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ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

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Abstract

The European Conference on Infections in Leukemia (ECIL) provides recommendations for diagnostic strategies and prophylactic, pre-emptive or targeted therapy strategies for various types of infection in patients with hematological malignancies or hematopoietic stem cell transplantation recipients. Meetings are held every two years since 2005 and evidence-based recommendations are elaborated after evaluation of the literature and discussion among specialists of nearly all European countries. In this manuscript, the ECIL group presents the 2015-update of the recommendations for the targeted treatment of invasive candidiasis, aspergillosis and mucormycosis. Current data now allow a very strong recommendation in favor of echinocandins for first line therapy of candidemia irrespective of the underlying predisposing factors. Anidulafungin has been given the same grading as the other echinocandins for hemato-oncological patients. The beneficial role of catheter removal in candidemia is strengthened. *Aspergillus* guidelines now recommend the use of either voriconazole or isavuconazole for first line treatment of invasive aspergillosis, while first line combination antifungal therapy is not routinely recommended. As only few new data were published since the last ECIL guidelines, no major changes were brought to mucormycosis recommendations.

Introduction

ECIL is the result of a collaboration between the European Organization for Research and Treatment of Cancer (EORTC), the European Society for Blood and Marrow Transplantation (EBMT), the European Leukemia Net (ELN) and the International Immunocompromised Host Society (ICSH). First recommendations for the treatment of *Candida* and *Aspergillus* infections in hematological patients have been published in 2007 after ECIL-1 and have then been updated at ECIL-2 and ECIL-3.[1, 2] First recommendations for the diagnosis and treatment of mucormycosis have been published after ECIL-3.[3] ECIL-4 updates for antifungal therapy were only available as slides on the websites of these participating societies without publication of a manuscript considering lack of substantial new data and the limited modifications compared to the latest publication.

With respect to the targeted treatment of fungal infections, the goals for ECIL-5 were to update the recommendations with analysis of the new data for invasive candidiasis, aspergillosis and mucormycosis in hematological patients. The update was also necessary to change the prior 5-level grading (A to E) used during the ECIL 1 to 4 for the strength of recommendations for *Candida* and *Aspergillus* infections into a 3-level grading (A to C) already used during ECIL-3 for the first recommendation for mucormycosis (Table 1).[1-3] The grading for quality of evidence has not been modified.

Methods

ECIL-5 meeting was held in September 2013 and involved 57 experts from 21 countries including three non-European countries. Conclusion slides of ECIL-5 were available on the websites of EORTC, EBMT, ELN and ICHS. ECIL-6 meeting was held in September 2015 with the presence of 55 experts from 24 countries including four non-European countries (see collaborator list at the end of the text).

At both ECIL-5 and ECIL-6 meetings, the antifungal therapy working group made a search for new publications regarding treatment of invasive candidiasis, aspergillosis and mucormycosis. The group was divided in three subgroups, each being responsible for one of each fungal infection type. The literature search was performed in Pubmed and Cochrane databases. Abstracts presented at major congresses during the previous two years were also retrieved and integrated in the ECIL recommendation. All recommendations referring to an abstract, however, were classified as provisional until the publication of the final manuscript.

The working group presented its recommendations during the plenary session at ECIL-5 meeting and then incorporated the suggestions coming from the assembly. In case of absence of full consensus, a vote was organized and final decision was based on majority of votes from the full ECIL-5 assembly. The updated recommendations were presented on the next day during a second plenary session for final approval. Recommendations were graded based on the strength of recommendations (three-level scale: A, B, or C) and quality of evidence (three-level scale: I, II, or III) as detailed in Table 1.

The manuscript of ECIL-5 was taken on hold on after debates had emerged on differences between ECIL and European Society for Clinical Microbiology and Infectious Diseases (ESCMID) / European Confederation of Medical Mycology (ECMM) recommendations on guidelines for prophylaxis and treatment of invasive aspergillosis (draft presented at ECCMID 2014).[4] Two joint meetings were subsequently held (December 2014 and April 2015) to identify the differences and the exact reasons for these differences. The aim was not to modify the recommendations made by each of the two groups but rather to add explanations on the differences in the manuscript. For further clarification, a joint presentation was given at ECIL-6 by members of the ECIL group and of the ESCMID/ECMM group. This resulted in a delay of publication of the ECIL-5 recommendations and the ECIL assembly approved during the ECIL-6 plenary session a new search for publications or abstracts until September 2015 with inclusion of all relevant data on aspergillosis, candidiasis and mucormycosis for a full update of the guidelines. Final approval by the majority of the members of the group was obtained in the Fall of 2015. The actual manuscript includes updates from both ECIL-5 and ECIL-6 and is called ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients.

