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REVIEW

Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2014

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Abstract

There is a strong argument for the use of antifungal prophylaxis in high-risk patients given the significant mortality associated with invasive fungal disease, the late identification of these infections, and the availability of safe and well-tolerated prophylactic medications. Clinical decisions about which patients should receive prophylaxis and choice of antifungal agent should be guided by risk stratification, knowledge of local fungal epidemiology, the efficacy and tolerability profile of available agents, and estimates such as number needed to treat and number needed to harm. There have been substantial changes in practice since the 2008 guidelines were published. These include the availability of new medications and/or formulations, and a focus on refining and simplifying patient risk stratification. Used in context, these guidelines aim to assist clinicians in providing optimal preventive care to this vulnerable patient demographic.

Introduction

Invasive fungal disease (IFD) represents a significant challenge to the management of patients with haematological malignancies and those undergoing haemopoietic stem cell transplantation (HSCT).[1] It results in an inability to deliver curative treatment and substantial morbidity and mortality (with up to 75% mortality at 1 year[2,3])

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despite modern antifungal treatments.[3] Antifungal prophylaxis thus represents an important 'preventive' strategy for managing patients at high risk of developing an IFD, particularly those undergoing intensive treatments.

Assessing the benefit or cost-effectiveness of antifungal prophylaxis is difficult. The number needed to treat (NNT) and number needed to harm (NNTH) – as well as an individual patient's IFD risk – is typically used to help guide clinical decision making, with current expert opinion favouring an NNT of around 20 for optimal benefit.[4,5] If NNTH is smaller than NNT, a prophylactic strategy is not appropriate. When applying this concept locally, clinicians need to be cognisant of deficiencies in local diagnostics as these can impact the background rate of IFD detection, which may falsely lower or elevate NNT. An alternative to universal mould-active prophylaxis in at-risk patients is a diagnostic-driven early therapy approach.[6] This strategy, however, is limited to centres with the appropriate laboratory infrastructure.

Changing fungal epidemiology at both a population-wide and local level remains an important consideration. Broadly, since the introduction of fluconazole and itraconazole prophylaxis in high-risk patients, there has been a change in epidemiology with *Aspergillus* species replacing *Candida* species as the most common fungal pathogen.[1,2,7,8] Between sites, there is also a variability in the incidence and etiology of IFDs, which will impact the decision to use prophylaxis *and* subsequent choice of agent.[2,3,8,9]

The current guidelines serve as an update to those previously published in 2008.[10] They incorporate new information and highlight agents and approaches currently under investigation.

Methodology

Questions asked

We aimed to address the following questions:

1 What updates have been published since 2008 to assist the stratification of patients into low-, intermediate- or high-risk groups for IFD?

2 What new information exists on the efficacy and tolerability of available agents to help guide their use in this setting?

Search strategy

A literature review was performed using PubMed to identify papers published since 2007 that pertained to risk factors for, and prophylaxis of, IFD in haematology and HSCT patients. Search terms included (in combination) 'haematology', 'haemopoietic cell transplant', 'fungal infection', 'antifungal prophylaxis' and 'risk factors'.

Evidence and recommendations for antifungal prophylaxis in adult patients

Assigning IFD risk to adult patients

Risk stratification is a key to identifying patients that should be considered for antifungal prophylaxis. However, the number of potential risk factors, as well as their interactions in any individual patient, does make risk stratification complex.[11] A classification of risk according to the underlying disease alone is provided in Pagano *et al.*[12] Several other accepted risk factors for IFD (including age, disease stage, treatment type and intensity, and immune status) are presented in Tables 1 and 2, with Table 1 stratifying the level of risk imposed by each.

The IFD risk model shown in Table 1 was based on patients not receiving mould prophylaxis[11] and was subsequently validated by testing a group of haematology patients receiving intensive chemotherapy or HSCT for *Aspergillus* by polymerase chain reaction (PCR).[13] While fludarabine alone is not an established risk factor for IFD, its inclusion in the table highlights the role of agents that cause lymphopenia. Individual factors predisposing to or adding to risk for mould infection are shown in Table 2.

Clinical risk assessment profiles identify the following two groups of patients as those at highest risk of developing an IFD:[12]

- Patients receiving intensive chemotherapy for acute myeloid leukaemia (AML) or myelodysplastic syndromes
- Patients with corticosteroid-requiring graft-versus-host disease (GVHD) following allogeneic HSCT.

With regard to GVHD, the risk of IFD appears particularly prominent in patients with (i) either high-grade (grade 3 or 4) or steroid-refractory/dependent acute GVHD and (ii) chronic GVHD, particularly if it developed as a late complication of acute GVHD.

