38(6b):477-95.
    Not applicable, no advice on primary antifungal prophylaxis

Nichols WG. Management of infectious complications in the hematopoietic stem cell transplant recipient. J Intensive Care Med. 2003 Nov-Dec;18(6):295-312.
    Not applicable, for use in fungal treatment review.

Playford EG, Webster AC, Sorrell TC, Craig JC. Systematic review and meta-analysis of antifungal agents for preventing fungal infections in liver transplant recipients. Eur J Clin Microbiol Infect Dis. 2006 Sep;25(9):549-61.
    Not applicable, not a guideline, systematic review.

Playford EG, Webster AC, Sorrell TC, Craig JC. Antifungal agents for preventing fungal infections in non-neutropenic critically ill and surgical patients: systematic review and meta-analysis of randomized clinical trials. J Antimicrob Chemother. 2006 Apr;57(4):628-38.
    Not applicable, not a guideline, wrong patients population.

Playford EG, Webster AC, Sorell TC, Craig JC. Antifungal agents for preventing fungal infections in solid organ transplant recipients. Cochrane Database Syst Rev. 2004(3):CD004291.
    Not applicable, wrong patient population.

Reinbolt RE, Shenk AM, White PH, Navari RM. Symptomatic treatment of infections in patients with advanced cancer receiving hospice care. J Pain Symptom Manage. 2005 Aug;30(2):175-82.
    Not applicable, not a guideline, focus on treatment not prophylaxis.

Rolston KVI. The infectious diseases society of America 2002 guidelines for the use of antimicrobial agents in patients with cancer and neutropenia: Salient features and comments. Clinical Infectious Diseases. 2004 15 Jul;39(SUPPL. 1):S44-S8.
    Applicable, IDSA guideline.

Segal BH, Freifeld AG, Baden LR, Brown AE, Casper C, Dubberke E, et al. Prevention and treatment of cancer-related infections. J Natl Compr Canc Netw. 2008 Feb;6(2):122-74.
    Applicable, NCCN guideline.

Segal BH, Almyroudis NG, Battiwalla M, Herbrecht R, Perfect JR, Walsh TJ, et al. Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. Clin Infect Dis. 2007 Feb 1;44(3):402-9.
    Not applicable, not a guideline, review article.

Slavin MA, Heath CH, Thursky KA, Morrissey CO, Szer J, Ling LM, et al. Antifungal prophylaxis in adult stem cell transplantation and haematological malignancy. Intern Med J. 2008 Jun;38(6b):468-76.
    Applicable.

Slavin MA. Introduction to the updated Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting, 2008. *Intern Med J*. 2008 Jun;38(6b):457-67.
Not applicable, not a guideline, no advice on antifungal prophylaxis, how to develop a guideline

Sugar AM. Empiric treatment of fungal infections in the neutropenic host. Review of the literature and guidelines for use. Arch Intern Med. 1990 Nov;150(11):2258-64.
Not applicable, focus on treatment not prophylaxis.

Thursky KA, Playford EG, Seymour JF, Sorrell TC, Ellis DH, Guy SD, et al. Recommendations for the treatment of established fungal infections. Intern Med J. 2008 Jun;38(6 B):496-520.
Not applicable, for use in fungal treatment review.

Trifilio S, Verma A, Mehta J. Antimicrobial prophylaxis in hematopoietic stem cell transplant recipients: Heterogeneity of current clinical practice. Bone Marrow Transplantation. 2004 Apr;33(7):735-9.
Not applicable, not a guideilne, review article.

Weinstock DM, Boeckh M, Boulad F, Eagan JA, Fraser VJ, Henderson DK, et al. Infections in immunocompromised patients. Postexposure prophylaxis against varicella-zoster virus infection among recipients of hematopoietic stem cell transplant: unresolved issues. *Infection Control & Hospital Epidemiology*. 2004;25(7):603-8.
Not applicable, no advice on antifungal prophylaxis.

West F, Mitchell SA. Evidence-based guidelines for the management of neutropenia following outpatient hematopoietic stem cell transplantation. *Clin J Oncol Nurs*. 2004 Dec;8(6):601-13.
Not applicable, focus on empiric therapy and treatment not prophylaxis.

