Yeast Infections

15

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15.1 Introduction

Invasive fungal disease (IFD) caused by yeasts and yeast-like pathogens are important infection-related complications in patients with underlying haematological malignancy, specifically after both autologous and allogeneic hematopoietic stem cell transplantation (HSCT). Donor sources such as the umbilical cord or mismatched unrelated donors have expanded HSCT availability but with increased risk of IFD (Kontoyiannis et al. 2010). The epidemiology of yeast infections varies with antifungal prophylaxis practices and varies by geographical region. Nonetheless, bloodstream *Candida* infections (candidaemia) and other forms of invasive candidiasis (IC) remain the most common IFD (Kontoyiannis et al. 2010; Cornely et al. 2015). *Cryptococcus* and more uncommon pathogens such as *Trichosporon*, *Geotrichum*-like, *Rhodotorula, Saccharomyces cerevisiae* or *Malassezia* and species also cause serious infections (Kontoyiannis et al. 2010; Chitasombat et al. 2012; Chaaban et al. 2014). Accurate diagnosis will assist with selection of best practice antifungal therapy and other treatment. In this chapter, we focus on the management of yeast infections in haematological malignancy. The aetiology, risk factors and diagnostic approaches are also briefly discussed.

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15.2 *Candida* Infections

15.2.1 Epidemiology, Risk Factors and Clinical Features

IC in the setting of haematology and HSCT carries with it both high mortality (≈40%) and excess hospital-related costs (Ananda-Rajah et al. 2012; Cornely et al. 2015). Its occurrence has long been substantively reduced by widespread use of azole prophylaxis in cancer chemotherapy and in HSCT conditioning regimens

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(Slavin et al. 1995). Estimates from after 2010 indicate an incidence of IC in patients with underlying haematological malignancy of 1.4 cases/1000 admissions in one study (Gamaletsou et al. 2014) with the Transplant Associated Infections Surveillance Network (TRANNET) noting an incidence of 1% and 1.1% at 6 and 12 months, respectively, after HSCT (Kontoyiannis et al. 2010). An incidence of fungaemia of 1.55% in HSCT was reported in Europe with 90% of such infections due to *Candida* spp. (Cornely et al. 2015). Variation in IC rates depends on differences in local practices and transplant conditioning regimens.

Risk factors for IC in patients with haematological malignancy are well known. Especially pertinent are status of underlying cancer, neutropenia, older age, corticosteroid use, recent HSCT (<6 months), recent broad-spectrum antibiotic use, total parenteral nutrition (TPN) and intensive care unit (ICU) admission (Slavin et al. 2010; Hoenigl et al. 2012; Hsu et al. 2015). Established candidaemia risk factors including disruption of the gastrointestinal mucosa after chemotherapy, radiotherapy or surgery also apply to haematology patients as does placement of a central venous access device (CVAD) (Slavin et al. 2010; Andes et al. 2012). The shift in epidemiology from *Candida albicans* to non-*albicans Candida* spp. is particularly well manifested. Specifically, *Candida glabrata*, *Candida krusei* and other non-*albicans Candida* spp. are more common in HSCT patients compared with, e.g. solid organ transplant recipients (Lockhart et al. 2011). *C. glabrata* is associated not only with traditional candidaemia risk factors but also with prior azole exposure (Alexander et al. 2005; Trubiano et al. 2015). This species is not only less susceptible to azole antifungals but, in some countries, associated with both echinocandin and multi-drug resistance (Alexander et al. 2013; Wang et al. 2015; McCarty et al. 2018)), which impacts the choice of treatment (**see below**). Clinicians should also be alert to previously rare but emerging species, most recently *Candida auris* with its associated multidrug-drug resistant characteristics (reviewed in (Forsberg et al. 2019).

Clinical features of IC and non-*Candida* yeast infections in haematology patients are summarized in Table 15.1. Clinical presentation as candidaemia remains the most common. As patients are often receiving antifungal prophylaxis, candidaemia is typically occurring as "breakthrough" infection accounting for up to 50% of IFD in HSCT patients (Slavin et al. 2010; Cornely et al. 2015) and may be associated with resistance to one (most often the azoles) or more classes of antifungal drugs (Alexander et al. 2013). IC per se has been reported as an independent predictor of death in HSCT (Falagas et al. 2006; Hsu et al. 2015).

Other clinical syndromes include disseminated IC, which is now uncommon. Patients may present with persistent fever after neutrophil

Table 15.1 Clinical syndromes of yeast and yeast-like pathogens in haematological malignancy and hematopoietic stem cell recipients

	Clinical syndrome							
Pathogen	Fungaemia	Lung	Abdominal disease	Skin/soft tissue	CNS	Eye	Cardiac	Hepato-splenic
Candida spp.	+++	+[a]	+++	+	+	++	+	+++
Cryptococcus spp.	+	+++	+	+	+++	+	+	+
Trichosporon spp.	+++	+[a]	++	++	+	+	+	++
Geotrichum-like spp.	+++	+[a]	++	++	+	+	+	++
Rhodotorula spp.	+++	+[a]	+	+	+	+	+	+
Saccharomyces spp.	+++	+[a]	+	+	+	+	+	+
Malassezia spp.	+++	+[a]	+	+++	+	+	+	+

Abbreviations: *CNS*, central nervous system

+, relatively uncommon; ++, common; +++, very common

[a]Lesions occurring by haematogenous dissemination responsible for bilateral nodular lesions

