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Consensus guidelines for the treatment of invasive mould infections in haematological malignancy and haemopoietic stem cell transplantation, 2014

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Key words
invasive mould disease, antifungal therapy, aspergillosis, mucormycosis, emerging fungal infection.

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Abstract

Mould species represent the pathogens most commonly associated with invasive fungal disease in patients with haematological malignancies and patients of haemopoietic stem cell transplants. Invasive mould infections in these patient populations, particularly in the setting of neutropenia, are associated with high morbidity and mortality, and significantly increase the complexity of management. While *Aspergillus* species remain the most prevalent cause of invasive mould infections, *Scedosporium* and *Fusarium* species and the Mucormycetes continue to place a significant burden on the immunocompromised host. Evidence also suggests that infections caused by rare and emerging pathogens are increasing within the setting of broad-spectrum antifungal prophylaxis and improved survival times placing immunosuppressed patients at risk for longer. These guidelines present evidence-based recommendations for the antifungal management of common, rare and emerging mould infections in both adult and paediatric populations. Where relevant, the role of surgery, adjunctive therapy and immunotherapy is also discussed.

Introduction

The increasing prevalence of cancer and advances in therapeutic practices have led to a growing population at risk for invasive mould disease (IMD). As the use of antifungal prophylaxis has become more widespread and improved survival times place patients at risk for longer, uncommon fungal pathogens have also emerged, further complicating clinical management. Patients with haematological malignancies and haemopoietic stem cell transplantion (HSCT) patients carry the greatest burden of invasive fungal diseases. Mould species are now the predominant fungal pathogens in this population, with invasive aspergillosis (IA) the most common.[1–3] There is wide regional and institutional variability in incidence rates of IMDs, most likely due to differences in local practices and other institution-specific factors.[4] These include use of antifungal prophylaxis, variable diagnostic intensity reflecting the frequency and timing of investigations,[5,6] infection-control practices, preference for reporting clinical (i.e. possible) or microbiologically confirmed (i.e. probable/proven) IMDs and geoclimatic factors.[7]

The treatment guidelines presented here represent an update of the previous consensus guidelines published in 2008.[8] The current recommendations extend on the previous guidelines by considering the evidence base for both adult *and* paediatric populations. It should be noted,

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Table 1 Recommended dosing for antifungal treatment of invasive mould infections in adult and paediatric patients

	Adult	Child
Amphotericin B		
Conventional amphotericin B	1.0–1.5 mg/kg IV, daily	1.0–1.5 mg IV, daily
L-AMB	3 mg/kg IV, daily†	3 mg/kg IV, daily†
ABLC	5 mg/kg IV, daily	5 mg/kg IV, daily
Azoles		
Fluconazole	400–800 mg orally or IV, daily	12 mg/kg orally or IV, daily
Voriconazole	6 mg/kg IV, 12-hourly for 24 h (loading dose) then 4 mg/kg IV or orally, 12-hourly (maintenance) Therapeutic drug monitoring is recommended‡	Children 2–<12 years or young adolescents (12–14 years) weighing <50 kg: 9 mg/kg IV, 12-hourly for 24 h (loading dose) then 8 mg/kg IV, 12-hourly OR 9 mg/kg (max 350 mg) orally, 12-hourly (maintenance)[9,10] Older adolescents or young adolescents weighing > 50 kg: as per adult dosing
Posaconazole§	200 mg orally, 6-hourly (or 400 mg orally, 12-hourly on discharge) Therapeutic drug monitoring is recommended.‡	The optimal dose of oral posaconazole in young children has not been determined. In adolescents, the adult dose can be used. In young children, therapeutic drug monitoring must be used to optimise therapy.
Echinocandins		
Caspofungin	70-mg loading dose then 50 mg IV, daily	70 mg/m^2 loading dose then 50 mg/m^2 IV, daily
Anidulafungin	200 mg IV as a single loading dose then 100 mg IV, daily	3 mg/kg IV as a single loading dose then 1.5 mg/kg IV, daily
Micafungin	100–150 mg IV, daily	2–4 mg/kg IV, daily
Acenes and derivatives		
Terbinafine	250 mg orally, 12-hourly	Consider 62.5 mg orally, daily in children ≤20 kg, 125 mg orally, daily for children 20–40 kg and 250 mg orally, daily in children ≥40 kg¶

†Higher doses of L-AMB are recommended in invasive mucormycosis (see text for details). ‡See accompanying optimising drug therapy guidelines by Chau *et al*., 2014 (appearing elsewhere in this supplement) for TDM details. §Intravenous preparation is now available through special access scheme. Phase III trials in adults using a loading dose of 300 mg IV, 12-hourly for 24 h followed by 300 mg IV, daily thereafter, are currently underway. No paediatric data exist. ¶The optimal paediatric dose of terbinafine for invasive mycosis has not been identified, but it is well tolerated between 2 and 17 years. Expert opinion should be sought. Dosing shown in table is based on systemic therapy for onychomycosis. ABLC, amphotericin B lipid complex; IV, intravenous; L-AMB, liposomal amphotericin B; TDM, therapeutic drug monitoring.

however, that there remains a paucity of data specific to the paediatric setting; the recommendations provided here for adults should be cautiously applied to children by paediatricians familiar with the literature. The recommendations provided here should be used in conjunction with the accompanying consensus guidelines for antifungal prophylaxis, diagnosis and therapeutic drug monitoring (also published in this supplement). The recommended adult and paediatric dosing for the antifungal agents referred to throughout these guidelines is shown in Table 1.

Methodology

Questions asked

In preparing this update, we aimed to address the following questions:

1 What is the current status of treatment strategies for IA, scedosporiosis, fusariosis and mucormycosis based on new evidence published in the literature over the last 5 years?
2 What new and emerging moulds are causing human disease in the haematology/oncology population?
3 What is the role of combination therapy in the treatment of IMD?

