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Recommendations for the treatment of established fungal infections

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Abstract

Evidence-based guidelines for the treatment of established fungal infections in the adult haematology/oncology setting were developed by a national consensus working group representing clinicians, pharmacists and microbiologists. These updated guidelines replace the previous guidelines published in the Internal Medicine Journal by Slavin *et al.* in 2004. The guidelines are pathogen-specific and cover the treatment of the most common fungal infections including candidiasis, aspergillosis, cryptococcosis, zygomycosis, fusariosis, scedosporiosis, and dermatophytosis. Recommendations are provided for management of refractory disease or salvage therapies, and special sites of infections such as the cerebral nervous system and the eye. Because of the widespread use newer broad-spectrum triazoles in prophylaxis and empiric therapy, these guidelines should be implemented in concert with the updated prophylaxis and empiric therapy guidelines published by this group.

This section of the guidelines is dedicated to the management of established invasive antifungal infections (IFI) in the adult haematology/oncology setting. Our recommendations are based on the antifungal agents licensed for use in Australia at the time of writing, and are organized according to pathogen.

Where there is a radiological abnormality on computed tomography (CT)/high resolution computed tomography (HRCT) without early microbiological confirmation, clinicians should consider the most common clinical scenario. Microbiological confirmation with histology and/or culture should be pursued in all cases where the patient's clinical status permits additional investigations, such as bronchoscopy and/or biopsy. Newer diagnostic modalities such as polymerase chain reaction (PCR), galactomannan (GM) testing and molecular sequencing, are becoming increasingly available, particularly at specialist centres, and will play an increasing role in identifying probable and proven fungal infections. They are discussed in detail in the previous section of the guidelines by Morrissey *et al.*

When considering the possibility of mould infections, *Aspergillus* is still the most likely organism within the Australasian setting.

Yeasts

Candidaemia and invasive candidiasis (IC)

IC, including candidaemia, is an increasingly common, costly, and potentially fatal infection, particularly among the immunocompromised and critically ill.

Candida albicans accounts for around 50% of invasive *Candida* isolates in Australia, followed by *C. parapsilosis* (20%), *C. glabrata* (15%), *C. tropicalis* (5%), *C. krusei* (4%) and *C. dubliniensis* (2%).[1] Many factors can influence the

epidemiology (and species distribution) of candidaemia. For example, the proportion of candidaemia episodes caused by *C. albicans* is low among haematology patients (31%) but high among intensive care patients (62%).[2] Exposure to fluconazole is associated with an increased likelihood of *C. glabrata* and *C. krusei*,[3–6] whereas total parenteral nutrition and central venous catheters are associated with *C. parapsilosis*.[7] Regional variations also occur,[2] emphasizing the need for clinicians to be aware of local fungal epidemiology when instituting empirical or pre-emptive treatment.

The portal of entry for *Candida* species is generally intravascular devices or the gastrointestinal tract.[8] However, the relative importance of these routes is difficult to ascertain in individual patients.

Despite new antifungal drugs and advances in the supportive management of critically ill patients, candidaemia remains associated with crude and attributable mortalities of 40–70% and 30–50%, respectively, prolonged lengths of stay and excess costs of around USD 40 000 per episode.[2,9–11] All episodes of candidaemia and IC should be considered clinically significant (level III-3 evidence). Antifungal therapy should be initiated as early as possible, as delays in antifungal therapy are associated with poorer clinical outcomes, including increased mortality (level III-3 evidence).[12,13]

The following guidelines address the management of candidaemia and IC in adult patients. We do not provide recommendations for antifungal therapy in children (these are covered elsewhere[14], the treatment of superficial candidiasis (including mucocutaneous candidiasis and oesophageal candidiasis) and candiduria, or early antifungal intervention strategies (such as prophylactic, pre-emptive or empirical therapy) for IC.

The role of laboratory investigations

Traditional culture-based diagnostic techniques are relatively insensitive and slow; however, newer techniques, such as beta-D-glucan and PCR are not sufficiently validated, standardized or routinely available. Accurate identification of an infecting *Candida* species is highly predictive of likely antifungal susceptibility and aids the selection of antifungal agents (see Table 1).[15] Many *Candida* species, including *C. albicans*, *C. parapsilosis* and *C. tropicalis*, are reliably susceptible to fluconazole, whereas others, such as *C. glabrata* and *C. krusei*, display reduced susceptibility or resistance to fluconazole. Antifungal susceptibility testing is increasingly performed in microbiology laboratories on a routine basis, particularly in the setting of IC, and may provide useful clinical information (e.g. when evaluating a failed clinical response or treating infections involving non-*albicans Candida* species).[15] Antifungal susceptibility testing, however, does have limitations, including a relatively slow turnaround time and imperfect clinical correlation. Host immune status and concurrent illnesses, the presence of persistent underlying infective foci and pharmacokinetic parameters all influence clinical outcomes so drug susceptibility does not guarantee clinical success, although drug resistance usually predicts clinical failure.

Evidence-based treatment recommendations

Clinical efficacy of antifungal agents for the treatment of candidaemia and IC

Clinical efficacy data for fluconazole (level I evidence) and voriconazole (level II evidence) in the treatment of IC are available from comparative randomized trials with AmB-D.[16–19] These trials included predominantly non-neutropenic patients with candidaemia (although a minority had neutropenia and/or non-candidaemic IC). Efficacy was assessed by the resolution of the clinical manifestations of IC and negative sterile site cultures. The trial findings were consistent; the triazole had similar – but not superior – efficacy to AmB-D but significantly reduced nephrotoxicity.[19,20] A meta-analysis of trials comparing fluconazole with AmB-D also found no significant differences in efficacy between these two agents across a range of clinical and microbiological outcomes.[20]

The efficacy of echinocandins in IC has been assessed in three published randomized trials (level II evidence): caspofungin versus AmB-D,[21] micafungin versus L-AMB[22] and anidulafungin versus fluconazole.[23] Both caspofungin and micafungin were not inferior to the AmB preparations (AmB-D and L-AMB, respectively) but were associated with significantly less infusion reactions and nephrotoxicity. Anidulafungin was associated with significantly greater clinical and microbiological efficacy than fluconazole in the modified intention-to-treat population. However, anidulafungin's superiority should be interpreted with caution, as a possible study bias could not be excluded. Data from a recent head-to-head comparative trial of two echinocandins (caspofungin at standard doses and micafungin at two different doses: 100 or 150 mg daily) revealed similar clinical and microbiological outcomes across the three treatment arms in the primary intention-to-treat analysis as well as similar safety and tolerability (abstract only).[24]

The lipid-associated AmB preparations for the treatment of IC have not been well studied. Although L-AMB was not inferior to micafungin in a single trial (level II evidence),[22] the success rates associated with L-AMB in the modified intention-to-treat population were similar[18,21] – but in some cases, worse than those

Table 1 Patterns of susceptibility to licensed antifungal agents among the major *Candida* species†

	Amphotericin B	Caspofungin	Fluconazole	Voriconazole
C. albicans	S	S	S	S
C. glabrata	S	S	S-DD to R	S to I
C. krusei	S	S	R	S to I
C. parapsilosis	S	S (‡I)	S	S
C. tropicalis	S	S	S	S

Table adapted from Ostrosky-Zeichner and Pappas, 2006.[58]
†Patterns of susceptibility are based on results of ≥75% of clinical isolates.
‡Intermediate susceptibility is rarely reported.

historically associated with AmB-D.[17,19] The only other comparative data available for a lipid-associated AmB formulation arise from an unpublished trial of amphotericin B lipid complex (ABLC) versus AmB-D; similar outcomes were reported for the two agents (abstract only).[25]

Given the poor outcomes associated with invasive mycoses, combination antifungal therapy in IC remains an area of active interest. Fluconazole combined with AmB-D was compared with fluconazole alone in a randomized trial for the treatment of IC.[26] Although patients randomized to combination therapy had a significantly greater overall success rate and greater clearance of yeasts from blood cultures than those randomized to fluconazole alone, they also had significantly lower baseline APACHE II scores, an important determinant of outcome. Despite this imbalance, this trial demonstrated that the combination of AmB-D and fluconazole was at least as effective as fluconazole alone and dispelled concerns that this combination might exert an antagonistic effect (level II evidence).

