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European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia

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The European Conference on Infections in Leukaemia (ECIL) updated its guidelines on antifungal prophylaxis for adults using the grading system of IDSA. The guidelines were extended to provide recommendations for other haematological diseases besides AML and recipients of an allogeneic haematopoietic stem cell transplantation (HSCT). Posaconazole remains the drug of choice when the incidence of invasive mould diseases exceeds 8%. For patients undergoing remission-induction chemotherapy for AML and myelodysplastic syndrome (MDS), fluconazole can still offer an alternative provided it forms part of an integrated care strategy that includes screening with biomarkers and imaging. Similarly, aerosolized liposomal amphotericin B combined with fluconazole can be considered for patients at high risk of invasive mould diseases but other formulations of the polyene are discouraged. Fluconazole is still recommended as primary prophylaxis for patients at low risk of invasive mould diseases during the pre-engraftment phase of allogeneic HSCT whereas only a moderate recommendation could be made for itraconazole, posaconazole and voriconazole for patients at high risk. Posaconazole is strongly recommended for preventing invasive mould disease post-engraftment but only when graft-versus-host disease (GvHD) was accompanied by other risk factors such as its severity, use of an alternative donor or when unresponsive to standard corticosteroid therapy. The need for primary prophylaxis for other patient groups was less clear and should be defined by the estimated risk of invasive fungal disease (IFD).

Introduction

In 2005, the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the European LeukemiaNet (ELN) and the International Immunocompromised Host Society (ICHS) inaugurated the European Conference on Infections in Leukaemia (ECIL). Its main goal was to elaborate guidelines or recommendations for the management of infections due to bacteria, viruses and fungi among leukaemia patients as well as those undergoing haematopoietic stem cell transplantation (HSCT) and to identify unmet needs and areas for further research.[1] The prevention of invasive fungal disease (IFD) has been one of the key topics from the beginning.[1,2] Since 2006, all proposed guidelines

Table 1. Quality of evidence and strength of recommendations

Quality of evidence		Strength of recommendation	
I	Evidence from at least one properly randomized controlled trial.	A	Good evidence to support a recommendation for or against use.
II	Evidence from at least one well-designed clinical trial without randomization; from cohort or case-controlled analytic studies (preferably from more than one centre); multiple time-series studies; or from dramatic results from uncontrolled experiments.	B	Moderate evidence to support a recommendation for or against use.
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports from expert committees.	C	Poor evidence to support a recommendation.

and updates on this topic have been made publicly available through the web sites of these four organizations and via publications in peer-reviewed international journals both for adults[2,3] and children.[4]

The ECIL committee aims to update its guidelines regularly based on the available evidence. During the fifth and sixth meetings (19–21 September 2013 and 11–12 September 2015, Nice, France), guidelines on antifungal prophylaxis for adults were extensively revised, according to a methodology that was previously described,[1,3] and the final slide set was made available on the ECIL web site (www.ecil-leukaemia.com).

Compared with the previous versions, including the one published in 2011,[3] major changes included: (i) the implementation of a novel IDSA grading system that condensed the strength of recommendation from five to three levels (Table 1); and (ii) extending the recommendations to other haematological diseases besides AML and recipients of an allogeneic HSCT. In fact, due to new therapeutic approaches including biotherapies, IFD has recently been reported more frequently in many haematological diseases, including lymphoproliferative disorders.[5] Hence, the group considered it useful for the haematology community to extend its analysis and recommendations for primary antifungal prophylaxis in these populations. Of note, separate guidelines on antifungal prophylaxis for patients with aplastic anaemia have been recently published by the aplastic anaemia working party of the EBMT.[6] Also recently, specific guidelines on the use of biomarkers for diagnosis of IFD,[7] the prevention of infections due to *Pneumocystis jirovecii*[8] and the management of IFD in the paediatric population[4] have been published elsewhere.