The 2014 Italian Group for Bone Marrow Transplantation also recommends that the following patient groups be considered at 'high risk' of acquiring an IFD: patients receiving stem cell transplantation with cord blood transplants; patients with either mismatched-related or matched-unrelated donors, with additional risk factors (defined as cytomegalovirus (CMV) disease or recurrent CMV infection or iron overload); and patients receiving allogeneic stem cell transplantation for acute leukaemia with active disease at the time of transplant.[14]

Patients undergoing 'intensive' therapy regimens for other haematological conditions may also be at a higher risk of IFD. For example, a high rate of IFD (incidence of 28% with fluconazole prophylaxis) has been observed in

Table 1 Invasive fungal disease risk groups (adapted from multiple sources[8,11,13–15])

High risk: >10% incidence IFD	Neutrophils <0.1 × 10^9/L for >3 weeks[16] or <0.5 × 10^9/L for >5 weeks
	Unrelated, mismatched or cord blood donor HSCT
	GVHD
	Corticosteroids >1 mg/kg prednisolone equivalent and neutrophils <1 × 10^9/L for >1 week
	Corticosteroids >2 mg/kg prednisolone equivalent >2 weeks†
	High-dose cytarabine‡
	Fludarabine use in highly treatment-refractory patients with CLL or low-grade lymphoma§
	Alemtuzumab use, especially in highly treatment-refractory patients with CLL or lymphoma§[17]
	ALL
	AML
Intermediate risk: ~10% incidence of IFD	Neutropenia 0.1–0.5 × 10^9/L for 3–5 weeks
	Neutropenia 0.1–0.5 × 10^9/L for <3 weeks with lymphopenia (lymphocytes <0.5 × 10^9/L)
Low risk: ~2% incidence of IFD	PBSC autologous HSCT
	Lymphoma

†Other authors have described prednisolone equivalent of >1 mg/kg/day for 2 weeks or 0.25–1 mg/kg/day for 4 weeks in allogeneic HSCT[2]. ‡Some authors question whether the high rates of IFDs seen with high-dose cytarabine may be contributed to by concurrent fludarabine. §Represent additions to 2008 table. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukemia; GVHD, graft versus host disease; HSCT, haemopoietic stem cell transplant; IFD, invasive fungal disease; PBSC, peripheral blood stem cell; TBI, total body irradiation.

patients receiving intensive chemotherapy (e.g. hyper-CVAD) for acute lymphoblastic leukaemia (ALL).[15]

Clinicians should also keep in mind that risk factors for IFDs are dynamic, and risk status can evolve in an individual patient, particularly at phase-specific time points following allogeneic HSCT. For example, patients classified as low or intermediate risk (e.g. those with myeloma[22] and chronic lymphocytic leukaemia (CLL)) may move into a higher-risk group with advanced disease, prolonged or profound neutropenia, prolonged corticosteroid use, and in the case of CLL, use of alemtuzumab.[17]

Recommended use of prophylaxis in adults based on risk classification

Patients at high risk of invasive mould infections should receive mould-active prophylaxis (level II evidence, grade A recommendation).

Prophylaxis directed at *Candida* species is appropriate in patients where neutropenia is less protracted (e.g. less than 14 days in duration) but where mucosal integrity may be compromised (level III evidence, grade C recommendation).[23]

Where neutropenia is transient, mucosal integrity is preserved, and when immunosuppression is not extensive (such as standard intensity chemotherapy for lymphoma), antifungal prophylaxis is not routinely required (level III evidence, grade C recommendation).

Please refer to Table 3 for a summary of recommendations by risk classification.

Table 2 Individual risk factors for invasive mould infection

Antibiotics[11]
Older age[11]
Central venous catheter[11]
Iron overload[18]
Recent CMV reactivation[19]
Ganciclovir use[20]
Lower respiratory tract viral infection[21]
Environmental exposure to mould[12,18]

CMV, cytomegalovirus.

Timing of prophylaxis for adults

Aside from allogeneic HSCT,[7] the optimal timing of initiation of prophylaxis is unclear. Most studies commence prophylaxis during administration of chemotherapy, although to avoid drug interactions, particularly with itraconazole and cyclophosphamide, itraconazole may be commenced on day of stem cell infusion.[24] Cessation is generally recommended following resolution of risk, which in acute leukaemia corresponds with neutrophil reconstitution (>0.5 or 1.0 × 10^9/L) (level II evidence, grade C recommendation).

Allogeneic transplant recipients should continue antifungal prophylaxis until at least day 75 (in the absence of GVHD), unless precluded by toxicity (level II evidence, grade B recommendation). For patients with GVHD, prophylaxis should be continued for 16 weeks or until corticosteroid dose is less than 10 mg daily prednisolone equivalent (level IV evidence, grade C recommendation).

Therapeutic drug monitoring in adults

The need for, and utility of, therapeutic drug monitoring (TDM) in patients receiving antifungal prophylaxis is

Table 3 Classification of risk and recommended prophylaxis for adults

Risk classification	Clinical examples (level of evidence, grade of recommendation)	Recommended prophylaxis
High risk	Acute leukaemia or myelodysplasia, with remission induction and re-induction chemotherapy (II, A)	Mould-active prophylaxis
	Severe GVHD: steroid dependent or refractory or grade 3 or 4 (II, A)	
	Extensive chronic GVHD (II, A)	
	Allogeneic HSCT with expected neutropenia >14 days (III, C)	
Low risk	Selected autologous HSCT† (II, C)	Anti-*Candida* prophylaxis
	Allogeneic HSCT with expected neutropenia <14 days (II, A)	
	Patients receiving intensive/dose-escalated therapy for lymphoma (IV, D)	
Very low risk	Standard chemotherapy for lymphoma (III, C)	No prophylaxis
	Chronic myeloid leukaemia (IIIC)	
	Other myeloproliferative neoplasms (III, C)	

†'Selected' refers to autologous HSCT with higher risk of mucositis and thus *Candida* infection (e.g. those with recent aggressive salvage chemotherapy or receiving multi-agent regimens). GVHD, graft-versus-host disease; HSCT, haemopoietic stem cell transplant.

discussed in the accompanying optimising drug therapy guidelines by Chau *et al*. 2014 (appearing elsewhere in this supplement). However, as failures are associated with inadequate levels, TDM in specific groups may be beneficial. Please refer to Chau *et al*. 2014 for a more detailed discussion of the available evidence for TDM and agent-specific recommendations.

