**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 hematologic 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 made to mucormycosis recommendations.

**Introduction**

The European Conference on Infections in Leukemia (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 hematologic patients were published in 2007 after the first conference (ECIL-1) and have then been updated at ECIL-2 and ECIL-3. First recommendations for the diagnosis and treatment of mucormycosis have been published after ECIL-3. First updates for antifungal therapy were only available as slides on the websites of these participating societies without publication of a manuscript in consideration of the 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 hematologic patients. The update was also necessary to change the prior 5-level grading (A to E) used during the ECILs 1 to 4 for the strength of recommendations for Candida and Aspergillus infections into the 3-level grading (A to C) already used during ECIL-3 for the first recommendation for mucormycosis (Table 1). The grading for quality of evidence has not been modified.

**Methods**

The ECIL-5 meeting was held in September 2013 and involved 57 experts from 21 countries, including 3 non-European countries. Slides of the conclusions of the ECIL-5 were made available on the websites of the EORTC, EBMT, ELN, and ICHS. The ECIL-6 meeting was held in September 2015 with the presence of 55 experts from 24 countries, including 4 non-European countries (see list of collaborators at the end of this Review).

At both the ECIL-5 and the 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 into 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 into 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 the ECIL-5 meeting and then incorporated the suggestions coming from the assembly. In cases in which full consensus was not obtained, the decision was put to the vote, and the final decision was based on a 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 on the basis of the strength of recommendations (5-level scale: A, B, or C) and quality of evidence (3-level scale: I, II, or III), as detailed in Table 1.

The manuscript of the ECIL-5 was put on hold after a debate arose 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 the ECMM 2014). 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 the ECIL-6 by members of the ECIL group and of the ESCMID/ECMM group. This resulted in a delay in publication of the ECIL-5 recommendations and during the ECIL-6 plenary session, the ECIL assembly approved 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 Autumn 2015. The current manuscript includes updates from both the ECIL-5 and the 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 the hematologic population as well as the general population of patients. Although hematologic patients are the main focus of the recommendation, this distinction is maintained because available data from the original randomized controlled trials mainly include non-neutropenic patients. Chronic infections are not considered. Twenty-two major publications were identified (Tables 2 and 3). Fifteen reported primary results from clinical trials. One publication analyzed results of a subgroup of cancer patients from a previously published trial. One publication reported the analysis of pooled data from 2 trials previously published with a focus on patients with an underlying malignancy. All these studies were published before the ECIL-4. Since then, 5 studies have been 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 versus azole-based regimen for *C. parapsilosis* candidemia. These publications were the reasons for the change in guidelines. Characteristics of these studies and main results are shown in Tables 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 et al. showed that, in the univariate analysis, neutropenia was one of the factors significantly and negatively associated both with clinical outcome and with survival. 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 (Odds Ratio (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). The strength of recommendation is the same (A) for anidulafungin, caspofungin and micafungin and is also the same for the overall and the hematologic population. However, the quality of evidence is lower for hematologic 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 4 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. Therefore, the grading is now similar (A II) for all three echinocandins.
for the treatment of invasive candidiasis in hematologic patients.

Liposomal amphotericin B has also been graded A I for the overall population and A II for hematologic patients due to similar efficacy in comparison to micafungin. 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 alternatives for first-line treatment in the 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 72 hours of an echinocandin-based regimen compared to anazole-based therapy for patients with C. parapsilosis candidemia. 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 five days of intravenous (iv) therapy. 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. 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. 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). The recommendation is, therefore, to rapidly remove the catheter in the overall population (grade A II) as well as in hematologic 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.

