ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients

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Abstract

This part of the EFISG guidelines focuses on non-neutropenic adult patients. Only a few of the numerous recommendations can be summarized in the abstract. Prophylactic usage of fluconazole is supported in patients with recent abdominal surgery and recurrent gastrointestinal perforations or anastomotic leakages. *Candida* isolation from respiratory secretions alone should never prompt treatment. For the targeted initial treatment of candidaemia, echinocandins are strongly recommended while liposomal amphotericin B and voriconazole are supported with moderate, and fluconazole with marginal strength. Treatment duration for candidaemia should be a minimum of 14 days after the end of candidaemia, which can be determined by one blood culture per day until negativity. Switching to oral treatment after 10 days of intravenous therapy has been safe in stable patients with susceptible *Candida* species. In candidaemia, removal of indwelling catheters is strongly recommended. If catheters cannot be removed, lipid-based amphotericin B or echinocandins should be preferred over azoles. Transoesophageal echocardiography and fundoscopy should be performed to detect organ involvement. Native valve endocarditis requires surgery within a week, while in prosthetic valve endocarditis, earlier surgery may be beneficial. The antifungal regimen of choice is liposomal amphotericin B +/− flucytosine. In ocular candidiasis, liposomal amphotericin B +/− flucytosine is recommended when the susceptibility of the isolate is unknown, and in susceptible isolates, fluconazole and voriconazole are alternatives. Amphotericin B deoxycholate is not recommended for any indication due to severe side effects.

Keywords: Candidiasis, Guideline, non-neutropenic, prophylaxis, treatment

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Introduction

Invasive candidiasis remains a challenging complication, which frequently occurs in patients with one or more underlying diseases or surgical interventions. In recent point prevalence studies, a candidaemia incidence of 6.9 per 1000 ICU patients was reported, and 7.5% of ICU patients received antifungal therapy [1,2]. Candidaemia increases mortality rates in the range of 20–49% [3,4], but still there are many open management questions.

The unmet medical needs surrounding candidaemia and invasive candidiasis are defined in general from diagnosis to prophylaxis, empiric and pre-emptive strategies to treatment. So far, the scientific community has not achieved to accurately predict invasive candidiasis and thus to define populations that benefit from prophylaxis or early treatment [5]. Although it is well known that treatment is being initiated too late in the majority of patients, identification of the optimal time point to commence antifungal therapy remains challenging [6,7]. Intertwined with this problem is insufficient support of reliable mycological assays preventing timely and diagnosis-driven early treatment initiation [173].

With the diversity of various groups of patients with organ involvement beyond the bloodstream, a body of diverse evidence on the best treatments and infectious diseases management decisions, for example, treatment duration is provided.

In the light of the medical need to analyse the scientific evidence in the field of invasive *Candida* diseases, the ESCMID European Fungal Infection Study Group (EFISG) developed comprehensive practical guidance for microbiologists and clinicians to facilitate evidence-based decision making.

This guideline follows the clinical events in a chronological order. Prophylaxis in patient populations at risk for invasive *Candida* disease is followed by fever- and diagnosis-driven approaches to early therapy and finally targeted therapy. Important clinical questions on catheter management to step-down strategies are being addressed. Specific situations in deep tissue candidiasis are cherished, and for each topic, a table lists the medical/scientific evidence.

Methods

An expert group (OAC, MB, TC, JG, BJK, OL and WM) was set up by EFISG and searched the literature. Documents and views were shared by email, teleconferences, and face-to-face meetings during 2010–2012. Once a first consensus was reached, the preliminary recommendations were presented to the whole group, that is, the other authors, discussed, developed further, and finalized as a group consensus. The methods to evaluate the quality of evidence and to reach group consensus recommendations are described in this issue of *Clinical Microbiology and Infection* [172]. Definition of the strength of recommendation is given in Table 1. The quality of the published evidence is defined in Table 2. Grouping quality of evidence into three levels only may lead to diverse types of published evidence being assigned specifically a level II. To increase transparency in the evaluation of the evidence, we added an index (Table 2) to the level II recommendations, where appropriate. Of note, the strength of recommendation and the quality of evidence were assigned in two separate evaluations, thus allowing, for example, a recommendation strongly supporting a procedure even if there is a lower level of evidence.

Results

Prophylaxis

Antifungal prophylaxis has been discussed as a promising approach in ICU patients. At this moment, the optimal target population for antifungal prophylaxis remains unknown, as this question has not been sufficiently addressed in clinical trials. Some special populations though have been enrolled in randomized clinical trials, and recommendations for these can be given.

TABLE 1. Definition of the strength of recommendation

Grade	ESCMID EFISG
A	Strongly supports a recommendation for use
B	Moderately supports a recommendation for use
C	Marginally supports a recommendation for use
D	Supports a recommendation against use

TABLE 2. Definition of the quality of evidence

ESCMID EFISG
Level
I Evidence from at least one properly designed randomized, controlled trial
II Evidence from at least one well-designed clinical trial, without randomization, from cohort or case-controlled analytical studies (preferably from >1 centre); from multiple time series or from dramatic results of uncontrolled experiments
III Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies or reports of expert committees
Index (for quality of evidence II)
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)

Evidence. Patients who had undergone abdominal surgery recently and who had recurrent gastrointestinal perforations or anastomotic leakages were treated either with fluconazole 400 mg/day or with placebo in order to prevent intraabdominal *Candida* infection. The rate of intraabdominal candidiasis was significantly lower in the fluconazole prophylaxis group. This clinical trial exhibited high technical quality, but was performed in a very high baseline incidence population and is limited by enrolling 43 evaluable patients only [8]. In a small non-comparative trial, standard dosed caspofungin was evaluated in the same indication, but no evidence can be derived [9]. In a large prophylaxis trial, critically ill surgical patients with an expected ICU stay of ≥3 days were randomized to receive either fluconazole 400 mg/day or placebo. The primary endpoint was the time to fungal infection, which was significantly delayed in the fluconazole prophylaxis group. The trial was well designed and enrolled 260 patients. A limitation of the study is the inclusion of presumed invasive fungal infection, defined for example, by repeatedly positive urine cultures and catheter tips with ≥15 yeast colonies, into the primary endpoint [10]. In another study, patients ventilated for 48 h and expected to remain ventilated for another ≥72 h received selective digestive decontamination with polymyxin B, neomycin and vancomycin and were randomized to receive fluconazole 100 mg/day or placebo. This trial was well designed, and 204 patients were randomized. Candidaemia was more successfully prevented in fluconazole recipients, but the selective digestive decontamination regimen used in this clinical trial is not a standard in most countries [11–13]. Meta-analyses of the clinical trials above and some other studies on highly selected populations found fluconazole 400 mg/day to be superior to placebo in preventing invasive fungal infection in critically ill surgical patients [14–18]. A more recent clinical trial compared caspofungin 50 mg/day with placebo for prophylaxis in a highly selected population of ventilated patients receiving antibiotics, having a central venous catheter and fulfilling at least one of the following criteria: parenteral nutrition, dialysis, major surgery, pancreatitis, systemic steroids or other immunosuppressant medication. The primary endpoint of this trial was the incidence of proven and probable invasive candidiasis according to EORTC/MSG definitions [19]. The investigators found a trend only towards a reduced incidence of invasive candidiasis [5]. Other antifungals have been evaluated in prophylactic indications [20–22]. For ketoconazole 200 mg/day, evidence of prophylactic benefit is weak while adverse events and drug interactions limit its use in general [22]. The same is true for itraconazole 400 mg/day [21]. Nystatin 4 Mio IU/day has been evaluated, but concept and patient setting are basically outdated [20]. Intravenous amphotericin B and the echinocandins have not been sufficiently evaluated in this indication [23]. Antifungal prophylaxis in solid organ transplant recipients is not part of this guideline.

