PROPHYLACTIC ANTI-FUNGALS IN HAEMATOLOGICAL DISORDERS: newer advances

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RATIONALE FOR ANTIFUNGAL PROPHYLAXIS IN HAEMATOLOGICAL DISORDERS

Patients of haematological malignancies are predisposed to serious invasive infections associated with increased risk of mortality.

Causes:

1. Secondary immunodeficiency due to underlying disease:

a. Neutropenia (risk of serious bacterial infection, and if prolonged- fungal infection)

b. T-cell dysfunction (risk of fungal and viral infection)

c. Hypogammaglobulinemia

2. Secondary immunodeficiency due to therapy related causes:

a. drug-induced (cytotoxic and biologic) (e.g B-cell depleting therapies)

b. Radiation induced

c. Graft vs host disease

Known risks of infections:

- Hypogammaglobulinemia is a predictor of shorter overall survival in CLL
- infections are the leading cause of death in patients with CLL, MM and NHL who develop SID
- Infections related to SID may account for up to 50% of deaths of patients with CLL
- They contribute to up to 22% and 33% of deaths of patients with MM and NHL, respectively

1. Andersen MA, Vojdeman FJ, Andersen MK, et al.Hypogammaglobulinemia in newly diagnosed chroniclymphocytic leukemia is a predictor of early death.Leuk Lymphoma. 2016;57(7):1592–1599
2. Nucci M, Anaissie E. Infections in patients with mul-tiple myeloma in the era of high-dose therapy andnovel agents. Clin Infect Dis. 2009;49(8):1211–1225
3. Ostrow S, Diggs CH, Sutherland J, et al. Causes ofdeath in patients with non-Hodgkin's lymphoma.Cancer. 1981;48(3):779–782
4. Oscier D, Dearden C, Eren E, British Committee forStandards in Haematology, et al. Guidelines on thediagnosis, investigation and management of chroniclymphocytic leukaemia. Br J Haematol. 2012;159(5):541–564.RISK FACTORS FOR SEVERE INFECTIONS71

Infection/risk in haematological malignancies

TABLE 3 Percentages of patients with CLL, MM, and NHL who had infections (any grade and grade ≥3), neutropenia (any grade or grade ≥3), or hypogammaglobulinemia.

Malignancies		Any grade neutropenia*		Grade ≥3 neutropenia*		Any grade infections*		Grade ≥3 infections*		Hypogamma*
Studies (n)		Mean	Range	Mean	Range	Mean	Range	Mean	Range	Range
CLL	17	36.3	9.4–64.0	29.8	3.0–60.0	51.3	14.4–69.1	19.8	6.4–39.0	0.0–15.3
MM	38	36.4	9.8–85.5	23.2	2.0–80.0	35.9	0.0–68.0	16.3	0.0–50.2	–
NHL	34	35.4	3.2–87.5	38.7	0.0–100.0	31.1	4.0–81.0	11.3	0.9–38.0	5.9
Total	89	36.0	3.2–87.5	29.6	0.0–100.0	36.7	0.0–81.0	15.9	0.0–50.2	0.0–15.3

*The reporting criteria for time to adverse events differed across studies.
Neutropenia grades: grade 1, less than the lower limit of normal–1,500 per mm3; grade 2, 1,499–1,000 per mm^3; grade 3, 999–500 per mm^3; grade 4, <500 per mm^3; grade 5, death.
Infection grades: grade 1, –; grade 2, localized, local intervention indicated; grade 3, IV antibiotic, antifungal, or antiviral intervention indicated, interventional radiology or operative intervention indicated; grade 4, life-threatening consequences e.g., septic shock, hypotension, acidosis, or necrosis; grade 5, death.
CLL, chronic lymphocytic leukemia; hypogamma, hypogammaglobulinemia; IV, intravenous; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; –, not reported.

Jolles S, Giralt S, Kerre T, Lazarus HM, Mustafa SS, Ria R, et al. Agents contributing to secondary immunodeficiency development in patients with multiple myeloma, chronic lymphocytic leukemia and non-Hodgkin lymphoma: A systematic literature review. Frontiers in Oncology [Internet]. 2023 Feb 7 [cited 2024 Mar 17];13.

Table 1. Novel targeted therapies: immune sequelae.

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG [1]	Neutropenia
CD20	Rituximab Ofatumumab Obinutuzumab	+++	-	+	++ [2]
CD52	Alemtuzumab	++	+++	+	+ [3]
CD38	Daratumumab	+	+	-	+
SLAMF7	Elotuzumab	-	-	-	-
CD19/CD3	Blinatumomab	+++	+	++	++
BTK	Ibrutinib Acalabrutinib Zanubrutinib	++	-	+	+
PI3K	Idelalisib Copanlisib Duvelisib	++	+	-	+
JAK	Ruxolitinib	-	+	-	-
BCL-2	Venetoclax	-	-	-	++

Plus signs indicate relative effect (e.g., mild, moderate, significant). [1] Hypogammaglobulinemia. [2] Late neutropenia may occur (median time 175 days, Dunleavy et al.). [3] Neutropenia typically resolves in 2–4 weeks.

Little JM, Weiss Z, Hammond SP. Invasive Fungal Infections and Targeted Therapies in Hematological Malignancies. Journal of Fungi. 2021 Dec 10;7(12):1058–8.

Malignancies	Studies (n)	Any grade neutropenia*		Grade ≥3 neutropenia*		Any grade infections*		Grade ≥3 infections*		Hypogamma*
		Mean	Range	Mean	Range	Mean	Range	Mean	Range	Range
Rituximab (as doublets, triplets etc.)										
CLL	7	46.6	20.9–64.0	36.2	3.0–60.0	64.0	59.0–69.0	23.8	6.4–39.0	–
NHL	17	53.0	17.4–87.5	51.9	11.1–92.5	33.0	10.0–53.3	8.5	0.9–23.0	–
Total	24	51.6	17.4–87.5	46.7	3.0–92.5	38.7	10.0–69.0	15.8	0.9–39.0	–
Rituximab (as monotherapy)										
CLL	2	20.9	20.9	7.0	7.0	–	–	15.0	11.0–19.0	–
NHL	7	14.1	3.4–22.0	8.5	2.4–14.9	23.0	7.0–36.1	3.6	2.0–4.4	5.9
Total	9	15.2	3.4–22.0	8.2	2.4–14.9	23.0	7.0–36.1	8.1	2.0–19	5.9
Bortezomib (as doublets, triplets etc.)										
MM	14	36.2	18.1–73.4	24.8	9.2–42.7	25.9	9.6–48.4	8.5	3.8–13.5	–
NHL	1	17.4	17.4	11.1	11.1	53.3	53.3	10.8	10.8	–
Total	15	33.1	17.4–73.4	23.7	9.2–42.7	31.4	9.6–53.3	8.8	3.8–13.5	–
Bortezomib (as monotherapy)										
MM	7	42.5	42.5	10.6	2.0–25.0	8.8	8.8	16.9	3.7–30.0†	–
NHL	2	25.0	25.0	5.9	5.9	–	–	–	–	–
Total	9	33.8	25.0–42.5	9.6	2.0–25.0	8.8	8.8	16.9	3.7–30.0	–

