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REVIEW ARTICLE OPEN

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Primary antifungal prophylaxis in hematological malignancies. Updated clinical practice guidelines by the European Conference on Infections in Leukemia (ECIL)

Livio Pagano[1,2]✉, Georg Maschmeyer[3], Frederic Lamoth[4], Ola Blennow[5,6], Alienor Xhaard[7], Manuela Spadea[8,9], Alessandro Busca[10], Catherine Cordonnier[11], Johan Maertens[12] On behalf of ECIL*

At the 10th European Conference on Infections in Leukaemia (ECIL), the guidelines for antifungal prophylaxis in pediatric and adult patients with hematological malignancies (HM) were updated and some changes introduced. Regarding acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) patients undergoing remission induction chemotherapy, a B-II grading has been assigned to isavuconazole, micafungin, and caspofungin, based on non-randomized studies that have shown efficacy in preventing invasive fungal diseases (IFD). Regarding high-risk MDS patients treated with azacytidine, prophylaxis with posaconazole during the first four cycles of treatment is supported in the literature. Prophylaxis is not indicated in patients treated for myeloproliferative neoplasms (NPM), acute lymphoid leukemia (ALL), and Hodgkin lymphoma (HL). For patients with chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL), prophylaxis is not generally indicated. For patients with multiple myeloma (MM), prophylaxis is not indicated and the limited epidemiological data available do not support the use of prophylaxis in subjects treated with bispecific antibodies. For patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT), no substantial changes were made, apart from the addition of isavuconazole with grading B-II in the post-engraftment period. In patients undergoing auto-HSCT, antifungal prophylaxis is not indicated. Previous ECIL guidelines did not include CAR-T cells. The expert panel proposes to endorse the use of anti-mold prophylaxis in high-risk patients during pre-infusion and post-infusion, while in low-risk patients, anti-yeast prophylaxis can be recommended (B-II). For pediatric hematology patients, based on newly published data, caspofungin received a B-I grading as mold-active prophylaxis. Moreover, patients with ALL with insufficient treatment response during induction therapy, and children older than 12 y.o are now considered at high risk for IFD and are recommended to receive antifungal prophylaxis.

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INTRODUCTION

In 2005, the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the European Leukemia Net (ELN), and the International Immunocompromised Host Society (ICHS) inaugurated the European Conference on Infections in Leukemia (ECIL). Its main goal was to establish guidelines or recommendations for the management of infections due to bacteria, viruses, parasites, and fungi in patients with leukemia and in patients undergoing hematopoietic stem cell transplantation (HSCT) [1]. The prevention of invasive fungal disease (IFD) has been one of the key topics from the beginning [1, 2].

The ECIL committee aims to update their guidelines regularly based on current available evidence. During the fifth and sixth meetings (2013 and 2015), guidelines on antifungal prophylaxis for adults were extensively revised, and during the ninth meeting (2021) recommendations for antifungal prophylaxis in pediatrics were developed [1, 3].

An update of previous recommendations was already done in 2018 [4], but over the last few years, several new antineoplastic drugs have been introduced into clinical practice for all hematological malignancies (i.e. BCL-2 inhibitors, FLT-3 inhibitors in acute myeloid leukemias, Bruton Tyrosine Kinase inhibitors (BTKIs) other new tyrosine kinase inhibitors (TKIs), bispecific

[1]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Università Cattolica del Sacro Cuore, Roma, Italia. [2]Divisione di Ematologia Geriatrica ed Emopatie Rare, Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Roma, Italia. [3]Charité University Hospital Berlin, Berlin, Germany. [4]Infectious Diseases Service and Institute of Microbiology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. [5]Department of Infectious Diseases, Karolinska Universitetssjukhuset, Stockholm, Sweden. [6]Department of Medicine, Karolinska Institutet, Stockholm, Sweden. [7]Hematologie greffe, hopital Saint-Louis, APHP, Universite Paris Cite, Paris, France. [8]Department of Pediatric and Publich Health Sciences, University of Turin, Turin, Italy. [9]Regina Margherita Children's Hospital, Turin, Italy. [10]Trapianto Cellule Staminali, AOU Citta' della Salute e della Scienza, Turin, Italy. [11]University Paris-Est Créteil, 94000 Créteil, France. [12]Department of Haematology, Department of Microbiology, Immunology and Transplantation, University Hospitals Leuven, Leuven, Belgium. *A list of authors and their affiliations appears at the end of the paper. ✉email: livio.pagano@unicatt.it

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Table 1. Evidence-based medicine grading system according to the European Society for Clinical Microbiology and Infectious Diseases (ESCMID).

Strength of recommendation (SoR)	
Grade	Definition
A	ECIL strongly supports a recommendation for use
B	ECIL moderately supports a recommendation for use
C	ECIL marginally supports a recommendation for use
D	ECIL supports a recommendation against use
Quality of evidence (QoE)	
Level	Definition
I	Evidence from at least 1 properly designed randomized, controlled trial (orientated on the primary endpoint of the trial)
II	Evidence from at least 1 well-designed clinical trial (including secondary endpoints), without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
Added index for source of level II evidence	
Index	Source
r	Meta-analysis or systematic review of randomized controlled trials
t	Transferred evidence, that is, results from different patient cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trial
a	Published abstract (presented at an international symposium or meeting)

monoclonal antibodies). In addition, new cellular therapy procedures, such as chimeric-antigen receptor T (CAR-T) cell treatments, are now increasingly used. Therefore, at the ECIL-10 meeting in September 2024, a detailed review of the recent literature was conducted, with the agreed proposals summarized in this review.