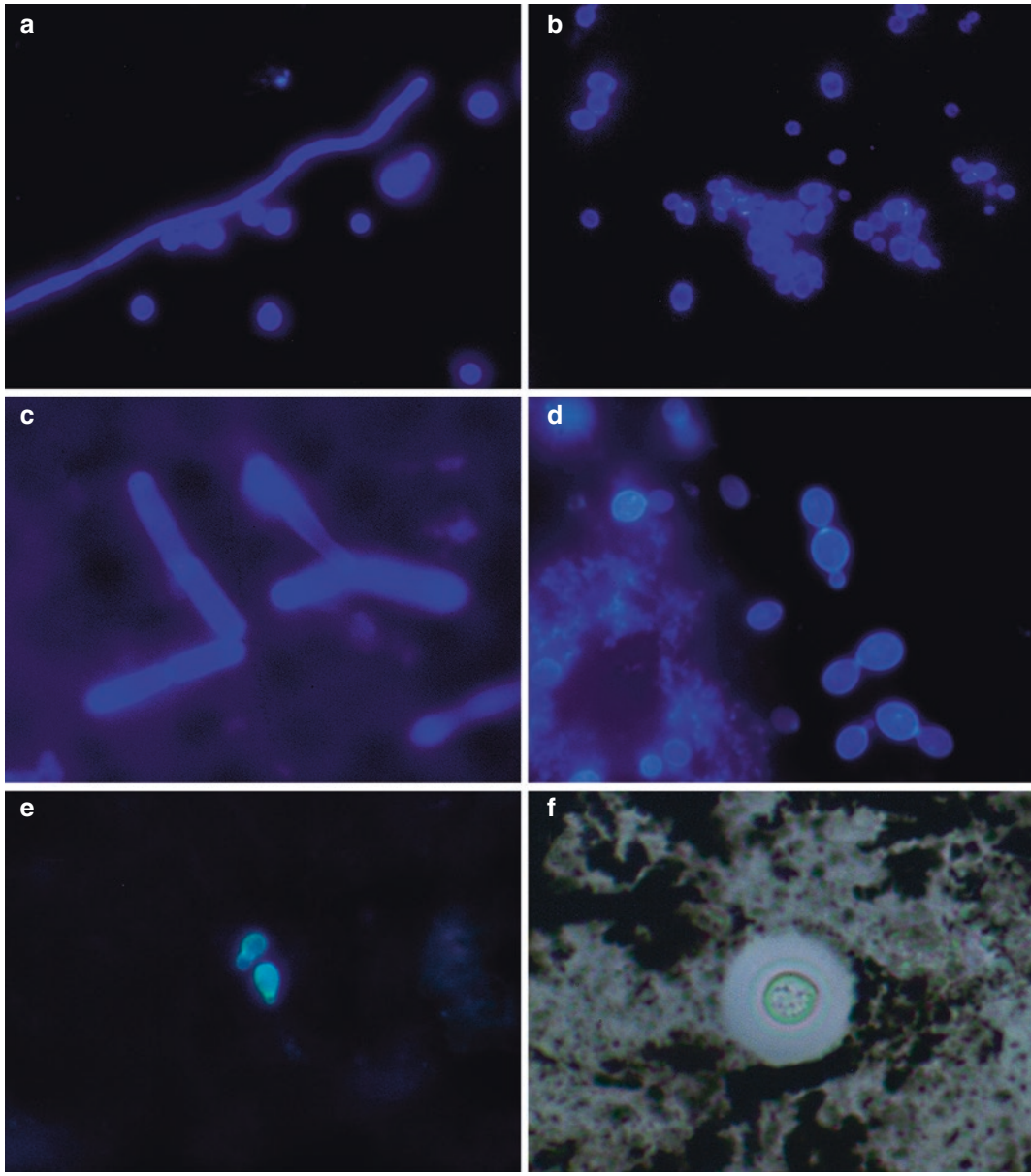

Fig. 15.1 Microscopic examination of *Candida* and non-*Candida* yeasts responsible for infections in haematology. (**a**) *Candida albicans* from a blood culture (x400 magnification, calcofluor staining), (**b**) *Candida glabrata* from a blood culture (x400 magnification, calcofluor staining), (**c**) *Saprochaete clavata* from a blood culture (x400 magnification, calcofluor staining), (**d**) *Rhodotorula mucilaginosa* from a blood culture (x1000 magnification, calcofluor staining), (**e**) *Malassezia pachydermatis* from a sinus aspirate (×400 magnification, calcofluor staining), (**f**) *Cryptococcus neoformans* from a bronchoalveolar lavage (×400 magnification, India ink examination)

recovery, accompanied by lesions (abscesses) in the kidneys, liver, spleen and lungs. A subset of patients may have hepato-splenic candidiasis, with lesions confined to the liver and spleen (Rammaert et al. 2012). Culture of affected tissue is often negative although yeasts and granulomatous changes are a clue for histopathological examination (Fig. 15.1).

15.2.2 Diagnostic Approaches

Diagnosis of IC still mostly relies on culture-based approaches. For candidaemia, blood cultures are the cornerstone of diagnosis and allow an isolate for antifungal susceptibility testing (Arendrup et al. 2012). Blood cultures for IC, although specific, lack sensitivity (<50%), and all forms of IC are limited by delayed time to positivity of result (2–3 days) (Clancy and Nguyen 2013).

Hence, non-culture-based methods are often used to assist with diagnosis. Of these, the serum beta-D-glucan (BDG) test can be a useful adjunctive tool in haematologic malignancy and other patients. However, in general and encompassing all haematologic patient groups, its widespread use is limited by variable sensitivity (50–100%) and specificity (45–100%) as well as negative predictive value (NPV; 73–100%). Specificity can be improved by obtaining two consecutive BDG results but at the expense of sensitivity. Importantly, more extensive studies of its utility in the haematology setting are required. While meta-analyses clearly point out very high sensitivity and specificity of the test for diagnosing IC, the test may be less sensitive in certain settings, with only 36% of candidaemia detected at the time of diagnosis in one study (Angebault et al. 2016). In another study of haematology patients, serum BDG testing had insufficient sensitivity for detecting breakthrough candidaemia (Abe et al. 2014). In part, the wide range of performance may be explained by difficulties of performing the test, which is prone to contamination. Since BDG is a panfungal biomarker, a positive test should prompt investigations for other IFDs, such as invasive aspergillosis or pneumocystosis (Karageorgopoulos et al. 2011). A detailed discussion of the serum BDG test is beyond the scope of this chapter and information relating to its incorporation into diagnostic algorithms are found in the Infectious Diseases Society of America guidelines for managing candidiasis (Pappas et al. 2016) and in one meta-analysis (Karageorgopoulos et al. 2011). For the present, where employed, serial testing is recommended with interpretation of results in conjunction with clinical and laboratory parameters.