Malignancies	Studies (n)	Any grade neutropenia*		Grade ≥3 neutropenia*		Any grade infections*		Grade ≥3 infections*		Hypogamma*
		Mean	Range	Mean	Range	Mean	Range	Mean	Range	Range
Ibrutinib (as doublets, triplets etc.)										
CLL	2	39.4	35.5–43.3	27.8	18.6–37.0	–	–	–	–	15.3
NHL	1	42.9	42.9	33.0	33.0	42.9	42.9	38.0	38.0	–
Total	3	40.6	35.5–43.3	29.5	18.6–37.0	42.9	42.9	38.0	38.0	15.3
Ibrutinib (as monotherapy)										
CLL	2	15.1	9.4–20.7	8.1	4.1–12.1	49.7	49.7	–	–	0.0
NHL	1	16.0	16.0	13.0	13.0	–	–	–	–	–
Total	3	15.4	9.4–20.7	9.7	4.1–13.0	49.7	49.7	–	–	0.0
Lenalidomide (as doublets, triplets etc.)										
MM	10	32.5	15.0–61.3	23.0	8.0–54.1	52.5	46.7–59.4	19.5	6.0–41.0	–
NHL	1	36.1	22.1–50.0	–	–	–	–	–	–	–
Total	11	33.4	15.0–61.3	23.0	8.0–54.1	52.5	29.0–59.4	19.5	6.0–41.0	–
Lenalidomide (as monotherapy)										
MM	3	71.0	71.0	29.7	13.0–43.0	–	–	25.7	5.0–50.2	–
NHL	2	15.7	15.7	20.1	20.1†	29.0	29.0	10.8	10.8	–
Total	5	43.4	15.7–71.0	27.3	13.0–43.0	29.0	29.0	22.0	5.0–50.2	–
Dexamethasone (as doublets, triplets etc.)										
MM	21	34.2	9.8–73.4	22.5	5.9–54.1	46.8	9.6–68.0	18.4	6.0–41.0	–
NHL	3	10.8	3.2–22.1	34.8	0.0–100.0†	51.6	36.0–81.0	12.7	11.3–14.1	–
Total	24	30.5	3.2–73.4	23.3	0.0–100.0	48.6	9.6–81.0	17.7	6.0–41.0	–
Dexamethasone (as monotherapy)										
MM	1	20.1	20.1	16	16	52.7	52.7	32.7	32.7	–

*The reporting criteria for time to adverse events differed across studies.
†Not all studies reported values for both any grade and grade ≥3 events; this has led to the situation where in some categories, individual studies reported higher levels of grade ≥3 events than other studies did for any grade events, leading to the average of grade ≥3 events being higher than the average for any grade events.
Neutropenia grades: grade 1, less than the lower limit of normal–1,500 per mm^3; grade 2, 1,499–1,000 per mm^3; grade 3, 999–500 per mm^3; grade 4, <500 per mm^3; grade 5, death.
Infection grades: grade 1, –; grade 2, localized, local intervention indicated; grade 3, IV antibiotic, antifungal, or antiviral intervention indicated, interventional radiology or operative intervention indicated; grade 4, life-threatening consequences e.g., septic shock, hypotension, acidosis, or necrosis; grade 5, death.
CLL, chronic lymphocytic leukemia; hypogamma, hypogammaglobulinemia; IV, intravenous; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; –, not reported.

Fungal diseases in haematological diseases

- Invasive fungal infections (IFIs) are a major cause of morbidity and mortality, particularly in patients with hematological malignancies
- The most common fungi causing invasive infections in this setting are Aspergillus spp. and Candida albicans
- but non-C. albicans and a growing number of other organisms (e.g. Zygomycetes, Trichosporon, Fusarium spp.) are found increasingly

Ruhnke A, Bohme A, Diagnosis of invasive fungal infections in hematology and oncology—guidelines from the Infectious Diseases Working Party in Haematology and Oncology of the German Society for Haematology and Oncology (AGIHO)

- The highest incidences have been reported in allogeneic hematopoietic cell transplant (HCT) recipients and in patients with acute myeloid leukemia (AML) receiving induction remission chemotherapy
- Recent studies have shown a high incidence of IFD in patients with acute lymphoid leukemia (ALL)
- Emergence of a new group at risk: patients with chronic lymphoproliferative diseases receiving ibrutinib

1. Pagano, L.; Busca, A.; Candoni, A.; Cattaneo, C.; Cesaro, S.; Fanci, R.; Nadali, G.; Potenza, L.; Russo, D.; Tumbarello, M.; et al. Risk stratification for invasive fungal infections in patients with hematological malignancies: SEIFEM recommendations. *Blood Rev.* **2017**, *31*, 17–29.
2. Cornely, O.A.; Leguay, T.; Maertens, J.; Vehreschild, M.J.G.T.; Anagnostopoulos, A.; Castagnola, C.; Verga, L.; Rieger, C.; Kondakci, M.; Härter, G.; et al. Randomized comparison of liposomal amphotericin B versus placebo to prevent invasive mycoses in acute lymphoblastic leukaemia. *J. Antimicrob. Chemother.* **2017**, *72*, 2359–2367.
3. Nucci, M. Epidemiology of invasive fungal disease in haematologic patients. *Mycoses* **2021**, *64*, 252–256
4. Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib. *Blood* **2018**, *131*, 1955–1959.

Table 2. Novel targeted therapies: risk of invasive fungal in

Target	Agents	Risk for IFI
BTK	Ibrutinib Acalabrutinib Zanubrutinib	High
CD52	Alemtuzumab	High
PI3K	Idelalisib Copanlisib Duvelisib	Moderate/High
CD19/CD3	Blinatumomab	Moderate
BCL-2	Venetoclax	Moderate
CD20	Rituximab Ofatumumab Obinutuzumab	Moderate/Low
JAK	Ruxolitinib	Moderate/Low
SLAMF7	Elotuzumab	Low
CD38	Daratumumab	Low
FLT3	Midostaurin Gilterinib	Low

Little JM, Weiss Z, Hammond SP. Invasive Fungal Infections and Targeted Therapies in Hematological Malignancies. Journal of Fungi. 2021 Dec 10;7(12):1058–8.