Of note, none of the trials proved a reduction in overall or attributable mortality. All trials were lacking power to address the potential emergence of less azole-susceptible strains during prophylaxis. Apart from historical control studies in intensive care and abdominal surgical populations, this has been shown in prophylactic settings in haematology during substantially longer azole exposure periods [24–26]. Selection of less-susceptible strains remains a caveat against broadly using antifungals in populations where substantial benefit has not been proven.

Recommendations. Fluconazole prophylaxis against invasive candidiasis is recommended in patients who recently underwent abdominal surgery and had recurrent gastrointestinal perforations or anastomotic leakages. For further recommendations, refer to Table 3.

Fever-driven approach (empiric)

We defined empiric therapy as a fever-driven approach in the clinical situation of a patient at risk for invasive candidiasis who is persistently febrile with no microbiological evidence of infection.

Evidence. The value of initiating antifungal therapy in this situation has been addressed in a number of retrospective studies. Incubation time [27] and time from first positive blood culture drawn to initiation of empiric antifungal therapy correlated with mortality increases [6,28]. Similarly, in a population-based retrospective study, empiric antifungal treatment was associated with higher survival rates, if the isolate turned out to be susceptible to the empiric regimen [29]. Another retrospective study in patients with septic shock due to any cause found empiric antifungal therapy was given infrequently, and those with invasive fungal infection not receiving empiric antifungals had a statistically significantly higher mortality [7].

Although uncontrolled, all of these studies suggest that initiating empiric therapy may be beneficial to reduce overall mortality, but none could identify reliable triggers for antifungal treatment. They analysed patients with candidaemia but not the whole population of febrile patients.

One randomized double-blind placebo-controlled clinical trial evaluated fluconazole 800 mg/day in 270 adult ICU patients with an APACHE II score >16. Rates of invasive candidiasis were not statistically different between the two groups. The primary endpoint was driven by resolution of

TABLE 3. Recommendations on antifungal prophylaxis in ICU patients

Population	Intention	Intervention	SoR	QoE	References	Comment
Recent abdominal surgery AND recurrent gastrointestinal perforations or anastomotic leakages	To prevent intraabdominal *Candida* infection	Fluconazole 400 mg/day	B	I	[8]	Placebo *N* = 43
		Caspofungin 70/50 mg/day	C	II_u	[9]	Single arm *N* = 19
Critically ill surgical patients with an expected length of ICU stay ≥3 day	To delay the time to fungal infection	Fluconazole 400 mg/day	C	I	[10]	Placebo *N* = 260
Ventilated for 48 h and expected to be ventilated for another ≥72 h	To prevent invasive candidiasis/candidaemia	Fluconazole 100 mg/day	C	I	[162]	Placebo *N* = 204 SDD used
Ventilated, hospitalized for ≥3 day, received antibiotics, CVC, and ≥1 of: parenteral nutrition, dialysis, major surgery, pancreatitis, systemic steroids, immunosuppression	To prevent invasive candidiasis/candidaemia	Caspofungin 50 mg/day	C	II_a	[5]	Placebo *N* = 186 EORTC/MSG criteria used
Surgical ICU patients	To prevent invasive candidiasis/candidaemia	Ketoconazole 200 mg/day	D	I	[22]	Placebo *N* = 57
Critically ill patients with risk factors for invasive candidiasis/candidaemia	To prevent invasive candidiasis/candidaemia	Itraconazole 400 mg/day	D	I	[21]	Open *N* = 147
Surgical ICU with catabolism	To prevent invasive candidiasis/candidaemia	Nystatin 4 Mio IU/day	D	I	[20]	Placebo *N* = 46

SoR, Strength of recommendation; QoE, Quality of evidence; ICU, intensive care unit; CVC, central venous catheter; IU, international units.
The table displays the published evidence; therefore, other available antifungal agents are not mentioned here.

fever, and empirical fluconazole treatment did not improve outcome when compared with placebo [30].

Recommendations. Early treatment of presumed fungaemia is presumably associated with higher survival rates, but the optimal time point for initiating empiric antifungal treatment remains undetermined. Due to lack of data, no recommendation can be given for choosing a specific drug for fever-driven therapy. In general, such choice should be based on local epidemiology and drug–drug interactions in the individual patient and should be made among the same drugs as recommended for candidaemia. Further recommendations are given in Table 4.

Diagnosis-driven approach (pre-emptive)

We defined pre-emptive therapy as therapy triggered by microbiological evidence of candidiasis without proof of invasive fungal infection.