Molecular methods to detect *Candida* in blood or blood cultures have likewise been developed but methodologies are not standardized, limiting their routine use. Data to support its routine use in HSCT are also lacking. Nguyen et al. found that PCR was more sensitive than blood cultures for diagnosis of intra-abdominal candidiasis, although there were no haematology/HSCT patients included in that study (Nguyen et al. 2012). Also, one FDA-approved assay, the T2 magnetic resonance (T2MR) assay, is available in the USA and Europe, which has the advantage of detecting *Candida* in whole blood specimens as opposed to blood cultures. A multicentre study, which included HSCT recipients (43% of study patients), showed a sensitivity of 91%, specificity of 98% and NPV of 99% for *Candida* spp. with time to negativity reduced to 4.4 hours (cf. 2–5 days (Mylonakis et al. 2015). However, test sensitivity was much lower in other real-life studies (Muñoz et al. 2018; White et al. 2018). Hence, whilst holding promise, experience with this new method is limited and results should be interpreted in a clinical context.

15.2.3 Treatment

The treatment principles for IC and candidaemia in the haematology and HSCT setting are similar to those provided in clinical practice guidelines for other populations (Cornely et al. 2012; Chen et al. 2014; Pappas et al. 2016).

15.2.3.1 Empirical Antifungal Treatment and General Practice Considerations

Empirical therapy should be tailored to local epidemiology and *Candida* species distribution. In addition, the site of infection, patient's clinical status and history of antifungal exposure and—if known—*Candida* colonization status may assist in the choice of antifungal agent. Although the value of empirical therapy is debated, it is clear that delay in appropriate antifungal treatment is associated with poor outcomes (Taur et al. 2010). Hence, it is reasonable for patients at high risk for IC with no explanation for fever or clinical symp-

toms to be treated with antifungal drugs on an empirical basis.

For candidaemia, treatment recommendations for patients who are neutropenic, or who are hemodynamically unstable, or who have had recent azole exposure (e.g. as antifungal prophylaxis) include an echinocandin (micafungin, caspofungin or anidulafungin) or a lipid formulation of amphotericin B (e.g. liposomal amphotericin B [L-AMB]) as primary treatment; however, voriconazole can be used in situations in which additional mould coverage is required (Chen et al. 2014; Pappas et al. 2016). Should the patient be non-neutropenic and haemodynamically stable, treatment with fluconazole is an acceptable alternative to the above (Cornely et al. 2012; Pappas et al. 2016). If a patient was recently colonized with *Candida* spp., consideration of the relevant species-specific susceptibility profiles is recommended. If recent echinocandin exposure has occurred/there are concerns about echinocandin resistance, the empirical use of L-AMB or voriconazole is recommended (Pappas et al. 2016). That said, available data do not indicate less favourable outcomes associated with empiric fluconazole and voriconazole, compared with lipid amphotericin formulations or an echinocandin; however, many experts favour the latter, which are fungicidal and sometimes better tolerated, as first-line agents in neutropenic patients (Pappas et al. 2016). Doses of antifungals commonly used to treat IC are shown in Table 15.2; isavuconazole use is not included in the table but briefly discussed (in Sect. X 1.4). Removal of CVADs as early as possible is strongly recommended (Andes et al. 2012). When this is not possible, an echinocandin is preferred for its anti-biofilm activity (Pappas et al. 2016).

For all cases of IC, screening for involvement of the eye, heart, abdomen and other organs is indicated. The incidence of ocular candidiasis in patients with candidaemia is estimated at 12.5–26% and if there is retinal disease at diagnosis, an echinocandin should not be used alone as this drug class does not achieve therapeutic levels in vitreous fluid in contrast to azoles (Khalid et al. 2014; Pappas et al. 2016). Antifungals excreted through the renal tract, e.g. fluconazole and 5-flucytosine, are more effective in *Candida* pyelonephritis, cystitis and fungal balls. Intra-abdominal candidiasis may be difficult to diagnose and should be suspected at least, particularly in the event of major gastrointestinal surgery. Repeat blood cultures to ensure that fungaemia has cleared during antifungal therapy should be performed. In general, the duration of therapy for candidaemia without metastatic complications is 2 weeks after established clearance of *Candida* from the bloodstream and with resolution of clinical symptoms attributable to candidaemia (Pappas et al. 2016).

The frequency of *Candida* endocarditis is difficult to estimate due to differences in clinical practice and differential use of transthoracic vs. transoesophageal echocardiography but varies between 4.2 and 17% (Lefort et al. 2012; Fernández-Cruz et al. 2015). Echocardiography is strongly recommended, especially in the presence of prosthetic cardiac valves.

15.2.3.2 Targeted Antifungal Treatment and Treatment of Invasive Candidiasis Conditions

For candidaemia, antifungal therapy should be modified according to the causative pathogen and its antifungal susceptibility profile with targeted "step-down" therapy. In the event of infections due to an azole-susceptible isolate, fluconazole (12 mg/kg loading dose then 6 mg/kg daily) can be used for step-down therapy even if the patient is neutropenic but clinically stable and, for example, has documented bloodstream clearance; voriconazole (see Table 15.2 for doses) may also be used (Pappas et al. 2016). Other azoles, e.g. posaconazole or isavuconazole, are alternatives in this context but historically there is far less (although growing) experience with their use in IC. The choice of azole should always be guided by the organism's susceptibility profile. Where the isolate is not azole-susceptible, then echinocandin or lipid amphotericin B therapy should be continued.

