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REVIEW

Consensus guidelines for the treatment of yeast infections in the haematology, oncology and intensive care setting, 2014

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Abstract

Pathogenic yeast forms are commonly associated with invasive fungal disease in the immunocompromised host, including patients with haematological malignancies and patients of haemopoietic stem cell transplants. Yeasts include the *Candida* spp., *Cryptococcus* spp., *Pneumocystis jirovecii* and some lesser-known pathogens. *Candida* species remain the most common cause of invasive yeast infections (and the most common human pathogenic fungi). These guidelines present evidence-based recommendations for the antifungal management of established, invasive yeast infections in adult and paediatric patients in the haematology/oncology setting. Consideration is also given to the critically ill patient in intensive care units, including the neonatal intensive care unit. Evidence for 'pre-emptive' or 'diagnostic-driven antifungal therapy' is also discussed. For the purposes of this paper, invasive yeast diseases are categorised under the headings of invasive candidiasis, cryptococcosis and uncommon yeast infections. Specific recommendations for the management of *Pneumocystis jirovecii* are presented in an accompanying article (see consensus guidelines by Cooley *et al*. appearing elsewhere in this supplement).

Introduction

These guidelines discuss management of established invasive yeast infections in adult and paediatric patients in the haematology/oncology setting and in the critically ill patient in intensive care units (ICUs), including the neonatal ICU (NICU). These recommendations update those published previously[1] and are based on antifungal agents currently licensed for use in Australia. Invasive yeast diseases are categorised under the headings of invasive candidiasis, cryptococcosis and uncommon yeast infections.

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Methodology

Questions asked

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

1 What is the optimal treatment for systemic yeast infection in adults and children?

2 What is the optimal dose and duration of antifungal treatment?

3 What investigations and adjunctive therapies improve outcomes?

Search strategy

A literature review was performed using PubMed to identify papers published since 2007 that pertained to the treatment of yeast infections in patients with haematological malignancy, patients of haemopoietic

Table 1 Factors predisposing patients to candidaemia

Population	Risk factor
All patients	Prior abdominal surgery
	Intravascular catheters
	Parenteral nutrition
	Use of broad spectrum antibiotics
	Immunosuppression, including corticosteroid therapy
	Acute renal failure
	Diabetes
	Transplantation
	Haemodialysis
	Pancreatitis
ICU patients	Prolonged stay in ICU
	Candida colonisation, particularly multifocal
	High Acute Physiology and Chronic Health Evaluation II (APACHE II) score
	Blood transfusions
	Low birth weight and prematurity for neonatal ICU
	Necrotising enterocolitis for neonatal ICU

stem cell transplantation (HSCT) and critically ill patients in an intensive care setting. Search terms included 'candidiasis', 'candidaemia', '*Candida*', 'cryptococcosis', '*Cryptococcus neoformans*', '*Cryptococcus gattii*', 'yeast and diagnosis, treatment and management'.

Invasive candidiasis and candidaemia

Candida species are the most common cause of invasive yeast infections. Invasive candidiasis (IC) includes bloodstream infection (i.e. candidaemia), deep-seated tissue infection or both. Most studies have focused on candidaemia. In Australia, the incidence of candidaemia (2001–2004) has been estimated at 1.81 cases per 100 000 of population.[2] *Candida albicans* accounted for approximately 50% of invasive *Candida* isolates, followed by *C. parapsilosis* (20%), *C. glabrata* (15%), *C. tropicalis* (5%), *C. krusei* (4%) and *C. dubliniensis* (2%).[2] In the NICU, *C. albicans* and *C. parapsilosis* predominate.[3] IC, including candidaemia, has a high attributable mortality (30–71%) and morbidity.[2,4–7] Multiple risk factors for IC have been identified (see summary in Table 1 and recent reviews by Yapar 2014 and Delaloye and Calandra 2014),[8,9] with immunocompromised and critically ill patients at particularly high risk. Antifungal therapy should be started early, since treatment delays are associated with worse clinical outcomes and increased mortality (Level III evidence, grade B recommendation).[10–12]

Laboratory investigations for diagnosis of IC

Blood cultures

Cultures of blood and other clinical specimens remain the cornerstone of diagnosing IC. However, they are insensitive and relatively slow (taking at least 2–3 days),[13,14] and are positive in only 63–83% of cases of IC[15,16] and 50% of deep-seated IC.[16]

Antifungal susceptibility

Accurate identification of *Candida* spp. is predictive of likely antifungal susceptibility (or resistance) and aids selection of antifungal agents (see Table 2 for common susceptibility patterns of major *Candida* spp.). In Australia, most species, including *C. albicans*, *C. parapsilosis* and *C. tropicalis*, are typically susceptible to fluconazole,[22] while those with reduced susceptibility include *C. glabrata* and *C. krusei*.[17,18,23] The emergence of multi-drug resistance in *C. glabrata*, involving all azoles and echinocandins,[19,20] is of particular concern. Though the correlation is imperfect, susceptibility testing is often routinely performed against clinically significant isolates (level III-3 evidence, grade C recommendation) and can help guide therapy.

Non-culture approaches

Non-culture-based diagnostics are more sensitive and rapid than culture. However, they do not recover

Table 2 Common antifungal susceptibility patterns of the major *Candida* species[17–21]

Species	Amphotericin B	Echinocandins†	FLU	ITRA	VORI‡
C. albicans	S	S	S§	S	S
C. glabrata	S	S¶	S-DD to R††	S-DD to R	S to R
C. krusei	S	S	R	S-DD to R	S to R
C. parapsilosis	S	S to R‡‡	S	S	S
C. tropicalis	S	S	S	S	S

†Susceptibility pattern is similar for all the echinocandins (anidulafungin, micafungin, caspofungin). ‡In general, posaconazole has similar susceptibility patterns as voriconazole. §Resistance of *C. albicans* to fluconazole is approximately 5%. ¶Resistance of *C. glabrata* to the echinocandins appears to be emerging. ††Cross-resistance to azoles occurs in >10% of *C. glabrata* isolates. ‡‡Higher minimum inhibitory concentration values and poor activity against *C. parapsilosis* biofilms. FLU, fluconazole; ITRA, itraconazole; R, resistant; S, susceptible; S-DD, susceptible dose-dependent; VORI, voriconazole.

organisms and may not allow identification to species level. They are also expensive and, in the case of *Candida* PCR assays, not yet standardised. They do have value as complementary tests, as they can increase diagnostic yields and direct diagnostic-driven antifungal therapy.