METHODOLOGY

The methodology of the ECIL conferences has previously been reported [1, 3].

A working group of experts in the field was nominated several months in advance of the biennial conference and was charged with reviewing the literature published since the last update of the guidelines.

A literature review was performed using the PubMed database for publications up from September 2015 and the working group co-authoring this manuscript reviewed all publications identified. 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 EBM grading system of ESCMID (Table 1) [5].

The working group compiled a slide set discussed in several consecutive online group meetings and electronic communication until two weeks before the ECIL-10 plenary meeting held on September 20th, 2024. The final slide set, approved by all group members, was sent by email to all ECIL-10 participants before the plenary. On the day of the meeting (September 20, 2024), the slides were presented by the working group and interactively discussed during a plenary session. The comments made during the plenary discussion were reviewed by the members of the working group in a closed session and recommendations revised accordingly.

The final set of recommendations was thereafter discussed with the ECIL-10 plenary until consensus was reached.

The approved slide set was published on the ECIL website (https://ecil-leukaemia.com/en/resources/resources-ecil), with comments invited for over a month (November 2024). All members of the working group then approved the final set of recommendations.

The final manuscript has been written and revised by all co-authors.

ACUTE MYELOID LEUKEMIA (AML)

Two new major issues have been addressed since the publication of the previous ECIL guidelines on antifungal prophylaxis [4].

Oral isavuconazole has been studied for primary antifungal prophylaxis in 65 patients undergoing remission induction chemotherapy in an open-label phase II study [6]. One patient developed a proven IFD and another 3 a probable IFD. When compared with posaconazole and voriconazole in a retrospective analysis of 277 patients with newly diagnosed AML, the incidences of breakthrough IFD were 2.9% for posaconazole, 4.8% for voriconazole, and 5.7% for isavuconazole ($p = 0.55$) [7]. While isavuconazole is not approved for antifungal prophylaxis in Europe (nor in the United States), the expert panel consider that isavuconazole may be considered for antifungal prophylaxis in selected adult patients undergoing remission induction therapy for AML and for whom posaconazole is not appropriate (e.g., liver function abnormalities, QTc prolongation, drug-drug interactions, intestinal absorption issues).

The benefit from systemic antifungal prophylaxis in patients undergoing consolidation chemotherapy for AML was retrospectively analyzed in a large SEIFEM study [8]. Among 2588 adult and pediatric patients, invasive aspergillosis was diagnosed in 34/1137 (2.9%) patients receiving no antifungal prophylaxis, compared with 22/1451 (1.5%) patients who were given antifungal prophylaxis ($p = 0.01$). The number needed to treat to prevent one invasive aspergillosis was 71 patients [8]. Systemic antifungal prophylaxis has been given a B-IIu recommendation for AML patient undergoing consolidation chemotherapy.

For patients undergoing AML treatment with one of the newer systemic agents such as venetoclax, FLT3 inhibitors, or ivosidenib,

the recommendations on indications and the proper selection of agents for systemic antifungal prophylaxis, as given by the ECIL-9 guideline [9], are reinforced by the present updated guideline. Recommendations for appropriate dose adjustments in case of relevant pharmacological drug-drug interactions were thereby addressed as well.

Beyond these issues, the grading of recommendations has been modified for itraconazole (from B-I to C-I) and micafungin (from C-II to B-II), and a recommendation for "super bioavailable" (SUBA)-itraconazole has been added (C-II).

In comparison to posaconazole, itraconazole was shown to be less effective and less reliable concerning drug levels than posaconazole in AML patients [10, 11]. As SUBA-itraconazole has become available, "classic" itraconazole has been slightly downgraded (C-I).

SUBA-itraconazole has been clinically investigated for pharmacokinetics, tolerability, and safety in several cohort studies including patients with hematologic malignancies and allogeneic HSCT recipients as well as solid organ transplant recipients [12, 13].

In our former recommendations, echinocandins as a group were graded as "C-II", because of their narrower spectrum of antifungal activity when compared to amphotericin B and most triazoles, and sparse clinical data on their use as antifungal prophylaxis in patients with hematologic malignancies. As more detailed data for the efficacy and safety of micafungin are now available for AML and myelodyplastic syndromes (MDS) patients as well as for allogeneic HSCT recipients, micafungin has now been upgraded to B-II [14–16].

Table 2 shows the new recommendations compared to those suggested during ECIL-5.

Myelodysplastic Syndromes (MDS)

For patients with low-risk MDS receiving transfusion-supportive treatment or treated with growth factors (i.e. erythropoietin), no increased risk of IFD has been reported, and therefore no antifungal prophylaxis is indicated (D-I). The introduction of luspatercept does not change this recommendation. The COMMANDS study comparing luspatercept versus erythropoietin which enrolled over 600 patients, did not report any case of IFD [17].