Table 15.3 summarizes the various forms of the suggested treatment for non-candidaemia IC including ocular candidiasis, central nervous

Table 15.2 Doses of commonly used antifungal agents in the treatment of invasive candidiasis in adults and children

Antifungal agent	Route	Recommended dose (adults)	Recommended dose (children)
Amphotericin B deoxycholate	IV	0.6–1 mg/kg daily	0.7–1 mg/kg daily
Liposomal amphotericin B	IV	3 mg/kg daily	3 mg/kg daily
5-flucytosine[a,b]	IV or oral	25 mg/kg 6 hourly	25 mg/kg 6 hourly
Fluconazole[b]	IV or oral	Loading: 12 mg/kg (single dose) Maintenance: 6–12 mg/kg daily	12 mg/kg daily
Voriconazole[c]	IV or oral	Loading: 6 mg/kg twice daily (2 doses) Maintenance: 4 mg/kg twice daily	Loading: 9 mg/kg twice daily (2 doses) Maintenance: 8 mg/kg twice daily
Caspofungin	IV	Loading: 70 mg daily (single dose) Maintenance: 50 mg daily	50 m/m^2 daily
Anidulafungin	IV	Loading: 200 mg daily (single dose) Maintenance: 100 mg daily	Loading: 3 mg/kg (single dose) Maintenance: 1.5 mg/kg daily
Micafungin	IV	Loading: Not required Maintenance:100 mg daily	Loading: Not required Maintenance: 2–4 mg/kg daily

Adapted from Chen et al. (2014). Also see full approved Product Information for individual antifungal agents
Abbreviations: *IV*, intravenous
[a]Trough levels required to achieve clinical efficacy (>25 mg/L) and peak levels to avoid toxicity (<100 mg/L)
[b]Require dose adjustment in renal impairment
[c]Therapeutic drug monitoring is required with trough levels to achieve clinical efficacy and peak levels to avoid toxicity (lower and upper limits vary with laboratory and should be individualized to patient)

system (CNS) disease, endocarditis and urinary tract candidiasis. Where appropriate, e.g. in endocarditis, combined antifungal therapy and surgery is the optimal treatment and should be employed. In cases of chorioretinitis with vitritis, vitrectomy has the advantage of reducing fungal burden and draining fungal microabscesses (Pappas et al. 2016). In *Candida e*ndocarditis, although there are some reports of successful outcomes with medical treatment alone, consensus expert opinion is to always consider early cardiac surgery (Lefort et al. 2012). Echinocandins have a central role in treating *Candida* endocarditis because of their good biofilm penetration (Fiori et al. 2011).

For initial antifungal therapy of hepatosplenic candidiasis or disseminated infection, the IDSA guidelines (Pappas et al. 2016) recommend the use of a lipid amphotericin formulation or an echinocandin followed by step-down therapy with an azole, preferably fluconazole (Table 15.3). The Australia and New Zealand Mycoses Interest Group recommendations (Chen et al. 2014) also provide the option of using an azole (fluconazole) up front if the isolate is fluconazole-susceptible. The role of voriconazole, posaconazole and isavuconazole (see later) as initial therapy in treating this entity is uncertain. Hepatosplenic disease often requires prolonged treatment and may be accompanied by persistent fever, which may also be caused by immune reconstitution inflammatory syndrome (IRIS) and some authors have advised the short term (1–2 weeks) in certain clinical settings (Rammaert et al. 2012; Pappas et al. 2016).

The identification and management of end-organ complications of IC are important to maximize the long-term treatment success. Where neutropenia is expected to resolve, granulocyte infusions have been used to bridge a period of profound neutropenia but in the absence of RCTs, their efficacy is uncertain (Safdar et al. 2004).

15.2.3.3 Candida Auris

C. auris has emerged as a cause of nosocomial candidaemia and IC, with high mortality rates (reviewed in (Forsberg et al. 2019)). Infections occur in all patient populations, including in the setting of haematological malignancies. This species is typically resistant to fluconazole, and variably susceptible to other azoles, amphotericin and

Table 15.3 Summary of recommendations for treatment of *Candida* infections other than candidaemia in haematological malignancy

Clinical entity	Preferred agents	Alternative agents	Minimum duration	Comments
Ocular candidiasis (endophthalmitis)	c-AMB (0.7–1 mg/kg daily) or L-AMB (3–5 mg/kg/ daily) plus 5-FC (25 mg/kg 4 times daily) for fluconazole-resistant isolates *OR* Fluconazole (12 mg/kg loading dose then 6–12 mg/kg daily) for fluconazole-susceptible isolates	Voriconazole 6 mg/kg loading dose twice daily for 2 doses then 4 mg/kg twice daily	Four to six weeks and until ocular lesions have resolved	1. If vitritis, add either intravitreal c-AMB (5–10 ug/0.1 mL sterile water) or voriconazole, 100 ug/0.1 mL sterile water 2. Consider vitrectomy 3. Echinocandins are not recommended as single agents due to poor ocular penetration but have been used in combination with lipid formulations of amphotericin B
Endocarditis	Lipid amphotericin B formulations (3–5 mg/kg daily) f ± 5-FC (25 mg/kg 4 times daily) *OR* High-dose echinocandin (caspofungin 150 mg daily or micafungin 150 mg daily or anidulafungin 200 mg daily)	Step-down therapy to fluconazole (12 mg/kg loading dose then 6–12 mg/kg daily) for isolates that are fluconazole-susceptible *OR* Voriconazole (6 mg/kg loading dose for 2 doses then 4 mg/kg twice daily) or posaconazole[a], for isolates susceptible to these agents and non-susceptible to fluconazole	Six weeks	1. For all patients, valve replacement is recommended; treatment should be continued for at least 6 weeks after surgery. 2. If surgery is not possible, long-term suppressive therapy with fluconazole or an alternate azole. 3. For prosthetic valve endocarditis, long-term suppressive fluconazole (6–12 mg/kg daily) is recommended (fluconazole-susceptible isolates).
Hepatosplenic (chronic disseminated candidiasis)	Lipid formulation of AMB 3–5 mg/kg daily followed by an azole (fluconazole 6 mg/kg daily is preferred, if isolate is fluconazole-susceptible).	An echinocandin followed by an azole (fluconazole 6 mg/kg daily is preferred, if isolate is fluconazole-susceptible).	Several weeks of initial therapy followed by typically several months of azole therapy.	Therapy should continue until lesions resolve on repeat imaging, which is usually several months.

