INTERNAL MEDICINE JOURNAL

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doi:10.1111/imj.15589

SUPPLEMENT ARTICLE

Consensus guidelines for the diagnosis and management of invasive candidiasis in haematology, oncology and intensive care settings, 2021

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Key words
invasive candidiasis, candidaemia, antifungal therapy, consensus guidelines, diagnosis, prevention.

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Abstract

Patients with haematological malignancies, haemopoietic stem cell transplant recipients and patients requiring admission to intensive care settings are at high risk for invasive candidiasis (IC). Over the past decade, there has been increased reporting of non-*albicans* species and fluconazole resistance in Australia. These guidelines provide updated evidence-based recommendations for the diagnosis and management of IC in adult and paediatric haematology, oncology and intensive care settings. Optimal pharmacological and non-pharmacological management are discussed. Recent studies strengthen the recommendation for an echinocandin agent as first-line therapy for high-risk patients with IC. Mortality benefit has also been demonstrated for non-pharmacological management, including removal of central venous catheters, infectious diseases consultation and use of care bundles. Healthcare facilities managing immunocompromised patient populations should therefore adopt implementation strategies for these multimodal interventions.

Introduction

These guidelines discuss laboratory diagnosis, management and prevention of invasive candidiasis (IC), including candidaemia, in adult and paediatric haematology and oncology patients, and in critically ill patients in intensive care units (ICU). Recommendations update those published previously[1] and are based on laboratory methods and antifungal agents currently available for use in Australia and New Zealand.

Since the previous guidelines, *Candida auris* has emerged internationally, particularly affecting high-risk patient populations. Included in these guidelines is a discussion of the role of antifungal stewardship (AFS) and infection control measures. Prophylaxis and therapeutic drug monitoring (TDM) are briefly discussed as relevant to IC, with detailed recommendations provided in the accompanying antifungal prophylaxis (Teh *et al.* 2021)[280] and optimising antifungal therapy (Chau *et al.* 2021)[281] guidelines, both of which can be found elsewhere in this supplement. Taxonomic changes reflect sequencing differentiation, and many previously known *Candida* species have been reassigned to non-*Candida* genera. In order to maintain consistency throughout the guidelines, we refer to the currently accepted and valid species name used in clinical practice for the organism. The reader is referred to Table 1 for revised

Funding: None.
Conflicts of interest: None.

Table 1 Taxonomic changes to nomenclature for previously grouped *Candida* spp. (adapted from Borman and Johnson[2])

Previous name	Revised name
Candida bracarensis	*Nakaseomyces bracarensis*†
Candida catenulata	*Diutina catenulata*
Candida eremophila	*Pichia eremophila*
Candida etchellsii	*Starmerella etchellsii*
Candida fabianii	*Cyberlindnera fabianii*
Candida famata	*Debaryomyces hansenii*
Candida fermentati	*Meyerozyma caribbica*
Candida glabrata	*Nakaseomyces glabrata*†
Candida inconspicua	*Pichia cactophila*
Candida infanticola	*Wickerhamiella infanticola*
Candida kefyr	*Kluyveromyces marxianus*
Candida krusei	*Pichia kudriavzevii*
Candida guilliermondii	*Meyerozyma guilliermondii*
Candida lambica	*Pichia fermentans*
Candida lipolytica	*Yarrowia lipolytica*
Candida lusitaniae	*Clavispora lusitaniae*
Candida nivariensis	*Nakaseomyces nivariensis*†
Candida norvegensis	*Pichia norvegensis*
Candida pararugosa	*Wickerhamiella pararugosa*
Candida pelliculosa	*Wickerhamomyces anomalus*
Candida pintolopesii	*Kazachstania telluris*
Candida pseudorugosa	*Diutina pseudorugosa*
Candida pulcherrima	*Metschnikowia pulcherrima*
Candida rugosa	*Diutina rugosa*
Candida sorbosivorans	*Starmerella sorbosivorans*
Candida utilis	*Cyberlindnera jadinii*

†Did not have a MycoBank number at the time of writing and is not yet formally approved.

nomenclature. The terms candidiasis and IC will be utilised to refer to the clinical syndromes of invasive infection caused by *Candida* and *Candida*-like organisms. The term candidaemia will be utilised to refer to bloodstream infection (BSI) caused by *Candida* and *Candida*-like organisms. Where the term *Candida* is employed throughout the guideline, this refers to both *Candida* and *Candida*-like organisms.

Methodology

Questions asked

These guidelines address the following questions:

1 How has the epidemiology of IC changed?
2 What is the optimal collection and processing of blood and other cultures?
3 What is the role of susceptibility testing in the diagnosis and management of IC?
4 What is the role of non-culture-based diagnostic tests in the diagnosis and management of IC?
5 What is the role of prophylaxis to prevent IC?
6 What are the optimal pharmacological approaches for the management of IC?
7 What are the pharmacological considerations in paediatric IC?
8 What are the optimal non-pharmacological approaches for the management of IC?
9 What are the recommended infection prevention measures for *C. auris* and other species in haematology/oncology and intensive care settings?

Search strategy

A literature review was performed to identify papers published between 2014 and 2020 pertaining to the diagnosis, management and prevention of *Candida* infections in haematology/oncology populations, recipients of haemopoietic stem cell transplant and critically ill patients in ICU settings. Search terms included 'candidaemia', 'candidemia', 'candidiasis', '*Candida*', together with key terms 'diagnosis', 'treatment', 'management' and 'prevention'.

Question 1: How has the epidemiology of IC changed?

Immunocompromised patient populations are at high risk for IC, including BSI (candidaemia) and deep-seated infection. Worldwide, these are among the most common hospital-acquired infections,[3–7] and the increasing incidence of candidaemia has been reported in several recent studies.[3,8] In Australia, the incidence has increased from 1.81 to 2.41 cases per 100 000 population between 2001 and 2015.[3,9] While endogenous flora most commonly contribute to clinical infection, nosocomial acquisition may occur, particularly for *C. auris*.[10,11] The importation of *C. auris* has highlighted the need to consider relevant risk factors including travel history.[10,11]

Major factors for IC include underlying haematological malignancy and critical illness (Box 1). Deep-seated candidiasis in the absence of candidaemia is most frequently related to an intra-abdominal focus, for which risk factors include gastrointestinal or hepatobiliary surgery and liver or gastrointestinal disease.[12,21,22] Reported all-cause mortality for candidaemia has remained unchanged over the last decade (27.7% in 2006; 31% in 2017).[3,9,22] Poorer outcomes have been observed in the setting of an unknown source for candidaemia, extremes of age, haematological malignancy, lymphopenia, organ failure, absence of recent surgery, prolonged antibiotic therapy and ICU admission.[22–24] Patients with neutropenia and IC in the setting of haematological or solid organ

Box 1 Risk factors for invasive candidiasis[12–20]

- Immunocompromised state
  - Haematological malignancy
  - Neutropenia
  - Inherent or primary immune deficiency
  - Solid organ or haemopoietic stem cell transplantation
  - Chemotherapeutic agents, particularly those associated with mucositis
  - Receipt of corticosteroid therapy
- Gastrointestinal tract disease
  - Gastrointestinal malignancy
  - Liver disease
  - Recent surgery, particularly abdominal or hepatobiliary
- Intensive care unit admission
- Intravenous agents
  - Receipt of total parenteral nutrition
  - Transfusion
  - Intravenous drug use
- Presence of indwelling medical devices
  - Central venous catheter (CVC)
  - Indwelling urinary catheter
  - Tenckhoff catheter
- Extremes of age
  - Elderly
  - Neonates
  - Very low birthweight infants
- Receipt of broad-spectrum antibiotic agent/s
- Trauma and burns patients

Species-specific risk factors include association of *C. parapsilosis* complex infection with the presence of a CVC, association of *C. tropicalis* with haematology populations, and association of *C. auris* with admission to a healthcare facility with known *C. auris* outbreak, presence of indwelling medical devices and the use of antifungal agents.

malignancy have a 15–20% rate of lower clinical response to antifungal therapy.[25–27]

In Australia, IC due to non-*albicans* species is increasingly reported, particularly *Candida glabrata* complex (Table 2). An increase in acquired fluconazole resistance has been observed in *Candida tropicalis* but otherwise remains uncommon, while echinocandin resistance is rare (Table 3).[3] In contrast to international reports, only sporadic cases of *C. auris* infection or colonisation have been noted in Australia.[11,36,37]

The burden and spectrum of illness differs in paediatric populations. Rates of candidaemia in infants and neonates are high compared with other groups, with an annual incidence of 4.39 per 100 000 in neonates and 0.92 per 100 000 in children (aged 1 month to 16 years) reported in Australia between 2000 and 2004.[13] Overall mortality in paediatric patients is 10–14.4%, increasing up to 22% for neonates.[13,38–42] The distribution of species is also different in neonates and children. Although *C. albicans* remains predominant in neonates,[38,40] non-*albicans* *Candida* species