Yahav D, Gafter-Gvili A, Muchtar E, Skalsky K, Kariv G, Yeshurun M, et al. Antiviral prophylaxis in haematological patients: systematic review and meta-analysis. *European Journal of Cancer*. 2009 Dec;45(18):3131-48.
Not applicable, not a guideline, no advice on antifungal prophylaxis.

Zitella LJ, Friese CR, Hauser J, Gobel BH, Woolery M, O'Leary C, et al. Putting evidence into practice: prevention of infection. Clinical Journal of Oncology Nursing. 2006 Dec;10(6):739-50.
Not applicable, not a guideline.

Appendix E: Primary Literature Search Strategy

Search Strategies

Medline

The search strategy for MEDLINE (1950 to **September 8, 2011** retrieved **3750** references of which **3665** were unique and not duplicated in our other searches. We used a combination of MeSH and free text terms for

Set	History	Results	Comments
1	exp Neoplasms/ or Bone Marrow Transplantation/ or exp Stem Cell Transplantation/ or neutropenia/	2333548	Neoplasm/Transplantation Population Terms
2	exp Antifungal Agents/	129301	Antifungal terms
3	1 and 2	13497	Base Clinical Set 1
4	Chemoprevention/ or (prophylax* or prophylact*).mp.	112359	Prophylaxis terms
5	1 and 4	21081	Base Clinical Set 2
6	3 or 5	33297	Final Base Clinical Set
7	randomized controlled trial.pt. or randomized controlled trials as topic/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or ((singl* or doubl* or trebl* or tripl*) adj5 (mask* or blind*)).mp. or (placebo* or random*).mp. or (rct or rcts).mp.	762374	Study Design/Methodology terms
8	6 and 7	3750	Evidence filtered Final results

EMBASE

The search strategy for EMBASE (1996 to **2011 Week 35**) retrieved **3704** references of which **2386** were unique and not duplicated in our other searches. We used a combination of EMBASE and free text terms for

Set	History	Results	Comments
1	*tissue transplantation/ or exp *bone marrow transplantation/ or exp *cell transplantation/ or exp *stem cell transplantation/ or exp *neoplasm/ or *neutropenia/	2112149	Neoplasm/Transplantation Population Terms
2	exp *Antifungal Agent/	91611	Antifungal terms
3	1 and 2	5452	Base Clinical Set 1
4	*prophylaxis/ or (prophylax* or prophylact*).mp.	161987	Prophylaxis terms
5	1 and 4	21297	Base Clinical Set 2
6	3 or 5	25961	Final Base Clinical Set
7	ct.fs. or randomized controlled trial/ or double blind	654944	Study Design/Methodology terms

	procedure/ or single blind procedure/ or triple blind procedure/ or (rct or rcts or ((singl: or doubl: or tripl: or trebl:) and (mask: or blind:))).mp.		
8	6 and 7	3704	Evidence filtered Final results

EBM Reviews – Cochrane Central Register of Controlled Trials

The search strategy for CCTR (3rd **Quarter 2011**) retrieved **2170** references of which **196** were unique and not duplicated in our other searches. This database consists exclusively of RCTs so no study design terms were used. This database does not allow for publication date limits as references are added as they are found by Cochrane. We used a combination of MeSH, EMBASE and free text terms for

Set	History	Results	Comments
1	exp Neoplasms/ or Bone Marrow Transplantation/ or exp Stem Cell Transplantation/ or neutropenia/ or exp cell transplantation/	36654	Neoplasm/Transplantation Population Terms
2	exp Antifungal Agents/ or exp Antifungal Agent/	5326	Antifungal terms
3	1 and 2	516	Base Clinical Set 1
4	prophylaxis/ or chemoprevention/ or (prophylax* or prophylact*).mp.	16574	Prophylaxis terms
5	1 and 4	466	Base Clinical Set 2
6	3 or 5	2170	Final Results

Appendix F: External Review and Consultation Process

The draft guideline was reviewed in a two stage process; content review and stakeholder review.