This review summarizes the proposals agreed upon at ECIL-5 and ECIL-6. During the revision process, the group identified several important issues that made gathering of the evidence difficult. These included the fact that a significant number of antifungal prophylaxis studies date from the late 1980s and early 1990s when standards of study design and conduct were less exact, no biomarkers were available and there was no agreed definition of IFD. There were also few well-executed, prospective, blinded, controlled trials with adequate numbers of patients to ensure sufficient statistical power, particularly for those that did not include patients with AML and allogeneic HSCT recipients. In addition, different doses of the same drug (e.g. fluconazole doses ranged from 50 mg/day[9] to 400 mg/day[10]) as well as different routes of administration [e.g. itraconazole orally[11] or intravenously (iv)[12]] were used. The primary aims of studies also differed widely with only proven and probable IFD being a common endpoint.[2,13,14] Finally, despite many years of use,[15] and a large volume of published data, the true impact of high-efficiency particulate air (HEPA) filtration in reducing infectious complications including IFD remains unclear.[16]

Methods

The methodology of the ECIL conferences has been previously reported.[1] A working group of experts in the field was created several months in advance of the biennial conference and was charged with reviewing the literature published since the last update of the previous guidelines. Additionally, for the new topics addressing the non-AML, non-HSCT patients, subgroups were designed to review the literature about the risk of IFD in these specific populations and to assess the need for antifungal prophylaxis. Recommendations drawn from data available only as abstracts were provisionally graded, pending the publication of the full papers. The quality of evidence and strength of recommendation were graded according to the IDSA grading system (Table 1).

Recommendations

AML

Patients with AML or myelodysplastic syndrome (MDS) who undergo successive cycles of myelosuppressive chemotherapy (e.g. cytarabine plus an anthracycline) have multiple risk factors for developing IFD, including, but not limited to, advanced age, prolonged and profound neutropenia and monocytopenia, use of purine analogues (e.g. fludarabine), the presence of indwelling catheters, alimentary mucositis and individual genetic susceptibilities.[17] Moreover, recently identified pre-admission factors in AML patients, such as COPD, profession-related or hobby exposure to fungal pathogens, the lack of HEPA filtration, influenza H1N1 infection and a lack of response to induction chemotherapy may further increase the risk.[18,19] A clear epidemiological shift towards mould infections has also been observed worldwide following the introduction of fluconazole prophylaxis in the early 1990s. *Aspergillus* has become the dominant species in Europe with the incidence of invasive aspergillosis in AML ranging from 5% to 24%, while rates of candidaemia are <2%.[20] In a European multicentre prevalence study (the PIMDA Audit involving 17 countries), the overall rate of proven and probable aspergillosis in patients with AML receiving induction chemotherapy was 8.1%, though considerable variation in

Table 2. Azole prophylaxis in patients with AML

First author, citation and year	Setting	Design of the study (number of patients included in each arm)	Percentage of IFD		Absolute risk reduction of IFD	Percentage of deaths		Absolute risk reduction of death
			control group	experimental group		control group	experimental group	
Winston *et al.*[10] 1993	AML	Placebo ($n = 132$). Fluconazole oral 400 mg q24h or iv 200 mg q12h ($n = 123$).	8	4	0.04	3	1	0.02
Menichetti *et al.*[11] 1999	AML Autologous HSCT	Placebo ($n = 204$). Itraconazole oral solution 2.5 mg/kg q12h ($n = 201$).	4	2	0.02	9	7	0.02
Rotstein *et al.*[28] 1999	AML/MDS Autologous HSCT	Placebo ($n = 151$). Fluconazole oral 400 mg q24h ($n = 153$).	21	6	0.15	10	10	0.00
Harousseau *et al.*[27] 2000	AML/MDS	Placebo plus amphotericin B 2g q24h ($n = 276$).	5	3	0.02	8	6	0.02
	Autologous HSCT	Itraconazole oral solution 2.5 mg/kg q12h plus placebo ($n = 281$).						
Glasmacher *et al.*[26] 2006	AML	Fluconazole oral 400 mg q24h ($n = 246$).	2	2	0.0	3	2	0.01
	Autologous HSCT	Itraconazole oral solution 2.5 mg/kg q12h ($n = 248$).						
Cornely *et al.*[13] 2007	AML/MDS	Fluconazole oral 400 mg q24h or itraconazole oral solution 200 mg q12h ($n = 298$).	8	2	0.06	22	16	0.06
		Posaconazole oral suspension 200 mg q8h ($n = 304$).						