Evidence. Several studies have addressed diagnosis-driven therapy on grounds of detecting (1,3)-β-D-glucan in serum or plasma. In a study on 46 ICU patients without infection or with confirmed bacterial or fungal infection, glucan test results (G-test; Associates of Cape Cod, East Falmouth, MA, USA) correlated with infection, but not with fungal infection. The authors suggested using the test to rule out invasive fungal infection [31]. This was the key finding in a study using the Fungitell™

TABLE 4. Recommendations on fever-driven and diagnosis-driven therapy of candidaemia and invasive candidiasis

Population	Intention	Intervention	SoR	QoE	References
Adult ICU patients with fever despite broad-spectrum antibiotics and APACHE II >16	To resolve fever	Fluconazole 800 mg/day	D	I	[30]
ICU patients persistently febrile, but without microbiological evidence	To reduce overall mortality	Fluconazole or echinocandin	C	II_u	[28] [163] [164] [7] [27]
ICU patients with candida isolated from respiratory secretions	To cure invasive candidiasis or candidaemia early	Any antifungal	D	II_u	[42]
ICU patients with positive (1,3)-β-D-glucan test[a]	To cure invasive candidiasis or candidaemia early	Any antifungal	C	II_u	[39] [31] [37] [35] [32] [36] [34] [33]
Any patient with *Candida* isolated from a blood culture	To cure invasive candidiasis	Antifungal treatment	A	II	[46] [47] [48] [49]

APACHE, acute physiology and chronic health evaluation.
[a]The (1,3)-β-D-glucan tests have low specificity and sensitivity with false-positive results in the presence of haemodialysis, other fungal or bacterial infection, wound gauze, albumin or immunoglobulin infusion.

(Assoc. of Cape Cod) test, too [32]. Another group of investigators found glucan (Fungitec™; Seigakaku Kogyo, Tokyo, Japan) testing useful in predicting invasive fungal infection, but in a very small population of 32 patients only [33]. During twice weekly monitoring in long-term ICU patients, glucan concentrations (Glucatell™; Cape Cod) were higher in individuals with proven fungal infection than in those without. As patients with invasive fungal infection had more bacterial infections and other intercurrent complications, the test result could still not clearly distinguish between both groups [34]. Similar results were found in a surgical ICU patient group (N = 57) and in a mixed ICU population (N = 95) where higher glucan concentrations (Fungitell™) were found in those with invasive candidiasis, but still the positive predictive value was limited [35,36]. Findings from a retrospective study on a larger number of patients (N = 871) were in favour of the test (Fungitell™), but documented generally higher glucan concentrations in patients on haemodialysis and in those receiving albumin or intravenous immunoglobulin infusions [37]. Other reasons for positive test results in the absence of invasive candidiasis have been described due to (1,3)-β-D-glucan-containing cell walls of a variety of fungi, for example, *Aspergillus* or *Histoplasma* [32,38]. Indeed, the Fungitell™ assay has been suggested useful in the diagnosis of pneumocystis pneumonia as well [39]. A discussion of glucan tests and their cut-offs to positivity can be found in the ESCMID Candida Guidelines on Diagnostic Procedures in this issue [173]. In some of the studies above, it has been stated that a negative glucan test practically rules out invasive candidiasis. Currently, the glucan tests cannot reliably confirm invasive candidiasis, although there may be a role as part of a set of diagnostic tools and patient characteristics.

Recommendations on mannan and anti-mannan antibody detection is part of the EFISG guideline on diagnosis of invasive candidiasis [173].

A controversial issue is the initiation of antifungal therapy upon *Candida* isolation from respiratory secretions. Two forms of pulmonary candidiasis have been distinguished, that is, pulmonary abscesses resulting from haematogenous spread during candidaemia, especially in febrile neutropenic patients, and direct invasion of bronchial and lung tissues. Most articles on the topic of pulmonary candidiasis were published in the 1970s and 1990s. There are hardly any data on ICU populations, but case series of patients with haematological malignancy and stem cell recipients [40,41]. While *Candida* can frequently be isolated from respiratory secretions, it appears that *Candida* invading the lung tissue is a very rare event. In a recent prospective autopsy study (N = 232) on ICU patients, a total of 58% had proven pneumonia. Regardless of whether *Candida* had been isolated pre-mortem or not, in neither case histopathological proof of *Candida* tissue invasion was found [42].

Recommendations. Candida isolation from respiratory secretions should never trigger treatment, but rather be interpreted as one site of colonization among others. (1,3)-β-D-glucan detection in serum or plasma prompting antifungal treatment is marginally supported. Detailed recommendations are given in Table 4.

Targeted treatment

Candida isolated from a single peripheral blood culture or a single central-line blood culture defines candidaemia [19,43,44]. Previous definitions may have described asymptomatic patients with a blood culture positive for *Candida*, and it has been debated whether there are patients who do not need antifungal treatment despite a positive blood culture [45]. This appears to be a very rare clinical situation, as usually blood cultures are triggered by a clinical sign, for example, fever. Each case of candidaemia, even from surveillance blood cultures in asymptomatic patients requires targeted treatment [46–49].

Evidence. A plenitude of well-designed clinical trials evaluated antifungals for the initial treatment of candidaemia and invasive candidiasis. Amphotericin B deoxycholate clearly is a very potent drug against *Candida*, but the well-documented significant toxicity justifies a recommendation against using this compound [50–55]. In the past, several approaches aimed at reducing toxicity, for example, continuous intravenous administration, but efficacy of this strategy in candidiasis remains unclear [56]. Amphotericin B lipid complex has been evaluated in candidaemia, but the single randomized trial to date has been published as abstract only. Amphotericin B lipid complex appeared to be less nephrotoxic than the deoxycholate formulation although not more effective [57], findings which were supported by a phase IV study [58]. As opposed to laboratory-confirmed adverse events, clinically defined side effects, such as infusion-related fever and chills, tend to be underestimated in uncontrolled post-marketing studies. When ABLC was compared to liposomal amphotericin B in persistently febrile neutropenic patients, infusion-related adverse events occurred very frequently [59]. Data on amphotericin B colloidal dispersion stem from a non-randomized, non-comparative study describing nephrotoxicity in the same range as found with amphotericin B lipid complex [60]. Liposomal amphotericin B and amphotericin B deoxycholate have not been compared directly in patients with candidaemia. But, liposomal amphotericin B appears at least as effective, but less toxic than the deoxycholate formulation when considering results from a large clinical trial on candidaemia and invasive candidiasis evaluating liposomal amphotericin B and micafungin [61]. Compared to micafungin,

efficacy was similar, but renal toxicity was higher with liposomal amphotericin B [61,62]. Caspofungin when compared to amphotericin B deoxycholate was as effective, but significantly less toxic [55]. A clinical strategy became feasible, which avoided amphotericin B toxicity without losing efficacy. Two doses of micafungin (100, 150 mg/day) were compared with caspofungin in a phase III trial. All three regimens were similarly effective and safe [63]. While all echinocandin trials above proved statistical non-inferiority of the experimental study drug as compared to standard regimens, anidulafungin was found to be superior over fluconazole [64]. In particular, the outcomes for patients with *Candida albicans* were significantly better with anidulafungin (81%) than with fluconazole (62%). The latter result remained valid in a subsequent subgroup analysis of ICU patients: global response for anidulafungin 67% vs. fluconazole 47% [65].

