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ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT)

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Abstract

Fungal diseases still play a major role in morbidity and mortality in patients with haematological malignancies, including those undergoing haematopoietic stem cell transplantation. Although *Aspergillus* and other filamentous fungal diseases remain a major concern, *Candida* infections are still a major cause of mortality. This part of the ESCMID guidelines focuses on this patient population and reviews pertaining to prophylaxis, empirical/pre-emptive and targeted therapy of *Candida* diseases. Anti-*Candida* prophylaxis is only recommended for patients receiving allogeneic stem cell transplantation. The authors recognize that the recommendations would have most likely been different if the purpose would have been prevention of all fungal infections (e.g. aspergillosis). In targeted treatment of candidaemia, recommendations for treatment are available for all echinocandins, that is anidulafungin (AI), caspofungin (AI) and micafungin (AI), although a warning for resistance is expressed. Liposomal amphotericin B received a BI recommendation due to higher number of reported adverse events in the trials. Amphotericin B deoxycholate should not be used (DII); and fluconazole was rated CI because of a change in epidemiology in some areas in Europe. Removal of central venous catheters is recommended during candidaemia but if catheter retention is a clinical necessity, treatment with an echinocandin is an option (CII_c). In chronic disseminated candidiasis therapy, recommendations are liposomal amphotericin B for 8 weeks (AIII), fluconazole for >3 months or other azoles (BIII). Granulocyte transfusions are only an option in desperate cases of patients with *Candida* disease and neutropenia (CIII).

Keywords: Candida, European, guideline, haematopoietic stem cell transplantation, malignancies

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Introduction

Infectious complications remain a major obstacle in the successful treatment of patients with malignant diseases. This part of the ESCMID guidelines focuses on the special need of this patient population with malignancies that had received chemotherapy or radiotherapy. *Candida* diseases played a pivotal role in the past in patients with malignancies [1–3]. In an Italian study, patients with AML and ALL developed candidaemia at incidence rates of 2–3% and 4–5%, respectively [4]. In one German hospital, candidaemia remains a disease with a high fatality rate [5]. Studies report an overall mortality risk as high as 38% with an attributable mortality of 19% [2]. Risk factors such as previous triazole exposure, age, high APACHEII scores, renal failure and neutropenia contribute to these high mortality rates [2,6]. A change in the *Candida* species epidemiology also needs special attention since fluconazole sensitive *C. albicans* is not the sole cause of disease [2,7]. Therefore, *Candida* diseases deserve special attention in this high-risk population. We included recommendations for haematopoietic stem cell transplant recipients, which is an integral part of the guideline. This guideline is divided into four parts: prophylaxis, pre-emptive/empirical therapy strategies, targeted treatment and specific situations in patients with malignancies.

Numerous guidelines have been published to date and have usually included all fungal diseases [8–11]. Here, we focus on Candida diseases with diagnostic procedures and recommendations for treatment. This guideline was originally edited as described previously by the first 4 authors and later reviewed and edited by the entire EFISG (ESCMID Fungal Infection Study Group) guideline group [155].

Other fungal diseases, for example aspergillosis in this patient population will also need special attention. The authors recognize that other filamentous fungal infections besides aspergillosis play a more pivotal role in the morbidity and mortality in this patient population (e.g. agents of mucormycosis) [12–16]. Therefore, the recommendations for prophylaxis and empirical/pre-emptive therapy would possibly direct our guideline recommendation in a different direction because this guideline focuses solely on *Candida* diseases.

The same grading system for the strength of recommendation and its documented quality of evidence are used throughout of this guideline as in the majority of the EFISG guidelines. The explanations and abbreviations used in this document are given in Table 1.

TABLE 1. Strength of the EFISG Recommendation and Quality of Evidence. Two parts: Strength of a Recommendation (SoR) and Quality of Evidence (QoE)

Strength of a recommendation	
Grade A	ESCMID strongly supports a recommendation for use
Grade B	ESCMID moderately supports a recommendation for use
Grade C	ESCMID marginally supports a recommendation for use
Grade D	ESCMID supports a recommendation against use
Quality of Evidence	
Level I	Evidence from at least one properly designed randomized, controlled trial
Level II*	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

*Added index:
$_r$: Meta-analysis or systematic review of randomized controlled trials.
$_t$: Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation.
$_h$: Comparator group is a historical control.
$_u$: Uncontrolled trial.
$_a$: Published abstract (presented at an international symposium or meeting).