the incidence rate was noted between participating countries and centres.[21]

Given these high numbers, preventative measures have been proposed. Apart from avoiding construction and renovation activities as well as heavily contaminated items (such as potted plants, soil and pepper) and protective isolation in HEPA-filtered rooms to prevent exposure, primary antifungal chemoprophylaxis has been recommended and is now a well-established practice in many European haematology centres.[22,23]

Selection of studies

Given an expected incidence of IFD of around 8%, we considered studies with <200 patients to be underpowered to assess the potential benefit of primary antifungal prophylaxis; therefore, although published, these were not included in our analysis. For randomized studies that used a fluconazole or an itraconazole arm, only those trials that used fluconazole at 400 mg q24h or itraconazole oral solution at 2.5 mg/kg q12h (or iv at 200 mg q12h) were included. The itraconazole capsule formulation yields poor bioavailability and was not significantly different from the respective comparator drugs in three randomized clinical studies.[9,24,25] All studies using any formulation of amphotericin B were evaluated during the previous ECIL meetings and no change was necessary since our previous recommendations, as there is still no standard dose or frequency.[3] Finally, few properly designed studies with echinocandins have been undertaken in this patient population. Moreover there has been no systematic analysis of studies involving only patients with AML/MDS. Table 2 summarizes details of the six studies that were included in our updated analysis.[10,11,13,26–28] Epidemiological surveys have reported much lower incidences (0%–5%) of IFD during consolidation chemotherapy, especially among patients achieving morphological remission, than has been reported during the remission-induction phase, although the intensity of consolidation may impact on this risk.[29] In general, we do not recommend primary antifungal prophylaxis beyond remission-induction chemotherapy (a similar policy was used in a clinical trial[13]), unless patients are to undergo re-induction chemotherapy or intensified consolidation therapy.

ECIL recommendations (Table 3)

Similar to previous ECIL recommendations, azoles are considered the first choice for primary antifungal prophylaxis for patients receiving intensive remission-induction chemotherapy for AML or MDS. Based on the results of a large, though open-label study, posaconazole is the drug of choice (A-I), given either as an oral suspension (200 mg q8h)[13] or as a gastroresistant tablet (300 mg

Table 3. ECIL recommendations on primary antifungal prophylaxis in adult patients with AML and MDS undergoing intensive remission-induction chemotherapy[a]

Antifungal agent	Grading	Comments
Posaconazole oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1	A-I	Recommended if baseline incidence of mould infections is high. Given the increased absorption of the tablet, it is likely that the need for therapeutic drug monitoring will become restricted to specific populations (e.g. severe mucositis).
Fluconazole 400 mg q24h	B-I	Only recommended if the incidence of mould infections is low. Fluconazole may be part of an integrated care strategy together with a mould-directed diagnostic approach.
Itraconazole oral solution 2.5 mg/kg q12h	B-I	Recommended if baseline incidence of mould infections is high. May be limited by drug–drug interactions or patient tolerability. It is recommended to monitor serum drug concentrations.
Voriconazole 200 mg q12h	B-II	Recommended if baseline incidence of mould infections is high. It is recommended to monitor serum drug concentrations.
All echinocandins	C-II	Insufficient data on efficacy and tolerability.
Liposomal amphotericin B	C-II	Insufficient data on dose, frequency and duration, as well as on efficacy and tolerability.
Lipid-associated amphotericin B	C-II	Insufficient data on dose, frequency and duration, as well as on efficacy and tolerability.
Aerosolized liposomal amphotericin B (10 mg twice weekly)	B-I	Only when combined with fluconazole 400 mg q24h.
Amphotericin B deoxycholate	A-II against	
Aerosolized amphotericin B deoxycholate	A-I against	

[a]Primary antifungal prophylaxis might be considered during intensified consolidation therapy (see text).