Expert Content Reviewer Feedback:

Initally, the guideline was reviewed by a panel of experts in pediatric hematology/oncology and infectious disease. A total of 17 experts were contacted to review the document. Eleven of 17 experts responded. The experts were asked to complete a questionnaire; their responses and the panel's responses, including changes to the draft guideline, are summarized below.

Question	Response
Role in care of children with cancer?	Oncologist – 36.4% Infectious Disease Physician – 36.4% Pharmacist – 18.2% Infectious Disease and Hematology/Oncology – 9%
Currently following a guideline on primary antifungal prophylaxis?	No – 27.3% Yes – 72.7%
Rationale for guideline clear?	Strongly agree or agree – 100%

Children's Cancer & Blood Disorders

Is there a need for this Canadian guideline?	Strongly agree or agree – 81.8%
	Neither agree nor disagree – 18.2%
Literature search complete?	Strongly agree or agree – 81.8%
	Disagree – 18.2%
Evidence described relevant?	Strongly agree or agree – 90.9%
	Neither agree nor disagree – 9.1%
Methods used to summarize effective?	Strongly agree or agree – 100%
Results interpreted in accordance with your own interpretation?	Strongly agree or agree – 81.9%
	Neither agree nor disagree – 9.1%
	Disagree – 9.1%
Draft recommendations are clear?	Strongly agree or agree – 90.9%
	Disagree – 9.1%
Agree with draft recommendations as stated?	Strongly agree or agree – 54.6%
	Neither agree nor disagree – 18.2%
	Disagree – 27.3%
Comfortable recommending use of the guideline in own institution?	Strongly agree or agree – 63.7%
	Neither agree nor disagree – 18.2%
	Disagree – 18.2%
Likely to adopt for own practice?	Likely – 45.5%
	Not sure 18.2%
	Not likely – 27.3%
	Not Applicable – 9.1%

Comments:

Comment	Response
The guidelines are insufficiently specific regarding what IFI are to be prevented; that is C/IC vs. IA. The risks for C/IC and for IA are very different and involve quite different pathogeneses.	Information added to introduction.
The guidelines have not examined the context in which IFIs occur and the risks that are associated with context (e.g. C/IC during post-remission consolidation for AML, or pre-engraftment IA risk associated with autoHSCT using protocol-driven HGFs).	It was outside the scope of the document to examine each context; clarified in introduction.
There is often a failure to include consideration of institutional event rates for the IFIs of interest in the policy-related decision making	Introduction modified to address this.
Many of the breakthrough IFIs reported in clinical trials are due to pathogens that should be susceptible to the prophylaxis agent. This suggests that in many (but not all) cases other factors (such as those that are host-related) may "trump" the drug's ability to protect the patients at highest risk.	Introduction modified to address this.
Pre-emptive ("early") therapy strategies based upon surrogate marker detection are being examined as alternatives to chemoprophylaxis.	This was outside the scope of the guideline.
My recommendations are to re-articulate more specifically what is being targeted for prevention, the period of risk over which prevention is expected to be effective, the clinical and treatment contexts within which prevention is expected to be effective, and the specific institutional event rates that a given prevention strategy is intended to impact (and by what order of magnitude).	This was clarified where possible throughout the document.
Use of a chemoprophylaxis strategy based upon one anti-fungal class	This was added to