With regard to *Candida,* all three echinocandins exhibit a broad spectrum activity; acquired resistance is rare, although there has been a first large epidemiological evaluation describing acquisition of resistance genes in *Candida glabrata* [66]. There is an ongoing debate on whether echinocandins are appropriate for treating *Candida parapsilosis*, because minimal inhibitory concentrations are found to be higher than those of other *Candida* species. Overall, that is, clinical and microbiological, response rates in *C. parapsilosis* infection were not statistically significantly different throughout the echinocandin trials: for caspofungin/amphotericin B, the success rates were 70% and 65%, for micafungin/liposomal amphotericin B 89.2% and 86.7%, for caspofungin/micafungin 100/150 rates were 64.3%, 75.9% and 71.4%, and for anidulafungin/fluconazole, they were 64% and 83% [55,61,63]. However, there were numerically higher numbers of persistent fungaemia due to *C. parapsilosis* during caspofungin as compared to amphotericin B deoxycholate treatment [55], and during standard dose caspofungin as compared to high dose, that is, 150 mg/day, caspofungin [67], and the eradication rate in *C. parapsilosis* fungaemia was lower with anidulafungin than with fluconazole [64]. It is important to note that none of these trials were powered to detect such differences.

Two further aspects we considered important when interpreting the latter trial are (i) the microbiological eradication rate as well as the overall success rate in *C. albicans* infection was higher with anidulafungin than with fluconazole and (ii) *Candida krusei* infection was excluded from the anidulafungin trial, because of fluconazole being the comparator drug [64].

In the clinical trials, all three echinocandins were well tolerated and appeared very safe. Micafungin though carries a warning label against use unless other antifungals are not appropriate by the European Medicines Agency, which reflects results of rats developing liver tumours after very long and high-dosed exposure [68]. This statement has elicited some debate in terms of its relevance to humans, but has not been withdrawn or disproved so far.

An advantage of the echinocandin class is the low potential for drug–drug interactions. For anidulafungin, no interactions have been described, and for micafungin, very few relevant interactions need to be considered [68,69]. Co-administering caspofungin with rifampin lowers caspofungin exposure, and it has been recommended to increase the dose of caspofungin in the rare cases, where both drugs need to be administered concomitantly. In addition, caspofungin dose has to be increased in patients with a high body weight [70].

For many years, fluconazole was considered the drug of choice for candidaemia [71–73]. This was based on a great number of clinical trials evaluating fluconazole in this indication [52–54,64,74–76]. As anidulafungin was superior over fluconazole in patients with candidaemia, especially those infected with *C. albicans*, we do no longer consider fluconazole as the drug of choice [64]. Fluconazole was inferior in the subgroup of patients with high APACHE scores and is known to have a limited spectrum of activity, being inactive against *C. krusei* and being considered hardly active in *C. glabrata* infection. Microbiologically, it might though be the better drug against *C. parapsilosis*, which is supported by a trend towards better outcomes in the comparative trial [64], but clinical proof is not in support of this. There have been no trials with sufficient power to assess non-inferiority of echinocandins for *C. parapsilosis*. In a large clinical trial, voriconazole was non-inferior to amphotericin B deoxycholate followed by fluconazole [43], and voriconazole offers an important additional treatment option for first-line and salvage situations [77,78]. Still there are certain limitations, that is, the multiple drug–drug interactions [79], the limit of the intravenous use to 14 days duration [79] and the variable pharmacokinetics of the drug [80]. Itraconazole yielded negative results when compared to fluconazole [76]. There are no published data on posaconazole treatment of candidaemia.

Very few clinical trials used combination treatment. Lipid-based amphotericin B was supplemented with placebo or efungumab, a monoclonal antibody targeting heat shock protein 90 (HSP-90), in 139 patients. The study design and analysis drew substantial criticism for (i) enrolling an ill-defined patient population, for example, symptomatic candiduria, (ii) enrolling patients with negative fungal cultures and (iii) excluding patients from the efficacy population who died while on treatment [81]. Furthermore, the trial allowed extensive prior antifungal treatment, used a short, 10-day, treatment time until response evaluation and did not specify

the proportion of patients receiving which type of lipid-based amphotericin B formulation.

The combination of amphotericin B deoxycholate and fluconazole has been as effective as fluconazole monotherapy in a randomized trial, but patients had an increased risk of toxicity and no survival benefit [74]. A small study (N = 72) comparing fluconazole with amphotericin B deoxycholate and 5-flucytosine showed no difference in overall response to treatment [75].

Recommendations. Targeted treatment of candidaemia with echinocandins is strongly recommended. The recommendation for liposomal amphotericin B or voriconazole is less stringent, and fluconazole is recommended with marginal strength only, except for *C. parapsilosis*. For detailed recommendations, refer to Table 5.

Duration of targeted treatment, step-down to oral treatment and diagnostics in candidaemia

Evidence. The duration of treatment depends on the extent of organ involvement. In a population without documented organ involvement, treatment aims to clear the infection and at the same time to avoid deep-organ involvement. This can be achieved by treating for 14 days after the end of candidaemia [82]. To determine the end of candidaemia, at least one blood culture per day should be taken until culture results come back negative. Treatment can probably be simplified by stepping down to oral fluconazole after 10 days of intravenous treatment, if the patient is stable, tolerates the oral route and if the species is susceptible [55,63,64].

The diagnostic procedures to detect organ involvement comprise transoesophageal echocardiography, fundoscopy and search for a thrombus. A recent observational study found infectious endocarditis in 8.3% of patients with candidaemia; the majority of these patients had no well-established risk factors, that is, vascular prosthesis or persistent candidaemia [83].