A novel approach to combination antifungal therapy for IC was recently reported. A randomized trial exploring the use of either L-AMB or ABLC in combination with human recombinant monoclonal antibody directed against heat shock protein 90 demonstrated significantly greater clinical and microbiological response and significantly less IC-attributable mortality than the lipid-associated AmB preparation alone.[27] Although some concerns have been raised about these trial data,[28] this therapy may herald a promising new approach to the management of IC if the results are confirmed by further trials.

Collectively, these trial data suggest similar efficacy for the treatment of IC, both between and within the polyene, triazole and echinocandin classes,[29] although the latter two classes are significantly better tolerated. The theoretical advantage that fungicidal agents (such as the polyenes or the echinocandins) may have over fungistatic agents (such as the triazoles) has not been realized clinically.

Selecting the initial antifungal regimen – clinical considerations

The potential for infection with an antifungal-resistant Candida *spp.* Given its proven clinical efficacy, low toxicity, relatively low cost and availability for both parenteral and enteral administration, fluconazole justifiably remains the preferred antifungal agent to treat IC in most settings (grade A recommendation).[29] However, susceptibility to fluconazole cannot be fully assumed until species identification and/or antifungal susceptibility testing has been performed. *C. albicans* generally remains susceptible to fluconazole but this is not true of all non-*albicans Candida* species. *C. glabrata*, which ranks among *Candida* spp. as the second or third most common cause of IC,[30,31] often displays reduced susceptibility (generally referred to as susceptible but dose dependent, implying the requirement for increased fluconazole exposure to achieve clinical efficacy[15] or resistance to fluconazole. Other species, most notably *C. krusei*, are intrinsically resistant to fluconazole and require treatment with an alternative agent.

Antifungal therapy tends to be initiated upon – if not prior to – notification from the laboratory that yeasts have been identified by microscopic examination of blood cultures or other sterile site specimen(s). Thus, information regarding species identification and antifungal susceptibility testing is generally unavailable to guide initial antifungal choice. Although clinical factors alone do not accurately predict infection with a non-*albicans Candida* spp. or a fluconazole-resistant *Candida* spp.,[32] local epidemiological patterns of IC, the patient's prevalent colonizing *Candida* spp., and prior azole exposure should be considered when selecting EAFT (grade C recommendation).[6]

Haemodynamically unstable or neutropenic patients. Empirical therapy with a reliably broad-spectrum anti-*Candida* agent, such as an echinocandin should be initiated in patients with IC who are haemodynamically or otherwise

clinically unstable unless there is a strong suspicion of an azole-susceptible pathogen (e.g. recent colonizing flora) (grade C recommendation). In this setting, fungicidal therapy offers theoretical advantages although there are no data to demonstrate superior clinical efficacy of a fungicidal agent (such as a polyene or an echinocandin) over a fungistatic agent (such as a triazole) (grade D recommendation).

Similar considerations exist for neutropenic patients with IC who are often clinically unstable and who are likely to have received antifungal prophylaxis with an azole drug, increasing the likelihood of infection with an azole-resistant pathogen. In such patients, an antifungal agent other than fluconazole is preferred as initial therapy (grade C recommendation).[15]

Patients with renal or hepatic dysfunction. Please refer to the section of the guidelines by Worth *et al.* on p. 521 for a detailed discussion of drug exposure and dose adjustment in the setting of organ dysfunction.

Potential for drug interactions and/or nephrotoxicity. Please refer to the section of the guidelines by Worth *et al.* on p. 521 for a detailed discussion of drug-related toxicity and antifungal drug interactions.

Cost. Oral fluconazole and AmB-D are both relatively cheap. In comparison, the newer agents are 30–90 times more expensive.

Modifying the initial antifungal regimen

Following the initiation of an empirical antifungal regimen for IC, any subsequent clinical and microbiological information should be reviewed to help guide ongoing treatment.

Microbiological data. Within 30–45 min of the detection of yeasts by microscopy from a positive blood culture or other sterile site specimen, a presumptive species identification based on the germ tube result should be available. A presumptive identification of *C. albicans*, based on a positive germ tube test, would support a clinical decision to continue, or change to, fluconazole. On the other hand, a negative result, presumptively a non-*albicans Candida* spp., may indicate – but not necessarily prove – a fluconazole-resistant organism, such as *C. glabrata* or *C. krusei*. Full identification, necessitating a further 24–48 h, is required to confirm or exclude this possibility.

Species identification can, with reasonable accuracy, predict antifungal susceptibility (see Table 1)[15] and should guide clinical decisions regarding the most appropriate antifungal agent. An AmB-D preparation, an echinocandin, or possibly voriconazole would be appropriate for *C. glabrata* or *C. krusei* (grade C recommendation), whereas fluconazole is suitable for most other *Candida* spp. (grade A recommendation). Formal antifungal susceptibility testing will provide further adjunctive information, particularly when the clinical response to a particular regimen has been poor, or when a change to fluconazole from another regimen is contemplated.

It should be noted that antifungal susceptibility testing has only been clinically validated for fluconazole, and not for the polyenes, other triazoles or the echinocandins. Furthermore, reporting of susceptibility does not ensure clinical success, whereas resistance usually predicts failure.

Clinical response parameters. The clinical response should be assessed carefully following the initiation of any antifungal regimen. A lack of improvement in haemodynamic parameters, temperature, other systemic or local clinical signs of infection, white cell count, or other inflammatory parameters, should prompt consideration of several important possibilities: antifungal resistance, persistence or development of an intravascular or deep infective focus, or the effects of underlying immunosuppression. In these circumstances, the routine removal of all potentially infected intravascular catheters, discussed in more detail later, is generally advocated. A poor clinical response also demands a thorough clinical search for potential intravascular foci, such as intravascular catheters, vascular grafts or heart valves, or other deep foci, such as hepatosplenic lesions, osteomyelitis, undrained collections or seeding of prosthetic material. In this setting, the routine collection of follow-up blood cultures to document persistent or breakthrough candidaemia can provide valuable information.

If the clinical response to an initial regimen of fluconazole is suboptimal, we recommend changing to a broader-spectrum agent, such as a polyene or an echinocandin, while investigating for persistent deep infective foci and await species identification and/or results of antifungal susceptibility tests (grade D recommendation). However, the time frame over which a favourable clinical response should be expected has not been clearly defined.

Where the clinical response to fluconazole *is* satisfactory and the pathogen is subsequently identified as *C. glabrata*, fluconazole may still be appropriate therapy. Several studies report similar clinical outcomes when fluconazole is used to treat candidaemia due to *C. albicans* and other fluconazole-susceptible *Candida* species as well as candidaemia due to *C. glabrata*.[33,34] Indeed, a significant proportion of *C. glabrata* isolates demonstrate *in vitro*

susceptibility to fluconazole[35] while isolates with reduced susceptibility may be adequately treated with a higher dose (e.g. 12 mg/kg/day) (grade C recommendation).[15]

On the other hand, a poor clinical response to fluconazole in the setting of *C. glabrata* or the identification of *C. krusei*, regardless of clinical response, should prompt a change to an alternative agent (grade C recommendation).

Ancillary management decisions

Routine removal of intravascular catheters. There are no randomized trials evaluating the benefit of routine vascular catheter removal as ancillary management of candidaemia, though limited observational data suggest it may have a mortality benefit.[36] Intravascular catheters, however, are strongly associated with *C. parapsilosis* infection[7] and should be promptly removed if a patient returns positive isolates for this species (grade D recommendation).

The removal of vascular catheters has also been shown to expedite the clearance of *Candida* species from the blood[37] although *post hoc* observational data from randomized trials have failed to demonstrate any clinical benefit.[21,22,26] Despite these conflicting findings, the early removal of vascular catheters – where possible – is generally advocated in the setting of candidaemia (grade C recommendation).[15,38,39]

Follow-up blood cultures. Persistent or breakthrough candidaemia may occur with a persistent infective focus (such as an infected intravascular device, endocarditis or a collection), significant immunosuppression or a resistant organism.[40,41] In these circumstances, follow-up blood cultures may provide potentially important information and help inform clinical decision making (grade C recommendation).