Candida antigen and antibody detection

The role of serum *Candida* antigen and antibody detection as an early marker of IC is uncertain. The best results have been obtained with a combined mannan/anti-mannan antibody assay (Platelia; Bio-Rad, Marnes-la-coquette, France). While combined testing may be useful in earlier diagnosis of hepatosplenic candidiasis, it is less useful for detecting candidaemia (level II evidence, grade C recommendation),[24] and is not currently available in Australia.

ß(1,3)-D-glucan detection

The detection in serum of the fungal cell wall component ß(1,3)-D-glucan (BDG) for the diagnosis of candidaemia and IC is well studied (see summary by Perfect, 2013),[25] but is not used locally due to cost. This assay, however, has been used to guide pre-emptive antifungal therapy. A single-centre study of twice-weekly BDG surveillance among high-risk ICU patients for >3 days reported a positive predictive value (PPV) of 30% for IC (sensitivity 100%, specificity 75%) with a negative predictive value (NPV) of 100%.[26] The study also found pre-emptive anidulafungin to be safe and associated with good outcomes. In light of more contemporary data, a re-evaluation of the role of BDG surveillance in Australia and New Zealand is warranted.

Polymerase chain reaction(PCR)-based tests

Nucleic acid amplification assays for *Candida* include those that detect all fungi (e.g. Panfungal PCR[27]) and those that specifically detect *Candida* spp.; however, these lack methodological standardisation. PCR results can precede positive blood culture results by 1 day to 4 weeks.[28,29] The combination of blood culture *and* BDG or PCR tests had superior sensitivities to blood cultures in isolation (79% and 98%, respectively). Hence, these assays may represent useful adjuncts.[16]

Identifying patients at high risk of invasive candidiasis

The efficacy of diagnostic-driven antifungal therapy strategies in ICU patients was established by a 2004 study, in which fluconazole – administered to patients with a predefined *Candida* colonisation index of ≥0.5 based on number of colonised sites[30] – significantly decreased the incidence of IC.[31] Risk factors for invasive candidiasis in the critically ill patient are summarised in Table 1. These patients may benefit from empirical anti-candida therapy (level III evidence, grade C recommendation).

Treatment of invasive candidiasis and candidaemia

When choosing empirical or pre-emptive treatment, knowledge of local epidemiological patterns of IC, the patient's prior therapy and prevalence of antifungal resistance is important. In Australia, the proportion of candidaemia caused by *C. albicans* is relatively high among ICU patients (about 62%) but low among haematology patients (31%).[2,17,18,21] Total parenteral nutrition (TPN) and central venous catheters (CVCs) are associated with *C. parapsilosis*.

Exposure to fluconazole or broad-spectrum antimicrobials is associated with an increased likelihood of fluconazole-resistant *Candida* spp.[18,32–34] Similarly, exposure to echinocandins is associated with echinocandin resistance[35,36] and selection for less susceptible *Candida* spp.[33]

When last examined in 2008, the prevalence of fluconazole resistance in *Candida* spp. was stable in Australia.[37] Globally, resistance to echinocandins is very uncommon among wild-type *C. albicans*, *C. parapsilosis* and *C. tropicalis*, occurring in just 0.4% of cases of candidaemia in France (2005–2010)[36] and 0–0.6% of cases in the Asia-Pacific region (2010–2011).[38] However, elsewhere, resistance in *C. glabrata*, with cross-resistance to all echinocandins, has been reported with rates of up to 28%.[39] These differences may relate to the varying methodology and criteria employed in different countries to define resistance and/or to differing antifungal usage patterns. In Australia, clinical resistance to the echinocandins appears uncommon.

Initial therapy for invasive candidiasis and candidaemia

Amphotericin B and the triazoles

Studies pre-2008 focused on the use of conventional amphotericin B (amphotericin B deoxycholate [AmB-D]), fluconazole[40–44] and voriconazole[45] for the treatment of IC and are reviewed in the previous guidelines.[1] In children and neonates, both azoles and amphotericin B preparations have been shown to be effective for the treatment of IC in open-label studies (see review by Blyth and colleagues, 2007[46]), but studies comparing different

antifungal classes are lacking. The only randomised controlled trial (RCT) comparing azoles to amphotericin B for the treatment of IC in children is a trial of 23 neonates with candidaemia.[47] Patients were randomised to receive AmB-D 1 mg/kg/day or fluconazole 5 mg/kg/day, with no reported difference in outcomes. A 2010 Cochrane review of the treatment of suspected (prolonged fever and neutropenia) and proven IC identified four RCTs comparing AmB-D with lipid formulations of amphotericin and one trial comparing itraconazole with fluconazole for candidaemia.[48] No difference in outcomes between the studies was observed but the patient groups were heterogeneous and the studies largely underpowered.