Some prospective studies addressed ocular candidiasis as complication of candidaemia. The diagnostic approach was usually based on weekly eye examinations. Immunosuppression and repeatedly positive blood cultures are risk factors

TABLE 5. Recommendations on initial targeted treatment of candidaemia and invasive candidiasis in adult patients

Intervention	SoR	QoE	References	Comment
Anidulafungin 200/100 mg	A	I	[64]	Consider local epidemiology (*Candida parapsilosis*, *Candida krusei*), less drug–drug interactions than caspofungin
Caspofungin 70/50 mg	A	I	[67] [55] [63]	Consider local epidemiology (*C. parapsilosis*)
Micafungin 100 mg	A	I	[61] [63]	Consider local epidemiology (*C. parapsilosis*), less drug–drug interactions than caspofungin, consider EMA warning label
Amphotericin B liposomal 3 mg/kg	B	I	[61] [62]	Similar efficacy as micafungin, higher renal toxicity than micafungin
Voriconazole 6/3 mg/kg/day[a,b]	B	I	[43] [78] [77]	Limited spectrum compared to echinocandins, drug–drug interactions, limitation of IV formulation in renal impairment, consider therapeutic drug monitoring
Fluconazole 400–800 mg[a]	C	I	[165] [53] [74] [54] [64] [76] [75] [73] [72]	Limited spectrum, inferiority to anidulafungin (especially in the subgroup with high APACHE scores), may be better than echinocandins against *C. parapsilosis*
Amphotericin B lipid complex 5 mg/kg	C	II_a	[57] [58]	
Amphotericin B deoxycholate 0.7–1.0 mg/kg	D	I	[50] [51] [165] [53] [54] [55]	Substantial renal and infusion-related toxicity
Amphotericin B deoxycholate plus fluconazole	D	I	[74]	Efficacious, but increased risk of toxicity in ICU patients No survival benefit
Amphotericin B deoxycholate plus 5-fluorocytosine	D	II	[75]	
Efungumab plus lipid-associated amphotericin B	D	II	[166]	
Amphotericin B colloidal dispersion	D	II_a	[60]	
Itraconazole	D	II_a	[76]	
Posaconazole	D	III	No reference found	

EMA, European Medicines Agency.
Comparative clinical trials did not prove a survival benefit of one treatment over another. Primary intention of treating candidaemia is clearing the blood stream.
[a]Not all experts agreed, SoR results from a majority vote.
[b]The licensed maintenance dosing is 4 mg/kg/day.

for eye involvement and should prompt fundoscopic evaluation [84,85]. Other risk factors coincided with those for candidaemia [86]. In a large clinical trial, fundoscopy revealed ocular candidiasis in 16% of patients with candidaemia, the majority had eye involvement upon diagnosis of candidaemia and additional cases were detected during treatment. Most of the patients had chorioretinitis while endophthalmitis was uncommon (1.6%) [43,87].

In patients with a central venous catheter or a peripherally inserted central catheter, the possibility of a thrombus should be taken into account.

Recommendations. For uncomplicated candidaemia, treatment duration of 14 days after the end of candidaemia is recommended. The end of candidaemia should be determined by at least one blood culture per day until negativity. Transoesophageal echocardiography and fundoscopy should be performed to detect organ involvement. Switching to oral treatment can be considered after 10 days of intravenous therapy. For detailed recommendations, refer to Table 6.

Catheter-related blood stream infection

In general, indwelling lines need to be removed early after diagnosing catheter-related candidaemia; however, removal or exchange is not always possible. As the predominant mode of device-related infections is likely biofilm formation [88], certain differences in antifungal activity on *Candida* grown in biofilms vs. planktonic cells may help decision making. Liposomal amphotericin B, amphotericin B lipid complex, caspofungin and micafungin were active against *Candida* cells in biofilms, while cells were resistant towards amphotericin B deoxycholate, fluconazole, ravuconazole and voriconazole [89]. In animal models, amphotericin B lipid complex and anidulafungin reduced candida cell numbers in biofilms, while fluconazole did not [90,91].

Evidence. Duration of candidaemia: In a prospective randomized clinical trial comparing fluconazole with amphotericin B deoxycholate for candidaemia in non-neutropenic patients [53], the exchange of catheters – not over a guidewire – within the first 24 h was associated with a shorter duration of candidaemia [92]. A *post hoc* analysis of two pooled phase III trials comparing micafungin to caspofungin or liposomal amphotericin B (N = 842) did not find an improved time to mycological eradication, if central venous catheters were removed within 24 or 48 h [61,63,93].

Impact of catheter removal on mortality: Catheter removal was identified as a protective factor in a prospective study on 272 episodes of candidaemia [94]. A population-based study analysing 345 cases of candidaemia concluded that catheter removal was associated with an improved probability of survival [95,96]. In a retrospective analysis on 92 patients with cancer, removal of non-tunnelled central venous catheters ≥72 h after diagnosis of candidaemia was associated with a significantly decreased survival rate, [97] and in a univariate analysis on 244 ICU patients with candidaemia, catheter removal within 24 h was associated with better survival [73]. Early removal of central venous catheters, that is, within 24 or 48 h, had no impact on survival at 28 or 42 days in the *post hoc* analysis of the two pooled micafungin phase III trials [93]. However, in a recent individual patient level (n = 1915) pooled analysis of seven prospective randomized controlled trials for treatment of invasive candidiasis and candidaemia, the removal of a central venous catheter was associated with decreased mortality (OR, 0.50; 95% CI, 0.35–0.72, p = 0.0001) [98].

Recommendations. In candidaemia, removal of indwelling intravascular catheters is strongly recommended. When catheter removal is not possible, lipid-based amphotericin B formulation or an echinocandin is preferable. For detailed recommendations, refer to Table 7.

TABLE 6. Recommendations on the duration of targeted treatment, step-down to oral treatment and diagnostics in candidaemia

Population	Intention	Intervention	SoR	QoE	References
Candidaemia with no organ involvement detected	To avoid organ involvement	Treat for 14 days after the end of candidaemia	B	II	[82]
		Take at least one blood culture per day until negative	B	III	No reference found
	To detect organ involvement	Transoesophageal echocardiography	B	II_a	[83]
		Fundoscopy	B	II	[87] [84] [85] [86]
		If CVC, PICC or intravascular devices, search for thrombus	B	III	No reference found
Any	To simplify treatment	*Step-down to fluconazole after 10 days of IV, if species is susceptible, patient tolerates PO, and patient is stable	B	II	[64] [55] [63]

CVC, central venous catheter; PICC, peripherally inserted central catheter.
*If *C. parapsilosis* is identified, step-down to fluconazole may occur earlier.

Urinary tract infection

Candiduria is commonly encountered in hospitalized patients, particularly those with a urinary catheter. Candiduria is indicative for a wide spectrum of conditions which may or may not require treatment.

