Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2021

Introduction

In the seven years since the publication of the last guidelines, the treatment of malignancies has undergone a paradigm shift with the increasing use of targeted oral therapies (e.g. Bruton's tyrosine kinase [BTK] inhibitors) and the advancement of immune-based therapies (e.g. immune checkpoint inhibitors [ICI], chimeric antigen receptor [CAR] T cell therapy).[1-3] These therapeutic advances have led to significant improvements in disease prognosis and survival; however, in haematological malignancy, they also appear to be associated with new potential risks for invasive fungal disease (IFD).[4] Other well-established risks for IFD, such as prolonged neutropenia and graft-versus-host disease (GVHD), remain relevant and unchanged from previous guidelines.[5]

The landscape for the prevention and treatment of IFD has also evolved with the development of new antifungal therapies, as well as new formulations of established agents, for treatment and prophylaxis.[6, 7] Selection of the optimal prophylactic agent is now impacted by new challenges, such as the emergence of the multi-drug resistant fungal pathogen *Candida auris*, increasing rates of antifungal resistance in *Aspergillus* spp., and the changing epidemiology of invasive candidiasis and non-*Aspergillus* moulds.[8-10]

The current guidelines take all of these developments into account and serve as an update to the 2014 guidelines.[5] Primary antifungal prophylaxis is recommended for disease groups associated with a high risk of IFD. Not surprisingly, the higher the baseline prevalence of

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IFD, the more marked the beneficial effect of prophylaxis is.[11] When implementing prophylaxis regimens, consideration must also be given to institutional epidemiology, and relevant adjustments made. Most of the available evidence for prophylaxis relates to haematological malignancies, and this is the primary focus of these guidelines. For solid organ tumours, the need for prophylaxis remains undefined and expert advice should be sought on an individual case-by-case basis.

Methodology

Questions asked

This update addresses the following questions:

1. What new therapies for haematological malignancies are associated with potential risk for IFD and what are the new risk groups?
2. Is there new evidence to support and guide the use of established prophylactic agents?
3. What are the new options for antifungal prophylaxis?
4. How does the use of mould-active antifungal prophylaxis impact diagnostic testing?
5. What critical drug-drug interactions do clinicians need to be aware of and what is the need for therapeutic drug monitoring (TDM) in the era of targeted and immune-based therapies?
6. How do antifungal resistance patterns affect choice of prophylaxis?
7. What special considerations are required in the paediatric setting?
8. How could antifungal prophylaxis recommendations be implemented into practice?

9. Are there new approaches to defining risk for IFD?

Search strategy

A comprehensive literature search was performed utilising PUBMED to address the questions previously outlined. The search encompassed studies published since 2013 and utilised the following terms in combination: 'haematology', 'malignancy', 'haemopoietic stem cell transplantation', 'haematopoietic stem cell transplantation', 'leukaemia', 'myeloma', 'lymphoma', 'risk factors', 'antifungal', 'prevention', 'prophylaxis', and 'invasive fungal infection'.

Question 1 What new therapies for haematological malignancies are associated with potential risk for IFD and what are the new risk groups?

Recommendations

- Due to the absence of high-level evidence, the routine use of antifungal prophylaxis is not recommended for the majority of patients undergoing treatment with new haematological treatments; rates of IFD with new therapies are summarised in Table 2. Antifungal prophylaxis should be considered on an individual patient risk model (see Table 3).
- For patients receiving new generation immunomodulatory, monoclonal antibody therapy for relapsed and refractory myeloma, prophylaxis with fluconazole could be considered [Marginal recommendation, Level III evidence].
- For patients undergoing CAR-T cell therapy, prophylaxis with fluconazole should be considered [Strong recommendation, Level II evidence].
- For patients deemed at higher risk of fungal infection (e.g. due to severe neutropenia or multiple lines of therapy, treatment of cytokine release syndrome), mould-active azole prophylaxis could be considered [Moderate recommendation, Level II evidence].
- For patients with a prior history of IFD, secondary prophylaxis should be administered [Marginal recommendation, Level III evidence].

Given recent advances in the treatment of haematological malignancies and the potential association between these newer agents and IFD risk, this section discusses new advances in the treatment of haematological malignancies, their potential association with risk for IFD

and the resultant recommended approach to prevention of IFD. Established risk groups for IFD are summarised in Table 1.

Targeted and immunomodulatory drug therapies

Since the publication of the previous guidelines, an increasing number of targeted agents have become available as standard of care options for the treatment of both haematology and medical oncology patients. Such agents, through their effects on immune function, may increase the risk of IFD.[12] Reported rates of IFD accompanying the use of these agents vary according to the patient group being treated (i.e. treatment naïve versus relapsed/refractory malignancy); previous treatments used, including number of lines of therapy; and whether these agents are used in combination with other therapies, especially conventional chemotherapy that induces mucositis or prolonged neutropenia.

Ibrutinib, a BTK inhibitor commonly used for the treatment of chronic lymphocytic leukaemia (CLL) and other B-cell lymphoproliferative disorders, interrupts B-cell receptor signalling and also results in hypogammaglobulinaemia. There is an association between ibrutinib therapy and risk of IFD. A retrospective study of 378 patients receiving ibrutinib (monotherapy in 84% of cases) reported an IFD rate of 4.2%, with the majority of IFD cases lacking classical risk factors such as neutropenia or corticosteroid usage.[13] Local, real-world data suggests an IFD rate as high as 12.1% in patients treated with ibrutinib monotherapy in the setting of relapsed/refractory CLL.[14] These findings contrast the 1% IFD rate reported in the randomised, phase 3 RESONATE study.[15] The majority of fungal infections reported were invasive aspergillosis with a predilection for central nervous system (CNS) involvement (40%).[16] Most patients developed IFD within three to six months of starting ibrutinib.

Substantially higher IFD rates of 38.9% (7/18) have been observed in the context of primary CNS lymphoma treated with ibrutinib, potentially due to the concomitant use of chemotherapy and corticosteroid agents.[17] This emphasises the additional risk imposed when combining BTK inhibition with other immunosuppressive therapies.

Cases of IFD, including *Pneumocystis jirovecii* pneumonia, have been reported in association with the use of other tyrosine kinase inhibitors such as Janus kinase (JAK) inhibitors,[18, 19] phosphatidylinositol 3-kinase (PI3K) inhibitors,[20] B-cell lymphoma 2 (BCL-2) inhibitors (venetoclax)[21] and mammalian target of rapamycin (mTOR) inhibitors.[22] In retrospective studies, the use of hypomethylating agents such as azacitidine in patients with myelodysplastic syndromes and acute myeloid leukaemia (AML), has been associated with an IFD risk of up to 8.3% – consistent with the risk posed by treatment of the underlying disease.[23, 24] The greatest IFD risk was observed amongst patients who had received prior intensive chemotherapy.