Invasive candidiasis

Like previous ECIL recommendations, the current guidelines for invasive candidiasis cover hematological population as well as the general population of patients. Although hematological patients are the main focus of the recommendation, this distinction is kept because available data from original randomized controlled trials mainly include non-neutropenic patients. Chronic infections are not considered. Twenty-two major publications have been identified (Tables 2 and 3).[5-26] Fifteen reported primary results from clinical trials.[5-11, 13-17, 19, 20] One publication analyzed results of a subgroup of cancer patients from a previously published trial.[12] One publication reported the analysis of pooled data from two trials previously published with a focus on patients with an underlying malignancy. [21] All these studies have been published before ECIL-4. Since then, five studies were identified, including one patient-level quantitative review of 7 published trials on invasive candidiasis, one pooled patient-level data analysis from 5 prospective trials on anidulafungin, one systematic review of 17 randomized clinical trials focusing on invasive candidiasis in neutropenic patients, one prospective non-comparative trial evaluating a strategy of early oral switch from anidulafungin for

invasive candidiasis and one observational study comparing the initial use of echinocandin-based vs. azole-based regimen for *C. parapsilosis* candidemia.[22-26] These publications were the reasons for the change in guidelines. Characteristics of these studies and main results are shown in Table 2 and 3.

The number of neutropenic patients included in each of these studies was low and limited the level of evidence of the recommendation for this group of patients. The review published by Andes and al. showed that in the univariate analysis, neutropenia was one of the factors significantly and negatively associated both with clinical outcome and with survival.[22] In the multivariate analysis, however, the effect of neutropenia disappeared, but there was a significant association of immunosuppressive therapy (including steroids) with lower survival. Other factors significantly associated with lower survival were the APACHE score, infection by *C. tropicalis* and age, while treatment with an echinocandin (OR 0.65, 95% CI 0.45-0.94, p=0.02) and catheter removal were both significantly associated with better survival (OR 0.50, 95% CI 0.35-0.72, p=0.0001).

Based on the patient-level quantitative analysis by Andes et al., echinocandins must be considered as first-line choice for invasive *Candida* infections before species identification (table 4).[22] The strength of recommendation is the same (A) for anidulafungin, caspofungin and micafungin and is also the same for overall and hematological population. However, the quality of evidence is lower for hematological patients (II) compared to the overall population, as the number of neutropenic patients recruited in the clinical trials was low. A recent communication on a patient-level pooled analysis of one randomized clinical trial and four open label studies focusing on anidulafungin in 46 neutropenic patients with candidemia showed comparable response and survival rates to those observed with caspofungin and micafungin in other studies.[25] Therefore, the grading is now similar (A II) for all three echinocandins for the treatment of invasive candidiasis in hematological patients.

Liposomal amphotericin B has also been graded A I for overall population and A II for hematological patients due to similar efficacy in comparison to micafungin.[15, 21] However, its safety profile is less favorable and therefore liposomal amphotericin B should be considered as an alternative in case of contraindication to echinocandins. Fluconazole and voriconazole are potential alternative for first line treatment in overall population provided there is no previous exposure to azoles and the infection is not severe (fluconazole).

After species identification, susceptibility testing should guide the treatment. In general, echinocandins remain the drug of choice except for *C. parapsilosis* where fluconazole is more appropriate (table 5). However, a recent observational study reported no difference in 30-day mortality and persistent candidemia at 72h of an echinocandin-based regimen compared to an azole-based therapy for patients with *C. parapsilosis* candidemia.[26] Therefore, the continuing use of echinocandins might be

considered in patients with a clinical and microbiological response. When *Candida* species is azole-susceptible, step-down to fluconazole can be considered in stable patients after 5 days of iv therapy.[24] In patients with *Candida krusei* infection, switch to oral voriconazole is an option.

Although the role of catheter removal in the management of candidemia has long been controversial, most recent studies suggest a beneficial effect on outcome.[6-8, 10, 11, 15, 16, 20, 26-33] Garnacho-Montero et al. showed in a large number of candidemia that early adequate therapy and removal of central venous line were independently associated with lower mortality.[34] The patient-level quantitative analysis by Andes et al. also demonstrated in a multivariate analysis that removal of catheter was associated with a decreased mortality [OR 0.50; 95% CI 0.35-0.72; p=0.0001].[22] The recommendation is therefore to remove rapidly the catheter in overall population (grade A II) as well as in hematological patients (grade B II) irrespective of the *Candida* species. If central venous catheter cannot be removed, treatment should include an echinocandin or a lipid formulation of amphotericin B due to their better activity on *Candida* biofilms.[35-37]

Invasive *Aspergillus* infections

Nine prospective trials (only 4 being randomized comparative trials) have been published before ECIL-4 and were the basis of the previous guidelines for first-line therapy in invasive aspergillosis (Table 6).[38-46] An additional paper reported a post-hoc analysis of the trial comparing standard dose of liposomal amphotericin B to high-dose of liposomal amphotericin B.[47] This post-hoc analysis comparing outcome in possible versus mycologically documented aspergillosis underscored the limited number of mycologically documented infections but did not lead to any change in the grading for liposomal amphotericin B. A second post-hoc analysis was performed on the voriconazole versus amphotericin B deoxycholate trial.[48] Integration of the results of baseline galactomannan detection tests performed after primary analysis and re-categorization according to the 2008 EORTC/MSG definition criteria allowed to identify more mycologically documented cases of invasive aspergillosis.[49] Conclusions of this post-hoc analysis were similar to those of the primary analysis and therefore its results did not affect the grading for voriconazole and for amphotericin B deoxycholate.