q24h following a loading dose of 300 mg q12h on the first day)[30] since the rate of proven and probable IFD was reduced from 8% to 2% and the rate of invasive aspergillosis from 7% to 1%.[13] The tablet formulation offers advantages when compared with the oral suspension, including better bioavailability, no clinically relevant food effect, higher serum concentrations and once-daily dosing.[31] Of note, a cyclodextrin-containing iv formulation (300 mg q24h following a loading dose of 300 mg q12h on the first day) is also available.[32] Although it is likely that the need for therapeutic drug monitoring of posaconazole tablets will diminish, it is still recommended until more 'real-life experience' is gained (see recommendations by the ECIL-6 antifungal drug monitoring working group at www.ecil-leukaemia.com). It should also be noted that, although the efficacy of posaconazole prophylaxis was clearly superior to that of fluconazole ($P = 0.001$), the same was not true for prophylaxis with itraconazole ($P = 0.22$).[13] Nevertheless, itraconazole was given only a B-I recommendation because the drug is less well tolerated, evokes more drug–drug interactions and serum levels should be monitored.[11,26,27] There are no large studies of voriconazole prophylaxis among patients with AML/MDS but the drug was given a B-II recommendation for 200 mg q12h based on results inferred from data during the pre-engraftment neutropenic phase in allogeneic HSCT recipients (see below). Finally, in centres with a low incidence of invasive mould disease (i.e. below 8% based on the PIMDA study[21]), fluconazole (400 mg q24h) is still a valid option (B-I), provided it forms part of an integrated care strategy that includes an early mould-directed diagnostic approach combining biomarker screening and imaging.[33] Of note, although the concomitant administration of anthracyclines (doxorubicin, daunorubicin and idarubicin) and azoles is not contraindicated, azole antifungals exhibit selective inhibition of efflux transporters that might alter the transport kinetics of anthracyclines.[34] As the interaction effect is unknown, an anthracycline washout period of 24 h is considered prudent before starting azole prophylaxis.

The recommendations for echinocandins and for iv lipid formulations of amphotericin B remain unchanged because there is still insufficient data on dose, frequency and duration as well as on efficacy and tolerability (C-II).[3] The only exception is aerosolized liposomal amphotericin B (10 mg twice weekly), when given in combination with oral fluconazole (400 mg q24h to prevent yeast infection) (B-I).[35] Finally, we strongly discourage the use of conventional amphotericin B, either as an aerosol (A-I against the use) or as an iv solution (A-II against the use) when lipid formulations are available.

MDSs

While subgroups of MDS patients receive intensive AML-like therapy, with or without allogeneic HSCT, most patients receive only supportive care treatment (transfusions, erythropoiesis-

stimulating agents), lenalidomide (e.g. chromosome 5q deletion) or hypomethylating agents (azacitidine or decitabine). However, these low- and intermediate-risk MDS patients usually present with multiple spontaneous or acquired risk factors of infection, including long-lasting neutropenia and functional neutrophil defects, impairment of B cells, T cells and NK cells with decreased antibody production, (transfusion-related) iron overload and older age-associated comorbidities.[36] Nevertheless, in studies treating MDS patients with hypomethylating agents or lenalidomide, IFD is only rarely mentioned as a complication, or not at all.[36] Vice versa, in three prospective European registries of invasive mould disease, MDS represents only a small fraction of the enrolled haematology population.[37–39] Recently, a retrospective single-centre analysis of 948 courses of azacitidine in 121 consecutive AML/MDS patients reported a low incidence of proven/probable IFD of only 0.21% per azacitidine treatment cycle and 1.6% per patient treated for the whole series, with slightly higher incidences (0.73% and 4.1%, respectively) among patients with severe neutropenia.[40]

Hence, ECIL does not recommend primary antifungal prophylaxis in patients with low-to-intermediate risk MDS (excluding those patients undergoing intensive AML-like induction and/or allogeneic HSCT) as they have a low risk (<2%) of IFD. Moreover, they typically have prolonged neutropenia for months and even years; this would imply a very prolonged prophylaxis, a situation that has been associated with an increased risk of acquired antifungal resistance. Nonetheless, this underscores the need for collecting solid epidemiological data, especially in prospective therapeutic trials.