Echinocandins

The efficacy of the echinocandins for the treatment of IC in adults has been assessed by four RCTs comparing: (i) caspofungin versus AmB-D,[49] (ii) micafungin versus lipsomal amphotericin B (L-AMB),[50] (iii) anidulafungin versus fluconazole[51] and (iv) micafungin versus caspofungin.[52] Caspofungin and micafungin were not inferior to AmB-D and L-AMB, respectively, but were associated with significantly fewer infusion reactions and nephrotoxicity.[49,50] Anidulafungin was associated with significantly greater clinical and microbiological efficacy than fluconazole in a modified intention-to-treat population.[51] However, the superior efficacy of anidulafungin should be interpreted with caution, as a possible study bias could not be excluded. Further, fluconazole was given at a dose of 400 mg/day, which may not achieve the required ratio of area under the curve to minimum inhibitory concentration (AUC : MIC) target in all patients with candidaemia.[53] A comparative trial of caspofungin at standard doses and micafungin at doses of 100 or 150 mg daily had similar clinical and microbiological outcomes across the three treatment arms in the primary intention-to-treat analysis, as well as similar safety and tolerability.[52] *C. parapsilosis* has comparatively higher MICs to echinocandins than other *Candida* species, but studies[54] suggest echinocandin treatment may be successfully used to treat *C. parapsilosis* infections (level III evidence, grade C recommendation). In children with IC, there have been only two RCTs published comparing an echinocandin with another class of antifungal drug.[55,56] The first study of 106 patients (age range: birth to 16 years) compared micafungin 2 mg/kg with L-AMB 3 mg/kg, and showed similar treatment success (73% and 76%, respectively). The second study involving 32 neonates compared caspofungin 2 mg/kg with AmB-D 1 mg/kg, and showed a superior composite success rate with caspofungin (87% vs 42%, respectively). However, this endpoint included discontinuation due to adverse events, and both studies showed increased infusion-related adverse events and nephrotoxicity (albeit temporary) in the amphotericin groups.

Several authors have also examined the pooled results of antifungal treatment studies. One review compared the outcomes of 1195 patients receiving AmB-D, L-AMB, fluconazole, voriconazole and the echinocandins.[57] A multivariate analysis found that only CVC removal and receipt of an echinocandin were associated with survival and clinical success.[57] However, this analysis has been criticised on the basis of the number of patients excluded due to lack of outcome data and the prolonged time period over which the studies were conducted (1989–2006).[58–60] Conversely, the analyses of Gafter-Gvili *et al*. 2008[44] and Mills *et al*. 2009[61] of RCTs assessing the treatment of IC and candidaemia over a similar time period, did not show an improvement in all-cause mortality for patients receiving echinocandins compared to other antifungals. However, Gafter-Gvili *et al*. 2008 did conclude that echinocandins and AmB-D had a lower rate of microbiological failure than fluconazole.[44] There have been no meta-analyses of echinocandin use in children.

Evidence-based treatment recommendations for adults

The superiority of echinocandins over other agents for the treatment of candidaemia has not been conclusively proven, although they are associated with fewer adverse events than AmB-D and fluconazole.[44] Based on the analysis of Andes *et al*. 2012[57] and the reduced propensity for adverse events,[44] echinocandins received the highest level of recommendation for the initial treatment of candidaemia in the ESCMID guidelines,[62] as they do in the current guideline (see Table 3 for a summary of recommendations and Table 4 for dosing guidance).

Initial therapy with an echinocandin is favoured in the critically ill or haemodynamically unstable patient (level III evidence, grade B recommendation), as well as in the setting of neutropenia (level IV evidence, grade D recommendation), or where a biofilm infection or azole resistance is suspected (level IV evidence, grade D recommendation). An analysis of anidulafungin versus fluconazole supports this approach.[51] Kett *et al*., 2011 evaluated outcomes in 163 patients with severe sepsis (in ICU or with Apache II scores >15) and a better global response was observed at the end of treatment with anidulafungin compared to fluconazole, with a trend to lower mortality at day 14 (10% vs. 20%, $P = 0.08$), although day 28 mortality (20% vs. 24%) was not significantly different.[63] This study was a post-hoc analysis and not designed to examine the question of superiority in critically ill patients. The results, therefore, are not definitive. An analysis of outcomes in Spanish critical

Table 3 Recommended antifungal therapy for adult patients with candidaemia or invasive candidiasis†

Candida spp.	Clinical scenario/patient type	Antifungal agent						
		Azole		Echinocandin‡			Amphotericin B§	
		Fluconazole	Voriconazole	Anidulafungin	Caspofungin	Micafungin	L-AMB	AmB-D
Unknown organism or species	Critically ill OR neutropenic OR risk factors associated with azole resistance	NR	C	A	A	A	B	C
	Risk factors associated with echinocandin resistance and one of the following: critically ill OR neutropenic	NR	C	NR	NR	NR	B	C
	Clinically stable with no risks for azole or echinocandin resistance	B	C	A	A	A	C	C
Fluconazole susceptible *Candida* spp.	Critically ill OR neutropenic	B	B	A	A	A	B	C
	Clinically stable	A	B	A	A	A	B	B
C. glabrata	Critically ill	NR	NR	A	A	A	B	C
	Clinically stable	B¶	B¶	A	A	A	B	C

†Most recommendations in children, unless otherwise stated, would be considered Grade C at best, due to the paucity of dedicated paediatric randomised data. ‡There are limited data about the pharmacokinetics, safety and efficacy of anidulafungin in children. If an echinocandin is required, caspofungin or micafungin would be favoured. §Conventional amphotericin B-associated toxicity is less common in children than in adults. It should be considered at the same level as lipid formulations in children with candidaemia or invasive candidiasis. ¶Provided *C. glabrata* isolate is not azole resistant. AmB-D, amphotericin B deoxycholate; L-AMB, liposomal amphotericin B; NR, not recommended.

care patients suggests appropriate treatment, as well as catheter removal, improves survival.[64] In the setting of endophthalmitis and central nervous system (CNS) infection, echinocandins should not be used due to poor drug penetration (level III evidence, grade C recommendation).[65] See Table 5 for treatment recommendations when infection involves difficult sites.