In the setting of variable antifungal prophylaxis use (i.e. either an azole, echinocandin, or none), the use of hypomethylating agents in combination with the BCL-2 inhibitor venetoclax for newly-diagnosed and relapsed or refractory AML, was associated with an overall IFD rate of 12.6%.[25] The IFD rate in newly-diagnosed AML was 5.0%.[25] The addition of an fms-like tyrosine kinase (FLT3) inhibitor (midostaurin, gilterinib) to standard chemotherapy for the treatment of FLT3-positive AML has been demonstrated to improve survival.[26, 27] However, the impact on IFD rates beyond that expected of the underlying AML remains undefined. In an early clinical trial, an IFD rate of 5% was reported.[26] These targeted agents, particularly BTK inhibitors and BCL-2 inhibitors, have significant CYP3A4 interactions with azole antifungals, necessitating their dose adjustment.[3]

IFD rates of 3.8–5.6% were reported in patients with multiple myeloma (MM) treated with first-generation immunomodulatory drugs and proteasome inhibitors.[28, 29] The rate of invasive mould infection was less than 1.0%.[28] An IFD rate of 15% was reported in patients who had received three or more lines of therapy, including conventional chemotherapy.[28] In contrast, a recent study of a heavily-treated MM patient cohort (median five lines of therapy) treated with next-generation immunomodulatory drugs, proteasome inhibitors and new anti-CD38/SLAM-F7 monoclonal antibody therapies, reported a low overall IFD rate of 3.4%.[30] The rates ranged from 2.3–7.0% per the specific drug classes. Patients with IFD had received more lines of therapy and all proven IFD cases involved yeasts, i.e. cryptococcal infection and *Pichia kudriavzeveii* (formerly *Candida krusei*).[30]

Adoptive T-cell therapies

Adoptive T-cell therapies such as CAR T cell therapy and bi-specific constructs such as bi-specific T-cell engagers (BiTE) (e.g. blinatumomab) have now become standard of care in relapsed, high-grade B-cell malignancies: CAR T cell therapy for diffuse large B-cell lymphoma and paediatric acute lymphoblastic leukaemia (ALL), and blinatumomab for ALL. Patients receiving these therapies have often had multiple prior lines of therapy, including HSCT, which may influence their fungal infection risk. Other agents such as fludarabine may be administered prior to CAR T cell infusion, which may further increase fungal infection risk.[31-35]

CAR T cell therapy

Rates of infective toxicity appear similar in patients receiving CAR T cell therapy or other salvage therapies. Bacterial infections are a larger concern, occurring in 23% of patients receiving CAR T cell therapy, predominately during the first 28 days following CAR T cell infusion. IFD rates in trials of ALL and B-cell lymphoma have ranged between 5–13%

depending on the disease group.[31, 32, 36] In a dedicated study of infectious complications with CAR T cell therapy, 5% of patients developed a fungal infection in the setting of fluconazole prophylaxis.[4] An IFD rate of 7% has also been reported with the use of micafungin prophylaxis in ALL patients managed with CAR T cell therapy.[37] Patients with ALL appear to be at a higher risk of infection if they have received four or more prior lines of therapy, been treated with higher CAR T cell therapy doses, developed cytokine release syndrome (CRS) or used systemic corticosteroid agents during their CAR T cell therapy.[4, 38, 39] Potentially, a subset of patients with prolonged neutropenia or with higher-grade CRS requiring additional immunosuppressive treatments (e.g. corticosteroid agents) may be at higher risk for mould infections.

Bi-specific immune engagers

At time of publication, blinatumomab is the only bi-specific immune engaging agent in clinical practice and is indicated for patients with ALL, both relapsed/refractory disease and minimal residual disease. Blinatumomab is only modestly myelosuppressive and does not cause mucotoxicity. However, it can be associated with neutropenia and risk of infection can be compounded by prior therapies received. Fungal infection is relatively rare; however, early development of neutropenia has been associated with an increased risk of possible fungal infection.[35, 40]

Rates of IFD associated with these emerging cancer therapies and potential new risk groups are summarised in Table 2 and recommended approaches to prophylaxis are summarised in Table 3. There should be an increased awareness of the potential risk and clinicians should have a low threshold for initiating investigations for suspected IFD in the setting of compatible symptoms such as persistent fever or pulmonary infiltrates.

Question 2 Is there new evidence to support and guide the use of established prophylactic agents?

Recommendations

- Posaconazole remains recommended as a first-line agent for IFD prophylaxis in high-risk patients [Strong recommendation, Level I evidence].
- Voriconazole is considered to be an alternate agent for IFD prophylaxis due to higher rates of adverse events (e.g. liver function abnormalities) and variable metabolism [Strong recommendation, Level II evidence].
- Use of micafungin could be considered during periods of neutropenia in high-risk patients if use of azoles is contraindicated or in the setting of expected poor gastrointestinal absorption [Moderate recommendation, Level II evidence].
- Itraconazole is considered to be an alternate agent due to a lower number of clinical trials and cohort studies [Moderate recommendation, Level II evidence].
- Use of liposomal amphotericin B could be considered if use of azoles is contraindicated due to drug-drug interactions, adverse events or poor absorption [Moderate recommendation, Level II evidence].

Posaconazole

Posaconazole remains the preferred agent for prophylaxis against IFD in high-risk patients with AML or for those undergoing allogeneic HSCT.

Network meta-analyses of randomised controlled trials of triazole prophylaxis confirm posaconazole's efficacy for the prevention of proven or probable IFD and invasive

aspergillosis, reducing the requirement for empiric antifungal therapy and all-cause mortality compared to fluconazole and itraconazole.[41-43] Although posaconazole was not significantly better than voriconazole for prevention of IFD and invasive aspergillosis, it was the highest-ranked agent for achieving these outcomes in two published network meta-analyses.[41, 43] When evaluated, its use appears to be cost-effective compared to voriconazole.[41]

Cohort studies evaluating posaconazole against voriconazole, itraconazole or micafungin consistently report lower rates of IFD with posaconazole ranging from 0–5% versus 5–11%.[44-48] For patients undergoing HSCT, observational cohort studies have shown that rates of breakthrough IFD during prophylaxis with posaconazole suspension remain low at between 3–8%.[49, 50] Cohort studies of AML patients report similarly low rates of proven or probable breakthrough IFD (0–7%).[45, 51, 52]

Voriconazole

Voriconazole is an alternate agent for IFD prophylaxis. Meta-analyses show no significant difference between posaconazole and voriconazole efficacy for the prevention of proven or probable IFD and invasive aspergillosis.[41-43] However, a significantly higher risk for treatment-related liver abnormalities was noted, compared to other azoles.[41, 43] In the same analysis, this agent is ranked second as an effective prophylaxis agent.[41] In cohort studies of AML patients, the use of voriconazole prophylaxis was associated with an IFD rate of 3–5%.[48, 53, 54] Due to variable metabolism, CYP2C19 testing prior to commencement could assist with dose selection (please refer to the accompanying optimising antifungal therapy and TDM guidelines by Chau *et al*. 2021, which can be found elsewhere in this supplement).[55, 56]

Itraconazole

Since the 2014 guidelines, a new formulation of itraconazole has been introduced (see later discussion). The only new data supporting the use of intravenous itraconazole or its solution are from a few cohort studies reporting IFD rates of 1–7% for HSCT patients and 5% for patients with AML.[53, 57, 58]

Micafungin

There have been further studies evaluating the use of micafungin during the neutropenic period in HSCT patients. In two trials, the rate of IFD was not significantly different when assessed against fluconazole and itraconazole at 7.3% and 4.4%, respectively.[57, 59] Adverse event rates were significantly higher with itraconazole.[57] Different doses have been assessed but, in general, dosing with 100–150 mg intravenous (IV) daily followed by oral voriconazole or posaconazole on discharge, led to proven or probable IFD rates of between 1–4%.[60-62] In the AML cohort, the rate was 6.3%.[47] Overall, use of micafungin could be considered during the neutropenic period in high-risk patients if use of azoles is contraindicated or there are concerns about absorption.