Routine ophthalmological examination. Ophthalmological examination should be routinely performed to detect candidal endophthalmitis (grade C recommendation).[42] Non-specific retinal lesions are found in 10–20% of candidaemic patients;[43] whether such lesions represent underlying comorbid conditions or candidal chorioretinitis is best determined by serial ophthalmological examination through dilated pupils, preferably by an ophthalmologist. The optimal timing of ophthalmological examination has not been defined, but expert opinion suggests an examination should be performed after initial control of the candidaemia (grade D recommendation).[15]

Duration of therapy

There are no prospective data on the optimal duration of therapy for IC.[44] For candidaemia, expert opinion generally recommends treatment for 14 days following the last positive sterile site culture or following resolution of clinical features of infection[15] and has been the approach adopted in most comparative trials (grade C recommendation).[17,19,21,26] There is even less experience for other forms of IC: expert opinion recommends similar durations for peritonitis, and 6 weeks or longer, for difficult-to-treat deep foci such as endocarditis, endophthalmitis, mediastinitis or osteomyelitis (grade D recommendation).[15]

Route of administration of antifungal therapy

The IV route is preferred for the initiation of antifungal therapy to ensure that adequate blood and tissue levels are achieved. Following a satisfactory clinical and microbiological response, changing from IV to oral antifungal therapy is appropriate – assuming a susceptible organism to the oral agent, a functioning gastrointestinal tract and a reasonable expectation of compliance (grade B recommendation).

Invasive candidiasis in difficult sites

Hepatosplenic (chronic disseminated) candidiasis. Hepatosplenic candidiasis is generally encountered in the context of myeloablative chemotherapy and prolonged neutropenia. The optimal antifungal regimen remains undefined, although experience with AmB-D with or without 5-flucytosine (5-FC), fluconazole, lipid-associated AmB preparations and caspofungin has been reported (all level IV evidence). Prolonged antifungal therapy over several months is required, and should be continued until radiological resolution has been achieved and until further episodes of intensive myeloablative or immunosuppressive therapies have been completed (grade D recommendation).

Central nervous system disease. Most data in this clinical setting are based on observational reports of AmB-D.[45,46] AmB-D 0.7–1 mg/kg/day plus 5-FC 25 mg/kg four times a day is recommended as initial therapy for central nervous system (CNS) candidiasis (grade D recommendation). 5-FC is often added to the treatment course due to its ability to penetrate the blood–brain barrier.[47] This combined regimen allows the administration of amphotericin B at lower doses and for a shorter duration, minimizing its nephrotoxicity. However, the use of 5-FC is limited by its myelotoxicity in patients with haematological malignancies.

L-AMB, 3 mg/kg/day, is an alternative to AmB-D. L-AMB has better penetration into brain tissue in animal models than other lipid formulations of amphotericin.[48]

Table 2 Summary of recommendations for antifungal therapy in adult patients with candidaemia or invasive candidiasis

Clinical setting	Recommended antifungal therapy† (Grade of recommendation)	Alternative agents† (Grade of recommendation)
Candidaemia or invasive candidiasis involving unknown or yet to be identified *Candida* species: not haemodynamically unstable, not neutropenic, and no risk factors associated with azole-resistant *Candida* spp.	Fluconazole (A)	Caspofungin (B) OR Voriconazole (B) OR Lipid-associated formulation of amphotericin B (C) OR Amphotericin B deoxycholate (A)
Candidaemia or invasive candidiasis involving unknown or yet to be identified *Candida* species: haemodynamically unstable, neutropenic, or risk factors associated with azole-resistant *Candida* spp.	Caspofungin (B) OR Lipid-associated formulation of amphotericin B (C)	Voriconazole (B) OR Amphotericin B deoxycholate (A)
Candidaemia or invasive candidiasis involving *Candida* species known (or likely) to be susceptible to fluconazole	Fluconazole (A)	Caspofungin (B) OR Voriconazole (B) OR Lipid-associated formulation of amphotericin B (C) OR Amphotericin B deoxycholate (A)
Candidaemia or invasive candidiasis involving *Candida* species known (or likely) to be resistant to fluconazole	Caspofungin (B) OR Lipid-associated formulation of amphotericin B (C)	Voriconazole (B) OR Amphotericin B deoxycholate (B)

†See Table 3 for recommended doses.

While voriconazole has good cerebrospinal fluid (CSF) and brain tissue penetration,[49] there are limited data reported for its use in CNS infections due to *Candida* spp. Fluconazole penetrates the blood–brain barrier better than AmB-D but is less able to sterilize CSF and eradicate brain parenchymal infection.[50]

Due to the high risk of relapse, treatment should be continued for at least 4 weeks after resolution of CSF findings, radiological signs and neurological symptoms (grade D recommendation).[50]

Endophthalmitis. *Candida* spp. are the most common cause of fungal endophthalmitis. Treatment requires systemic antifungal therapy and surgical debridement (vitrectomy) with intra-vitreal antifungal therapy (amphotericin B, 10 μg) if vitritis is present.

Amphotericin B plus 5-FC is recommended for first-line systemic therapy (grade D recommendation).[51] L-AMB, fluconazole and voriconazole are alternative agents (grade D recommendation).[52–57]

A summary of our recommendations, based on the above evidence and antifungal agents approved for use in Australia as of October 2006, is presented in Table 2. Recommended doses for the various antifungal agents are listed in Table 3.

Cryptococcus

Cryptococcosis is typically associated with T-lymphocyte deficiency, especially acquired immune deficiency syndrome (AIDS). Although cryptococcal disease is uncommon in haematopoietic stem cell recipients (HSCT) recipients and patients with solid organ malignancy,[59] underlying haematological malignancies, especially Hodgkin lymphoma disease, chronic lymphocytic leukaemia

Table 3 Recommended doses of licensed antifungal agents for *Candida*†

Agent	Preparation	Recommended dose
Amphotericin B deoxycholate	IV	0.6–1.0 mg/kg daily
Liposomal amphotericin	IV	3–5 mg/kg daily
Amphotericin B lipid complex	IV	3–5 mg/kg daily
Fluconazole	Oral, IV	400 mg (6–12 mg/kg) daily
Voriconazole	Oral, IV	6 mg/kg every 12 h for 24 h, then 4 mg/kg every 12 h
Caspofungin	IV	70 mg daily for 24 h, then 50 mg daily

†Also see full Product Information. IV, intravenous.

and non-Hodgkin lymphoma, account for 15–40% of cases in HIV-negative patients.[59–61]

Pulmonary disease is more likely to manifest as interstitial or alveolar infiltrates in the immunocompromised host rather than as mass lesions (which is characteristic of infection in the immunocompetent patient).[60] This finding is consistent with failure of the host immune response to contain the infection.

Disseminated infection involving the CNS, skin or other sites, is relatively common.[59,60,62] Thus, regardless of clinical presentation, the extent of dissemination should be established early by obtaining sputum, blood, urine and CSF cultures, testing for cryptococcal antigen in the serum and CSF and performing a cerebral CT or magnetic resonance imaging (MRI).

Relapse of CNS infection occurs in approximately 4% of immunosuppressed, HIV-negative patients despite consolidation therapy and is not always culture-positive.[62] This observation raises the possibility that the response to antifungal therapy may be associated with an immune reconstitution inflammatory syndrome (IRIS)-like illness, similar to that observed in organ transplant recipients and patients with AIDS.[63,64]

Antifungal susceptibility testing is not routinely recommended for cryptococcosis, as primary resistance is rare and correlations between the minimum inhibitory concentration and clinical response have not been established.[65] Susceptibility testing may be useful, however, in cases of relapse, if primary therapy has failed and in patients presenting with cryptococcosis after receipt of prolonged therapy with fluconazole.

Evidence-based treatment recommendations

The choice of antifungal treatment for cryptococcal disease depends on both the anatomical sites involved and the immune status of the host. All HIV-negative, immunocompromised hosts should be treated as for CNS cryptococcosis, regardless of the site of involvement, because of the likelihood of dissemination (see recommendations below). The concept of induction (to rapidly reduce the cryptococcal burden), consolidation (to remove residual fungi) and maintenance therapy (to prevent relapse) was first introduced[66] and validated[67] by random controlled trials (RCT) in patients with AIDS (level II evidence). These studies form the basis of the recommendations below (see Table 4 for summary).