ALL

An IFD rate of 6.5% has been reported in the retrospective SEIFEM-2004 analysis of 1173 adults undergoing treatment for ALL with invasive aspergillosis and candidiasis being most frequent.[41] Given the retrospective nature of the analysis and the complexity of diagnosing IFD, the true incidence may well be underestimated. While prophylaxis with azole antifungals has become a standard of care for other patient groups at similar risk (e.g. AML), there is currently no approved standard of care for patients with ALL. Moreover, the European Working Group for Adult ALL (EWALL) recommends against the use of mould-active azoles because of potentially hazardous neurotoxic interactions with *Vinca* alkaloids, a key component of the antineoplastic polychemotherapy.[42] In the absence of convincing efficacy and toxicity data, cautious use of fluconazole prophylaxis to prevent yeast infections may be considered (C-III).

Chronic myeloproliferative neoplasms (MPNs)

Based upon a few recent epidemiological studies, there appears to be no increased risk of IFD in patients with CML treated with tyrosine kinase inhibitors (TKIs) or in other conventionally treated MPN patients.[43] Primary antifungal prophylaxis is therefore not recommended. However, MPN patients who are undergoing intensive AML-like chemotherapy for accelerated/blast phases or who are receiving an allogeneic HSCT should be managed according to the respective guidelines. Of note, drug interactions with azole antifungals need to be considered in patients who develop an IFD while receiving TKIs.[44]

Multiple myeloma

Patients with myeloma tend to have several risk factors for developing IFD, including the frequent use of high doses of corticosteroids (and resulting hyperglycaemia), myeloma-related innate immunodeficiency involving various arms of the immune system, disease-related comorbidities (e.g. renal insufficiency) and poor marrow function when heavily pre-treated.[45] Nevertheless, although case series of IFD have been described, several large epidemiological studies and prospective registries uniformly reported very low incidences (<1%) of yeast and mould infections among those receiving conventional combination chemotherapy.[37–39,41]

In recent years, the treatment of myeloma has undergone major changes with immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies and autologous HSCT becoming the new standard of care. No prospective studies have specifically addressed the problem of IFD among patients receiving these novel agents but a recent retrospective study of a cohort of 372 Australian patients recorded an overall low rate of 2.4% with an invasive mould infection rate of 0.8%.[46] These rates are comparable to those reported in other studies during the last decade.

The introduction of novel life-prolonging therapies has transformed myeloma from an 'acute' to a chronic disease with the resultant cumulative exposure to several lines of these immunosuppressive treatments increasing the risk of fungal infection as well as expanding the spectrum of potential opportunistic pathogens.[47] However, the overall incidence remains low (<2%).[46] Consequently, pending further epidemiological data, primary antifungal prophylaxis is not recommended for patients being treated for myeloma.

CLL

Patients with CLL are prone to infections because of both the disease-associated humoral immunodeficiency (related to stage and duration of disease) and the additional immunosuppression resulting from therapy with corticosteroids, cytotoxic drugs (alkylating agents and purine analogues), monoclonal antibodies (rituximab, alemtuzumab, ofatumumab and obinutuzumab), lenalidomide and kinase inhibitors (ibrutinib and idelalisib).[48] Most patients develop bacterial or viral infections rather than IFD.[48] Epidemiological data on fungal infections (excluding *P. jirovecii*) are scarce.[37,38,41,43,49,50] A retrospective multicentre Italian study (SEIFEM-2004) reported an IFD incidence rate of 0.5%.[41] Given this low attack rate, primary antifungal prophylaxis is not recommended, although it might be considered for patients with prolonged neutropenia (>6 months), elderly patients and those with advanced and unresponsive CLL disease. However, long-term toxicity and selection pressure are important issues, especially given the very protracted suppressed immunity.