Liposomal amphotericin B

Evidence supporting the use of liposomal amphotericin B (L-AMB) remains limited. A recent randomised trial of L-AMB at 5 mg/kg twice a week compared to placebo for prophylaxis in ALL reported no difference in the rate of proven or probable IFD (7.9% vs. 11.7%; P = 0.24); however, a significantly higher rate of adverse events led to interruption of L-AMB in 20.3% of patients.[63] *Post hoc* analysis did report a trend for lower IFD rates in patients who were administered L-AMB prophylaxis (7.6 vs. 14.4%; P = 0.07).[63] In a cohort study of Australian ALL patients, use of L-AMB at a median dose of 100 mg three times per week had a similar rate of IFD to posaconazole (6% vs. 7%), and a lower rate compared to both fluconazole (14.3%) and no prophylaxis (21%).[64] At this stage, evidence supporting its use

remains poor but this agent could be considered in the setting of azole intolerance or contraindication. Optimal dosing of this agent for prophylaxis requires further evaluation. Doses ranging from 50–200 mg, three times per week, have been used.

Recommendations by risk group and grading of evidence for the selection and dosing of an antifungal prophylactic agent are summarised in Table 4.

Question 3 What are the new options for antifungal prophylaxis?

Recommendations

- Isavuconazole is not recommended as a first-line agent for prophylaxis against IFD in high-risk patients due to higher reported rates of IFD in cohort studies. Its use can be considered if azoles are contraindicated (e.g. QTc prolongation) [Moderate recommendation, Level II evidence].
- There is insufficient evidence to support use of the new formulation of itraconazole as a first-line agent for prophylaxis against IFD [Moderate recommendation, Level II evidence]. However, it is used in several Australian centres.
- Oral posaconazole remains recommended as a first-line agent for IFD prophylaxis in high-risk patients (tablets are preferred but in some cases, suspension may be necessary, in which case, prescribers should consult with pharmacy regarding levels and dosing) [Strong recommendation, Level I evidence]. Intravenous formulation is an option for continuation of posaconazole prophylaxis in the setting of poor or limited oral intake.

Isavuconazole

Isavuconazole is a recently introduced broad-spectrum triazole antifungal agent. It has been licensed for the treatment of invasive mould disease on the basis of non-inferiority compared to voriconazole in the SECURE trial and for the treatment of mucormycosis, either as primary treatment or for treatment of infection refractory or intolerant to other antifungals, based on a mixed group of patients in the VITAL study.[6, 65] Based on its broader spectrum of activity and improved side-effect profile, it is being evaluated as prophylaxis in

patients with AML and allogeneic HSCT in prospective trials. In an early phase 2 dose-escalation study, the rate of breakthrough invasive fungal infection was 10%.[66]

Results from its use as prophylaxis, as reported in prospective studies, retrospective studies and case reports, have been variable.[67-71] In a mixed population of relapsed refractory and HSCT patients, a breakthrough rate of 5.8% was reported.[70] However, the use of isavuconazole as prophylaxis in newly-diagnosed AML was associated with a rate of 7.9%. This is higher than the rate reported with posaconazole (2.7%), but is not statistically significant ($P = 0.06$).[68] Posaconazole was used for a longer period in patients with a longer duration of neutropenia.[68] A prospective single-centre, single-arm, primary prophylaxis study in AML and myelodysplastic syndrome reported an overall breakthrough rate of 18.0% with a proven/probable rate of 6.0%.[71] Half the patients were receiving treatment with oral targeted anti-leukaemic agents such as venetoclax, which has CYP3A4-mediated drug-drug interactions when co-administered with other azoles.[71]

Use of isavuconazole as prophylaxis in the setting of relapsed or refractory AML has been associated with breakthrough rates of between 12–18.5%,[68, 69] higher than that reported with posaconazole and voriconazole (5.5%).[68] When performed in a subset of patients, isavuconazole levels appeared to be adequate.[68, 70, 71] In the majority of cases, breakthrough infections were due to *Aspergillus* spp. and *Mucor* spp.[68, 69] The use of isavuconazole following micafungin prophylaxis in HSCT patients has been associated with an IFD rate of 3.1%. In this study all IFD were bloodstream infections with *Candida parapsilosis* and *Candida glabrata*.[72] Tolerability appears to be good with a low risk of QTc prolongation in the setting of potential drug-drug interactions.[71] Evidence from trials being conducted may provide further clarity.

Currently, the use of isavuconazole as a first-line agent for prophylaxis in patients with AML and HSCT cannot be recommended due to higher observed IFD rates in uncontrolled cohort studies. Its use could be considered in the setting of intolerance or if use of other azoles is contraindicated.

New formulation of itraconazole

A novel formulation of itraconazole (SUper BioAvailability [SUBA]-itraconazole) has been approved in Australia since 2014.[73, 74] At the time of the 2014 guidelines, only data from healthy volunteer studies were available on the SUBA-itraconazole formulation, which demonstrated that this formulation is not affected by gastric pH with dosing recommendations differing from the previous conventional itraconazole capsule formulation.[75] However, recently there have been a number of small cohort studies demonstrating good tolerability and levels in the therapeutic range using SUBA-itraconazole in haematology and HSCT recipients.[76, 77] One small prospective cohort (n = 57) compared SUBA-itraconazole for primary prophylaxis in an allogeneic HSCT cohort to itraconazole oral solution. Therapeutic concentrations were achieved significantly more quickly in the SUBA-itraconazole group (median of six days versus 14 days) with therapeutic concentrations achieved in 69% vs. 21% of patients ($P < 0.01$). Of note, there were no treatment failures due to gastrointestinal intolerance, which has previously limited the use of conventional itraconazole formulations.[76] In another small retrospective cohort study (n = 74) of myeloma, AML, ALL, autologous and allogeneic HSCT patients, therapeutic concentrations were achieved at a median of seven days by 87% of patients.[76] The incidence of IFD reported in both studies was low at 3% and 1% respectively; however, the studies were too small to accurately assess efficacy. It should be noted that despite the manufacturer's recommendation to use half the relative dose of the conventional capsules, both studies

used SUBA-itraconazole at the recommended dose range of the itraconazole oral solution (i.e. 200 mg twice daily with TDM used to monitor levels and dose-adjust accordingly).