Table 2 Aetiology of candidaemia in Australia (2001–2015)[3,9,13]

Candida species	ACS1† 2001–2004 ($n = 1095$)	ACS2‡ 2014–2015 ($n = 549$)
C. albicans	47%	44%
C. glabrata complex	15%	27%
C. parapsilosis complex	20%	17%
C. tropicalis	5%	4%
P. kudriavzevii	4%	2%
Uncommon *Candida* and *Candida*-like species§	6%	5%

†Australian candidaemia study 1 (ACS1) included 143 neonates and children, isolates were 42% *C. albicans*, 4% *C. glabrata* complex, 38% *C. parapsilosis* complex, 2% *C. tropicalis*. ‡Australian candidaemia study 2 (ACS2) included 23 cases in ≤14 years old. §Includes *C. dubliniensis*, *D. hansenii* (previously *C. famata*), *K. marxianus* (previously *C. kefyr*), *M. guilliermondii*, *Y. lipolytica* (previously *C. lipolytica*), *C. lusitaniae*, *W. anomalus* (previously *C. pelliculosa*), *C. quercitrusa* and *D. rugosa* (previously *C. rugosa*).

have become the predominant cause of invasive, paediatric candidiasis.[40–44] The proportion of *C. albicans* declines as the age of paediatric patients increases.[39,40]

Question 2: What is the optimal collection and processing of blood and other cultures?

Recommendations

- For adults, 40–60 mL of blood should be collected when investigating possible candidaemia (Strong recommendation, Level II evidence).
- Blood cultures should be repeated following the detection of candidaemia in order to document clearance and guide the duration of therapy (Strong recommendation, Level II evidence).[45,46]
- To increase diagnostic yield, direct microscopy of other sterile specimens should be performed in addition to fungal culture (Strong recommendation, Level III evidence).[45] The use of Calcofluor White greatly assists with visualising fungal elements.

Blood cultures are positive in approximately 40% of IC episodes (range 21–71%).[21] Low sensitivity is due to a low concentration of *Candida* in blood, containment of organisms at sites of deep infection, clearing of yeast cells from the circulation, and the difficulty in neonates and children of obtaining sufficient volume for adequate detection by blood culture. Between 26% and 54% of blood cultures positive for *Candida* have <1 colony forming unit/mL.[47] When serial blood cultures are collected, only 60% of candidaemia events are detected by the first blood culture.[48] Yield of blood culture for detecting *Candida* is dependent on the volume of blood

Table 3 Antifungal susceptibility patterns of the major *Candida* species[28–35]

Species	Amphotericin B†	Echinocandins‡	Fluconazole	Voriconazole	Posaconazole†
C. albicans	WT	S	S§	S	WT
C. glabrata complex	WT	S¶	S-DD to R††	WT	WT to NWT
P. kudriavzevii	WT	S	IR	S-I	WT
C. parapsilosis complex	WT	S to R	S-SDD	S	WT
C. tropicalis	WT	S	S-SDD	S-I	WT

†Clinical breakpoints not currently available. ECV are not available for isavuconazole, though it is likely to be broadly similar to posaconazole. ‡Susceptibility pattern is similar for all licensed echinocandin agents (anidulafungin, micafungin, caspofungin). §Resistance within *C. albicans* to fluconazole is approximately 5%. ¶Resistance of *C. glabrata* complex to the echinocandins has increased from 2001 to 2016[32]; ††Cross-resistance to azoles occurs in 5–10% of *C. glabrata* complex isolates. ECV, epidemiological cut-off values; NWT, non-wild type (based on ECV); IR, intrinsically resistant; R, resistant; S, susceptible; S-DD, susceptible dose-dependent; WT, wild type.

collected. In adults, a total of 40–60 mL of blood divided across 2–3 blood culture sets should be collected when testing for possible candidaemia (*Strong recommendation, Level II evidence*). In automated blood culture systems, most *Candida*-positive blood cultures flag within 2–3 days, and incubation for more than 5 days is not routinely required (*Strong recommendation, Level II evidence*).[49,50] In an attempt to reduce the time for identification, molecular and proteomic techniques (matrix-assisted laser-desorption/ionisation-time of flight mass spectrometry (MALDI-TOF MS)) applied to positive blood cultures are increasingly used.[51,52] Culture of sterile sites by direct aspiration may assist in distinguishing infection from colonisation. Culture of tissue or fluid from non-sterile sites (e.g. bronchoalveolar lavage/washings or drain tube cultures) may contain colonising yeasts and therefore requires cautious interpretation. More than 14 days of incubation is not required to recover *Candida* isolates for non-blood culture specimens.[53] Isolates from sterile sites should be identified to species level.

Laboratory diagnosis and monitoring

Culture of tissue or fluid is required to prove a diagnosis of IC. Clinical specimens should be collected in a sterile container with a small amount of sterile, preservative-free saline to keep the specimen moist. Histopathology findings may also indicate infection. In addition to haematoxylin and eosin-stained sections, periodic acid-Schiff or silver staining of tissue assists in diagnostic yield. Therefore, if IC is suspected, it is important to communicate this to the laboratory on request forms. Tissue forms present as budding yeasts or pseudohyphae.

Question 3: What is the role of susceptibility testing in the diagnosis and management of IC?

Recommendations

- Susceptibility testing should be routinely performed on clinically significant isolates (i.e. those from sterile sites and as determined in consultation between the clinician and the clinical microbiologist), particularly where there has been previous antifungal exposure or where a species that is intrinsically associated with resistance (e.g. *C. glabrata*) has been cultured (Strong recommendation, Level II evidence).
- Susceptibility results of invasive isolates should be reviewed periodically to provide insight into any change in susceptibility profiles and inform clinical practice (e.g. antifungal choices) (Strong recommendation, Level II evidence).

Identification of *Candida* species is important, given the likely antifungal susceptibility profiles of certain species (Table 3). In infections acquired in Australia and New Zealand, most species, including *C. albicans* and *Candida parapsilosis* complex, are susceptible to fluconazole,[3,54,55] while those with reduced fluconazole susceptibility include *C. glabrata* complex and *C. tropicalis*.[3,28,54] *Pichia kudriavzevii* (previously *Candida krusei*) is intrinsically resistant to fluconazole. Multi-drug resistance in *C. glabrata* complex (involving all azoles and echinocandins),[29,30] multi-drug resistance in *C. parapsilosis* complex,[56] and resistant isolates of *C. auris* have all been reported,[57] including rare cases from Australia.

Clinical Laboratory Standards Institute (CLSI)-based antifungal susceptibility testing and European Committee on Antimicrobial Susceptibility Testing (EUCAST)-based methods are used in Australasian laboratories.[58] Values generated by one method must not be interpreted using the criteria of the other.[58] The most commonly used yeast susceptibility method in Australasia, the Sensititre® YeastOne® (TREK Diagnostic Systems, West Sussex, UK), is a CLSI-based method. For many species-antifungal agent pairings, there are insufficient data to allow the determination of clinical breakpoints. This limitation has been, in part, addressed by the determination of epidemiological cut-off values (ECV) to differentiate 'wild-type' isolates (those without acquired resistance mechanisms) and 'non-wild-type' isolates (those more

likely to harbour acquired resistance). Updated ECV including those of less common *Candida* species (CLSI 2020, EUCAST 2020), and susceptibility profiles of uncommon yeasts,[59] have recently been published.

Question 4: What is the role of non-culture-based diagnostic tests in the diagnosis and management of IC?

Non-culture-based tests are more sensitive and rapid than blood culture. However, testing does not enable identification to species level or susceptibility testing. Furthermore, these tests are costly and in the case of *Candida* polymerase chain reaction (PCR) assays, non-standardised. Therefore, non-culture-based tests should be used as an adjunct to culture-based diagnostics. Performance characteristics are summarised in Table 4.

Molecular approaches

Nucleic acid amplification assays for *Candida* include those that detect all fungi (e.g. panfungal PCR) and those that specifically detect *Candida* species. Currently, these tests lack methodological standardisation. PCR results precede positive blood culture results by an average of 2.2 days (range 0.5–8 days).[61] Overall sensitivity and specificity for IC are 73% and 91%, respectively,[62] and in neonates 87.5% and 81.6% respectively.[63] Increased sensitivity of PCR over blood culture has been demonstrated in neonates, where PCR was positive in 27/150 (17.4%) cases of culture-negative sepsis.[63] High negative predictive value in low prevalence (2–10%) settings means that PCR-based tests can rule out IC with a high degree of certainty and may assist AFS programmes by allowing the cessation of empirical therapy or the withholding of therapy (in the first place) with a pre-emptive approach.[60] There are limited data on the performance of PCR in paediatric patients.