Anti-Candida prophylaxis in allogeneic haematopoietic stem cell transplantation

The intention of the EFISG recommendations for prophylaxis in allogeneic haematopoietic stem cell transplantation is to look at the possibility of reducing morbidity and mortality due to *Candida* diseases. Obviously, the authors recognize that the recommendations would have been significantly different if the purpose would have been prevention of all fungal infections (e.g. aspergillosis). The prescribing physician should be aware of these interpretations. Different immune deficient situations, often referred to as the 'net state of immunosuppression', need to be appreciated during the course of allogeneic haematopoietic stem cell transplantation [17]. During the early post-transplantation phase, neutropenia is a major finding in these patients. Criteria for selecting prophylaxis throughout the various phases after transplantation should be a low toxicity profile and good efficacy. For the purpose of reducing morbidity, various antifungal agents have similar outcomes as fluconazole and have therefore received a similarly strong recommendation. But the strength of recommendation by the EFISG when including all possible fungal infections (i.e. aspergillosis) would be most likely different.

For prevention during the early neutropenic phase after transplantation, almost all available azoles are scored as highly recommended. Indeed, several publications demonstrated a reduction in morbidity for *Candida* diseases [18–23]. Later studies utilized voriconazole in comparison with itraconazole or fluconazole as comparators [24,25]. Despite

the absence of noninferiority testing in the recent voriconazole trials, an equal outcome compared with fluconazole is assumed and therefore voriconazole received an AI recommendation for the prevention of *Candida* disease. Posaconazole was not tested in a trial during the early phase of allogeneic haematopoietic stem cell transplantation but the duration and severity of neutropenia is very similar to that observed during induction chemotherapy for AML therapy [26]. Because of this implied evidence, posaconazole received an AII_t recommendation. Micafungin and caspofungin were the only echinocandins so far assessed in prophylaxis and demonstrated similar efficacy to fluconazole in transplant recipients [27]. Chou *et al.* used caspofungin in allogeneic stem cell recipients. In this retrospective study, 7.3% of the 123 patients developed a fungal disease. Two of the nine cases with fungal disease were *Candida tropicalis* and *Candida glabrata* infections [28].

In addition to the early neutropenic phase, another time period plays historically an important role after allogeneic haematopoietic stem cell transplantation, that is, the first 100 days after transplantation. During this period, patients are also prone to fungal diseases but not all antifungal agents (e.g. micafungin and posaconazole) have been tested during this period [27]. Historically, a few azoles were able to reduce morbidity and mortality, especially fungal-attributable mortality, during this phase [18,19]. However, other trials examined the value of prophylaxis beyond the neutropenic phase to include this first 100 days period. As for the voriconazole prophylaxis trial that was performed during the first 100 days after transplantation, it had a similar outcome to fluconazole [24]. Therefore, the AI recommendation with the intention to reduce morbidity in invasive candidiasis is ascribed to voriconazole and fluconazole. In the well-known trials by Goodman *et al.* [18] and Slavin *et al.* [19], survival advantage was driven by reduced mortality to *Candida* disease. In the trial performed by Marr *et al.* [22], itraconazole demonstrated superiority to fluconazole but no mortality difference was noted. Itraconazole was associated with significantly more toxicity and this explains a weaker strength of recommendation for itraconazole than fluconazole. It remains unclear whether patients without GVHD and recovered neutrophils need anti-*Candida* prophylaxis during the first 100 days after transplantation.

Another important intention for the outcome of patient care is the survival advantage when using antifungal agents as prophylaxis. Again, during the early phase of neutropenia, all azoles except fluconazole received a lower recommendation (C). During the first 100 days after transplantation, only fluconazole compared with placebo was able to demonstrate a survival advantage in *Candida* diseases [18,19]. Both voriconazole trials did not demonstrate any mortality difference [24,25]. The overall death rate in the Cornely *et al.* [26] trial was significantly lower in patients with posaconazole, and therefore, posaconazole received a slightly stronger grade of recommendation. Finally, during moderate to severe graft-versus-host disease, posaconazole received a weaker BI recommendation. In the Ullmann *et al.* [29] trial, posaconazole had an identical outcome regarding *Candida* infection compared with fluconazole, but the rate of fungal-related death was lower with posaconazole and consequently posaconazole received a slightly higher recommendation, although the *Candida*-associated death rate was not clear. The association between intention and the dosage of the intervention, including strength of recommendation, are noted in Table 2.

Another important scenario of immunosuppression plays a significant role in the outcome in the transplant recipient. Due to increased immunosuppressive therapy during the latter phase (beyond 100 days) in patients with graft-versus-host disease, slow T-cell recovery and increased risk of fungal infections is obvious. The trial by Ullmann *et al.* [29] demonstrated that posaconazole and fluconazole were equally efficacious in preventing candida infections. Other drugs were rated weaker (Table 2). Itraconazole and amphotericin B deoxycholate received a weaker recommendation because of a weaker safety profile [22,30–32].