Review of literature since 2008 for the use of specific prophylactic antifungal agents in adult patients

For a review of the literature up to 2008, please refer to the previous guidelines.[10] Table 4 provides evidence-based recommendations to help guide clinicians' choice of agent and dosing.

Posaconazole Oral posaconazole remains the preferred agent for use in high-risk patients due to its broad anti-mould activity and low-breakthrough IFD rates.[8,9,26] It is the only mould-active agent to demonstrate a survival advantage in a randomised trial in AML patients.[9] However, the oral posaconazole suspension used in that trial (the only formulation currently available in Australia) can be difficult to reliably administer in patients with GVHD of the gastrointestinal tract and mucositis, with absorption most questionable in patients experiencing vomiting, diarrhoea or colitis.[27] Further information

Table 4 Recommendations for the use and dosing of specific antifungal agents for prophylaxis (grade of evidence)

Risk group	Agent	Alternative agents
High risk	Posaconazole (A)	Voriconazole (B)
		Itraconazole (B)
		Liposomal amphotericin B (C)
		Micafungin† (B)
		Caspofungin (C)
Low risk	Fluconazole (B)	Itraconazole (B)
		Echinocandins (B)

Agent	Recommended dose for adult patients	Recommended dose for paediatric patients
Posaconazole	200 mg orally, 8-hourly	>13 years: 200 mg orally, 8-hourly plus TDM
Voriconazole	200 mg orally or IV, 12-hourly	2 years to <12 years or 12–14 years and weighing <50 kg: 8 mg/kg (day 1, 9 mg/kg) IV, 12-hourly or 9 mg/kg orally, 12-hourly plus TDM
		≥15 years or aged 12–14 years and weighing ≥50 kg: 4 mg/kg (day 1, 6 mg/kg) IV, 12-hourly or 200 mg orally, 12-hourly plus TDM
Fluconazole	200–400 mg orally or IV, daily	6–12 mg/kg (max 400 mg) orally or IV, daily
Itraconazole	200 mg orally, 12-hourly	2.5 mg/kg orally, 12-hourly plus TDM
Liposomal amphotericin B	See text (adult section) for dosing recommendations	See text (paediatric section) for dosing recommendations
Echinocandins	See text (adult section) for dosing recommendations	See text (paediatric section) for dosing recommendations

†Although a randomised controlled trial has compared micafungin and fluconazole prophylaxis, this study was not adequately powered to establish anti-mould efficacy.[25] IV, intravenous; TDM, therapeutic drug monitoring.

on optimising posaconazole exposure and monitoring drug levels is available in the accompanying optimising drug therapy guidelines by Chau *et al*. 2014 (appearing elsewhere in this supplement).

Hepatotoxicity occurs in approximately 10% of patients.[28] In the prophylaxis studies, the rate of disturbance of liver function tests for patients with GVHD was 15% (compared with 8% in the fluconazole arm)[26] and for patients with AML, 7% (compared with 3% in the itraconazole/fluconazole arm).[9]

In November 2013, the Food and Drug Administration in the USA approved posaconazole delayed-release tablets enabling once daily dosing (following a loading dose), which results in more reliable serum levels: serum levels >500 ng/mL are achieved in most AML and HSCT recipients.[29] This formulation, as well as an intravenous (IV) preparation of posaconazole, may address some of the problems with administration and absorption associated with the suspension. However, it is not yet marketed for use in Australia.

Voriconazole Voriconazole is an alternative to posaconazole as it exhibits mould activity and is also available in an IV formulation. In myeloablative HSCT recipients at standard risk for early death or relapse, one randomised, double-blind study of voriconazole (n = 305) and fluconazole (n = 295) concluded that fungal-free survival rates (the primary endpoint) were similar at 180 days.[30] Both arms underwent weekly to twice weekly screening with galactomannan (GM), and prophylaxis was administered for 100 or 180 days in higher-risk patients. The median number of days patients remained on the study drug was 91 for fluconazole and 96 for voriconazole. There was a trend towards fewer IFDs, fewer *Aspergillus* infections and less empiric antifungal therapy with voriconazole prophylaxis than fluconazole prophylaxis. Notably, fluconazole and voriconazole were similarly tolerated with the same proportion of withdrawals due to adverse events (AEs) at a similar median time. This study indicates that voriconazole prophylaxis is safe in HSCT patients. It is not clear whether the low incidence of IFDs observed in this study was due to selection of a cohort at low risk of mould infections, the GM surveillance or the efficacy of prophylaxis. However, with an overall incidence of proven and probable IFDs of 6.3% at day 180, these patients did not appear as high risk as those examined in other studies. This study provides no evidence to change the standard practice of fluconazole prophylaxis in standard-risk HSCT in the first 75 days post-transplant.[7] In HSCT recipients where the incidence of *Aspergillus* is higher, voriconazole prophylaxis may be an option, although this study did not examine such a selected high-risk group.