The T2 Magnetic Resonance (T2MR) assay uses nanotechnology to identify five *Candida* spp. with *Candida* species-specific sequences following cell lysis and amplification of pan-*Candida* primers.[64] Using spiked blood cultures, the assay has an estimated sensitivity and specificity for candidaemia of 91% and 98% respectively.[64] Unlike the impact on blood culture yield, administration of antifungal agents has a minimal effect on the sensitivity of T2MR.[64] More clinical data are required to determine the role this assay has in routine practice.

Candida antigen and antibody detection

The role of serum *Candida* antigen and antibody detection as an early marker of IC is yet to be defined. A combined mannan/anti-mannan antibody assay (Platelia™; Bio-Rad, Marnes-la-coquette, France) has reported sensitivity and specificity of 58% and 93% respectively,[65] and the assay may be positive 6–7 days before blood culture.[65] While combined testing may be useful in the earlier diagnosis of hepatosplenic candidiasis, it is less so for detecting candidaemia. These assays are not currently available in Australia.

1,3-β-D-glucan detection

The detection in serum of the fungal cell wall component of *Candida* species 1,3-β-D-glucan (BDG) for the diagnosis of candidaemia and IC has been previously reviewed,[66–68] with sensitivity and specificity reported as 75–80% and ~80% respectively. For ICU patients, sensitivity and specificity were 81% and 61% respectively.[69] Testing has been used to guide pre-emptive antifungal therapy, with a modest positive predictive value of 30%.[70] In a meta-analysis of neonatal studies, sensitivity and specificity were 89% (95% confidence interval (CI): 80–94%) and 60% (95% CI: 53–66%), respectively, with substantial variability between studies. Using a higher positivity threshold of 120 pg/mL, sensitivity and specificity were 81% (95% CI: 75–88%) and 80% (95% CI: 75–88%) respectively.[71] The performance of BDG in children is limited.[72] Cut-offs are yet to be determined and may need to be higher than in adult populations.[73] High BDG levels have been reported in the setting of fungal colonisation in the absence of invasive disease.[74,75]

Role of TDM in managing *Candida* infections

TDM has been used to support management of invasive fungal infections (IFI) including IC, particularly for azole agents with a well-characterised exposure–response

Table 4 Performance of non-culture-based tests to screen for *Candida* infection in adults in low-prevalence settings (adapted from Johnson *et al.*[60])

	Serum 1-3-β-D-Glucan	Serum mannan/anti-mannan	Blood T2Candida	Blood PCR *Candida* spp.
Sensitivity	80%	58%	91%	73%
Specificity	80%	93%	98%	95%
PPV†	9%	13%	0.5%	17%
NPV†	>99%	99%	>99%	99%

†2% prevalence. NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value.

relationship and unpredictable pharmacokinetic profile.[76] TDM is discussed in detail in the accompanying optimising antifungal therapy guidelines by Chau *et al.* (2021)[281], which can be found elsewhere in this supplement.

Question 5: What is the role of prophylaxis to prevent IC?

Recommendations

- Fluconazole prophylaxis is recommended for very low birth weight infants in units with a high incidence of IC (Strong recommendation, Level II evidence).
- Prophylactic and pre-emptive antifungal therapy is not recommended for ICU patients. Empirical antifungal therapy may be considered in patients with septic shock, multi-organ failure and at least two extra-intestinal sites of *Candida* colonisation (Moderate recommendation, Level III evidence).

Risk factors for IC are well-described (Box 1). Stratification of haematology patients is discussed in the accompanying antifungal prophylaxis guidelines by Teh *et al.* (2021)[280], which can be found elsewhere in this supplement. In addition to patients with underlying haematological malignancy, neonatal and ICU cohorts are high-risk populations for IC.

Neonates

In very low birth weight infants, fluconazole prophylaxis results in a relative risk reduction in the incidence of IC of between 50% and 80%.[77] A meta-analysis in 2016 demonstrated fluconazole prophylaxis to be effective and safe, reducing the incidence of IC (odds ratio (OR) 0.2; 95% CI: 0.08–0.51) and *Candida* colonisation (OR 0.28; 95% CI: 0.18–0.41) compared with placebo.[78] International guidelines support prophylaxis for IC prevention with fluconazole twice weekly for 6 weeks in neonates <1000 g birth weight admitted to neonatal ICU with high (>2%) IC incidence.[46,79]

Patients in the ICU

Assessment of efficacy of antifungal prophylaxis in ICU cohorts prior to positive cultures has been confounded by the use of non-standard definitions and heterogenicity of study populations. A joint taskforce of the European Societies of Intensive Care Medicine and Clinical Microbiology and Infectious Diseases has published management guidelines for IC in critically ill patients.[45] Prophylaxis is defined as antifungal agents administered to critically ill patients with risk factors but without suspicion of fungal infection; pre-emptive treatment as that administered to patients with risk factors and with a diagnosis based on fungal biomarkers (e.g. BDG); empirical therapy as treatment given in patients with specific risk factors and with signs and symptoms of infection, though again, without positive microbiological cultures; and targeted or directed therapies as treatments based on microbiological confirmation of an invasive *Candida* infection.

Use of azole antifungal agents to prevent fungal infections in the ICU setting has failed to demonstrate a mortality benefit, despite some reduction in the incidence of IFI.[80] A randomised, placebo-controlled trial of caspofungin prophylaxis or pre-emptive therapy in ICU patients with sepsis, multi-organ failure and risk factors for IC, found no reduction of IC or mortality with either approach.[81] Empiric therapy with micafungin in patients admitted to ICU with septic shock decreased the mean time from shock onset to appropriate therapy from 40.5 to 10.6 h ($P = 0.001$) and significantly increased the proportion of patients receiving appropriate antifungal therapy within 12 h (69.2% vs. 6.7%; $P = 0.001$). However, hospital mortality and length of stay were not reduced.[82] In this study, the number of septic shock patients that needed to be treated with empiric antifungal therapy for one patient with *Candida*-related septic shock to receive appropriate treatment was high at 19.6. Similarly, empirical micafungin did not increase fungal infection-free survival when examined in non-neutropenic patients with ICU-acquired sepsis, *Candida* colonisation at multiple sites and multi-organ failure.[83]

Question 6: What are the optimal pharmacological approaches for the management of IC?

Recommendations

- Recommended initial antifungal therapies are summarised in Tables 5 and 9, prescribing recommendations provided in Table 6 and recommendations for the treatment of IC syndromes provided in Table 7.

The range of antifungal therapies for candidaemia with or without IC syndromes remains unchanged since the 2014 guidelines. Of emerging therapies, isavuconazole has failed to demonstrate non-inferiority to standard therapy and rezafungin is yet to complete phase three clinical trials.[147,148] The rest of this section presents the updated evidence for the use of echinocandins, azoles and amphotericin B in candidaemia, as well as duration of therapy.

Table 5 Recommended first-line antifungal therapy for adult patients with candidaemia prior to susceptibility testing

Clinical state	Antifungal agent (SoR/QoE)															
	Azole				Echinocandin						Amphotericin B formulation					
	Fluconazole		Voriconazole		Anidulafungin		Caspofungin		Micafungin		L-AMB†		D-AMB			
Critically ill or neutropenic	B	II	NR		A	I	A	I	A	I	B	I	C	II		
Clinically stable with no neutropenia or risk factors for azole resistance	B	II	C	II	A	I	A	I	A	I	B	II	C	II		

†Liposomal amphotericin B has equivalent efficacy to echinocandins (though a higher rate of toxicity) and is an alternative agent in high-risk patients where echinocandins cannot be used or resistance suspected.[25,84,85] D-AMB, amphotericin B deoxycholate; L-AMB, liposomal amphotericin B; NR, not recommended; QoE, quality of evidence; SoR, strength of recommendation.

Echinocandins

Several studies support superiority of echinocandins in the treatment of IC, even for azole-sensitive isolates in critically ill and neutropenic patients.[46,149–152] The phase 3, randomised, double-blind, non-inferiority ACTIVE trial compared caspofungin and voriconazole oral stepdown to isavuconazole (initial intravenous and oral step-down) for the primary treatment of IC in 450 patients.[148] Outcome was assessed according to overall response to therapy, defined as mycological eradication and clinical cure or improvement. Isavuconazole failed to reach the non-inferiority threshold of 15%. Successful outcome at the end of intravenous therapy was 60.3% in the isavuconazole and 71.1% in the caspofungin arm, respectively (adjusted difference 10.8%; 95% CI: 19.9–1.8). The trend to a higher success rate with caspofungin was seen across all APACHE II scores. Median time to clearance of candidaemia, all-cause mortality and safety were similar between each group.