Invasive Aspergillus infections

Nine prospective trials (only 4 being randomized comparative trials) had been published before the ECIL-4 and provided the basis of the previous guidelines for first-line therapy in invasive aspergillosis (Table 6). An additional paper reported a post-hoc analysis of the trial comparing standard dose of liposomal amphotericin B to high-dose liposomal amphotericin B. 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. 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 more mycologically documented cases of invasive aspergillosis to be identified. 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 the ECIL-5, results from the comparative study of voriconazole plus anidulafungin versus voricona-
### 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 | N of pts with cancer | N of pts with IS therapy | N of pts with Neutropenia |
|-----------------------------|------------------------------------------------------------|------------------------|----------|----------------------|--------------------------|--------------------------|
| Rex, 1994<sup>4</sup>       | RCT; candidemia; pts with neutropenia or hematologic cancer excluded | Fluconazole (400 mg) | 103      | 33                   | 22                       | 0                        |
|                             | d-AmB (0.5-0.6 mg/kg)                                       |                        | 103      | 32                   | 24                       | 0                        |
| Nguyen, 1995<sup>5</sup>    | Prospective observational; candidemia; any Candida species excluded | d-AmB (mostly 0.5-0.7 mg/kg) | 227      | 107                  | NA                       | NA                       |
|                             | Fluconazole (50-800 mg)                                     |                        | 67       | 32                   | NA                       | NA                       |
| Anaissie, 1996<sup>6</sup>  | RCT; candidemia and other acute invasive candidiasis including urinary tract infections; any Candida species excluded | Fluconazole (400 mg) | 75       | 43                   | NA                       | 20<sup>6</sup>            |
|                             | d-AmB (25-50 mg; 0.67 mg/kg) for neutropenic pts            |                        | 67       | 42                   | NA                       | 20<sup>6</sup>            |
| Anaissie, 1996<sup>7</sup>  | Matched cohort study; candidemia; any Candida species; only cancer pts excluded | Fluconazole (200-600 mg) | 45       | 45                   | NA                       | 11<sup>6</sup>            |
|                             | d-AmB (0.3-1.2 mg/kg)                                       |                        | 45       | 45                   | NA                       | 11<sup>6</sup>            |
| Phillips, 1997<sup>8</sup>  | RCT; candidemia; C. krusei and C. glabrata infections excluded | Fluconazole (800 on day 1 then 400 mg) | 50       | 10                   | 16                       | 0                        |
|                             | d-AmB (0.6 mg/kg)                                           |                        | 53       | 12                   | 22                       | 0                        |
| Mora-Duarte, 2002<sup>9</sup> | RCT; candidemia or deep-seated infections; any Candida species; neutropenic pts excluded | Caspofungin (70 mg on day 1 then 50 mg) | 109      | 30                   | 28                       | 14                       |
|                             | d-AmB (0.6-1.0 mg/kg)                                       |                        | 115      | 38                   | 18                       | 10                       |
| Rex, 2003<sup>10</sup>      | 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<sup>11</sup> | Invasive candidiasis in cancer pts; subgroup analysis of #6; numbers of pts not consistent with primary manuscript | Caspofungin (70 mg on day 1 then 50 mg) | 41       | 41                   | NA                       | 14                       |
|                             | d-AmB (0.6-1.0 mg/kg)                                       |                        | 33       | 33                   | NA                       | 10                       |
| Kullberg, 2005<sup>12</sup> | RCT; candidemia; any Candida species; neutropenic pts excluded | Voriconazole (12 mg on day 1 then 6 mg/kg) | 248      | 248                  | NA                       | 0                        |
|                             | d-AmB (0.7-1.0 mg/kg) then fluconazole (400 mg)             |                        | 122      | NA                   | NA                       | 0                        |
| Ostrosky-Zeichner, 2005<sup>13</sup> | 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<sup>14</sup>     | 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<sup>15</sup>   | 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<sup>16</sup>   | RCT; candidemia or deep-seated infections; C. krusei infections excluded; second publication on factors associated with improved outcome in C. albicans infections | Anidulafungin (200 mg on day 1 then 100 mg) | 127      | 28                   | 18                       | 3                        |
|                             | Fluconazole (800 mg on day 1 then 400 mg)                   |                        | 118      | 27                   | 27                       | 4                        |
| Queiroz-Telles, 2008<sup>17</sup> | 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<sup>18</sup>    | RCT; candidemia or deep-seated infections; safety as primary objective; any Candida species | Caspofungin (70 mg on day 1 then 50 mg) | 104      | 27                   | 29                       | 7                        |
|                             | Caspofungin (150 mg)                                        |                        | 100      | 33                   | 29                       | 8                        |
| Cornely 2011<sup>19</sup>   | Analysis of pooled data from #12 and 13 restricted to cancer pts | Micafungin (100 mg), micafungin (150 mg), caspofungin (70 mg on day 1 then 50 mg), L-AmB (3 mg/kg) | 1087     | 359                  | NA                       | 114                      |
| Andes, 2012<sup>20</sup>    | 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<sup>21</sup>    | Systematic review of 17 RCT; focus on candidemia and deep-seated infections in neutropenic pts | d-AmB, d-AmB + fluconosine, L-AmB, ABLC, ketoconazole, fluconazole, voriconazole, caspofungin, micafungin, anidulafungin | 5675     | NA                   | NA                       | 342                      |
Invasives aspergillosis while all other combinations were graded C. Therefore, the combination of voriconazole plus anidulafungin was graded C for primary therapy of invasive aspergillosis. 11.6% in favor of combination; that had not been originally planned, 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 graded 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.