Invasive fungal disease incidence: studies in novel therapy recipients

Target	Indication	Reference	Ref No.	Manifestations of IFI
BTK	PCNSL	Lionakis et al.	[63]	IFI incidence 44%; 7 cases of IA including 2 involving CNS; 1 PJP
	CLL NHL	Varughese et al.	[64]	IFI incidence 4.2%; 8 cases of IA; 3 PJP, 1 concurrent IA + PJP, 1 cryptococcosis; 1 *Candida albicans* fungemia
	CLL NHL	Ghez et al.	[65]	33 cases of IFI amongst 16 centers over 4 years; 27 cases IA with 11 involving CNS; 4 cryptococcosis; 1 PJP
	CLL NHL	Rogers et al.	[66]	IFI incidence 3%; 12 cases of IA included 1 involving CNS; 2 mucormycosis; 1 cryptococcosis; 1 blastomycosis; 1 histoplasmosis
	CLL	Frei et al.	[67]	IFI incidence 2.5%; 13 cases of IA; 2 cases invasive candidiasis; 5 cryptococcosis; 1 histoplasmosis; 1 PJP; 1 *Fusarium* infection
PI3K	CLL	Zelenetz et al.	[68]	1 patient died from pulmonary mycosis; 4 cases of PJP
	NHL	Dreyling et al.	[69]	IFI incidence 2%; 1 case of IA; 2 PJP
CD19/CD3	ALL	Kantarjian et al.	[57]	IFI incidence 10% in blinatumomab group; 6 cases of IA; 2 mucormycosis; 1 PJP
BCL-2	AML	Aldoss et al.	[70]	IFI incidence 12.6%; 7 cases of IA; 5 cases of mucormycosis; 2 *Scedosporium*; 1 *Penicillium*
	CLL	Davids et al.	[71]	IFI incidence 2%; 2 cases of IA; 3 cases oral/esophageal candidiasis; 2 PJP

Little JM, Weiss Z, Hammond SP. Invasive Fungal Infections and Targeted Therapies in Hematological Malignancies. Journal of Fungi. 2021 Dec 10;7(12):1058–8.

Risk stratification-2014 guidelines

- Risk stratification is a key to identifying patients that should be considered for antifungal prophylaxis

- Clinical risk assessment profiles identify the following two groups of patients as those at highest risk of devel-oping an IFD

1. Patients receiving intensive chemotherapy for acute myeloid leukaemia (AML) or myelodysplastic syndromes
2. Patients with corticosteroid-requiring graft-versus-host disease (GVHD) following allogeneic HSCT

With regard to GVHD, the risk of IFD appears particularly prominent in patients with

(i) either high-grade(grade 3 or 4) or steroid-refractory/dependent acuteGVHD and

(ii) chronic GVHD, particularly if it developedas a late complication of acute GVHD

Additional risk groups:

- Patients receiving stem cell transplantation with cord blood trans-plants
- patients with either mismatched-related ormatched-unrelated donors, with additional risk factors(defined as cytomegalovirus (CMV) disease or recurrent CMV infection or iron overload)
- patients receiving allogeneic stem cell transplantation for acute leukaemia with active disease at the time of transplant
- Patients undergoing ‘intensive’ therapy regimens forother haematological conditions may also be at a higher risk of IFD

Recommended use of prophylaxis in adults based on risk classification 2014

- Patients at high risk of invasive mould infections should receive mould-active prophylaxis (level II evidence, grade A recommendation).
- Prophylaxis directed at Candida species is appropriate inpatients where neutropenia is less protracted (e.g. less than 14 days in duration) but where mucosal integrity may be compromised (level III evidence, grade C recommendation)
- Where neutropenia is transient, mucosal integrity is preserved, and when immunosuppression is not extensive (such as standard intensity chemotherapy for lymphoma), antifungal prophylaxis is not routinely required(level III evidence, grade C recommendation)

Risk stratification: 2014

Table 1 Invasive fungal disease risk groups (adapted from multiple sources[8,11,13-15])

High risk: >10% incidence IFD	Neutrophils <0.1 × 10⁹/L for >3 weeks[16] or <0.5 × 10⁹/L for >5 weeks
	Unrelated, mismatched or cord blood donor HSCT
	GVHD
	Corticosteroids >1 mg/kg prednisolone equivalent and neutrophils <1 × 10⁹/L for >1 week
	Corticosteroids >2 mg/kg prednisolone equivalent >2 weeks†
	High-dose cytarabine‡
	Fludarabine use in highly treatment-refractory patients with CLL or low-grade lymphoma§
	Alemtuzumab use, especially in highly treatment-refractory patients with CLL or lymphoma§[17]
	ALL
	AML
Intermediate risk: ~10% incidence of IFD	Neutropenia 0.1–0.5 × 10⁹/L for 3–5 weeks
	Neutropenia 0.1–0.5 × 10⁹/L for <3 weeks with lymphopenia (lymphocytes <0.5 × 10⁹/L)
Low risk: ~2% incidence of IFD	PBSC autologous HSCT
	Lymphoma

†Other authors have described prednisolone equivalent of >1 mg/kg/day for 2 weeks or 0.25–1 mg/kg/day for 4 weeks in allogeneic HSCT[2]. ‡Some authors question whether the high rates of IFDs seen with high-dose cytarabine may be contributed to by concurrent fludarabine. §Represent additions to 2008 table. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukemia; GVHD, graft versus host disease; HSCT, haemopoietic stem cell transplant; IFD, invasive fungal disease; PBSC, peripheral blood stem cell; TBI, total body irradiation.

Individual risk factors: 2014

Table 2 Individual risk factors for invasive mould infection

Antibiotics[11]
Older age[11]
Central venous catheter[11]
Iron overload[18]
Recent CMV reactivation[19]
Ganciclovir use[20]
Lower respiratory tract viral infection[21]
Environmental exposure to mould[12,18]

CMV, cytomegalovirus.

Timing of starting prophylaxis

- Most studies commence prophylaxis during administration of chemotherapy

(to avoid drug interactions, particularly with itraconazole and cyclophosphamide, itraconazole may be commenced on day of stem cell infusion)

- Cessation is generally recommended following resolution of risk, which in acute leukaemia corresponds with neutrophil reconstitution (>0.5 or 1.0×109/L)
- Allogeneic transplant recipients should continue anti-fungal prophylaxis until at least day 75 (in the absence of GVHD)
- For patients with GVHD, prophylaxis should be continued for 16 weeks or untilcorticosteroid dose is less than 10 mg daily prednisolone equivalent

Agents for different risk classes: broad groups

Table 3 Classification of risk and recommended prophylaxis for adults

Risk classification	Clinical examples (level of evidence, grade of recommendation)	Recommended prophylaxis
High risk	Acute leukaemia or myelodysplasia, with remission induction and re-induction chemotherapy (II, A) Severe GVHD: steroid dependent or refractory or grade 3 or 4 (II, A) Extensive chronic GVHD (II, A) Allogeneic HSCT with expected neutropenia >14 days (III, C)	Mould-active prophylaxis
Low risk	Selected autologous HSCT† (II, C) Allogeneic HSCT with expected neutropenia <14 days (II, A) Patients receiving intensive/dose-escalated therapy for lymphoma (IV, D)	Anti-*Candida* prophylaxis
Very low risk	Standard chemotherapy for lymphoma (III, C) Chronic myeloid leukaemia (IIIC) Other myeloproliferative neoplasms (III, C)	No prophylaxis

†'Selected' refers to autologous HSCT with higher risk of mucositis and thus *Candida* infection (e.g. those with recent aggressive salvage chemotherapy or receiving multi-agent regimens). GVHD, graft-versus-host disease; HSCT, haemopoietic stem cell transplant.