precludes use of members of that class for therapy.	implementation considerations.
The recommendations are based solely upon evidence gathered from prospective randomized clinical trials. Although this is clearly the strongest form of evidence, some important evidence can also be obtained from retrospective or epidemiologic reports esp. when the population of interest have never been included in a prospective trial ("absence of evidence is not evidence of absence").	The search strategy and inclusion / exclusion criteria were decided by the committee and outlined in the methods.
Marks has been published in BJH in the meantime	Reference amended.
Ref. 92 is misspelled	Corrected.
I think the guideline choices are the obvious ones given the data we have. There are choices, and one could come up with different recommendations based on geographical differences in fungal species seen in the patient groups.	This was added to the introduction and implementation considerations.
I just had some concerns about the conclusions made from these data. Specifically I was concerned about using primarily adult literature to quantify level of evidence (A,B,C) for each of the recommendations. In reality most of the recommendations had no or little pediatric data to support the recommendation.	In the evidence tables, trials were separated into pediatric, combined adult/pediatric and adult trials to clarify where the evidence was drawn from.
There are several instances where the terms "allogenic" and "allogeneic" are used with respect to HSCT. I suggest selecting one (my preference is allogeneic) and use it throughout the document.	This was corrected throughout the document to "Allogeneic".
Your guideline search strategy failed to pick up several key guidelines: there are at least 3 IDSA guidelines that are applicable: Patterson for Candida, Walsh for Aspergillus, Freifeld for Febrile Neutropenia, all of which address fungal prophylaxis, and the ASBMT infection prevention guideline by Tomblyn endorsed by multiple international societies, which also address fungal prophylaxis.	The ASBMT guideline by Tomblyn was identified by our search and was one of the guidelines referenced frequently in our guideline. The other guidelines focused primarily on treatment.
I also did not see any recommendations regarding posaconazole levels (as we know that azoles are notorious and need close monitoring).	This was beyond the scope of the guideline.
Recommendation 1.1	
Galactomannan testing combined with fluconazole in this population considered necessary to support early diagnosis of *Aspergillus* infections. While success with this test may vary many programs now consider this standard of care.	This was added to the scope of the guideline
Micafungin approved dose of 50 mg considered insufficient by some practitioners	There is a separate section discussing the echinocandin dosing in recommendation 1.1. The recommendation is based on the evidence from clinical trials.
Duration of prophylaxis - How will engraftment (time to end antifungal therapy) be defined? - Does the committee consider immune deficit of all donor types (cord vs. MRD vs. MUD vs. mismatch donors). Had the committee considered using immune reconstitution (T-cell counts or something else?) as being a reasonable surrogate for decreased fungal risk?	Introduction modified to address several of these issues. It was beyond the scope of the guideline to look at all clinical situations.
Drug interactions, adherence issues, LFT abnormalities, etc can be	The rationale for our

overcome and given the large body of data supporting prophylaxis through +75, I am not sure there is sufficient evidence of safety for stopping at engraftment.	recommendation is outlined in the section on "duration" in Recommendation 1.1.
Study comments Itraconazole studies frequently had insufficient dosing for therapeutic benefits to be realized (e.g. 200 mg IV daily Marr et al 2004)	This was clarified.
Percent of pediatric patients in many studies not provided, compromising the ability to assess relevance to target population (can it be added to all studies in some manner?)	An extra line stating the number of pediatric patients was added to each trial in the tables.
Percent of pediatric patients in many studies not provided, compromising the ability to assess relevance to target population (can it be added to all studies in some manner?)	As above.
I also would stress the therapeutic drug monitoring (TDM) in children receiving posaconazole	This was beyond the scope of the guideline.
To my opinion, itra, vori and liposomal ampho B would be alternatives for primary prophylaxis until engraftment (question: is engraftment really sufficient? many guidelines recommend prophylaxis until "immune recovery", which needs a certain number of T/CD4 cells)	Discussion of alternative agents was clarified. Rationale for duration outlined in section on "duration".
Recommendation 1.2	
Galactomannan testing combine with fluconazole considered necessary to provide early warning of aspergillus infections. While success with this test may vary many programs now consider this standard of care.	This was beyond the scope of the guideline; scope amended.
Allo HSCT with GVHD: I do not think that fluconazole would be an alternative to posa (see comment above). Here I would rather give itra (+TDM) or vori (+TDM).	This is discussed in the guideline. It is acknowledged that these patients are at increased risk for mold infections but there is insufficient evidence to recommend anti-mold agents over fluconazole, although this might change when more data becomes available. A section was added to the discussion indicating that in centers with high rates of mold infection, a mold-active agent could be considered although data is lacking.
I would not use non-mold-active prophylaxis for the highest risk patients. For instance, in alloHSCT patients with GVHD (by far the highest risk group), giving children less than 13 yo fluconazole is not the best option. While I agree there is no posaconazole dose known just yet, another mold-active drug could be used.	As above.
Recommendation 3	
Posaconazole must be given with a high fat food to optimize absorption and provide adequate drug levels to prevent mold	This was added to the discussion.

