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ORIGINAL ARTICLE

European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3—2009 Update

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In 2005, several groups, including the European Group for Blood and Marrow Transplantation, the European Organization for Treatment and Research of Cancer, the European Leukemia Net and the Immunocompromised Host Society created the European Conference on Infections in Leukemia (ECIL). The main goal of ECIL is to elaborate guidelines, or recommendations, for the management of infections in leukemia and stem cell transplant patients. The first sets of ECIL slides about the management of invasive fungal disease were made available on the web in 2006 and the papers were published in 2007. The third meeting of the group (ECIL 3) was held in September 2009 and the group updated its previous recommendations. The goal of this paper is to summarize the new proposals from ECIL 3, based on the results of studies published after the ECIL 2 meeting: (1) the prophylactic recommendations for hematopoietic stem cell transplant recipients were formulated differently, by splitting the neutropenic and the GVHD phases and taking into account recent data on voriconazole; (2) micafungin was introduced as an alternative drug for empirical antifungal therapy; (3) although several studies were published on preemptive antifungal approaches in neutropenic patients, the group decided not to propose any recommendation, as the only randomized study comparing an empirical versus a preemptive approach showed a significant excess of fungal disease in the preemptive group.
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Introduction

Hematology patients and hematopoietic stem cell transplant (HSCT) recipients represent a population at high risk for invasive fungal disease (IFD). Given the high morbidity and mortality of *Candida* and *Aspergillus* infections, the availability of new antifungals and the rich scientific production on this topic, there is a need for a regular update of consensus guidelines.

In 2005, several groups, including the European Group for Blood and Marrow Transplantation, the European Organization for Treatment and Research of Cancer, the European Leukemia Net and the Immunocompromised Host Society created the European Conference on Infections in Leukemia (ECIL). These groups are all involved in the management and research programs in leukemia and HSCT and realized the need for European guidelines on the management of infections in these patients. The main goal of ECIL, since its first edition in 2005, is to elaborate guidelines—or recommendations—for the management of infections in hematology patients. From the beginning of ECIL, IFD has been chosen as one of the main topics and has been addressed in three parts: antifungal prophylaxis in high-risk hematology patients, empirical antifungal therapy and treatment of invasive *Candida* and *Aspergillus*

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infections. The first sets of slides of ECIL guidelines were made available on the websites of the four involved bodies in 2006 and the corresponding papers were published in the *European Journal of Cancer* in 2007.[1–3] The slide sets of the ECIL 1 (2005) guidelines were updated in 2007, after the ECIL 2 meeting. The ECIL 3 meeting was held in September 2009. The expert group of ECIL 3 updated the previous version of the guidelines, based on studies published from October 2007 to September 2009. The updated slide sets of ECIL 3 have been available on the websites of the four organizations involved in ECIL since December 2009.[4] This article summarizes the main changes or new items on the management of IFD in hematology patients implemented in the ECIL 3 guidelines when compared with the previous version published in 2007. It also comments on the similarities and differences between ECIL and the Infectious Diseases Society of America (IDSA) guidelines for *Candida*[5] and *Aspergillus*[6] infections, published in the meantime.

Materials and methods

The methodology of the ECIL conferences has been previously described.[7] The organization committee of the conference initially defined the topics, and the main questions to be addressed by the working groups. Each working group consisted of three to six international experts identified on the basis of knowledge and publications in the selected topics, who worked under the guidance of a designated group leader. The working groups on IFD were the same in 2005, 2007 and 2009. They reviewed the literature published since the last conference, to analyze the new data and prepare proposals for changes or additions in the previous recommendations. The groups were asked to use medical subject heading terms (http://www.nlm.nih.gov/mesh/MBrowser.html) as keywords to search articles published up to the date of the conference, in Medline, PubMed or Cochrane databases. Abstracts presented during the period 2007–2009 at annual meetings of the American Society of Hematology, the Interscience Conference on Antimicrobial Agents and Chemotherapy, the European Society of Clinical Microbiology and Infectious Diseases, the American Society of Clinical Oncology and the European Group for Blood and Marrow Transplantation were also screened. The guidelines drawn from data available only as abstracts were provisionally graded, pending the publication of the full papers. The quality of evidence and strength of recommendations were graded according to the IDSA (Table 1).[8]

Results

Antifungal prophylaxis

Primary prophylaxis. The guidelines of ECIL 1 are available in Maertens *et al*.[1] and their 2007 update appears in the slide set. The ECIL 3 guidelines for primary antifungal prophylaxis are summarized in Table 2. They were split into guidelines for allogeneic HSCT patients and guidelines for leukemia patients receiving chemotherapy.

Allogeneic HSCT. The ECIL 2 guidelines graded both fluconazole and posaconazole as the only 'AI' drugs for allogeneic HSCT on the basis of placebo-controlled trials with fluconazole[9–11] and the more recent trial with posaconazole.[12] However, we realized at ECIL 3 that this recommendation was confusing, because of the fact that fluconazole does not protect against mould infections,[13] and that the clinical trials with fluconazole and posaconazole had different designs. The posaconazole versus fluconazole study[12] included patients from the onset of GVHD requiring systemic immunosuppressive therapy, so that there are no data on the use of posaconazole during the initial phase—neutropenic phase—of transplant. On the other hand, the risk of mould infection, although higher during the GVHD phase than during the neutropenic phase, is also relevant during the initial phase. Therefore, the ECIL 3 Working Group has proposed to provide phase-specific guidelines for HSCT recipients: (1) fluconazole is highly recommended in the initial phase, but only when combined with a mould-directed diagnostic approach (for example, galactomannan-based or CT-scan-based) or a mould-directed therapeutic approach (for example, empirical antifungal therapy) for centers not having HEPA-filtered rooms and/or having a high baseline incidence of invasive mould infections. (2) Posaconazole is the drug of choice at onset of acute or chronic GVHD. However, the working group recommended therapeutic drug monitoring, especially in patients with intestinal GVHD. During GVHD, fluconazole becomes less relevant (CI), because of the high risk of mould disease.

Since 2007, the results of two controlled studies of primary prophylaxis with voriconazole have been

Table 1 Quality of evidence and strength of recommendations according to the Infectious Diseases Society of America grading system[8]

Quality of evidence	*Strength of recommendations*
I—Evidence from at least one well-executed randomized trial II—Evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies (preferably from more than one center; multiple time-series studies; or dramatic results from uncontrolled experiments III—Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports from expert committees	A—Strong evidence for efficacy and substantial clinical benefit: strongly recommended B—Strong or moderate evidence for efficacy, but only limited clinical benefit: generally recommended C—Insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (for example, drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches: optional D—Moderate evidence against efficacy or for adverse outcome: generally not recommended E—Strong evidence against efficacy or of adverse outcome: never recommended

Table 2 ECIL 3 Guidelines on antifungal primary prophylaxis in hematology patients (the items in bold italic have been introduced at ECIL 3)

Antifungal drug	*Grading*	*Comments*
Leukemia patients, induction chemotherapy		
Fluconazole (50–400 mg/day)	CI	Azoles should not be used empirically in case of prevoius azole prophylaxis Combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections
Itraconazole oral solution (2.5 mg/kg b.i.d.)	CI	May be limited by drug interactions and/or patient tolerability Azoles should not be used empirically in case of prior azole prophylaxis It is recommended to monitor serum drug concentrations
Posaconazole (200 mg t.i.d.)	AI	Azoles should not be used empirically in case of previous azole prophylaxis It is recommended to monitor serum drug concentrations
Echinocandins IV	Insufficient data	
Polyenes IV	CI	Includes low doses of conventional ampho B and lipid formulations
Aerosolized liposomal ampho B combined with oral fluconazole	***BI***	***The ECIL recommendation for aerosolized amphotericin B deoxycholate is DI***
Allogeneic HSCT recipients, initial neutropenic phase		
Fluconazole (400 mg q.d. i.v. or oral)	AI	Azoles should not be used empirically in case of previous azole prophylaxis Combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections
Itraconazole (200 mg i.v. followed by oral solution 200 mg b.i.d.)[a]	BI	May be limited by drug interactions and/or patient tolerability Azoles should not be used empirically in case of previous azole prophylaxis It is recommended to monitor serum drug concentrations
Posaconazole	No data	
Voriconazole (200 mg b.i.d. oral)	***Provisional AI***	***Grading pending the publication of the full paper***
Micafungin (50 mg q.d. i.v.)	CI	
Polyenes i.v.	CI	Includes low doses of conventional ampho B and lipid formulations
Aerosolized liposomal ampho B combined with oral fluconazole	***BII***	***The ECIL recommendation for aerosolized ampho B deoxycholate is DI***
Allogeneic HSCT recipients, GVHD phase		
Fluconazole (400 mg q.d. i.v. or oral)	CI	Azoles should not be used empirically in case of previous azole prophylaxis
Itraconazole (200 mg i.v. followed by oral solution 200 mg b.i.d.)[a]	BI	May be limited by drug interactions and/or patient tolerability Azoles should not be used empirically in case of prior azole prophylaxis It is recommended to monitor serum drug concentrations
Posaconazole	AI	Azoles should not be used empirically in case of previous azole prophylaxis It is recommended to monitor serum drug concentrations
Voriconazole (200 mg b.i.d. oral)	***Provisional AI***	***Grading pending the publication of the full paper***
Echinocandins i.v.	Insufficient data	
Polyenes i.v.	CI	Includes low doses of conventional ampho B and lipid formulations
Aerosolized liposomal ampho B combined with oral fluconazole	***Insufficient data***	

Abbreviation: ECIL = European Conference on Infections in Leukemia.
[a]In case the i.v. form of itraconazole is not available, the treatment will start with the oral solution, 200 mg b.i.d.

presented.[14,15] In a cohort of 600 allogeneic HSCT recipients, the double-blinded Wingard study[15] compared voriconazole (200 mg b.i.d. p.o. or i.v.) versus fluconazole (400 mg q.d. p.o. or i.v.) given for 100 days after transplant, and up to 180 days in case of steroid treatment, or CD4 cell count $<200/\mu l$ in case of T-cell-depleted graft. In all, 91% of the patients had good disease-risk status. The primary end point was fungal-free survival at 180 days. There was no difference in terms of safety between the two arms, nor in the primary objective (75 versus 78%, non-significant). However, the rates of microbiologically proven or probable IFD were lower in the voriconazole group than in the fluconazole group (13 versus 23, $P=0.049$), although there was only a trend for a lower number of cases of aspergillosis in the voriconazole group. The second study[14] compared voriconazole (200 mg b.i.d.) versus itraconazole (200 mg b.i.d.) in 489 patients receiving allogeneic HSCT after a myeloablative or reduced-intensity conditioning, for at least 100 days, and up to 180 days. The primary objective was assessed on a composite end point, including survival at 180 days after transplant and no proven or probable breakthrough IFD and no discontinuation of the study drug for more than 14 days during the 100-day prophylactic period. The voriconazole arm met the criteria for superiority in the primary end point when compared with the itraconazole arm (49.1 versus 34.5%, $P=0.0004$). The median duration of voriconazole prophylaxis was longer (97 days) than that of itraconazole (68 days), likely because of significantly more gastrointestinal adverse events (nausea, vomiting and diarrhea) in the itraconazole group. However, the main concern with this study is the low rate of proven or probable IFD (three in the voriconazole arm and six in the itraconazole arm).

In contrast with the posaconazole trial, these two studies evaluate the benefit of voriconazole during both most important phases (neutropenia and GVHD) at risk of IFD after HSCT. However, likely because of the selection of a majority of good-risk patients and different study timing,

the incidence of IFI in both voriconazole studies was low when compared with the posaconazole study, being, respectively, 6%[15] and 1.8%[14] versus 7.1%.[12] Considering the results of these two studies, and pending the publication as full papers, the ECIL 3 group recommended the use of voriconazole in both phases of HSCT (initial neutropenic and GVHD phase) with a provisional AI grading.

The usually recommended duration of an antifungal primary prophylaxis in allogeneic HSCT is 90–100 days. It is usually accepted that primary prophylaxis should be continued beyond day +100 in case of persisting GVHD and/or ongoing immunosuppressive therapies at this time. This is the way the posaconazole[12] and the voriconazole[14,15] studies have been designed. However, it is not possible from these studies to fix a recommended duration of prophylaxis in case of GVHD. In the posaconazole study,[12] the median duration of study drug administration in the posaconazole arm was 111 days from inclusion.

Leukemia patients receiving chemotherapy. The previous ECIL conference[1] had graded different drugs for primary prophylaxis in leukemia patients receiving induction or consolidation chemotherapy. Azoles were considered the first option (Table 2). There were insufficient data to recommend primary prophylaxis with candins, and i.v. polyenes were graded CI. Since 2007, new data are available from a double-blind, placebo-controlled trial on aerosolized liposomal amphotericin B (L-ampho B) combined with fluconazole.[16] Aerosols were given twice weekly at the dose of 10 mg of L-ampho B during the neutropenic phase of leukemia chemotherapy, autologous HSCT or allogeneic HSCT. In all, 272 adults were randomized, including 49% with acute myeloid leukemia or myelodysplastic syndrome and 77% housed in HEPA-filtered rooms. The incidence of proven or probable aspergillosis (according to the first version of the European Organization for Treatment and Research of Cancer-MSG definitions) was significantly reduced in the aerosol group when compared with the placebo group (6/139 versus 18/132 in the modified intention-to-treat analysis, $P=0.005$). However, in both groups, discontinuation of the aerosols was frequent (35% in the L-ampho B group versus 27% in the placebo group), mainly because of difficulties in accepting the inhalation system, intolerance or technical problems with the aerosol delivery system. Despite this observation, because of the significant difference in the incidence of aspergillosis, the Working Group recommended this prophylactic strategy for chemotherapy-induced neutropenia in leukemia patients (BI). Because of the low number of allogeneic HSCT patients in the trial, a weaker grading of recommendation was given for the neutropenic phase of HSCT (BII).

Secondary prophylaxis. Secondary prophylaxis aims at preventing relapse of a previous IFD, or the onset of another IFD, during a new at-risk period, defined as either a prolonged neutropenic phase, usually chemotherapy-induced, or a phase of severe immunosuppression, mainly after allogeneic HSCT. There is no comparative study on secondary prophylaxis, as there is no standard approach in this setting. Only retrospective studies were available until recently, using various antifungals, including voriconazole, caspofungin or liposomal amphotericin B. Two large retrospective studies in allogeneic HSCT recipients[17,18] strongly suggested the protective effect of a secondary antifungal prophylaxis on the rate of IFD occurring after HSCT. More recently, the first prospective study on secondary prophylaxis was conducted with voriconazole in a cohort of 45 allogeneic HSCT recipients with a previous history of IFD, mainly aspergillosis.[19] Only 3 out of 45 patients developed an IFD during the first year after transplant. Therefore, although no randomized study has evaluated secondary antifungal prophylaxis in such high-risk patients, most transplant centers recognize its potential for decreasing the risk of IFD after HSCT, and so did the ECIL panel, who graded the recommendation for secondary prophylaxis as 'AII'. For the drug selection, no specific recommendation was formulated, considering that the choice should be based on the causative fungal pathogen of the previous IFD and the previous response to antifungal agents.

Empirical and preemptive antifungal treatment in neutropenic patients

Empirical antifungal therapy. Late diagnosis and antifungal therapy is associated with severe morbidity and high mortality of IFD in hematological patients. Empirical therapy aimed at treating IFD before progression to overt disease has been historically defined as the administration of antifungal agents in neutropenic patients with persistent fever despite 4–7 days of broad-spectrum antibacterial therapy, or with relapsing fever.[2] Although used as standard of care in most hematology centers and endorsed by international guidelines, this strategy has never been compared with placebo or other antifungal strategies. The larger study that established the use of empirical antifungal therapy compared with an open non-placebo-controlled design the addition of amphotericin B deoxycholate to antibacterial therapy with the continuation of antibacterial therapy alone. On the basis of available evidence from underpowered studies for the efficacy of empirical antifungal therapy in reduction of IFD and IFD-associated mortality, the recommendation for this strategy was graded with BII at ECIL 1. On the other hand, on the basis of large prospective randomized studies comparing two drugs for empirical antifungal therapy in persistent or relapsing fever, L-ampho B and caspofungin were recommended with AI grading,[20,21] ampho B lipid complex or colloidal dispersion, itraconazole and voriconazole with BI grading, and ampho B deoxycholate with BI and DI grading, respectively, in the absence and presence of renal impairment or nephrotoxic comedications (Table 3). However, the majority of these trials used a composite end point including defervescence, a nonspecific sign of response and toxicity as major drivers of therapeutic success, whereas assessment of the efficacy on IFD or IFD-related mortality was limited to low numbers of patients.

Few new data on empirical antifungal therapy were published between 2007 and 2009. No study has evaluated the empirical strategy *per se*—versus placebo—and the grading of recommendation remained unchanged (BII). The new studies either evaluated the efficacy and safety of antifungal drugs in noncomparative trials,[22] or compared

Table 3 ECIL 3 guidelines on empirical antifungal treatment in neutropenic patients with persistent or relapsing fever (the updated items are reported in bold italic)

Antifungal agent	*Daily dose*	*Level of recommendation*	*CDC grading Level of evidence for*	
			Efficacy	*Safety*
Liposomal ampho B	3 mg/kg	A[a]	I	I
Caspofungin	50 mg	A[a,b]	I	I
ABCD	4 mg/kg	B[c]	I	I
ABLC	5 mg/kg	B[c]	I	I
Itraconazole	200 mg i.v.	B[b,e]	I	I
Voriconazole	2 × 3 mg/kg i.v.	B[b,d,e]	I	I
Micafungin	***100 mg***	***B***	***II***	***II***
Ampho B deoxycholate	0.5–1 mg/kg	B[c]/D[f]	I	I
Fluconazole	400 mg i.v.	C[b,e,g]	I	I

Abbreviations: ABCD = amphotericin B colloidal dispersion; ABCL = amphotericin B lipid complex; ECIL = European Conference on Infections in Leukemia; FDA, Food and Drug Administration; HSCT = hematopoietic stem cell transplant.
[a]A double-blind, randomized trial comparing caspofungin 50 mg/m^2 ($n = 56$) with liposomal ampho B 3 mg/kg/day ($n = 25$) (published in abstract form) suggests a provisional grading BII for children; the constitution of a pediatric group specifically addressing antifungal prophylaxis and therapy in children will be considered for the 2011 update of ECIL guidelines.
[b]No activity against mucorales.
[c]Infusion-related toxicity (fever, chills, hypoxia).
[d]Failed the 10% noninferiority cut-off when compared with liposomal AmB (and thus not approved by the FDA for this indication), but first-line therapy for aspergillosis, effective therapy for candidiasis and efficacious for prevention of breakthrough IFI.
[e]Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class.
[f]B in the absence of or D in the presence of risk factors for renal toxicity (for example, impaired renal function at baseline, nephrotoxic comedication including cyclosporin or tacrolimus in allogeneic HSCT recipients, aminoglycoside antibiotics, history of previous toxicity).
[g]No activity against *Aspergillus* and other moulds. Not approved by the FDA for this indication.

two different antifungals.[23,24] Maertens *et al*.[24] conducted a prospective, multicenter, double-blind trial comparing caspofungin (70 mg/m^2 on day 1, then 50 mg/m^2/day) with L-ampho B (3 mg/kg/day) (randomization ratio 2:1) in neutropenic children aged 2–17 years, remaining febrile after 96 h of antibacterial therapy, or with relapsing fever. A total of 79 children entered the study, 54 in the caspofungin group and 25 in the L-ampho B group. The primary end point was safety, and there was no significant difference between groups in terms of drug-related adverse events. There was also no significant difference in efficacy, which was assessed as a composite end point. On the basis of these data, pending their publication as a full paper and the constitution of a new working group for specific assessment of the evidence of antifungal therapy in pediatric patients, empirical caspofungin has been recommended with a provisional BII grading in children. Two studies on empirical micafungin were recently published.[23,25] The first reported a historical comparison between caspofungin ($n = 161$) and micafungin ($n = 173$) in three North-American centers:[23] in-hospital mortality (7.5 and 7.4%) and incidence of IFD (10.6 and 13.7%) were not significantly different between the two groups. The second study is a prospective, noncomparative trial, conducted in 277 neutropenic adults, including one-third of HSCT recipients, from 87 Japanese centers.[22] Micafungin (50–150 mg/day) was administered either after >48 h of persistent fever ($n = 88$), or for the treatment of possible ($n = 63$), probable[38] or proven[8] IFD. Efficacy was within the range of previous empirical trials, with an 80.7% response rate based on a composite end point for all patients and 86.3% (44/51 patients) for those treated in empirical indication. Drug-related adverse events occurred in 27% of all treated patients (liver toxicity in 81% of cases), and serious toxicity was observed in 4.3 of cases. On the basis of these two studies, ECIL 3 included empirical micafungin in the revised recommendations (BII). Regarding two observational studies on itraconazole[25] and caspofungin,[26] they were not considered to provide new data requiring a revision of previous recommendations of ECIL for these antifungal drugs.

Preemptive antifungal therapy. The ECIL questionnaire sent to European centers in 2005 already highlighted that the combination of persistent fever with a specific clinical presentation (for example, pneumonia) or a biological marker of IFD (for example, galactomannan antigenemia) does influence the choice of the antifungal drug.[2] This suggests that the empirical antifungal strategy, although recommended as the standard of care, is being challenged by the clinicians, because of the poor specificity of fever in neutropenic patients, the availability of new noninvasive procedures for early diagnosis of infection, the toxicity and the costs associated with a broad and maybe unnecessary use of new antifungal drugs.

Preemptive strategies have been currently developed for targeting the administration of antifungal agents in high-risk neutropenic patients with early IFD—selected on the basis of risk factors, clinical presentation, imaging and biological markers—to decrease the toxicity, cost and possibly emerging fungal resistance associated with the nonselective empirical approach.[27] However, as a standard definition of preemptive antifungal strategy is lacking, the reported studies used different criteria and approaches. In 2005, Maertens *et al*.[28] published the first noncomparative study in 136 high-risk neutropenic patients on the feasibility of a preemptive antifungal approach using the combination of a daily assessment of serum *Aspergillus* galactomannan antigenemia, pulmonary CT scan and bronchoalveolar lavage The authors reported an estimated reduction of the use of antifungals from 35% (expected rate if the empirical approach would have been used) to 7.7% of 117 persistent or relapsing febrile neutropenic episodes. In addition, the strategy identified invasive aspergillosis in 10/19 neutropenic episodes without fever (7% of the study population), which would have been missed by the fever-driven empirical approach. No undetected cases of invasive aspergillosis were identified. However, the overall incidence of proven or probable IFD in this series (22/136 episodes of prolonged neutropenia, 16%) was in the highest range of previous series in neutropenic patients. Only two randomized studies were published on the comparison of an empirical versus a preemptive approach.[29,30] Using a pan-fungal blood PCR assay twice weekly, Hebart *et al*.[30]

compared an empirical approach with administration of L-ampho B in persistent or recurrent fever and a preemptive approach starting L-ampho B in patients with either two positive consecutive PCR tests or one positive PCR test combined with clinical symptoms consistent with IFD, including persistent fever. In all, 409 allogeneic HSCT recipients were included and followed during the first 100 days of transplant. Surprisingly, although the aim of a preemptive approach is to focus the administration of antifungals to patients with early IFD, this PCR-based strategy led to the administration of antifungals in 45% of the patients versus 30% using the traditional empirical approach. More importantly, the PCR- and clinically-based approach was not associated with a significant reduction of proven IFD (4% on day 30). There was only a trend for a reduced IFD-related mortality on day 30 of transplant (0.5 versus 2.4%), but no difference on day 100. Cordonnier *et al*.[29] prospectively compared a classical empirical approach with a preemptive approach with administration of ampho B-deoxycholate or L-ampho B in patients with a clinical focus consistent with IFD (for example, pneumonia, acute sinusitis), shock, or with a positive serum galactomannan test, screened twice weekly. A total of 293 patients with an expected duration of neutropenia >10 days and no previous IFD were randomized. The primary end point was survival 14 days after recovery from neutropenia. The survival rates were 97.3% in the empirical group versus 95.1% in the preemptive group, showing the noninferiority of the preemptive approach for overall survival. However, the incidence of IFD was significantly higher in the preemptive group than in the empirical group (9.1 versus 2.7%, $P<0.02$; IFD-related mortality 2.1 versus 0%, $P=0.11$), mainly because of IFD occurring in the subgroup of patients receiving induction chemotherapy for acute leukemia who had the longest duration of neutropenia (median: 26 days). Therefore, although the number of patients receiving antifungals and the duration of antifungal administration were significantly reduced by the preemptive approach, the authors concluded that this strategy is safe in patients with neutropenia duration <10 days, but is associated with an increased risk of IFD in those with prolonged neutropenia, especially during the induction phase of acute leukemia. Five single-center observational noncomparative studies have been published on preemptive approaches, using different clinical, radiological and microbiological criteria and antifungal drugs, in a series of 53–159 neutropenic episodes or patients.[31–35] They all suggest that the administration of antifungals is likely reduced by a preemptive strategy when compared with what would have been expected by using an empirical strategy. However, a noncomparative and retrospective design is a limitation of these reports. Although one of the advantages of a preemptive therapy could be to identify afebrile patients with early IFD, who are missed by a fever-driven empirical approach, this potential benefit has been poorly illustrated in the literature.

Gathering all these data, the ECIL group decided not to grade a recommendation for the preemptive approach, considering a possible excess of risk for occurrence of IFD in particular during prolonged neutropenia,[29] the lack of defined standard criteria for starting antifungal therapy, and the variability of results between studies. Pending improved scientific evidence, this strategy has to be considered as an experimental approach. Many parameters, which may influence its efficacy and safety, including patient population, duration of neutropenia, local fungal epidemiology, type and timing of investigations, risk of diagnostic work-up, and choice and time of start of the antifungal regimen need to be defined. The ECIL group encourages prospective, comparative, randomized, preemptive studies aimed at standardizing clinical, biological and imaging criteria for starting antifungal therapy. These studies should also assess the cost-effectiveness of the strategy, considering that the costs saved by the decreased use of antifungals may be counter-balanced by the increased costs of the diagnostic procedures.

Antifungal therapeutic management of invasive aspergillus and candida infections

Aspergillosis. Two prospective, open studies with caspofungin in first-line treatment of invasive aspergillosis were recently presented: one in non-HSCT patients[36] and one in HSCT recipients.[37] Both used standard doses of caspofungin (70 mg on day 1 followed by 50 mg/day). In the first study,[36] 129 patients with hematologic malignancies were enrolled; 61 were eligible with the criteria for proven or probable, microbiologically documented aspergillosis. Most of them had acute leukemia and 85% were neutropenic. The rate of complete plus partial response was 20/61 (33%), which was below the working hypothesis of >35%. The 12-week survival was 53%. The second study[37] enrolled 42 allogeneic HSCT recipients. In all, 24 recipients were eligible, that is, with microbiologically documented proven or probable aspergillosis. The rate of complete plus partial response was 10/24 (42%) and the 12-week survival was 50%. Because of accrual problems, the study was terminated early. Caspofungin was previously graded CIII, as first-line therapy of invasive aspergillosis at ECIL 2. Considering the recent data, the group upgraded caspofungin in this indication to CII.

Two retrospective studies were also recently available: one compared amphotericin B lipid complex with L-ampho B and mixed primary and salvage treatments.[38] The response rates were poor in both groups, but the patients had mostly advanced disease. The nephrotoxicity of amphotericin B lipid complex seemed to be higher than that of L-ampho B. This study was considered to provide no data justifying changing the previous ECIL recommendations on amphotericin B lipid complex and L-ampho B in the treatment of invasive aspergillosis. A retrospective study was run by Cesaro *et al*.,[39] including 40 children treated with various combinations including caspofungin, 20 for primary and 20 for salvage therapy. A favorable response rate was observed in 21 (53%) patients. The recommendations on the use of combinations for the treatment of invasive aspergillosis were not modified (DIII for first line and CII for salvage).

Candidiasis. Only one study has been published on the treatment of invasive candidiasis since the ECIL 2 guidelines.

This double-blind study compared two doses of caspofungin (70 mg on day 1 followed by 50 versus 150 mg/day) in 204 patients with proven invasive candidiasis.[40] A minority of patients (60/204) had an active malignancy, only 15 were neutropenic and 10 were transplant patients. The incidence of drug-related adverse events (19%), as well as the incidence of adverse events leading to discontinuation (2%), was similar in both groups. There was no benefit of the high dose of caspofungin on the overall response, time to clear blood cultures or 8-week mortality rate. Therefore, in the absence of any benefit of the high dose, the group proposed no changes to the previous recommendations for a standard dose of caspofungin.

Discussion

Owing to the availability of new antifungal drugs, the publication of large randomized trials and changes in the fungal epidemiology in hematology patients, there is a need for consensus guidelines for the medical community in charge of immunocompromised patients. This was the goal of the ECIL 1 and ECIL 2 conferences, whose conclusions were published in 2007.[3] Recently, the IDSA published updates of the aspergillosis [6] and candidiasis[5] management guidelines. The conclusions of the North-American and European panels were very consistent, especially on the optimal choices of antifungal drugs in first-line therapy. It should be noticed that some minor discrepancies between the ECIL and the IDSA guidelines—for example, the grading of L-ampho B in the first-line therapy of aspergillosis—may be explained by the use of two different grading systems: whereas the ECIL guidelines used the IDSA grading score with three levels of evidence (I–III) and five levels of recommendations (A–E), the last version of the IDSA guidelines[5,6] used a more recent rating system derived from the Canadian Task Force and shared with the United Stated Public Health Service, with the same three levels of evidence, but with only three levels of recommendations. For example, a 'C' grading means 'optional' in the ECIL guidelines and 'poor evidence to support a recommendation' in the IDSA guidelines.

Most of the large, important trials were available at the time the IDSA expert group and the ECIL 2 expert group elaborated their guidelines, especially for first-line treatment of invasive aspergillosis[41,42] and candidiasis.[42–46] Both panels met similar difficulties in analyzing the literature on some topics, for example, the use of new antifungal drugs for candidemia in neutropenic patients, as few data are available on this specific population. However, despite these difficulties, their conclusions were very close.

ECIL 3 was held in September 2009, when some new data were available. The main changes discussed at the ECIL 3 update meeting and included in the revised recommendations were the following:

A different way to present the prophylactic guidelines for fungal infections in allogeneic HSCT recipients, splitting the neutropenic and GVHD phases first, then integrating recent data on voriconazole primary prophylaxis, using a provisional recommendation pending the final publications. We also introduced the use of L-ampho B aerosols combined with fluconazole in acute leukemia patients.

The use of micafungin as an alternative for empirical antifungal treatment in febrile neutropenic patients and a provisional grading for empirical caspofungin in children.

Due to lack of evidence, the group was cautious about preemptive antifungal approaches. No recommendations about clinical selection criteria, type and timing of noninvasive diagnostic procedures, choice and time of start of the antifungal regimen were formulated. To improve the scientific evidence of this strategy, the ECIL group encourages the development of well-designed, large, prospective, randomized trials.

The use of caspofungin in first-line therapy of invasive aspergillosis was analyzed on the basis of two open prospective studies.[36,37] While the result of one of these studies was below the initial hypotheses of efficacy, the studies were not comparative with one of the first choice drugs and enrolled only a limited number of patients especially in the allogeneic HSCT recipients group, the results of these trials did not challenge the actual places of voriconazole or L-ampho B in this indication.

Finally, as there are still no results from a prospective randomized trial on combination therapy in invasive aspergillosis, the ECIL group has considered it irrelevant to give any recommendation on the use of combination in first line.

Conclusion

The ECIL panel, gathering four major international bodies working on infections in leukemia and HSCT patients, aims at regularly updating evidence-based guidelines on antifungal strategies as a helpful tool for the medical community in clinical management of hematological patients.

Conflict of interest

JM is a consultant for Astellas Pharma, Gilead Sciences, Merck Sharp & Dohme, Pfizer and Schering-Plough and has received grants from Pfizer, Merck Sharp & Dohme, Cephalon and Gilead. OM received unrestricted research grants from and/or was consultant to Gilead Sciences, Merck, Sharp & Dohme, Pfizer and Schering-Plough. RH has received a grant from Pfizer and has been consultant for Astellas Pharma, Gilead Sciences, Merck Sharp & Dohme, Pfizer and Schering-Plough. OAC received research grants from Astellas, Basilea, Bayer/Schering, Celgene, Genzyme, Gilead, Medac, Menarini, Merck/Schering-Plough, Merck/Serono, Mölnlycke, Novartis, Optimer, and Pfizer, and Quintiles, is a consultant to Astellas, Basilea, Bayer/Schering, F2G, Gilead, Medac, Merck/Schering-Plough, Mölnlycke, Optimer, and Pfizer, and served at the speakers' bureau of Astellas, Gilead, Merck/Schering-Plough, Pfizer, SpePharm, and United Medical. UF received unrestricted research grants from and/or was consultant to Gilead

Sciences, Merck, Sharp & Dohme, Pfizer, and Schering-Plough. BG received travel grants from Pfizer, Gilead Sciences, MSD and Astellas Pharma. WJH received research grants from Astellas, Basilea, Gilead, Merck/Schering-Plough and Pfizer, is a consultant to Novartis, Merck/Schering-Plough and Pfizer, and served at the speakers' bureau of Astellas, Gilead, Merck/Schering-Plough and Pfizer. CLF received grants from Pfizer and Gilead. She served at the speakers' bureau of Gilead, Pfizer and MSD. PR has received grants and research supports from Pfizer, and has been a consultant to Pfizer, Schering-Plough, Gilead Sciences and Merck Sharp & Dohme. AT has been a consultant to MSD, Schering-Plough, Gilead and Pfizer. CC has received grants and research supports from Pfizer, Gilead Sciences and Merck Sharp & Dohme, has been a consultant to Pfizer, Schering-Plough, Gilead Sciences, Merck Sharp & Dohme and Astellas-Pharma, and served at the speakers' bureau of Gilead Sciences, Merck/Schering-Plough and Pfizer. PF declares no conflict of interest.

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References

1 Maertens J, Frere P, Lass-Flörl C, Heinz W, Cornely OA. Primary antifungal prophylaxis in leukaemia patients. *Eur J Cancer* 2007; Suppl 5: 43–48.
2 Marchetti O, Cordonnier C, Calandra T. Empirical antifungal therapy in neutropenic cancer patients with persistent fever. *Eur J Cancer* 2007; Suppl 5: 32–42.
3 Herbrecht R, Flückiger U, Gachot B, Ribaud P, Tiebaut A, Cordonnier C. Treatment of invasive candida and invasive aspergillus infections in adult haematological patients. *Eur J Cancer* 2007; Suppl 5: 49–59.
4 ECIL Guidelines for the management of bacterial, fungal and viral infections 2009. http://www.ichs.org/Ecilslides/ECIL%203%20Empirical%20Antifungal%20Therapy%20Update%202009.pdf.
5 Pappas PG, Kauffman CA, Andes D, Benjamin DK, Calandra TF, Edwards JE *et al*. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **48**: 503–535.
6 Walsh TJ, Anaissie EJ, Dennin DW, Herbrecht R, Kontoyaiannis DP, Marr K *et al*. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **46**: 327–360.
7 Cordonnier C, Calandra T. The first European Conference on infections in leukaemia: why and how? *Eur J Cancer* 2007; Suppl 5: 2–4.
8 Kish MA. Guide to development of practice guidelines. *Clin Infect Dis* 2001; **32**: 851–854.
9 Goodman JL, Winston DJ, Greenfield RA, Chandrasekar PH, Fox B, Kaizer H *et al*. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med* 1992; **326**: 845–851.
10 Marr KA, Seidel K, Slavin MA, Bowden RA, Schoch HG, Flowers ME *et al*. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. *Blood* 2000; **96**: 2055–2061.
11 Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch HG, Feldman AR *et al*. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation—a prospective, randomized double blind study. *J Infect Dis* 1995; **171**: 1545–1552.
12 Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR *et al*. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med* 2007; **356**: 335–347.
13 Robenshtok E, Gafter-Gvili A, Goldberg E, Weinberger M, Yeshurun M, Leibovici L *et al*. Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation: systematic review and meta-analysis. *J Clin Oncol* 2007; **25**: 34.
14 Marks DI, Kibbler C, Pagliugi A, Ribaud P, Solano C, Heussel CP *et al*. Voriconazole vs Itraconazole for primary prophylaxis of invasive fungal infection in allogeneic hematopoietic cell transplant (HCT) recipients. In: *49th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2009*; San Francisco, CA 2009.
15 Wingard JR, Carter SL, Walsh TJ, Kurtzberg J, Small TN, Gersten ID *et al*. Results of a randomized, double-blind trial of Fluconazole vs Voriconazole for the prevention of invasive fungal infections in 600 allogeneic blood and marrow transplant patients. In: *49th American Society of Hematology Annual Meeting and Exposition; 2007*. American Society of Hematology: Atlanta, GA, 2007, p 163.
16 Rijnders BJ, Cornelissen JJ, Slobbe L, Becker MJ, Doorduijn JK, Hop WC *et al*. Aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: a randomized, placebo-controlled trial. *Clin Infect Dis* 2008; **46**: 1401–1408.