Search strategy

A literature review was performed using PubMed to identify papers published since 2007 that pertained to the treatment of invasive mould infections (IMD) in patients with haematological malignancy and patients of HSCT. Search terms included 'aspergillosis', 'aspergillus', 'zycomycosis', 'zygomycetes', 'mucormycosis', 'mucormycetes', 'fusariosis', 'fusarium', 'scedosporiosis',

'scedosporium', 'hyalohyphomycetes', 'paecilomyces', 'acremonium', 'trichoderma', 'geosmithia argillacea', 'schizophyllum commune', 'phaeohyphomycetes', 'bipolaris', 'cladophialophora', 'exophiala' and 'alternaria'.

Invasive aspergillosis

Background

IA remains the most frequent IMD in immunocompromised patients, particularly those with haematological malignancy and patients of solid organ transplants or HSCT.[11] The incidence of IA has decreased in the setting of improved diagnostic testing, the use of mould-active antifungal prophylaxis and the availability of newer antifungal agents with increased efficacy and better tolerance.[12] Despite this, morbidity and mortality rates remain significant.[11,12] Risk factors for IA include prolonged neutropenia, solid organ transplantation, HSCT (especially when complicated by graft-versus-host disease (GVHD)), the use of high-dose corticosteroids, iron overload and infection with immunomodulating viruses, such as cytomegalovirus (CMV).[11,13,14]

Aspergillus species have the ability to cause severe invasive infections in almost every major organ system. The lung is the most frequent site of infection; more than 75% of patients have pulmonary IA alone, and a further 10% have evidence of infection in the lung and other sites, including the sinuses, central nervous system (CNS), skin and soft tissue, eyes, and heart.[11] *Aspergillus fumigatus* remains the species most frequently responsible for IA; other species, such as *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus terreus*, are less frequently observed.[9,11]

Antifungal therapy for IA

IA should be treated promptly and aggressively. Many clinicians advocate commencement of antifungal therapy upon first suspicion of disease.

Two randomised controlled trials (RCT) have demonstrated comparable response rates for voriconazole and liposomal amphotericin B (L-AMB), although no head-to-head comparison has been performed.[9,15] In the first RCT, intravenous (IV) followed by oral voriconazole was compared with conventional amphotericin B for the primary treatment of IA. Voriconazole led to more successful outcomes (53% vs. 32%) and improved survival at 12 weeks (71% vs. 58%).[9] In addition, voriconazole was better tolerated with fewer severe drug-related adverse events.

The second RCT compared different doses of L-AMB in highly immunocompromised patients.[15] A response rate of 50% and a 12-week survival rate of 72% was reported for the lower L-AMB dose (3 mg/kg, daily).[15] This dose was also associated with a lower incidence of nephrotoxicity and hypokalaemia than the higher dose of 10 mg/kg.[15] A re-evaluation of the response rates 4 years later using the revised European Organization for Research and Treatment of Cancer/Mycosis Study Group criteria found higher survival rates at 12 weeks for possible versus probable/proven cases in the 3 mg/kg group (82% vs. 58%; $P = 0.006$) compared with the 10 mg/kg group (65% vs. 50%; $P = 0.15$).[16]

Other agents with activity against *Aspergillus* include other forms of amphotericin B, other mould-active azoles (e.g. itraconazole, posaconazole) and echinocandins. The choice of agent should be influenced by: (i) prior use of mould-active azole prophylaxis; (ii) existing comorbidities, particularly renal impairment; (iii) the likelihood of an azole-resistant *Aspergillus* infection or (iv) likely presence of another causative fungus (e.g. a mucormycete).

Given the lack of data comparing voriconazole with lipid formulations of amphotericin B, the latter may be considered as an alternative primary therapy to voriconazole in some patients, particularly those who develop IA while receiving a mould-active azole or those intolerant to voriconazole (grade C recommendation). A lipid formulation of amphotericin B is preferred in most populations due to the lower risk of nephrotoxicity and expected length of therapy.[17,18]

An echinocandin as first-line therapy for IA has been studied in both HSCT patients[19] and patients with haematological malignancy.[20] A small, phase 2, open-label trial in adults with mycologically documented proven or probable IA post-HSCT, complete or partial responses, were observed in 33% of study participants at 12 weeks and 42% at end of therapy, with 50% survival at 12 weeks.[19] In the second study, complete or partial responses were observed at the end of therapy in 33% of patients with haematological malignancy, with 53% survival at 12 weeks.[20] While no head-to-head comparison has been performed, echinocandins should be considered second-line therapy after voriconazole and a lipid form of amphotericin (grade D recommendation).

Antifungal susceptibility varies among different *Aspergillus* species. Some species, such as *Aspergillus terreus* and *Aspergillus nidulans*, are relatively resistant or resistant to amphotericin B.[21,22] Azole resistance in *Aspergillus fumigatus* is increasingly described in Europe and in Asia, most often due to mutations in the *CYP51A* gene.[23] The development of resistance in patients on long-term azole therapy, especially those with chronic respiratory infections, and *de novo* infection with resistant species can occur. Large-scale surveillance has not yet been

undertaken inAustralia, but of clinical isolates of *Aspergillus fumigatus*, 4.3% had a voriconazole minimum inhibitory concentration (MIC) of ≥2 mg/L, the current recommended clinical breakpoint for this species (S. Kidd and D. Ellis, National Mycology Reference Centre, pers. comm., 2014). An attempt to obtain specimens for culture and routine susceptibility testing of any invasive specimens is recommended in order to establish the antifungal susceptibility profile of common aspergillus species (grade D recommendation). Although not a significant problem at present, ongoing surveillance is also integral to track the emergence of antifungal resistance in *Aspergillus* species in Australia.