For patients with high-risk MDS receiving intensive AML-like induction (and consolidation) chemotherapy treatment, the recommendation to administer antifungal prophylaxis has not changed (A-I) [4]. The situation is different for intermediate and high-risk patients receiving treatment with azacytidine. A review of the literature in recent years shows an increased risk of IFD, especially during the first 4 cycles of treatment with an incidence ranging from 3% to 12% [18]. When antifungal prophylaxis was administered in most patients, the rate of IFD was 3-8% [18–20], while in series where the proportion of patients receiving antifungal prophylaxis was very low, the rate of IFD rised to 8-12% [21–27]. The new recommendation for these patients is therefore to use antimold prophylaxis during the first 4 cycles of azacytidine treatment (B-IIu).

CHRONIC MYELOPROLIFERATIVE NEOPLASMS

Regarding patients with chronic myeloid leukemia treated with TKIs (imatinib, dasatinib, nilotinib, ponatinib, asciminib) and Philadelphia chromosome-negative myeloproliferative neoplasms, including those treated with ruxolitinib [28–34] an increased risk of IFD is not reported and antifungal prophylaxis is not indicated (D-I).

Table 3 shows the new recommendations compared to those suggested during ECIL-5.

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Adults with ALL are usually treated with an intensive polychemotherapy regimen inducing prolonged neutropenia and receive corticosteroids. Therefore, these patients are at risk of developing IFD. The incidence of IFD in this population varies between 4 and 18%, which is rather similar compared to that observed in AML [35]. Although TKIs (e.g. imatinib, nilotinib, ponatinib) used for the treatment of Philadelphia chromosome-positive ALL have been associated with IFD, the actual IFD incidence seems to be low (< 1%) [36]. Novel specific monoclonal antibody therapies used for ALL (e.g. blinatumomab, inotuzumab ozogamicin) have not been associated with a higher IFD incidence compared to the standard of care in randomized controlled trials [37, 38].

Antifungal prophylaxis in this population is hampered by the drug-drug interaction between triazoles and vincristine, an important component of most ALL chemotherapy regimens. Concomitant use of triazoles may result in increased vincristine-related neurotoxicity because this later drug is metabolized by the CYP3A4 cytochrome. Studies in children with ALL suggest a significantly higher risk of vincristine-related neurotoxicity with voriconazole or itraconazole, while the use of fluconazole seems to be safer [39, 40]. However, data on adults are lacking. Studies assessing the efficacy of antifungal prophylaxis in ALL adult patients for the prevention of IFD are heterogeneous and scarce [41–43]. One randomized controlled study failed to demonstrate the benefit of twice weekly intravenous liposomal amphotericin B (5 mg/kg) versus placebo with a higher incidence of drug-related adverse events in the treatment arm [44].

Antifungal prophylaxis with a mold-active triazole, such as voriconazole or posaconazole, is not recommended because of interactions which could increase the toxicity of vincristine (D-II). Although data are still lacking, isavuconazole might be considered with caution, considering its lower inhibitory effect on CYP3A4 (C-III). Similarly, fluconazole might be considered with caution for prevention of yeast infection (C-III). Alternative anti-mold prophylaxis (e.g. liposomal amphotericin B, echinocandins) might be considered in high-risk patients (i.e. prolonged chemotherapy-induced neutropenia), but no benefit has been shown to date. No antifungal prophylaxis is recommended for ALL patients receiving only TKIs (D-III) (Table 4).

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

The incidence of IFD in patients with CLL is overall low (0.5 to 3%) and varies according to the type of treatment [45–48]. These patients present with a large and diverse spectrum of immunosuppression, from untreated patients with different degrees of neutropenia, patients treated with corticosteroids, anti-BCL2 (e.g. venetoclax), or BTKIs (e.g. ibrutinib). Treatment with ibrutinib or other BTKIs is associated with the highest IFI incidence in this population (2 to 3%) [46, 49, 50]. One small retrospective analysis showed a significantly lower IFD incidence among ibrutinib-treated CLL patients receiving antifungal prophylaxis (mainly fluconazole) versus no prophylaxis [51].

Antifungal prophylaxis is not routinely recommended in CLL patients (D-III) but may be considered in selected refractory cases with prolonged neutropenia or BTKIs therapy (C-II). In the case of co-administration of venetoclax, antifungal prophylaxis should be avoided or used cautiously because of drug-drug interactions (i.e. adjustment of venetoclax dosing is needed with therapeutic drug monitoring of the antifungal agent) (Table 4).

MYELOMA

Reported IFD incidences in myeloma patients treated with conventional chemotherapy combinations have been low (< 1%) despite the presence of risk factors for IFD such as high doses of corticosteroids, disease-related comorbidities, myeloma-related innate immunodeficiency and, in treatment-experienced patients, poor marrow function [52]. Since the publication of the previous ECIL guidelines, treatment with combinations of immunomodulatory

Table 2. Recommendations for antifungal prophylaxis in patients with AML receiving intensive remission induction/reinduction chemotherapy.