Lymphoma

Patients with lymphoma tend to be at low risk of IFD. In the aforementioned SEIFEM-2004 study, including 844 patients with

Table 4. ECIL recommendations on primary antifungal prophylaxis in adult allogeneic HSCT recipients: pre-engraftment period

	Pre-engraftment risk of mould infections	
Antifungal agent	low	high
Fluconazole 400 mg q24h	A-I	
Posaconazole oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1	B-II	B-II
Itraconazole oral solution 2.5 mg/kg q12h	B-I	B-I
Voriconazole 200 mg q12h	B-I	B-I
Micafungin 50 mg q24h	B-I	C-I
Caspofungin and anidulafungin	no data	no data
Liposomal amphotericin B	C-II	C-II
Aerosolized liposomal amphotericin B (10 mg twice weekly) plus fluconazole 400 mg q24h	C-III	B-II
Fluconazole 400 mg q24h		A-III against

Hodgkin's disease and 3475 patients with non-Hodgkin's disease, the incidence of IFD was 0.7% and 1.6%, respectively.[41]

Autologous HSCT

Patients undergoing autologous HSCT, for whatever underlying condition, are at low risk of IFD. Primary antifungal prophylaxis is not recommended, although fluconazole (400 mg q24h) should be considered to prevent mucosal *Candida* infection during the neutropenic phase (B-III).[50–53]

Allogeneic HSCT

In line with the ECIL-3 recommendations, the working group again proposed to provide phase-specific recommendations for HSCT. Indeed, recently, the Italian HSCT group described different risk factors for IFD during the pre- and post-engraftment period. Active leukaemia, cord blood transplantation and prior fungal infection are major risk factors during the pre-engraftment period.[54] In addition, alternative donor HSCT recipients with at least one of the following factors [iron overload, early or recurrent cytomegalovirus infection, acute graft-versus-host disease (GvHD), delayed engraftment (more than 3 weeks neutropenia), high dose corticosteroids (2 mg/kg or more) for more than 1 week] are at high risk of IFD during engraftment.[54] However, centres that perform a high number of low-risk HSCT transplants may still have a low incidence of fungal infections primarily involving moulds. This serves to emphasize that centres offering allogeneic HSCT should know their own incidence and epidemiology of IFD and be aware that construction works may alter environmental exposure.[55]

With regard to the post-engraftment phases, acute and chronic GvHD historically represent major risk factors for IFD. However, it should be emphasized that GvHD in itself is not an indication for mould-active prophylaxis. A subanalysis revealed significantly different risk profiles: grade III–IV acute GvHD, grade II acute GvHD of alternative donor transplants, GvHD unresponsive to standard corticosteroid therapy and acute GvHD followed by chronic GvHD have all been identified as high-risk conditions for mould infection. Conversely, in patients with grade II GvHD responsive to steroid therapy after an HLA-compatible sibling donor transplant and in those with chronic GvHD not preceded by acute GvHD, the risk of IFD was significantly lower.[54] In addition, secondary neutropenia and recurrent cytomegalovirus infections in an alternative donor HSCT should be considered as high-risk conditions after engraftment.[54] Finally, increasing age (>40 years) is an additional risk factor for mould infections in patients with acute GvHD receiving steroids.[56]

Pre-engraftment period (Table 4)

Fluconazole (400 mg/day) is still recommended for centres with a low incidence of mould infections (i.e. below 5%, the reported incidence in allogeneic HSCT in the PIMDA audit[21]) but only when combined with a mould-directed diagnostic approach (biomarker and/or CT scan-based) or a mould-directed therapeutic approach (empirical antifungal therapy) (A-I).[33] Centres with a higher incidence of mould infections should adopt an alternative approach (A-III).

Voriconazole had been given a provisional A-I recommendation for primary antifungal prophylaxis in allogeneic HSCT at ECIL-3 before the full publication of the studies of Wingard *et al.*[14] and Marks *et al.*[57] However, the first study (voriconazole versus fluconazole) ultimately failed to show a difference in fungal-free survival, overall survival, incidence of IFD, invasive aspergillosis, empirical use of antifungals and toxicity between study arms.[14] In addition, the majority of the study population consisted of low-risk HSCT recipients. The second study (voriconazole versus itraconazole oral solution following 2 days of iv loading) showed the superiority of voriconazole for the primary composite endpoint. Although there was no difference in incidence of proven/probable invasive fungal infection (IFI; 1.3% versus 2.1%) or survival to day 180 (81.9% versus 80.9%) for voriconazole and itraconazole, respectively, voriconazole was better tolerated and could be given for significantly longer durations, with less need for other systemic antifungals.[57] The low rate of proven and probable fungal diseases was another concern. Therefore, the provisional recommendation was changed to B-I.