Posaconazole: tablet and intravenous formulation

Posaconazole modified-release tablet and intravenous (IV) formulation have been licensed in Australia since 2014 and 2015, respectively. The tablet is listed on the Pharmaceutical Benefits Scheme (PBS) for prophylaxis of IFD in specific high-risk groups, namely patients with anticipated neutropenia while receiving chemotherapy for AML or myelodysplastic syndrome, and patients with acute (grade II–IV) or extensive-chronic GVHD receiving intensive immunosuppressive therapy following an allogenic HSCT. The evidence for its efficacy in these settings is extrapolated from the prophylaxis studies using posaconazole oral solution.[78, 79] Advantages of the tablet formulation are once-daily dosing, higher drug exposure than with the oral solution,[80] and no requirement for concurrent intake of fatty food to improve absorption.[81] The safety profile is similar between the two formulations.[7] Although, gastric pH was not thought to influence absorption (which occurs in the small intestine), recent studies in patients with haematological malignancies or HSCT receiving posaconazole tablets as prophylaxis have indicated that proton pump inhibitors and corticosteroid agents (>0.7 mg/kg daily) may lead to lower plasma concentrations with the tablet formulation.[82]

In real-life studies reporting trough levels in approximately 230 haematological malignancy or HSCT patients receiving posaconazole tablets, between 3–18% of patients had sub-therapeutic levels, defined as <700 ng/ml with prophylaxis and <1000 ng/ml with treatment.[83-86] These studies may be biased towards detecting lower levels, as levels were not routinely measured in all series reported and when performed, it was due to clinical concerns about absorption or failure. Correlations with higher posaconazole levels and

hepatotoxicity were not clearly seen in these real-world studies, although one small report linked trough levels >1,830 ng/ml and pre-existing liver damage with grade 3–4 liver injury.[84] In these studies, breakthrough infection did not always occur within the context of low levels, indicating that host factors continue to play a role in prophylaxis failure.

IV posaconazole remains an option for continuing posaconazole administration when oral medication cannot be taken (e.g. severe mucositis, nausea, vomiting, GVHD of the gut or a requirement to remain fasting). In one study, IV posaconazole was given as antifungal prophylaxis to 237 neutropenic patients with AML, myelodysplastic syndrome or recipients of allogeneic HSCT.[87] The dose was 300 mg of posaconazole IV twice daily on day 1, followed by 300 mg IV once daily for at least five days followed by a switch to the oral suspension. The mean posaconazole trough level on day 6 was 1320 ng/mL and posaconazole was well tolerated.[87] A real-life study of patients treated for haematological malignancy and HSCT recipients – the majority of whom received prophylaxis – reported a median trough level of 1.16 (0.69–2.06) mg/L, taken 3–7 days after commencement. The median duration for prophylaxis was 10 days. No severe adverse events specifically attributable to IV posaconazole were documented, although six courses were curtailed due to potential toxicity.[88]

Question 4 How does the use of mould-active antifungal prophylaxis impact diagnostic testing?

The performance of diagnostic tests for fungal infection is highly dependent on pre-test probability and incidence of IFD.[89] Primary antifungal prophylaxis in high-risk patients successfully reduces the incidence of proven or probable IFD to around 5%, with a corresponding reduction in test performance, in particular galactomannan (GM) testing.[44, 51, 90, 91] The utility of performing serum GM or *Aspergillus* PCR testing for IFD surveillance in the setting of primary antifungal prophylaxis appears to be limited.[89-91] However, these assays remain useful as part of a diagnostic-driven algorithm for suspected breakthrough IFD in high-risk patients.[91, 92] The impact of antifungal prophylaxis on the performance of a range of diagnostic tests is discussed in further detail in subsequent sections of these guidelines.

Question 5 What critical drug-drug interactions should clinicians be aware of and what is the need for TDM in the era of targeted and immune-based therapies?

Recommendations

- Dose adjustment of targeted therapies is required in the setting of major CYP3A4 interaction [Strong recommendation, Level II evidence].
- Use of CYP testing may assist with ascertainment of target drug level (refer to the accompanying optimising antifungal therapy and TDM guidelines by Chau *et al*. 2021, which can be found elsewhere in this supplement).
- Due to real-world evidence of sub-therapeutic drug levels in up to 20–30% of patients, TDM is still important for new formulations of azole antifungal agents [Marginal recommendation, Level III evidence].

With the introduction of novel targeted therapies for hematological malignancies and HSCT, managing the drug-drug interactions associated with azole antifungals requires careful consideration. Of particular note, when using a strong CYP3A4 inhibitor, such as posaconazole, itraconazole or voriconazole, in combination with novel targeted therapies that are major CYP3A4 substrates such as venetoclax and ibrutinib, manufacturer recommendations of up to 75% dose reductions of the novel agents are indicated.[3, 93, 94] However, other commonly used novel agents such as midostaurin and gilteritinib are considered weak/moderate CYP3A4 substrates and dose adjustment is not recommended.[95, 96] Therefore, manufacturer recommendations and/or specialist advice should be considered before using azoles in combination with novel targeted therapies. There is also growing

evidence that agents such as letermovir and flucloxacillin, significantly reduce voriconazole concentrations.[97, 98] These potential interactions further emphasise the importance of TDM of azole antifungal agents, particularly during changes in concomitant medications, as well as during periods of critical illness such as intensive care unit (ICU) admissions.[99] In addition, despite superior level attainment from new oral and IV formulations of posaconazole,[7, 100] post-marketing experience has reported subtherapeutic serum trough concentrations in approximately 20–30% of haematology patients.[84, 88, 101] Therefore, ongoing use of TDM for these new formulations should be considered. For further information, please refer to the accompanying optimising antifungal therapy and TDM guidelines by Chau *et al*. 2021, which can be found elsewhere in this supplement.

Question 6 How do antifungal resistance patterns affect choice of prophylaxis?

Recommendation

- The antifungal prophylaxis recommendations in this guideline take into account currently available data on antifungal resistance rates and patterns; however, a local organisational approach for ongoing surveillance of the rates and epidemiology of IFD in high-risk patients is important for guiding effective prophylaxis choice [Strong recommendation, Level II evidence].

Clinicians continue to be challenged by the changing epidemiology of fungal infections over time, emergence of multi-drug resistant fungi such as *Candida auris*, and primary antifungal resistance in human and environmental isolates.

The epidemiology of *Candida* spp. infection continues to evolve with increasing use of azoles and echinocandins. A nationwide surveillance of candidaemia revealed a 1.7-fold increase in the proportion of candidaemia due to *Candida glabrata*.[10] *Candida glabrata* is now responsible for up to 30% of candidaemia[102] and is the leading cause of candidaemia in haematology patients.[103] Between 13–23% of *Candida glabrata* isolates are fluconazole-resistant, a key consideration in lower-risk patients receiving fluconazole prophylaxis. Multi-drug resistance remains uncommon in isolates responsible for candidaemia but azole resistance is at 17% and thus ongoing surveillance is vital.[10]

In the last five years, *Candida auris* has emerged as a healthcare-associated, multi-drug resistant yeast, which has caused significant outbreaks in multiple countries around the world. It is an effective coloniser of the hospital environment and patients, causing invasive

infection (predominantly candidaemia).[9] *Candida auris* is resistant to at least two antifungal drug classes in nearly 25% of cases.[9] At last count, less than 10 cases of this infection have been reported in Australia.[9, 104] An Australasian diagnostic, infection prevention and clinical management approach to this infection has recently been developed with multi-stakeholder involvement.[9]

Multi-triazole-resistant *Aspergillus fumigatus* have been isolated in up to 30% of clinical isolates in countries overseas.[105] A 13-year review of *Aspergillus fumigatus* isolates in the National Mycology Reference Laboratory detected only two isolates carrying the TR34/L98H mutation of *CYP51A*.[105] Fortunately, rates of azole resistance in *Aspergillus fumigatus* isolates in Australia appear to be low at 2% of clinical isolates in a limited screen of human, animal and environmental isolates.[106] No azole-resistant isolates were detected in animal or environmental isolates.[106] Testing of clinical isolates of non-*Aspergillus* fungal pathogens in Australia has confirmed expected susceptibility patterns for the isolated species.[107]

In the setting of antifungal prophylaxis, between 6–17% of IFD episodes were due to non-*Aspergillus* moulds, which have intrinsic resistance to a range of azole antifungals.[108-110] In a national study, *Scedosporium* spp. and mucormycetes were the dominant species, contributing up to 80% of IFD caused by non-*Aspergillus* moulds, with underlying haematological malignancy associated with significantly higher odds of mortality.[110] Increasing use of mould-active antifungal prophylaxis will contribute to changing epidemiology of IFD in high-risk patients and active surveillance of breakthrough IFD should continue to guide choice of antifungal prophylaxis.