Intention	Intervention	SoR	QoE	ECIL 5-6
Prevent IFD in AML patients, excluding allogeneic HSCT	posaconazole, tablet 300 mg q24h p.o. (q12h on day 1)	A	I[1]	A-I
	amphotericin B, liposomal, inhalation[*2,3] 10 mg twice weekly	B	I	B-I
	fluconazole[4] 400 mg q24h, p.o. or i.v.	B	I	B-I
	voriconazole 6 mg/kg/12 h first day then 4 mg/kg q12h, i.v. or p.o.	B	IIu	B-II
	isavuconazole[2] 200 mg q8h p.o. first 2 days then 200 mg q24h	B	IIt	NR
	micafungin 50 mg q24h i.v.	B	II u,t	NR
	amphotericin B, liposomal, i.v.[2] 1-3 mg/kg q24h	C	II	C-II
	caspofungin[2] 50 mg q24h i.v. (70 mg on day 1, 70 mg q24h in patients >80 kg)	B	IIt	NR
	itraconazole 2.5-7.5 mg/kg q24h i.v. or 200 mg q24h p.o.	C	I	B-I
	SUBA-itraconazole 200 mg q12h p.o.	C	IIt	NR

AML acute myeloid leukemia, *IFD* invasive fungal disease, *HSCT* hematopoietic stem cell transplantation, *NR* No recommendation.
1 = recommendation for AML under remission induction chemotherapy; 2 = no approval for prophylaxis of IFD; 3 = formulation not approved; 4 =Only recommended if the incidence of mold infections is low. Fluconazole may be part of an integrated care strategy together with a mold-directed diagnostic approach.
*Should be combined with systemic fluconazole.
Amphotericin deoxycholate is not approved for prophylaxis and should not be considered due to drug-related toxicity.

Table 3. Recommendations for antifungal prophylaxis in patients with MDS, CML, and MPN.

Population	Intervention	SoR	QoE	ECIL 5-6
MDS low-/intermediate No chemotherapy	Any prophylaxis	D	I	No recommendation
MDS Intermediate/High treated as AML with intensive chemotherapy	posaconazole prophylaxis 300 mg q24 p.o. (q12h on day 1)	A	I	As for AML
MDS Intermediate/High Treated with Azacytidine	posaconazole prophylaxis during the first 4 azacytidine courses	B	IIu	No recommendation
CML Treated with TKIs	Any prophylaxis	D	I	No recommendation
MPN No chemotherapy	Any prophylaxis	D	I	No recommendation
MPN Treated with Ruxolitinib	Any prophylaxis	D	I	No recommendation

MDS Myelodysplastic Syndromes, *CML* Chronic Myeloid Leukemia, *MPN* Myeloproliferative Neoplasms, *AML* acute myeloid leukemia, *TKIs* tyrosine kinase inhibitors.

drugs, proteasome inhibitors, monoclonal antibodies, and autologous HSCT have been the standard of care. While no prospective study specifically reporting on IFD in this setting has been published, retrospective studies have reported a somewhat higher IFD incidence than with conventional chemotherapy, 2.7%, 3.5%, and 5.6%, respectively [46, 53–60]. Recently, two new types of antibody treatments have been introduced, bispecific antibodies activating a T-cell response by binding to both myeloma cells and T-cells, and B-cell binding antibodies conjugated with a cytotoxic compound (antibody-drug compound, ADC). Although neither prospective trials nor retrospective studies of treatment with bispecific antibodies have reported the exact numbers of IFD, their overall incidence after excluding Pneumocystis pneumonia has been low (< 2%) [47, 61–64]. The only registered ADC is belantamab mafotidin, which has now been withdrawn as a single agent but is currently under consideration as part of a combination treatment. The incidence of IFD was not specifically reported in the treatment trials leading to its registration, but the total infection rates were low with a 3% total incidence of pulmonary infections in the largest trial including 218 patients [61]. Routine antifungal prophylaxis is thus not recommended in myeloma patients, regardless of treatment with bispecific antibodies (D-II) (Table 4). Expert panels suggest to consider mold active prophylaxis in high-risk populations such as prolonged neutropenia or prolonged steroid treatment or secondary prophylaxis (no trials).

NON-HODGKIN LYMPHOMA (NHL)

Patients with NHL have an overall low IFD incidence (0.5 to 3%) [46, 47]. The incidence among NHL patients receiving BKTIs (e.g.

Table 4. Recommendations for antifungal prophylaxis in patients with ALL, CLL, NHL, HL and MM.

Population		Intervention	SoR	QoE	ECIL 5-6
ALL	TKIs	Any prophylaxis	D	III	No data
	Chemotherapy including vincristine	posaconazole voriconazole	D	II	Against
		isavuconazole 200 mg q8h p.o. first 2 days then 200 mg q24h	C	III	No data
		Fluconazole 400 mg q24h, p.o. or i.v.	C	III	C-III
CLL	Conventional treatment	Any prophylaxis	D	III	No recommendation
	Refractory treated BTKIs and/or venetoclax	Mold-active prophylaxis	C	II	No recommendation
NHL	Treated with chemotherapy	Any prophylaxis	D	II	No recommendation
	Refractory treated BTKIs or high doses steroids	Mold-active prophylaxis	C	II	No recommendation
	Treated with Bispecific antibodies	Any prophylaxis	D	II	No data
HL	Treated with chemotherapy	Any prophylaxis	D	II	No recommendation
MM	Treated with IMiDs	Any prophylaxis	D	II	No recommendation
	Treated with Bispecific antibodies	Any prophylaxis	D	II	No data

ALL Acute Lymphoblastic Leukemia, *CLL* Chronic Lymphocytic Leukemia, *NHL* non-Hodgkin's Lymphoma, *HL* Hodgkin's Lymphoma, *MM* Multiple Myeloma, *BTKIs* Bruton tyrosine kinase inhibitors; *IMiDs* immunomodulatory drugs.

ibrutinib) is roughly similar (about 1.5%) [49]. Some factors have been associated with a higher risk of IFD, such as primary refractoriness, use of two or more previous treatment lines, and occurrence of neutropenia [62].