CNS and disseminated cryptococcosis

Amphotericin B (≥0.7 mg/kg/day) plus 5-FC (100 mg/kg/day) for 2 weeks (induction therapy), followed by

Table 4 Summary of recommendations for the treatment of cryptococcosis

Clinical setting	Recommended first-line antifungal therapy (Grade of recommendation)	Alternative agents (Grade of recommendation)	Comments
CNS and disseminated cryptococcosis	Induction therapy: AmB-D ≥0.7 mg/kg/day plus 5-FC 100 mg/kg/day for two weeks (B) Consolidation therapy: fluconazole 400 mg/day for 8–10 weeks (B) Suppressive therapy: fluconazole 200 mg/day for 6–12 months (B)	Induction therapy: AmB-D alone (B) Third line: 5-FC 100 mg/kg/day plus fluconazole 800 mg/day (B)	L-AMB may be substituted for AmB-D in cases of renal dysfunction. Monitor EUC, LFTs, FBC if patient receives 5-FC for >2 weeks. Measure serum 5-FC levels 2 h post-dose. Adjust dose to maintain serum level between 30–80 mg/L.[75] Induction therapy with fluconazole alone is generally not recommended due to relatively slow responses (D)[73,83]
Isolated, asymptomatic or mildly symptomatic pulmonary disease, not severely immunosuppressed	Fluconazole 400 mg/day for 6–12 months (D)		Treat because of high risk of dissemination
Relapse of CNS disease	Re-induction with AmB-D 0.7 mg/kg/day plus 5-FC 100 mg/kg/day (D); consolidation therapy with fluconazole 600–800 mg/day (D)	If unable to tolerate AmB-D formulation: 5-FC plus fluconazole 800 mg/day (D) OR High-dose fluconazole (800 mg/day)	Consider increasing AmB-D to 1 mg/kg/day or L-AMB to 5 mg/kg/day (D)

5-FC, flucytosine; AmB-D, amphotericin B deoxycholate; CNS, central nervous system; EUC, electrolyte and creatinine; FBC, full blood count; L-AMB, liposomal amphotericin B; LFTs, liver function tests.

fluconazole (400 mg/day) for 8–10 weeks (consolidation therapy) and then followed by a lower dose of fluconazole (200 mg/day) for 6–12 months (suppressive therapy), is recommended to treat the immunocompromised host with disseminated disease or CNS involvement (grade B recommendation).

If AmB-D is contraindicated because of nephrotoxicity, L-AMB is the best alternative for induction therapy although the optimal dose of L-AMB is yet to be established. A single RCT compared L-AMB, 4 mg/kg/day, with AmB-D, 0.7 mg/kg/day; L-AMB resulted in significantly earlier sterilization of the CSF and reduced nephrotoxicity compared with AmB-D although the overall efficacy of the two drugs was similar (level II evidence).[68] A larger study (published in abstract form only), showed no improvement in CSF sterilization with L-AMB, 3 or 6 mg/kg/day, compared with AmB-D, 0.7 mg/kg/day (level III-1 evidence).[69] A L-AMB dose of 3–4 mg/kg/day, therefore, is recommended (grade C recommendation).

Induction therapy may be continued for another 2–4 weeks ('extended induction therapy'), depending on clinical response, if one or more poor prognostic factors are present, or for another 4–8 weeks if the patient is unable to tolerate 5-FC or its use is contraindicated (e.g. in the presence of marrow failure).[68,70,71] Poor prognostic factors include haematological malignancy, reduced mental status, neurological signs or abnormal brain imaging at presentation, renal or liver failure,[62] culture-positive CSF at 2 weeks, high cryptococcal load at presentation (CSF and serum antigen titres >1:512) and disseminated disease.[59,61,62,72]

Options for salvage therapy in patients with persistent cryptococcosis include increasing the dose of AmB-D, adding fluconazole (e.g. 800 mg/day) (P.G. Pappas *et al.*, unpubl. data) or trialling a combination of fluconazole 400–800 mg/day and 5-FC 100 mg/kg/day (note: this combination may induce toxicity).[73,74]

Itraconazole 200 mg/day may be used for consolidation or maintenance therapy in individuals who cannot tolerate fluconazole (grade C recommendation).[66]

Cryptococcal pneumonia

Patients who present with localized pneumonia and mild-moderate symptoms without severe immunosuppression may be treated with an azole antifungal, preferably fluconazole 400 mg/day, for 6–12 months (grade C recommendation).[62,75,76] Those with severe immunosuppression or diffuse infiltrates should be treated as for CNS cryptococcosis (see recommendations above) (grade D recommendation).

Ancillary therapy

In addition to systemic antifungal therapy, clinicians should aim to minimize immunosuppression; reducing the dose of prednisolone (or its equivalent) to 10 mg/day, if possible, may result in improved outcomes.[75]

Intracranial pressure (ICP) should be closely monitored in patients with cryptococcal meningoencephalitis. The management of elevated ICP in this setting is discussed elsewhere.[75,77]

Treatment of CNS relapse

For the purpose of these guidelines, relapse is defined as the recurrence of clinical symptoms or a positive cryptococcal culture after cessation of initial therapy or during receipt of maintenance fluconazole. Cerebral imaging should be performed to rule out hydrocephalus, cerebral oedema or cerebral infarct, followed by CSF examination. If the CSF culture is negative, an increase in the CSF cryptococcal antigen titre is consistent with relapse. IRIS should be considered in culture-negative patients with no demonstrated rise in CSF cryptococcal antigen titres if immunosuppressive therapy has recently been reduced or ceased.[63,64]

Patients with relapsed cryptococcosis should receive re-induction therapy with AmB-D plus 5-FC followed by higher doses of fluconazole (600–800 mg/day) for consolidation therapy (grade D recommendation).[78–80] Voriconazole (200–400 mg bd)[81] or posaconazole (200 mg qid or 400 mg bd)[82] for 10–12 weeks may also be suitable for salvage therapy (grade D recommendation).

There are no prospective data to support recommendations for the treatment of IRIS. Short-term anti-inflammatory therapy is indicated in those patients presenting with major manifestations of IRIS (e.g. CNS inflammation or significant inflammatory reactions elsewhere). Case reports have documented success with steroids (0.5–1 mg/kg prednisolone equivalent dose) and non-steroidal anti-inflammatory agents (level IV evidence).[63,64]

Aspergillus and other moulds

Invasive aspergillosis

IA is an important cause of morbidity and mortality in immunocompromised patients, particularly patients with haematological malignancy and transplant recipients. While the incidence of IA has decreased with changes in transplantation practices, improved diagnostic strategies, the introduction of antifungal prophylaxis and better supportive care of high-risk patients (e.g. acute

leukaemia and allogeneic stem cell transplantation),[84] the overall mortality rate for IA remains high, approaching 90% in stem cell recipients and patients with cerebral or disseminated IA.[85]

IA commonly affects the respiratory tract (including the sinuses) but may also cause disseminated and CNS disease. Angioinvasion, haemorrhagic infarction and intra-alveolar haemorrhage are often seen in neutropenic and HSCT patients, whereas inflammatory necrosis is predominant in non-neutropenic patients.[86] IA is usually categorized as acute (<1 month disease before diagnosis), subacute (>1 month disease before diagnosis) or chronic (>3 months disease before diagnosis).[87]

Aspergillus fumigatus accounts for approximately half of all isolates. *A. flavus*, the second most common isolate, causes chronic granulomatous sinusitis, keratitis and cutaneous disease, as well as wound infections and osteomyelitis following trauma.[88] *A. terreus* is less commonly isolated, often in nosocomial outbreaks, but is noteworthy for its refractoriness to amphotericin B therapy.[89]

Major risk factors for IA include prolonged neutropenia, corticosteroid use, HSCT and solid organ transplantation, moderate to severe graft versus host disease (GVHD), cytomegalovirus infection, gancyclovir therapy, iron overload[90] and systemic immunosuppression.[91,92,93,94,95]

The current guidelines provide recommendations for the treatment of proven, probable or possible IA in patients with malignancy. They are not intended to provide detailed information on the pathogenesis or diagnosis of IA. Please refer to the section of the guidelines by Morrissey *et al.* on p. 477 for information on diagnostic strategies.