There is a role for initial therapy with fluconazole where the patient is clinically stable and the isolate is likely to be susceptible to fluconazole (level II evidence, grade B recommendation). The recommended loading dose of fluconazole is 800 mg (12 mg/kg) followed by 400 mg/day (6 mg/kg/day).[98] However, this may be suboptimal in some patients due to high *Candida* MIC or patient pharmacokinetics. While optimisation of AUC : MIC > 25 is recommended (level III evidence, grade C recommendation), fluconazole levels are not commonly performed in routine practice.[72,99]

Table 4 Recommended doses of licensed antifungal agents for *Candida*†

Agent	Preparation	Recommended dose adults	Recommended dose children	Recommended dose neonates
Anidulafungin	IV	200 mg, daily for 24 h then 100 mg, daily	3 mg/kg loading dose on day 1 then 1.5 mg/kg, daily	3 mg/kg loading dose on day 1 then 1.5 mg/kg, daily
Caspofungin	IV	70 mg/day for 24 h then 50 mg, daily	50 mg/m^2, daily	25 mg/m^2, daily
Micafungin	IV	100 mg, daily	2–4 mg/kg, daily	10 mg/kg, daily
Amphotericin B deoxycholate	IV	0.6–1 mg/kg, daily	0.7–1 mg/kg, daily	0.5–1 mg/kg, daily
Liposomal amphotericin	IV	3 mg/kg, daily	3 mg/kg, daily	3 mg/kg, daily
Amphotericin B lipid complex	IV	3–5 mg/kg, daily	5 mg/kg, daily	5 mg/kg, daily
Fluconazole	Oral/IV	12 mg/kg, daily for 24 h then 6–12 mg/kg, daily	12 mg/kg, daily	25 mg/kg loading dose on day 1, then 12 mg/kg/day
Voriconazole	Oral/IV	6 mg/kg, 12 hourly for first 24 h then 4 mg/kg, 12 hourly	9 mg/kg, 12 hourly day 1 then 8 mg/kg, 12 hourly + TDM	4–6 mg/kg, 12 hourly (data from case series, not PK studies)
Itraconazole	Oral		2.5 mg/kg, 12 hourly + TDM	No data

†Also see full approved Product Information for individual antifungal agents. IV, intravenous; PK, pharmacokinetic; TDM, therapeutic drug monitoring.

Table 5 Treatment of invasive candidiasis in difficult sites†

Clinical setting	Recommended agents	Alternative agents	Comments
Hepatosplenic (chronic disseminated) candidiasis	Fluconazole 400 mg, daily (6 mg/kg) if stable L-AMB 3–5 mg/kg, daily or AmB-D 0.5–0.7 mg/kg, daily if unstable, followed by fluconazole	An echinocandin followed by fluconazole	• Prolonged neutropenia is a risk factor[66] • Continue antifungal therapy while receiving immunosuppression and until imaging abnormalities resolve (usually at least 6 months)[67–70] • There is limited evidence supporting the use of corticosteroids for persisting fevers in this setting[67,70]
CNS candidiasis (meningitis or intracerebral abscesses[71])	L-AMB 3–5 mg/kg, daily ± 5-flucytosine 25 mg/kg, 6-hourly followed by fluconazole 400–800 mg, daily	Fluconazole 400–800 mg, daily (6–12 mg/kg)	• Continue therapy until at least 4 weeks after resolution of radiological signs and neurological symptoms[72,73] • Remove intraventricular devices[71,72] • There are limited data on posaconazole, voriconazole or echinocandins for CNS candidiasis[74–77]
Ocular candidiasis	AmB-D 0.7–1 mg/kg, daily *plus* 5-fluorouracil 25 mg/kg, 6-hourly[62,72] *or* fluconazole 400–800 mg, daily (6–12 mg/kg)	L-AMB 3–5 mg/kg, daily *or* voriconazole 6 mg/kg, 12-hourly for two doses then 3–4 mg/kg, 12-hourly[78–80]	• Treat for 4–6 weeks and until ocular lesions have resolved[72,81] • Consider intravitreal antifungal therapy or surgical vitrectomy in the presence of vitritis • Echinocandins are not recommended due to concerns regarding their ocular penetration[81]
Candida osteomyelitis	Fluconazole 400 mg, daily (6 mg/kg) or L-AMB 3–5 mg/kg, daily followed by fluconazole[82–86]	An echinocandin followed by fluconazole	• Treat for 6–12 months[82,83,87] • Adjunctive surgery may be required[72]
Candida septic arthritis	Surgical intervention is essential[72] Fluconazole 400 mg, daily (6 mg/kg) or L-AMB 3–5 mg/kg, daily followed by fluconazole[84,85,88–90]	An echinocandin followed by fluconazole, *or* voriconazole[62,72]	• Treat for a minimum of 6 weeks • Removal of the prosthesis is usually required in prosthetic joint infections; if not removed, long-term suppressive therapy is recommended[62,72]
Candida endocarditis	Surgical intervention is recommended[62,72] L-AMB 3–5 mg/kg, daily ± 5-fluorouracil *or* an echinocandin[91–95]	Fluconazole can be used as suppressive therapy but should not be used alone in initial treatment[96,97]	• Treat for at least 6 weeks[62,72] • For those who do not undergo valvular surgery, use lifelong suppressive fluconazole 400–800 mg, daily (6–12 mg/kg) • Surgery is particularly important in prosthetic valve endocarditis[62,72]
Symptomatic *Candida* cystitis or pyelonephritis	Cystitis: fluconazole 200 mg, daily Pyelonephritis: fluconazole 200–400 mg, daily	AmB-D ± flucytosine, *or* flucytosine alone Echinocandins reserved for resistance or intolerance	• Continue therapy for 14 days • Amphotericin B bladder irrigation now infrequently used
Candidal urinary tract fungal ball	Fluconazole 200–400 mg, daily *or* AmB-D 0.5–0.7 mg/kg, daily ± flucytosine 25 mg/kg, 6-hourly		• Surgery often required ± local irrigation using endoscopic methods

AmB-D, amphotericin B deoxycholate; CNS, central nervous system; CVC, central venous catheter; L-AMB, liposomal amphotericin B. †All recommendations are grade D, based on level 4 evidence.