Combination antifungal therapy for IA

Given the significant morbidity and mortality of IA despite optimal therapy, there has been significant interest in the potential benefits of combination antifungal therapy. Recent *in vitro* and animal studies support the use of combination therapy, particularly with a broad-spectrum azole and an echinocandin.[24,25] Several case series, most frequently combining an echinocandin with either voriconazole or L-AMB, have been described.[26–28] In a case series of 47 patients with confirmed IA who experienced failure or intolerance to voriconazole, Marr *et al*. reported improved 3-month survival with voriconazole and caspofungin compared with historic controls treated with voriconazole alone (hazard ratio, 0.42; 95% confidence interval 0.17–1.1; $P = 0.048$).[28]

The role of combination therapy was examined in a prospective, double-blind clinical trial in 454 adult allogeneic HSCT patients and patients with haematological malignancies with proven or probable IA. All subjects received voriconazole and either anidulafungin (200 mg IV on day 1 followed by 100 mg daily) or placebo.[29] Combination therapy was administered for at least 2 weeks with at least 5 weeks of antifungal therapy prescribed to all subjects. Combination therapy showed no additional benefit: 6-week mortality was not significantly different in the combination group (19.3% vs. 27.5%; $P = 0.09$), nor was there a significant difference in 12-week or aspergillosis-associated mortality. In the combination arm, 32.6% of subjects were considered to have a global response (judged by a composite of clinical and radiological responses) compared with 43.0% of subjects receiving monotherapy.[29] Based on current evidence, combination therapy should not be used as first-line therapy (grade D recommendation).

Salvage therapy for IA

Salvage therapy refers to treatment provided in the setting of disease that is refractory to a standard antifungal regimen or drug intolerance.[30,31] Patients are considered refractory to initial antifungal therapy if, after at least 7 days of therapy, there is evidence of progression on two or more of the following grounds: clinical (e.g. persistence of fever), radiologic (e.g. progression of infiltrates and/or appearance of new infiltrates) or mycologic (e.g. persistence of positive cultures).[32] However, even when using these criteria, evaluation of response to therapy is difficult for several reasons. Persistent fever in an immunocompromised patient may be due to another cause while cough and haemoptysis may worsen in the setting of neutrophil recovery.[30] Likewise, the size and number of lesions on radiological imaging may increase in the initial stages of therapy, making it difficult to imply treatment failure on radiological grounds alone.[33] Given the difficulty in evaluating response to therapy and the heterogeneity of patients with refractory aspergillosis, salvage therapy studies should be interpreted with caution.[30]

Options for salvage therapy include lipid formulations of amphotericin B, caspofungin and posaconazole. A successful outcome was observed in 42% of patients with IA refractory to or intolerant of amphotericin B or itraconazole, who were prescribed 800 mg daily of posaconazole.[34] A favourable response was also observed in 45% of adults with IA refractory or intolerant to amphotericin B or itraconazole who were then prescribed caspofungin.[35] Limited data suggest that certain combinations of antifungal agents may provide an additional benefit. In a retrospective, single-centre study of 31 HSCT patients with proven or probable IA refractory to primary therapy, favourable responses were seen in 77% of patients receiving a combination of posaconazole and caspofungin.[36] In contrast, another retrospective study of patients with haematological malignancy and proven or probable IA refractory to primary therapy demonstrated that a combination of L-AMB and an echinocandin (21% response) offered no advantage over either echinocandins alone (28%) or L-AMB alone (9%) when all study endpoints were considered.[37]

Surgical management of IA

In the modern antifungal era, the role of surgery remains uncertain. Evidence supports improved outcomes in CNS, eye and cardiac infections.[38–40] Early surgical therapy may be beneficial in lesions that are close to critical structures (e.g. great vessels, pericardium) or those involving the chest wall. Debridement may also assist in managing complicated infections, including skin, soft tissue, bone and joint aspergillosis. Early surgical resection of isolated lesions prior to an episode of intensive chemotherapy or HSCT may also be of benefit.

Management of *Aspergillus* infections in problematic sites (CNS, eyes, renal tract and heart)

Treatment of IA involving the brain, eyes, renal tract or heart valves deserves specific consideration. Infection of the CNS is associated with very high mortality.[41,42] The optimal treatment of CNS aspergillosis has not yet been defined, although treatment success has been reported with both mould-active azoles and lipid preparations of amphotericin B. Penetration into brain tissue by conventional amphotericin B and echinocandins is poor compared with mould-active azoles, particularly voriconazole.[43] In CNS aspergillosis, clinical response rates as high as 35% have been observed with voriconazole.[44] Based on these data, voriconazole is the preferred agent for CNS aspergillosis (grade D recommendation).

The majority of successful outcomes reported have occurred in patients managed with both systemic antifungals *and* surgery, suggesting that surgical debridement may play an important role in CNS aspergillosis.[38] *Aspergillus* meningitis occurs less frequently than CNS involvement and is seen more often in immunocompetent hosts.[45] Voriconazole is recommended as first-line therapy in this setting (grade B recommendation), although case reports have cited treatment success with other agents, including amphotericin B.[45]

Similar factors influence the management of *Aspergillus* endophthalmitis, which comprises systemic antifungal therapy (voriconazole or L-AMB), surgical debridement (vitrectomy) and/or intravitreal injection of an antifungal agent (voriconazole or L-AMB).[40] Fluconazole, voriconazole and flucytosine achieve adequate therapeutic intravitreal concentrations, whereas the echinocandins and amphotericin B formations do not. In sight-threatening infections, intravitreal injection of voriconazole or AmB-d should be performed to ensure that appropriate drug levels in the posterior segment are rapidly achieved. Surgical debridement should be considered to decrease the burden of infection and remove infection inaccessible to systemic antifungals.[40]

Aspergillosis involving the renal tract is rare and may be parenchymal, usually involving the kidney through haematogenous spread, or pelvic, such as fungal balls within the bladder or renal pelvis.[41] The choice of antifungal agent depends on the presentation. For pelvic disease, agents with good urinary excretion are preferred. Voriconazole and echinocandins have low concentrations in the urine compared with flucytosine.[46] Local irrigation of amphotericin B and high-dose systemic amphotericin B have been used successfully.[41]

Aspergillus endocarditis and cardiac device-related infections are rare.[39] Risk factors include underlying cardiac abnormalities, prosthetic valves, malignancy, solid organ transplants and HSCT.[39,47] A review of more than 50 cases of *Aspergillus* endocarditis suggests that optimal treatment requires aggressive surgical debridement, combined with antifungal therapy; in one case series, only 2/53 cases (4%) were successfully treated with antifungal therapy alone.[39] Voriconazole is suggested as first-line therapy, but the appropriate duration of antifungal therapy has not been evaluated (grade D recommendation).