Evidence-based treatment recommendations

Initial therapy

IA should be treated promptly and aggressively and many clinicians advocate commencing antifungal treatment upon first suspicion of disease. Any empirical or prophylactic therapy being used at the time of diagnosis will influence the initial choice of antifungal agent.

For decades, AmB-D was considered the standard antifungal agent for the treatment of IA. It is now recognized that voriconazole is superior in efficacy to AmB-D for the primary treatment of IA (level II evidence); in a large, well-conducted, randomized trial comparing voriconazole and AmB-D for the primary treatment of acute IA, voriconazole led to better responses (53% versus 32%) and improved survival (71% versus 58%) at 12 weeks. Voriconazole was also better tolerated than AmB-D. This study has been criticized, however, as the median duration of treatment was 77 days in the voriconazole arm compared with 10 days in the AmB-D arm,[96] although patients who switched from AmB-D to other licensed antifungal agents, including L-AMB, also did worse.[97]

Infection with amphotericin-resistant species

A. terreus and *A. nidulans* are both resistant to amphotericin B.[89,98] Voriconazole is recommended as first-line therapy for these infections (grade D recommendation).

CNS, eye and extrapulmonary disease

Conventional amphotericin B (AmB-D) is not recommended for cerebral aspergillosis (grade D recommendation). Case reports, however, have cited success with lipid formulations of amphotericin B,[99] itraconazole[100] and voriconazole.[101,102] As more experience has been cited with voriconazole in this setting, this agent is recommended as first-line therapy (grade D recommendation).

Fungal endopthalmitis due to *Aspergillus* species requires systemic antifungal therapy (voriconazole or L-AMB), surgical debridement (vitrectomy) and intravitreal antifungal therapy.[103]

Alternative treatment options when voriconazole cannot/should not be used

While voriconazole has good bioavailability and an acceptable toxicity profile,[104] its clinical use can be limited by its potential for drug interactions and drug-related hepatotoxicity (see the topic section by Worth *et al.* on p. 521 for further details). Alternative agents for the treatment of IA are discussed below.

The choice of agent will depend on host factors such as antifungal prophylaxis history and risk of nephrotoxicity and zygomycosis. For example, a lipid formulation of amphotericin B is recommended as first-line therapy for patients with diabetes, iron overload or an infection involving the sinuses or eye, as these patient groups are at a higher risk of zygomycosis.

Conventional amphotericin B. AmB-D has been used extensively in the treatment of aspergillosis with an overall efficacy of approximately 32%. Its narrow therapeutic window and attendant toxicities, however, are well recognized; a 2-week course will lead to infusion-related toxicity in around 60% of patients and renal impairment in 80% of patients.[105]

Although there are strategies to manage these toxicities (e.g. saline loading, potassium-sparing diuretics and premedication with antihistamines, steroids and pethidine),

AmB-D is still often poorly tolerated, particularly in patients requiring prolonged, high-dose (above 0.5 mg/kg/day) courses.

Nephrotoxicity may be irreversible in patients with multiple risk factors for renal impairment and can have a dramatic impact on secondary costs (morbidity, mortality and length of stay).[106] Studies have shown that continuous infusion may reduce the risk of nephrotoxicity and infusion reactions; however, these studies were not powered to evaluate efficacy as well (level II evidence).[107,108]

There is no evidence to support the use of doses greater than 1.5 mg/kg/day.

Lipid formulations of amphotericin B. Lipid formulations of amphotericin B allow higher doses of amphotericin to be given compared with AmB-D. Liposomal formulations are likely to be at least as efficacious as AmB-D (with response rates averaging approximately 50%) but have a more favourable safety profile. Lipid forms of amphotericin B are therefore recommended for patients at high risk of nephrotoxicity (grade B recommendation).

Two underpowered RCTs have compared conventional amphotericin with lipid preparations in probable or proven IA. The first study compared Ambisome® 5 mg/kg/day with AmB-D 1 mg/kg/day for the first-line treatment of IA. Response rates were 50% and 27%, respectively, after 14 days.[109] The other study compared ABLC 6 mg/kg/day with AmB-D 1–1.5 mg/kg/day; response rates were 52% and 51%, respectively. While the rate of renal toxicity was lower and time to onset of nephrotoxicity longer in the ABLC group, the rate of infusion-related reactions was high (53%).[110]

For predominantly pulmonary IA, 3 mg/kg/day of low-dose L-AMB is as effective as higher doses (10 mg/kg/day) (level II evidence)[111] and has a lower incidence of nephrotoxicity and hypokalaemia.

Lipid formulations of amphotericin B should be considered for patients:

- With existing renal impairment
- Who have received, or are likely to proceed to, an allogeneic SCT (these patients are five times more likely to develop nephrotoxicity)
- Who have previously or are currently receiving two or more nephrotoxic agents (e.g. cyclosporin, aminoglycosides)[112]
- Who have received prolonged therapy with high-dose AmB-D
- With an underlying disease state associated with renal impairment (e.g. diabetes, sepsis)[113]

Echinocandins. The echinocandins are active, both *in vitro* and *in vivo*, against *Aspergillus* species. Caspofungin was the first agent in the echinocandins class to be studied for the treatment of IA. The first clinical study, a study of 83 patients with proven or probable IA who were refractory to, or intolerant of, standard anti-*Aspergillus* therapy, reported an overall response rate of 41%.[114]

A more recent study evaluating caspofungin as first-line therapy of proven or probable pulmonary IFI in 32 consecutive patients with a haematological malignancy reported a response rate of 58%.[115]

We recommend caspofungin as an alternative agent for the treatment of IA in subjects intolerant or refractory to voriconazole and/or AmB-D (grade D recommendation).

Posaconazole. One open-label, multicentre study evaluated posaconazole as monotherapy in patients with IA and other mycoses who were refractory to or intolerant of conventional antifungal therapy.[116] The overall success rate was 42% for posaconazole recipients versus 26% for control subjects. Posaconazole has also demonstrated activity against *Aspergillus* species refractory to other triazoles.[117]

While posaconazole has not been studied as initial therapy for IA, the above results demonstrate that posaconazole is an alternative to salvage therapy for patients with IA who are refractory to, or intolerant of, previous antifungal therapy (grade D recommendation).

IA and other IFI after mould-active prophylaxis

Breakthrough IA is uncommon with mould-active prophylaxis – occurring in approximately 1% of patients receiving posaconazole[118] and in 1–2% of patients receiving voriconazole.[119,120] Zygomycoses and other non-*Aspergillus* mould infections have also been reported in patients receiving voriconazole or posaconazole prophylaxis.[120–123]

The possible causes of a breakthrough infection include subtherapeutic levels of prophylactic voriconazole or posaconazole and resistance to triazoles. Intra-patient variability in drug levels and drug exposure is well documented with triazoles and may be influenced by concomitant drugs or malabsorption due to mucositis or ileus. In such cases, drug levels may be suboptimal and should be measured to ensure adequate prophylaxis.[124] (Please refer to the section of the guidelines by Worth *et al.* on p. 521 for further detail.)