Specific agents for different risk groups: 2014

Table 4 Recommendations for the use and dosing of specific antifungal agents for prophylaxis (grade of evidence)

Risk group	Agent	Alternative agents
High risk	Posaconazole (A)	Voriconazole (B) Itraconazole (B) Liposomal amphotericin B (C) Micafungin† (B) Caspofungin (C)
Low risk	Fluconazole (B)	Itraconazole (B) Echinocandins (B)

Agent	Recommended dose for adult patients	Recommended dose for paediatric patients
Posaconazole	200 mg orally, 8-hourly	>13 years: 200 mg orally, 8-hourly plus TDM
Voriconazole	200 mg orally or IV, 12-hourly	2 years to <12 years or 12–14 years and weighing <50 kg: 8 mg/kg (day 1, 9 mg/kg) IV, 12-hourly or 9 mg/kg orally, 12-hourly plus TDM ≥15 years or aged 12–14 years and weighing ≥50 kg: 4 mg/kg (day 1, 6 mg/kg) IV, 12-hourly or 200 mg orally, 12-hourly plus TDM
Fluconazole	200–400 mg orally or IV, daily	6–12 mg/kg (max 400 mg) orally or IV, daily
Itraconazole	200 mg orally, 12-hourly	2.5 mg/kg orally, 12-hourly plus TDM
Liposomal amphotericin B	See text (adult section) for dosing recommendations	See text (paediatric section) for dosing recommendations
Echinocandins	See text (adult section) for dosing recommendations	See text (paediatric section) for dosing recommendations

Evidence in favour of agents: 2014 data

- Posaconazole:

- preferred agent for use in high-risk patients due to its broad anti-mould activity and low-breakthrough IFD rates

- only mould-active agent to demonstrate a survivaladvantage in a randomised trial in AML patients

- rate of disturbance of liver function tests for patients with GVHD was 15% and for patients with AML, 7%

- Once daily dosing (after loading) and IV preparations are also available

- Voriconazole:

- alternative to posaconazole as it exhibits mould activity and is also available in an IV formulation

Evidence in favour of agents: 2014 data

- Itraconazole:

- Itraconazole (n=255) was compared with voriconazole (n=234) in an open-labelled, randomisedstudy in allogeneic HSCT recipients with a composite endpoint of efficacy and tolerability.

- no difference between the two agents in terms of the study's efficacy endpoints(overall 180-day survival and incidence of proven or probable IFDs

- greater number of itraconazolepatients received other systemic antifungals (42% vs30%)

- Intolerance was reported in up to one-third of thosetaking itraconazole irrespective of formulation (can be alleviated by using other newly available forms- Lozanoc/Sporanox

Evidence in favour of agents: 2014 data

- Liposomal amphotericin B

- used in the setting of azole intolerance or chemotherapy drug interactions (such as those observed with vincristine in ALL)

- scarce data in favour of its tolerability

- Twice-weekly aerosolised liposomal amphotericin B was examined in one randomised, placebo-controlledstudy in 271 haematology patients who wereneutropenic after chemotherapy.

- Invasive aspergillosiswas significantly reduced in the treatment group

Evidence in favour of agents: 2014 data

- Echinocandins

- favourable safety profile in high-risk patients

- lack broad spectrum anti-mould activity

- a recent study found that micafungin 150 mg daily was as effective as fluconazole 400 mg daily prophylaxis at 4 weeks for patients under-going allogeneic HSCT

- Similar results have been observed with caspofungin 50 mg daily

- These studies generally examined short-term prophylaxis whenyeast infections predominate over Aspergillus infections

- A cohort analysis of 152 AML patients receiving remission induction chemotherapy (2009-2011) found echinocandin-based prophylaxis was associated with higher breakthrough IFD rates than voriconazole/posaconazole prophylaxis

Recent update in guidelines

Primary prophylaxis of invasive fungal diseases in patients with haematological malignancies: 2022 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO)

Jannik Stemler[1,2,3], Sibylle C. Mellinghoff[1,2,3], Yascha Khodamoradi[4], Rosanne Sprute[1,2,3], Annika Y. Classen[1,3], Sonja E. Zapke[5], Martin Hoenigl[6], Robert Krause[6], Martin Schmidt-Hieber[7], Werner J. Heinz[8], Michael Klein[9], Philipp Koehler[1,2], Blasius Liss[5,10], Michael Koldehoff[11,12], Christoph Buhl[13], Olaf Penack[14,15], Georg Maschmeyer[16], Enrico Schalk[17], Cornelia Lass-Flörl[18], Meinolf Karthaus[19], Markus Ruhnke[20], Oliver A. Cornely[1,3,21,22] and Daniel Teschner[23,24]*

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update

Randy A. Taplitz, Erin B. Kennedy, Eric J. Bow, Jennie Crews, Charise Gleason, Douglas K. Hawley, Amelia A. Langston, Loretta J. Nastoupil, Michelle Rajotte, Kenneth V. Rolston, Lynne Strasfeld, and Christopher R. Flowers

Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2021

Benjamin W. Teh,[1,2,3] Daniel K. Yeoh,[2,3,4] Gabrielle M. Haeusler,[1,2,3,5,6] Costas K. Yannakou,[7] Shaun Fleming,[8] Julian Lindsay[2,3,9] and Monica A. Slavin,[1,2,3,10] Australasian Antifungal Guidelines Steering Committee*

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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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ASCO/IDSA clinical practice guideline (2018)

- The risk of infection increases with the depth and duration of neutropenia
- with the greatest risk occurring in patients who experience profound, prolonged neutropenia after chemotherapy, which is most likely to occur in the period before engraftment during HSCT and after induction chemotherapy for acute leukemia
- severely or profoundly neutropenic patients may present with suspected infection in an afebrile state or even hypothermic

Risk stratification in neutropenic patients- IDSA/ASCO

Table 2. Factors to Consider in Assessing Risk of a Febrile Neutropenic Episode in Patients Undergoing Cytotoxic Chemotherapy for Malignancy