As shown by the 2 post-hoc analyses, survival was substantially lower in mycologically-documented infections compared to possible cases. 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 made on this issue.

The clinical trial comparing the new triazole isavuconazole versus voriconazole for primary therapy of invasive aspergillosis could not be discussed during the ECIL-5 as results were only presented as an abstract in 2014. However, the group could review the data from these abstracts during the ECIL-6 meeting. Isavuconazole appears to be 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 (Table 7). As the full paper was 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.

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 were discussed during the ECIL-5 and the ECIL-6. Rhizopus, Mucor, Lichtheimia (previously classified as Absidia), Cunninghamella, Rhizomucor, Apophysomyces, and Saksenaea are the genera most frequently involved in human disease. Cunninghamella species is more virulent in experimental models and may be associated with a higher mortality rate in patients. So far, there has not been enough evidence that identification of mucormycosis to the genus and/or species level helps guide antifungal treatment.

Species identification remains, nevertheless, important for outbreak investigations. 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 (reverse halo sign on chest CT-scan) factors 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 microscopic, culture and/or histopathological 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. Although these new approaches are very promising for an earlier diagnosis, no grading for their use can be given yet due to the lack of data.

Amphotericin B, posaconazole and isavuconazole are the most potent agents in vitro. Currently, no validated minimum inhibitory concentration breakpoints for any of the drugs are available and thus determination of susceptibility categories is not possible for the agents of mucormycosis. The ECIL-3 recommendations for the treatment of mucormycosis were mostly based on retrospective studies, registry data and small prospective non-controlled studies. Few new data are available for the treatment of mucormycosis since the ECIL 4 and, therefore, the current recommendations are very similar (Table 9).
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                   | Fluconazole d-AmB | No difference in response rates | No difference in survival | Fluconazole better tolerated |
| Nguyen, 1995                | Fluconazole d-AmB | Fluconazole as efficacious as d-AmB | No difference in survival | Fluconazole better tolerated |
| Anaissie, 1996              | Fluconazole d-AmB | Similar for fluconazole and d-AmB | No difference in survival | Fluconazole better tolerated |
| Phillips, 1997              | Fluconazole d-AmB | Similar for fluconazole and d-AmB | No difference in survival rates | Fluconazole better tolerated |
| Mora-Duarte, 2002           | Caspofungin d-AmB | Caspofungin not inferior to d-AmB | Similar survival and relapse rate | Less clinical and laboratory drug-related adverse events |
| Rex, 2003                   | 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              | Voriconazole d-AmB then fluconazole | Voriconazole not inferior to d-AmB/fluconazole cultures | Similar survival and time to clear blood cultures receiving voriconazole | Less all-cause adverse events in patients receiving voriconazole |
| Kullberg, 2005              | 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     | 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                  | 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                | Micafungin L-AmB | Micafungin not inferior to L-AmB | Similar survival and time to clear blood cultures adverse events in pts receiving micafungin | Less clinical and biological drug-related adverse events in pts receiving micafungin |
| Reboli, 2007a and Reboli, 2011a | Micafungin (100 mg) Micafungin (150 mg) Caspofungin | Similar for the three arms in neutropenic pts | No significant difference in survival; similar response rates and caspofungin | Same safety profile for both doses of micafungin and caspofungin |
| Queiroz-Telles, 2008        | Micafungin L-AmB | Similar for both treatments of the age | Similar survival; efficacy independent discontinuation in L-AmB arm | More adverse events leading to treatment discontinuation in L-AmB arm |
| Betts, 2009a                | 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 |
| Cornelly, 2011a             | 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, 2012a                | 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 |
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. 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 hematologic malignancy or cancer (HR: 3.15; 95% CI: 1.12-8.91; P=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 any recommendation for 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. Thirty-two patients received this combination of posaconazole with liposomal amphotericin B given at 10 mg/kg/day combined with surgery when surgery was appropriate. This combination 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 hematologic malignancy or cancer (HR: 3.15; 95% CI: 1.12-8.91; P=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 any recommendation for the administration of such a high dose of 10 mg/kg/day.

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

| Overall population | Hematologic patients |
|--------------------|----------------------|
| Antifungal therapy |                       |
| Miconazole          | A I                  | A II |
| Anidulafungin       | A I                  | A II |
| Caspofungin         | A I                  | A II |
| Liposomal amphotericin B | B II   | B II |
| Amphotericin B lipid complex | B II   | B II |
| Amphotericin B colloidal dispersion | A II   | A II |
| Amphotericin B deoxycholate | C I    | C II |
| Liposomal amphotericin B | B II   | B II |
| Amphotericin B lipid complex | B II   | B II |
| Amphotericin B colloidal dispersion | B II   | B II |
| Amphotericin B deoxycholate | C I    | C II |
| Fluconazole         | A I                  | C III |
| Voriconazole        | A I                  | B II |
| Catheter removal    | A II                 | B II |

**Note**: See warning box in European label; provisional grading; close monitoring for adverse events is required; “not in severely ill unstable patients;” “not in patients with previous azole exposure;” 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 | Hematologic patients |
|-----------------|--------------------|----------------------|
| *C. albicans*   | Echinocandin\*     | A I                  | Echinocandin\*     | A II |
|                 | Fluconazole        | 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*   | Echinocandin\*     | A I                  | Echinocandin\*     | 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*     | Echinocandin\*     | A II                 | Echinocandin\*     | 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 I                  | Fluconazole         | A III |
|                 | Echinocandin\*     | B II                 | Echinocandin\*     | B III |

\*Same grading for anidulafungin, caspofungin, micafungin; \*not in severely ill patients; if echinocandin-based regimen introduced before species identification and patient responding clinically and microbiologically (sterile blood cultures at 72 h), continuing use of echinocandin might be considered.
tericin B (n=27) or amphotericin B lipid complex (n=5). Only 3 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 (Table 10).

**Discussion and conclusions**

An update of the ECIL antifungal treatment recommendations was needed as there were important new data, and also because of necessary changes in the ECIL grading system so as to be in harmony with other ECIL recommendations. The most important data for invasive candidiasis came from a large review of patients included in 7

| Table 6. Trials for first-line therapy of invasive aspergillosis: main characteristics and outcome. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| 1st author, year, reference | Type of study | Patient population | Antifungal agent (daily dose) | N of pts | Mycological documentation | Favorable response rate | 12-week survival |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Ellis, 1998a | RCT | Hematologic malignancy, HSCT | L-AmB (1 mg/kg) | 41 | 8 (20%) | 58% | 58% |
| Caillot, 2001a | Prospective, non-comparative | Hematologic 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, 2002a | RCT, double blind | Hematologic malignancy, HSCT, other IS condition, COPD | d-AmB (1-1.5 mg/kg) | 86 | 81 (94%) | 35% | 45% |
| Herbrecht, 2002a | RCT | Hematologic malignancy, HSCT, other IS conditions | d-AmB (1-1.5 mg/kg) Voriconazole (iv, 2x6 mg/kg on day 1 then 2x4 mg/kg then oral 2x200 mg) | 133 | 84 (63%) | 32% | 50% |
| Candoni, 2005a | Prospective, non-comparative | Hematologic malignancy, HSCT | Caspofungin | 32 | NA | 56% | 53% |
| Cornely, 2007a | RCT, double blind | Hematologic malignancy, HSCT, other IS condition | L-AmB (3 mg/kg) L-AmB (10 mg/kg for 14 days then 3 mg/kg) | 107 | 41 (40%) | 50% | 72% |
| Viscoli, 2009a | Prospective, non-comparative | Hematologic malignancy | Caspofungin (70 on day 1 then 50 mg) | 61 | 61 (100%) | 33% | 53% |
| Herbrecht, 2010a | Prospective, non-comparative | Allogeneic HSCT | Caspofungin | 24 | 24 (100%) | 42% | 50% |
| Cornely, 2011a | Prospective dose-escalation study | Hematologic malignancy, HSCT, other IS condition | Caspofungin (70-200 mg) | 46 | 26 (57%) | 57% | 72% |
| Herbrecht, 2015a | Post-hoc analysis of study published in 2002 | Hematologic malignancy, HSCT, other IS conditions | d-AmB (1-1.5 mg/kg) Voriconazole (iv, 2x6 mg/kg on day 1 then 2x4 mg/kg then oral 2x200 mg) | 164 | 113 (69%) | 19% | 55% |
| Marr, 2015a | RCT, double blind | Hematologic malignancy, HSCT | Voriconazole (iv, 2x6 mg/kg on day 1 then 2x4 mg/kg then oral 2x300 mg) Voriconazole (iv, 2x6 mg/kg on day 1 then 2x4 mg/kg then oral 2x300 mg) + Anidulafungin (200 on day 1 then 100 mg) | 142 | 142 (100%) | 43% | 61% |
| Maertens, 2015a | RCT, double blind | Hematologic malignancy, HSCT, other IS condition | Isavuconazole (2x200 on day 1 and 2 then 200 mg) Voriconazole (iv, 2x6 mg/kg on day 1 then 2x4 mg/kg then oral 2x200 mg) | 143* | 143* | 62% | 70% |

*aNumbers of patients refer to the modified intent to treat population when available or to the intent to treat population; 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; favorable response rate includes only complete and partial responses; two-month survival rates; intent to treat population; time point not specified (median follow up 10 months); includes also other mold infections (4 and 2 in 3 mg/kg and 10 mg/kg arm, respectively); after exclusion of the 6 other mold infections; 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). A BCD: amphotericin B colloidal dispersion; A BLC: 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.
The multivariate analysis now allows a very strong recommendation in favor of an echinocandin for the first-line therapy of candidemia irrespective of the underlying predisposing factors. The controversy on the beneficial role of catheter removal can now be considered to be resolved. The 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.

ECIL-6 guidelines now include the results of these 2 clinical trials and should help clinicians in their treatment decision making. Since few new data have been published since the last ECIL guidelines, no major changes were made to mucormycosis management. Importantly, the posology and indication of antifungal agents reported in the current guidelines do not necessarily reflect those licensed by the European Medicines Agency (EMA), but are the result of a consensus-based analysis of available literature within the ECIL group.

There has been controversy about some discrepancies between the ECIL-5 and the ESCMID recommendations for invasive aspergillosis in hematologic patients. These differences were identified during a joint meeting and an ESCMID representative was invited to discuss them at the ECIL-6 meeting. Most differences were minor and mostly reflected a difference in grading system. The ECIL Aspergillus recommendations are restricted to hematologic patients who represent more than 90% of the patients included in the major clinical trials.41,49,50,51 No subgroup of hematologic patients deserving specific recommendation for Aspergillus infection treatment has been identified by the ECIL group. In contrast, the ESCMID group had a broader approach considering all other conditions predisposing to invasive aspergillosis, grading the diagnostic procedures, and including environmental measures in the prevention, also providing a grade for specific infection sites. In addition, the ESCMID group also segregated the hematologic patients into 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 the 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 change other than this update was required.

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

| Management includes antifungal therapy, surgery and control of underlying conditions | Grade | Comments |
|----------------------------------------------------------------------------------|-------|----------|
| Antifungal therapy                                                               |       |          |
| Amphotericin B deoxycholate                                                       | C II  |          |
| Liposomal amphotericin B                                                          | B II  |          |
| Amphotericin B lipid complex                                                       | B II  |          |
| Amphotericin B colloidal dispersion                                               | C II  |          |
| Posaconazole                                                                     | C III |          |
| Combination therapy                                                              | C III |          |
| Control of underlying condition                                                   | A II  |          |

| Surgery                                                                          |       |          |
|----------------------------------------------------------------------------------|-------|----------|
| Rhino-orbito-cerebral infection                                                   | A II  |          |
| Soft tissue infection                                                             | A II  |          |
| Localized pulmonary lesion                                                        | B III |          |
| Disseminated infection                                                            | C III |          |
| Hyperbaric oxygen                                                                 | C III |          |

| Recommendation against use                                                         |       |          |
|----------------------------------------------------------------------------------|-------|----------|
| Combination with deferasirox                                                      | A II  |          |

| CNS: central nervous system. |

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

| 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. * |       |          |

*Both comments apply to the oral solution but may not apply to the solid oral formulation.

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