Antifungal prophylaxis is not routinely recommended in patients with NHL (D-II) but might be considered in selected patients with refractory lymphoma and/or repeated intensive chemotherapies with neutropenia or high dose steroids or BTKI therapy (C-II) (Table 4).

HODGKIN LYMPHOMA (HL)

The risk for IFD tends to be low in patients with Hodgkin lymphoma. Two recent nationwide epidemiological studies in hospitalized HL patients reported a total IFD incidence of 0.5% in Australia and a 0.5% incidence of pulmonary aspergillosis in Spain [47, 63]. In line with previous recommendations, routine antifungal prophylaxis is not recommended (D-II) (Table 4).

ALLOGENEIC HSCT (ALLO-HSCT)

The main practice change since the previous ECIL recommendations [4] has been the development of haplo-identical allo-HSCT using post-transplantation cyclophosphamide (haplo/PTCy) as graft-versus-host-disease (GVHD) prophylaxis. Retrospective studies on haplo/PTCy allo-HSCT report a one-year incidence rate of IFD ranging from 6 to 17% [64–68]. In two retrospective studies, the IFD incidence (especially invasive mold infections) was significantly higher in haplo/PTCy than in patients transplanted from HLA-matched related and/or unrelated donors receiving calcineurin inhibitors with or without anti-thymocyte globulin (ATG) [66, 67]. However, as the reported IFD rates remained within the range of those in post allo-HSCT outside of the haplo/PTCy setting, haplo/PTCy was still considered at low risk of IFD by the expert panel. As previously highlighted, [4] allo-HSCT centers should monitor the incidence and epidemiology of IFD and be aware that construction works may alter environmental exposure, which may warrant local adaptation of primary antifungal prophylaxis strategy.

The use of isavuconazole as primary antifungal prophylaxis in allo-HSCT recipients has been reported in two prospective open-label studies [69, 70]. The reported rates of breakthrough IFD were low (3–5%) while the treatment was well tolerated (discontinuation rate for toxicity: 2–7%). Data are insufficient to recommend isavuconazole as first-line prophylaxis; however, the expert panel proposes to endorse the ASTCT (American Society of Transplantation and Cellular Therapy) recommendations allowing the use of isavuconazole in cases of QT prolongation, or intolerance to voriconazole or posaconazole (B-II) [71].

In Tables 5 and 6, the main changes in antifungal prophylaxis recommendation are reported (with two additional references in Table 5 [72, 73]).

ANTI-CD19 CHIMERIC ANTIGEN RECEPTOR (CAR) T CELLS

Previously published ECIL guidelines did not include CAR-T cells [4]. The EBMT/JACIE (Joint Acreditation Committee International Society for Cellular Therapy (ISTC) EBMT) and EBMT/ASTCT guidelines recommend the use of an anti-*Candida* prophylaxis and suggest discussing an anti-mold prophylaxis in case of prolonged neutropenia and/or steroid use [74, 75].

Retrospective studies, along with two literature reviews, report a 1–15% incidence of IFD in patients treated with anti-CD19 CAR-T cells [76–80]. These studies highlight a significant association between the occurrence of cytokine release syndrome (CRS) and a higher incidence of infections, attributed to the use of systemic immunosuppressive agents. In the literature review by Garner et al. [80], a combination of pre-and post-infusion factors seemed to increase the risk of IFD. The panel endorses the proposal of Garner et al., published after the EBMT/ASTCT recommendations, and integrating new data not available at the time of publication of the EBMT/ASTCT recommendations. The use of anti-mold prophylaxis is thus proposed to patients with pre-infusion (such as neutropenia, previous IFD, previous allo-HSCT, refractory disease) and post-infusion (CRS/immune effector cell-associated neurotoxicity syndrome [ICANS] necessitating steroid therapy and/or tocilizumab, prolonged neutropenia, use of alternative immunosuppressive agent) risk factors for mold infections, while patients without these risk factors could receiveanti-yeast prophylaxis (B-II) [80].

AUTOLOGOUS HSCT

In the previous ECIL recommendations, patients undergoing autologous HSCT, for whatever underlying condition, were

Table 5. Recommendations for allo-HSCT recipients: pre-engraftment.