(continued)

Table 15.3 (continued)

Clinical entity	Preferred agents	Alternative agents	Minimum duration	Comments
CNS (meningitis/ brain abscess)	L-AMB 3–5 mg/kg daily ± 5FC 25 mg/ kg four times daily followed by fluconazole 12 mg/ kg loading dose, then 6–12 mg/kg daily	Fluconazole 12 mg/ kg loading dose, then 6–12 mg/kg daily	Until resolution of all neurological symptoms and radiological abnormalities	Infected devices, e.g. drains, shunts, should be removed if possible; if dev ices cannot be removed, c-AMB could be administered through the device into the ventricles (0.01–0.5 mg in 2 mL 5% dextrose in water). There are limited data for the use of posaconazole, voriconazole or the echinocandins for CNS candidiasis (Lutsar et al. 2003; Kang et al. 2009). Echinocandin and posaconazole penetrate poorly into the CNS
Candida osteomyelitis	Fluconazole 6 mg/kg daily) *OR* An echinocandin (caspofungin 50 mg daily or micafungin 100 mg daily or anidulafungin 100 mg daily) for at least 2 weeks followed by fluconazole 6 mg/kg daily	Lipid formulation of AMB 3–5 mg/kg/ daily for at least 2 weeks followed by fluconazole 6 mg/kg daily	Six to 12 months	Surgical debridement in selected cases of osteomyelitis
Candida septic arthritis	Fluconazole 6 mg/ kg/daily OR An echinocandin (as for "*Candida* osteomyelitis" for 23 weeks followed by fluconazole 6 mg/ kg daily for 4 weeks	A lipid formulation of AMB 3–5 mg/kg/ daily for 2 weeks followed by fluconazole 6 mg/kg daily for 4 weeks	Six weeks	Surgical drainage in all cases of septic arthritis Removal of infected joint prosthesis. If not possible, long-term suppressive therapy is recommended (fluconazole is preferred, if the isolate is fluconazole-susceptible).
Candida cystitis (symptomatic) or pyelonephritis	Fluconazole 3–6 mg/ kg day if isolate is fluconazole-susceptible c-AMB 0.3–0.6 mg/ kg daily ± 5FC (25 mg/kg 4 times daily for 1–7 days if fluconazole-resistant	Echinocandins are reserved for instances of drug resistance or drug intolerance	If fluconazole: 2 weeks If c-AMB ± 5FC: 1–7 days	AMB bladder irrigation is uncommonly used.

(continued)

Table 15.3 (continued)

Clinical entity	Preferred agents	Alternative agents	Minimum duration	Comments
Candida urinary tract fungal ball	As for *Candida* cystis and pyelonephritis	–	As for *Candida* cystis and pyelonephritis	Surgery is usually required ± local irrigation of c-AMB 25–50 mg in 200–500 sterile water via endoscopic methods
Intra-abdominal candidiasis[b]	Echinocandin (caspofungin 70 mg loading dose, then 50 mg daily; micafungin 100 mg daily; anidulafungin 200 mg loading dose, then 100 mg daily)	Fluconazole 12 mg/kg loading dose, then 6 mg/kg daily *OR* Amphotericin B lipid formulation 3–5 mg/kg daily) *OR* Voriconazole 6 mg/kg loading dose for 2 doses then 4 mg/kg twice daily	Duration of therapy should be individualized according to source control and clinical response	Choice of antifungal agent should be the same as for candidaemia and be guided by drug susceptibility results. Surgical drainage of abscess and debridement of necrotic tissue is recommended.

Adapted from Cornely et al. 2012; Chen et al. 2014; Pappas et al. 2016)
Abbreviations: *5-FC*, 5-flucytosine; *AMB*, amphotericin B; *c-AMB*, amphotericin B deoxycholate; *CNS*, central nervous system; *L-AMB*, liposomal amphotericin B
[a]Suggested dose is posaconazole slow release tablets; 300 mg daily with TDM
[b]excluding hepatosplenic candidiasis

the echinocandins. Lockhart et al. reported on 54 isolates in a US study; 93% were fluconazole-resistant, 35% were amphotericin B-resistant, 7% were echinocandin-resistant, with 41% of isolates being resistant to two drug classes (Lockhart et al. 2017). At present, although some isolates have elevated minimal inhibitory concentrations (MICs) to echinocandins, this drug class remains the first-line antifungal therapy for *C. auris* candidaemia (Chowdhary et al. 2017). Following susceptibility testing, treatment should be adapted if necessary. The recommended duration of antifungal therapy for IC is similar to that for *Candida* spp. and where indicated, CVADs should be removed (Vallabhaneni et al. 2015). As *C. auris* can persist in the environment, aggressive infection control measures are recommended (Biswal et al. 2017).

15.2.4 New Drugs for Treatment of Candidiasis

Several agents including compounds with novel mechanisms of action are under clinical evaluation or development for treatment of candidiasis to address the limitations of drug resistance in certain *Candida* species and adverse effects of current antifungals. A detailed discussion is found in recent reviews (Wiederhold 2017; Gonzalez-Lara et al. 2017).

Current evidence for the most recently marketed triazole drug, isavuconazole, in the treatment of candidiasis has not provided data as robust as that obtained for this agent's place in the treatment of mucormycosis or aspergillosis. The ACTIVE study compared the efficacy of isavuconazole with that of caspofungin and the results failed to meet criteria for non-inferiority of isavuconazole (summarized in (Wilson et al. 2016)). Based on these data, it is not possible to position isavuconazole as initial treatment for IC but it may be reasonably used as an oral option for step-down in patients who cannot receive another azole due to tolerability or spectrum of activity limitations (Astellas Pharma US, Inc., Available from https://newsroom.astellas.us/news-releases. Accessed 01/2019).

Drugs undergoing evaluation for treatment of candidiasis include rezafungin (Cidara Therapeutics, San Diego, USA), a long-acting

echinocandin with potent in vitro activity against *Candida* spp. and which is associated with low frequency of development of mutations in hot spot regions of the *Candida FKS1* and *FKS2* genes (Wiederhold 2017). A phase 2 randomized double-blind study is in progress comparing the efficacy of rezafungin with caspofungin (± fluconazole step-down therapy) in patients with candidaemia (summarized in Gonzalez-Lara et al. 2017). Ibrexafungerp (Scynexis Inc., Jersey City, NJ) is another glucan synthase inhibitor, which can be administered orally and exhibits potent activity against *Candida* spp. including azole- and echinocandin-resistant isolates, and also inhibits the biofilms of *C. auris* (Larkin et al. 2017; Schell et al. 2017). Results of a phase 2 study for treatment of IC are pending. The tetrazole compounds, inclusive of VT-1161 and VT-1598, are fungal-specific inhibitors of cyp51 also with good in vitro activity against *Candid*a spp. Larger-scale data on their efficacy in IC in humans are pending (Wiederhold 2017).