Duration of antifungal therapy for IA

The optimal length of therapy for IA remains uncertain. RCT generally assess response at 12 weeks. Treatment for 6–12 weeks, or until immune recovery, or resolution of clinical/radiological evidence of disease, is most frequently recommended (grade C recommendation).[48] Secondary prophylaxis during periods of intense immunosuppression is also recommended (grade D recommendation). Therapeutic drug monitoring of azole agents throughout the treatment period is recommended. Please refer to the accompanying optimising drug therapy guidelines by Chau *et al.*, 2014 (appearing elsewhere in this supplement) for details.

Mucormycosis

Background

Mucormycosis is a term used to describe infections caused by saprophytic fungi of the class Mucormycetes, which are saprophytes of soil and decaying plant and vegetable matter.[49] Mucormycetes are further classified into two orders: Mucorales, comprising the genera *Rhizopus, Mucor, Absidia*, *Saksenaea*, *Rhizomucor, Apophysomyces* and *Cunninghamella*, and Entomophthorales, which include the genera *Basidiobolus* and *Conidiobolus*.[50] Mucorales have a worldwide distribution and are commonly associated with angioinvasive disease in immunocompromised hosts. In contrast, pathogenic fungi of the order Entomophthorales have a mostly tropical and subtropical distribution, and are commonly associated with chronic cutaneous and subcutaneous infections in immunocompetent individuals.[51,52]

Mucormycete infections follow inhalation, ingestion or percutaneous inoculation of spores. Such infections have the potential to disseminate, especially in the immunocompromised host undergoing high-intensity chemotherapy or immunosuppression.[53] Risk factors for mucormycosis include poorly controlled diabetes mellitus, injecting drug use, iron overload, prolonged neutropenia or corticosteroid use, major trauma,

prematurity and malnourishment.[51] Clinical outcomes are closely related to a patient's overall health and the control of their underlying disease.[49]

Over the last two decades, Mucormycetes have emerged as significant fungal pathogens in patients undergoing treatment for haematological malignancy or HSCT.[54,55] Risk factors for mucormycosis in these patients include severe GVHD, complicated diabetes, increased age, male gender, high corticosteroid dose and prior history of CMV or respiratory virus disease.[56–58] The use of voriconazole for the prevention and treatment of IA in high-risk haematology patients has also been associated with an increased risk of mucormycosis in several observational studies.[59–61] This association, however, was not apparent in a recent RCT investigating the safety and efficacy of voriconazole prophylaxis.[62] Voriconazole has no clinically useful *in vitro* activity against Mucormycetes[63] and may therefore select for fungal species within this class.

Antifungal therapy for mucormycosis

The optimal treatment of mucormycosis has not been defined, owing to the lack of appropriate prospective and RCT. Amphotericin B deoxycholate (AmB-d) at maximum tolerable doses (1–1.5 mg/kg/day) was historically the antifungal treatment of choice prior to the availability of less nephrotoxic lipid formulations of amphotericin B. Lipid formulations of amphotericin B, starting at 5 mg/kg/day, are now preferred as first-line therapy (level III-3 evidence), with a higher initial dose of 10 mg/kg/day recommended in cases of CNS disease (grade C recommendation).[64] Although the dose of lipid formulations may be increased to 15 mg/kg/day for severe and/or refractory disease,[65] pharmacokinetic data suggest that increasing the dose of L-AMB beyond 10 mg/kg/day does not achieve higher serum concentrations (level III-3 evidence).[66] Significantly lower mortality (49% vs. 83%; $P = 0.03$) has been reported when amphotericin-based treatment is initiated within 5 days of clinical diagnosis, underscoring the importance of timely therapy.[67]

The extended-spectrum triazole, posaconazole, has demonstrated activity against Mucormycetes *in vitro*[68,69] and shown more limited activity *in vivo*, especially for *Rhizopus oryzae*, when tested in a neutropenic murine model.[70,71]

Until recently, first-line therapy with posaconazole was not recommended over L-AMB formulations for several reasons, including the availability of an oral preparation only and all its attendant issues: less predictable pharmacokinetics, especially in patients with mucositis or diarrhoea; the longer time it takes (5–7 days) to reach steady-state concentrations; and experimental data suggesting less activity in severe or disseminated disease (level III-3 evidence, grade B recommendation).[64] However, an IV preparation of posaconazole has just become available for compassionate use within Australia, which is likely to increase its use.

Based on observational data, posaconazole may have a role in patients who require ongoing maintenance therapy (level III-3 evidence).[64] Maintenance therapy is indicated in patients with residual tissue-based infection or with risk factors that are not readily modifiable. In these patients, therapeutic drug monitoring should be conducted where possible.[64]

Combination antifungal therapy for mucormycosis

The use of various combinations of antifungal agents to treat mucormycosis (azoles, echinocandins or both plus amphotericin B) has been described but only in murine and small retrospective clinical studies.[72]

The rationale for echinocandin-amphotericin B combination therapy is underpinned by the fact that *Rhizopus oryzae*, the most common clinical isolate implicated in mucormycosis, expresses β(1,3)-D-glucan synthase, the target enzyme for echinocandins.[73] One small retrospective study showed a significant survival advantage in patients treated with amphotericin B lipid complex (ABLC) and caspofungin for rhino-orbito-cerebral mucormycosis, albeit in a predominantly diabetic population.[74] Given the paucity of high-quality evidence and the uncertain efficacy and safety of this strategy, combination polyene-echinocandin therapy cannot currently be recommended (grade D recommendation).