Anti-*Candida* prophylaxis in autologous haematopoietic stem cell transplantation and in severe and prolonged neutropenia

In the autologous transplant setting, only the neutropenic phase can be considered a possible risk situation for *Candida* diseases. But with the improvement of autologous transplantation procedures over time, antifungal prophylaxis is not recommended for autologous transplantation recipients [33]. Nevertheless, in centres with a high incidence of *Candida* disease, prophylaxis could remain an option, but based on recent data only a weak C recommendation is provided for itraconazole and posaconazole (C) [26,34]. The group was not able to provide a recommendation when antibody treatment is co-administered (e.g. rituximab) due to the lack of data, and obviously, there seems to be no increased risk of fungal infections. There is indirect evidence for a survival advantage in prophylaxis for invasive candida disease, which is only available from the Cornely *et al.* [26] trial for patients with severe and prolonged neutropenia. None were studied with other drugs for *Candida* disease in autologous stem cell recipients. In general, autologous haematopoietic stem cell transplantation is not considered a high-risk situation for patients.

TABLE 2. Anti-*Candida* prophylaxis for allogeneic haematopoietic stem cell recipients

	Intention: Morbidity reduction		Intention: Survival improvement		
	SoR	QoE	SoR	QoE	References
Intervention (anti-Candidal prophylaxis) during the neutropenic phase					
Fluconazole 400 mg qd if no prophylaxis is considered	A	I	A	I	[18–20,22,23]
Itraconazole* 2.5 mg/kg oral solution tid	B	I	C	I	[22,23]
Posaconazole* 200 mg tid	A	II_t	B	II_t	[26,29]
Voriconazole* 200 mg bid	A	I	C	I	[24]
Caspofungin* 70/50 mg qd	C	II_u	C	III	[28]
Micafungin* 50 mg qd	A	I	C	I	[27]
Anidulafungin	NR	ND	NR	ND	
Liposomal amphotericin B 50 mg every other day iv, 100 mg/weekly	B	II	C	III	[38,39]
Intervention (anti-Candidal prophylaxis) during the first 100 days without GVHD and neutrophil recovery					
Fluconazole 400 mg qd	A	I	A	I	[18–20,22,23]
Itraconazole* 2.5 mg/kg oral solution tid	B	I	C	I	[22,23]
Posaconazole* 200 mg tid	C	III	C	III	[26,29]
Voriconazole* 200 mg bid	A	I	C	I	[24]
Caspofungin* 70/50 mg qd	C	II_u	C	II_u	[28]
Micafungin* 50 mg	C	III	C	III	[27]
Anidulafungin	NR	ND	NR	ND	
Liposomal amphotericin B 50 mg every other day iv, 100 mg/weekly	C	III	C	III	[38,39]
Intervention (anti-Candidal prophylaxis) in GVHD					
Fluconazole 400 mg qd	A	I	C	I	[18–20,22,23]
Itraconazole* 2.5 mg/kg oral solution tid	C	I	C	I	[22,23]
Posaconazole* 200 mg tid	A	I	B	I	[29], equal outcome regarding *Candida* disease
Voriconazole* 200 mg bid	B	I	C	I	[24] equal outcome regarding *Candida* disease
others	NR	ND	NR	ND	ND

NR, no recommendation; ND, no data available.
*Decision was based on comparative trials with fluconazole.

TABLE 3. Anti-Candida prophylaxis outside of allogeneic haematopoietic stem cell transplantation (e.g. autologous haematopoietic stem cell transplantation or chemotherapy induced neutropenia)

		Autologous HCT		Severe and prolonged neutropenia		
Intention	Situation	Intervention	SoR/QoE	Intervention	SoR/QoE	References
Reduce morbidity and mortality (during and after high dose chemotherapy)		Any prophylaxis	DIII	Any prophylaxis	DIII	[33]
Additional antibody treatment (e.g. rituximab)		Any prophylaxis	DIII	Any prophylaxis	DIII	
Morbidity reduction or survival advantage*	Neutropenia*	Fluconazole	ND	Fluconazole	CI	For autologous HCT: [26, 34]
		Itraconazole	CII	Itraconazole	CI	For neutropenia: [26, 32, 35-38, 40–43]
		Posaconazole	CIIt	Posaconazole	CIIt	
		Voriconazole	ND	Voriconazole	ND	
		Anidulafungin	ND	Anidulafungin	ND	
		Caspofungin	ND	Caspofungin	CI	
		Micafungin	ND	Micafungin	ND	
		Nystatin	DIIt	Nystatin	DII	
		Any amphotericin B formulation	ND	Any amphotericin B formulation	DI	

*If an institution wishes prophylaxis, weak recommendations for selected antifungal agents are provided.
ND, no data.

The treatment of numerous other malignant diseases causes neutropenia in varying degrees of severity and duration. Prophylaxis in this patient population is usually administered only if the patient develops profound and prolonged neutropenia. Again, our group does not support prophylaxis for the prevention of *Candida* diseases in this setting (prophylaxis: DII).