Question 7 What special considerations are required in the paediatric setting?

Recommendations

- Indications for antifungal prophylaxis in children (adapted from Lehrnbecher *et al.*, 2020)[11] are provided in Table 6.
- Where antifungal prophylaxis is indicated, a mould-active agent is recommended [Strong recommendation, Level I evidence].
- The choice of mould-active agent will depend on age, potential drug interactions and patient location (inpatient versus outpatient), with preference given to mould-active azoles or echinocandins [Strong recommendation, Level II evidence].
- Intermittent liposomal amphotericin is an alternative option for children in whom azole prophylaxis is not tolerated or contraindicated and daily echinocandin administration is not feasible [Marginal recommendation, Level III evidence].
- Where antifungal prophylaxis is indicated, administer during periods of observed or expected severe neutropenia [Strong recommendation, Level II evidence].
- Secondary prophylaxis is recommended for children with proven or probable IFD undergoing subsequent immunosuppression, particularly during intensive phases of chemotherapy [Moderate recommendation, Level III evidence]. For agent selection and duration, specialist infectious diseases advice is recommended.
- Dosing recommendations in children are summarised in Table 7.

New therapies for haematological malignancy and new patient risk groups in children

Since the publication of the previous guidelines, the risk factors for IFD in children have been further refined (Table 5).[5] In addition to previously recognised associations, including haematological malignancy, prolonged neutropenia, high-dose corticosteroids and severe-acute (grade II or above) or chronic GVHD, age (>7.5 years) has now also been identified as a risk factor.[111] In an Australian, multisite, 10-year cohort study of IFD in children, IFD prevalence in AML and HSCT cohorts was 28.2% and 11.7%, respectively.[112, 113] IFD prevalence was <5% in autologous HSCT recipients (3.1%) and children with solid tumours (4.4%). Amongst ALL patients, IFD prevalence was 23.5% for relapsed/refractory ALL, 14.5% for high-risk ALL and 7.3% for standard-risk ALL, with IFDs more common during induction, consolidation and delayed intensification phases.[112] Across both relapsed and non-relapsed ALL, mould infections were more common than non-mould infections. These data suggest that a tailored prophylaxis approach is required for patients with ALL, taking into consideration disease risk status, chemotherapy intensity, remission status and phase of treatment.

There are limited data on risk of IFD with targeted and adoptive T-cell therapies in children. For an overview of adult data and approach to prophylaxis in both adults and children, please refer to earlier discussion on this topic, as well as Table 3. In a review of infective complications in 83 children and young adults receiving CAR T cell therapy, one patient (1.2%) developed a proven IFD in the first 30 days, although it is unclear if this was a new infection or progression of a previously documented probable pulmonary invasive mould infection.[114]

New evidence for established prophylactic agents in children

An international clinical practice guideline for antifungal prophylaxis in children with cancer or HSCT has been recently published.[11] Underpinning these recommendations were rigorous and comprehensive systematic reviews addressing: (i) which paediatric patients should routinely receive antifungal prophylaxis and (ii) what agents should be used. Only randomised clinical trials were considered and evidence rated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Below is a summary of the new evidence for prophylaxis in children. For a review of the paediatric literature up to 2014, please see the previous Australian guidelines.[5] For a comprehensive review of all published randomised control trials investigating antifungal prophylaxis in adult and paediatric patients, please refer to the recently published paediatric antifungal guidelines.[11]

Mould-active azoles

In a systematic review and meta-analysis, predominantly adult pooled data found a significant reduction in proven or probable IFD, mould infection or invasive aspergillosis in patients receiving any mould-active azole compared to fluconazole.[11] Compared to echinocandins, there was no difference in proven or probable infections or mortality, although there were more adverse effects in the group receiving mould-active azole prophylaxis. TDM is recommended for children receiving mould-active azoles. Please refer to the accompanying optimising antifungal therapy and TDM guidelines by Chau *et al*. 2021, which can be found elsewhere in this supplement.

Posaconazole

Since 2014, observational studies of children with cancer or following HSCT have reported a breakthrough proven/probable IFD rate between 0–4.3% with posaconazole.[115-119] Many of these breakthrough IFDs occurred in the setting of subtherapeutic levels and all studies included children less than 12 years of age where data are specifically lacking.

In Australia, posaconazole suspension and modified-release tablets are approved for use in children ≥13 years of age. There are emerging pharmacokinetic-population studies to guide dosing of both formulations in younger children (<13 years) (Table 7).[100, 120] Poor attainment of target levels using the suspension are reported[115, 119, 121-123] and tablets are preferred when this is possible (see discussion on new evidence for established agents in children).[100, 121] Where suspension is necessary, higher doses, increasing dose fractionation (e.g. four times daily [QID] dosing rather than three times daily [TDS]) and co-administration with a fatty meal are recommended.[124]

Voriconazole

Since 2014, observational studies of children with cancer or following HSCT have reported a breakthrough proven/probable IFD rate between 0–12% with voriconazole.[125-128] In the study reporting a 12% breakthrough rate, patients received voriconazole doses of between 5–10 mg/kg/day,[128] which is below the currently recommended dose (Table 7).[129]

Itraconazole

Since 2014, observational studies of children with haematological malignancy or following HSCT have reported a breakthrough proven/probable IFD rate between 0–3.2%with itraconazole.[116, 117, 130] No studies included patients receiving SUBA-itraconazole.

Amphotericin B

The aforementioned clinical practice guidelines for antifungal prophylaxis in children with cancer or HSCT includes a recommendation against the routine use of amphotericin B for prophylaxis based on a meta-analysis of randomised controlled trial data showing amphotericin B was not more effective than fluconazole in preventing IFD (risk ratio 0.99; 95% CI: 0.52–1.88) but was associated with more adverse effects (risk ratio 5.63; 95% CI: 1.17–27.02).[11] However, while this recommendation includes both conventional and lipid formulations, only one randomised controlled trial investigated the lipid formulation and none assessed liposomal amphotericin B (L-AMB) specifically.

Liposomal amphotericin B

Despite the limited supporting data, intermittent L-AMB continues to be prescribed for prophylaxis, particularly where triazole prophylaxis is not tolerated or contraindicated and daily IV echinocandins are not feasible.[131] Since 2014, observational studies report a breakthrough proven/probable IFD rate with L-AMB of between 0–8%[125, 132-134] and mild renal toxicity of between 8.8–22%.[132, 134] Optimal dosing for prophylaxis remains unknown, and varied doses, including 1 mg/kg thrice weekly, 2.5 mg/kg twice weekly and 3–5 mg/kg thrice weekly, have been used.[134-136]

Echinocandins

Echinocandins are considered a suitable option, alongside mould-active triazoles, for primary prophylaxis with similar efficacy in preventing proven/probable IFD.[11]

Caspofungin

A recent randomised controlled trial assessing the efficacy of echinocandin prophylaxis in 517 children and young adults with AML found a significant reduction in proven/probable

IFD with caspofungin compared with fluconazole (3.1% vs. 7.2%; $P = 0.03$).[137] Both agents were well tolerated.