Itraconazole (200 mg iv q24h, followed by oral solution 200 mg q12h versus fluconazole) provided better protection against invasive mould infections with similar protection against candidiasis. There was no difference in fungal-free or overall survival. However,

Table 5. ECIL recommendations on primary antifungal prophylaxis in adult allogeneic HSCT recipients: post-engraftment period

Antifungal agent	High risk GvHD
Posaconazole oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1	A-I[a,b]
Itraconazole oral solution 2.5 mg/kg q12h	B-I[b]
Voriconazole 200 mg q12h	B-I[b]
Micafungin 50 mg q24h	C-II
Caspofungin and anidulafungin	no data
Liposomal amphotericin B	C-II
Aerosolized liposomal amphotericin B (10 mg twice weekly) plus fluconazole 400 mg q24h	no data
Fluconazole 400 mg q24h	A-III against

[a]No difference with placebo was seen in patients with chronic GvHD.[59]
[b]It is recommended to monitor serum drug concentrations.

drug toxicities and tolerability limited its usefulness as a prophylactic agent (B-I).[12]

Although there are no specific large, prospective studies of posaconazole prophylaxis during the pre-engraftment phase, the drug (oral solution 200 mg q8h or gastroresistant tablet/iv formulation 300 mg q24h following a loading dose of 300 mg q12h on the first day) was given a B-II recommendation based on results inferred from data during the neutropenic phase in AML/MDS patients.[13]

Data for the echinocandins are limited to micafungin (50 mg iv q24h). The study comparing micafungin versus fluconazole had significant shortcomings, including the overrepresentation of a low-risk population (resulting in an unusually low incidence of fungal infections) and the lack of a pre-defined work-up for diagnosing IFD.[58] Hence, prophylaxis with micafungin has been given a B-I recommendation for centres with a low incidence of mould infections and C-I recommendation for those with a high incidence.

The addition of aerosolized liposomal amphotericin B to fluconazole is not recommended for centres with a low incidence of mould infections (C-III), although there is some evidence to do so in higher risk centres (B-II).[35] Iv liposomal amphotericin B for prophylaxis was given a C-II recommendation.

Post-engraftment period (Table 5)

Given the significantly increased risk of invasive mould infection during GvHD (and its associated high mortality), we strongly recommend against the use of fluconazole for prophylaxis in patients with high-risk GvHD (A-III).

Based on the results of a large, double-blind study, posaconazole (oral solution or gastroresistant tablet/iv formulation) is the drug of choice for antifungal prophylaxis (A-I).[59] However, no difference is observed in patients with (limited or extensive) chronic GvHD.[59]

The C-II recommendation for micafungin is based on the low number of patients with GvHD in the randomized study and the low incidence of mould infections.[58] There are no data available for caspofungin and anidulafungin.

Iv liposomal amphotericin B is given a C-II recommendation and, as there are no data available, we offer no recommendation for aerosolized liposomal amphotericin B plus fluconazole for this phase of transplant.

Discussion

In light of the constantly changing fungal epidemiology and the availability of new clinical data, ECIL aims to update its guidelines for antifungal prophylaxis regularly based on the best available data. ECIL-5 also adopted a different grading system from that used in the previous version published in 2011, allowing only three levels for grading the strength of the recommendation.