In nontransplantat settings, all recommendations are very similar to those for autologous transplantation. There is only very weak evidence for the use of azole prophylaxis against *Candida* diseases for the group of azoles. The study by Glasmacher *et al.* [32] saw no difference between fluconazole and itraconazole. Another randomized placebo-controlled study demonstrated the superiority of itraconazole for

TABLE 4. Empiric therapy to treat possible *Candida* disease: All situations causing severe and prolonged neutropenia

Intention	Intervention	Allogeneic HCT included	SoR	QoE	References
Morbidity reduction	Liposomal amphotericin B (3 mg/kg/day)	Yes	A	I	[44,45,47,55]
	Caspofungin (70 mg on day 1 then 50 mg)	Yes	A	I	[46,47]
	Amphotericin B colloidal dispersion (4 mg/kg/day)	Yes	C	I	[54]
	Amphotericin B lipid complex (5 mg/kg/day)	Yes	B	I	[55]
	Itraconazole (200 mg iv q12h on day 1 & 2 then 200 mg iv/day)	ND	B	I	[56,57]
	Voriconazole (2 × 6 mg/kg on day 1 then 2 × 3 mg/kg/day)§	Yes	B	I	[48]
	Fluconazole (400 mg/day)	ND	C*	I*	[52,53]
	Amphotericin B deoxycholate (0.5–1.0 mg/kg/day)	Yes	D	II_c	[44,54,56,57]
	Micafungin (100 mg)	Yes	B	II	[49,50]
	Anidulafungin	ND	NR		No data

*Limited use since fluconazole has no mould activity. Application requires appropriate work-up to rule out mould disease.
NR, no recommendation; ND, no data available, §, dosis according to trial [48].

preventing superficial fungal infection in patients with haematological malignancies and neutropenia [35]. Only one study by Menichetti *et al.* [36] demonstrated a significant lower incidence of fungaemia due to *Candida* species in 0.5% of itraconazole recipients and in 4% of placebo recipients, a difference of 3.5 percentage points (95% CI, 0.5–6%; p <0.01). Obviously, no overall survival advantage in *Candida*-associated mortality was noted.[36,37] In the trial by Penack *et al.* [38], low dose of liposomal amphotericin B did not significantly prevent *Candida* infections. In a similar but smaller trial by Cordonnier *et al.* [39], only one of twenty-nine patients developed probable *Candida* disease. Other trials utilized various comparators (e.g. amphotericin B/nystatin or fluconazole vs. itraconazole), but none demonstrated superiority [40,41]. Nystatin, an oral polyene, cannot be recommended as prophylaxis [42]. Only one retrospective trial where micafungin was assessed as prophylaxis led to a significant decrease in the occurrence of IFI (from 12.3% to 1.5%, p 0.001) [43] (Table 3).

Secondary prophylaxis is not indicated in cases of prior candidaemia without any sign of deep-seated infection when patients are exposed to a new immunosuppressive therapy or where prolonged neutropenia is induced by chemotherapy, autologous or allogeneic HCT. The strength of recommendation for secondary prophylaxis in patients with a history of deep-seated invasive *Candida* disease (not candidaemia alone) was rated C III.

Empiric or pre-emptive (diagnostic driven) antifungal therapy

In patients expected to suffer prolonged duration of neutropenia [>10 days] (induction and consolidation chemotherapy of AML/MDS and autologous, or allogeneic transplantation) fever occurs frequently and is usually treated primarily with broad-spectrum antibacterial agents. If the patient does not defervesce after at least 3–4 days of antibacterial treatment, the presence of an undetected fungal infection is assumed and antifungal therapy is usually added with the intention of preventing further morbidity or death (AII) [44]. Extensive diagnostic workup is required to exclude a clinically or mycological documented infection which might require specific therapy.

Again, similar to the prophylactic indication, a challenge in providing recommendations was the fact that empirical treatment is not only given for the intention of treating as early as possible an undetected *Candida* disease, but also any kind of fungal infection (e.g. filamentous fungal infections). With regards to a reduction in morbidity, liposomal amphotericin B and caspofungin received an AI recommendation [44–47] (Table 4). Voriconazole failed to demonstrate noninferiority when compared to liposomal amphotericin B but in a subset analysis of high-risk patients no differences were noted [48]. In a prospective but one-armed trial with micafungin, not a single patient receiving empiric treatment developed a breakthrough fungal infection [49]. In a retrospective trial comparing micafungin and caspofungin, breakthrough *Candida* diseases were detected at a rate of 0.7% and 2.8%, respectively [50]. Amphotericin B deoxycholate and fluconazole were not recommended for empirical treatment despite the existence of adequate studies in the past, because of toxicity in the first case, and narrow spectrum of action in the second case [51–53]. The differences in the grading of amphotericin B formulations lie solely in the different toxicity profiles [54–56]. Amphotericin B colloidal dispersion causes infusion-related events similar in frequency and intensity to amphotericin B deoxycholate and in a direct double-blind comparison trial amphotericin B lipid complex was more toxic than liposomal amphotericin B [54,55]. The use of itraconazole provided some promising results in a noncomparator trial and in a recent published trial compared with amphotericin B [56,57]. In the latter trial, itraconazole had a better outcome. The major limitation for fluconazole was

the lack of antimould activity. Therefore, if fluconazole is used, it remains essential to rule out a mould infection by the *Aspergillus* galactomannan index (GMI) ELISA and chest and sinus CT scan.