Tashiro *et al*. conducted a meta-analysis of five randomised control studies of therapy for IC between 1997 and 2015.[25] Treatment success was compared for initial therapy with any echinocandin to either azoles (fluconazole or isavuconazole) or polyenes (standard or lipid formulations of amphotericin B). Candidaemia accounted for 84.1% of infections and 90.2% of patients were non-neutropenic. Overall treatment success rates were significantly higher in patients receiving an echinocandin compared to non-echinocandin therapy (risk ratio (RR) = 1.14; $P = 0.0003$), and the success rate of echinocandin therapy was significantly higher than azole (RR = 1.2; $P = 0.001$) but not polyene therapy (RR = 1.2; $P = 0.06$). Similarly, in the subset of patients with candidaemia, there was a significantly higher treatment success rate with echinocandin compared to azole therapy (RR = 1.16; $P = 0.01$), but no significant difference was observed between echinocandin and polyene therapies. Subgroup analysis of 138 neutropenic patients identified lower overall success rate for both echinocandin and non-echinocandin treatments (57.1% and 44.1%) compared to non-neutropenic patients (75.2% and 67.1%). While echinocandin therapy had a significantly higher success rate than non-echinocandin therapy in non-neutropenic patients (RR = 1.12; $P = 0.006$), this was not observed in the setting of neutropenia (RR = 1.24; $P = 0.21$), possibly related to small numbers.

Patient-level data from six studies assessing anidulafungin efficacy for candidaemia and IC was assessed by Kullberg *et al*.[153] The global success rate at the end of intravenous therapy was 76.4%, with higher success rates in patients with deep-seated tissue candidiasis and resolved neutropenia (79% and 80% respectively) than in patients with persistent neutropenia (54%). *Candida* species did not influence outcome, and notably, the success rates in *C. parapsilosis* complex and *P. kudriavzevii* infections were 78% and 74%, respectively, comparable to *C. albicans* (78%). On multivariate analysis, factors associated with treatment failure were neutropenia (OR 2.6) and higher APACHE II scores (OR 1.1).

In contrast, the majority of observational and cohort population-based studies have failed to demonstrate mortality benefit with echinocandin compared to azole therapy.[22,154,155] An exception is a Spanish observational study focused on intensive care patients with documented candidaemia.[156] Initial therapy with caspofungin compared to an azole significantly reduced 30- and 90-day mortality, with an OR of 0.32 and 0.5 after multivariable analysis. There is little evidence comparing the efficacy of individual echinocandins. Micafungin and anidulafungin were compared in a retrospective single centre study of intensive care patients with candidaemia or IC.[157] Ninety-day survival was higher in patients receiving micafungin. However, on multivariate analysis, antifungal therapy did not predict mortality.

Azole therapy as first-line antifungal therapy

Studies suggesting equivalent efficacy of azoles to echinocandins as initial therapy are generally observational, include smaller numbers, or include IC patients

Table 6 Recommended dosing of antifungal agents for treatment of invasive candidiasis[1,86–94]

	Preparation	Loading dose (Day 1)	Maintenance dose	Hepatic impairment	Renal impairment	CRRT	Obesity
Fluconazole							
Adult	IV/oral	800 mg (up to 12 mg/kg/day in critical illness)	400–800 mg (6 mg/kg in critical illness) daily; use up to 12 mg/kg if SDD	NSR	200–400 mg daily if CrCl <50 mL/min; 200–400 mg daily after IHD	300–400 mg twice daily (9 mg/kg/day)	No adjustment, dose on total body weight
Child	IV/oral	Not required	12 mg/kg daily	NSR	NSR	NSR	NSR
Neonate	IV	25 mg/kg	12 mg/kg daily	NSR	NSR	NSR	NSR
Voriconazole							
Adult	IV/oral	6 mg/kg twice daily	4 mg/kg twice daily (TDM)	Child-Pugh A/B/C: loading 50–100%; maintenance 1–2 mg/kg twice daily (C: no more than 1 mg/kg) (TDM)	No dosage adjustment; oral formulation recommended as potential SBECD accumulation with IV formulation in renal impairment and CRRT		Dose on adjusted body weight
Child (2 years to <12 years OR 12–14 years and weight <50 kg)†	IV/oral	9 mg/kg PO twice daily	8 mg/kg IV twice daily (TDM)	Child-Pugh A/B: reduce maintenance by 50% (C: NSR) (TDM)	NSR; oral formulation recommended as potential SBECD accumulation with IV formulation in renal impairment and CRRT		Dose on adjusted body weight
Neonate (<30 days of age)	Not routinely used in neonates. There is limited dosing information regarding the neonate population. IV doses of 12–20 mg/kg/day in two or three divided doses have been used.						
Posaconazole							
Adult	IV/oral (MR tablet)	300 mg twice daily	300 mg daily (TDM)	Child-Pugh A/B/C: usual dose	No dosage adjustment	No dosage adjustment (TDM)	No weight adjustment
Child 1–18 years‡	IV§	10 mg/kg twice daily (max 300 mg/dose)	10 mg/kg daily (max 300 mg/day) (TDM)	NSR	NSR	TDM	NSR
Neonate	IV	NSR	NSR	NSR	NSR	NSR	NSR
Anidulafungin							
Adult	IV	200 mg	100 mg daily (increase by 50–75% in critical illness)	Child-Pugh A/B/C: usual dose	No dosage adjustment	No dosage adjustment	Increase both loading and maintenance dose by 50%
Child	IV	3 mg/kg (max 200 mg/day)	1.5 mg/kg daily (max 100 mg/day)	NSR	NSR	NSR	NSR
Neonate	IV	3 mg/kg	1.5 mg/kg daily	NSR	NSR	NSR	NSR
Caspofungin							
Adult	IV	70 mg	50 mg daily (consider increase to 70 mg daily in critical illness)	Child-Pugh B: reduce maintenance to 35 mg daily	No dosage adjustment	No dosage adjustment	>80 kg: increase to 70 mg daily
Child >3 months	IV	70 mg/m^2 (max 70 mg)	50 mg/m^2 daily (max 50 mg or 70 mg in critical illness)	Child-Pugh B: reduce maintenance by 50%	No dosage adjustment	NSR	NSR
Neonate	IV	Not required	25 mg/m^2 daily	NSR	NSR	NSR	NSR
Micafungin							
Adult	IV	Not required	100 mg daily (consider increasing to 150 mg daily in critical illness)	NSR	No dosage adjustment	NSR	>75 kg: increase daily dose by 50–75%; up to 200 kg: dose = weight + 42

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Table 6 *Continued*

	Preparation	Loading dose (Day 1)	Maintenance dose	Hepatic impairment	Renal impairment	CRRT	Obesity
Child	IV	Not required	2–4 mg/kg daily (max 100–150 mg/day in critical illness)	NSR	No dosage adjustment	NSR	NSR
Neonate	IV	Not required	10 mg/kg daily†	NSR	NSR	NSR	NSR
Lipid formulations of amphotericin B							
Liposomal AmB							
Adult	IV	Not required	3 mg/kg daily	NSR; enhanced LF monitoring recommended	No dosage adjustment	No dosage adjustment	Dose based on adjusted body weight
Child	As above						
Neonate	As above						
ABLC							
Adult	IV	Not required	3–5 mg/kg daily	NSR	NSR	NSR	Dose based on adjusted body weight
Child	IV	Not required	5 mg/kg daily				
Neonate	IV	Not required	5 mg/kg daily				
Amphotericin B deoxycholate							
Adult	IV	Not required	0.6–1.0 mg/kg daily	NSR	Not recommended	Not recommended	Use the higher of 100 kg dosing or adjusted body weight
Child	IV	Not required	0.7–1.0 mg/kg daily	NSR	NSR	NSR	NSR
Neonate	IV	Not required	0.5–1.5 mg/kg daily	NSR	NSR	NSR	NSR
Flucytosine							
Adult	IV/oral	Not required	25 mg/kg four times daily (TDM)	NSR	NSR	NSR	Dose based on ideal body weight (TDM)
Child	IV/oral	Not required	25 mg/kg four times daily (TDM)	NSR	NSR	Dose adjustment required if CrCl <40 mL/min	NSR
Neonate	IV/oral	Not required	Week 1 of life: 25 mg/kg three times daily; otherwise, four times daily (TDM)	NSR	NSR	Dose adjustment required if CrCl <40 mL/min	NSR

†Dosing is extrapolated to children 1 month to <2 years old in the absence of robust data. ‡For paediatric dosing of oral posaconazole, use modified-release tablets if able to swallow tablets, >30 kg, use loading dose of 300 mg twice daily, then 300 mg daily from Day 2 onwards (TDM), use oral suspension if tablets not suitable: 1 to 6 years old: 200 mg four times daily; 7 to 12 years old: 300 mg four times daily; ≥13 years old: 200 mg four times daily (TDM), consult local tertiary pharmacy/AMS services. §Not licensed in children <18 years of age. ABLC, amphotericin lipid complex B; AmB, amphotericin B; AMS, antimicrobial stewardship; CRRT, continuous renal replacement therapy; CrCl, creatine clearance; HD, haemodialysis; IC, invasive candidiasis; IHD, intermittent haemodialysis; IV, intravenous; LF, liver function; MR, modified release; NSR, no specific recommendations (due to limited data); PO, per oral; SBECD, sulfobutylether-beta-cyclodextrin; SDD, susceptible dose dependent; TDM, therapeutic drug monitoring.