Itraconazole Itraconazole (n = 255) was compared with voriconazole (n = 234) in an open-labelled, randomised study in allogeneic HSCT recipients with a composite endpoint of efficacy and tolerability.[31] While it did show a difference in its composite endpoint, as a result of better voriconazole tolerability, there was no difference between the two agents in terms of the study's efficacy endpoints (overall 180-day survival and incidence of proven or probable IFDs). Unlike the study of Wingard *et al*. discussed previously,[30] systematic GM testing was not performed in this study, and thus, it is possible that the overall incidence of proven/probable IFDs (1.3% for itraconazole and 2.1% for voriconazole) was underestimated.[31] It is also worth noting that a greater number of itraconazole patients received other systemic antifungals (42% vs 30%). Intolerance was reported in up to one-third of those taking itraconazole irrespective of formulation (capsule or solution). Rates of intolerance may be alleviated by a novel capsule formulation recently approved. This new formulation, Lozanoc®, is not affected by gastric pH, and dosing recommendations differ from the capsule formulation currently in widespread use (Sporanox®). Please refer to the accompanying optimising drug therapy guidelines by Chau *et al*., 2014, appearing elsewhere in this supplement, for further information. Retrospective studies of itraconazole's use in Australia have also demonstrated its efficacy although breakthrough rates vary between centres.[8,32]

Liposomal amphotericin B Liposomal amphotericin B prophylaxis has been used in the setting of azole intolerance or chemotherapy drug interactions, such as those observed with vincristine in ALL, despite a paucity of evidence. Older studies are summarised in the previous guideline.[10]

In a prospective phase II trial, 48 AML patients undergoing induction chemotherapy received high-dose liposomal amphotericin B (15 mg/kg) initially and again after 15 days of neutropenia.[33] Although this was primarily a tolerability study, the rate of IFDs was 8.3%. A prospective study of 40 patients randomised to either posaconazole or weekly liposomal amphotericin B (7.5 mg/kg) in HSCT had insufficient numbers to clarify the comparative efficacy of the two agents.[34] However, 53% of patients treated with liposomal amphotericin B had to discontinue treatment due to renal toxicity versus 5% in the posaconazole group. This contrasts with the experience of another group who used liposomal amphotericin B (7.5 mg/kg weekly) in allogeneic HSCT recipients receiving high-dose prednisolone for GVHD. The study was not randomised and included only 42 patients. Five patients (12%) had reversible nephrotoxicity leading to temporary treatment

discontinuation during the median 7 weeks of exposure to liposomal amphotericin B.[35] The optimal dose for prophylaxis requires clarification.

Liposomal amphotericin B studies in progress include the following:

- Paediatric acute leukaemia induction – oral voriconazole versus IV liposomal amphotericin B 0.5 mg/kg daily, three times per week (NCT00624143)
- Adult acute leukaemia induction – IV liposomal amphotericin B (1 mg/kg daily vs 3 mg/kg three times per week vs 10 mg/kg weekly) (NCT00451711)
- A multi-centre, randomised, double-blind study of liposomal amphotericin B (5 mg/kg daily, twice weekly) compared with placebo in newly diagnosed ALL patients undergoing first remission induction. Intensive monitoring with *Aspergillus* GM and PCR is incorporated in each study arm (NCT01259713).

While IV liposomal amphotericin B is often used for prophylaxis in settings where an azole cannot be used (due to toxicity or drug interactions), it remains uncertain whether it is as effective as azole prophylaxis. The optimal dosing regimen is also unclear although some Australian centres have used a dose of 100 mg three times a week based on older studies discussed in the previous guideline.[10]

Twice-weekly aerosolised liposomal amphotericin B was examined in one randomised, placebo-controlled study in 271 haematology patients who were neutropenic after chemotherapy. Invasive aspergillosis was significantly reduced in the treatment group.[36] Despite the positive finding of this study, aerosolisation of liposomal amphotericin B has not been widely adopted, possibly due to the need for an advanced nebuliser system.

Echinocandins

Despite a favourable safety profile in high-risk patients, there is reluctance to use echinocandins for prophylaxis as they lack broad spectrum anti-mould activity. Similar to a larger study using 50 mg of micafungin daily discussed in the 2008 guidelines,[25] a recent study found that micafungin 150 mg daily was as effective as fluconazole 400 mg daily prophylaxis at 4 weeks for patients undergoing allogeneic HSCT.[37] As there were only 52 patients in each arm, it is possible that the sample size was too small to detect a difference. Similar results have been observed with caspofungin 50 mg daily.[38,39] The above studies generally examined short-term prophylaxis when yeast infections predominate over *Aspergillus* infections. A cohort analysis of 152 AML patients receiving remission induction chemotherapy between 2009 and 2011 found echinocandin-based prophylaxis (agents and doses not specified) was associated with higher breakthrough IFD rates than voriconazole/posaconazole prophylaxis.[40]

Use of prophylactic agents in special populations

Many drugs used in the haematology/oncology population will interact with antifungal medications, which may impact the choice of antifungal prophylaxis. For further information, please consult the accompanying optimising drug therapy consensus guidelines by Chau *et al*. 2014 (appearing elsewhere in this supplement). Some specific patient types and clinical scenarios are also considered here.