A consensus criteria defining pre-emptive (sometimes also called 'diagnostic driven') treatment of fungal infections in cancer patients does not exist. The term 'pre-emptive treatment' is associated more with filamentous fungi infections than with *Candida*-associated diseases. This approach is not driven by persistent fever or neutropenia but rather by galactomannan antigen detection in serum and/or BAL fluid or high-resolution CT scan in high-risk patients [58]. The role 1,3-ß-D-glucan and PCR testing for aspergillosis/candidiasis remains controversial [59,60]. Whether or not any kind of infiltrate in the presence of *Aspergillus* galactomannan should trigger antifungal therapy is still debatable, although few experts would not add an antifungal agent in all of these situations. Some experts wait for *Aspergillus* associated typical radiographic signs [halo, wedge shaped, air crescent or cavity] before starting treatment [58]. Other authors are more flexible [61,62]. Basically, no recommendation can be given at this point on the choice between the empirical and pre-emptive approach.

No clinical trial has been performed to compare antifungal drugs for this indication, and therefore, no recommendation can be made. The main studies which tested the pre-emptive approach used liposomal or deoxycholate formulation of amphotericin B or voriconazole [61–63]. As treating pre-emptively should mean treating at an early phase of disease, drugs approved for the treatment of fungal diseases might be effective or at least should be evaluated.

In summary, no data exist regarding whether or not *Candida* diseases can be managed by pre-emptive anti-Candida therapy. If *Candida* disease is the main concern and the patient is not on azole prophylaxis, then fluconazole might be a good choice. However, in contrast to the ICU setting, no trial has prospectively assessed the role of *Candida* spp. colonization or 1,3-ß-D-glucan in these patients [64]. 1,3-ß-D-glucan was assessed previously in a meta-analysis by Lamoth *et al.* [65] The group concluded that two consecutive positive antigen tests in patients with haemato-oncological patients demonstrate a high specificity, positive predictive value but a low sensitivity. Therefore, the test needs to be combined with clinical and radiological assessments and microbiological findings [65].

Mucosal oropharyngeal or oesophageal candidiasis

Mucosal candidiasis does not play a significant role for morbidity or mortality in haematological malignancies. The occurrence of oropharyngeal or oesophageal candidiasis is more inconvenient than threatening for the patient and usually easy to treat. For a rapid response, oral azoles, for example fluconazole, are recommended (AI) [66]. Physicians should keep in mind that azole-resistant *Candida* species can be selected during therapy even without prolonged treatment periods [67,68]. Other azoles can then be used [69–74]. Topical polyenes treatment is recommended for mild forms as in nonimmunocompromised patients [66,75–78].

Oral candidiasis with dysphagia and thoracic pain when swallowing is suggestive of oesophageal involvement. In this situation, topical treatment is not recommended (topical polyene treatment for oesophagitis: DIII). Cases refractory to fluconazole can be treated with any other azole if MIC tests suggest susceptibility [70,71,79–82]. In the event of severe or refractory disease, intravenous antifungals such as an echinocandin or liposomal amphotericin B might be indicated [83–90] (Table 5). It is essential to identify the species causing candidiasis to ensure susceptibility to the chosen agent [91]. This is a minimum requirement in immune-compromised patients, because resistance might have developed and a mixed aetiology might be possible.

Targeted treatment of invasive candidiasis/candidaemia

Treatment of invasive candidiasis or candidaemia should always focus on the success of treatment with improved survival. Once the diagnosis of candidaemia is established, blood cultures should be drawn on a daily basis until negativity for at least two consecutive samples (B I). Treatment should at least continue for 14 days after the last positive blood culture [92]. Individuals who have negative blood cultures for more than 14 days but remain neutropenic at approximately day 28 (or are not expected to recover from neutropenia) should be evaluated for the resolution of clinical signs and symptoms including exclusion of endocarditis and endophthalmitis by appropriate examination. But defining an exact and appropriate duration of therapy is still an issue of debate.