Evidence-based treatment recommendations for children and neonates

The principles guiding the choice of antifungal agent in children are similar to those discussed for adults – in short, give due regard to local epidemiology and severity of illness. No adequately powered comparative trials have been performed in the paediatric and neonatal setting. Recommendations about treatment choice are therefore derived from the limited paediatric data, adult studies and expert opinion.

Antifungal dosing cannot be extrapolated from adult studies, as children have a greater volume of distribution, higher drug elimination and different toxicity profiles, and these variables change during childhood (see Table 4 for dose recommendations). There has been a paucity of specific pharmacokinetic studies in children and neonates. A study of fluconazole in immunocompromised

children over 5 years showed that doubling the dose to 12 mg/kg/day was required for equivalence to the adult dose (400 mg/day), due to rapid drug elimination.[100] In neonates, slower elimination of fluconazole necessitates increased intervals between doses and a loading dose has been recommended to achieve therapeutic levels on day 1.[101,102] Voriconazole also needs higher comparative dosing in children (who have linear elimination of the drug) than in adults (non-linear), as demonstrated in a group of immunocompromised children aged 2–12 years where a dose of 8 mg/kg twice daily was shown to be equivalent to an adult dose of 4 mg/kg twice daily.[103] Itraconazole, conversely, needs no dose adjustment with 2.5 mg/kg twice daily shown to be effective in paediatric HIV patients with oropharyngeal candidiasis.[104] Amphotericin B, in both its conventional and lipid formulation, has similar pharmacokinetics in neonates and children as in adults with lipid formulation doses of 2.5–5 mg/kg daily recommended.[105] The few recent pharmacokinetic studies in children have focused on the echinocandins. Caspofungin has a more comparable AUC to adult dosing in both children and neonates when dosed using body surface area rather than weight, with 50 mg/m¬¬^{2}/day in children aged 2–11 years equivalent to an adult dose of 50 mg/day.[103,106] Anidulafungin is faecally excreted so is an attractive option in patients with hepatic or renal failure. It needs no dose adjustment, with 1.5 mg/kg/day in immunocompromised children and neonates equivalent to an adult dose of 100 mg/day.[107,108] Micafungin has high drug elimination in young patients and in immunocompromised children aged 2–12 years, requiring doses of 4 mg/kg/day for adult equivalence.[98] Doses of 10 mg/kg/day are required in neonates to ensure CNS penetration.[109]

Candida glabrata: a problematic organism

C. glabrata is prevalent in many regions[110] and has potential to be cross-resistant to both the triazoles and echinocandins.[35,38,110] This is due to increased transporter genes,[111] increased expression of efflux pumps[112] and the propensity for biofilm formation.[113] Further, *C. glabrata* exists in a haploid state and hence is more prone to mutations.[114] Indeed, some features of resistant *C. glabrata* may allow for increased virulence.[115] Treatment, therefore, may be a challenge. These data argue strongly for rapid identification of the species causing the candidaemia, as well as antifungal susceptibility testing of all isolates.[35]

Treatment of invasive candidiasis in difficult sites

Treatment recommendations for hepatosplenic, central nervous system (CNS), ocular, bone and joint, endocarditis and urinary tract candidiasis are summarised in Table 5.

Candida spp. are the most common causes of fungal endocarditis,[116] which has a higher mortality than non-fungal endocarditis.[91] Candidaemia is complicated by endocarditis in up to 17.7% of cases when transoesophageal echocardiogram (TOE) is routinely performed.[92]

In the absence of surgery, increased mortality rates have been seen in some cohorts[116,117] but not in others,[91,92] although most data was obtained prior to the availability of the echinocandins. Combined surgical and antifungal therapy is the optimal treatment and should be employed where possible. There have been reports of successful medical treatment with caspofungin in a small number of patients in whom surgical intervention was not possible.[92,93] The potential efficacy of echinocandin drugs is increasingly recognised in the treatment of fungal endocarditis due to their biofilm penetration.[118–120]

Duration and route of administration of antifungal therapy

There are no prospective data on the optimal duration of therapy for IC[121] and recommendations are largely based on expert opinion in both adults and children. The identification and management of ongoing infective foci, and of end-organ complications of IC, are important to maximise the long-term success of therapy. Several important ancillary management decisions should be considered (these are summarised in Table 6). For candidaemia with deep-tissue infection, treatment with systemic antifungal agents for 14 days following the last positive sterile site culture and resolution of clinical features of infection is recommended;[62,72] this approach has been adopted in most comparative trials (level III evidence, grade C recommendation).[45,50,52,131] Expert opinion recommends similar durations for peritonitis, but 6 weeks or longer for difficult-to-treat deep foci such as endocarditis, endophthalmitis, mediastinitis or osteomyelitis (grade D recommendation).[72]

The intravenous route is preferred for the initiation of antifungal therapy to ensure adequate blood and tissue levels are achieved. Following satisfactory clinical and microbiological response, changing from intravenous to oral antifungal therapy is appropriate, assuming susceptibility to the oral agent and a functioning gastrointestinal tract (level III evidence, grade C recommendation).[132]

Cryptococcosis

Cryptococcosis is predominantly caused by two species, *Cryptococcus neoformans* (serotypes A [*C. neoformans* var. *grubii*], D [*C. neoformans* var. *neoformans*] and AD) and