Posaconazole-amphotericin B combination therapy cannot be recommended either, given insufficient clinical data and the lack of clear benefit shown when this approach was used in experimental murine mucormycosis (grade D recommendation).[75,76]

Salvage therapy for mucormycosis

Observational clinical studies suggest that posaconazole may provide effective salvage therapy for patients who are refractory to and/or intolerant of amphotericin B.[77,78] However, these studies should be interpreted with caution, as subjects treated with salvage therapy may be fitter (having already survived at least 7 days with their fungal disease). Further, if the observed clinical deterioration leading to salvage therapy was paradoxical in nature (i.e. due to immune reconstitution rather than refractory disease), any successful outcomes reported for posaconazole may be due, in part, to the initial amphotericin treatment.[64]

Ancillary therapy for mucormycosis

The successful management of mucormycosis relies on early diagnosis, urgent surgical debridement of devitalised tissue, the control (or reversal) of medical risk factors (e.g. immunosuppression, diabetes mellitus, iron overload) and the timely initiation of appropriate antifungal therapy.

Several treatment modalities are often required to achieve optimal outcomes. Surgical debridement and antifungal therapy have been shown to achieve a lower fatality rate than antifungal therapy with an amphotericin-based regimen alone.[79] In general, positive responses to antifungal therapy are associated with timely surgery and no worsening or improvement of underlying conditions.

Adjuvant therapies with granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon, granulocyte CSF (G-CSF) and/or hyperbaric oxygen have been used in some patients, but there are no controlled studies to help define their wider use.

Given the importance of iron in the pathogenesis of mucormycosis, the potential benefit of iron chelation therapy with deferasirox in disease management has been a focus of research interest. A phase 2, randomised, placebo-controlled trial comparing the safety and efficacy of L-AMB plus deferasirox to L-AMB plus placebo failed to show a clinical benefit with adjunctive deferasirox, despite promising results from earlier preclinical and clinical studies.[80,81] Excess mortality at 90 days has been reported in patients receiving deferasirox in the absence of drug-related toxicity.[82] However, a disproportionate number of patients with leukaemia and neutropenia in the interventional arm of this study may have accounted for the observed differences.[82] The use of deferasirox cannot be recommended until a phase 3 study establishes its safety and efficacy in the treatment of mucormycosis (grade D recommendation).

Duration of antifungal therapy for mucormycosis

Treatment duration in mucormycosis is often unclear. The duration of amphotericin therapy will depend on the site of infection, recovery of host immunity and the response to treatment. Prolonged, high-dose amphotericin for as long as possible until clinical and radiological resolution seems practical (grade D recommendation). Lipid formulations of amphotericin B, such as L-AMB or ABLC, may be required for weeks in cases of cerebral infection, disseminated disease or prolonged neutropenia.

The decision to switch to oral monotherapy with posaconazole (salvage or maintenance therapy) will depend on the patient's response to amphotericin therapy, the presence and severity of any toxicities, and the concurrent or recent use of drugs known to interact with azoles (e.g. vinca alkaloids). Amphotericin should not be ceased until adequate posaconazole levels have been reached. Please refer to accompanying optimising drug therapy guidelines by Chau *et al*., 2014 (also appearing in this supplement) for further details.

The duration of posaconazole should be individualised according to response and the risk of relapse in the setting of continuing immunosuppression. Patients who are neutropenic and/or receiving immunosuppressants should continue on posaconazole until the immunosuppressants have been weaned, neutrophil counts have recovered and the clinical and radiological signs of infection have resolved. Posaconazole during further cycles of chemotherapy may be indicated for secondary prophylaxis. Clinicians should refer to the accompanying consensus guidelines for antifungal prophylaxis located elsewhere in this supplement for further details (Fleming *et al*. 2014).

Fusariosis

Background

Fusarium is an emerging cause of opportunistic mycosis, with most invasive infections occurring in the immunocompromised host. In this group of patients, fusarial infections are often disseminated and associated with very high mortality rates (40–50%), despite the availability of liposomal amphotericin and newer azoles.[83–87]

Fusarium species are ubiquitous in the environment. Found in soil, plant debris and vegetation, they cause infection in both humans and plants. Widespread use of azoles has the potential to induce resistance in *Fusarium* species.[88]

In humans, the major risk factors for fusarial infection include haematological malignancy, lung transplant and burns, but regional differences in incidence are apparent.[89] The most commonly reported infecting species are *Fusarium solani* complex (60% of cases) and *Fusarium oxysporum* (20%).[83,84,86,87,90] The best outcomes are usually seen with *Fusarium verticillioides*. Accurate species identification beyond the species complex is difficult, but techniques, such as DNA sequencing, improve identification and are recommended for epidemiological studies and where morphological identification does not establish species.[91] Matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry is not a satisfactory procedure as yet.

The most common sites of infection are skin, from direct contact with spores, and sinopulmonary structures,

from inhalation of spores.[87,92] Infection of central venous catheters or from contaminated medical fluids rarely occurs.[93] *Fusarium* species have the capacity to conidiate adventitiously and disseminate systemically, leading to multiple cutaneous lesions (70–90% of patients), sinus and lung disease (70–80% of patients), and positive blood cultures in 50–58% of cases.[94,95] Dissemination may cause endophthalmitis, septic arthritis, meningitis and fungal endocarditis, among other clinical syndromes.[96] Breakthrough infections may occur with resistant strains during treatment with echinocandins and voriconazole, or while on posaconazole prophylaxis.[97,98]

Imaging techniques are non-specific. Blood cultures and tissue biopsy are the most specific diagnostic tests, and pan-fungal polymerase chain reaction, galactomannan and β(1,3)-D-glucan assays may all be positive.[99,100]

Factors associated with increased mortality include disseminated infection (metastatic skin lesions and fungaemia), persistent neutropenia, stem cell transplantation and ongoing corticosteroid use, although in studies by Nucci and colleagues, only persistent neutropenia and corticosteroid use remained significant after multivariate analysis.[90,101,102] Strategies to prevent fusarial infection during immunosuppression include good skin care, avoidance of skin breakdown and minimising immunosuppression.