Secondary prophylaxis

In patients with a documented history of suspected or confirmed IFD, secondary prophylaxis is recommended, employing the agent used to treat the initial infection provided it was well tolerated and effective (level III evidence, grade B recommendation).[41] Therapeutic dosing should be used.[42]

Renal impairment

Drug toxicities are presented in the accompanying optimising drug therapy guidelines by Chau *et al*., 2014 (appearing elsewhere in this supplement). Liposomal amphotericin B is potentially nephrotoxic. Close attention to fluid and electrolyte status is advised. Despite the animal data suggesting potential nephrotoxicity of IV voriconazole, recent data have not shown an association with acute kidney injury in patients of renal impairment.[42–44]

Hepatic impairment and azole associated transaminitis

Azole antifungals are metabolised by the liver and hepatotoxic. Thus, in the presence of moderate to severe hepatic dysfunction, a change to either liposomal amphotericin B (for mould activity) or an echinocandin should be considered (grade D recommendation). Elevation of hepatic transaminases occurs in approximately 10% of patients on itraconazole or a second-generation azole, with grade 3–4 hepatotoxicity (5× upper limit of normal) occurring infrequently (as per full prescribing information).[45] It is unclear at what level of transaminitis the azole should be discontinued. The potential benefit and harm of discontinuation should be considered.

Photosensitivity and skin cancers

It should be noted that immunosuppressed patients receiving prolonged voriconazole therapy (e.g. more than

1 year) in conjunction with ongoing immunosuppression have developed photosensitivity and skin cancer, particularly squamous cell carcinoma.[46]

Intensive care unit admission

Mould-active antifungal prophylaxis is recommended for neutropenic haematology or HSCT patients with multi-organ failure managed in the intensive care unit (ICU; level II evidence, grade C recommendation). An echinocandin agent, with a good safety profile, may be used if other agents cannot be used due to potential toxicity (grade D recommendation).[47] A mould-active azole agent should be resumed if toxicity improves or resolves (grade D recommendation).

Solid tumour

There is insufficient evidence to support the routine use of antifungal prophylaxis in patients with solid tumours, outside the intensive care setting (level III evidence, grade C recommendation).

Tyrosine kinase inhibitors in ALL/blast crisis CML

The metabolism of tyrosine kinase inhibitors (TKI), such as imatinib, dasatinib or nilotinib, is affected by azole antifungals. For this reason, TDM, close attention to liver function and dose modification, if required, are advised (grade D recommendation).[48] In view of the potential for prolonged QT interval and arrhythmias with the combination of TKIs and azoles, monitoring of electrocardiograms may be warranted. Patients with reduced left ventricular ejection fraction or electrolyte disturbances, or who are taking antibiotics, such as fluoroquinolones, may be at risk.[49]

Sorafenib for FMS-like tyrosine kinase inhibition in AML

Triazole antifungals directly interfere with the activity of FMS-like tyrosine kinase 3 inhibitors, such as sorafenib. Consequently, liposomal amphotericin B is the preferred antifungal agent for these patients (grade D recommendation).[50]

Vincristine

Azole antifungals inhibit the metabolism of vincristine through cytochrome P450 (CYP) 3A4, leading to excess vinca alkaloid exposure.[51] For more information, please refer to the accompanying optimising drug therapy guidelines by Chau *et al*., 2014 (appearing elsewhere in this supplement).

Environmental factors

When managing patients at high risk of IFDs, close attention should be paid to minimising risk of fungal spore exposure. This should include utilisation of high-efficiency particulate air filtration and positive-pressure room ventilation for in-patients. Out-patients should be advised to avoid exposure to soils and dust, and to wear N95 particulate filtering masks if the risk of exposure is considered high. Particular care needs to be exercised where there is significant building activity around a facility as this increases the risk of exposure to airborne fungi. For further information, please refer to the accompanying quality factors guidelines by Chang *et al*. 2014 (appearing elsewhere in this supplement).

Evidence and recommendations for antifungal prophylaxis use in paediatric patients

Children with cancer are as vulnerable to IFD as adults. However, there is substantially less evidence for the efficacy of prophylaxis in children. Most of the available literature is derived from adult or combined adult and paediatric trials (with children usually no younger than 12 years). Risk stratification remains fundamental to identifying those children who should be considered for antifungal prophylaxis and for distinguishing which agent (anti-mould vs anti-candida) should be used. As paediatric cancer treatment protocols are continually evolving, and new chemotherapy agents and combinations are trialled, ongoing IFD surveillance is strongly recommended.

Assigning IFD risk to paediatric patients

Factors contributing to an increased risk for IFD in children are similar to adults (Tables 1 and 2). However, stratification and prophylaxis regimens do vary due to important differences in IFD epidemiology, underlying conditions, chemotherapy regimens and pharmacokinetics of antifungal agents. The 4th European Conference for Infections in Leukaemia summarised the risk of IFD in children according to patient population (Table 5).[52] This classification is based on data from several paediatric studies, including an Australian publication,[55] and is in keeping with recent systematic reviews.[52,54,56]

While there is agreement that children at highest risk of IFD include those with relapsed acute leukaemia, AML, post-allogeneic HSCT, GVHD and severe aplastic