At the time of ECIL-5, results from the comparative study of voriconazole plus anidulafungin versus voriconazole plus placebo were only available in an abstract form. The results have been discussed with a provisional grading that could be transformed in a definite grading as no additional data available in the full paper suggested a need for change in provisional recommendations.[50] This study failed to reach the primary endpoint of decreased all-cause mortality at week 6 (difference of -8.2% in favor of combination, p value = 0.087). However, in a subgroup of patients with an invasive aspergillosis documented by positive galactomannan in either serum or bronchoalveolar lavage, 6-week all-cause mortality was lower in patients receiving combination therapy (difference of -11.6% in favor of combination, p value = 0.037). A large majority of the ECIL members felt that this subgroup

analysis, not planned at the origin, was not sufficient to give a stronger recommendation although this subgroup included 80% of the modified intent-to-treat population. Therefore the combination of voriconazole plus anidulafungin was graded C I for primary therapy of invasive aspergillosis while all other combinations were grade C III in the absence of well-designed studies for first line therapy.

Table 6 summarizes the main characteristics and results of the various studies. Importantly, very few studies had a large number of patients with a mycological documentation.[40, 41, 50] As shown by the two post-hoc analyses, survival was substantially lower in mycologically documented infections compared to possible cases.[47, 48] Therefore studies with a limited number of documented cases cannot lead to the strongest recommendations. As no study specifically addressed management of breakthrough aspergillosis after failure of posaconazole or voriconazole prophylaxis, no recommendation could be provided on this issue.

The clinical trial comparing the new triazole isavuconazole versus voriconazole for primary therapy of invasive aspergillosis could not be discussed during ECIL-5 as results were only presented as an abstract form in 2014. However, the group could review these abstracts data during the ECIL-6 meeting. Isavuconazole appears as effective as voriconazole for the treatment of invasive aspergillosis and has a better safety profile. Therefore, a grade A I similar to the grading for voriconazole has been given to isavuconazole. As the full paper has been published shortly after the meeting and confirms the results, the provisional grading attributed during the meeting has been transformed into a definite grading in this manuscript.[51]

Currently, amphotericin B deoxycholate is considered to have no role in the treatment of invasive aspergillosis when more effective and less toxic agents are available. Its limited efficacy and its poor safety profile led to a recommendation against its use. No substantial change has been made for second line therapy in the absence of new data (table 8).

Mucormycosis

Diagnostic and therapeutic strategies have been discussed during the ECIL-5 and ECIL-6. *Rhizopus*, *Mucor*, *Lichtheimia* (previously classified as *Absidia*), *Cunninghamella*, *Rhizomucor*, *Apophysomyces*, and *Saksenaea* are the genera most frequently involved in human disease.[52] *Cunninghamella* species is more virulent in experimental models and may be associated with a higher mortality rate in patients.[53]

So far, there is not enough evidence that identification of mucormycosis to the genus and/or species level helps guiding antifungal treatment.[54, 55] Species identification remains nevertheless important for outbreak investigations.[56] However, the differentiation between mucormycosis and other invasive mold infection is of critical importance as it has major therapeutic implications.

While epidemiological aspects and some clinical (sinus disease, concomitant diabetes, occurrence under voriconazole therapy) and radiological factors (reverse halo sign on chest CT-scan) may help to suspect mucormycosis, the diagnosis remains difficult and biopsy of the lesion is often required. Identification of the pathogen most often comes from microscopy, culture and/or histopathology examination of relevant samples. New diagnostic approaches include molecular testing on serum and various other clinical samples including formalin fixed tissues, MALDI-TOF and Mucorales-specific T-cell detection.[57-64] Although these new approaches are very promising for an earlier diagnosis, no grading for their use can be given so far due to the lack of data.

Amphotericin B, posaconazole and isavuconazole are the most potent agents in vitro.[65-67] Currently, no validated minimum inhibitory concentrations breakpoints for any of the drugs are available and thus determination of susceptibility categories is not possible for the agents of mucormycosis. ECIL-3 recommendations for the treatment of mucormycosis were mostly based on retrospective studies, registry data and small prospective non-controlled studies.[3, 68-77] Few new data are available for the treatment of mucormycosis since ECIL 4 and therefore, the current recommendations are very similar.

A prospective non-comparative trial assessed the efficacy and safety of first-line therapy with high-dose liposomal amphotericin B given at 10 mg/kg/day combined with surgery when appropriate.[78] This trial demonstrated efficacy of high-dose liposomal amphotericin B plus surgery in mucormycosis with a survival rate of 62% at week 12. The only factor associated with mortality was the presence of hematological malignancy or cancer [HR: 3.15; 95% CI: 1.12 – 8.91; 0.02]. Renal impairment of any degree was observed in 40% of the patients but was transient in most of them. These results confirm the beneficial role of liposomal amphotericin B but do not yet allow recommending the administration of such a high dose of 10 mg/kg/day.