Antifungal agent	Pre-engraftment risk of mold infection		ECIL 5-6	
	low	high	low	High
Fluconazole 400 mg q24h	A-I [a]	D-III	A-I [a]	A-III against
Posaconazole tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1 or oral solution 200 mg q8h	B-II	B-II	B-II	B-II
Itraconazole 2.5–7.5 mg/kg q24h i.v. or 200 mg q24h p.o	B-I	B-I	B-I	B-I
Voriconazole 6 mg/kg q12h first day then 4 mg/kg q12h i.v. or p.o.	B-I	B-I	B-I	B-I
Micafungin 50 mg q24h	B-I	C-I	B-I	C-I
Caspofungin and anidulafungin	no data	no data	no data	no data
Liposomal amphotericin B	C-II		C-II	C-II
Aerosolized liposomal amphotericin B (10 mg twice weekly) in combination with systemic fluconazole 400 mg q24h	C-III		C-III	B-II
Isavuconazole 200 mg q24h following a loading dose of 200 mg q8h on days 1 and 2 [b]	B-II	B-II	no data	no data

[a]only when combined with a mold-directed diagnostic approach (biomarker and/or CT scan-based)or a mold-directed therapeutic approach (empirical antifungal therapy).
[b]Isavuconazole can be used as second-line mold active prophylaxis, in case of intolerance to posaconazole / voriconazole, or QTc prolongation.
Pre-engraftment risk of mold infection as previously defined: high risk includes active leukemia, cord blood transplantation and unrelated donor [72]. Haploidentical HSCT using post-transplantation cyclophosphamide should be considered at low risk (B-II) In case of prior IFD, secondary prophylaxis should be tailored according to the previous documentation [73].
HSCT hematopoietic stem cell transplantation.

Table 6. Recommendations for allo-HSCT recipients: post-engraftment.

Antifungal agent	Steroid treated acute GVHD	ECIL 5-6
Posaconazole tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1, or oral solution 200 mg q8h	A-I [a, b]	A-I [a, b]
Itraconazole 2.5-7.5 mg/kg q24h i.v. or 200 mg q24h p.o	B-I [b]	B-I [b]
Voriconazole 6 mg/kg q12h first day then 4 mg/kg q12h i.v. or p.o.	B-I [b]	B-I [b]
Micafungin 50 mg q24h	C-II	C-II
Caspofungin and anidulafungin	no data	no data
Liposomal amphotericin B	C-II	C-II
Aerosolized liposomal amphotericin B (10 mg twice weekly) in combination with systemic fluconazole 400 mg q24h	no data	no data
Fluconazole 400 mg q24h	D-III	D-III
Isavuconazole 200 mg q24h following a loading dose of 200 mg q8h on days 1 and 2 [c]	B-II	no data

After engraftment, in patients without GVHD, fluconazole can be continued until D + 75.
[a] No difference compared with placebo was seen in patients with chronic GVHD.
[b] It is recommended to monitor serum drug concentration.
[c] Isavuconazole can be used as second-line mold active prophylaxis, in case of intolerance to posaconazole/voriconazole, or QTc prolongation.

considered 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) [4]. There are no recommendations for change for autologous HSCT recipients.

PRIMARY ANTIFUNGAL PROPHYLAXIS IN PEDIATRIC HEMATOLOGICAL MALIGNANCIES

Mold-active antifungal prophylaxis is recommended for pediatric patients at high risk of IFD (incidence ≥10%), encompassing a subgroup of children with ALL, though their specific risk profile is less precisely defined [81].

A recent analysis of 6316 children with ALL enrolled in the international AIEOP-BFM ALL2009 trial reported an incidence of proven/probable IFDs at 3.8%, with a 12-week mortality rate of 11.2% [82]. In this cohort, 68% of infections were mold-related, with significant risk factors for IFD being ≥12 years of age and insufficient treatment response. A diagnoses of proven/probable IFD were associated with a elevated hazard ratio for event-free survival and overall survival [82]. Consequently, older children (≥ 12 years) with ALL and those with insufficient treatment response are identified as being at elevated risk for IFD and are now recommended to receive antifungal prophylaxis.

Since the 2021 update by ECIL, advances in pediatric antifungal development have been significant. A recent multicenter, non-randomized, open-label, phase 1b dose-escalation trial demonstrated that posaconazole intravenous solution (IV) and powder for oral suspension (PFS) were well tolerated in children, with safety profiles similar to adults [83]. Following this dose-finding trial, the European Medicines Agency (EMA) approved posaconazole IV and PFS in 2021 for high-risk patients aged ≥2 years and

weighing ≤40 kg, including those with AML/MDS or undergoing HSCT with GVHD [84]. Delayed-release tablets were approved for patients ≥2 years and >40 kg with the same conditions [84], although oral suspension remains unapproved by EMA [85].

Additionally, a prospective, randomized, open-label trial among pediatric allo-HSCT patients found caspofungin to be as effective as voriconazole and other triazoles in preventing IFD, including aspergillosis, with a 1.4% infection rate across both trial arms [86]. Hence, the caspofungin grade of recommendation has been updated to a B-I.

FUTURE PROSPECTS

The characteristics of an 'ideal' agent for antifungal prophylactic use include (a) broad spectrum of activity - covering both yeast and mold pathogens - with low risk of development of resistance, (b) availability in oral and parenteral formulations, (c) low potential for clinically problematic drug-drug interactions, (d) low risk of acute and chronic treatment-limiting toxicities, and (e) predictable pharmacokinetics. Several molecules with antifungal activity with a novel mechanism of action are currently in various stages of clinical development [87]. These new molecules tackle some of the shortcomings of the currently available aramamentarium.