Resistance of *A. fumigatus* clinical isolates to triazoles has been reported with increasing frequency and the genetic mechanism identified. This may also cause prophylaxis to fail; however, the clinical significance of this is still uncertain.[122]

If an IFI is suspected in a patient receiving prophylactic azole therapy (with adequate serum levels documented),

a lipid formulation of amphotericin B (5 mg/kg/day) is recommended as first-line therapy (grade C recommendation). The identity of the organism should be actively pursued with bronchoalveolar lavage (BAL), biopsy or resection. However, diagnostic tests such as the GM enzyme immunoassay should be interpreted with caution as mould-active agents may decrease their sensitivity.[125]

Refractory disease and salvage therapy

Patients are considered refractory to initial antifungal therapy if there is worsening of two or more of the following response criteria after at least seven days of therapy: clinical, radiologic and/or mycologic (persistence of positive cultures).[126] However, evaluation of response to therapy in IA is difficult for several reasons. There may be multiple reasons why an immunocompromised patient has a persistent fever or other signs that suggest infection. Moreover, localized signs and symptoms of fungal infection may be blunted by immunosuppressive agents (e.g. corticosteroids) or by the underlying immunodeficiency.[126] Serial radiological imaging in proven *Aspergillus* infection will always become worse before it improves, usually after 9–14 days; both the number and size of the lesions may increase, making it difficult to imply treatment failure in the first 2 weeks of treatment on radiological grounds alone.[127,128]

Options for salvage therapy include posaconazole, lipid forms of amphotericin B or caspofungin. The response rates for salvage therapy (posaconazole,[116] caspofungin,[114] lipid formulations of amphotericin[129] or combination therapy; see discussion below) are all around 40%.

Salvage therapy studies should be interpreted with caution for several reasons.[126,130] Prior therapy is likely to impact on the response to the new agent, particularly if slow release from tissue depots is a feature of the previous drug (e.g. lipid formulations of amphotericin B). Furthermore, only patients who have survived initial therapy can enter salvage therapy trials; for this reason alone, patients may be more likely to achieve a positive outcome. Likewise, while immunity may improve over time, many salvage studies do not take into account the role of neutrophil recovery when interpreting results.

Combination therapies

Despite the development of new classes of antifungal agents with novel mechanisms of action, the clinical outcome of proven IFIs, particularly in immunocompromised hosts, remains unsatisfactory. While there is growing enthusiasm for the potential use of combination antifungal therapies, clinical data do not consistently support the superiority of any particular antifungal combination for the treatment of patients with proven or probable IA. Furthermore, retrospective comparisons and non-contemporaneous cohorts limit what may be interpreted from these reports. There is only one published prospective randomized trial of combination therapy. In this phase 3 trial, 18 patients with proven IA were randomized to receive AmB-D 0.5 mg/kg/day, with or without 5-FC.[131] The study was prematurely terminated due to poor outcomes; only one patient in the AmB-D arm and two in the combination arm survived.

In a review of the published literature up to 2001, Steinbach *et al.*, identified 128 reports of combination antifungal therapy.[132] The most frequently reported combinations (reflective of antifungal use pre-2001) were: AmB-D and 5-FC (49%), AmB-D and itraconazole (17%) and AmB-D and rifampicin (11%). Sixty-four per cent of patients (n = 249) on combination therapy were reported to have improved. This figure is higher than the usually quoted 34% response rate for monotherapy; however, variable or unspecified criteria were used to assess the response to combination treatment.

More recently, several case series have reported variable responses to combinations of voriconazole, lipid formulations of amphotericin and the echinocandins. In summary, voriconazole and caspofungin in combination resulted in better survival at 3 months compared with voriconazole alone, but this finding did not persist at 12 months.[133] Addition of itraconazole to L-AMB showed no benefit over historical controls treated with L-AMB alone,[134] while addition of caspofungin to L-AMB for progressive IA resulted in a limited response rate of 18%.[135] A 35% overall response rate was reported when micafungin was added to standard antifungal therapies to treat refractory IA in paediatric and adult MBT recipients.[136]

In conclusion, there is currently no evidence that combination therapies provide any additional benefit over optimal doses of voriconazole or L-AMB used as monotherapy for primary or salvage therapy.

Duration of therapy

There is no evidence to support a pre-specified duration of therapy for IA although many trials assess response to treatment at 12 weeks. Continuing antifungal therapy for several months, in combination with serial radiological imaging, seems reasonable.

Patients who have recovered from an episode of IA should receive secondary prophylaxis with a mould-active agent if further immunosuppression is anticipated (grade C recommendation).[137] Please refer to the section of the guidelines by Slavin *et al.* (pp 468–476) for further details.

Table 5 Summary of recommendations for the treatment of definite, probable and possible invasive aspergillosis

Clinical setting	Recommended first-line antifungal therapy (Grade of recommendation)	Alternative agent	Comments
Invasive pulmonary aspergillosis	Voriconazole IV 6 mg/kg bd for 24 h (loading dose) then 4 mg/kg IV bd or 200–300 mg po bd (maintenance) (B)	Liposomal amphotericin 3 mg/kg/day (B) OR Conventional amphotericin (AmB-D) 1.0–1.5 mg/kg/day (C)*	Caution with voriconazole if concomitant use of cytochrome P450 inducers, vinca alkaloids, tacrolimus or significant hepatic dysfunction. Conventional amphotericin should be avoided in patients at risk of nephrotoxicity, or with pre-existing renal impairment
Infection with *Aspergillus* isolates known to be amphotericin resistant	Voriconazole IV 6mg/kg bd for 24 h (loading dose) then 4 mg/kg IV bd or 200–300 mg po bd (maintenance) (D)		Amphotericin B resistant isolates include *A. terreus*, *A. nidulans*, *A. ustus*
CNS or disseminated disease	Voriconazole IV 6 mg/kg bd for 24 h (loading dose) then 4 mg/kg IV bd or 200–300 mg po bd (maintenance) (D) An intra-vitreal injection of amphotericin (10 μg) is recommended for endopthmalmitis (D)	L-AMB 3 mg/kg/day (D)	L-AMB is preferred due to its ability to achieve higher concentrations in the blood and brain than amphotericin B and its other lipid formulations
Refractory or salvage therapy	Lipid form of amphotericin 3 mg/kg/day (C) Caspofungin 70 mg loading dose then 50 mg/day (C) Posaconazole 200 mg po qid (C)		Posaconazole can be dosed at 400 mg po bd after 7–10 days
Development of suspected IFI while receiving voriconazole or posaconazole prophylaxis	Lipid form of amphotericin B 5 mg/kg/day (D)		

AmB-D, amphotericin B deoxycholate; CNS, central nervous system; IFI, invasive fungal infection; IV, intravenous; L-AMB, liposomal amphotericin B; po, oral.

Please see Table 5 for a summary of these recommendations.

Zygomycosis

Zygomycosis is an opportunistic infection caused by saprophytic fungi of the class *Zygomycetes*, which are typically found in soil and decaying plant and vegetable matter.[138] These infections produce angioinvasive disease and are prone to disseminate. They evolve from inhalation, ingestion or the percutaneous inoculation of spores into a predisposed host, e.g. during immunosuppression.[139] Clinical outcomes are closely related to a patient's overall health and the control of their underlying diseases.[139]

Over the last decade, *Zygomycetes*, particularly fungi belonging to the order Mucorales (which cause mucormycosis), have emerged as significant fungal pathogens in patients undergoing treatment for haematological malignancy or HSCT. This trend may be associated with the more widespread use of voriconazole for the prevention and treatment of IA in patients undergoing intensive chemotherapeutic or conditioning regimens.[140,141,123] Voriconazole has no *in vitro* activity against *Zygomycetes* and may therefore select for this class of fungi.

Evidence-based treatment recommendations

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

Optimal treatment of zygomycosis has not been defined, owing to the lack of appropriate prospective trials. AmB-D at maximum tolerable doses (1–1.5 mg/kg/day) has traditionally been the antifungal treatment of choice. Prolonged use, however, is often limited by nephrotoxicity. Lipid formulations of amphotericin B starting

at 5 mg/kg/day are now preferred as first-line therapy (grade C recommendation). The dose may be increased to 15 mg/kg/day for severe and/or refractory disease (grade D recommendation).[129,142]

Unlike other azoles, the newer, extended-spectrum triazole, posaconazole, has demonstrated both *in vitro* and *in vivo* activity against *Zygomycetes*.[143–145] Observational studies suggest that posaconazole may provide effective salvage therapy for patients who are refractory to or intolerant of amphotericin B.[82,146,147] However, some *Zygomycetes* spp. are less susceptible to posaconazole than others;[148] posaconazole had no effects against *Rhizopus oryzae* and only partial benefit against *Absidia corymbifera* in infected mice, although the clinical significance of this in humans is unknown.[143,144]

While posaconazole is an attractive alternative for patients who cannot tolerate or do not respond to amphotericin B products, its clinical use may be limited by:

1. The lack of an IV preparation; posaconazole is only available in oral (liquid) form.
2. The requirement for a second antifungal agent that can deliver effective therapy while waiting to achieve adequate posaconazole levels; an 800 mg dose (administered in 4 divided doses daily) will usually take 7–10 days to achieve steady state levels.[149]
3. Potential drug–drug interactions; although posaconazole is metabolized via uridine diphosphate (UDP)-glucuronidation, it is also a CYP3A4 inhibitor, and may interact with other drugs, particularly tacrolimus and cyclosporine.
4. The availability of posaconazole drug assays for therapeutic monitoring; these tests are not routinely available across all institutions.