A short paper presented data from a retrospective analysis of a combination of posaconazole and a lipid formulation of amphotericin B.[79] Thirty-two patients received this combination of posaconazole with liposomal amphotericin B (27 patients) or amphotericin B lipid complex (5 patients). Only three

of them were treated with this combination in first line. Overall response rate was 56% but a large proportion of patients (59%) died before day 90. The low number of patients, the retrospective nature of the study and the high mortality rate at day 90 only allowed for a B III recommendation for this combination for salvage therapy of mucormycosis.

Discussion and conclusions

Update of the ECIL antifungal treatment recommendations were needed as there were important new data and also because of necessary changes in the ECIL grading system to be in harmony with other ECIL recommendations. Most important data for invasive candidiasis come from a large review at a patient level of seven major trials.[22] The multivariate analysis allows now a very strong recommendation in favor of an echinocandin for the first line therapy of a candidemia irrespective of the underlying predisposing factors. The controversy on the beneficial role of catheter removal can now be considered as resolved. Most interesting new data were the publication of a first line combination study in invasive aspergillosis and the results of a randomized comparative trial comparing isavuconazole to voriconazole. *Aspergillus* guidelines now include the results of these two clinical trials and should help clinicians in their treatment decision making. Since few new data were published since the last ECIL guidelines, no major changes were brought to mucormycosis management. Of note, posology and indication of antifungal agents reported in the current guidelines do not necessarily reflect those licensed by the Europe Medicines Agency (EMA) but are the result of a consensus-based analysis of available literature within the ECIL group.

Controversy has been raised about some discrepancies between ECIL-5 and the ESCMID recommendations for invasive aspergillosis in hematological patients. These differences have been identified during a joint meeting and an ESCMID representative was invited to discuss them at ECIL-6 meeting. Most differences were minor and mostly reflected a difference in grading system The ECIL *Aspergillus* recommendations are restricted to hematological patients that represent more than 90% of the patients included in the major clinical trials.[41, 43, 50, 51] No subgroup of hematological patients deserving specific recommendation for *Aspergillus* infection treatment has been identified by ECIL group. In contrast, the ESCMID group had a broader approach considering all other conditions predisposing to invasive aspergillosis, and grading the diagnostic procedures and the prevention including environmental measures and providing also a grade for specific infection sites. In addition, the ESCMID group also segregated the hematological patients in subgroups and provided specific grading for each of them, with usually weaker recommendations when there was not a sufficient

number of patients with these specific underlying conditions included in the clinical studies. Finally and importantly, some data were not available at the time of ECIL-5 meeting but were in the public domain when the ESCMID group met. In September 2015, the ECIL-6 group was able to incorporate the new data and this has helped to reduce the apparent differences with the ESCMID guidelines. Therefore, neither the ECIL group nor the ESCMID group felt any other change than this update should be required.

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Table 1: Evolution over time of the grading system used for treatment of invasive *Candida* and *Aspergillus* infections

Strength of recommendations		
Grade	**ECIL-1 to 4**	**ECIL-5 and 6**
A	Strong evidence for efficacy and substantial clinical benefit: Strongly recommended	Good evidence to support a recommendation for use
B	Strong or moderate evidence for efficacy, but only limited clinical benefit: Generally recommended	Moderate evidence to support a recommendation for use
C	Insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (e.g. drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches: Optional	Poor evidence to support a recommendation for use
D	Moderate evidence against efficacy or for adverse outcome: Generally not recommended	Omitted
E	Strong evidence against efficacy or of adverse outcome: Never recommended	Omitted
Quality of evidence		
Grade	**ECIL-1 to 6 (no change)**	
I	Evidence from $\geq$ 1 properly randomized, controlled trial	
II	Evidence from $\geq$ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytical studies (preferably from > 1 center); from multiple time-series; or from dramatic results from uncontrolled experiments	
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	

Table 2: Trials for first line therapy of invasive candidiasis: critical inclusion and exclusion criteria, treatment and relevant characteristics of the patients