Table 6 Recommendations for ancillary management measures in candidaemia

Recommendation	Grade	Comment
Early removal of vascular catheters where possible[62,72,122]	B	Removal of catheters, ideally within 48 h, may have a mortality benefit[18,64,123] and expedites clearance;[124] it is particularly important in *C. parapsilosis* infection, which is usually catheter associated
When catheter removal is not possible, an echinocandin[118,125] or L-AMB[119,126] is recommended for biofilm penetration	D	
Follow-up blood cultures are advised to ensure clearance of infection[72]	C	Persistent or breakthrough candidaemia may suggest a persistent infective focus or a resistant organism;[127,128] ocular candidiasis is correlated with longer duration of candidaemia[78]
Ophthalmological examination should be routinely performed in all patients within the first week of antifungal therapy[72,129]	C	Findings consistent with ocular candidiasis, often chorioretinitis, are found in 10–20% of patients with candidaemia[78,130]
Serial ophthalmological examinations may be required	C	In persistent candidaemia, a repeat ophthalmological examination may detect ocular candidiasis[78,129]
Echocardiography should be performed in patients with persistent candidaemia or those with risk factors for endovascular infection[91,92,116]	C	Risk factors for endocarditis include pre-existing valve disease,[116] CVC access[92] and persistently positive blood cultures for *Candida* spp.[91]

Cryptococcus gattii (serotypes B and C).[133] The predilection of *Cryptococci* for the central nervous system (CNS) can lead to life-threatening meningoencephalitis.[134]

Antifungal susceptibility of *Cryptococcus*

MICs of amphotericin B, 5-flucytosine, fluconazole, voriconazole and posaconazole have been reported.[135,136] However, routine susceptibility testing is not recommended (level IV evidence, grade D recommendation), as primary resistance to antifungal drugs is uncommon in Australia.[137] There are no standardised MIC breakpoints and MIC levels have not been shown to correlate with clinical outcomes. As molecular type VGI predominates (overwhelmingly) in Australia, routine susceptibility testing is not indicated (level IV evidence, grade D recommendation).[138]

Diagnosis of cryptococcosis

Based on recent studies, laboratory investigations in patients with cryptococcal infection in any site – except in patients with small pulmonary cryptococcomas and negative serum cryptococcal antigen (CrAg) tests – should include blood cultures, cerebrospinal fluid (CSF) examination and an assessment of patient risk factors (including CD4/CD8 lymphocyte counts, HIV antibody status and other causes of immunosuppression) (level IV evidence, grade D recommendation).[139,140]

Management of cryptococcosis

Initial management of cryptococcosis requires both antifungal therapy and control of raised intracranial pressure (ICP). Measuring the opening pressure via lumbar puncture is important (level III evidence, grade C recommendation), as raised ICP is associated with increased morbidity and mortality.[139] The only RCTs of antifungal therapy in cryptococcosis have been conducted in HIV-infected patients with *C. neoformans* meningitis. The choice of initial antifungal regimen depends on the site and severity of infection and the immune status of the host. Antifungal therapeutic recommendations for adults and children are summarised in Table 7. Where relevant, doses of immunosuppressive agents should be reduced slowly[139] while balancing the risk of developing cryptococcosis-associated immune reconstitution inflammatory syndrome (C-IRIS).

Treatment of *C. neoformans* infection

Meningoencephalitis

Combination therapy with AmB-D 1 mg/kg/day and 5-FC 100 mg/kg/day is associated with superior outcomes.[142] Liposomal amphotericin B (L-AMB) may be used in place of AmB-D at 3–6/kg/day (level II evidence, grade B recommendation).[143,144] The lower dose (3 mg/kg) may be used when administered concurrently with 5-FC.[145]

In HIV-infected individuals, a repeat lumbar puncture to check for CSF sterility is prudent prior to switching from induction to consolidation antifungal therapy and prior to commencing combination antiretroviral therapy (cART) (level III evidence, grade C recommendation).[146,147] Guidance on consolidation and maintenance therapy is summarised in Table 7 and discussed in more detail elsewhere.[139]

L-AMB and AmB-D are both considered Category B drugs during pregnancy; concurrent 5-flucytosine

Table 7 General recommendations for the antifungal treatment of central nervous system and pulmonary cryptococcosis due to *C. neoformans and C. gatti* (adapted from Perfect *et al*., 2010[139] and Chen *et al*., 2013[141])