15.3 Non-*Candida* Infections

Large surveillance studies have shown that non-*Candida* fungaemia accounted for 1.1% (out of 4000 fungaemia cases) in Denmark to 5.1% (of 3668 fungaemia cases) in France (Arendrup et al. 2014). Indeed, the proportion of non-*Candida* infections varies between countries and centres ranging from 2.3% in India to up to 24.9% in Thailand. Frequencies are higher in tropical areas such as Mexico, Brazil and Asia (Lin et al. 2018). In a recent report from Asia analysing 1 year of yeast isolates in blood (total 2155 isolates) from 25 centres, non-*Candida* isolates represented 8.1% of the total (Lin et al. 2018), which included 5.1% of *Cryptococcus*, 1.1% of *Trichosporon*, 0.5% of *Rhodotorula*, 0.3% of *Kodamaea ohmeri* and 0.2% of *Malassezia* species.

Recommended antifungal treatments for non-*Candida* yeast infections in haematology patients are summarized in Table 15.4.

15.3.1 *Cryptococcus* Infections

Cryptococcus are encapsulated basidiomycetous yeasts. More than 70 species have been described but only few are associated with human infections including the two major species *Cryptococcus neoformans* and *C. gattii*. Cryptococcosis used to be typically observed in HIV-positive patients with CD4 counts below 200/mm3. However, cryptococcosis in immunocompromised non-HIV-infected patients is an increasingly reported entity parallel to a decrease in incidence of cryptococcosis in HIV-positive patients in the presence of highly effective antiretroviral treatment (O'Halloran et al. 2017). However, cryptococcosis seems to be relatively uncommon in haematology patients. In one study, underlying leukaemia was present in 2% of HIV-negative patients with cryptococcosis (Baddley et al. 2008). In a more recent study in California and Florida, describing prevalence of cryptococcosis over a 7-year period, non-HIV non-transplant cases of cryptococcosis represented 39.4% of the total cases (George et al. 2018), with 8.2% of the cases occurring in the setting of

Table 15.4 Therapeutic options for cryptococcosis and rare yeast infections in patients with haematological malignancies

Organism	First line	Other option
Cryptococcus spp.	AmB + 5FC	AmB + fluconazole
Trichosporon spp.	Voriconazole	Fluconazole
M. capitatus/*S. clavata*	AmB ± 5FC	Voriconazole + caspofungin
Rhodotorula spp.	AmB ± 5FC	/
Saccharomyces spp.	AmB ± 5FC	Fluconazole
Malassezia spp.	AmB	Fluconazole

Lipid formulations of amphotericin B (AmB) are preferred due to renal toxicity of deoxycholate amphotericin B. 5-FC, 5-flucytosine is myelotoxic and should be considered carefully in haematology patients

haematological malignancy. Mortality is higher in non-HIV patients than in HIV patients (Bitar et al. 2014; George et al. 2018). Among haematology patients, acute leukaemia (50%) and non-Hodgkin's lymphoma (17.8%) were the most prevalent underlying diseases (Pagano et al. 2004). The administration of corticosteroids and the presence of diabetes mellitus seem to be strong risk factors (Pagano et al. 2004). Clinical presentation can vary from isolated pulmonary infection to cryptococcal meningitis and/or dissemination with fungaemia (Dromer et al. 2007). In HIV-negative patients, pulmonary localization was present in half of the patients, meningoencephalitis in 70% of the patients and dissemination in 38% of the patients (Dromer et al. 2007).

Diagnosis of cryptococcosis relies on direct examination, culture of clinical specimens and *Cryptococcus* antigen detection. Direct examination with India ink wet mount allows visualization of yeasts with their surrounding capsules (Arendrup et al. 2012). Culture can be performed on Sabouraud dextrose agar, but differentiation from ascomycetous yeasts can be difficult although *Cryptococcus* colonies tend to be more mucous. Identification can be done by subculture onto canavanin-glycine-bromothymol (CGB) medium (to differentiate between *C. neoformans* and *C. gattii*) (Kwon-Chung et al. 1982) and species identification can either be achieved accurately by Maldi-tof mass spectroscopy analysis (McTaggart et al. 2011; Firacative et al. 2012) or by molecular identification (Diaz et al. 2005). Culture may be negative in those prior exposed to antifungal drugs and culture plates should be incubated for up to 3 weeks at 30 °C. Another way to diagnose cryptococcosis is to detect soluble *Cryptococcus* antigen (glucuronoxylomannan) in biological fluids (whole blood, plasma, serum) or CSF. Antigen detection in serum is presumptive of active infection and in CSF of cryptococcal meningitis (Temstet et al. 1992). Different methods exist for detection of the antigen including latex agglutination, enzyme-linked immunosorbent assays (ELISA) and most recently a lateral flow assay (LFA). In HIV-negative patients, the LFA has been evaluated in comparison to the latex agglutination test with 100% sensitivity (Jitmuang et al. 2016). A high antigen titre (>1/512) in blood has been correlated with disease severity in CNS infections (Dromer et al. 2007; Perfect et al. 2010).

Cryptococcus spp. are intrinsically resistant to echinocandins but susceptible to amphotericin B, 5-flucytosine and fluconazole. Although fluconazole is frequently used to treat cryptococcosis, at present, antifungal susceptibility testing is not recommended on the initial isolate (Perfect et al. 2010). A recent study suggests that there is no correlation between fluconazole MICs and patient outcome upon fluconazole treatment (Vena et al. 2018).

In non-HIV non-transplant patients with meningoencephalitis or disseminated infection, the latest guidelines recommend the use of a combination of amphotericin B deoxycholate plus 5-flucytosine for more than 4 weeks (induction therapy) followed by fluconazole 400–800 mg/d for 8 weeks (consolidation therapy) and then fluconazole 200 mg/d for 6–12 months (Perfect et al. 2010). Lipid formulations of amphotericin B should be used in place of amphotericin B deoxycholate, if available. The myelotoxicity of 5-flucytosine is often a major concern in haematology patients. Therapeutic drug monitoring of 5-flucytosine should be performed to prevent drug toxicity. In non-HIV immunosuppressed patients with *Cryptococcus* infection in whom meningitis and dissemination have been ruled out, fluconazole (400 mg/d) for 6–12 weeks is recommended (Perfect et al. 2010).