Factors Related To	Factor	Effect on Risk	
Patient characteristics	Advanced age	Risk increases if age ≥ 65 years[17]	
	Performance status	Risk increases if ECOG performance score ≥ 2[17]	
	Nutritional status	Risk increases if albumin < 35 g/L[18,19]	
	Prior FN episode	Risk in cycles 2-6 is four-fold greater if FN episode occurs in cycle 1[20]	
	Comorbidities	FN odds increase by 27%, 67%, and 125% for one, two, or three or more comorbidities, respectively[17,21]	
Underlying malignancy	Cancer diagnosis	Diagnosis	Reported FN rates (%)
		Acute leukemia/MDS	85.0-95.0[22-25]
		High-grade lymphoma	35.0-71.0*[26]
		Soft tissue sarcoma	27.0 (95% CI, 19.0 to 34.5)[20,21,27,28]
		NHL/myeloma	26.0 (95% CI, 22.0 to 29.0)[20,21,27,28]
		Germ-cell carcinoma	23.0 (95% CI, 16.6 to 29.0)[20,21,27,28]
		Hodgkin lymphoma	15.0 (95% CI, 6.6 to 24.0)[20,21,27,28]
		Ovarian carcinoma	12.0 (95% CI, 6.6 to 17.7)[20,21,27,28]
		Lung cancers	10.0 (95% CI, 9.8 to 10.7)[20,21,27,28]
		Colorectal cancers	5.5 (95% CI, 5.1 to 5.8)[20,21,27,28]
		Head and neck carcinoma	4.6 (95% CI, 1.0 to 8.2)[20,21,27,28]
		Breast cancer	4.4 (95% CI, 4.1 to 4.7)[20,21,27,28]
		Prostate cancer	1.0 (95% CI, 0.9 to 1.1)[20,21,27,28]
	Cancer stage	Risk increases for advanced stage (≥ 2)[4]	
	Remission status	Risk increases if not in remission[24,29]	
	Cancer treatment response	Risk is lowest if patient has a CR	
		If patient has a PR, FN risk is greater for acute leukemia than for solid tissue malignancies[24]	
		FN risk is higher if persistent, refractory, or progressive disease despite treatment[30,31]	
Treatment of malignancy	Cytotoxic regimen	Risk is higher with regimens that administer:	
		Anthracyclines at doses ≥ 90 mg/m^2	
		Cisplatin at doses ≥ 100 mg/m^2	
		Ifosfamide at doses ≥ 9 g/m^2	
		Cyclophosphamide at doses ≥ 1 g/m^2	
		Etoposide at doses ≥ 500 mg/m^2	
		Cytarabine at doses ≥ 1 g/m^2	
		High dose density	
		Anthracycline + taxane, and cyclophosphamide or gemcitabine, for breast cancer	
	Dose intensity	Increased risk if > 85% of scheduled doses are administered[29,32]	
	Degree and duration of GI and/or oral mucositis	Risk is greatest if NCI mucositis grade is ≥ 3 (GI) or if peak score on OMAS is ≥ 2[26,33,34]	
	Degree and duration of cytopenia	Profound, protracted neutropenia	ANC < 100/μL for ≥ 7 days[35-37]
		Lymphopenia	ALC < 700/μL (ANC surrogate)[27,38]
		Monocytopenia	AMC < 150/μL (ANC surrogate)[39]

Definitions for this guideline

- Fever
- Fever in neutropenic patients is defined as a single oral temperature of 38.3°C (101°F) or a temperature of 38.0°C (100.4°F) sustained over a 1-hour period

- Neutropenia
- Neutropenia is defined as an absolute neutrophil count <1,000/mL
- severe neutropenia as absolute neutrophil count <500/mL
- profound neutropenia <100/mL
- The period of neutropenia is considered protracted if it lasts for >7 days.

Recommendations for antifungal prophylaxis (IDSA-ASCO):

- Antifungal prophylaxis with an oral triazole or parenteral echinocandin is recommended for patients who are at risk for profound, protracted neutropenia, such as most patients with AML/MDS or undergoing HSCT (strength- moderate)
- Antifungal prophylaxis is recommended during the expected period of neutropenia in those patients who are anticipated to have profound, protracted neutropenia and grade III or IV mucositis where the risk for invasive candidiasis is high
- Patients with high risk of invasive candidiasis will require Fluconazole
- Patients with high risk of invasive mold infection will require mold-active agents- echinocandins and other azoles (posaconazole, voriconazole, isavuconazole)

- A mold-active triazole is recommended where the risk of invasive aspergillosis is . 6%, such as in patients with AML/ MDS during the neutropenic period associated with chemotherapy
- Invasive mold infection risk is now observed to be greater in late-stage post-allogeneic SCT, and a mold-active antifungal should be considered in this context (eg, posaconazole) and/ or in the context of GVHD.
- Prophylaxis is recommended, eg, TMPSMX—for patients receiving chemotherapy regimens associated with . 3.5% risk for pneumonia from Pneumocystis jirovecii (eg, those with > 20 mg prednisone equivalents daily for >1 month or those on the basis of purine analogs

Evidence from literature:

- An updated Cochrane review, which included 29 trials of antifungal prophylaxis and three trials of empirically administered antifungals in patients with cancer with neutropenia found no significant difference between antifungals and placebo or no treatment of all cause mortality at approximately 3 months (RR, 0.94; 95% CI, 0.81 to 1.09)
- however, there was a significant effect for death related to fungal infection (RR, 0.52; 95% CI, 0.38 to 0.71) and invasive infections (RR, 0.50; 95% CI, 0.39 to 0.64)
- Baseline rates of fungal infections in the control groups were 7.6% (all patients receiving HSCT and chemotherapy) and 20% (patients receiving HSCT only)

Gøtzsche PC, Johansen HK: Routine versus selective antifungal administration for control of fungal infections in patients with cancer. Cochrane Database Syst Rev 2014:CD000026, 2014

- A retrospective review of the medical records of 740 patients with melanoma who received immune checkpoint blockers found that serious infection occurred in 54 patients (7.3%). The main risk factors for infection were the receipt of corticosteroids and/or infliximab
- Evidence is emerging about the risk of infection with newer cancer therapy options.

Del Castillo M, Romero FA, Arguello E, et al: The ¨ spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. Clin Infect Dis 63:1490-1493, 2016

Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation: systematic review and meta-analysis

E Robenshtok, A Gafter-Gvili, E Goldberg, M Weinberger, M Yeshurun, L Leibovici, and M Paul.

Review published: 2007.

- 64 RCTs were included (n=13015, 6157 receiving treatment and 6498 control)
- Allocation generation and concealment were adequately reported in 16 studies
- 26 studies were double blind

- All cause mortality
- Reported in 31 studies
- Mortality at end of follow up/30 day mortality significantly reduced in patients treated with systemic antifungals (in comparison to no prophylaxis) (RR 0.84, 95% CI, 0.74-0.95,p=0.007 for end of follow up and RR 0.79, 95% CI, 0.68-0.92, p=? For 30 day mortality)
- Meta regression however showed only one significant association, and that was between patients of acute leukaemia and RR for mortality at the end of the follow up
- 33 studies reported significant differences in fungus-related mortality (RR 0.55, 95% CI, 0.41-0.74, $p<0.0001$) between patients on prophylactic systemic antifungals and those who are not on any prophylaxis

- Comparison of two systemic antifungals agents
- 7 studies compared fluconazole with Itraconazole
- Significant increase in adverse effects with itraconazole (study discontinued)
- 3 studies compared fluconazole and AMB
- Significant reduction in IFI with fluconazole compared to AMB (RR 0.47, 95% CI) with AMB showing more adverse effects
- 2 studies compared posaconazole with fluconazole
- Borderline reduction in all cause mortality (RR 0.77, CI 95%)
- Significant reduction in fungus-related mortality (RR 0.25), documented IFI (RR 0.47) and invasive aspergillus infection (RR 0.22)

- Concerns about results
- Majority of studies had wide confidence intervals, ration>1, questionable reliability
- Should be considered when interpreting the results

- Conclusions drawn from the study-

-antifungals prophylaxis should be offered to patients receiving allogenic HSCT

- Should be offered to patients with acute leukaemia during induction chemotherapy and other groups with high risk to develop IFI
- Recommendations could not be made in cases of autogenic HSCT recipients