Antifungal therapy for fusariosis

In vitro susceptibility testing has shown intrinsic resistance to fluconazole, itraconazole and the echinocandin class, while susceptibility to amphotericin B, voriconazole and posaconazole is unpredictable.[86,87,103–105] Strains resistant to L-AMB but susceptible to voriconazole have been described. Given the scarcity of fusarial infections, there are no studies that directly compare the clinical efficacy of different antifungal agents against *Fusarium* spp. or the precise correlation between *in vitro* susceptibility and clinical outcomes. Therefore, antifungal drug management is based upon results from retrospective studies or subgroup analysis of larger drug comparison studies.

Early reports of disease responding to high-dose amphotericin B (1.0–1.5 mg/kg IV, daily) treatment or failing to progress were promising.[65,106] However, results from later series (L-AMB or ABLC at least 5 mg/kg, daily) have been less successful, with 32–46% response rates in patients with haematological malignancy and HSCT patients (level IV evidence).[90,102,107] In large case series, complete or partial responses to voriconazole were reported in 45–47% of patients, with a worse outcome in those who were neutropenic at the start of therapy (5–36%).[83,84,107] In the absence of comparative studies, it is currently not possible to recommend one of these agents over another as empiric therapy.

Combination antifungal therapy for fusariosis

More recently, case reports have documented success with dual antifungal therapy (L-AMB and voriconazole).[108,109] However, the evidence is mixed with one case series showing no benefit, while another single-centre series found a higher mortality (level IV evidence).[83,87] The outcomes reported are also likely to be confounded somewhat by the severity of the underlying disease state.

Salvage therapy for fusariosis

Breakthrough *Fusarium* infections can occur with amphotericin B therapy.[102,107] Several case reports and case series have described the use of voriconazole with reasonable outcomes in this clinical setting (45% partial or complete response at week 16 or end of treatment) (level IV evidence).[110,111] More recently, posaconazole has been used for this purpose, also with reasonable outcomes (48% partial or complete response at end of treatment) (level IV evidence).[112] Only patients who were intolerant of, or had disease that was refractory to, amphotericin B and/or its lipid formulations qualified for these studies. There are two case reports of a combination of terbinafine and amphotericin B apparently giving some benefit as salvage therapy.[113,114]

Ancillary treatment for fusariosis

Expert opinion recommends a combination of medical therapy, surgical debridement and immune suppression reversal where practicable (grade D recommendation).[85]

Management of fusarial infections in problematic sites (CNS and eyes)

Voriconazole may be used to treat CNS and eye disease due to *Fusarium* species, although successful therapy is limited to case reports.[111] Lipid formulations of amphotericin remain an alternative. There are occasional case reports on the use of posaconazole in this clinical setting.[115]

Duration of antifungal treatment for fusariosis

No studies have compared a fixed time period for antifungal administration, but at least 12 weeks of therapy is often required.[107,112] Therapy should be ceased only once immunosuppression has resolved and there is clear evidence of clinical and radiological improvement (grade D recommendation).

Scedosporiosis

Background

Mycoses caused by *Scedosporium* species continue to be emergent in a wide variety of patient groups, particularly within immunosuppressed populations.[116–119] An increase in the severity of host immunosuppression due to more aggressive chemotherapy regimens, and possibly changes to antifungal prophylaxis regimens, is likely to have contributed to the emergence of these infections.[120]

Until recently, there were only two medically relevant species: *Scedosporium apiospermum* (the anamorph of *Pseudallescheria boydii*) and *Scedosporium prolificans*. Modern molecular approaches have now identified and classified a broad range of *Scedosporium* species pathogenic for humans. Of these, three are the most frequently recovered from clinical specimens: *Scedosporium prolificans* (now *Lomentospora aurantiacum*), *Scedosporium apiospermum* and *Scedosporium aurianticum*.[118,121,122] All these fungi are found in the environment.

While all *Scedosporium* spp. are potentially pathogenic, especially in immunosuppressed populations, *Scedosporium prolificans* is particularly virulent in patients with haematological malignancy and neutropenia, and patients of bone marrow transplantation (BMT).[117–119] In these cancer populations, qualitative or quantitative deficits of macrophages and granulocytes within pulmonary tissue may result in failure to control germination of inhaled *Scedosporium* spp., with unchecked proliferation of hyphae and conidia proliferation resulting in haematogenous dissemination.[117] Consequently, *Scedosporium apiospermum* and especially *Scedosporium prolificans* may cause bloodstream infection and disseminated disease – a pattern of illness that is rare in the non-compromised host. Isolation of *Scedosporium* spp. from the respiratory tract may represent colonisation or local pulmonary infection or be associated with subsequent dissemination.[117–119,121,123,124] Localised disease (e.g. mycetoma, joint infections, ocular infections) may occur in cancer populations, and *Scedosporium* spp. may also cause infection in hosts with normal immune systems, such as pulmonary infection in drowning and soft tissue infections following traumatic inoculation injury.

Scedosporium spp. infection in the haematological malignancy and BMT setting most often occurs during neutropenia, although it may occur later in BMT with GVHD.[117,123] Hallmark features of disseminated scedosporiosis in these patients include fever (90%) and evidence of dissemination with focal CNS symptoms (40%), appearance of rash (30%), and positive blood cultures (72%); occurrence of the latter three features portends a very poor prognosis.[119,123]

Successful treatment of *Scedosporium* spp. infections is likely to depend on several factors, including localised virus disseminated (or CNS) infection, species of *Scedosporium* (e.g. worse outcomes are typically observed with *Scedosporium prolificans* than *Scedosporium apiospermum*), underlying immune suppression status and failure to recover from granulocytopaenia.[117–119] *In vitro*, interactions between polymorphonuclear leukocytes (PMN) and antifungal drugs, as well as CSFs, have demonstrated additive increase in damage to *Scedosporium* spp. hyphae.[117]