Host risk group or clinical setting	First-line antifungal therapy (level of evidence/grade of recommendation)	Alterative agents for antifungal therapy (level of evidence/grade of recommendation)	Comments (level of evidence/grade of recommendation)
Cryptococcus neoformans			
CNS infection			
HIV-infected individuals	Induction therapy: L-AMB 3 mg/kg, daily (*or* AmB-D 1 mg/kg, daily) *plus* 5-flucytosine 100 mg/kg, daily for 2 weeks (II, B) Consolidation therapy: fluconazole 400 mg, daily (6 mg/kg, daily) for 8 weeks (II, B) Maintenance therapy: fluconazole 200 mg, daily for ≥1 year (II, B)	Induction therapy: L-AMB 3 mg/kg, daily (*or* AmB-D 1.0 mg/kg, daily) alone for 4–6 weeks (III, B) OR L-AMB 3 mg/kg, daily (*or* AmB-D 1 mg/kg, daily) *plus* fluconazole (III, B)[19] OR 5-flucytosine 100 mg/kg, daily *plus* fluconazole 800 mg, daily (III, B) Maintenance therapy: itraconazole 400 mg, daily for at least 12 months (II, C)[69]	In patients with impaired renal function, L-AMB is preferred (IV, D). Induction therapy with fluconazole alone is not recommended due to suboptimal clinical response (III, C).[17,21] Where there is no alternative, then higher doses of fluconazole (800 to 1200 mg, daily) may be used, either as monotherapy (II, C) or, if possible, in combination with 5-flucytosine (II, C)
Organ transplant patients	Induction therapy: L-AMB 3 mg/kg, daily (*or* ABLC 5 mg/kg, daily) *plus* 5-flucytosine 100 mg/kg, daily for 2 weeks (III, C) Consolidation therapy: fluconazole 400–800 mg, daily for 8 weeks (III, B) Maintenance therapy: fluconazole 200–400 mg, daily for 12 months	Induction therapy: L-AMB 6 mg/kg, daily *or* ABLC 5 mg/kg, daily *or* AmB-D 0.7–1.0 mg/kg, daily for 4–6 weeks (III, C)	L-AMB is the preferred amphotericin B formulation as induction therapy (IV, D)[69]
Non-HIV infected, non-transplant hosts	Induction therapy: L-AMB 3 mg/kg, daily (*or* AmB-D 0.7–1.0 mg/kg, daily) *plus* 5-flucytosine 100 mg/kg, daily for ≥4 weeks (III, C) Consolidation therapy: fluconazole 400–800 mg, daily for 8 weeks (III, C) Maintenance therapy: fluconazole 200 mg, daily for 6–12 months (III, C)	Induction therapy: L-AMB 3 mg/kg, daily *or* AmB-D 0.7–1.0 mg/kg, daily for ≥6 weeks (III, C)	Although the term 'maintenance' therapy is used, therapy aims to be curative
Children: immunocompromised	Induction therapy: L-AMB 3 mg/kg, daily (*or* AmB-D 1 mg/kg, daily) *plus* 5-flucytosine 100 mg/kg, daily for 2 weeks Consolidation therapy: fluconazole 12 mg/kg, daily for 8 weeks Maintenance therapy: fluconazole 6 mg/kg, daily 6–12 months	Induction therapy: L-AMB 3 mg/kg, daily *plus* 5-flucytosine 100 mg/kg, daily for 2 weeks	An LP should be done at the end of induction to ensure CSF sterility and the induction phase should be continued until sterility of CSF is achieved
Children: immunocompetent	Induction therapy: AmB-D 1.0 mg/kg, daily *plus* 5-flucytosine (100 mg/kg, daily) for 4 weeks Consolidation therapy: fluconazole 12 mg/kg, daily for 8 weeks Maintenance therapy: fluconazole 6 mg/kg 6–12 months	Induction therapy: L-AMB (5 mg/kg, daily) *plus* 5-flucytosine (100 mg/kg, daily) for 4 weeks	An LP should be done at the end of induction to ensure CSF sterility and the induction phase should be continued until sterility of CSF is achieved
Pulmonary cryptococcosis without cns involvement			
Immunocompetent patients with mild disease	Fluconazole 400 mg, daily for 6–12 months (III, C)	—	—
Immunosuppressed patients and immunocompetent patients with severe lung disease	Same as for CNS disease Duration of therapy 12 months (III, C)	—	—
Cryptococcus gatti			
CNS infection	Induction: L-AMB 3 mg/kg, daily (*or* AmB-D 0.7–1.0 mg/kg, daily) *plus* 5-flucytosine 100 mg/kg, daily for at least 6 weeks (IV, D) Consolidation/maintenance: Fluconazole 400 mg, daily for 12–18 months (III, C)[141]	—	Induction therapy with fluconazole monotherapy is not recommended due to a high probability of treatment failure (IV, D)[141] Surgical excision of mass lesions where appropriate (IV, D)
Pulmonary cryptococcosis without CNS involvement	Induction therapy: L-AMB 3 mg/kg, daily (*or* AmB-D 0.7–1.0 mg/kg, daily) *plus* 5-flucytosine (100 mg/kg, daily) for 2 weeks (IV, D) Consolidation/maintenance therapy: Fluconazole 400 mg, daily for 6–12 months (IV, D)[141]	—	For mild lung disease in the absence of immunosuppression, fluconazole monotherapy 400–800 mg, daily for 6–12 months may be considered[141]

L-AMB, liposomal amphotericin B; AmB-D, amphotericin B deoxycholate; ABLC, amphotericin B lipid complex; LP, lumbar puncture; CSF, cerebrospinal fluid; CNS, central nervous system.

(Category C) should be discussed. Fluconazole (Category C) should be avoided until after delivery (level IV evidence, grade D recommendation).[148]

There is a lack of studies addressing treatment in children; recommendations are extrapolated from adult studies and represent expert opinion.[149]

Pulmonary infection

Immunocompetent patients with mild or no symptoms may be treated with fluconazole 400 mg/day, for 6–12 months (level III evidence, grade C recommendation).[139,150,151] Those with immunosuppression, large

cryptococcomas or diffuse infiltrates should be treated as for cryptococcal meningitis (level III evidence, grade C recommendation).

Non-meningeal, non-pulmonary cryptococcosis

There are no clinical trial data on the treatment of patients with non-meningeal, non-pulmonary cryptococcosis. Other guidelines suggest that in the absence of immune suppression, fluconazole 400 mg/day (6 mg/kg/day) for 6–12 months may be used (level IV evidence, grade D recommendation). In immunosuppressed patients, treatment doses and duration are in line with those presented for cryptococcal meningitis.

Treatment of *C. gattii* infection

There are no clinical trial data on the management of *C. gatti* infection; recommendations are based on expert opinion and case series (level IV evidence, grade D recommendation). The IDSA guidelines recommend similar induction regimens and durations of therapy to those used for *C. neoformans*.[139] However, a recent Australian retrospective case series of 86 cases of *C. gattii* (largely CNS cryptococcosis), indicated that induction therapy with amphotericin B and 5-flucytosine for at least 6 weeks and a prolonged total duration of therapy (at least 12–18 months) enabled clinical cure (level IV evidence, grade D recommendation).[141] For disease restricted to the lung, combination amphotericin B and 5-flucytosine is recommended for 2 weeks followed by fluconazole, although in mild lung disease without immunosuppression, fluconazole monotherapy may also achieve cure (level IV evidence, grade D recommendation).