It is recommended that for patients who are on prophylaxis that the class of drugs for antifungal treatment be changed (C III). In prospective trials, only a few neutropenic patients were enrolled [93–97]. This consideration reduces the level of our recommendation in comparison with intensive care patients. Caspofungin and micafungin trials included approximately 10% neutropenic patients [94–96]. The outcome of these patients was also favourable, and therefore, both agents received an AII_t recommendation. Anidulafungin

TABLE 5. Treatment of mucosal oropharyngeal or oesophageal candidiasis. Identification of *Candida* species would be desirable

Diseases	Intension	Intervention	SoR/QoE	References
Oropharyngeal	Eradication	Nystatin suspension (non-neutropenic, mild presentation)	CII_t	[76,77]
		Miconazole buccal	BII_t	[78]
		Fluconazole	AI	[66,75]
		Itraconazole solution	BII_t	[72–74]
		Posaconazole	AII_t	[69,70]
		Voriconazole	BIII	[71]
		Echinocandins (anidulafungin, caspofungin) only in very severe and refractory cases	BIII	[84,149,150]
		Liposomal amphotericin B as an option only in very severe and refractory cases	CIII	
Oesophageal	Eradication	Fluconazole	AII_t	[81,82,151–153]
		Itraconazole	BII_t	[72,80,82]
		Posaconazole	AII_t	[70]
		Voriconazole	AIII	[71]
		Topical treatment	DIII	
		Echinocandins (anidulafungin, caspofungin and micafugnin) or liposomal amphotericin B only in very severe and refractory cases	BII_t	[84–90]

on the other hand received a marginally weaker recommendation (BII_t) because there were <3% neutropenic patients in this trial [97]. The extensive usage of echinocandins could trigger resistance against this class of antifungal agents in the future because some areas in the world have demonstrated an increase in *C. parapsilosis* which usually has higher MICs compared with other *Candida* species [98,99]. Despite good sensitivity results, first reports demonstrate caution on the usage of echinocandins [100,101]. These are some of the reasons for species discrimination and susceptibility testing which are highly recommended in these settings.

Fluconazole, once considered gold standard in the treatment of candidaemia received a weaker recommendation despite positive outcomes in a number of trials [92,102]. These trials are considered out-dated, especially when considering the risk of the development of resistance. In recent publications, previous fluconazole or triazole exposure and gastrointestinal tract surgery are risk factors for fluconazole-resistant candidaemia. In addition to invasive ventilation, renal impairment, age >65 years and steroids and triazole exposure are considered risk factors for death [6,103]. Therefore, fluconazole should only be considered as a step-down treatment option in neutropenia when the *Candida* species isolates demonstrate susceptibility to fluconazole. Other azoles had only limited data and because of this, itraconazole and posaconazole in particular, cannot be recommended for treatment [104]. On the other hand, more data exist for voriconazole and it may be considered as an option [105,106]. Despite equal outcome when compared to micafungin, liposomal amphotericin B received only a BII recommendation due to its higher nephrotoxicity profile [96,107]. Due to different toxicity profiles and weak data of other lipid formulations of amphotericin B, a C grading for the recommendation for treating invasive candidiasis or candidaemia is given [108–112]. Extensive nephrotoxicity, consecutive higher mortality and other unacceptable toxicity are factors that make amphotericin B deoxycholate not recommendable for treatment (DII) [30,31] (Table 6).

If patients were receiving fluconazole or liposomal amphotericin B, a switch to an echinocandin might be desirable (BII_t). Basically, there is no adequately powered randomized trial for this situation neither for neutropenic patients nor for stem cell transplant recipients but the identification of the *Candida* species and susceptibility testing could be helpful for making a decision (e.g. *Candida krusei*)(BIII).

In vitro and animal data of antifungal combinations seem to improve the efficacy of antifungal treatment. In humans, especially neutropenic patients this outcome is not so clear-cut.

TABLE 6. Targeted treatment of invasive candidiasis/candidaemia in patients with malignancies, usually with neutropenia

Intention	Intervention	SoR	QoE	Comment	References
Morbidity reduction and survival improvement	Fluconazole	C	II_t	Caution regarding resistance. Fluconazole should rather be considered as a step-down treatment option	[92,93,102]
	Itraconazole	D	III	Only abstract in non-neutropenics	[154]
	Posaconazole	D	III	One case report in a non-neutropenic	[104]
	Voriconazole	C	II_t	Alternative agent due to better susceptibility data in comparison with fluconazole but limited clinical data	[105,106]
	Amphotericin B colloid dispersion	C	III	Considerable nephrotoxicity	[111,112]
	Amphotericin B deoxycholate	D	II_t	Unacceptable toxicity	[30,31,44,93,94]
	Amphotericin B lipid complex	C	II_a	Considerable nephrotoxicity	[108,110]
	Anidulafungin	B	II_t	<3% of the participants were neutropenic	[97]
	Caspofungin	A	II_t	~10% of the participants were neutropenic	[94,95]
	Liposomal amphotericin B	B	II_t		[96,107]
	Micafungin	A	II_t	~10% of the participants were neutropenic consider EMA warning	[95,96]

Only a few combinations have been studied without any improved outcome. Combination of amphotericin B deoxycholate and 5-flucytosine is not recommended due to its toxicity and erratic pharmacokinetics [113–115]. Efungumab and a lipid formulation amphotericin B are also not recommended because flaws in the design of the study hampered outcome [116]. Efungumab is not an approved or marketed drug. The combination of amphotericin B deoxycholate and fluconazole was studied as a sequential therapy and did not demonstrate any improvement to the comparators [105]. There was even more toxicity in the amphotericin B group despite a median of only 3 days of amphotericin B deoxycholate exposure. Another trial assessed whether this combination was antagonistic [117]. Due to its similar outcome, this combination can be considered an option (CII_t). Other combinations were not studied but the expert opinion is that antifungal combinations might be useful in severe deep-seated infections (e.g. abdominal infection, CNS and endocarditis, CIII).