Scedosporium spp., particularly *Scedosporium prolificans*, are amongst the most resistant fungi to currently available antifungal drugs.[107,117,118] Rodriguez-Tudela *et al*. found that treatment with antifungal drugs had no impact on outcomes from *Scedosporium prolificans* infections; however, it was not clear how many of these patients received tertiary azole therapy. Importantly, only nine of 72 patients with disseminated *Scedosporium prolificans* infection survived, only two of whom received voriconazole therapy, and all of whom were either not granulocytopaenic or had recovered from this.[119] In another retrospective study by Troke *et al*., infections with *Scedosporium* spp. (including CNS disease) could be treated successfully with voriconazole; again, successful outcomes occurred more frequently with *Scedosporium apiospermum* (64%) than *Scedosporium prolificans* infections (44%). These success rates, however, included localised infections (with an inherently much better prognosis) as well as disseminated ones.[118] Mortality is documented to be as high as 90% for both species, but this is especially true for *Scedosporium prolificans* if disease is invasive, disseminated or involves fungaemia.[110]

Antifungal therapy for scedosporiosis

The optimal antifungal treatment for Scedosporium infections is unclear. While no validated interpretive breakpoints for *Scedosporium* spp. have been defined, *Scedosporium apiospermum* and particularly *Scedosporium prolificans* are both intrinsically resistant *in vitro* to multiple antifungal drugs. Amphotericin-based therapies (monotherapy or combination therapy) appear to be inferior to azole-based therapies against both species.[117,118,125–127] Antifungal use should be guided by susceptibility testing when available as this may be associated with better outcomes (grade D recommendation).[117]

The extended-spectrum triazoles are active *in vitro* against *Scedosporium apiospermum* with cross-resistance observed among all the azoles except posaconazole.[126] Voriconazole appears most potent against *Scedosporium apiospermum* with a median MIC (MIC_{50}) of 0.25 μg/mL and MIC range 0.01–2 μg/mL. In contrast, *Scedosporium*

prolificans is often resistant to all tested antifungal agents, although individual isolates may demonstrate low MICs to one or more agents (e.g. median MIC_{50} to voriconazole is 4 μg/mL, range 0.06–32 μg/mL, while posaconazole has variable MICs but is generally less active than voriconazole).[107,123,127] Other newer-generation azoles (currently unavailable in Australia), including albaconazole and ravuconazole, may also have some activity.[117,127] Limited data ($n = 6$) from a 2008 survey of the voriconazole global clinical trials database (Pfizer) suggest that voriconazole MICs may not increase over time in patients with persistently positive cultures for *Scedosporium prolificans*.[118]

Miltefisone, a phospholipid drug typically used to treat leishmaniasis, has demonstrated *in vitro* activity against moulds, with greatest activity against *Scedosporium* spp., particularly in combination with a triazole.[128,129]

Combination therapy for scedosporiosis

In vitro, there is evidence that azoles and terbinafine act synergistically against *Scedosporium prolificans*; voriconazole and terbinafine are synergistic in more than 85% of *Scedosporium prolificans* strains *in vitro*, with a 16-fold reduction in MICs.[8,125,130] Synergy may also exist for *Scedosporium prolificans* with other combinations of drugs, including amphotericin and pentamidine, voriconazole and micafungin, and amphotericin and micafungin, although the clinical usefulness of these interactions is unknown.[117,128]

Although there are no trials comparing monotherapy with combined therapy (prospectively or as case reviews), it is recommended that clinicians use voriconazole with terbinafine, based on *in vitro* observations and case reports (grade D recommendation).

Ancillary therapy for scedosporiosis

Ancillary management of Scedosporium infections may include surgery and immunotherapy.

Surgical debridement of localised disease is recommended, although this is usually not possible in the setting of disseminated disease (grade D recommendation).[117]

Multiple case reports describe survival of disseminated scedosporiosis in the setting of resolution of neutropenia. Given this, and particularly that disseminated *Scedosporium prolificans* disease is nearly always fatal in the absence of neutrophil recovery, efforts to restore circulating PMN should be made; use of CSF has been described in survivors.[117,119,131] Cytokines, most notably GM-CSF and IFN-γ, may additively increase PMN damage of scedosporium hyphae. While G-CSF use has been described in case reports of survivors, animal models have not shown consistently positive benefit.[119] Granulocyte transfusions have theoretical merit; however, no description of PMN transfusions exists for scedosporiosis.[131]

Duration of antifungal therapy for scedosporiosis

There is no evidence to support a pre-specified duration of therapy, particularly for invasive disease; however, patients who survive *Scedosporium* spp. infection have generally received >1 month of therapy and often prolonged courses of treatment (beyond 2 years).[117,118] Continuing antifungal therapy for several months and/or until immune recovery seems reasonable (grade D recommendation).

Infections from rare and emerging fungi

Background

There is increasing evidence that invasive fungal infections caused by filamentous pathogenic fungi, other than *Aspergillus*, *Scedosporium* and *Fusarium* species, and the Mucormycetes, are increasing.

Many of these fungi have limited pathogenic potential in the healthy host. Profound and prolonged immunosuppression that may accompany more aggressive treatment regimens for cancer chemotherapy and organ transplantation increases the risk of infection with these fungi. Furthermore, broad-spectrum antifungal prophylaxis may select for less common fungi, which may be intrinsically resistant to agents used for prophylaxis.

The causative fungi fall within two broad categories: the hyalohyphomycetes and the phaeohyphomycetes. Besides *Scedosporium* and *Fusarium* species, less common hyalohyphomycete pathogens include *Paecilomyces* species and *Acremonium* species.[132] Emerging pathogens in this group include *Trichoderma*[133–135] species and, more recently, *Geosmithia argillacea*[136,137] and *Schizophyllum commune*.[138]

Phaeohyphomycetes are distinguished by the production of melanin in cell walls, resulting in dark pigmentation of the fungal colonies. Multiple species are reported to cause invasive human infection, including case clusters; however, the most commonly isolated species include *Bipolaris*, *Cladophialophora*, *Exophiala* and *Alternaria* species.

Pneumonia and disseminated disease (with isolation of the fungi from blood cultures) are the more common clinical manifestations of infection.[139] However, as with other moulds, some infections involve the sinuses, skin and occasionally other organs, such as the brain and eye.