Evidence. Asymptomatic candiduria has been followed long term, but no adverse consequences have been described [99]. Funguria resolved without specific treatment in 76% of a large (N = 861) clinical cohort [100]. In a well-designed trial, fluconazole was superior over placebo in clearing candiduria, but at 2-week follow-up candiduria rates were similar between both groups. Removal of the urinary catheter was the most promising intervention [101]. Bladder irrigation appeared as a rarely used alternative, if treatment is judged necessary [100,102]. In symptomatic candida cystitis, fluconazole has been advocated as well as amphotericin B deoxycholate with or without 5-flucytosine, but clinical data are sparse for all these approaches [100,103]. In the rare cases of fungus balls, surgical intervention is the only promising treatment option [104,105]. Echinocandins do not achieve high urine concentrations and are thus rarely considered in urinary tract infection. Some cases though have successfully been treated with caspofungin. These were partly candidaemias with concomitant candiduria and partly infections limited to the urinary tract [106]. For candida pyelonephritis, fluconazole and amphotericin B deoxycholate each with or without flucytosine may be used, but clinical trials have not been performed.

Recommendations. Asymptomatic candiduria should not be treated, while symptomatic cystitis should be treated with fluconazole, if the isolate is susceptible. Fungus balls or casts in the pyelum or urinary bladder need surgical intervention. To cure pyelonephritis fluconazole as well as lipid-based amphotericin B are recommended either alone or in combination with flucytosine. For detailed recommendations, refer to Table 8.

Ocular candidiasis

Ocular candidiasis may cause pain or disturbed vision, but should rather be diagnosed prior to becoming clinically symptomatic [86,107]. There are two forms of ocular candidiasis. Chorioretinitis is the inflammation of the choroid and the retina, while endophthalmitis is the inflammation of the vitreous body. Fungal endophthalmitis may develop from chorioretinitis as advanced disease and is associated with poor visual outcomes [108]. Most publications in this field report on individual cases or small series, and not all clearly differentiate between the two forms of ocular involvement.

Evidence. Amphotericin B deoxycholate has been advocated for ocular candidiasis, but dosing information was not always disclosed in the early reports [107,109,110]. Amphotericin B deoxycholate followed by fluconazole has been used successfully to treat ocular involvement in the voriconazole phase III trial [43,87]. Information on amphotericin B lipid complex use in ocular candidiasis is sparse. One case of breakthrough ocular candidiasis during amphotericin B lipid complex treatment has been described [111], and another case in which amphotericin B lipid complex was successfully used with concomitant flucytosine [112]. In a rabbit model evaluating the penetration of amphotericin B deoxycholate, liposomal amphotericin B and amphotericin B lipid complex, the highest penetration into the eye was achieved with the liposomal formulation [113,114]. Intravitreal injection of amphotericin B deoxycholate 5–10 μg dissolved in 0.1 mL sterile water is part of standard approaches and frequently combined with systemic antifungals and surgery [110,115].

All three echinocandins appear to have limited penetration into the eye [116–118]. With caspofungin treatment, varying outcomes have been reported, some patients failed treatment [116,119], while only two patients have been described who responded successfully [120,121].

Successful use of fluconazole has been reported in case series, where it was used at doses varying from 100 to 400 mg

TABLE 7. Recommendations on catheter management in candidaemia

Population	Intervention	SoR	QoE	References
Central venous catheter can be removed	Remove indwelling lines (not over a guidewire)	A	II_r	[98]
Central venous catheter cannot be removed	Echinocandin, liposomal amphotericin B or amphotericin B lipid complex	B	II_r	[98] [90] [89] [91] [93] [92]
	Azole or amphotericin B deoxycholate	D	II_r	[95] [98] [73] [97] [96] [94]

Interventions are intended to clear candidaemia and to improve survival.

TABLE 8. Recommendations on *Candida* urinary tract infections

Population	Intention	Intervention	SoR	QoE	References
Asymptomatic	To clear candiduria	None[a]	A	II_u	[100] [99]
		Fluconazole 200 mg for 14 days[b]	C	I	[100] [101]
		Removal of urinary catheter	B	I	[101]
		Amphotericin B deoxycholate bladder irrigation	C	$II_{r,u}$	[100] [102]
Cystitis	To cure	Fluconazole[b]	A	III	[100]
		Amphotericin B deoxycholate +/– flucytosine	B	III	
Fungus balls	To cure	Surgical intervention	A	III	[104] [105]
Pyelonephritis	To cure	Caspofungin 70/50 mg for 9–28 days	C	III	[106]
		Fluconazole +/– flucytosine[b]	A	III	No reference found
		Lipid-based amphotericin B +/– flucytosine	A	III	No reference found

[a]In pre-operative patients, treatment is indicated to suppress candiduria.
[b]If species is susceptible.

for at least two and up to 8 weeks. A number of these patients were treated with concomitant systemic amphotericin B deoxycholate [122–125]. Overall fluconazole 400 mg alone appeared to be effective in less-advanced disease [126].

In advanced disease, a combined strategy of surgical intervention with intraocular amphotericin B deoxycholate, and systemic fluconazole has successfully been applied [110]. Systemic antifungal treatment duration varied between 2 and 12 weeks [110,127]; an individual decision will usually take reduction of immunosuppression and the extent of ocular candidiasis into consideration.

More recently, intravitreal voriconazole has been evaluated, and in animal models, doses of 25 mg/L vitreous, that is, 100 μg absolute in an adult human eye, were found to be safe [126,128]. Published cases were frequently treated with combined approaches, so that the efficacy of voriconazole monotherapy has not yet been defined [126,129,130]. In the *post hoc* analysis of eye involvement in the voriconazole phase III trial on candidaemia, treatment was successful in most cases, but endophthalmitis was rare [87].

Recommendations. In ocular candidiasis, liposomal amphotericin B either alone or combined with flucytosine is recommended when the susceptibility of the isolate is unknown. In susceptible isolates fluconazole or voriconazole are the drugs of choice. In the case of vitreal involvement, vitrectomy and intravitreal injection of amphotericin B are recommended in addition to systemic therapy. For details, refer to Table 9.

Candida meningitis

Candida meningitis is a rare disease, and only very few reports have been published. Prognosis is generally poor [131].

Evidence. Liposomal amphotericin B has been combined with flucytosine for 10 weeks, followed by fluconazole for 5 weeks in a neonate [132]. In another neonate, a *Candida* isolate was resistant to flucytosine, and liposomal amphotericin B was combined with fluconazole for a total of 4 weeks [133]. Amphotericin B deoxycholate/flucytosine treatment had failed in the latter patient [133]. However, it is unclear to what extent these experiences can be extrapolated applied to adults. In a series of HIV-infected patients with candida meningitis, amphotericin B deoxycholate was frequently combined with flucytosine, and four of five patients were treated successfully [131]. In two other series, 27 of 34 patients survived after similar treatments [134,135]. In some cases, individualized maintenance regimens were given [131,134]. In the more recent case reports, amphotericin B deoxycholate toxicity frequently forced to replace it with the liposomal amphotericin B.