Adjunctive management of cryptococcosis

Raised intracranial pressure

Many patients with cryptococcal meningitis have raised ICP (defined as a CSF pressure of >25 cm H_20).[152] Early detection and reduction of raised ICP is critical, as this has been associated with increased mortality and neurological sequelae.[140,152–154] Therapeutic LPs should be undertaken at daily intervals until the CSF pressure is ≤20 cm H_20 or <50% of the initial opening pressure.[139,152,155,156] If repeated LPs fail to control CSF pressure, CSF shunts or drains are recommended (level IV evidence, grade D recommendation), although the optimal timing and efficacy of these procedures have not been examined systematically.[157,158]

Surgical management

Cerebral and pulmonary cryptococcomas may occur in both *C. neoformans* and *C. gattii* disease. Lesions causing mass effects, such as pressure on vital structures or bleeding, should be excised where practicable (level IV evidence, grade D recommendation).

Exogenous interferon (INF)

There have been two randomised studies of exogenous IFN-gamma as adjuvant therapy for cryptococcal meningitis. One showed a non-significant trend towards improved CSF clearance of cryptococci[159] and the other demonstrated faster rates of fungal clearance but no change in mortality.[160] Further evidence is required before recommendations for the use of IFN-gamma in cryptococcosis can be made.

Corticosteroid and other therapies

Steroids have been used, apparently successfully, in patients with cryptococcal meningitis – mostly in *C. gattii* infections and cases of C-IRIS or CNS mass lesion with significant oedema.[141,161] An international multicentre study of cryptococcal meningitis in 800 HIV-infected patients receiving 6 weeks of adjunctive therapy with dexamethasone is currently underway (ISRCTN59144167). Acetazolamide is not recommended, as it has been associated with adverse outcomes in *C. neoformans* cryptococcal meningitis.[162]

Cryptococcal persistence and relapse

In cryptococcal meningitis, persistent infection may be defined as persistently positive CSF cultures after 4 weeks of an effective antifungal regimen.[139] In such cases, prolongation of induction therapy should be considered. Similarly, re-induction therapy should be given to those with microbiological relapse and a higher consolidation dose of fluconazole (600–800 mg/day) is recommended (level IV evidence, grade D recommendation). Voriconazole (200–400 mg BD)[163] or posaconazole (200 mg QID or 400 mg BD)[164] for 10–12 weeks may be suitable for salvage therapy (level IV evidence, grade D recommendation). There are no studies comparing the efficacy of the newer azoles with that of fluconazole. Antifungal susceptibility testing is recommended in microbiological relapse (level IV evidence, grade D recommendation).

Cryptococcosis-associated immune reconstitution inflammatory syndrome (C-IRIS)

C-IRIS has been reported in apparently normal hosts with *C. gatti* infection, particularly those with a lower CD4 + T-cell count, brain involvement and concurrent

Table 8 Antifungal therapy for rare yeast infections by organism group

Organism(s)	Preferred antifungal agents	Strength of recommendation	Comments
Geotrichum candidum	Amphotericin B† ± 5-flucytosine	C-III	No data for fluconazole (high MICs); low MIC values for voriconazole, limited human data[169–171]
Kodameae ohmeri	Amphotericin B†	C-III	Most (though limited clinical experience with amphotericin B†);[172,173] elevated azole MICs for some isolates[174,175]
Rhodotorula spp.	Amphotericin B† ± 5-flucytosine	B-III	*In vitro* susceptibility only to these two agents; *in vitro* resistance to all azoles and echinocandins[176,177]
Trichosporon spp.	Voriconazole	C-III	Preferred therapy but scarce data; *in vitro* resistance to fluconazole, 5-flucytosine and amphotericin B† reported[178,179]

†Refers to amphotericin B deoxycholate and its lipid formulations. MIC, minimum inhibitory concentration.

brain-meninges-lung involvement.[141] It also occurs in solid-organ transplant patients.[165] However, C-IRIS is best studied in AIDS-associated cryptococcal meningitis, where it presents as clinical worsening or an apparently new presentation of cryptococcal disease after commencement of cART.[166,167]

There are no prospective clinical trials to help guide the management of C-IRIS but in symptomatic CNS infection, especially in the presence of mass effect, corticosteroids have been used. Recommended doses are 0.5–1.0 mg/kg/day of prednisone equivalent over 2–6 weeks with gradual tapering of the dose (level IV evidence, grade D recommendation). Antifungal therapy should be continued.

Rare yeast infections

Rarer yeast pathogens include *Malassezia*, *Rhodotorula*, *Trichosporon*, *Geotrichum*, *Kodamaea* and *Saccharomyces* species. Common colonisers of the skin and mucosal surfaces, these pathogens rarely result in invasive infections except in severely immunosuppressed individuals. DNA sequencing is required for identification to species level. Rare yeast infections represent 1.1–5.1% of fungal isolates in Europe.[168] The incidence of rare yeast infections is not known in Australia but is likely to be low.

There are no trial data to guide treatment and MIC breakpoints are lacking. In general, all these rare yeast species (except *Saccharomyces* and *Kodamea ohmeri*) are regarded as intrinsically resistant to the echinocandins.[168] The European Society for Clinical Microbiology and Infectious Diseases (ESCMID)/ECMM Joint Committee has formulated guidelines for first-line antifungal therapy.[168] These are summarised in Table 8.

Implications for research

Continued epidemiological surveillance studies are required to understand the evolution of yeast ecology and antifungal resistance. Improved diagnostics and treatment strategies to direct antifungal therapy in high-risk ICU patients are necessary.

Conclusion

Invasive yeast infections are a significant cause of morbidity and mortality in immunocompromised patients and the critically ill host. The usefulness of available tests to facilitate early diagnosis and diagnostic driven treatment is explored here. When choosing empirical or pre-emptive treatment, knowledge of local epidemiological patterns, a patient's prior therapy and prevalence of antifungal resistance is important. Evidence-based recommendations to help guide choice and dose of antifungal agent have been provided with consideration of ancillary management measures, where relevant.

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