Table 5 Paediatric IFD risk groups

High risk (≥10%)	Acute myeloid leukaemia
	Recurrent/relapsed acute leukaemia
	Allogeneic HSCT
	Allogeneic with acute grade 1–4 GVHD or chronic extensive GVHD
	Severe aplastic anaemia
Low risk (≤5%)	Acute lymphoblastic leukaemia†
	Non-Hodgkin lymphomas
	Autologous HSCT
Sporadic occurrence‡	Paediatric solid tumours
	Brain tumours
	Hodgkin's lymphoma

†Depending on the treatment protocol and additional risk factors, in particular prolonged neutropenia, use of corticosteroids and local prevalence data, risk for IFD may exceed 5–10%. ‡Consider that sporadic occurrence is not equal to no risk. Adapted from Groll *et al*.,[52] Science *et al*., 2014[53] and Dvorak *et al*.[54] GVHD, graft-versus-host disease; HSCT, haemopoietic stem cell transplant.

anaemia,[53,54,56] there is some discordance regarding risk in ALL. Depending on the institution, rates of IFD in this population vary from 1%[57] to 10% or more.[55,58] Rates of up to 11% have also been reported in infants with ALL.[59] In an Australian paediatric series, as many as 30% of children with high-risk ALL (defined according to age, white cell count, blast count, minimal residual disease, immunophenotype and unfavourable cytogenetics, and treated with an intensive regimen not currently followed) had a proven or probable IFD (yeast 15%, mould 15%) as compared with 6% (yeast only) in the low-risk ALL group. This suggests that burden and type of fungal disease are related to treatment protocol and disease risk. Similar variability was also seen in children with AML with intensive induction associated with significantly higher rates of fungal infections, as compared with standard induction treatment.[60] Despite the variability in quoted incidence of IFD in ALL, children with standard-risk ALL are generally considered low risk for IFD.[53]

In addition to variability in the reported rates of IFD, there are differences in the reported frequency of mould versus *Candida* infections between institutions. In children with AML, *Aspergillus* was the most common pathogen in a European study,[61] while *Candida* species were more frequently documented in an Australian study at a single centre[55] and in a large Canadian study of 341 children across 15 centres.[62] The influence of chemotherapy regimen and underlying disease on type of IFD is also important. *Aspergillus* tends to be documented more frequently than *Candida* in patients with recurrent acute leukaemias,[55,63] moderate to severe GVHD[53] and severe aplastic anaemia,[64] while *Candida* species often predominate in ALL,[57,65] including infant ALL[59] and autologous HSCT.[66]

Recommended use of prophylaxis in paediatric patients based on risk classification

Primary antifungal prophylaxis is recommended when the underlying incidence of IFD exceeds 10% (expert opinion).[52,67] Where the incidence is below 10%, consideration should be given to prophylaxis for those conditions where a clear benefit has been shown, as for autologous transplant with prolonged neutropenia.[68,69] When implementing prophylaxis regimens, consideration must also be given to institutional epidemiology and relevant adjustments made.

Recommendations for fluconazole, posaconazole and voriconazole prophylaxis in children are based on results from randomised controlled trials conducted predominantly in adults. Please refer to the preceding section of this paper and the 2008 guidelines for a detailed discussion of these trials.[10] A comprehensive review of the literature is also available in the recently published paediatric antifungal guidelines from Europe and Canada.[52,67] Notably, these guidelines differ with regard to the level of evidence assigned to each recommendation. In applying the grading of the Australian National Health and Medical Research Council, most recommendations, unless otherwise stated, would be considered grade C at best due to the paucity of dedicated paediatric randomised data.[70] While it is sensible to rely on adult data in this situation, clinicians should pay particularly close attention to adverse effects, drug interactions and TDM.

Due to high mortality associated with invasive mould infections (predominantly *Aspergillosis*), mould-active prophylaxis has been recommended for patients at highest risk of these infections (grade of recommendation as for adults). Itraconazole or voriconazole, with TDM, is recommended for children <13 years of age as there is an absence of pharmacokinetic (PK) data for posaconazole in this age group. In contrast, a 2014 publication recommends fluconazole for children <13 years with an increased risk of invasive mould infections.[53] These recommendations (Table 6) are based on results of a meta-analysis that did not show an overall survival benefit of anti-mould prophylaxis compared with fluconazole in patients with cancer or HSCT[71] and a randomised trial that compared fluconazole with voriconazole prophylaxis after allogeneic HSCT.[30] This trial, which included both adults and children, found no significant difference in fungal-free or overall survival. Of note, this trial incorporated intensive monitoring for IFD and used paediatric doses of voriconazole lower than those currently recommended.

The risk of IFD is high in children with AML,[55] although in contrast with adults, *Candida* infections predominate.[62] Therefore, although a survival benefit of posaconazole, in

Table 6 Recommendations for antifungal prophylaxis in children

Risk classification	Clinical examples	Recommended prophylaxis	Alternative agent
High (requiring mould-active prophylaxis)	High-intensity treatment for recurrent/ relapsed acute leukaemia Severe GVHD (steroid dependent or refractory or grade 3 or 4) Extensive chronic GVHD Severe aplastic anaemia	<13 years†: itraconazole or voriconazole ≥13 years: Posaconazole	Itraconazole Liposomal-amphotericin B Echinocandin
Intermediate (requiring non-mould-active prophylaxis)	High risk: Allogeneic HSCT AML‡ Low risk: Autologous HSCT (where expected ANC <500 for >10 days)	Fluconazole§	Echinocandin§ Itraconazole Liposomal-amphotericin B
Low	ALL¶ NHL	No prophylaxis Consider fluconazole when neutrophils expected to be <0.5 for >3 weeks	—