Chronic disseminated candidiasis

Chronic disseminated candidiasis or hepato-splenic candidiasis is a very specific syndrome in patients with malignant diseases. The disease usually occurs after the recovery of neutrophils due to previous chemotherapy. The diagnosis of chronic candidiasis is challenging when prior candidaemia has not been documented. Imaging by ultrasound examination demonstrates a weaker sensitivity in comparison with CT or MRI [118–121]. Only one study could show a higher sensitivity utilizing MRI in comparison with CT [118]. But despite adequate imaging techniques, the confirmation of the diagnosis by biopsy remains troublesome. Histology with culture positivity is seldom. No comparator trials in regard to morbidity improvement or survival advantage have been performed or published. Antigen detection [e.g. mannan/antimannan or 1,3-ß-D-glucan) are probably helpful, but data in this situation are scarce [122]. Histology requires the use of special staining (Gomori) and immunohistochemistry and molecular-genetic workup is highly recommended.

In terms of treatment, only a few case series have been published [96,123–126]. The experience of treatment is currently only anecdotal. Lipid formulations of amphotericin B might be a good choice because of potential accumulation in the reticulo-endothelial system [127]. Frequently, sequential approaches are employed empirically, for example liposomal amphotericin B followed by prolonged treatment of fluconazole. The disease has been recently considered to be an inflammatory immune reconstitution syndrome [128]. There are interesting publications that suggest the co-administration of steroids at the beginning of treatment [129,130]. The duration of antifungal treatment appears to be at least 8 weeks. Again the use of amphotericin B deoxycholate is not encouraged (Table 7).

Biofilms and central venous catheters

Central venous catheters (CVC) play a major role in the care of this patient population. Once inserted, the removal or replacement might threaten the life of the patient because of frequently experienced thrombocytopenia. Upon review of the published data, a negative outcome during therapy by not removing the central venous catheter early appears only to occur in the situation where echinocandins were not used [6,94–97,131,132]. In the recently published trials, where the central venous catheter was retained, the outcome was similar but the numbers noted in those trials were low [94,95,97]. Additionally, these trials demonstrated an equal outcome in *C. parapsilosis* disease despite other publications indicating higher MICs [133,134]. As *C. parapsilosis* is associated with catheter infections, removal would be desirable.

On the other hand, if catheter retention is clinical necessary, treatment with an echinocandin remains an option. Nevertheless, persistence of positive blood cultures for yeast should prompt removal of a central venous catheter. Velasco and Bigni [135] saw in their study by multivariate analysis that comorbidities and neutropenia were independently associated with mortality in adults and not CVC removal. In a trial by Liu *et al.*, early catheter removal is associated with better survival. In this trial, the retention of the catheter, high APACHE II score or thrombocytopenia was associated with a higher mortality rate [131]. Nucci *et al.* [136] looked especially on the outcome in terms of CVC removal and reported no differences between the groups being given caspofungin, micafungin or liposomal amphotericin B. But

TABLE 7. Treatment of chronic disseminated candidiasis

Intention	Intervention	Duration	SoR/QoE	Comments	Reference
Eradication	Fluconazole	Reported duration minimum 3 months	BIII	[125,126]	[125,126]
	Other azoles (if susceptibility is expected)		BIII	Lacking data	ND
	Amphotericin B deoxycholate		DIII	Toxicity issues	[30,31]
	Lipid formulations of amphotericin B	8 weeks	AIII	Better exposure	[96,124]
Defervesce	Steroid therapy	Until defervesce	CIII		[129,130]

TABLE 8. Treatment of *Candida* Biofilm and catheter-related candidaemia

Intention	Intervention	SoR/QoE	Comment	Reference
Survival advantage	Early catheter removal	AII_u	Retention and high APACHE II and thrombocytopenia also associated with higher mortality.	[131,132,137]
Morbidity reduction	Catheter retention	CII_t	Patients in trials treated with echinocandins and CVC retention had equal outcome (low numbers)	[94–97]
	If catheter retention use echinocandins or liposomal amphotericin B, not azoles or amphotericin B deoxycholate	CII_t	Worse outcome in non echinocandins trials	[94–97,137]
	Other implanted hardware (pace-maker, port-a-cath)	CIII	Keep unless proven associated with candidaemia. No published data available	ND

another work by Andes *et al.* [137] saw in review of seven clinical trials that improved survival and greater clinical success is associated with the use of an echinocandin and removal of the CVC. A few in vitro studies indicate that echinocandins penetrate *Candida* biofilm better than other antifungal agents [138,139]. A more clinically challenging question is how to handle other implanted hardware, for example pacemaker, port-a-cath. Unless an association could be provided, in cases with implanted hardware and with candidaemia, retention of the hardware is appropriate but no published data are available. Unfortunately, no reliable symptom or sign associated with hardware is available (Table 8).