infections with the current suspension dosage form.	
5 of 20 trials contain MDS patients and given the age of most patients this is likely to represent secondary MDS which may have different risk factors than that found in younger children (< 16 or < 13). Would consider the evidence in this group 2B or 2C.	It was decided to keep the evidence rating as 1B.
I agree with your recommendation for fluconazole for AML pts. However, I believe you overstate the strength of the evidence for that. Only one study was favorable (the Rotstein study) and the rest did not show a substantive benefit. Moreover, if I recall correctly, the definition of IFI was unconventional for that study with Candida UTIs being considered IFI, not the case for other studies and if those were removed, the rates of Candidemia were not different.	The evidence was kept as 1B; however, the points raised were added to the discussion.
I believe a caution about the posaconazole use in AML should be mentioned. Although there were not differences in all adverse events in the Cornely trial (not surprising since adverse events are nearly universal in intensive chemotherapy), there were significantly more SAEs attributable to the study drug (6% vs. 2%, P <0.05). In that trial 42% of pts got additional chemo during the study drug; what I have repeatedly requested is a breakdown of whether those occurred in the subset of those who got the second course of chemo, suggestive of a deleterious interaction of posa with certain chemo agents, a well described occurrence with other extended spectrum azoles. The sponsor has not looked at that issue. You may want to caution the reader that this is an issue not well studied.	This was added to the discussion under the posaconazole section.
Pts with AML/MDS -the C17 guidelines recommend for pts 1 months-19 years of age fluconazole; posaconazole would be an alternative for patients >= 13 years of age. My concern: what about institutions with relevant mold infections? Fluconazole is not active against molds. Therefore, I would itraconazole (+TDM) and liposomal ampho B (intermittent dosage) as alternative in this age group; the latter is based on the RCT by Penack in adults; Bochennek et al reported on an observational study in children with intermittent liposomal ampho B in AML patients (CMI, 2011; 17:1868)	A statement was added to the discussion section cautioning that anti-mold agents may be superior in centers with high rates of mold infections, but there is insufficient evidence to make a general recommendation for mold-active agents at this time.
Recommendation 4	
The patient mix in these studies is very heterogeneous and contains many acute leukemia (AML and ALL should be broken out separately due to the differences in disease and therapy) and autologous transplants which are likely to have a different fungal risk than solid tumors and lymphoma with myelosuppressive regimens. How have these confounding groups been accounted for in the assessment?	This is identified as a limitation. All studies group these patient populations together and it was not possible to separate out.
Patients with ALL, given the prevalence in pediatrics and nature of corticosteroid use (frequent and prolonged) should be broken out as a separate population for review. If this is felt to be unnecessary than a state should be added to explain why this is the case.	A separate comment on ALL was added to the discussion.
There is some evidence from non-RCT trials that may be useful. For example, while there is no trial that demonstrates that pediatric patients with relapsed ALL or with severe aplastic anemia benefit from antifungal prophylaxis, but this may be because no trial has ever	This was beyond the scope of the guideline. The search strategy and inclusion criteria were defined and the decision was to

been undertaken in these populations. And yet we know from retrospective reports that patients with these diagnoses are at very high risk for developing an IFI. That is why I don't "strongly" agree with recommendation 4.1, though I do strongly agree with all of the others.	use only RCTs.
I am struck by your silence about ALL, the chief group of pts this guideline would be applicable to. Why? do you intend the neutropenia > 7 days to be for this? If so, i suggest being explicit. There is a subgroup of pediatric ALL on high doses of steroids at high risk for IFI. In particular you should caution the dangers of drug interactions, especially itra, vori, and presumably posa with vincristine, cytoxan.	A separate comment on ALL was added to the discussion.