- Rezafungin, a second generation echinocandin with enhanced PK/PD pharmacometrics, is active in vitro against most wild-type and azole-resistant *Candida* species (including C. auris), *Aspergillus* species (including azole-resistant A. fumigatus and cryptic species) and *Pneumocystis jirovecii*. The drug has minimal risk of drug-drug interactions and has recently been approved for the treatment of candidemia and invasive candidiasis [88]. Its prophylactic efficacy and safety, when given intravenously once weekly, is currently being tested in a phase 3 randomized double-blind study versus a standard antimicrobial regimen (including fluconazole/posaconazole plus trimethoprim-sulfamethoxazole) in allo-HSCT recipients (The ReSPECT Study) [89].
- Ibrexafungerp, a first-in-class oral glucan synthase inhibitor (a triterpenoid), is approved for the treatment of recurrent vulvovaginal *Candida* infection. The spectrum of activity is similar to the spectrum of rezafungin, but also includes *Alternaria* and *Cladosporium* species. The drug is generally well tolerated with a low risk for drug-drug interactions [90]. Ibrexafungerp has not yet been studied as prophylactic agent but has the potential for use in primary prophylaxis (similar to rezafungin).
- The fungicidal orotomide olorofim is a potent inhibitor of fungal dihydroorotate dehydrogenase. The drug is given orally, has a good tissue distribution and is generally well tolerated. Although olorofim has activity against a variety of mold pathogens (excluding Mucorales species) and dimorphic fungi, the drug displays no activity against yeast pathogens [91]. As such, olorofim is not a good candidate for primary prophylaxis, but may be used for secondary prophylaxis in patients with well documented prior mold infections (e.g., scedosporiosis or aspergillosis).
- Fosmanogepix (the active moiety is manogepix) targets fungal glycosylphosphatidylinositol-anchored cell wall transfer protein 1, inhibiting cell wall synthesis causing loss of viability. Manogepix has a very broad spectrum of activity covering most clinically important fungal pathogens. The drug is available as an oral and IV formulation, has a wide tissue distribution and displays linear pharmacokinetics. The drug has favorable drug-drug interaction and safety profiles [92]. A phase 1 safety and PK study has been performed in neutropenic leukemia patients receiving the drug prophylactically [93]. Given these characteristics, the drug has potential for being investigated as prophylactic antifungal agent.
- Opelconazole is an azole with activity against *Aspergillus* species and other fungi including various *Candida* sp. (including C. auris), *Rhizopus oryzae*, *Cryptococccus neoformans*, *Chaetomium globosum*, *Penicillium chrysogenum* and *Trichophyton rubrum*. Opelconazole was specifically designed for inhaled delivery; the drug accumulates in the lung and has a long residence time in airway cells, potentially enhancing the ability of host cells to clear the fungus, both in treatment and in prophylaxis. Systemic exposure is very low (ratio of lung: systemic concentrations is ~7000:1), resulting in a low risk for drug-drug interactions [94].

CONCLUSION

IFDs remain potentially fatal events in patients with hematological malignancies undergoing chemotherapy, transplantation or cellular therapies. Identification of the main risk factors is necessary to establish appropriate antifungal prophylaxis.

In recent years, various antineoplastic drugs directed against specific surface proteins or molecular targets have been developed for almost all hematological malignancies. This has opened new therapeutic possibilities, but has also increased the population at risk of developing IFDs. Development of cellular therapies, i.e. CAR-T therapy, and increasing use of allo-HSCT has further expanded the number of patients at risk of IFD. The main differences in this updated ECIL guidelines is the inclusion of recommendations for these new risk groups, such as venetoclax combined with azacytidine in patients with AML, treatment with bispecific antibiodies, and CAR-T cell therapies.

We aimed to give solid indications based on randomized clinical trials, but in some cases, in the absence of randomized trials, clinical evidence from observational studies has been the base for a grading of recommendation (i.e. isavuconazole in AML).

New bispecific monoclonal antibodies have been introduced during the past 5 years for the treatment of myelomas and lymphomas, but current knowledge on the possible epidemiology of IFDs in these settings is still very limited and does not allow us to suggest any recommendation.

Until now, in Europe, lymphoma patients have been identified as receiving the most benefit from CAR-T cell therapies. However, the number of these procedures is constantly increasing, including myeloma and ALL patients, while their timing is changing, shifting from "the last line therapeutic change" to earlier treatment settings, and now being also used as a bridge to allo-HSCT.

The expectations for the near future are the introduction of new antineoplastic agents that will be more effective but which will also lead to increased immunosuppression. At the same time, we expect that new antifungals with greater efficacy and fewer pharmacological interactions will be available, which will hopefully have an important impact not only on the treatment of IFD but also on prophylaxis.

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All co-authors prepared a set of summary slides on each of the substances addressed in the manuscript, presented the slides at the ECIL-10 conference and revised the slide sets after the plenary discussion. LP prepared the manuscript, all co-authors revised the text and consented the final version.