1st author, Year, Reference	Type of study and critical inclusion and exclusion criteria	Treatment (daily dose)	N° of pts[a]	N° of pts[a] with		
				cancer	IS therapy	neutropenia
Rex, 1994[5]	RCT; candidemia; pts with neutropenia or hematological cancer excluded	Fluconazole (400 mg)	103	33	22	0
		d-AmB (0.5-0.6 mg/kg)	103	32	24	0
Nguyen, 1995[6]	Prospective observational; candidemia; any *Candida* species	d-AmB (mostly 0.5-0.7 mg/kg)	227	107	NA	NA
		Fluconazole (50-800 mg)	67	32	NA	NA
Anaissie, 1996[7]	RCT; candidemia and other acute invasive candidiasis including urinary tract infections; any C*andida* species	Fluconazole (400 mg)	75	43	NA	16[c]
		d-AmB (25-50 mg; 0.67 mg/kg for neutropenic pts)	67	42	NA	20[c]
Anaissie, 1996[8]	Matched cohort study; candidemia; any *Candida* species; only cancer pts	Fluconazole (200-600 mg)	45	45	NA	11[b]
		d-AmB (0.3-1.2 mg/kg)	45	45	NA	11[b]
Phillips, 1997[9]	RCT; candidemia; *C. krusei* and *C. glabrata* infections excluded	Fluconazole (800 on day1 then 400 mg)	50	10	16	0
		d-AmB (0.6 mg/kg)	53	12	22	0
Mora-Duarte, 2002[10]	RCT; candidemia or deep-seated infections; any *Candida* species; neutropenic pts excluded	Caspofungin (70 on day 1 than 50 mg	109	30	28	14
		d-AmB (0.6-1.0 mg/kg)	115	38	18	10
Rex, 2003[11]	RCT; candidemia; *C. krusei* infections excluded; neutropenic pts excluded	Fluconazole (800 mg)	107	20	29	0
		Fluconazole (800 mg) + d-AmB (0.6-0.7 mg/kg)	112	21	26	0
DiNubile, 2005[12]	Invasive candidiasis in cancer pts; subgroup analysis of #6; numbers of pts not consistent with primary manuscript	Caspofungin (70 on day 1 than 50 mg)	41	41	NA	14
		d-AmB (0.6-1.0 mg/kg)	33	33	NA	10
Kullberg, 2005[13]	RCT; candidemia; any *Candida* species; neutropenic pts excluded	Voriconazole (12 on day 1 then 6 mg/kg)	248	NA	NA	0
		d-AmB (0.7-1.0 mg/kg) then fluconazole (400 mg)	122	NA	NA	0
Ostrosky-Zeichner, 2005[14]	Prospective, non-comparative; monotherapy for de novo candidemia (n=72); monotherapy (n=25) or combination (n=29) for salvage therapy	Micafungin (<50->200 mg)	72	NA	NA	10

		Micafungin (>50->200 mg)	25	NA	NA	10
		Micafungin (>50->200 mg) + other agent	29	NA	NA	9
Kuse, 2007[15]	RCT; candidemia or deep-seated infections; any *Candida* species	Micafungin (100 mg)	264	85	111	34
		L-AmB (3 mg/kg)	267	90	111	28
Pappas, 2007[16]	RCT; candidemia or deep-seated infections; any *Candida* species	Micafungin (100 mg)	191	68	NA	22
		Micafungin (150 mg)	199	56	NA	17
		Caspofungin (70 on day 1 then 50 mg)	188	52	NA	11
Reboli, 2007[17] and Reboli, 2011[18]	RCT; candidemia or deep-seated infections; *C. krusei i*nfections excluded; second publication on factors associated with improved outcome in *C. albicans* infections	Anidulafungin (200 on day 1 then 100 mg)	127	28	18	3
		Fluconazole (800 on day 1 then 400 mg)	118	27	27	4
Queiroz-Telles, 2008[19]	RCT; candidemia or deep-seated infections; any *Candida* species; only pediatric pts	Micafungin (2 mg/kg limited to 100 mg)	48	NA	NA	6
		L-AmB (3 mg/kg)	50	NA	NA	13
Betts, 2009[20]	RCT; candidemia or deep-seated infections; safety as primary objective; any *Candida* species	Caspofungin (70 on day 1 then 50 mg)	104	27	29	7
		Caspofungin (150 mg)	100	33	29	8
Cornely 2011 [21]	Analysis of pooled data from #12 and 13 restricted to cancer pts	Micafungin (100 mg), micafungin (150 mg), caspofungin (70 on day 1 then 50 mg), L-AmB (3 mg/kg)	1067	359	NA	114
Andes, 2012[22]	A pt level quantitative review of #1, 6, 7, 8, 11, 12, 13; candidemia and deep-seated infections; any *Candida* species	Fluconazole, d-AmB, L-AmB, d-AmB + fluconazole, d-AmB then fluconazole, voriconazole, caspofungin anidulafungin, micafungin	1915	410	440	139
Kanji, 2013[23]	Systematic review of 17 RCT; focus on candidemia and deep-seated infections in neutropenic pts	d-AmB, d-AmB + flucytosine, L-AmB, ABLC, ketoconazole, fluconazole, voriconazole, caspofungin, micafungin, anidulafungin	5675	NA	NA	342
Vasquez, 2014[24]	Prospective, non-comparative, evaluating iv to oral step-down strategy; candidemia or deep-seated infections; any *Candida* species	Anidulafungin (200 on day 1 then 100 mg), possible switch to oral fluconazole (400 mg) or voriconazole (200 mg bid) after day 5	250	NA	NA	9
Herbrecht, 2014[25]	Pooled analysis of a RCT and 4 non-comparative open label studies; candidemia; focus on neutropenic pts treated with anidulafungin	Anidulafungin (200 on day 1 then 100 mg)	46	NA	NA	46
Fernandez-Ruis 2015[26]	Prospective non-interventional population-based study; *C. parapsilosis* candidemia.	Azole-based (42%), echinocandin-based (24.7%), amphotericin B-based (19%), combination therapy (14.4%). Dose not specified.	194[d]	61[d]	72[d]	7[d]

[a] Numbers of patients refer to the modified intent to treat population when available or to the intent to treat population; for this reason and due to some inconsistencies numbers may be different in primary manuscript and in pooled analysis. [b] Neutropenia defined by less than 1000/µL; [c] neutropenia defined by less than 500/µL; [d] number of episodes

Abbreviations: ABLC: amphotericin B lipid complex; d-AmB: deoxycholate amphotericin B; IS: immunosuppressive (including steroids); L-AmB: liposomal amphotericin B; pt(s): patient(s); RCT: randomized controlled trial

Table 3: Trials for first line therapy of invasive candidiasis: outcomes

1st author, Year, Reference	Treatment	Response rate at end of therapy	Other efficacy outcomes	Safety profile
Rex, 1994[5]	Fluconazole d-AmB	No difference in response rates	No difference in survival	Fluconazole better tolerated
Nguyen, 1995[6]	Fluconazole d-AmB	Fluconazole as efficacious as d-AmB	No difference in survival	Fluconazole better tolerated
Anaissie, 1996[7]	Fluconazole d-AmB	Similar for fluconazole and d-AmB	No difference in survival	Fluconazole better tolerated
Anaissie, 1996[8]	Fluconazole d-AmB	Similar for fluconazole and d-AmB	No difference in time to defervescence, relapse and survival rates	Fluconazole better tolerated
Phillips, 1997[9]	Fluconazole d-AmB	Similar for fluconazole and d-AmB	No difference in survival rates	Fluconazole better tolerated
Mora-Duarte, 2002[10]	Caspofungin d-AmB	Caspofungin not inferior to d-AmB	Similar survival and relapse rate	Less clinical and laboratory drug-related adverse events with caspofungin
Rex, 2003[11]	Fluconazole Fluconazole + d-AmB	Improved success rate for the combination therapy	Similar time to failure and survival; higher rate of blood culture clearance with combination	Fluconazole monotherapy better tolerated than combination therapy
DiNubile, 2005[12]	Voriconazole d-AmB then fluconazole	Voriconazole not inferior to d-AmB/fluconazole	Similar survival and time to clear blood cultures	Less all-cause adverse events in patients receiving voriconazole
Kullberg, 2005[13]	Caspofungin d-AmB	Similar for caspofungin and d-AmB	Response rate lower in neutropenic than in non-neutropenic cancer pts	Caspofungin better tolerated than d-AmB
Ostrosky-Zeichner, 2005[14]	Micafungin Micafungin + other agent	High success rate for first line and salvage therapy	High success rate in neutropenic pts	No unexpected adverse event

Kuse, 2007[15]	Anidulafungin Fluconazole	Higher response rate for anidulafungin	Similar 6-week survival; higher microbiological response rate for anidulafungin; same conclusion for subgroup of *C. albicans* infections	More drug-related elevation in liver enzymes in patients receiving fluconazole
Pappas, 2007[16]	Micafungin L-AmB	Micafungin not inferior to L-AmB	Similar survival and time to clear blood cultures	Less clinical and biological drug-related adverse events in pts receiving micafungin
Reboli, 2007[17] and Reboli, 2011[18]	Micafungin (100 mg) Micafungin (150 mg) Caspofungin	Similar for the three arms	No significant difference in survival; similar response rates in neutropenic pts	Same safety profile for both doses of micafungine and caspofungin
Queiroz-Telles, 2008[19]	Micafungin L-AmB	Similar for both treatments	Similar survival; efficacy independent of the age	More adverse-events leading to treatment discontinuation in L-AmB arm
Betts, 2009[20]	Caspofungin (50 mg) Caspofungin (150 mg)	Similar for both doses of caspofungin	Similar survival and time to clear blood cultures	Safety not inferior for high-dose caspofungin
Cornely 2011[21]	Micafungin (100 mg), micafungin (150 mg), caspofungin, L-AmB	Similar response rate across the two trials and all treatment arms for pts with or without malignancy	Similar survival for all treatments groups for pts with or without malignancy	NA
Andes, 2012[22]	Fluconazole, d-AmB, L-AmB, d-AmB + fluconazole, d-AmB then fluconazole, voriconazole, caspofungin anidulafungin, micafungin	Higher response rate when use of echinocandin or central catheter removed; Lower response rate when greater Apache II score	Higher mortality when older age, greater Apache II score, immunosuppressive therapy, or *C. tropicalis* infection; Lower mortality when use of echinocandin or central venous catheter removed	NA
Kanji, 2013[23]	d-AmB, d-AmB + flucytosine, L-AmB, ABLC, ketoconazole, fluconazole, voriconazole, caspofungin, micafungin, anidulafungin	Trends favoring non-polyene compounds	NA	NA
Vasquez, 2014[24]	Anidulafungin, then fluconazole or voriconazole	Similar success rate for early switch (<7d) and MITT population across all *Candida* species	No difference in survival	Nausea and vomiting as the most frequent drug-related adverse events
Herbrecht, 2014[25]	Anidulafungin	Overall fifty-two percent success rate, lower when persistent neutropenia	Twenty-four percent all-cause mortality at day 28	NA
Fernandez-Ruis 2015[26]	Echinocandin-based Azole-based	NA	No difference in clinical failure (all-cause mortality between day 3 and 30 and persistent candidemia > 72h after start of antifungal therapy)	NA

Abbreviations: d-AmB: deoxycholate amphotericin B; L-AmB: liposomal amphotericin B; pts: patients

Table 4: ECIL-6 recommendations for initial first-line treatment of candidemia

	Overall population	**Hematological patients**
Antifungal therapy		
- Micafungin [a]	A I	A II
- Anidulafungin	A I	A II [b]
- Caspofungin	A I	A II
- Liposomal amphotericin B	A I	A II
- Amphotericin B lipid complex	B II	B II
- Amphotericin B colloidal dispersion	B II	B II
- Amphotericin B deoxycholate [c]	C I	C II
- Fluconazole [d,e]	A I	C III
- Voriconazole [d]	A I	B II
Catheter removal[f]	A II	B II

[a] See warning box in European label; [b] Provisional grading; [c] Close monitoring for adverse event is required ; [d] Not in severely ill unstable patients; [e] Not in patients with previous azole exposure; [f] if the catheter cannot be removed, use of an echinocandin or a lipid formulation of amphotericin B is recommended.

Table 5: ECIL-6 recommendations for first-line treatment of candidemia after species identification

***Candida* species**	**Overall population**		**Hematological patients**	
C. albicans	Echinocandins [a]	A I	Echinocandins	A II
	Fluconazole [b]	A I	Fluconazole	C III
	Liposomal amphotericin B	A I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	A II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	A II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. glabrata	Echinocandins [a]	A I	Echinocandins	A II
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. krusei	Echinocandins [a]	A II	Echinocandins [a]	A III
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
Oral stepdown	Voriconazole	B I	Voriconazole	C III
C. parapsilosis	Fluconazole	A II	Fluconazole	A III
	Echinocandins [c]	B II	Echinocandins	B III

[a] same grading for anidulafungin, caspofungin, micafungin ; [b] not in severely ill patients; [c] if echinocandin-based regimen introduced before species identification and patient responding clinically and microbiologically (sterile blood cultures at 72h), continuing use of echinocandin might be considered

Table 6: Trials for first line therapy of invasive aspergillosis: main characteristics and outcome

1st author, Year, Reference	Type of study	Patients population	Antifungal agent (daily dose)	N° of pts[a]	Mycological documentation[b]	Favorable[c] response rate	12-week survival
Ellis, 1998[38]	RCT	Hematological malignancy, HSCT	L-AmB (1 mg/kg)	41	8 (20%)	58%	58%[d]
			L-AmB (4 mg/kg)	46	12 (26%)	54%	51%[d]
Caillot, 2001[39]	Prospective, non-comparative	Hematological malignancy, HSCT, other IS condition	Itraconazole (iv, 2x200 for 2 days then 200 for 12 days then oral 2x200 mg)	31	14 (45%)	48%	87%
Bowden, 2002[40]	RCT, double blind	Hematological malignancy, HSCT, other IS condition, COPD	d-AmB (1-1.5 mg/kg)	86	81 (94%)	35%[d]	45%[d]
			ABCD (6 mg/kg)	88	75 (85%)	35%[d]	50%[d]
Herbrecht, 2002[41]	RCT	Hematological malignancy, HSCT, other IS conditions	d-AmB (1-1.5 mg/kg)	133	84 (63%)	32%	58%
			Voriconazole (iv, 2x6 mg/kg on day 1 then 2x4 mg/kg then oral 2x200 mg)	144	98 (68%)	53%	71%
Candoni, 2005[42]	Prospective, non-comparative	Hematological malignancy, HSCT	Caspofungin	32	NA	56%	53%[e]
Cornely, 2007[43]	RCT, double blind	Hematological malignancy, HSCT, other IS condition	L-AmB (3 mg/kg)	107[f]	41 (40%)[g]	50%	72%
			L-AmB (10 mg/kg for 14 days then 3 mg/kg)	94[f]	36 (39%)[g]	46%	59%
Viscoli, 2009[44]	Prospective, non-comparative	Hematological malignancy	Caspofungin (70 on day1 then 50 mg)	61	61 (100%)	33%	53%
Herbrecht, 2010[45]	Prospective, non-comparative	Allogeneic HSCT	Caspofungin	24	24 (100%)	42%	50%
Cornely, 2011[46]	Prospective dose-escalation study	Hematological malignancy, HSCT, other IS condition	Caspofungin (70-200 mg)	46	26 (57%)	57%	72%
Herbrecht, 2015[48]	Post-hoc analysis of study published in 2002	Hematological malignancy, HSCT, other IS conditions	d-AmB (1-1.5 mg/kg)	164	113 (69%)	19%	55%
			Voriconazole (iv, 2x6 mg/kg on day 1 then 2x4 mg/kg then oral 2x200 mg)	179	124 (69%)	51%	70%
Marr, 2012[50]	RCT, double blind	Hematological malignancy, HSCT	Voriconazole (iv, 2x6 mg/kg on day 1 then 2x4 mg/kg then oral 2x300 mg)	142	142 (100%)	43%	61%
			Voriconazole (iv, 2x6 mg/kg on day 1 then 2x4 mg/kg then oral 2x300 mg) + Anidulafungin (200 on day1 then 100 mg)	135	135 (100%)	33%	71%
Maertens, 2015[51]	RCT, double blind	Hematological malignancy, HSCT, other IS condition	Isavuconazole (2x200 on day 1 and 2 then 200 mg)	143[h]	143	62%	70%
			Voriconazole (iv, 2x6 mg/kg on day 1 then 2x4 mg/kg then oral 2x200 mg)	129[h]	129	60%	66%

[a] Numbers of patients refer to the modified intent to treat population when available or to the intent to treat population; [b] Includes positive microscopy or culture from relevant sites, positive histopathology, or positive galactomannan in serum, BAL or CSF as defined by EORTC/MSG 2008 criteria [49]; [c] Favorable response rate includes only complete and partial responses; [d] Two-month survival rates; [d] Intent to treat population; [e] time point not specified (median follow-up 10 months); [f] includes also other mold infections (4 and 2 in 3 mg/kg and 10 mg/kg arm respectively); [g] after exclusion of the 6 other mold infections. [h] includes also a few non-*Aspergillus* invasive mold diseases (5 in isavuconazole arm and 6 in voriconazole arm) and non-identified invasive mold disease (14 in isavuconazole arm and 15 in voriconazole arm).

Abbreviations: ABCD: amphotericin B colloidal dispersion; ABLC: amphotericin B lipid complex; COPD: chronic obstructive pulmonary disease; d-AmB: deoxycholate amphotericin B; HSCT: hematopoietic stem cell transplant; IS: immunosuppressive (including steroids therapy); L-AmB: liposomal amphotericin B; pt(s): patient(s); RCT: randomized controlled trial

Table 7: ECIL-6 recommendations for first-line treatment of invasive aspergillosis

	Grade	Comments
Voriconazole[a]	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (Initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole[a] + anidulafungin	C I	
Other combinations	C III	
Recommendation against use		
Amphotericin B deoxycholate	A I	Less effective and more toxic

[a]Monitoring of serum levels is indicated. In the absence of sufficient data for first line monotherapy, anidulafungin, micafungin and posaconazole have not been graded.

Table 8: ECIL-6 recommendations for salvage therapy of invasive aspergillosis

	Grade	Comments
Liposomal amphotericin B	B II	No data in voriconazole failure
Amphotericin B lipid complex	B II	No data in voriconazole failure
Caspofungin	B II	No data in voriconazole failure
Itraconazole	C III	Insufficient data
Posaconazole[a]	B II	No data in voriconazole failure
Voriconazole[a]	B II	If not used in 1st line
Combination	B II	Various studies and conflicting results

[a]Monitoring of serum levels is indicated, especially if posaconazole oral suspension is used.

Table 9: ECIL-6 recommendations for first line therapy of mucormycosis

	Grade	Comments
Management includes antifungal therapy, surgery and control of underlying conditions	A II	Multidisciplinary approach is required
Antifungal therapy		
- Amphotericin B deoxycholate	C II	
- Liposomal amphotericin B	B II	Daily dose: 5 mg/kg. Liposomal amphotericin B should be preferred in CNS infection and/or renal failure
- Amphotericin B lipid complex	B II	
- Amphotericin B colloidal dispersion	C II	
- Posaconazole	C III	No data to support its use as first line treatment. Alternative when amphotericin B formulations are absolutely contraindicated.
- Combination therapy	C III	
Control of underlying condition	A II	Includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy
Surgery		
- Rhino-orbito-cerebral infection	A II	
- Soft tissue infection	A II	
- Localized pulmonary lesion	B III	

- Disseminated infection	C III	Surgery should be considered on a case by case basis, using a multi-disciplinary approach
Hyperbaric oxygen	C III	
Recommendation against use		
Combination with deferasirox	A II	

Table 10: ECIL-6 recommendations for salvage and maintenance therapy of mucormycosis

	Grade	Comments
Salvage therapy		
- Management includes antifungal therapy, control of underlying disease and surgery	A II	
- Posaconazole	B II	
- Combination of lipid amphotericin B and caspofungin	B III	
- Combination of lipid amphotericin B and posaconazole	B III	
Maintenance therapy		
- Posaconazole	B III	Overlap of a few days with first line therapy to obtain appropriate serum levels. Monitoring of serum levels might be indicated[a]

[a] Both comments apply to the oral solution but may not apply to the solid oral formulation