IDSA/ASCO recommendations chart

Table 1. Summary of Recommendations for Antimicrobial Prophylaxis

Type of Prophylaxis	Population	Recommendation	Timing of Prophylaxis
Antibacterial	Patients at high risk of febrile neutropenia (Table 2) or profound, protracted neutropenia	Fluoroquinolone prophylaxis is recommended	During period of expected neutropenia
Antifungal	Patients at high risk of febrile neutropenia (Table 2) or profound, protracted neutropenia Patients with GVHD[14]	Oral triazole or parenteral echinocandin prophylaxis is recommended; a mold-active triazole is recommended when the risk of invasive aspergillosis is > 6%, such as in patients with AML/MDS or during treatment of GVHD[14]	During period of expected neutropenia
	Patients receiving chemotherapy regimens associated with > 3.5% risk for pneumonia from *Pneumocystis jirovecii* (eg, those with ≥ 20 mg prednisone equivalents daily for ≥ 1 month or those on the basis of purine analogs)	Prophylaxis, eg, trimethoprim-sulfamethoxazole (TMP-SMX), is recommended	Postmyeloid reconstitution or engraftment after stem-cell transplantation, particularly in the setting of postengraftment augmented immunosuppression (for the treatment of GVHD)

European guideline: ECIL (2018)

- Major changes from 2011 guidelines-

1. The implementation of a novel IDSA grading system that condensed the strength of recommendation from five to three levels
2. Extending the recommendations to other haematological diseases besides AML and recipients of an allogeneic HSCT

- Due to new therapeutic approaches including biotherapies, IFD has recently been reported more frequently in many haematological diseases, including lymphoproliferative disorders

Lortholary O, Gangneux JP, Sitbon K et al. Epidemiological trends in invasive aspergillosis in France: the SAIF network 2005–2007. Clin Microbiol Infect 2011; 17: 1882–9.

ECIL guideline for 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
- Risk factors

1. advanced age
2. prolonged and profound neutropenia and monocytopenia
3. use of purine analogues (e.g. fludarabine)
4. the presence of indwelling catheters, alimentary mucositis and individual genetic susceptibilities

Lupianez CB, Canet LM, Carvalho A ~ et al. Polymorphisms in host immunity-modulating genes and risk of invasive aspergillosis: results from the AspBIOmics Consortium.Infect Immun 2015; 84: 643–57.

- 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%

Donnelly JP, Cordonnier C, Cuenca-Estrella M et al. A European prospective invasive mould disease audit. In: Twenty-fourth European Congress of Clinical Microbiology and Infectious Diseases, 10–13 May 2014, Barcelona, Spain. Abstract P0028a

- 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
- Does not recommend primary antifungal prophylaxis beyond remission-induction chemotherapy, unless patients are to undergo re-induction chemotherapy or intensified consolidation therapy

Wang L, Hu J, Sun Y et al. Does high-dose cytarabine cause more fungal infection in patients with acute myeloid leukemia undergoing consolidation therapy. Medicine (Baltimore) 2016; 95: e2560.

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 ($n = 298$). Posaconazole oral suspension 200 mg q8h ($n = 304$).	8	2	0.06	22	16	0.06

Recommended regimen for AML (ECIL 2018)

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).

Poor tolerability

No large study

Insufficient data

ECIL guideline for MDS

- most patients receive only supportive care treatment (transfusions, erythropoiesis stimulating agents), lenalidomide (e.g. chromosome 5q deletion) or hypomethylating agents (azacitidine or decitabine).
- 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.

Toma A, Fenaux P, Dreyfus F et al. Infections in myelodysplastic syndromes. Haematologica 2012; 97: 1459–70.

- 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
- , 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

Pomares H, Arnan M, Sa´nchez-Ortega I et al. Invasive fungal infections in AML/MDS patients treated with azacitidine: a risk worth considering antifungal prophylaxis? Mycoses 2016; 59: 516–9.

ECIL guideline for ALL

- An IFD rate of 6.5% has been reported in the retrospective SEIFEM2004 analysis of 1173 adults undergoing treatment for ALL with invasive aspergillosis and candidiasis being most frequent.
- there is currently no approved standard of care for patients with ALL
- 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
- cautious use of fluconazole prophylaxis to prevent yeast infections may be considered (C-III)

ECIL guideline for ALL

- 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
- Primary antifungal prophylaxis is therefore not recommended
- 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
- drug interactions with azole antifungals need to be considered in patients who develop an IFD while receiving TKIs

Steinbach WJ, Marr KA, Anaissie EJ et al. Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. J Infect 2012; 65: 453–64

ECIL guideline for 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

- several large epidemiological studies and prospective registries uniformly reported very low incidences (1%) of yeast and mould infections among those receiving conventional combination chemotherapy

- Newer treatment options: immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies and autologous HSCT becoming the new standard of care
- Use of these new lines of drugs have transformed multiple myeloma in a chronic disease from an acute one leading to more prolonged exposure to infective agents and risk of infection

- But 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%
- primary antifungal prophylaxis is not recommended for patients being treated for myeloma.

Teh BW, Teng JC, Urbancic K et al. Invasive fungal infections in patients with multiple myeloma: a multi-center study in the era of novel myeloma therapies. Haematologica 2015; 100: e28–31

ECIL guideline for CLL

- Patients with CLL are prone to infections because of-

1. the disease-associated humoral immunodeficiency (related to stage and duration of disease)
2. additional immunosuppression resulting from therapy with corticosteroids, cytotoxic drugs (alkylating agents and purine analogues)
3. monoclonal antibodies (rituximab, alemtuzumab, ofatumumab and obinutuzumab)
4. lenalidomide
5. kinase inhibitors (ibrutinib and idelalisib).

- Most patients develop bacterial or viral infections rather than IFD
- A retrospective multicentre Italian study (SEIFEM-2004) reported an IFD incidence rate of 0.5%
- primary antifungal prophylaxis is not recommended
- It might be considered for patients with prolonged neutropenia (>6 months), elderly patients and those with advanced and unresponsive CLL disease

Pagano L, Caira M, Candoni A et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica 2006; 91: 1068–75

ECIL guideline for Lymphoma

- In SEIFEM-2004 study, including 844 patients with Hodgkin's disease and 3475 patients with non-Hodgkin's disease, incidence of IFD was 0.7% and 1.6%, respectively
- Antifungal prophylaxis was thus not recommended

HSCT recipients (autologous)

- Patients undergoing autologous HSCT 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)

HSCT recipients (allogenic)

- Phase-specific recommendations
- Active leukaemia, cord blood transplantation and prior fungal infection are major risk factors during the pre-engraftment period
- alternative donor HSCT recipients with at least one of the following factors are at high risk of IFD during engraftment

1. iron overload
2. early or recurrent cytomegalovirus infection
3. acute graft-versus-host disease (GvHD)
4. delayed engraftment (more than 3 weeks neutropenia)
5. high dose corticosteroids (2 mg/kg or more) for more than 1 week

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

- In post-engraftment phases, acute and chronic GvHD historically represent major risk factors for IFD
- GvHD in itself is not an indication for mould-active prophylaxis
- High risk factors-

1. grade III–IV acute GvHD
2. grade II acute GvHD of alternative donor transplants
3. GvHD unresponsive to standard corticosteroid therapy
4. acute GvHD followed by chronic GvHD

- Low risk factors

1. grade II GvHD responsive to steroid therapy after an HLA-compatible sibling donor transplant
2. chronic GvHD not preceded by acute GvHD

- Other risk factors-

1. Prolonged neutropenia
2. Recurrent cytomegalovirus infection
3. Age >40 years

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Posaconazole or Fluconazole for Prophylaxis in Severe Graft-versus-Host Disease