Micafungin

Since 2014, observational studies of micafungin prophylaxis (predominantly using 1 mg/kg/day) in children with cancer or undergoing HSCT, have reported breakthrough IFD rates of 1.5% and 12.8%.[125, 138-142] Serious drug-related adverse events were rare (0–3%).[138-142] Higher micafungin doses (2 mg/kg and 3 mg/kg daily)[143-145] and intermittent high-dose micafungin (up to 5 mg/kg weekly)[146, 147] have been assessed in observational paediatric studies, yet comparative data to support widespread use of these strategies are still lacking.[148]

Evidence for newer antifungal prophylactic agents and formulations in children

Please refer to earlier discussion on new options for antifungal prophylaxis in adults, including isavuconazole, tablet and IV formulations of posaconazole and SUBA-itraconazole. Specific paediatric data follows.

Isavuconazole in children

Published data on paediatric isavuconazole dosing, efficacy and safety is limited to small case series predominantly reporting on its use in the treatment of IFD rather than prophylaxis.[149-152] In the largest series to date, 29 children (median age 14.5 years) received isavuconazole 200 mg/day (>30 kg) or 100 mg/day (<30 kg) following initial loading (TDS dosing for 48 hours); no IFD occurred amongst five patients receiving isavuconazole for IFD prophylaxis.[149] Weight-based isavuconazole dosing for children aged 2–17 years of 10 mg/kg (maximum 372 mg) TDS for 48 hours and once daily thereafter has been proposed.[149]

New formulation of itraconazole in children

There are also limited data on SUBA-itraconazole dosing, efficacy and safety in children. A prophylactic dose of 2.5 mg/kg/day has been proposed based on a small paediatric cohort study.[153]

Posaconazole: tablet and intravenous formulation in children

In keeping with the adult literature, the administration of posaconazole modified-release tablets is associated with superior attainment of therapeutic levels in children compared to oral suspension.[100, 154-157] Attainment of target level (>700 ng/ml) in 94% (32/34) of children receiving modified-release tablets using weight-banded dosing has been reported (Table 7).[157]

In two small studies of IV posaconazole for IFD prophylaxis, attainment of target levels was reported in 95–100% of children using doses of 6–7 mg/kg/day.[158, 159] A new posaconazole powder formulation for suspension (PFS) was also assessed in children in one study, with attainment of target levels in 89–94% of patients and no serious drug related adverse effects.[158] Although not yet widely available, the PFS could replace liquid posaconazole for children unable to swallow tablets.

Impact of antifungal prophylaxis on diagnostic testing in children

While adult studies have suggested a reduced utility of GM for IFD screening in patients on mould-active prophylaxis,[90, 160, 161] paediatric specific data are lacking. Paediatric guidelines suggest the GM assay, particularly on bronchoscopy specimens, remains useful in children on mould-active prophylaxis with clinically-suspected IFD.[162, 163]

Significant drug-drug interactions and TDM in children

Vincristine and azole therapy remain problematic in children undergoing ALL treatment. Concomitant vincristine use with itraconazole or voriconazole is more problematic than with fluconazole.[164] With increasing use of posaconazole in the paediatric population, there are also reports of associated severe neuropathic pain,[165] myalgia and autonomic neuropathy in patients receiving concurrent vinka-alkaloids.[166]

Awareness of potential interactions with novel agents in paediatric leukaemia treatment is required when prescribing mould-active triazole prophylaxis. Inotuzomab and gemtuzumab are included in open studies for ALL and AML treatment respectively.[167-169] Monitoring of QT interval is recommended in the setting of concomitant triazole prophylaxis.[3] Venetoclax is increasingly used in children with relapsed or refractory leukaemia[170, 171] and dose reduction by up to 75% is recommended with concomitant triazole use.[3]

Rates of antifungal resistance and choice of prophylaxis in children

For detailed discussion, please refer to *Question 6*.

Question 8 How could antifungal prophylaxis recommendations be implemented into practice?

The adult and paediatric recommendations for antifungal prophylaxis outlined in these guidelines take into account the latest available evidence. While agents are licensed for use by the Therapeutic Goods Administration (TGA), not all agents are reimbursable for use as prophylaxis for all at-risk groups under the PBS, which will impact availability and their use, particularly in the paediatric population. For successful implementation, these guidelines will need to be adapted for use at a local institutional level. Early consideration of potential needs and barriers will facilitate local adaptation and adoption. Factors for consideration include haematology patient population (leukaemia, HSCT), use of targeted agents, haematology clinical trials, local epidemiology (i.e. incidence of IFD, pattern of fungal infection, rates of fungal resistance), and pharmacy cost and budgets. Expertise in infectious diseases, microbiology and pharmacology are required to implement these guidelines to optimise the use of prophylaxis and diagnosis of breakthrough infection.

Question 9 Are there new approaches to defining risk for IFD?

Antifungal prophylaxis is effective in reducing incidence of IFD but its use should be optimised and targeted to derive the most benefit. Accurate assessment of risk for IFD remains an ongoing challenge with new, emerging haematological treatments that are not associated with known risk factors such as prolonged neutropenia.[14]

Genetic polymorphisms of pattern recognition receptors or soluble acute phase reactants, critical components of mounting an innate response against IFD, have been associated with risk for invasive fungal infection.[172] In particular, single nucleotide polymorphisms (SNP) of genes that code for reduced expression or production of Toll-like receptor 4 (TLR4), Dectin-1, Pentraxin-3 and mannose-binding lectin (MBL), are significantly associated with increased risk for invasive aspergillosis in HSCT and patients with haematological malignancies (odds ratio between 2.8–7.3).[172, 173] To date, testing for known SNPs has not been translated into clinical practice to help identify higher-risk patients that may benefit from antifungal prophylaxis.

In the last several years there have been further advances in platforms for the use of genetic and functional immune profiling. By integrating genome-wide analysis and systems-level immune profiling (RNA sequencing and cytokine analysis), several genes such as the SERPINA1 and MAP3K8 genes, have been identified as potential markers for increased susceptibility to candidaemia.[174] Cytokine analysis has revealed that higher baseline interlukin-2 receptor (IL-2R) and monocyte chemoattractant protein-1 (MCP-1/CCL2) levels have been associated with higher rates of invasive aspergillosis.[175]

Due to increased understanding of intestinal microbiota, a relationship between stem cell transplant-related dysbiosis, expansion of pathogenic *Candida* species, and translocation and subsequent invasive bloodstream infection, has been established.[176] Progress has been made in identifying genetic markers, immune profiles and mycobiomes associated with increased risk for IFD. However, the use of testing for known SNPs associated with increased risk has not been evaluated for its impact in large prospective cohorts. Validation of potential newly identified biomarkers has yet to occur. While not yet ready for use in clinical practice, genetic and immune profiling offers great potential for guiding the optimal use of antifungal prophylaxis in the near future.