Fluconazole has been used in higher doses to treat *Candida* meningitis, when lower doses proved insufficient [136]. Published data on voriconazole use in *Candida* meningitis are sparse. In central nervous system, aspergillosis voriconazole is the drug of choice [137]. Brain tissue levels of voriconazole are satisfactory, but concentrations in cerebrospinal fluid are variable [138].

With caspofungin, a patient was cured from *Candida* meningitis refractory to amphotericin B deoxycholate and fluconazole [139], but poor penetration of echinocandins limit their use in central nervous system infection.

Recommendations. Due to lack of data, no strong recommendation can be given. Treatment should build on liposomal amphotericin B combined with flucytosine or with fluconazole if isolate is susceptible. For detailed recommendations, refer to Table 10.

TABLE 9. Recommendations on *Candida* chorioretinitis and endophthalmitis

Population	Intervention	SoR	QoE	References
Susceptibility of isolate unknown	Liposomal amphotericin B 5 mg/kg	B	III	[113] [114] [119]
	Liposomal amphotericin B plus flucytosine	B	III	No reference found
	Amphotericin B lipid complex plus flucytosine	B	III	[112]
	Amphotericin B deoxycholate 0.7–1.0 mg/kg (for 3–7 days), followed by fluconazole 400 mg	C	II	[87]
	Amphotericin B deoxycholate 0.6–1.0 mg/kg	C	II_r	[107] [109] [110]
	Amphotericin B lipid complex 5 mg/kg	C	III	[111]
	Amphotericin B deoxycholate plus flucytosine	C	III	No reference found
	Caspofungin 50–100 mg	D	II_u	[116] [120] [121] [119] [130]
Susceptible isolate	Fluconazole 400–800 mg	A	II_u	[122] [123] [124] [126] [125]
	Voriconazole 12/6 mg/kg IV, followed by 400 mg PO	A	II_u	[129] [87] [130] [119] [126] [128]
Vitreal involvement[a]	Amphotericin B deoxycholate 5–10 μg intravitreal injection	B	II_u	[110] [167] [115] [168]
	Vitrectomy plus intravitreal amphotericin B 5–10 μg, fluconazole 400 mg for ≥2 weeks	B	II_u	[110] [127] [125]
	Voriconazole 100 μg intravitreal injection	B	III	[128] [126]

Frequent eye examinations are needed to detect disease progression.
[a]Endophthalmitis requires local and systemic treatment plus surgery.

Candida endocarditis

Candida endocarditis may manifest as native valve endocarditis, prosthetic valve endocarditis or infection in the presence of pacemaker or other implanted material prone to biofilm formation. In general, prognosis is poor with 1-year mortality >50% and substantial relapse rates [140–142].

Evidence. In native valve *Candida* endocarditis, primary intention is to decrease mortality [140]. Retrospective data suggest that patients should undergo surgery within the first week [140,141,143]. Treatment regimens published are liposomal amphotericin B or caspofungin, either one has been combined with flucytosine [140,141]. In prosthetic valve *Candida* endocarditis, valve replacement surgery needs be performed as soon as possible [142,143]. In single cases where comorbidities prevented surgery, caspofungin and liposomal amphotericin B were used successfully with or without subsequent life-long suppressive therapy with fluconazole [142,144,145]. In patients with pacemakers, implantable defibrillators or assist devices, removal of the device appears mandatory [146].

TABLE 10. Recommendations on *Candida* meningitis

Intervention	SoR	QoE	References
Liposomal amphotericin B 3 mg/kg for 10 weeks + flucytosine 150 mg/kg for 10 weeks, followed by fluconazole 3 mg/kg for 5 weeks	B	III	[132]
Liposomal amphotericin B 3 mg/kg for 4 weeks + fluconazole 6 mg/kg for 4 weeks	B	III	[133]
Voriconazole 12/6 mg/kg[a]	C	III	[137] [138] [43]
Fluconazole 800 mg	C	III	[136] [169]
Amphotericin B deoxycholate 0.5–1.0 mg/kg for >2 weeks +/− flucytosine 30–120 mg/kg for >2 weeks	D	II_u	[131] [134] [133] [135]
Caspofungin 70/50 mg for 4 weeks, followed by fluconazole 400 mg for 2 weeks	D	III	[139] [170]

Interventions are intended to cure *Candida* meningitis.
[a]Therapeutic drug monitoring recommended.

Recommendations. In native valve *Candida* endocarditis, surgery within a week is recommended, and in prosthetic valve *Candida* endocarditis, even earlier surgery may be beneficial. The antifungal regimen of choice is liposomal amphotericin B, which can be combined with flucytosine. For detailed recommendations, refer to Table 11.

TABLE 11. Recommendations on *Candida* endocarditis

Population	Intention	Intervention	SoR	QoE	References
Native valve	To cure	Surgery within 1 week	A	II	[140] [143] [171]
		Liposomal ampho B +/− flucytosine for 6–8 weeks, followed by fluconazole	B	II	[171]
		Caspofungin +/− flucytosine	C	II	[171]
Prosthetic valve	To cure	Surgery within days	A	III	[142] [143]
Prosthetic valve, if surgery not possible	To cure	Liposomal amphotericin B 5 mg/kg	B	III	[142]
		Caspofungin 70/50 mg	B	III	[142]
	To suppress infection	Fluconazole 400–800 mg, life long	C	III	[142] [145]
Pacemaker, ICD, VAD	To cure	Removal	A	II	[146] [144]

ICD, implantable cardioverter defibrillator; VAD, ventricular assist device.
Surgery – even if restricted to removal of hardware – always needs to be combined with systemic antifungal treatment.