Stakeholder Feedback:

Secondly, the guideline was sent to all C[17] sites for stakeholder review. Similar to the content review process, the stakeholders were asked to complete a questionnaire; their responses and the panel's responses/guideline changes are summarized below. A total of 42 responses were received. All cancer centers across Canada had at least one representative with the exception of Cancer Care Manitoba.

Question	Response
Role in care of children with cancer?	Oncologist – 19% Infectious Disease Physician – 21.4% Nurse Educator – 7.1% Nurse Practitioner – 11.9% Pharmacist – 35.7% Other – 4.8%
Do you care for transplant patients?	No – 31.7% Yes – 68.3%
Currently following a guideline on primary antifungal prophylaxis?	No – 73.2% Yes – 26.8%
Is there a need for this Canadian guideline?	Strongly agree or agree – 93.5% Neither agree nor disagree – 6.5%
Literature search complete?	Strongly agree or agree – 93.5% Neither agree nor disagree – 6.5%
Results interpreted in accordance with your own interpretation?	Strongly agree or agree – 96.6% Neither agree nor disagree – 3.4%
Draft recommendations are clear?	Strongly agree or agree – 100%
Agree with draft recommendations as stated?	Strongly agree or agree – 86.2% Neither agree nor disagree – 6.9% Disagree – 6.9%

Question	Response
Comfortable recommending use of the guideline in own institution?	Strongly agree or agree – 79.3% Neither agree nor disagree – 13.8% Disagree – 6.9%
Likely to be supported by your colleagues?	Strongly agree or agree – 82.1% Neither agree nor disagree – 14.3% Disagree – 3.6%
Obstacles to implementing the guidelines at your institution?	
a) high local incidence of invasive mold infections	Strongly disagree or disagree – 74.1% Neither agree nor disagree – 7.4% Strongly agree or agree – 18.5%
b) concern about dosing as recommended	Strongly disagree or disagree – 74.1% Neither agree nor disagree – 11.1% Strongly agree or agree – 14.8%
c) reluctance to standardize practice	Strongly disagree or disagree – 74.1% Neither agree nor disagree – 18.5% Strongly agree or agree – 7.4%
d) recommendations conflict with current institutional policies	Strongly disagree or disagree – 77.8% Neither agree nor disagree – 7.4% Strongly agree or agree – 14.8%
e) Pre-printed and existing electronic order sets would need to be changed?	Strongly disagree or disagree – 77.8% Neither agree nor disagree – 22.2%
f) access to the recommended antifungal agents in our institution's formulary	Strongly disagree or disagree – 74.1% Neither agree nor disagree – 3.7% Strongly agree or agree – 22.2%
g) access to beta-glucan or galactomannan testing	Strongly disagree or disagree – 18.5% Neither agree nor disagree – 25.9% Strongly agree or agree – 55.6%
Likely to play an active role in contributing towards guideline implementation	Strongly agree or agree – 77.8% Neither agree nor disagree – 14.8% Strongly disagree or disagree – 7.4%
Likely to adopt for own practice?	Likely – 82.1% Unsure – 7.2% Not likely – 10.7%

Comments:

Comment	Response
Regarding patients with AML/MDS: Re recommendation on page 4, reiterated on page 29, could be interpreted to mean continuous prophylaxis during the whole course of chemotherapy including maintenance. The recommendation is clearer on page 37 where it is stated: '.... throughout the course of chemotherapy while they are neutropenic' is more precise	The document was modified to read "throughout course of chemotherapy while they are neutropenic".
The dose of fluconazole of 6-12 mg/kg is higher than we use outside of the newborn period. I am concerned about potential hepatic toxicity with the dose of 12 mg/kg, especially in the older children (close to age 13 yr). It is not uncommon that we have to reduce the dose from 400 mg to 200 mg in adolescents who are severely ill and on multiple drugs. I note that this dose range is based on the IDSA guideline for management of candidiasis yet that same document recommends a loading dose of 12 mg/kg followed by 6 mg/kg/dose for prophylaxis in neutropenia. That is the dose we use.	This is discussed in the dosing section of the recommendation.
what steps will be taken to evaluate the impact of these guidelines?	This is described in Appendix I - the key review criteria for monitoring and/or audit purposes.
What efforts will be made for posaconazole coverage?	This will be left to individual institutions.
Introduction mentions environmental strategies including avoidance of construction and renovation. Most of the times the physicians have no control on this. Do we change our practice of prophylaxis during these times?	This is beyond the scope of the guideline.
page 11, Figure 1. he numbers in text (para 2) and figure do not match.	Text adjusted accordingly.
Patient with HR ALL at least during induction tehrapy are likely emerging to be a population in need for antifungal prophylaxis. May be further studies should be directed to this population. thank you for the opportunity to review the guidelines.	This is addressed in the guideline. Appendix B (research gaps) was adjusted to address this research gap
Excellent review.....totally agree with recommendations. Invasive molds in Vancouver is one obstacle - but I think the guidelines as currently written reflect our current practice, and the guidelines include the caveats about IFI and the need to consider aspergillus coverage in certain situations - guidelines never replace tailoring treatment to the patients individual situation. Great Job! Look forward to them being published.	Caveats about IFI and mold infections included throughout guideline.
FYI - typo on page 21 (fluconazole dosing is 200 mg/kg/day in one place) I know that the literature is not clear, but it would be great if more guidance could be given re fluconazole dosing. 6 to 12 mg/kg/day is a big range. Are there patient factors that would influence the choice of dose?	This is beyond the scope of the guideline.
Suggest wording change for Health Question 3 to wording on page 37;	See comment 1.

change to AML/MDS should receive fluconazole 6-12 mg/kg/day throughout the course of chemotherapy while they are neutropenic. This would give us the option to start antifungals at a later time to avoid interactions.	
My only criticism is that if the authors claim to be using GRADE, they need to include the GRADE tables in the appendix. It appears that they perhaps just reached consensus based on the table they have added to Appendix C rather than actually applying the GRADE tool using the GRADE software. The reason why this is important is that the GRADE tables show the reader exactly how the quality of evidence was determined.	Although the software was not used, the system was still used to arrive at the evidence grades.
Posaconazole in recommendations summary but I am struggling to find it in the literature review or discussion of agents.	A separate heading for "Posaconazole" was added under the AML/MDS recommendation
Typos on page 24 - para 3 - prophylaxis.	Corrected.
page 28 1st line under fluconazole - need 'of' at the end of line,	Corrected.
2nd para under fluconazole 'the', not 'their'	Corrected.
Page 42 'Unfortunately, the all of' -> 'Unfortunately, all of',	Corrected.
'This is consistent ISDA' -> 'This is consistent with ISDA'.	Corrected.

Appendix G: Websites Searched for Guidelines and Standards

Web sites checked:

Canadian Cancer Academic Centers
Cancer Care Ontario: www.cancercare.on.ca
Professional Associations and Agencies
Children's Oncology Group: www.childrensoncologygroup.org* International Society of Pediatric Oncology: www.siop.nl*
Academic and Government Associated Websites
NCCN: www.nccn.org NCI: www.nci.nih.gov/cancertopics
Guideline Specific Websites
www.cancerindex.org Directory of Clinical Practice Guidelines National Guideline Clearing House National Comprehensive Cancer Network Cochrane Collaboration

Children's Cancer
& Blood Disorders

Appendix H: Tools for Application

Appropriate information and support will be provided to families so as to facilitate decision-making regarding the risks and benefits of antifungal prophylaxis when the guideline has been approved.

Appendix I: Organizational Barriers and Cost Implications

Potential organizational barriers/cost implications to applying the recommendations found in this guideline include:

- Inability to obtain antifungal agents

- Costs of some antifungal agents

Patient/ family preferences:

- Religious or other objection to antifungal prophylaxis

- Administration limitations of some antifungal agents (need for intravenous medication vs. oral)

Appendix J: Key Review Criteria for Monitoring and/or Audit Purposes

Key review criteria for monitoring/ audit include:

- Use of antifungal prophylaxis only for appropriate indications

- Extent of adherence to guideline recommendations

- Number of children requiring antifungal prophylaxis

- Number of children with invasive fungal infection and IFI related mortality