Whether posaconazole should be offered as primary therapy for zygomycosis instead of amphotericin B-based products is likely to be addressed by future prospective comparative trials.

Combination therapy

The use of various combinations of antifungal agents to treat zygomycosis (azoles, echinocandins, or both plus amphotericin B) has been described but only in case reports or in mice.[146] Antagonism has been described both *in vitro* and *in vivo* for triazole/polyene combinations but has not been reported in current animal studies.[150] The use of azoles following treatment with a polyene appears safe. Although the use of new antifungal agents with novel mechanisms of action in combination appears attractive – particularly for difficult-to-treat infections where morbidity and mortality remain high – clinical data are limited and no meaningful recommendations can be given at this time.

Duration of therapy

Treatment duration in zygomycosis is often not clear. 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 symptom 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 will depend on the patient's response to 'standard' 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). It may be used as step-down therapy following a satisfactory response to IV antifungal therapy or as salvage therapy if the patient has not responded to therapy. Some clinicians recommend that amphotericin should not be ceased until adequate posaconazole levels are attained, or in the absence of levels, until the patient has received at least 1 week of posaconazole therapy (grade D recommendation).

The duration of posaconazole should be individualized according to response and the risk of zygomycosis relapsing due to 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 (please refer to the section of the guidelines by Slavin *et al.* on p. 468 for further detail).

Scedosporium

Mycoses caused by *Scedosporium* species are an 'emerging' disease, particularly within immunosuppressed populations.[151] Changes in antifungal prophylaxis practices (e.g. the more widespread use of agents with activity against moulds but poor activity against *Scedosporium* species) and an increase in the severity of host immunosuppression due to more aggressive chemotherapy regimens are likely to have contributed to the emergence of *Scedosporium*.[152] *Scedosporium apiospermum* (the anamorph of *Pseudallescheria boydii*) and *S. prolificans* are the two species most commonly encountered by humans.[151,153]

Infection with *S. apiospermum* has been described for over a century. It causes cutaneous infections (including mycetoma) and occasionally deep-seated infections (e.g. CNS abscesses). More recently it has been described as a

cause of disseminated infection in immunosuppressed individuals.[154]

S. prolificans has only recently been described as a pathogen. It causes bone, joint and soft tissue infections in immunocompetent patients and disseminated infections in immunocompromised patients, e.g. acute myeloid leukaemia (AML) patients and HSCT recipients.[154] HSCT patients are at a particularly high risk of disseminated disease, including rash.[154] In such cases, infection may occur early after transplant (with neutropenia) or many months post transplant in the context of severe GVHD.[154] Disseminated disease is often associated with concurrent pulmonary infection.[151,155]

S. prolificans appears to be a more common cause of disseminated disease in Australia than *S. apiospermum*.[154] Mortality is documented to be as high as 80% for both species if disease is invasive, disseminated or involves fungaemia.[156,157]

Evidence-based treatment recommendations

The optimal antifungal treatment for *Scedosporium* infections is unknown. *S. apiospermum* and *S. prolificans* are both intrinsically resistant *in vitro* to multiple antifungal drugs, particularly *S. prolificans*, which often exhibits resistance to all currently available antifungal agents.[157–160]

Amphotericin-based therapies (monotherapy or combination therapy) appear to be inferior to azole-based therapies against both species (level III-3 evidence).[153,155]

The extended-spectrum triazoles are active *in vitro* against *S. apiospermum* with cross-resistance observed among all the azoles except posaconazole.[160] Voriconazole appears most potent against *S. apiospermum* with minimum inhibitory concentration in the range 0.12–0.5 μg/mL.[81,151,153,154]

S. prolificans is often resistant to even the newer extended-spectrum triazoles.[151,153,154] However, there is some *in vitro* evidence that azoles and terbinafine act synergistically against *S. prolificans* (level IV evidence).[161–164] Although there are no trials comparing monotherapy with combined therapy (prospectively or as case reviews), it is recommended that clinicians use these agents concurrently based on *in vitro* observations of a strong synergistic interaction (grade D recommendation).

Using an agent to which the organism has proven susceptible is associated with better clinical outcomes and drug susceptibility testing of isolates should be considered to help guide therapy (grade D recommendation).[151]

CNS disease and endophthalmitis

A solitary mass or multiple brain abscesses are the most frequent CNS manifestations of *Scedosporium* infections. Treatment recommendations are based on case reports.[165–168]

CNS and eye infections due to *S. apiospermum* should be treated with voriconazole while combination therapy (voriconazole *plus* terbinafine) is recommended for CNS/eye infections due to *S. prolificans* (grade D recommendation). Posaconazole is an alternative agent but has only been studied as salvage therapy.[169]

Duration of therapy

There is no evidence to support a pre-specified duration of therapy, particularly for invasive disease. However, continuing antifungal therapy for several months and/or until immune recovery seems reasonable (grade D recommendation).

Fusarium

Fusarium is an emerging cause of opportunistic mycoses. In immunocompromised hosts, fusarial infections are often disseminated and have very high mortality rates.[157,170] *Fusarium* species have the capacity to conidiate adventitiously. Dissemination of spores leads to multiple cutaneous lesions in 70–90% of patients, sinus and lung disease in 70–80% of patients and positive blood cultures in up to 60% of individuals.[171,172] Factors associated with increased mortality include disseminated infection (metastatic skin lesions and fungaemia), persistent neutropenia, stem cell transplantation and ongoing corticosteroid use,[173] although in the studies by Nucci *et al.*, only persistent neutropenia and corticosteroid use remained significant after multivariate analysis.[170,174] Mortality rates from fusarial infection remain high despite the availability of lipid formulations of amphotericin B and the newer azoles.[170] Strategies to prevent fusarial infection during immunosuppression include avoiding skin breakdown, good skin care and minimizing immunosuppression, where possible.[173]

Evidence-based treatment recommendations

Given the relative rarity of fusarial infections, there are no studies that directly compare the activity of different antifungal agents against *Fusarium* spp. Antifungal drug management is therefore based upon *in vitro* sensitivity testing and outcomes from retrospective studies or subgroup analysis of larger drug comparison studies. While drug sensitivity is species dependent, *Fusarium* spp, as a whole, generally demonstrate variable *in vitro* sensitivity to amphotericin B, voriconazole and posaconazole but are usually resistant to fluconazole, itraconazole and the echinocandin class.[157,158,175]

Successful treatment, in terms of disease response or non-progression, has been reported with high-dose amphotericin B (1.0–1.5 mg/kg IV daily) and ABLC (at least 5 mg/kg daily) in HSCT recipients and patients with haematological malignancy (level IV evidence).[129,176] There are currently limited data supporting voriconazole or posaconazole as initial therapy for fusariosis. While some authors suggest voriconazole is a viable alternative to amphotericin B and its lipid formulations,[81,156,157,171] others still favour amphotericin B-based regimens for initial therapy.[177,178] There have been no direct comparisons of amphotericin B (or its lipid formulations) and the newer azole agents. Thus, it is currently not possible to recommend one of these agents over another.

More recently, case reports have documented success with dual antifungal therapy (L-AMB and voriconazole) and some authors are now recommending combination therapy for managing the critically ill patient (level IV evidence).[179,180]

Salvage therapy

Breakthrough *Fusarium* infections can occur with amphotericin B.[81,174] 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 end of treatment or Week 16 of treatment) (level IV evidence).[156,181] 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).[182] Only patients who were intolerant of, or had disease that was refractory to, amphotericin B and/or its lipid formulations qualified for these studies.