TABLE 12. Recommendations on bone and joint candidiasis

Population	Intention	Intervention	SoR	QoE	References
Osteomyelitis/spondylodiscitis	To cure	Surgical debridement[a,b]	C	III	[147]
		Fluconazole 400 mg for 6–12 months[c]	A	II_u	[149] [148] [147]
		Liposomal amphotericin B 3 mg/kg or amphotericin B lipid complex 5 mg/kg for 2–6 weeks followed by fluconazole 400 mg for 5–11 months[c]	A	II_u	[149] [147]
		Posaconazole 800 mg for ≥6 weeks[c]	C	III	[150]
		Voriconazole 12/6 mg/kg for 6–12 weeks[c]	B	II_t	[78]
		Caspofungin 100 mg for 3 weeks, followed by fluconazole 400 mg for ≥4 weeks[c]	B	II	[120]
Arthritis	To cure	Liposomal Ampho B 3 mg/kg/ABLC 5 mg/kg 2 weeks, followed by fluconazole 400 mg for ≥4 weeks[c]	A	II_u	[154]
		Fluconazole 400 mg for ≥6 weeks[c]	A	II_u	[155]
		Voriconazole 12/6 mg/kg for ≥6 weeks[c]	B	III	[156]
		Caspofungin 70/50 mg for 6 weeks	C	II	[120] [152] [153]
Prosthetic joint infection	To cure	Prosthesis removal[b]	A	III	[154] [158] [157]
Prosthetic joint infection with prosthesis retention	To suppress infection	Fluconazole 400 mg, life long	A	III	[160] [161] [159] [157]

[a]Indications for surgery are, for example, instability or large abscess.
[b]Surgery needs to be combined with antifungal treatment.
[c]Treat longer if erythrocyte sedimentation rate or C-reactive protein not returned to normal.

Bone and joint candidiasis

Candida infections of bones and joints are grouped into osteomyelitis/spondylodiscitis, arthritis and prosthetic joint infection. No randomized clinical trials have been conducted, so that evidence for the best therapeutic approach is somewhat limited.

Evidence. Typical indications for surgical debridement in osteomyelitis or spondylodiscitis are instability or large abscesses. Usually, cases of *Candida* osteomyelitis are diagnosed by biopsy. Over the years, most experience has been gathered with amphotericin B formulations, sometimes combined with flucytosine, sometimes followed by fluconazole [147]. Today, in patients with osteomyelitis as well as spondylodiscitis due to a susceptible isolate, treatment can commence with liposomal or lipid complex amphotericin B to be followed by fluconazole [147], or – if isolate is susceptible – fluconazole monotherapy may be used from the beginning [147–149]. Posaconazole has been successfully used in a single case as add-on during unsuccessful caspofungin treatment [150]. Voriconazole treatment has been reported in three patients with *Candida* osteomyelitis [78]. In addition, in *Aspergillus* osteomyelitis, voriconazole was used either as the only antifungal or as maintenance following liposomal amphotericin B [151]. Use of echinocandins has not been reported, with the exception of four patients with osteomyelitis and/or septic arthritis successfully treated with caspofungin [120].

A case of *Candida* shoulder arthritis was cured with a 3-week course of caspofungin [152], and a knee arthritis was treated with 7 weeks of caspofungin added on to a failing fluconazole therapy [153]. The most prevalent joint prone to *Candida* infection is the knee. Standard treatment of knee arthritis due to *Candida* was an amphotericin B–based approach, which may have been supplemented with flucytosine [154]. More recently, fluconazole and voriconazole were used with success [78,155,156].

Joint prosthesis is an important risk factor for *Candida* arthritis, and prosthesis is mandatory [154,157,158]. If the prosthesis must be retained, life-long suppressive treatment should be tried. In some patients, surgery was considered not possible, and knee or hip prosthetic joint arthritis was cured with use of fluconazole alone [157,159–161]. Bias towards publishing the unusual and successful cases can be assumed, so that the standard approach remains prosthesis removal and an intensive course of systemic antifungals.

Recommendations. Treating osteomyelitis, spondylodiscitis or arthritis with fluconazole is strongly recommended if species is susceptible. Fluconazole may be preceded by an induction phase with lipid-based amphotericin B. If joint prosthesis cannot be removed, lifelong fluconazole suppressive therapy is indicated. For details, refer to Table 12.

Transparency Declarations

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

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, Immunexpress, Eli Lilly Suisse and Pfizer and received grant support from Baxter, bioMérieux, Merck Sharp and Dohme-Chibret AG and Roche Diagnostic. He has also received speaker's fees from MSD, Institut Pasteur and Gilead Sciences, travel support from Astellas, Pfizer and MSD.

J.G. has nothing to declare.

B.J.K. has received research grants from Bio-Mérieux and Cephalon. He is a consultant to Pfizer and is a member of the Gilead, MSD and Pfizer speaker's bureaus.

O.L. is a member of the MSD board, is a consultant for Astellas and Gilead Sciences and received grants or speaker's fees from MSD, Astellas, Gilead Sciences and Pfizer.

WM has received grant support from MSD and Pfizer. He had been an advisor to MSD and Pfizer. He has received honoraria for presentations on behalf of MSD/Schering Plough and Pfizer.

M.A. received research grants and honoraria for talks and consultancy from Merck, Pfizer and Gilead.

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.

J.B. has nothing to declare.

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

M.C.E. has received in the past 5 years grant support from Astellas Pharma, bioMerieux, Gilead Sciences, Merck Sharp and Dohme, Pfizer, Schering Plough, Soria Melguizo SA, Ferrer International, the European Union, the ALBAN program, the Spanish Agency for International Cooperation, the Spanish Ministry of Culture and Education, The Spanish Health Research Fund, The Instituto de Salud Carlos III, The Ramon Areces Foundation and The Mutua Madrileña Foundation. He has been an advisor/consultant to the Panamerican Health Organization, Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering Plough. He has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough.

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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.

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 and been paid investigator fees for a clinical trial by Pfizer.

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H.E.J. has nothing to declare.

C.L.-F. has received grant support in the past 5 years from Astellas Pharma, Gilead Sciences, Pfizer, Schering Plough and Merck Sharp and Dohme. She has been an advisor/consultant to Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering Plough. She has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough. Her travel and accommodation expenses have been covered by Astellas Pharma, Pfizer, Gilead Sciences, MSD and Schering-Plough.

G.P. has received research grants from Gilead, Pfizer, Astra Zeneca, Novartis, GSK, Astellas and MSD, has acted as paid consultant to Janssen Cilag, Gilead, Astellas and MSD and is a member of the Gilead, Astellas and MSD speaker' s bureaus. He has also received travel support from ESCMID, Gilead, Astellas and Pfizer.

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 conference support from Astellas Pharma, as well as consulted for Gilead Sciences and MSD.

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

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C.V. received grants as speaker/moderator in meetings sponsored by Pfizer, Gilead, MSD, Astellas, Abbott and BMS and received grants for participation in advisory boards by Gilead, Astellas, MSD and Pfizer. Further, he obtained research grants for his institution from Pfizer, MSD, Gilead, Abbott, Jansen, BMS, and Novartis. He is a 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). He has also received payment for educational presentations from Nadirex International (Pavia, Italy).

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