at lower risk for adverse outcomes.[22,154,158,159] However, azoles continue to have a role in the initial management of IC in specific patient populations, particularly those with low risk of mortality. In an attempt to guide rational azole use, studies have identified patients in whom fluconazole as initial therapy is unlikely to be successful. These include patients with haematological malignancy, mechanical ventilation, infection with *C. glabrata* or *P. kudriavzevii,* enteral nutrition, use of non-operative intubation/irrigation, longer time to start fluconazole therapy and prior use of antifungal therapies.[22,160]

Table 7 Management of IC syndromes in adults and children (excluding neonates)

Clinical setting	Recommended agents	SoR	QoE	Alternative agents	SoR	QoE	Comments	SoR	QoE
Hepatosplenic candidiasis (chronic disseminated) candidiasis)	LF-AMB or an echinocandin ≥2 weeks followed by an oral azole (choice according to susceptibilities; fluconazole for sensitive isolates)	C	III				Continue antifungal therapy while receiving immunosuppression and until hepatosplenic imaging abnormalities resolve (usually at least 6 months)[95–99]	C	III
							Cohort studies support the use of corticosteroids if fever persists for more than 1 week despite effective antifungal therapy and negative microbiological studies[95,98,100–103]	C	III
CNS candidiasis (meningitis or intracerebral abscesses)[104]	L-AMB 5 mg/kg daily ± flucytosine ≥2 weeks, followed by fluconazole 400–800 mg (6–12 mg/kg) daily	B	III	Fluconazole 800 mg daily (12 mg/kg) ± flucytosine	C	III	Continue therapy at least until stabilisation of symptoms and signs, radiological signs, and CSF abnormalities[46,105]	C	III
							Remove intraventricular devices[46,104]	C	III
							Voriconazole has excellent CSF penetration but clinical experience is limited[106]	C	III
							Intrathecal D-AMB has been used in refractory cases at doses of 0.01 mg to 1 mg in 2 mL of 5% dextrose daily[46,107]	C	III
Ocular candidiasis	Fluconazole 400–800 mg (6–12 mg/kg) daily or voriconazole	B	II	L-AMB 3–5 mg/kg daily plus flucytosine for fluconazole/ voriconazole resistant isolates[108–111]	B	III	Treat for 4–6 weeks and until ocular lesions have resolved[46,112]	B	II
							Consider intravitreal antifungal therapy for vitritis or macula involvement (D-AMB 5–10 μg in 0.1 mL sterile water, or voriconazole 100 μg in 0.1 mL sterile water)[46,112]	B	III
							Consider surgical vitrectomy in the presence of vitritis[46,112]	B	III
Candida osteoarticular infection	Fluconazole ± induction echinocandin ≥2 weeks	C	III	LF-AMB ≥2 weeks followed by fluconazole If the isolate is susceptible, voriconazole, posaconazole or itraconazole may be used for fluconazole-resistant infection	C	III	Treat native joint septic arthritis for ≥6 weeks[113]	B	II
							For prosthetic joint infection treated by two-stage revision, suggested antifungal duration has been ≥12 weeks between stages and ≥6 weeks after the second stage[114–116]	C	III
							Treat osteomyelitis for 6–12 months[117–119]	B	III

Table 7 *Continued*

Clinical setting	Recommended agents	SoR	QoE	Alternative agents	SoR	QoE	Comments	SoR	QoE
							Removal of prosthesis is suggested for prosthetic joint infection	A	II
							If removal of prosthesis not possible, chronic suppression with antifungals is recommended[120]	B	III
							Adjunctive surgery is indicated for septic arthritis and may be required for osteomyelitis[46]	B	III
Candida endocarditis and infection of implantable cardiac devices	LF-AMB 3–5 mg/kg daily ± flucytosine OR an echinocandin ≥2 weeks[121–125] followed by fluconazole 400–800 mg (6–12 mg/kg) daily[121,122,124–126]	B	II	If the isolate is susceptible, voriconazole or posaconazole may be used as step-down therapy for fluconazole-resistant infection	B	III	Valve surgery is recommended for valvular infection, and removal of the entire device is recommended for implantable cardiac device infection[127–129]	B	II
							Treat for ≥6 weeks for valvular endocarditis and ≥ 4 weeks for infection of implantable cardiac device[46,130,131]	B	II
							For those who do not undergo valvular surgery or removal of an infected implantable cardiac device, use long-term suppressive therapy	B	III
							Increased doses of echinocandins have commonly been used[124,132]	C	III
Symptomatic *Candida* cystitis or pyelonephritis or fungal balls[46,130,133]	Fluconazole 200 mg (3 mg/kg) daily (cystitis)	B	II	Flucytosine is an option for sensitive species which are fluconazole resistant where D-AMB is contraindicated, though resistance commonly develops	C	III	Continue therapy for 14 days; shorter courses of up to 7 days may be considered for D-AMB to limit toxicity	B	III
	Fluconazole 400 (6 mg/kg) daily for pyelonephritis	B	II	Echinocandins reserved for resistance or intolerance[134,135]	C	III	D-AMB bladder irrigation of 25–50 mg in 200–500 mL sterile water through nephrostomy tube can be considered for fluconazole-resistant fungal ball infection	C	III
	D-AMB 0.3–0.7 mg/kg daily for fluconazole-resistant species	B	III				Surgery is often required for fungal balls	B	II
							Indwelling catheters should be removed or replaced; also consider removal or	B	II

Table 7 *Continued*

Clinical setting	Recommended agents	SoR	QoE	Alternative agents	SoR	QoE	Comments	SoR	QoE
							replacement of stents and nephrostomy tubes		
Intra-abdominal candidiasis including peritoneal dialysis infection	Fluconazole for susceptible isolates	B	II	Echinocandins for empirical treatment, resistance or intolerance[136]	B	II	Treat if *Candida* species is isolated from an image-guided or surgically obtained intra-abdominal specimen	B	II
				If the isolate is susceptible, voriconazole or posaconazole may be used as step-down therapy for fluconazole-resistant infection	C	III	Source control with drainage and/or debridement is an important component of therapy[137–140]	A	II
							The peritoneal catheter should be removed in *Candida* peritoneal dialysis peritonitis[141]	A	II
							Empiric anti-*Candida* therapy may be considered in a patient at high risk of intra-abdominal candidiasis (e.g. necrotising pancreatitis, upper GI perforation, recurrent bowel leak) who is not improving with antibacterial therapy	B	II
							Treatment for ≥2 weeks, guided by clinical response[141]	B	II
Thoracic infection (empyema, mediastinitis, pericarditis)	Fluconazole for susceptible isolates	B	III	Echinocandins for empirical treatment, resistance or intolerance	B	III	Treatment is not recommended for *Candida* species isolated from the lower respiratory tract unless it represents disseminated infection (primary *Candida* pneumonia is very rare)[142–144]	B	II
				If the isolate is susceptible, voriconazole or posaconazole may be used as step-down therapy for fluconazole-resistant infection	C	III	Source control with drainage and/or debridement is an important component of therapy[145,146]	A	II
							Treatment for ≥2 weeks, guided by clinical response (for sternal osteomyelitis, see osteoarticular infection)	C	III

CNS, central nervous system; CSF, cerebrospinal fluid; D-AMB, amphotericin B deoxycholate; GI, gastrointestinal tract; L-AMB, liposomal amphotericin B; LF-AMB, lipid formulation of amphotericin B; QoE, quality of evidence; SoR, strength of recommendation.