CNS disease and endophthalmitis

Voriconazole may be used to treat CNS and eye disease due to *Fusarium* spp., although successful therapy is limited to case reports.[181,183] Lipid formulations of amphotericin remain an alternative. There is no data regarding the use of posaconazole in this clinical setting.

Duration of treatment

No studies have compared a fixed time period for antifungal therapy but at least 12 weeks' therapy is often required.[81,181,182] Therapy should only be ceased once immunosuppression has resolved and there is clear evidence of clinical and radiological improvement (grade D recommendation).

Ancillary management of mould infections

Reversal of immunosuppression

Aggressive efforts to minimize immunosuppression and neutropenia by reducing corticosteroid use are likely to improve patient outcomes.[151,154,170,171,176,184,185] While there are no clinical trials to support the use of granulocyte transfusions, cytokines (such as granulocyte colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF) and interferon gamma (IFN-γ)) or other putative immunostimulatory therapies in combination with antifungal agents for the treatment of invasive mould infections, case reports and small case series suggest these therapies may be useful in the setting of prolonged neutropenia and life-threatening infection if a patient is responding poorly to antifungal therapy.[155,186–191]

Surgical debridement

Prompt surgical debridement of localized fungal infection and devitalized tissue, where possible, may also contribute to survival, particularly when there is a clear nidus for the bulk of infection or *S. prolificans* or *Zygomycetes* are involved.[153,154,156,157,184,192] Surgical resection of localized pulmonary *Aspergillus* infection is recommended prior to allogeneic HSCT or if pulmonary vessels are threatened while resection of locally invasive *Aspergillus* infection is recommended before allogeneic HSCT (level IV evidence).[103,193]

Removal of intravascular catheters

IV lines may be a source of infections; removal is recommended in the setting of multiple positive blood cultures.

Invasive dermatophyte infections

Dermatophytosis (tinea or ringworm) of the scalp, glabrous skin and nails is caused by a closely related group of fungi known as dermatophytes, which have the ability to utilize keratin as a nutrient source.[194] Generally, no living tissue is invaded; the keratinized stratum corneum is simply colonized. However, the presence of the fungus and its metabolic products usually induce an allergic and inflammatory eczematous response in the host. The type and severity of the host response depend primarily on the species of dermatophyte causing the infection and, to some extent, on the immunological competence of the host. For example, AIDS, haematological malignancy and systemic corticosteroid therapy may play a significant role in predisposing patients to chronic dermatophyte infection.[194]

Table 6 Summary of treatment recommendations by pathogen

Pathogen	Clinical setting	Recommended antifungal therapy (grade of recommendation)
Zygomycetes	First-line therapy	Lipid formulation of amphotericin (Abelcet® 5 mg/kg/day or Ambisome® 5–15 mg/kg/day)† (C)
	Failed amphotericin B therapy, dose-limiting toxicity or step-down therapy after clinical response	Posaconazole 200 mg po qid with food‡ (C)
Scedosporium	*S. apiospermum*	First line: voriconazole§ (load with 6 mg/kg IV bd on day 1 then 4 mg/kg IV bd thereafter) (D)
		Second line: posaconazole 400 mg po bd *or* itraconazole 200 mg po bd (D)
	S. prolificans	Voriconazole (load with 6 mg/kg IV bd on day 1 then 4 mg/kg IV bd thereafter) (D)
		OR
		Itraconazole 200 mg po or IV bd (D)
		plus
		Terbinafine 250 mg po daily (D)
		Alternatively, use posaconazole 400 mg po bd instead of voriconazole§ or itraconazole (D)
Fusarium	Initial therapy	High-dose amphotericin B (1.0–1.5 mg/kg IV daily) or amphotericin B lipid complex (at least 5 mg/kg daily)† (D)
		OR
		Voriconazole§ (6 mg/kg bd IV for two doses then 4 mg/kg bd IV ongoing) (D)
	Breakthrough infection whilst receiving amphotericin-based therapy	Voriconazole§ (6 mg/kg bd IV for two doses then 4 mg/kg bd IV ongoing) (D)
		OR
		Posoconazole 400 mg po bd (D)
	Critically ill	Liposomal amphotericin† *plus* voriconazole§ (D)
Dermatophytes	Invasive infection	Terbinafine 250 mg/day (B)
		OR
		Itraconazole 200 mg/day (C)
	Chronic and/or widespread non-responsive tinea	Terbinafine 250 mg/day (B)
		OR
		Itraconazole 200 mg/day (C)

†Monitor renal function. ‡Posaconazole can be dosed at 400 mg bd after 7–10 days. §There can be significant interpersonal variability in plasma voriconazole levels due to polymorphisms in the cytochrome P450 (CYP450) enzymes involved in its elimination (CYP2C19, CYP2C9 and CYP3A4). Consider performing voriconazole levels in cases of serious IFI to ensure adequate systemic exposure.[205,206] IV, intravenous; po, oral.

Invasive dermatophyte infection, also known as 'dermatophyte pseudomycetoma' or 'Majocchi's dermatophyte granuloma', is an uncommon subcutaneous infection.[194–199] The latter may occur following the escape of fungal elements into the dermis due to the extrafollicular extension of infected hair follicles. Lesions tend to appear on the legs and are typically caused by *Trichophyton rubrum*.[195] Dermatophyte pseudomycetoma may be caused by trauma to the infected skin and/or rupture of infected hair follicles, which may introduce the dermatophyte into deep tissue. These infections are characterized by the presence of granulomas and pseudogranules, which are loose or compactly arranged hyphal elements embedded in a Splendore–Hoeppli-type eosinophilic sheath.[194,195] Several cases have been reported in immunosuppressed patients, mostly renal transplant recipients; *Microsporum canis, T. tonsurans* and *T. rubrum* were listed as aetiologic agents.[195–199]

Evidence-based treatment recommendations

Treatment of dermatophytosis is dependent on the clinical setting.[200] Uncomplicated single cutaneous lesions can be adequately treated with a topical antifungal agent. However, topical treatment of scalp and nail infections is often ineffective and systemic therapy is usually required

to cure these conditions. Chronic or widespread dermatophyte infections, acute inflammatory tinea and 'Moccasin' or dry type *T. rubrum* infection involving the sole and dorsum of the foot usually require systemic therapy.[200] Invasive dermatophyte infection or dermatophyte pseudomycetoma also require systemic therapy.[195–199] Ideally, the clinical diagnosis should be confirmed by mycologic testing before systemic antifungal treatment is commenced.

Many large, placebo-based and comparative clinical trials have evaluated the activity of terbinafine and itraconazole against dermatophytes that cause onychomycosis and tinea.[201–203] One double-blind, randomized, multicentre study (the LION study) compared the efficacy of continuous terbinafine 250 mg daily administered for 3 or 4 months with itraconazole pulse therapy 400 mg daily for 3 or 4 months (level II evidence).[202] This trial and others clearly showed terbinafine to be superior to itraconazole both *in vitro* and *in vivo* for dermatophyte onychomycosis. Terbinafine, thus, is recommended as first-line therapy while itraconazole is considered the next best alternative (grade B recommendation).[202,203]

Terbinafine is a fungicidal agent with a limited clinical spectrum of activity and acts primarily against dermatophytes.[204] It is well absorbed after oral administration and strongly lipophilic, becoming concentrated in the dermis, epidermis and adipose tissue.[204] It has been detected in the distil portion of nails after 4 weeks' treatment, indicating that diffusion from the nail bed is a major factor in drug penetration.[204] Oral terbinafine has become the drug of choice for dermatophytosis of the nail and can be used to treat dermatophytosis of the skin and/or scalp where topical treatment is considered inappropriate or has failed (grade A recommendation).[200,202,203]

Duration of treatment

In the immunocompetent host, the duration of antifungal treatment is dependent upon the site and extent of the infection, ranging from 2 weeks for interdigital tinea pedis, 4–6 weeks for widespread or chronic non-responsive dermatophytosis of the skin and/or scalp, to 12 weeks for nails.[200] However, there is no evidence to support a pre-specified duration of therapy for the immunosuppressed host; treatment times are invariably longer. Treatment should be continued until there is clinical and mycological cure (Table 6).

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