Conclusion

While there have been limited changes to recommendations for antifungal prophylaxis in adults since the last published guidelines, there has been a shift in the recognised risk groups and type of prophylaxis (mould versus non-mould) for children. New formulations have addressed some of the limitations of established agents, while the utility of newer antifungal agents for prophylaxis in high-risk groups remains unclear. New antifungal agents introduced for therapy such as rezafungin, are undergoing evaluation for use as prophylaxis.[177]

Evidence gaps remain around the need for antifungal prophylaxis in the setting of new haematological treatments such as BTK inhibitors and CAR T cell therapy, the choice of antifungal prophylaxis for ALL in adults and children, dosing of the newer formulations in children, and the role of long-acting antifungal agents. These are active issues for future research.

The rapid advances in immune-based haematological therapies with non-classical impact on immunity and risk for IFD highlights the need for new approaches for IFD risk assessment and early, active systems-based detection of new at-risk groups. Emergence of drug-resistant fungal pathogens requires ongoing active surveillance and knowledge of local IFD epidemiology in order to help tailor recommendations for choice of prophylaxis. While challenges remain, novel antifungal therapies in development offer new options and will change the prophylaxis landscape in the near future.[178]

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Figure legends

Nil

Tables

Table 1 Established risk groups for IFD and recommended antifungal prophylaxis coverage in adults

Risk level	Risk groups	Recommended prophylaxis[†]	SoR	QoE
High risk >10% incidence of IFD	Neutrophil <0.1 x 10^9/L for >3 weeks or <0.5 x 10^9/L for >5 weeks (e.g. allogeneic HSCT)	First line: Posaconazole	A	I
	Corticosteroids >1 mg/kg prednisolone equivalent and neutrophils <1 x 10^9/L for >1 week	Alternate agents: Voriconazole Itraconazole Micafungin		
	Corticosteroids >2 mg/kg prednisolone equivalent >2 weeks	Liposomal amphotericin		

		Isavuconazole		
	Unrelated, mismatched or cord blood allogeneic HSCT GVHD – extensive or severe AML – induction/reinduction ALL – induction/reinduction MDS			
Low risk Less than 5% incidence of IFD	Autologous HSCT (e.g. patients at high risk for mucositis) Allogeneic HSCT with expected neutropenia <14 days	First line: Fluconazole Alternate agents: Echinocandins	B	II (context dependent; level I evidence in setting of alloHSCT)

	Lymphoma (e.g. intensive/dose-escalated therapy)	Itraconazole		
Very low risk‡ Less than 5% incidence of IFD No mucositis	Other lymphoproliferative neoplasms (e.g. standard chemotherapy for lymphoma, induction therapy for myeloma, treatment-naïve CLL) Other myeloproliferative neoplasms Treatment for solid organ tumours	No prophylaxis	B	II

†Please refer to Table 4 for summary of recommendations and level of evidence supporting choice of antifungal prophylaxis agents. ‡Consider that low and/or sporadic occurrence is not equal to no risk and is dependent on underlying treatment regimen, previous and cumulative treatments. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; GVHD, graft vs. host disease; HSCT, haemopoietic stem cell transplantation; IFD, invasive fungal disease; MDS, myelodysplastic syndrome; QoE, quality of evidence; SoR, strength of recommendation

Table 2 Summary of IFD rates associated with emerging use of new generation cancer therapies

Therapy	Population	IFD rates	Comments
BTK inhibitor (e.g. ibrutinib)	Relapsed/refractory B-cell lymphoproliferative disorder	3–12%	Rates of 1% reported in clinical trials of BTK inhibitors
			Invasive aspergillosis with CNS involvement up to 40%
			Cryptococcus spp.
			Pneumocystis jirovecii pneumonia

	Primary CNS lymphoma	5–44%	In combination with corticosteroids and conventional chemotherapy
PI3K inhibitor (e.g. idelalisib)	Relapsed/refractory B-cell lymphoproliferative disorder	3%	*Pneumocystis jirovecii* pneumonia
BCL-2 inhibitor (e.g. venetoclax)	CLL	1%	*Aspergillus* spp., *Pneumocystis jirovecii* pneumonia
Hypomethylating agents (e.g. azacitadine)	MDS AML	5–13%	Rates higher in relapsed/refractory disease versus its use as front-line therapy

			Rate of 13% when used in combination with BCL-2 inhibitor venetoclax
			Aspergillus spp., *Candida* spp.
FLT-3 inhibitors (e.g. midostaurin, gliteritinib)	AML	5%	Limited data from clinical trial
Second generation IMiD, PI	Relapsed/refractory myeloma	2–7%	*Candida* spp., *Cryptococcus* spp.
CD38 or SLAMF7 monoclonal antibodies			
CAR T cell therapy	Relapsed/refractory ALL	5–8%	In the setting of fluconazole or micafungin prophylaxis

	Relapsed/refractory NHL		
			Rates up to 13% in patients with ALL
			Aspergillus spp., *Candida* spp., *Mucor* spp.
Bi-specific antibody therapies (e.g. blinatumomab)	Relapsed/refractory ALL Relapsed/refractory NHL	2%	Limited clinical trial data

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BCL-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukaemia; CNS, central nervous system; FLT-3, fms-like tyrosine kinase; IMiD, immunomodulatory drug therapy; IFD, invasive fungal disease; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; PI, proteasome inhibitor; PI3K, phosphatidylinositol 3-kinase; SLAMF7, signalling lymphocytic activation molecule F7

Table 3 Summary of key new haematological treatments and recommended approaches to prophylaxis in adults and children

Therapy	Patient group	Infection	Measures	SoR	QoE
Targeted therapies (e.g. BTK inhibitors)	Relapsed/refractory B-cell lymphoproliferative disorders	Yeast and mould infections	Need for prophylaxis should be determined taking into account recent therapy (e.g. fludarabine-based), ongoing immune suppression and presence/absence of previous IFD	B	II
Immunomodulatory drug therapy, monoclonal antibody therapy (CD38/SLAMF7)	Relapsed/refractory myeloma	Yeast infection	Need for prophylaxis should be determined by number of previous lines of therapy, risk factors for IFD such as prolonged neutropenia and presence/absence of previous IFD	C	III

CAR T cell therapy	Relapsed/refractory lymphoproliferative disorders	Yeast and mould infections	Yeast prophylaxis with fluconazole or micafungin Consider mould prophylaxis in the setting of prolonged neutropenia or additional treatments for high-grade cytokine release syndrome following CAR T cell therapy Previous therapies including recent allogeneic or autologous HSCT should be taken into account	A	II
Bi-specific antibody therapies	ALL	Yeast and	Need for prophylaxis should be determined taking into account recent therapy (e.g. fludarabine-based), ongoing	C	III

	Being evaluated for other aggressive B-cell lymphoproliferative disorders	mould infections	immune suppression and presence/absence of previous IFD

ALL, acute lymphoblastic leukaemia; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; HSCT, haemopoietic stem cell transplantation; IFD, invasive fungal disease; QoE, quality of evidence; SLAMF7, signalling lymphocytic activation molecule F7; SoR, strength of recommendation

Table 4 Recommendations for choice and dose of antifungal prophylaxis agent in adults

Risk group		Antifungal agent	SoR	QoE	Comments
High risk	First line	Posaconazole Oral (tablets) Loading with 300 mg twice daily on Day 1, followed by 300 mg daily	A	I	Intravenous formulation can be used to continue prophylaxis if poor oral intake/absorption
	Alternate agents	Voriconazole Oral or intravenous 4 mg/kg twice daily[†]	A	II	High rates of adverse events (liver function abnormalities); variable CYP metabolism
		Micafungin Intravenous	B	II	Could be used during periods of neutropenia if azoles