Azole therapy as step-down antifungal therapy

Azoles are recommended for step-down therapy after response to echinocandin therapy and when a susceptible organism is isolated.[27,46,130,161] The safety of voriconazole or fluconazole step-down therapy after 5 days of anidulafungin was evaluated by Vazquez *et al.* 2014.[162] Patients with candidaemia who were afebrile for greater than 24 h, had cleared *Candida* from the bloodstream, were hemodynamically stable, were non-neutropenic and able to tolerate oral therapy, received step-down therapy. Global response rate (clinical and microbiological response) was no different in early switch patients (commenced an azole by Day 7) when compared to patients who continued anidulafungin beyond 7 days, and response was not influenced by *Candida* species. In the intensive care setting, de-escalation to fluconazole has been found to be safe and effective for fluconazole-susceptible infections.[156]

Amphotericin B therapy

Amphotericin B formulations remain an alternative for initial or ongoing therapy. Since the previous guidelines, a meta-analysis by Osa *et al.*[163] have reported data from three randomised controlled trials comparing conventional amphotericin B to fluconazole or voriconazole. Disease severity was moderate (APACHE II score 13.1–16.1) and no patients were neutropenic. Treatment success rate was lower in the azole group compared to conventional amphotericin B, at a dose of 0.5–0.6 mg/kg (RR = 0.90; $P = 0.04$). However, mortality was not significantly different (RR = 0.87; $P = 0.19$). While renal failure was significantly less common with azoles than with amphotericin B (RR = 0.26; 95% CI 0.10–0.68), liver and electrolyte abnormalities were not significantly different. Keane *et al.*[26] reported a systemic literature review of critical care patients with IC and found no difference in treatment efficacy or mortality in patients receiving an amphotericin B formulation compared to those receiving an echinocandin or voriconazole.

Duration of antifungal therapy

Duration of therapy for uncomplicated candidaemia should be a minimum of 2 weeks after the first negative blood culture (*Strong recommendation, Level II evidence*). Duration of therapy for uncomplicated candidiasis should be a minimum of 2 weeks following the initial positive culture (*Moderate recommendation, Level III evidence*).

Timing and type of step-down therapy

Step down from echinocandin to oral fluconazole or voriconazole therapy may be considered if the following criteria are met: afebrile for greater than 24 h; clearance of *Candida* from the bloodstream; hemodynamic stability; non-neutropenic; ability to tolerate oral therapy; and isolation of an azole susceptible organism[27,46,130,156,161,162] (*Strong recommendation, Level II evidence*). Fluconazole is recommended as step-down therapy for fluconazole-susceptible species. Fluconazole or voriconazole are suggested step-down therapy for susceptible *C. glabrata* complex and voriconazole is suggested step-down therapy for susceptible *P. kudriavzevii*. Posaconazole may be used as an alternative to voriconazole when the latter is poorly tolerated. However, there are limited clinical data regarding the efficacy of posaconazole for treatment of *Candida* infections.

Treatment of IC syndromes

Expert advice should be sought for patients with focal *Candida* infections who may also have candidaemia or infection at multiple sites, when therapy should take into account recommendations for candidaemia and consider antifungal penetration of affected organs.

Antifungal drug choice for focal IC is influenced by fungicidal versus fungistatic activity of specific antifungal agents, potential for inhibition of biofilm formation, susceptibility of the *Candida* isolate, and penetration at the site in question. Treatment recommendations for focal IC (Table 7) are supported by observational studies rather than randomised controlled trials, and quality of evidence for all recommendations is low to moderate. Lipid formulations of amphotericin B and echinocandins have fungicidal activity[164,165] and inhibit biofilm formation,[166] and are therefore preferred agents for initial therapy for disseminated candidiasis, endocarditis, implantable cardiac device infection and prosthetic joint infection. Of note, some pharmacokinetic data included below and in Table 8 are from animal studies and from uninfected subjects, which may not reflect the augmented tissue penetration that can potentially occur in the setting of inflamed tissue within a focal site of infection.

Antifungal concentration ratios of cerebrospinal fluid (CSF) and brain to plasma are shown in Table 8. Among amphotericin B-based agents, CSF and brain concentrations are highest for liposomal amphotericin B (L-AMB),[191] which along with fungicidal activity, leads to a recommendation for its initial use in central nervous system (CNS) *Candida* infections. Flucytosine may be given as an adjunct as it has favourable CSF penetration, and fluconazole, given its favourable CNS penetration, can be utilised as step-down therapy.

The choroid and retina are highly vascular areas with presumed penetration by most antifungal agents. However, the vitreous humour is variably penetrated with vitreous to plasma concentration ratios in Table 8

Table 8 Antifungal penetration of tissue/sites (tissue:plasma ratio, unless otherwise expressed)

Antifungal	CSF	Brain	Vitreous	Urine
Fluconazole	0.52–0.82[167–169]	1.16–1.30[170]	0.70[171]	2.20–10.0[133,170]
Isavuconazole	0.00[172]	0.09–0.90[172–174]	No data	<0.5% of the total dose[175]
Itraconazole	<0.10[176]	0.20[177]	0.00–0.10[178]	0.00[179]
Posaconazole	<0.01[180–183]	0.05–0.22[180]	0.21[184]	<0.01[185]
Voriconazole	0.38–0.68[106,176,186–188]	Concentration 1.20–1.90 μg/g[186]	0.40[189]	0.01[190]
Amphotericin deoxycholate	0.00–0.04 (concentration 0.023 mg/L)[191,192]	0.18–0.26 (concentration 0.33–0.37 μg/g)[191]	0.07–0.38 (concentration 0.16 mg/L)[193,194]	21% of dose[195]
Liposomal amphotericin	<0.01 (concentration 0.03 mg/L)[191]	0.03 (concentration 1.99–1.84 μg/g)[191]	0.03 (concentration 0.47 mg/L)[193]	Low[133]
Amphotericin B Lipid Complex	0.01–0.03 (concentration 0.02 mg/L)[191,196]	0.27–0.41 (concentration 0.25–0.35 μg/g[191]	Concentration 0.27 mg/L[193]	Low[133]
Echinocandins	0.00[197,198]	0.10–0.20[199]	<0.01[112,197,200]	0.02–0.38† (concentration 0.04–0.61 mg/L)[134]
5-Flucytosine	0.74[201]	No data	0.34[202]	Concentration >30 mg/L[133,203]

†Ratio of the micafungin concentration of 24-h collected urine to the trough plasma concentration at steady state. CSF, cerebrospinal fluid.

demonstrating optimal penetration by fluconazole, voriconazole and flucytosine. Of the amphotericin B formulations, the highest vitreous concentrations are with L-AMB.[193] Fluconazole, voriconazole or L-AMB with flucytosine are therefore recommended therapy for chorioretinitis with or without vitritis.

Urine-to-plasma concentration ratios are favourable for fluconazole but not for other azoles. Urinary flucytosine concentrations are >30 mg/L[133,203] and lipid formulations of amphotericin B have low urinary concentrations,[133] while 21% of the total amphotericin deoxycholate dose is excreted in the urine.[195] Micafungin urinary concentrations may reach therapeutic pharmacokinetic/pharmacodynamic targets,[134] and there is evolving evidence of the effectiveness of echinocandins for urinary infection.[135] Fluconazole is the preferred agent for susceptible urinary tract infections, with amphotericin B deoxycholate (D-AMB) or flucytosine used for treatment of azole-resistant infections. Echinocandin therapy should be considered if there is intolerance or resistance to other agents.

New and emerging therapies

Several new agents for the treatment of candidiasis have been developed and these have recently been reviewed.[147] Purported advantages of these agents include availability as oral formulations, activity against resistant isolates, fungicidal activity, options for combination therapy, favourable pharmacokinetic/pharmacodynamic properties and reduced drug–drug interactions.[147,204–207] One of the most advanced in development is rezafungin (CD101), a novel semi-synthetic echinocandin that targets the BDG synthase through structural modification of an ether ring and is administered weekly by intravenous infusion. It is active against *C. auris* and *FKS* mutants.[147,205,206]

Question 7: What are the pharmacological considerations in paediatric IC?

Recommendations

- Recommendations for initial antifungal therapies are summarised in Table 9, with prescribing recommendations provided in Table 6.

Neonates

IC in neonates can be a more insidious presentation than in children or adults, with high frequency of disseminated disease affecting most tissues and organs, including the CNS. Given the low blood volumes available for culture and hence, low sensitivity of blood culture in neonates to detect candidaemia, isolated candiduria frequently heralds disseminated *Candida* infection and warrants treatment.[46] Although there are limited pharmacokinetic data, D-AMB is well tolerated in neonates and is not associated with a high risk for nephrotoxicity, such that it and fluconazole continue to be used for treatment of neonatal IC.[46,79,209] Lipid formulations of amphotericin B may have limited urinary penetration and concern about appropriate dosing,[210] but no significant difference in outcomes compared with D-AMB.[211] Flucytosine is not recommended in very low birth weight infants without careful TDM, haematological and biochemical monitoring, due to poor renal function and, thus, an increased risk of cytopenias.[46]

Table 9 Recommended first-line antifungal therapy for paediatric patients with candidaemia prior to susceptibility testing[208]

Clinical state	Antifungal agent (SoR/QoE)													
	Azole				Echinocandin						Amphotericin B			
	Fluconazole		Voriconazole		Anidulafungin		Caspofungin		Micafungin		L-AMB		D-AMB	
Critically ill or neutropenic														
Children and adolescents	B	II	C	II	B	II	A	I	A	I	A	I	C	II
Neonate	NR		NR		NR		C	III	B	II	B	II	B	II
Clinically stable with no neutropenia or risk factors for azole resistance														
Children and adolescents	B	I	C	II	C	II	A	I	A	I	B	II	C	II
Neonate	B	II	NR		NR		C	II	B	II	B	II	B	II

D-AMB, amphotericin B deoxycholate; L-AMB, liposomal amphotericin B; NR, not recommended; QoE, quality of evidence; SoR, strength of recommendation.