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ECIL MEMBERS WHO PARTICIPATED IN THE DRAFTING OF THESE RECOMMENDATIONS

Livio Pagano, Georg Maschmeyer, Frederic Lamoth, Ola Blennow, Alienor Xhaard, Manuela Spadea, Alessandro Busca, Catherine Cordonnier, Johan Maertens.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Livio Pagano.

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Manuela Aguilar Guisado[13], Murat Akova[14], Sophie Alain[15], Mahmoud Aljurf[16], Dina Averbuch[17], Francesco Baccelli[18], Ola Blennow[5,6], Nicole Blijlevens[19], Michael Boeckh[20,21], Alessandro Busca[10], Thierry Calandra[22], Simone Cesaro[23], Roy Chemaly[24], Francesca Compagno[25], Catherine Cordonnier[11], Rafael De La Camara[26], Thushan de Silva[27], Manuel Nuno Direito de Morais Guerreiro[28], Federica Galaverna[29], Carolina Garcia Vidal[30], Tobias Gedde-Dahl[31], Lidia Gil[32], Andreas Groll[33], Raoul Herbrecht[34], Hans Hirsch[35], Martin Hoenigl[36], Frederic Lamoth[4], Per Ljungman[37], Varun Mehra[38], Malgorzata Mikulska[39,40], Patricia Munoz[41], Anders Eivind Leren Myrhe[42], David Navarro[43], Dionysios Neofytos[44], Marcio Nucci[45,46], Chiara Oltolini[47], Agnieszka Piekarska[48], José Luis Pinana[49,50], Elena Reigadas Ramirez[41], Christine Robin[51], Alicja Sadowska-Klasa[52], Manuela Spadea[8], Ben Teh[53,54], Yuri Vanbiervliet[55] and Lewis White[56]

[13]Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Sevilla, Spain. [14]Medical Doctor, Hacettepe University, Ankara, Turkey. [15]Microbiology Department, Limoges University Hospital, Limoges, France. [16]Cancer Center for Excellence, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia. [17]Faculty of Medicine, Hebrew University of Jerusalem; Hadassah Medical Center, Jerusalem, Israel. [18]Pediatric Hematology and Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy. [19]Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands. [20]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, WA, USA. [21]Department of Medicine, University of Washington, Seattle, WA, USA. [22]Infectious Diseases Service, Department of Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. [23]Pediatric Hematology Oncology, Department of Mother and Child, Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy. [24]Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. [25]Pediatric Hematology/Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. [26]Hospital de la Princesa, Madrid, Spain. [27]Vaccines and Immunity Theme, MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine, London, UK. [28]Department of Hematology, Hospital Universitari i Politecnic La Fe, Valencia, Spain. [29]Department of

Pediatric Hematology and Oncology, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy. [30]Hospital Clinic, Infectious Diseases-IDIBAPS Department, Barcelona, Spain. [31]Clinic for Cancer Medicine, Hematology Department, Section for Stem Cell Transplantation, Oslo University Hospital, Rikshospitalet, Oslo, Norway. [32]Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poznan, Poland. [33]Infectious Disease Research Program, Center for Bone Marrow Transplantation and Department of Pediatric Hematology and Oncology, University Children's Hospital, Muenster, Germany. [34]Institut de Cancérologie Strasbourg Europe (ICANS), University of Strasbourg, Strasbourg, France. [35]Transplantation & Clinical Virology, University of Basel, Basel, Switzerland. [36]Abteilung für Infektionskrankheiten, Klinik für Innere Medizin, Medizinische Universität Graz, Graz, Österreich. [37]Dept of Cellular Therapy and Allogeneic Stem Cell Transplantation, Karolinska Comprehensive Cancer Canter, Karolinska University Hospital Huddinge and Dept of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden. [38]Department of Haematological Medicine, King's College Hospital NHS Foundation Trust, London, UK. [39]Division of Infectious Diseases, Department of Health Sciences (DISSAL), University of Genova, Genova, Italy. [40]IRCCS Ospedale Policlinico San Martino, Genova, Italy. [41]Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain. [42]Avdeling for blodsykdommer, Oslo universitetssykehus, Oslo, Norway. [43]Microbiology Service, Hospital Clínico Universitario, Valencia, Spain. [44]Division of Infectious Diseases, University Hospital of Geneva, Geneva, Switzerland. [45]Departament of Internal Medicine, Hospital Universitario, Universidade Federal do Rio de Janeiro, Río de Janeiro, RJ, Brazil. [46]Grupo Oncoclínicas, Río de Janeiro, Brazil. [47]Division of Infectious Diseases, ASST Grande Ospedale Metropolitano Niguarda, Piazza dell'Ospedale Maggiore, 3, 20162 Milan, Italy. [48]University Clinical Centre in Gdansk, Gdansk, Poland. [49]Department of Hematology. Hospital Clínico Universitario of Valencia, Valencia, Spain. [50]INCLIVA, Biomedical Research Institute, Valencia, Spain. [51]Department of Haematology, Assistance Publique des Hôpitaux de Paris, Henri Mondor Hospital, Créteil, France. [52]Department and Clinic of Hematology and Transplantology, Medical University of Gdańsk, Gdańsk, Poland. [53]Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia. [54]Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia. [55]Department of Hematology, University Hospitals Leuven, Leuven, Belgium. [56]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK