10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

An update on primary antifungal prophylaxis

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Final slide set
Post meeting

CONFERENCE
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EBM Categories

Category, grade		Definition
Strength of recommendation	A	Strongly supports a recommendation for use
	B	Moderate evidence to support a recommendation for use
	C	Poor evidence to support a recommendation
	D	Supports a recommendation against use
Quality of evidence—Level	I	Evidence from ≥1 properly randomized controlled trial
	II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results from uncontrolled experiments
	III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees
Quality of evidence—Index (for Level II)	r	Meta-analysis or systematic review of RCT
	t	Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation
	h	Comparator group is a historical control
	u	Uncontrolled trial
	a	Published abstract (presented at an international symposium or meeting)

ECIL 5 and 6 Recommendations 2013/2015 for AMLs

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).

Maertens et al, J Antimicrob Chemother 2018

AFP in AMLs receiving intensive remission induction/reinduction chemotherapy

Intention	Intervention	SoR	QoE	ECIL 5
Prevent invasive fungal infections in AML patients, excluding allogeneic hematopoietic stem cell transplantation	Posaconazole	A	I[1]	A-I
	Amphotericin B, liposomal, inhalation*[2,3]	B	I	B-I
	Fluconazole[4]	B	I	B-I
	Voriconazole	B	IIu	B-II
	Isavuconazole[2]	B	IIt	NR
	Micafungin	B	II u,t	NR
	Amphotericin B, liposomal, iv[2]	C	II	C-II
	Caspofungin[2]	B	IIt	NR
	Itraconazole, p.o. and i.v.	C	I	B-I
	SUBA-Itraconazole	C	IIt	NR

1 = recommendation for AML under remission induction chemotherapy; 2 = no approval for prophylaxis of invasive fungal infection; 3 = formulation not approved; 4 =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

*should be associate to fluconazole;

Footnote: amphotericin deoxycholate is not approved for prophylaxis and should not be considered due to drug-related toxicity

Antifungal Prophylaxis: Dosages

Drug	Dosage
Posaconazole, oral suspension	200 mg q8h p.o.
Posaconazole, tablet	300 mg q24 p.o. (q12h on day 1)
Posaconazole, i.v.	300 mg q24h i.v. (q12h on day 1)
Amphotericin B, liposomal, inhalation	10 mg twice weekly
Fluconazole	400 mg/24h/po or iv
Voriconazole	6 mg/kg/12h first day then 4 mg/kg q12h i.v./p.o.
Isavuconazole	200 mg/q8h first 2 days then 200 mg/24h
Micafungin	50 mg q24h i.v.
Amphotericin B, liposomal, i.v.	1-3 mg/kg q24h
Caspofungin	50 mg q24h i.v. (70 mg on day 1, 70 mg q24h in patients >80 kg)
Itraconazole, oral solution	2.5-7.5 mg/kg/d or 200 mg q24h
Itraconazole, capsules or i.v. formulation	200 mg q24h p.o. / i.v.
SUBA-itraconazole	200 mgq12h po

Antifungal Prophylaxis in AMLs Treated with «New Agents» combined with hypomethylating agents (see ECIL 9)

Population	Intention	Intervention	SoR	QoE
Venetoclax	Prevent IFD	Use triazole antifungal prophylaxis, if neutropenia ≥7 days is expected or present	**B**	**IIu,t**
	Prevent toxicity	Reduce dose of venetoclax by at least 75 % in combination with posaconazole or voriconazole and by 50% in combination with fluconazole or isavuconazole	**A**	**IIu,t**
Ivosidenib	Prevent IFD	If neutropenia ≥7 days is expected or present, use triazole antifungal prophylaxis concomitantly to ivosidenib	**B**	**III**
	Prevent toxicity	Reduce ivosidenib dose to 250 mg/day in combination with posaconazole or voriconazole	**B**	**III**

Antifungal prophylaxis in preventing invasive aspergillosis in AML patients undergoing consolidation therapy: SEIFEM

- Cases of IA observed **during consolidation** in adult/paediatric AML patients between 2011 and 2015, retrospectively collected in a multicentre Italian study
- Of **2588 patients**, 56 (2.2%) developed IA [43 probable (1.7%) and 13 proven (0.5%)]
- **IA diagnosed in 34/1137 (2.9%) patients receiving no AP and in 22/1451 (1.5%) who were given AP (p = 0.01)**
- NNT calculation: on average, 71 patients should have received AP (instead of no AP) for 1 additional patient to not have IA
- Overall mortality rate and mortality rate attributable to IA by day 120: 16% and 9%
- Multivariate analysis: **age ≥ 60 years** (OR 12.46, 95% CI 1.13-136.73; p = 0.03) and **high-dose cytarabine** treatment (OR 10.56, 95% CI 1.95-116.74; p = 0.04) **independently affected outcome**
- „AP appears to prevent IA from occurring during consolidation“

An AFP with posaconazole can be considered in consolidation phase of AML, especially in older patients or those receiveing high dose AraC : B IIt

Del Principe et al, J Antimicrob Chemother 2019

Recommendation for MDS, CML, and MPN

Population	Intention	Intervention	SoR	QoE	ECIL 5
MDS low-/ntermediate	No chemotherapy	No prophylaxis	D	I	No recommendation
MDS Intermediate/High	Treated as AML With intensive chemotherapy	Posaconazole prophylaxis	A	I	As for AML
MDS Intermediate/High	Treated with azacytidine	Posaconazole prophylaxis during the first 4 aza courses	B	IIu	No recommendation
CML	Treated with TKI	No prophylaxis	D	I	No recommendation
MPN	No chemotherapy	No prophylaxis	D	I	No recommendation
MPN	Treated with ruxolitinib	No prophylaxis	D	I	No recommendation

Acute lymphoblastic leukemia in adults - Recommendations

Previous recommendations:

ECIL [1]

- Against use of mold-active azoles (hazardous interactions with Vinca alkaloids)
- Cautious use of fluconazole to prevent yeast infection (C III)

ESCMID-ECMM-ERS [2]

- ALL induction: L-AMB D I

AGIHO / DGHO [3]

- ALL induction / re-induction included in «neutropenia >7 days»: posaconazole A I (strong only for AML)

Australasian Antifungal Guidelines Steering Committee [4]

- ALL induction / re-induction included in «high-risk»: A I

Proposed recommendations:

Mold-active azoles (voriconazole and posaconazole) are not recommended (hazardous interactions with Vinca alkaloids). **D II**

Cautious use of fluconazole and isavuconazole to prevent yeast infection (**C III)**

Alternative anti-mold prophylaxis (e.g. L-AMB, echinocandins) might be considered in high risk patients (induction chemotherapy, prolonged neutropenia) but no benefit has been shown

No prophylaxis for patients treated with TKIs **(D III)**

Chronic lymphoid leukemia - Recommendations

Previous recommendations:

ECIL [1]

- AF not recommended (might be considered in case of prolonged neutropenia, unresponsive CLL)

ESCMID-ECMM-ERS [2]

- No recommendation provided

ESCMID-ESGICH [3]

- Ibrutinib: AF not recommended (close monitoring)

ESMO [4]

- AF not recommended

AGIHO / DGHO [5]

- No recommendation provided (only venetoclax in AML: A II)

Australasian Antifungal Guidelines Steering Committee [6]

- Treatment-naïve CLL: no prophylaxis (B II)

Proposed recommendations:

AF prophylaxis not recommended (**D III**) but may be considered in selected cases with refractory CLL and prolonged neutropenia or BTKIs therapy (**C II**).

1. Maertens et al. *J Antimicrob Chemother* 2018; 73:3221-30; 2. Ullmann et al. *Clin Microbiol Infect* 2018; 24: e1-e38; 3. Reinwald et al. *Clin Microbiol Infect* 2018; 24:S53-S70; 4. Eichhorst et al. *Ann Oncol* 2021; 32:23-33; 5. Stemler et al. *J Antimicrob Chemother* 2023; 78:1813-26; 6. Teh et al. *Intern Med J* 2021; 51 Suppl 7:67-88

Non-Hodgkin Lymphoma - Recommendations

Previous recommendations:

ECIL [1]

- AF not recommended (low IFI incidence)

ESCMID-ECMM-ERS [2]

- No recommendation provided

ESCMID-ESGICH [3]

- Ibrutinib: AF not recommended (close monitoring)

AGIHO / DGHO [4]

- No recommendation provided

Australasian Antifungal Guidelines Steering Committee [5]

- Lymphoma intensive/dose-escalated therapy (low risk): FLC (ITZ or echinocandins) B II
- Lymphoma other (very low risk): no AF prophylaxis B II

Proposed recommendations:

AF prophylaxis not recommended (**D II**). Might be considered in selected patients with refractory lymphoma and/or repeated intensive chemotherapies with neutropenia or high doses steroids or BTKis therapy (**C II**)

1. Maertens et al. *J Antimicrob Chemother* 2018; 73:3221-30; 2. Ullmann et al. *Clin Microbiol Infect* 2018; 24: e1-e38; 3. Reinwald et al. *Clin Microbiol Infect* 2018; 24:S53-S70; 4. Stemler et al. *J Antimicrob Chemother* 2023; 78:1813-26; 5. Teh et al. *Intern Med J* 2021; 51 Suppl 7:67-88

Recommendations for Hodgkin' Lymphoma and Myeloma

- **HD**
  - ECIL 5 and 6: "Patients with lymphoma tend to be at low risk of IFD", with no specific recommendation given. **No change.**

- **Myeloma**
  - Conventional chemotherapy or IMIDs: **No prophylaxis**
  - Bispecific ab:
    - Data insufficient for recommendation
    - 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)
  - Belantamab
    - Low risk: No antifungal prophylaxis recommended or No recommendations can be made

Recommendations in alloHSCT recipients: pre-engraftment

Antifungal agent	Pre-engraftment risk of mould infection	
	low	high
Fluconazole 400 mg q24h	A-I [a]	D-III
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
Itraconazole oral solution 2.5mg/kg q12h	B-I	B-I
Voriconazole 200mg 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	
Aerosolized liposomal amphotericin B (10 mg twice weekly) associated with Fluconazole 400 mg q24h	C-III	
Isavuconazole 200 mg q24h following a loading dose of 200 mg q8h on days 1 and 2 [b]	no data	no data

[a] only when combined with a mould-directed diagnostic approach (biomarker and/or CT scan-based)

[b] Isavuconazole can be used as second-line mould active prophylaxis, in case of intolerance to posaconazole / voriconazole, or QTc prolongation (B-II)

Pre-engraftment risk of mould infection defined as in Girmenia et al, BBMT 2014: high risk includes active leukaemia, cord blood transplantation and unrelated donor. Haplo-identical HSCT using post-transplantation cyclophosphamide should be considered at low risk (B-II).

Centres offering allogeneic HSCT should know their own incidence and epidemiology of IFD and be aware that construction works may alter environmental exposure

In case of prior fungal infection, secondary prophylaxis should be tailored according to the previous documentation (ref Puerta Alcalde, Blood 2020)

Recommendations in alloHSCT recipients: post-engraftment

Antifungal agent	Steroids-treated acute GVHD
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]**
Itraconazole oral solution 2.5mg/kg q12h	**B-I [b]**
Voriconazole 200mg 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) associated with Fluconazole 400 mg q24h	**no data**
Isavuconazole 200 mg q24h following a loading dose of 200 mg q8h on days 1 and 2 [c]	**no data**
Fluconazole 400 mg q24h	**D-III**

After engraftment, in patients without GVHD, fluconazole can be continued until D+75

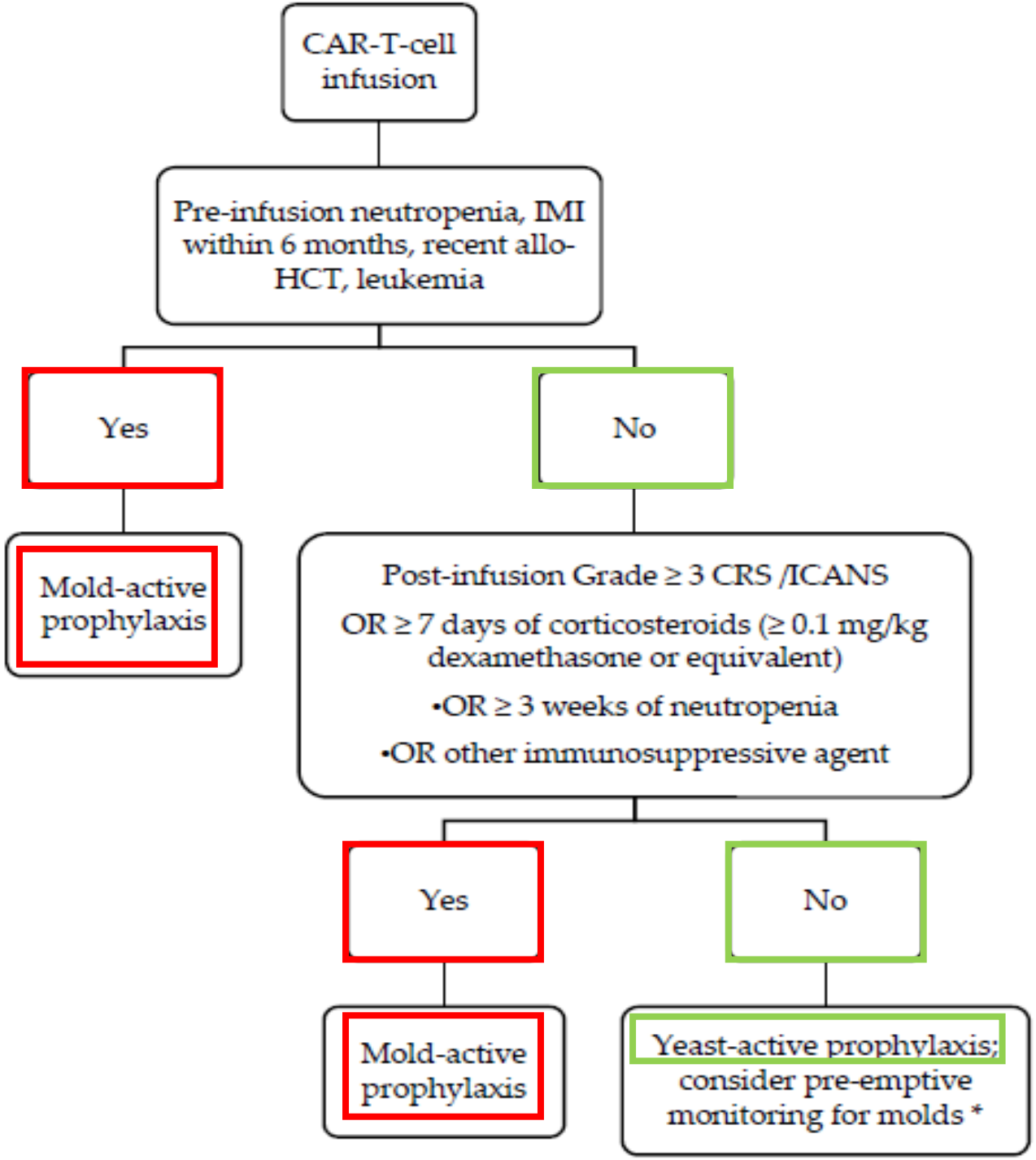
[a] No difference with placebo was seen in patients with chronic GVHD