Use of echinocandins is limited by low concentrations in the CNS and urinary tract, and so the data are limited for use in neonates. Micafungin is the only echinocandin approved for use in neonates. A systematic review showed 73% complete clinical response in IC[212] and a recent randomised controlled trial compared intravenous micafungin 10 mg/kg/day to intravenous D-AMB 1 mg/kg/day for ≥21 days (up to 28 days in infants without end-organ dissemination and up to 42 days in infants with end-organ dissemination) for infants aged 2–120 days with IC, of whom 25/30 enrolled were neonates. The trial was terminated early due to poor recruitment, at which time micafungin compared to D-AMB showed fungal-free survival of 60% versus 70%.[213] Higher doses of micafungin (4–10 mg/kg/d) in neonates are recommended because of increased clearance[211,214] and dose-dependent penetration into neonatal CSF.[215] Echinocandins should be administered to neonates only when CNS disease is excluded or if other recommended treatment fails. With the uncertainty about optimal dosing and limited studies, subtherapeutic antifungal dosing in neonates is frequent and widespread.[216]

Infants and children

The principles guiding the choice of antifungal agent in children are similar to those discussed for adults, with similar therapeutic considerations based on the local epidemiology and severity of illness. Antifungal dosing cannot be extrapolated from adult studies, as children have a greater volume of distribution, higher drug elimination and different toxicity profiles, all variables which change during childhood (see Table 6 for dose recommendations).

Echinocandins and L-AMB are the first-line agents in the treatment of IC and candidaemia both for immunocompetent and immunocompromised paediatric patients.[208] Since the 2014 Consensus Guidelines,[1] the few randomised controlled trials available show equivalent outcomes with echinocandins (mainly caspofungin) and L-AMB, and fewer adverse effects with echinocandins.[217,218] A recent meta-analysis, which included five randomised control trials of 354 patients (191 patients in the echinocandins group and 163 patients in the amphotericin B group), showed no differences in efficacy between the echinocandins and amphotericin B (D-AMB or L-AMB) in the treatment of IC in children (OR 1.38), although the echinocandin group had a significantly lower risk of discontinuing treatment than the amphotericin B group.[217] In children, echinocandin choice has been dictated by licensing in children and with limited safety and dosing data predominantly available for micafungin or caspofungin, these are favoured. Nonetheless, anidulafungin has emerging evidence for safety and efficacy with global response success rate of 70.8% in children and 68.8% in infants (1 month to 2 years of age), with similar pharmacokinetics to adults.[219]

Question 8: What are the optimal non-pharmacological approaches for the management of IC?

Recommendations

- Recommendations for non-pharmacological management are summarised in Table 10.

Central venous catheter (CVC) removal following candidaemia

The presence of a CVC presents a significant risk factor for candidaemia. Many observational studies have identified CVC removal as a key determinant of mortality, with improved clinical outcomes and reduced 7-day, 30-day and overall mortality following removal.[149,220–227] The impact of CVC removal on candidaemia-related mortality in the ICU population is variable, with some studies showing no[228] or only early survival benefit.[229] Catheter removal is particularly challenging in neutropenic patients, with these patients less likely to undergo CVC removal in several studies.

Table 10 Non-pharmacological management of candidaemia

Management	Recommendation	SoR	QoE
Vascular catheter removal	Early removal of vascular catheters where possible	A	I
	When catheter removal is not possible, an echinocandin or lipid formulation of amphotericin B is preferred for biofilm penetration	C	III
Infectious diseases consultation	All patients with candidaemia should receive an infectious diseases consultation	A	I
Echocardiography	TOE is preferred to TTE in patients with prosthetic heart valves and candidaemia	A	II
	Echocardiogram should be performed in in all patients with candidaemia and risk factors for endocarditis (e.g. prosthetic heart valves, implantable cardiac device, valvular heart disease, persistent positive blood cultures, new heart murmur, heart failure, embolic phenomena, prolonged presence of CVC)	B	III
	Echocardiogram should be considered for all patients with candidaemia	B	III
Ophthalmological review	Ophthalmological examination should be considered in all patients with candidaemia	B	III
	Ophthalmological examination is recommended for all neonates with candidaemia or candiduria	A	III
Bundles	Multimodal strategies for management of candidaemia should be implemented in healthcare settings	A	II
Antifungal stewardship	Healthcare facilities managing patients with invasive candidiasis and candidaemia should implement an antifungal stewardship programme inclusive of antifungal post-prescription review	A	II

CVC, central venous catheter; QoE, quality of evidence; SoR, strength of recommendation.

Optimal timing of CVC removal has not been determined. Lee *et al*. investigated the impact of delayed removal (retention more than 2 days after the onset of candidaemia) and found increased 30-day mortality related to delayed CVC removal (adjusted odds ratio (AOR) = 4.7).[230] Notably, a benefit of CVC removal was only apparent in patients with low Charlson Comorbidity Index, particularly in the presence of septic shock.

Echinocandins and lipid formulations of amphotericin B are effective against both planktonic and biofilm *Candida* populations, with activity demonstrated in animal models of CVC-related infections.[231–233] While yet to be demonstrated in human trials, this theoretical benefit has led to these agents being preferred treatment options in clinical circumstances where a CVC cannot be removed.

Echocardiogram

The reported incidence of infective endocarditis following candidaemia is between 1.9% and 11.5%.[22,229,234–237] Recurrence of candidaemia in those with endocarditis has been reported in up to 27% of cases[238] and mortality is approximately 50%.[235,238,239] Risk factors for endocarditis include valvular heart disease, prosthetic heart valves, injecting drug use, cancer chemotherapy, prolonged presence of CVC, prior bacterial endocarditis and an unknown source of infection.[234,240] Foong *et al*. reported an endocarditis incidence of 2.5% with candidaemia.[235] Patients with valvular heart disease had a seven-fold increased risk of endocarditis. Conversely, a reduced risk of endocarditis was noted in patients with a haematological malignancy, with infection due to *C. glabrata* complex and receipt of total parenteral nutrition therapy, with an AOR of endocarditis of 0.09, 0.17 and 0.38 respectively. Of the 47 patients with endocarditis, the initial investigation was transoesophageal echocardiogram (TOE) in 9 and transthoracic echocardiogram (TTE) in 38. Infective endocarditis (IE) was detected by TTE in 17/38 (45%) with the remaining 21 cases detected on subsequent TOE.

A prospective cohort study investigating routine echocardiography following 263 episodes of candidaemia[234] detected endocarditis in 11 cases, 3 of which were unsuspected. Of the 187 patients who underwent echocardiography, 11 (5.9%) had findings that indicated IE. The diagnostic yield of IE in patients with candidaemia was 2.9% (5/172) for TTE and 11.5% (10/87) for TOE. The prevalence of endocarditis was 33% in

patients with prosthetic heart valve, 9% in patients with at least one risk factor (valvular prosthesis, persistent candidaemia or previous valve disease) and 3.1% in those without risk factors.

Ophthalmological examination

Ocular candidiasis refers to endogenous *Candida* infection of the posterior chamber of the eye, manifesting as either chorioretinitis with or without macular involvement or chorioretinitis with extension into the vitreous (endophthalmitis).[241] Overall loss of visual acuity ranges from 30% to 55%, with a more favourable visual outcome for chorioretinitis than vitreous involvement. Reported rates of ocular candidiasis following candidaemia are highly variable, spanning 1–20%.[22,236,242–249]

One study of patients with candidaemia identified ocular lesions in 60/370 patients (16%).[108] Of these patients, 6 (10%) had vitreous involvement, 34 (57%) had probable chorioretinitis and 20 (33%) had possible chorioretinitis. In all, 82% were detected at baseline fundoscopy. However, a further 18% were detected on repeat fundoscopy. Only one patient was symptomatic at baseline. No episodes of chorioretinitis progressed to vitreous involvement, and all but two evaluable patients responded to medical therapy. Patients with ocular involvement had a longer duration of candidaemia than those without.

A more recent systematic review of 38 studies attributed discrepancies in incidence rates of ocular candidiasis to over-reporting and inconsistencies in the definition of endophthalmitis.[241] Application of rigorous definitions led to a reported incidence of vitreous involvement of 0.9% and chorioretinitis of 2.3%. Consequences of missing and not appropriately modifying therapy for ocular candidiasis may be loss of sight, and clinical stratification is limited by the largely asymptomatic nature of early ocular involvement, so ophthalmological assessment is recommended in all patients, particularly patients who do not rapidly clear blood cultures and patients with neutropenia. In patients with neutropenia, a repeat ophthalmological assessment after neutrophil recovery is suggested.