Diagnosis usually requires obtaining specimens (e.g. tissue, bronchoalveolar lavage) for culture and fungal

Table 2 Recommended antifungal therapy for treatment of invasive mould infections

Clinical setting	First-line agent (grade of recommendation)	Comments
Aspergillosis†		
Invasive pulmonary or extrapulmonary aspergillosis	Voriconazole (B) or Liposomal amphotericin B (C)	Caspofungin has demonstrated some efficacy (D). TDM advised with azoles
IA with an *Aspergillus* species known to be resistant to amphotericin B	Voriconazole (D)	Includes *Aspergillus terreus* and *Aspergillus nidulans* TDM advised with azoles
IA with suspected or proven azole resistance	Liposomal amphotericin B (D)	IA developed while receiving mould-active azole prophylaxis; high MIC to mould-active azoles on formal susceptibility testing
Refractory or salvage therapy	Liposomal amphotericin B (D) or Posaconazole (D) or Caspofungin (D)	There is limited evidence for the role of combination therapy.
Mucormycosis		
First-line therapy	Liposomal amphotericin B (B)	Monitor renal function Higher initial doses (5–10 mg/kg IV, daily) in CNS or disseminated disease
Second-line therapy (salvage or maintenance)	Posaconazole‡ (C)	TDM advised with azoles Once drug levels at steady state, change dosing schedule to 400 mg orally, 12-hourly
Fusarium		
Fusarium species	Voriconazole *or* a liposomal amphotericin B depending on exposure to previous antifungal therapy and patient tolerability (D) Posaconazole is an option for salvage therapy (D).	Reverse immune suppression where possible (D) Debride infected tissue (D)
Scedosporium		
Scedosporium prolificans *Scedosporium apiospermum*	Commence voriconazole with terbinafine (D) Voriconazole (D)	Use susceptibility testing when available to guide antifungal use (D). Synergy may exist for other combinations of drugs. Reverse immune suppression where possible; CSF use may be of benefit (D). Debride infected tissue (D)
Rare and emerging fungi		
Paecilomyces lilacinus	Voriconazole, posaconazole§ (D)[142]	
Paecilomyces variotii	Posaconazole (D)[143]	
Acremonium species	Voriconazole, amphotericin B§ (D)[132,144,145]	
Trichoderma species	Data limited (D)[133–135]	
Geosmithia argillacea	Echinocandins, posaconazole (D)[136,137]	
Phaeohyphomycetes¶ (*Bipolaris*, *Alternaria Cladophialophora* and *Exophiala* species)	Itraconazole, voriconazole, posaconazole (D)[146,147]	

†See text for recommendations for management of CNS and renal tract disease. ‡Intravenous preparation became available at time of writing for compassionate use. §Alternative agent to be considered, depending on antifungal susceptibility results.
¶Combination antifungal therapies have been used, although the optimal combinations are unknown. CNS, central nervous system; CSF, cerebrospinal fluid; IA, invasive aspergillosis; IV, intravenous; MIC, minimum inhibitory concentration; TDM, therapeutic drug monitoring.

identification. Non-culture-based diagnostic tools, such as the detection of serum galactomannan, lack the specificity to distinguish infection caused by the rare filamentous fungi from the more common causes (such as *Aspergillus* spp.). Molecular methods (amplification and sequencing of conserved fungal ribosomal internal transcribed spacer (ITS) regions) can assist where traditional methods based upon fungal morphology lack discrimination and in culture-negative cases where invasive fungal elements are seen on tissue histopathology.

Obtaining an accurate species identification is important as it allows for some prediction of the pathogen's antifungal susceptibility.

Antifungal therapy for rare and emerging fungi

Information on the treatment of infections caused by rare fungal pathogens is limited to case reports and non-randomised cohort studies, and clinicians should seek expert advice to optimise outcomes. In cases of suspected invasive fungal infection, clinicians should refer to the accompanying consensus guidelines for empiric antifungal therapy by Morrissey *et al*., 2014 (located elsewhere in this supplement).

When choosing an antifungal agent, clinicians should also take into consideration the site(s) of infection and their extent, potential for resection, drug penetration, and, in the case of breakthrough infections, prior antifungal therapy. Where clinical information is limited, choice of antifungal agent is usually extrapolated from *in vitro* susceptibility results. However, the challenges associated with the performance of susceptibility tests, especially outside the reference laboratory setting, as well as limited laboratory-standard guidelines for testing unusual fungi, do complicate the selection of antifungal therapy. Moreover, *in vitro* activity of tested antifungal agents, while providing some guidance, does not necessarily correlate with their *in vivo* efficacy.

The availability of newer-generation triazole antifungals (i.e. voriconazole and posaconazole) has expanded the available treatment options. *In vitro* susceptibility results and clinical experience have shown both voriconazole and posaconazole to be superior monotherapy options for many of the unusual fungal species. Therefore, clinicians should consider early use of the newer triazole agents (grade D recommendation). Therapeutic drug monitoring in those patients receiving voriconazole or posaconazole can assist in cases that are serious and associated with poor prognosis.[140,141]

Echinocandins (e.g. caspofungin, anidulafungin) are not recommended except in those situations where there is high suspicion that *G. argillacea* is the causative pathogen. This fungus causes invasive pulmonary infections, mostly in paediatric patients with chronic granulomatous disease (fungal morphology in cultures is suggestive of this pathogen).[136]

Pathogen-specific recommendations, based upon published experiences where possible, are provided in Table 2.

Combination therapy for rare and emerging fungi

While combination antifungal agents have been used on occasion for difficult cases,[129,133,139,146] there is little current evidence to recommend their routine use, and the optimal combinations are unknown.

Ancillary therapy for rare and emerging fungi

In general, treatment plans should, where possible, include reduction of immunosuppression, debridement of infected tissue and removal of infected devices, as well as antifungal therapy.

Conclusion

IMD is a significant cause of morbidity and mortality in immunocompromised patients. The increasing prevalence of cancer, as well as therapeutic advances leading to improved survival, is placing a growing cohort of patients 'at risk' and for longer periods. Given that these kinds of infections significantly add to the complexity of management, clinicians need to be aware of the treatment options available and the limitations of the current evidence base, particularly for less common and emerging mould infections.

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