15.3.2 *Trichosporon* Infections

Trichosporon spp. are basidiomycetous yeasts that are able to produce arthroconidia, blastoconidia, hyphae and pseudohyphae. These organisms are part of the normal flora on skin, respiratory tract or, uncommonly, the GI tract (Chagas-Neto et al. 2008). At least eight species are known to be associated with infection in humans out of 38 species described to date belonging to five clades (Chagas-Neto et al. 2008). The pathogenic species including *T. asahii*, *T. mucoides, T. cutaneum*, *T. asteroides*, *T.*

mucoides, *T. inkin*, *T. ovoides*, *T. domesticum* and *T. montevideense*. *Trichosporon* spp. can be identified using mycological culture and with phenotypic identification methods including urease testing on the colony (urease will be positive). Maldi-tof MS identification of *Trichosporon* spp. is accurate with most (>98%) of the tested strains representing 14 to 16 species correctly identified (Kolecka et al. 2013; de Almeida Júnior et al. 2014). Molecular identification using sequencing and comparison to public database can be performed accurately using the intragenic spacer (IGS) region (Sugita et al. 2002; Rodriguez-Tudela et al. 2005).

Cancer patients and more specifically patients with haematological malignancies largely comprise those at risk of trichosporonosis, with haematology patients representing more than 60% of cases reported in literature (Kontoyiannis et al. 2004; Girmenia et al. 2005). More specifically, patients most at risk were those with profound neutropenia (≤100/mmc) and/or those treated with chemotherapy for acute myeloid leukaemia. The outcome of trichosporonosis is poor, with crude mortality reported between 53 and 77% (Kontoyiannis et al. 2004; Girmenia et al. 2005; Suzuki et al. 2010). Negative outcome is associated with antibacterial use, bacterial bloodstream infection or coinfection, prophylactic/empirical antifungal therapy, admission to an intensive care unit, high APACHE II score and high dose of corticosteroid use (Kontoyiannis et al. 2004; Liao et al. 2015). A better outcome is associated with neutropenia recovery and removal of a CVAD when present (Liao et al. 2015). Fungaemia and or disseminated infection represent the main clinical presentations. *Trichosporon* infection has been associated with cross-reactions with *Aspergillus* galactomannan testing (Fekkar et al. 2009) and *Cryptococcus* antigen detection (Lyman et al. 1995; Liao et al. 2012). BDG detection have been associated with a low sensitivity with a maximum of 50% sensitivity in haematology patients with trichosporonosis, and rarely before positive blood cultures (Nakase et al. 2012).

All *Trichosporon* species share an intrinsic resistance to echinocandin drugs and *T. asahii* specifically is known to have increased MICs to amphotericin B and fluconazole (Rodriguez-Tudela et al. 2005). Triazole drugs are considered as the most effective drugs for *Trichosporon* infections (Arendrup et al. 2014). Specifically, voriconazole is considered as the most effective antifungal drug with a longer survival rate in patients (Kontoyiannis et al. 2004; Suzuki et al. 2010; Liao et al. 2015). Indeed, voriconazole displays a good in vitro activity against the most common *Trichosporon* species and a good outcome in animal models (Arendrup et al. 2014).

15.3.3 *Geotrichum*-like Infections

Geotrichum-like infections are due to few species including *Galactomyces candidus* (formerly known as *Geotrichum candidum*), *Magnusiomyces capitatus* (formerly known as *Trichosporon capitatum*, *Geotrichum capitatum* and *Blastoschizomyces capitatus*) and *Saprochaete clavata* (formerly known as *Geotrichum clavata*). All are ascomycetous urease-negative yeasts producing arthroconidia and hyphae. These organisms are considered part of the normal human mycobiome.

Galactomyces candidus has rarely been reported in haematology patients. On the other hand, *M. capitatus* and *S. clavata* infections are classically reported in patients with haematological malignancies with acute leukaemia as the main underlying disease (Girmenia et al. 2005; Vaux et al. 2014). Typically, patients develop fungaemia or disseminated disease (Girmenia et al. 2005; Arendrup et al. 2014). Identification is based on culture and identification of colonies using Maldi-tof mass spectrometry (Kolecka et al. 2013; Desnos-Ollivier et al. 2014) or by molecular approaches. *S. clavata* can be differentiated from *M. capitatus* using Maldi-tof (Kolecka et al. 2013; Desnos-Ollivier et al. 2014) and by ITS sequencing with a 96% similarity between both species (de Hoog and Smith n.d.). *S. clavata* infections have been probably underestimated because of easy misidentifications with *M. capitatus* (Desnos-Ollivier et al. 2014). *S. clavata* has been responsible for a nationwide outbreak in France

mostly in haematology patients with profound neutropenia. More than 60% of the patients were pre-exposed to echinocandins (Vaux et al. 2014). CVADs have been reported as a possible source of infection due to *M. capitatus* (Martino et al. 2004). Mortality is reported to be around 60% (Martino et al. 2004; Girmenia et al. 2005) to 70% (Vaux et al. 2014).

Galactomannan detection may be a useful adjunctive diagnostic tool in *M. capitatus* infections (Bonini et al. 2008), and serum BDG detection in *S. clavata* (Del Principe et al. 2016) or *M. capitatus* (Oya and Muta 2018) infections.

M. capitatus may have elevated MICs to fluconazole and to amphotericin B (Girmenia et al. 2003), is considered as susceptible to 5-flucytosine, itraconazole, voriconazole and posaconazole but is intrinsically resistant to the echinocandins (Vaux et al. 2014; Arendrup et al. 2014). Although no therapeutic strategy has been systematically compared, recommendations are to use amphotericin B with or without 5-flucytosine together with early catheter removal. Voriconazole could be a good alternative (Arendrup et al. 2014). Colony-stimulating factors, Interferon-gamma and granulocyte transfusions as adjuvant therapies have been successfully used (Arendrup et al. 2014).