Care bundles

Implementation of multimodal strategies (or 'care bundles') for the management of candidaemia results in improved process and outcome, including enhanced compliance with clinical guidelines and a survival benefit.[223] Bundle elements typically include between 5 and 10 interventions and may be grouped as a two-step bundle (i.e. initial and ongoing management of candidaemia).[226] Individual components are evidence-based and supported by local or international guidelines.[223,224,226,250,251] Examples of bundle elements include early removal of CVC, use of appropriate antifungal therapy (agent, dose and duration), collection of follow-up blood cultures until clearance of candidaemia, review of clinical efficacy following commencement of therapy and use of step-down oral therapy for uncomplicated infections.[158,250,251]

The efficacy of care bundles is associated with compliance with the elements of the bundle.[250] In large studies with high levels of compliance, a reduced mortality rate was demonstrated (OR 0.08–0.61), with the greatest impact on early (7–14 day) mortality.[226,251]

Infectious diseases consultation

Infectious diseases consultation has been demonstrated to significantly improve mortality at 30,[230,252,253] 60[230] and 90 days,[227,252] and overall survival.[254] A recent meta-analysis[252] of 10 studies found a reduction in mortality from 47.6% to 28.4% (pooled OR 0.41). Mejia-Chew *et al*. reported on the largest cohort analysis of 1694 episodes of candidaemia and identified that an adjusted hazard ratio (HR) of 0.81 (95% CI: 0.73–0.91; $P < 0.0001$) for mortality (survival benefit 19%) was associated with infectious diseases consultation. In this study, the number of infectious diseases consultations required to prevent one death from candidaemia was five.[227]

The impact of infectious diseases consultation appears to be associated with recognition of the significance of a positive culture and improved adherence to guidelines. When an infectious diseases consultation occurred, blood cultures were less frequently ignored and fewer patients had untreated candidaemia.[227,253] Higher rates of assessment for, and treatment of, complications of candidaemia were reported by Kobayashi *et al*., with increased rates of ophthalmological examination (pooled OR 6.1), echocardiogram (pooled OR 3.01) and CVC removal (pooled OR 3.27).[252] Two studies have reported that infectious diseases consultation reduced time to appropriate therapy and was associated with more rapid resolution of fungaemia.[230,254] In several studies, infectious diseases consultation was associated with higher rates of diagnosis of endocarditis or endophthalmitis.[227,230,254]

AFS and guideline implementation

Measuring the impact of AFS interventions in the management of candidaemia is confounded by the diversity of programmes and interventions. In a systematic review, Bienvenu *et al*. concluded that active intervention, such as post-prescription review, had more impact than guideline implementation.[255] Reported outcomes include reduced mortality,[256–258] reductions in time to appropriate antifungal therapy,[259–261] reduced antifungal consumption,[256–258,262] reduced number of patients

treated for IC,[256] improved guideline or bundle of care adherence,[260,263] increase in optimal antifungal prescribing[262,264,265] and reduced cost.[257,262] Implementation of an educational antimicrobial stewardship (AMS) programme focusing on appropriate antibacterial therapy resulted in a reduction in the incidence and mortality rate of hospital-acquired candidaemia.[266]

Studies have demonstrated a survival benefit of AFS programmes in individuals with IC. Rautemaa-Richardson *et al*. reported a fall in crude mortality due to IC from 45% to 19%, Kawaguchi *et al*. observed a non-significant decrease in 30-day mortality (40.9–30.0%) and in-hospital mortality (63.6–36.7%), and Martin-Gutierrez *et al*. reported a fall in 14-day crude death rate over a 9-year period from 0.044 to 0.0017 per 1000 bed days ($P = 0.09$).[256–258]

Significant improvements in prescribing parameters have been reported following implementation of AFS programmes, including increases in appropriate therapy,[265] optimal dosing[262] and reductions in inappropriate antifungal prescriptions.[255,256] Time to effective therapy has been observed to improve from median 13.5 to 1.3 h[261] and by 1.5 h in another study,[260] and overall reductions in antifungal consumption reported.[256,258]

Question 9: What are the recommended infection prevention measures for *C. auris* and other species in haematology/oncology and intensive care settings?

Recommendation

• If a case of *C. auris* is identified in a haematology/oncology or ICU population, infection prevention and control measures are required, including isolation, screening of close contacts and environmental cleaning (Moderate recommendation; Level III evidence).

Targeted prevention strategies have been employed to reduce the spread of infection in response to outbreaks of *Candida* infections in healthcare settings. For example, the requirement for enhanced hand hygiene in outbreaks of *P. kudriavzevii* candidaemia,[267] and a strong focus on prevention of CVC-related infections have been identified as effective in reducing rates of IC.[268] Recently, *C. auris* outbreaks have been reported in a range of healthcare settings, including ICU, general wards and haematology/oncology wards.[11,269–272] Given the risk of healthcare-associated transmission, antifungal resistance and potential mortality, infection prevention and control measures are recommended if a case of *C. auris* is identified in haematology units or ICU settings.[11,273] Patients colonised or infected with *C. auris* should be placed in a single room and managed using standard and contact precautions.[57]

Several strategies are required to curb transmission.[274] Such measures include timely identification of *C. auris* in clinical and screening specimens. Given the potential for phenotypic identification methods to misidentify *C. auris* as other *Candida* species, timely identification by laboratories requires confirmatory testing with MALDI-TOF MS (matrix-assisted laser desorption/ionisation-time of flight mass spectrometry) or molecular diagnostics.[57,275] Whole genome sequencing plays an important role in identifying clusters and transmission pathways.[37]

When an index case is identified, screening of close contacts is recommended. Potential contacts include patients treated on the same ward where and when a patient with *C. auris* was resident, and those who occupied a room recently vacated by a patient with *C. auris*.[276] In addition, screening of patients transferred from regions or facilities with recognised disease burden is another important element of prevention activities.[277] For screening purposes, composite bilateral swabs of axilla and groin, in addition to sampling of other sites of potential clinical infection (e.g. urine from catheterised patients), are recommended.[57,278]

Other prevention measures include optimal hand hygiene practices, environmental cleaning, cohorting of patients and healthcare workers, and avoiding the sharing of medical equipment.[57,276,279]

Implications for future research

Management of candidaemia is dependent on timely identification. Diagnosis rests largely upon appropriate collection of clinical specimens (tissue or fluid) for culture. Further studies focused on the utility of rapid and non-culture-based testing are required to determine specific roles in clinical practice. The emergence of *C. auris* and other *Candida* species with antifungal resistance has highlighted the need for surveillance programmes and laboratory networks to ensure that changes in epidemiology and susceptibility are identified. Implementation of non-pharmacological approaches to management has not been reviewed in Australia, and these require evaluation to support quality improvement activities. New antifungal agents are also required, and outcomes of clinical trials are awaited (e.g. rezafungin). Whole genome sequencing is likely to provide additional insight into antifungal resistance monitoring and characterisation of transmission dynamics where clusters of infection are identified (e.g. *C. auris*).

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Conclusion

Immunocompromised adult and paediatric populations are at high risk for IC, including BSI and deep-seated infection. In Australia, non-*albicans Candida* species have emerged as significant causes of candidaemia in haematology and ICU populations, with recent reports of drug-resistant isolates (e.g. *C. auris*). Culture of clinical specimens remains the gold standard for diagnostic testing, providing necessary identification to species-level as well as antifungal susceptibility testing. Non-culture-based tests have the potential to enable rapid and timely diagnosis, and negative predictive value is of clinical benefit in low-prevalence settings. Current evidence and local epidemiology support use of echinocandin agents as first-line therapy for candidaemia and following clinical improvement, azole agents used for step-down therapy according to species identification and review of antifungal susceptibility profile. Treatment approaches for specific IC syndromes (e.g. urinary tract, CNS, eye) should be based upon the need for fungicidal mode of action, biofilm activity, tissue penetration, as well as the need for surgical intervention. Notably, non-pharmacological management of IC is recommended to ensure improved patient outcomes, including infectious diseases review, use of multimodal care bundles, and implementation of antifungal stewardship programmes.

Acknowledgements

The authors would like to thank members of the Australasian Leukaemia & Lymphoma Group (ALLG), the Australasian Society for Infectious Diseases (ASID), the Australian & New Zealand Children's Haematology/Oncology Group (ANZCHOG), the Medical Oncology Group of Australia (MOGA) and the Haematology Society of Australia and New Zealand (HSANZ) for their review of the draft manuscript, and Dr. Candice O'Sullivan and Angelica Papanicolaou from Wellmark Pty Ltd. for their assistance in preparing the manuscript for submission.

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