Cytokines, colony-stimulating factors and granulocyte infusions for the treatment of invasive candidiasis or candidaemia

The question regarding the use of colony-stimulating factors or cytokines in the treatment of invasive candidiasis or candidaemia remains unanswered. No controlled trials are available and only anecdotal data from small numbers of patients exist. As persistent neutropenia is related to treatment failure, recovery from neutropenia substantiates the efficacy of antifungal agents [140–142]. Therefore, the use of colony-stimulating factors appears to be an option (C III). A recent Cochrane review indicates no mortality differences for all infections in patients suffering from neutropenia [143]. There is only a weak recommendation for granulocyte infusions, but the data are basically from children (CIII) [144–148]. This treatment might be considered an option in desperate cases.

Transparency Declarations

A.J.U. has received research grants from MSD (Schering Plough) and is/was an advisor or received lecture honorarium from Astellas, Aicuris, Basilea, Gilead, MSD and Pfizer.

M.A. received, during the past 5 years, research grants and honoraria for talks and consultancy from Merck, Pfizer and Gilead.

R.H. has been a consultant or at the advisory board for Astellas pharma, Basilea, Gilead Sciences, Merck Sharp and Dohme, Novartis, Pfizer and Schering Plough. He has been paid for talks on behalf of Astellas, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering Plough. He has received research support from Pfizer, travel support from Pfizer and Gilead, and investigator fees for a clinical trial from Pfizer.

C.V. received grants as speaker/moderator in meetings sponsored by Pfizer, Gilead, MSD, Astellas, Abbott, BMS and received grants for participation in advisory boards by Gilead, Astellas, MSD, Pfizer. Further, he obtained research grants for his institution from Pfizer, MSD, Gilead, Abbott, Jansen, BMS, Novartis. He is member of the SAG (Scientific Advisory Group) for antibacterials and antifungals of CHMP-EMA and consultant for Italian Medical Drug Agency Member of various levels of local Infection Control, Antibiotic Stewardship, Vaccine and HIV Committees (Genoa, Liguria, Italy), Nadirex International (Pavia, Italy).

M.C.A. has received grant support from Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering Plough. She has been a consultant or at the advisory board for Gilead Sciences, Merck Sharp and Dohme, Pfizer, Pcovery and Schering Plough. She has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough.

S.A.A. has received investigator initiated research grant support from Pfizer and speaker honoraria from Merck and Pfizer. She has been at the Advisory Board for Pfizer-Turkey.

M.B. has received research grants from Pfizer, MSD and Astellas and is/was an advisor or received lecture honorarium from Astellas, Angelini Farmaceutici, Astra Zeneca, Cubist, Aventis, Bayer, Cephalon, Cubist, Gilead, MSD, Novartis, Shionogi, Pfizer, Teva and Vifor.

J.B., J.G., H.E.J. has nothing to declare. T.C. is member of the Speaker bureau and is advisor or consultant for Astellas, Baxter; bioMérieux, EISAI, Evolva, Novartis, Merck Sharp and Dohme-Chibret AG, Pfizer. Grant support from Baxter, bioMérieux, Merck Sharp and Dohme-Chibret AG, Roche Diagnostic.

E.C. has participated as invited speaker to symposia organized by Gilead, Pfizer, Astellas, Merck, Novartis and he has been member of advisory boards for Astellas, Pfizer.

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J.P.D. has received grant support from Astellas, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering Plough. He has been a consultant or on an advisory board for Astellas, Gilead Sciences, Merck Sharp and Dohme and Pfizer. He has received remuneration for giving lectures on behalf of Gilead Sciences, Merck and Pfizer.

A.H.G. has received research support from Gilead, Merck and Schering. He has acted as speaker and/or consultant for Astellas, Cephalon, Gilead, Merck, Pfizer, Schering and Vicuron.

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M.D.R. has received grants, speaker's honoraria and travel support from ESCMID, Pfizer, Astellas, MSD and Gilead Sciences. He has also received book royalties from Blackwell Publishing and travel support from Astellas Pharma.

E.R. has received research support from Pfizer, Gilead, Merck, Enzon, Schering and he has made contributions in advisory boards of Gilead, Astellas, Pfizer, Merck, Schering. He has also been paid for talks on behalf of Gilead, Cephalon, Pfizer, Wyeth, Schering, Merck, Aventis and Astellas.

P.E.V. has received research grants and/or travel support and/or travel support from Pfizer, Astellas, Cephalon, Gilead Sciences, Merck and Schering Plough.

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