[b] It is recommended to monitor serum drug concentration

[c] Isavuconazole can be used as second-line mould active prophylaxis, in case of intolerance to posaconazole / voriconazole, or QTc prolongation (B-II)

AntiCD19 CART cells

Panel proposes to **endorse these recommendations (B II)**



Garner et al, J of Fungi 2021

Pediatric patients- proposed update

Previous recommendations:

ECIL 8 [1]

- ✓ Primary antifungal prophylaxis is strongly recommended for paediatric patients at high risk (≥10% estimated natural incidence) of invasive fungal disease including: acute myeloid leukaemia, recurrent leukaemia, acute lymphoblastic leukaemia at high risk of IFD * and those undergoing allogeneic HCT in the pre-engraftmen t and in the post-engraftment phase until immune reconstitution, or in situations of augmented immunosuppressive treatment in the context of graft-versus-host disease; augmented immunosuppression refers to the use of additional immunosuppressive interventions to control overt graft-versus-host disease and includes, but is not limited to, the use of glucocorticosteroids in therapeutic doses (≥0·3 mg/kg per day prednisone equivalent) or anti-inflammatory antibodies; attention to drug–drug interaction is needed, particularly with imm unosuppressive agents and vincristine

Proposed refinement of recommendations:

- ✓ **[...] * with insufficient treatment response during induction therapy, and children older than 12 y.o.** [2]

1. Groll et al. *The Lancet. Oncology* vol. 22,6 (2021): e254-e269.; 73:3221-30;
2. Lehrnbecher et al, Leukemia, 2023

Pediatric patients- proposed update

Previous recommendations:

ECIL 8 [1]

✓ Posaconazole: Patients aged 13 years or older: delayed-release tablets, 300 mg in one single daily dose (2 × 300 mg on day 1); patients aged 1 month to 12 years: oral suspension, starting dose 6 mg/kg three times daily

Proposed refinement of recommendations:

✓ Posaconazole **approved by EMA** in 2021 [2] for high-risk paediatric **patients from 2 years of age** with acute myeloid leukaemia/myelodysplastic syndrome **(AML/MDS)** and those with allogeneic haematopoietic cell transplantation **(HCT)** and graft-versus-host diseases **(GVHD)**

- ❖ **Delayed-release tablets, pts weighing more than 40 kg,** 300 mg in one single daily dose
- ❖ **iv solution , pts ≥2 years of age**, 6 mg/kg once daily (max. 300 mg; day 1: twice daily)
- ❖ **powder for delayed-release oral suspension, pts ≥2 years of age and ≤40 kg**: weight-based once-daily dosing (day 1: twice daily).
- ❖ **Oral suspension: still not approved by EMA**

No other changes are proposed for pediatric recommendations

1. Groll et al. *The Lancet. Oncology* vol. 22,6 (2021): e254-e269.; 73:3221-30;
2. Groll et al, Internat J of Antimic Agents, 2020

Pediatric patients- proposed update

Previous recommendations:

ECIL 8 [1]

Caspofungin: Potential new option for mould-active prophylaxis (no grading because data published after the meeting)

Proposed refinement of recommendations:

✓ Caspofungin[2]: **B I**

No other changes are proposed for pediatric recommendations

1. Groll et al. *The Lancet. Oncology* vol. 22,6 (2021): e254-e269.; 73:3221-30;
2. Dvorak et al, JPID, 2021

New antifungals

Drugs	Possible Indication in AF
Olorofim	Not in primary prophylaxis, possible in secondary prophylaxis
Fosmanogepix/Manogepix	Potential for primary prophylaxis (pending more efficacy data)
Rezafungin	Study ongoing of AFP in HSCT recipients
Ibrexafungerp	Potential for primary prophylaxis (~ rezafungin) (pending more efficacy data)
Opelconazole	Potential for primary prophylaxis (pending more efficacy data)