17 Fukuda T, Boeckh M, Guthrie K, Mattson DK, Owens S, Wald A *et al*. Invasive aspergillosis before allogeneic hematopoetic stem cell transplantation: 10 year experience at a single transplant center. *Biol Bone Marrow Transplant* 2004; **10**: 494–503.
18 Martino R, Parody R, Fukuda T, Maertens J, Theunissen K, Ho A *et al*. Impact of the intensity of the pretransplant conditioning regimen in patients with prior invasive aspergillosis undergoing allogeneic hematopoietic stem cell transplantation: a retrospective survey of the infectious diseases working party of the European Group for Blood and Marrow Transplantation. *Blood* 2006; **108**: 2928–2936.
19 Cordonnier C, Rovira M, Maertens J, Olavarria E, Faucher C, Bilger K *et al*. Voriconazole for secondary prophylaxis of invasive fungal infection in allogeneic stem cell transplant recipients: results of the VOSIFI study. *Hematologica* 2010 (in press).
20 Walsh TJ, Finberg RW, Arndt C, Hiemenz J, Schwartz C, Bodensteiner D *et al*. Liposomal Amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *N Engl J Med* 1999; **340**: 764–771.
21 Walsh TJ, Teppler H, Donowitz GR, Maertens J, Baden LR, Dmoszynska A *et al*. Caspofungin versus liposomal Amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* 2004; **351**: 1391–1402.
22 Tamura K, Urabe A, Yoshida M, Kanamaru A, Kodera Y, Okamoto S *et al*. Efficacy and safety of micafungin, an echinocandin antifungal agent, on invasive fungal infections in patients with hematological disorders. *Leuk Lymphoma* 2009; **50**: 92–100.
23 Kubiak X. Caspofungin vs micafungin for empirical therapy in adult neutropenic patients with persistent fever: a retrospective analysis. In: *48th ICAAC; 2008*. Washington, DC, 2008.
24 Maertens J, Madero-Lopez L, Reilly AF, Lehrnbecher T, Groll AH, Jafri HS; *et al*. Caspofungin vs liposomal AmB for empirical therapy in pediatric neutropenic patients with persistent fever: a randomized, double-blind, multicenter trial. *Pediatr Infect Dis J* **29**: 415–420.
25 Ohta K, Kosaka SN, Nakao Y, Kumura T, Hagihara K, Sakamoto E *et al*. Efficacy and safety of intravenous itraconazole as empirical antifungal therapy for persistent fever in neutropenic patients with hematological malignancies in Japan. *Int J Hematol* 2009; **89**: 649–655.
26 Lafaurie M, Lapalu J, Raffoux E, Breton B, Lacroix C, Socié G *et al*. High rate of breakthrough invasive aspergillosis among patients receiving caspofungin for persistent fever and neutropenia. *Clin Microbiol Infect* 2009 (e-pub ahead of print 3 September 2009).
27 Segal BH, Almyroudis NG, Battiwalla M, Herbrecht R, Perfect JR, Walsh TJ *et al*. Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostics adjuncts. *Clin Infect Dis* 2007; **44**: 402–409.
28 Maertens J, Theunissen K, Verhoef G, Verschakelen J, Lagrou K, Verbeken E *et al*. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. *Clin Infect Dis* 2005; **41**: 1242–1250.
29 Cordonnier C, Pautas C, Maury S, Vekhoff A, Farhat H, Suarez F *et al*. Empirical versus pre-emptive antifungal strategy in high-risk febrile neutropenic patients: a prospective randomized study. *Clin Infect Dis* 2009; **48**: 1042–1051.
30 Hebart H, Klingspor L, Klingebiel T, Loeffler J, Tollemar J, Ljungman P *et al*. A prospective ranomized controlled trial comparing PCR-based and empirical treatment with liposomal amphotericin B in patients after allogeneic stem cell transplant. *Bone Marrow Transplant* 2008; **43**: 553–561.
31 Riva E, Nosari A, Brizio A, Molteni A, Vanelli C, Gabutti C *et al*. In high risk acute leukemia patients, early antifungal therapy improves the outcome of invasive mould infections. In: *48th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2008*, Chicago, IL 2008.
32 Aguilar-Guisado M, Espigado I, Cordero E, Noguer N, Parody R, Pachon J *et al*. Empirical antifungal therapy in selected patients with persistent febrile neutropenia. *Bone Marrow Transplant* 2010; **45**: 159–164.
33 Barnes RA, White PL, Bygrave C, Evans N, Healy B, Kell J. Clinical impact of enhanced diagnosis of invasive fungal disease in high-risk haematology and stem cell transplant patients. *J Clin Pathol* 2009; **62**: 64–69.
34 Dignan FL, Evans SO, Ethell ME, Shaw BE, Davies FE, Dearden CE *et al*. An early CT-diagnosis based treatment strategy for invasive fungal infection in allogeneic transplant recipients using caspofungin first line: an effective strategy with low mortality. *Bone Marrow Transplant* 2009; **44**: 51–56.
35 Girmenia C, Micozzi A, Gentile G, Santilli S, Arleo E, Cardarelli L *et al*. Clinically driven diagnostic antifungal approach in neutropenic patients: a prospective feasibility study. *J Clin Oncol* 2010; **28**: 667–674.
36 Viscoli C, Herbrecht R, Akan H, Baila L, Sonet A, Gallamini A *et al*. An EORTC Phase II study of caspofungin as first-line therapy of invasive aspergillosis in haematological patients. *J Antimicrob Chemother* 2009; **64**: 1274–1281.
37 Herbrecht R, Maertens J, Baila L, Aoun M, Heinz W, Martino R *et al*. Caspofungin first-line therapy for invasive aspergillosis in allogeneic hematopoietic stem cell transplant patients: a European Organisation for Research and Treatment of Cancer study. *Bone Marrow Transplant* 2010 (e-pub ahead of print 11 January 2010; doi:10.1038/bmt.2009.334).
38 Hachem RY, Boktour MR, Hanna HA, Husni RN, Torres HA, Aliff C *et al*. Amphotericin B lipid complex versus liposomal amphotericin B monotherapy for invasive aspergillosis in patients with hematologic malignancy. *Cancer* 2008; **112**: 1282–1287.
39 Cesaro S, Giacchino M, Locatelli F, Spiller M, Buldini B, Castellini C *et al*. Safety and efficacy of a caspofungin-based combination therapy for treatment of proven or probable aspergillosis in pediatric hematological patients. *BMC Infect Dis* 2007; **18**: 28.
40 Betts RF, Nucci M, Talwar D, Gareca M, Queiroz-Telles F, Bedimo RJ *et al*. A multicenter, double-blind trial of a high-dose caspofungin treatment regimen versus a standard caspofungin treatment regimen for adult patients with invasive candidiasis. *Clin Infect Dis* 2009; **48**: 1676–1684.
41 Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW *et al*. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; **347**: 408–415.
42 Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J *et al*. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med* 2002; **347**: 2020–2029.
43 Kullberg BJ, Sobel JD, Ruhnke M, Pappas PG, Viscoli C, Rex JH *et al*. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. *Lancet* 2005; **366**: 1435–1442.
44 Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D *et al*. Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med* 2007; **356**: 2472–2482.
45 Kuse ER, Chetchotisakd P, da Cunha CA, Ruhnke M, Barrios C, Raghunadharao D *et al*. Micafungin versus liposomal

amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. *Lancet* 2007; **369**: 1519–1527.

46 Pappas PG, Rotstein CM, Betts RF, Nucci M, Talwar D, De Waele JJ *et al*. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis* 2007; **45**: 883–893.

Appendix

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