15.3.4 *Rhodotorula* Infections

Rhodotorula spp. are basidiomycetous yeasts containing red pigment. Although the genus contains up to 46 species, only three have been associated rarely with human infections, *R. mucilaginosa*, *R. glutinis,* and *R. minuta* (De Almeida et al. 2008; Tuon and Costa 2008). These organisms have been described as part of the normal microbiota. Infections to *Rhodotorula* seem to occur more frequently in tropical areas than in northern countries (Arendrup et al. 2014). Although rare in haematological malignancies, *Rhodotorula* spp. are increasingly recognized as emerging pathogens (De Almeida et al. 2008). In haematology, acute leukaemia and allogeneic HSCT are the main underlying diseases (García-Suárez et al. 2011; Potenza et al. 2018) with neutropenia as an important risk factor. Specifically, all cases were also associated with the presence of a CVAD. The presence of CVAD was also the main risk factor for *Rhodotorula* infection in two other case series (Kiehn et al. 1992; Zaas et al. 2003; Tuon et al. 2007). Numerous cases of breakthrough infection following fluconazole, posaconazole or echinocandins treatments have been reported (Arendrup et al. 2014; Potenza et al. 2018). These infections present mainly as fungaemia. Mortality has been reported to be 15–20% (De Almeida et al. 2008; García-Suárez et al. 2011; Potenza et al. 2018). In one study, mortality in haematology patients ranged from 0% in patients with lymphoma to 15.7% in acute leukaemia (De Almeida et al. 2008). Fungal culture is the main method of detecting and identifying this pathogen. Colonies are orange to salmon coloured, which make *Rhodotorula* spp. easily recognizable although other fungi such as *Sporobolomyces* spp. can also be orange coloured. Species identification relies on sequence analysis of the D1–D2 region of the 28S rDNA and of the ITS loci (Arendrup et al. 2014). Galactomannan testing has been shown to cross-react with *Rhodotorula* (Kappe and Schulze-Berge 1993).

Rhodotorula spp. are considered as resistant to the triazoles (fluconazole, voriconazole, posaconazole, itraconazole) and to echinocandins as MICs are especially high for these drugs. The MICs to amphotericin B and 5-flucytosine are low. Consequently, the treatment of choice will be any formulation of amphotericin B with or without 5-flucytosine. CVADs should be removed promptly.

15.3.5 *Saccharomyces* Infections

Saccharomyces cerevisiae is another ascomycetous yeast also known as "baker's yeast." It has low pathogenicity and is part of the normal gut flora. A genetically close-related species, *Saccharomyces boulardii*, is used in probiotic preparations for the prevention and treatment of diarrhoea in various settings. This organism is also closely related to *C. glabrata* and shares with it some phenotypic traits.

Saccharomyces fungaemia is rare but can be observed mainly in immunocompromised patients who have taken probiotic therapy (Arendrup et al. 2014). Out of 92 cases reported in the literature, fungaemia was the main clinical presentation and predisposing factors were similar to other *Candida* infections including the presence of a CVAD, and prior antibiotic therapy. *S. boulardii* infections accounted for half of all *Saccharomyces* infections and were exclusively fungaemia. These cases were mostly observed in non-immunocompromised hosts and were associated with better outcomes (Enache-Angoulvant and Hennequin 2005). Global mortality was 38%. Diagnosis is based on classical culture procedures. There are not enough data to put forward any recommendations on the use of fungal biomarkers to detect *Saccharomyces* infection but BDG may have utility as a biomarker (Yoshida et al. 1997).

Saccharomyces harbours intrinsically high MICs to amphotericin B and fluconazole. Treatment with fluconazole or amphotericin B has given favourable outcomes for 60% and 77% of cases, respectively (Arendrup et al. 2014). Amphotericin B with or without 5-flucytosine can be considered as the treatment of choice. *S. boulardii* probiotic treatments should also be stopped and CVAD removal discussed.

15.3.6 *Malassezia* Infections

Malassezia spp. are basidiomycetous lipid-dependent and lipophilic yeasts. These organisms are part of the normal microbiota specifically on skin. Fourteen species have been identified so far (Velegraki et al. 2015) with the four species, *M. globosa*, *M. restricta, M. pachydermatis* and *M. furfur* associated frequently with human infections. *M. pachydermatis* is the only *Malassezia* species that is not dependent on lipids to grow. It is able to grow on classical media like Sabouraud dextrose agar. *Malassezia* spp. are associated with a variety of skin diseases including pythiriasis versicolor, seborrhoeic dermatitis, dandruff, atopic eczema and folliculitis and, less commonly, onychomycosis (Gaitanis et al. 2012). Systemic infections have been described mainly in infants treated with parenteral nutrition (Gueho et al. 1987) and in infants or adults with various types of immunosuppression (Gaitanis et al. 2012). Patients, specifically those with in situ CVADs, are at risk of fungaemia (Morrison and Weisdorf 2000; Tragiannidis et al. 2010). Diagnosis relies on culture with the limitation that only *M. pachydermatis* can grow on classical media. For the other species, addition of lipid is required. The modified Dixon Agar is one specific medium that can be used in case of suspicion of *Malassezia* infection. Blood cultures are not optimized for *Malassezia* recovery except for the Isolator 10 system with subculture on lipid-containing media (Arendrup et al. 2014). Once grown, *Malassezia* species can be identified by Maldi-tof MS (Kolecka et al. 2014) and molecular tools (Velegraki et al. 2015). As these organisms are difficult to grow and require specific media, susceptibility testing has not been standardized and MICs are difficult to interpret. Fluconazole and amphotericin B are the preferred agents for treating *Malassezia* infections and where there is the most clinical experience. 5-Flucytosine and the echinocandins are inactive against *Malassezia* spp. and should not be used. CVAD removal and discontinuation of lipid-containing parenteral nutrition are part of the treatment of systemic infections (Arendrup et al. 2014).

15.4 Conclusion

Despite the use of prophylactic strategies in haematology, yeast infections remain the most prevalent invasive fungal infections in haematological malignancies. The use of these drugs impacts patients' ecology and is one of the possible reasons to explain the emergence of non-*Candida* infections due to organisms carrying intrinsic resistance to some of those antifungal drugs. These yeast infections are still associated with a high mortality rates (15 to 70% depending on the organism and the underlying disease), reinforcing that there is still room for improvement of prophylaxis, diagnostic and therapeutic strategies.

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