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- Phase 3, randomised, multicentre, double-blind and double-dummy, parallel-group, multinational trial
- Compared efficacy of posaconazole and fluconazole for prophylaxis against IFI in high risk GVHD patients after allogenic hematopoietic stem cell transplantation
- Independent data review committee- eight physicians with expertise in opportunistic infections in transplant recipients

- Subjects: males and females of 13 years and older, weight>34 Kg who had undergone allogenic HSCT if they develop acute GVHD, grade II-IV , or chronic extensive GVHD, or treated with intensive immunosuppressive therapy (high dose steroids >1 mg/Kg/day for acute GVHD, >0.8 mg/Kg/day every other day for chronic GVHD), ATG, or a combination of two or more immunosuppressive agents/therapies
- Excluded if they had a h/o proven/probable mould infection or suspected IFI at baseline, hepatic dysfunction (elevated ALT/AST or both)
- Excluded if there was drug to drug interaction with azoles

- Stratified according to GVHD status
- Randomly assigned to receive posaconazole oral suspension 200 mg TDS plus placebo capsule OD or fluconazole capsules 400 mg OD plus placebo oral suspension TDS for 112 days or protocol specified duration (until bIFI, adverse event requiring discontinuation, death)
- Exposure period- first dose to 7 days post-last dose
- Medication could be interrupted for up to 5 consecutive days without exclusion from the study

- Primary efficacy end point- incidence of proven/probable IFI as determined by the blinded data review committe (in the treatment period, among ITT population)
- Failure of prophylaxis- development of IFI within fixed treatment period of 112 days
- Other end points- proven/probable aspergillosis during fixed treatment period, bIFI during exposure period, overall mortality in ITT population, fungus-attributed mortality in ITT

- Laboratory evaluation for susceptibility to fungal isolates and testing for colonization- every 2 weeks
- Immunoassays for aspergillus galactomannan ag in serum
- Fungal colonisation at baseline and at the end of the treatment period
- Clinically significant change in susceptibility- increase of MIC by 4 times
- Plasma levels of posaconazole – liquid chromatography-tandem mass spectroscopy

- Safety assessment-
- Paired electrocardiographic and laboratory evaluation
- Monitored for 16 weeks+ additional 8 weeks
- Adverse effects noted
- Reasons for discontinuation noted (national cancer institute’s common toxicity criteria)

- RESULTS:

- Efficacy
- 62 cases (10%) of proven/probable IFI
- 43 in treatment period, 19 occurred after day 112
- Incidence of IFI in treatment period- 5.3% in posaconazole group and 9% in fluconazole group (OR for IFI in posaconazole group 0.56, CI 95%)
- Superiority was not demonstrated, but non-inferiority was established

- Majority if IFIs were invasive aspergillosis
- Posaconazole was superior to fluconazole in reducing invasive aspergillosis incidence (OR 0.31, CI 95%, p=0.006)
- Posaconazole was superior to fluconazole in reducing incidence of breakthrough proven or probable IFI (OR 0.30, CI 95%, p=0.004)
- Mean concentration of posaconazole- 1470 ng/mL in chronic GVHD and 958 ng/ml in acute GVHD
- There was a delay in onset of IFI in posaconazole group than fluconazole group (p=0.048)

- Fewer deaths in posaconazole group (p=0.048) and fungus-attributed death was even fewer (p=0.046)
- Colonisation- principal organism- C. Albicans and C. Glabrata
- Development of resistance more common in fluconazole group (17%) than in posaconazole group (5%)
- The safety issues: similar adverse effects related to therapy in both groups (36% in posaconazole vs 38% in fluconazole group)

Summery

- posaconazole was as effective as fluconazole in preventing all invasive fungal diseases in recipients of hematopoietic stem-cell transplants with severe GVHD who were receiving immunosuppressive agents during a 16-week period
- Posaconazole was superior to fluconazole in the prevention of invasive aspergillosis
- posaconazole was shown to be as safe and as acceptable as fluconazole
- posaconazole was significantly more effective in preventing invasive fungal infections during the exposure period than fluconazole
- Although posaconazole provided no advantage over fluconazole with respect to overall mortality, a difference in mortality due to invasive fungal infections was observed

Table 2. Proven or Probable Invasive Fungal Infections during the Fixed Treatment Period and the Exposure Period, According to Pathogen, among Patients Assigned to a Study Drug.

Pathogen or Pathogen Group	Posaconazole Group (N=301)	Fluconazole Group (N=299)	Odds Ratio (95% CI)	P Value
	no. (%)			
Fixed treatment period				
All proven and probable invasive fungal infections*	16 (5.3)	27 (9.0)	0.56 (0.30–1.07)	0.07
All invasive aspergillosis	7 (2.3)	21 (7.0)	0.31 (0.13–0.75)	0.006
Aspergillus (not otherwise specified)	0	5		
Aspergillus galactomannan antigen index	5	6		
A. fumigatus	2	5		
A. flavus	0	3		
A. niger	0	1		
A. terreus	0	1		
All candida species	4	4		
C. krusei	1	1		
C. albicans	0	1		
C. glabrata	2	1		
C. parapsilosis	0	1		
Candida (not otherwise specified)	1	0		
Other fungi	5	2		
Pseudallescheria boydii	1	0		
Rhizomucor miehei	0	1		
Trichosporon beigelii	1	0		
Scedosporium prolificans	1	0		
Mold (not otherwise specified)	2	1		

Table 2. (Continued.)

Pathogen or Pathogen Group	Posaconazole Group (N=291)	Fluconazole Group (N=288)	Odds Ratio (95% CI)	P Value
	no. (%)			
Exposure period†				
All proven and probable invasive fungal infections*	7 (2.4)	22 (7.6)	0.30 (0.12–0.71)	0.004
All invasive aspergillosis	3 (1.0)	17 (5.9)	0.17 (0.05–0.57)	0.001
Aspergillus (not otherwise specified)	0	4		
Aspergillus galactomannan antigen index	3	4		
A. fumigatus	0	6‡		
A. flavus	0	2		
A. niger	0	0		
A. terreus	0	1		
All candida species	1	3		
C. krusei	0	1		
C. albicans	0	1		
C. glabrata	1	1		
C. parapsilosis	0	0		
Candida (not otherwise specified)	0	0		
Other fungi	3	2		
P. boydii	1	0		
R. miehei	0	1		
T. beigelii	1	0		
S. prolificans	0	0		
Mold (not otherwise specified)	1	1		

* Cases of probable invasive aspergillosis confirmed on aspergillus galactomannan immunossay (Platelia Aspergillus EIA, Bio-Rad Laboratories) were included in this category.
† The total numbers of patients for the analysis of invasive fungal infections during the exposure period were 291 in the posaconazole group and 288 in the fluconazole group.
‡ An invasive fungal infection that developed in one patient on day 113 (while the patient was receiving the study drug) was not counted as occurring during the fixed treatment period (the interval beginning on the date of randomization and ending on day 112).