This updated version now provides recommendations for antifungal prophylaxis for wider groups of adults with haematological malignancies who are nonetheless considered to be at lower risk of IFD. Primary anti-mould prophylaxis is not recommended for patients suffering from myeloma, lymphoma, CLL, myelodysplastic disorders and chronic MPNs, even for those undergoing autologous HSCT (see specific recommendations for patients undergoing AML-like therapy and allogeneic HSCT). Nevertheless, fluconazole may be used to prevent mucosal yeast infections. This recommendation is based on the low incidence of IFD (usually <2%) reported in retrospective studies and a handful of prospective epidemiological surveys and registries. However, there is a real need for heightened awareness and vigilance to identify any changes in fungal epidemiology in view of the rapidly growing availability of novel therapeutic agents with immunosuppressive characteristics, mainly introduced for treating myeloma and lymphoproliferative disorders. For instance, in a recent French multicentre study on invasive aspergillosis, chronic lymphoproliferative disorders were the second most common underlying haematological disorder after acute leukaemia.[5] This could have been explained by the much higher frequency of lymphoproliferative disorders when compared with acute leukaemia in the general population but this observation should encourage a higher level of vigilance in this population who benefit from new therapeutic immunosuppressive approaches.

Although adults with ALL undergoing remission-induction therapy carry a significant risk of IFD, there is currently no approved primary antifungal prophylaxis for these patients. Mould-active azoles (itraconazole, voriconazole and posaconazole) should be avoided; these inhibit the metabolism of vincristine, leading to excess *Vinca* alkaloid exposure and severe neurotoxicity (including gastrointestinal toxicity, peripheral and autonomic neuropathy and seizures).[42] Following ECIL-5, results of a large, double-blind, randomized study, comparing liposomal amphotericin B 5 mg/kg

or placebo twice weekly during remission-induction therapy in adult ALL patients have been reported.[60] The IFD rate was 11.7% in the placebo arm and was not statistically significantly lower among those given liposomal amphotericin B (7.9%, $P = 0.24$).[60] However, until ECIL has had the opportunity to digest the full paper no recommendation has yet been given for prophylaxis with liposomal amphotericin B in these patients.

Recently, isavuconazole was approved for the treatment of invasive aspergillosis and mucormycosis. In the absence of studies, no recommendation can be given for its use in the prevention of fungal disease, although this compound carries some attractive features, including a better drug-interaction profile compared with other mould-active azoles.[61]

As previously mentioned, uncertainty about exposure and drug interactions are common when using azole antifungals. Therapeutic drug monitoring for voriconazole (plasma target 1 to 6 mg/L for prophylaxis) and posaconazole (plasma target >0.7 mg/L for prophylaxis) is therefore recommended (see recommendations by the ECIL-6 antifungal drug monitoring working group at www.ecil-leukaemia.com).

In 2014, 6 months after the ECIL-5 meeting, the Fungal Infection Study Group of ESCMID/European Confederation of Medical Mycology (EFISG/ECMM) presented a draft version of their guidelines on the management of *Aspergillus* diseases at their annual meeting.[62] Members of the ECIL-5 working party or plenary group also participated in the EFISG/ECMM endeavour and vice versa. At first glance, marked differences were noted when comparing both sets of recommendations of primary antifungal prophylaxis in haematology. However, following an in-depth analysis of both proposals, there appears to be good overall agreement. Minor incongruities were related to the use of a different, and more detailed, grading system by EFISG/ECMM including a different way of assigning the strength of recommendation. There were also differences in the approach towards specific patient populations (e.g. ECIL discriminates allogeneic HSCT recipients at low risk from those at high risk of mould infection). Also, EFISG/ECMM tended to provide a recommendation according to a specific intention (reduction of the incidence of IFD or reduction of mortality) whereas ECIL offers a more comprehensive recommendation. Finally, ECIL had decided to cover key aspects of the clinical management of fungal disease as standalone topics; for instance, the need for therapeutic drug monitoring has been extensively discussed at the most recent meeting (2015) and, pending the full publication, recommendations have been posted on www.ecil-leukaemia.com.

Finally, ECIL hopes it has maintained a good balance between scientific rigour on the one hand and clinical pragmatism on the other to reflect the fact that guidelines are intended to deal with commonly anticipated risks to patient populations rather than being a recipe suited to every individual case. The guidelines are offered as a guide to help physicians recognize the myriad of risks their patients face and take effective measures whenever possible so as to reduce those risks.

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