See Table 4 for dosing recommendations; see text for levels of evidence and grades of recommendations.
†Data for the use of posaconazole under the age of 13 years is limited (see text). Use in this age group should be assessed on an individual basis, and drug levels should be monitored. ‡For institutions with high rates of invasive mould infections in patients with AML, manage as for high risk requiring mould-active prophylaxis. §Level B evidence for allogeneic and autologous transplant. ¶ALL with highly intensive treatment regimens manage as autologous HSCT, unless prophylaxis mandated by trial protocol. ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; ANC, absolute neutrophil count; GVHD, graft-versus-host disease; HSCT, haemopoietic stem cell transplant; NHL, Non-Hodgkin's lymphoma. —, not applicable.

comparison with fluconazole or itraconazole, has been demonstrated in adults with AML,[9] fluconazole remains the recommended first-line antifungal prophylaxis agent in children. However, if local rates of invasive mould infection are high in this group, mould-active prophylaxis should be used. Given the results of the study by Cornely *et al.*, 2007, posaconazole could be considered for children over 13 years.[9]

There is no published evidence on the efficacy of antifungal prophylaxis in children with non-relapsed ALL. While the overall the risk of IFD in ALL is low, high-risk treatment protocols and dose-intense phases (i.e. induction and consolidation) may pose a greater than appreciated risk, and antifungal prophylaxis may be considered. It is also important to note that some paediatric trial protocols mandate antifungal prophylaxis, despite this lack of evidence. Pragmatically, these need to be acknowledged.

Timing of prophylaxis in paediatrics

The timing of prophylaxis in children is the same as for adults (please refer to earlier discussion).

Review of literature for the use of specific prophylactic antifungal agents in paediatric patients

Posaconazole The RCTs investigating posaconazole in patients with GVHD and AML included a total of 12 and 16 children (aged 13 to 18 years), respectively, and accounted for 2% of the study populations.[9,26] Although there is insufficient evidence to recommend the use of posaconazole in children aged less than 13 years, the limited PK data available suggest it may be safe and effective in this population. In a retrospective study, prophylactic posaconazole 4 mg/kg was given to 32 children under 12 years of age undergoing allogeneic HSCT. Posaconazole was well tolerated, and no proven or probable IFDs were observed (median trough level was 383 ug/L).[72] Adult posaconazole dosing regimens of 12 children greater than 8 years of age with posaconazole for treatment found similar trough concentrations to adults.[73] TDM is recommended in children with target trough concentrations ≥0.7 mg/L.[56] Please refer to the accompanying optimising therapy guidelines by Chau *et al.*, 2014 (appearing elsewhere in this supplement) for further information.

Voriconazole Two studies that found no difference in efficacy between voriconazole and fluconazole or itraconazole in HSCT both included small numbers of children.[30,74] One RCT in children with ALL and AML compared voriconazole with amphotericin B. The overall rate of IFD was low, with no significant difference between treatments. With no placebo comparison, the relative benefits are difficult to assess.[75] A retrospective cohort study compared voriconazole prophylaxis in 117 children with AML with 105 previously treated children, finding no difference in mould infection rates but a

different pattern of moulds isolated and an improved 90-day survival.[76] Important considerations for voriconazole are the potential for drug interactions (please refer to the accompanying optimising therapy guidelines by Chau *et al.*, 2014, appearing elsewhere in this supplement, for details) and associations with phototoxicity and risk of skin cancer with prolonged (>1 year) use.[46]

The weight-normalised clearance rate of voriconazole is faster in children than in adults.[77] As a result, currently recommended voriconazole doses are higher than those used in previous trials. TDM is advised because of considerable intra- and inter-patient variability in pharmacokinetics.[78] A voriconazole target trough concentration between 1.0 and 6.0 mg/L is recommended for prophylaxis and treatment (please refer to the accompanying optimising therapy guidelines by Chau *et al.*, 2014, appearing elsewhere in this supplement, further information).[56]

Itraconazole Several trials have compared itraconazole with fluconazole in HSCT, only a few of which included children.[79–81] A meta-analysis found fewer documented and suspected IFDs in itraconazole-treated patients but no significant difference in IFD-related or overall mortality.[82] In terms of anti-mould prophylaxis, only one study included children and found no difference in outcome, although more patients tolerated voriconazole for 100 days.[74] Because of its side effects, variable bioavailability, drug interactions and poor tolerability,[80] itraconazole prophylaxis has generally lost favour in children with malignancy.[53,80] However, when tolerated, its performance appears similar to that of voriconazole.[74,83] To optimise bioavailability, the liquid preparation of itraconazole should be used and administered on an empty stomach with acidic drinks (see accompanying optimising therapy guidelines by Chau *et al.*, 2014, also appearing in this supplement, for further information). Prophylaxis trials in children have generally used an itraconazole dose of 2.5 mg/kg twice daily. In most children, a steady state plasma level is reached after 2 weeks of itraconazole oral solution at a dose of 5 mg/kg daily.[84] TDM is also necessary with the suggested trough level of 0.5 ug/mL for prophylaxis and treatment (see accompanying optimising therapy guidelines by Chau *et al.*, 2014, also appearing in this supplement, for further information).[56]