	100–150 mg daily			contraindicated, poor oral intake/absorption
	Itraconazole Oral 200 mg twice daily	B	II	Less new data supporting its use compared to other azoles
	Liposomal amphotericin Intravenous 50–200 mg three times per week	B	II	Could be used if azoles contraindicated due to drug-drug interactions, adverse events, poor oral intake/absorption
	Isavuconazole Oral 200 mg three times per day for 48 hours followed by 200 mg daily	C	II	Higher rates of IFD in cohort studies; could be used if other azoles contraindicated due to

					adverse events such as QTc prolongation
Low risk	First line	Fluconazole Oral 200–400 mg daily	A	I	
	Alternate agents	Echinocandin Intravenous Dosing dependent on agent	A	II	
		Itraconazole Oral 200 mg twice daily	A	II	
Very low risk		No prophylaxis	B	II	

[†]Dose used in prophylaxis studies have been 200 mg twice daily; measure voriconazole levels to ensure achievement of target level (refer to accompanying optimising antifungal therapy and TDM guidelines by Chau *et al*. 2021, which can be found elsewhere in this supplement). CYP, cytochrome P450; IFD, invasive fungal disease; QoE, quality of evidence; QTc, corrected QT interval; SoR, strength of recommendation

Table 5 Updated risk groups for IFD in children (adapted from Groll *et al*. 2014,[136] Science *et al*. 2014,[179] Fisher *et al*. 2018[111] and Lehrnbecher *et al.* 2020[11])

Risk level	Clinical examples
High risk (>10%)	AML
	Recurrent/relapsed acute leukaemia
	High-risk ALL[†]
	Allogeneic HSCT
	Allogeneic with acute grade 2–4 GVHD or chronic extensive GVHD
Low risk (<5%)[‡]	Standard-risk or low-risk ALL[†]
	Non-Hodgkin lymphomas
	Autologous HSCT
Sporadic occurrence[‡]	Paediatric solid tumours
	Brain tumours
	Hodgkin's lymphoma
Unknown	CAR T cell therapy
	Other immunotherapy

[†]Key change from previous Australian antifungal prophylaxis guidelines based on TERIFIC study results.[112, 113] Note, high-risk ALL includes T-cell ALL, infant ALL, Philadelphia-positive ALL and high-risk B-cell ALL. [‡]Consider that low and sporadic occurrence is not equal to no risk and dependant on underlying chemotherapy regimen. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CAR,

chimeric antigen receptor; GVHD, graft-versus-host disease; HSCT, haemopoietic stem cell transplantation; IFD, invasive fungal disease

Table 6 Indications for primary antifungal prophylaxis in children based on clinical practice guideline by Lehrnbecher *et al.*, 2020.[11] Prophylaxis recommendations used with permission from lead authors and journal. Strength of recommendations adapted from Lehrnbecher *et al.*, 2020[11] to align with Australian guideline methodology. See in-text discussion for type of agent recommended.

Risk classification	Clinical example	Prophylaxis recommended	SoR	QoE
High-risk IFD	AML (*de novo* or relapsed)	Routine mould-active prophylaxis recommended†	A	I
	ALL (high-risk or relapsed)	Routine mould-active prophylaxis should be considered†	B	III

	Allogeneic HSCT (pre-engraftment[‡] and treatment of GVHD)	Routine mould-active prophylaxis recommended[†]	A	II
Low-risk IFD	ALL (standard risk)[§]	Routine prophylaxis not recommended	A	III
	Solid tumours[§]	Routine prophylaxis not recommended	A	II
	Most lymphomas[§]	Routine prophylaxis not recommended	A	II

	Autologous HSCT[§]	Routine prophylaxis not recommended	C	III

[†]Choice of mould-active agent will depend on age, potential drug interactions and patient location (e.g. inpatient versus outpatient), with preference given to mould-active azoles or echinocandins. [‡]Fluconazole is a reasonable alternative to a mould-active agent for patients undergoing allogeneic HSCT in the pre-engraftment phase, provided they do not have a history of proven or probable mould IFD and where local epidemiology supports its use. [§]Consider that low risk is not equal to no risk and dependant on underlying disease and chemotherapy regimen. For autologous HSCT, there is less certainty in the setting of tandem transplantations where the cumulative duration of neutropenia may be longer. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; GVHD, graft-versus-host disease; HSCT, haemopoietic stem cell transplantation; IFD, invasive fungal disease; N/A, not applicable; QoE, quality of evidence; SoR, strength of recommendation

Table 7 Suggested dosing for antifungal prophylaxis in children

Medication	Recommended dose	
Posaconazole[†]	Able to swallow tablets	Unable to swallow tablets
	Oral (modified-release tablets)	Oral (suspension)
	300 mg daily (>30 kg)[‡]	200 mg three times a day (≥13 years)
	For dosing options for children weighing <30 kg, please refer to Tragiannidis *et al*. 2019[157]	For dosing options for children <13 years, please refer to Boonsathorn *et al.* 2019[100]
Itraconazole[†]	Oral liquid	
	2.5 mg/kg (max 200 mg) twice daily	
Voriconazole[†]	2 to <12 years of age OR	≥15 years of age OR
	12–14 years of age and <50 kg:	12–14 years of age and >50 kg:
	Oral	Oral
	9 mg/kg (max 350 mg) twice daily	200 mg twice daily

	Intravenous 8 mg/kg twice daily (loading dose 9 mg/kg twice daily on Day 1)	Intravenous 4 mg/kg twice daily (loading dose 6 mg/kg twice daily on Day 1)
Micafungin	Intravenous 1 mg/kg (max 50 mg) daily	
Caspofungin	Intravenous 50 mg/m^2 (max 50 mg) daily (70 mg/m^2 loading dose on Day 1)	

Liposomal amphotericin B	Intravenous 1 mg/kg three times per week[180] or 3 mg/kg three times per week[134] or 2.5 mg/kg twice weekly[181]

†Adjust based on therapeutic drug monitoring target trough levels: posaconazole 0.7 mg/L; itraconazole 0.5–4 mg/L; voriconazole 1–5.5 mg/L.

‡Not TGA-approved for use in children <13 years of age in Australia. TGA, Therapeutic Goods Administration

Figures

Nil

Appendices

Nil

Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2021

Short title

Antifungal prophylaxis guidelines 2021

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Conflicts of interest

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Abstract

Antifungal prophylaxis can reduce morbidity and mortality from invasive fungal disease (IFD). However, its use needs to be optimised and appropriately targeted to patients at highest risk to derive the most benefit. In addition to established risks for IFD, considerable recent progress in the treatment of malignancies has resulted in the development of new 'at-risk' groups. The changing epidemiology of IFD and emergence of drug resistance continue to impact choice of prophylaxis, highlighting the importance of active surveillance

and knowledge of local epidemiology. These guidelines aim to highlight emerging risk groups and review the evidence and limitations around new formulations of established agents and new antifungal drugs. It provides recommendations around use and choice of antifungal prophylaxis, discusses the potential impact of the changing epidemiology of IFD and emergence of drug resistance, and future directions for risk stratification to assist optimal management of highly-vulnerable patients.

Keywords

antifungal prophylaxis, *Aspergillus*, *Candida*, stem cell transplantation, haematological malignancy