Liposomal amphotericin B Studies investigating amphotericin B as prophylaxis in paediatric patients are limited. Despite a paucity of evidence, it is often used in the setting of azole intolerance or chemotherapy drug interactions, such as with vincristine used in ALL. The optimal dose for prophylaxis remains unknown, with doses ranging from 1 mg/kg thrice weekly[85] to 3 mg/kg daily[86] used safely. Liposomal amphotericin is recommended over conventional amphotericin due to increased rates of toxicity with the latter.[87]

In children with high-risk haematological malignancies, a pilot study comparing liposomal amphotericin (1 mg/kg thrice weekly) with no prophylaxis found no difference in rates of proven/probable IFD.[85] Conversely, an observational study found a significant reduction in IFD in children treated with liposomal amphotericin (2.5 mg/kg twice weekly) compared with historical controls.[88] In another observational study, liposomal amphotericin prophylaxis was well tolerated, with 31 out of 32 courses completed successfully, as defined by absence of breakthrough IFD, no discontinuation due to AE and survival at end of treatment.[89]

In children undergoing allogeneic HSCT, 5% and 7% developed proven/probable IFD while receiving liposomal amphotericin at doses of 3 mg/kg daily and 10 mg/kg per week respectively.[86,90] A small randomised controlled trial, which included both adults and children, compared liposomal amphotericin 1 mg/kg daily with placebo. No significant difference in proven IFD was found, although the number of events in the placebo group was small.[91]

Echinocandins Micafungin and caspofungin have been investigated as prophylaxis in children, and doses of 1 mg/kg daily (max 50 mg) and 50 mg/m^2 daily, respectively, are recommended.[53,56] In a retrospective study of children with high-risk haematological malignancies, one out of 40 children receiving micafungin (3 mg/kg daily) developed a proven or probable IFD. No serious drug-related AEs were described at this dose.[92] In children undergoing allogeneic HSCT, a retrospective comparison of caspofungin (50 mg/m^2 daily) and liposomal amphotericin (1 mg or 3 mg/kg daily) did not show a difference in rates of proven/probable IFD, although patients treated with amphotericin had more drug-related AE.[39] In a prospective safety study of micafungin (2 mg/kg daily), one out of 38 children developed a proven/probable IFD, and no serious AEs were described.[93] In a large (n = 882) randomised study of patients undergoing allogeneic and autologous HSCT transplant, including 84 children, micafungin prophylaxis (1 mg/kg daily, max 50 mg) was associated with significantly lower rates of breakthrough IFD compared with fluconazole. In the paediatric sub-analysis, there was a trend towards fewer IFDs in the micafungin arm (69.2% vs 53.3%). Of note, this study was not adequately powered to establish anti-mould efficacy.[25]

Special paediatric populations

Recommendations regarding secondary prophylaxis, renal and hepatic impairment, ICU, solid tumours,

environmental factors and pharmacological interactions are the same as for adults (see earlier discussion).

Future research

There is a clear need for research into the role of prophylaxis in certain clinical settings where the risk of IFD may not remain static throughout the duration of therapy, as in the case of therapy intensification or attenuation. One such example is consolidation therapy in acute leukaemia in first complete remission. It has long been recognised that most IFD occurs during remission induction or re-induction therapy, rather than during consolidation therapy.[5,11] Factors suggested to impact on risk during consolidation are patient age, severity of mucositis with induction, duration of severe neutropenia with induction, number of induction cycles received, marrow cellularity post-induction, intensity of consolidation (which may impact on risk of mucositis, e.g. cytarabine dose +/– concomitant anthracycline) and time to count recovery (e.g. fludarabine exposure).[94] The effect of these factors on risk during consolidation should be examined as it may be more cost-effective to use fluconazole prophylaxis in lower-risk patients during consolidation therapy.[95]

The risk of IFD in patients receiving newer targeted cancer treatments, which do not rely on cytotoxic chemotherapies, is poorly characterised.[96,97] There are many new therapies in use, such as carfilzomib for myeloma, ibrutinib for CLL and obinutuzumab for B-cell malignancies, where the risk of IFD will need to be quantified.

Further, little is understood about risk of IFD in patients with advanced myeloma or lymphoma who have undergone multiple lines of treatment, or patients with myelodysplasia receiving azacitidine as primary therapy. These groups also require better identification of risk.

The identification of patient-specific risk factors for IFD is also an area for future study. Genetic profiling, particularly of genes relating to innate immunity in the patient – or, in the case of allogeneic HSCT, in the donor – is likely to play an increasingly important role.[98] Also, evaluation of immunological responses to IFD[22] and the role of the mycobiome may also prove to be of value.[99]

Conclusion

There have been substantial changes to the antifungal prophylaxis recommendations since 2008. These include the addition of new drugs and formulations (including voriconazole) and a focus on risk stratification over specific disease groups in order to simplify and clarify antifungal prescribing. We emphasise how important it is for each centre to understand its local fungal epidemiology, to identify species of fungal infection and to apply a risk stratification approach when deciding whether prophylaxis is appropriate or not. The thoroughness of the workup for IFD is critical – if diagnosis is not pursued, epidemiology cannot be understood. New developments in antifungal medications, including new formulations of posaconazole, may change future recommendations. The field of mycology remains an active and developing one within this patient population.

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