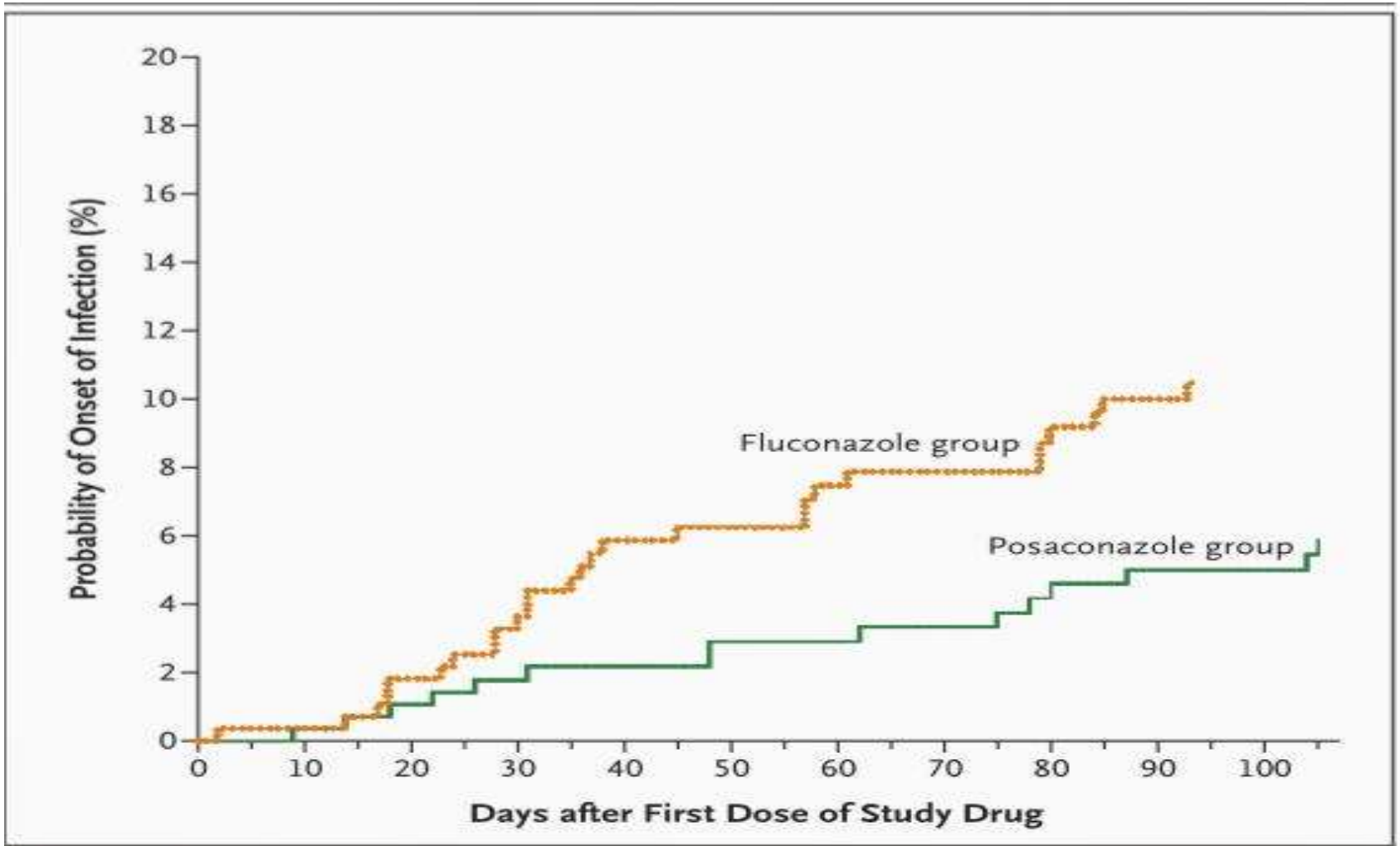

Figure 1. Time to Proven or Probable Invasive Fungal Infection.

All events not related to invasive fungal infections were considered censored; data on all patients were censored as of the end of the treatment period (day 112). The mean day of the onset of invasive fungal infection was day 102 in the posaconazole group and day 88 in the fluconazole group (P=0.048).

Table 4. Treatment-Related Adverse Events and All-Cause Mortality during the Observation Period.*

Event	Posaconazole Group (N=301)	Fluconazole Group (N=299)
	no. (%)	
Adverse events		
Total	107 (36)	115 (38)
Headache	3 (1)	8 (3)
Gastrointestinal disorders		
Diarrhea	8 (3)	12 (4)
Nausea	22 (7)	28 (9)
Vomiting	13 (4)	15 (5)
Liver and biliary disorders		
Bilirubinemia	8 (3)	5 (2)
Increased γ-glutamyltransferase	9 (3)	7 (2)
Increased hepatic enzymes	8 (3)	7 (2)
Increased aspartate aminotransferase	8 (3)	3 (1)
Increased alanine aminotransferase	9 (3)	4 (1)
Serious adverse events		
Total	40 (13)	29 (10)
Increased hepatic enzymes	6 (2)	1 (<1)
Increased γ-glutamyltransferase	5 (2)	3 (1)
Hepatocellular damage	4 (1)	0
Bilirubinemia	3 (1)	3 (1)
Abnormal hepatic function	0	3 (1)
Vomiting	4 (1)	1 (<1)
Nausea	4 (1)	0

Table 4. (Continued.)

Event	Posaconazole Group (N=301)	Fluconazole Group (N=299)
	no. (%)	
Deaths		
All causes		
During the observation period	76 (25)	84 (28)
During the fixed treatment period	58 (19)	59 (20)
During the exposure period†	22 (8)	24 (8)
Cause of death		
Adverse event	39 (13)§	37 (12)
Invasive fungal infection		
Complications of infection‡	4 (1)	12 (4)
Proven or probable infection§	2 (1)	11 (4)
Possible infection	2 (1)	1 (<1)
Progression of underlying disease or GVHD	31 (10)	33 (11)
Other	2 (1)	2 (1)

* Treatment-related adverse events were those that occurred at a frequency of at least 3% in either of the two groups. Treatment-related serious adverse events were those that occurred in at least three patients. Actual totals are also shown. (For further details on treatment-related serious events, see the Supplementary Appendix.) Deaths from all causes were those that occurred during the 24-week observation period. Invasive fungal infections were adjudicated by the data review committee in a blinded fashion. The cause of death was assessed by an investigator as one of the following: an invasive fungal infection, a cause other than an invasive fungal infection but in the presence of an invasive fungal infection, or a cause other than an invasive fungal infection (without evidence on autopsy of invasive fungal infection or with clinical evidence of the resolution of an invasive fungal infection).

† Data are for 291 patients in the posaconazole group and 288 in the fluconazole group. Only one adverse event was considered by an investigator to be related to the study drug. Ninety days after posaconazole was discontinued, only a single death from multiple-organ failure occurred after cyclosporine-associated thrombotic thrombocytopenic purpura–like syndrome developed; the death was considered by the investigator to be possibly related to treatment with posaconazole.

‡ P=0.046 by the log-rank test.

§ P=0.01 by the chi-square test.

Recommendations: pre-engraftment period

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

Recommendations: post-engraftment period

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.

Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2021

- Incorporated recommendations for patients receiving newer therapies for haematological disorders
- Due to the absence of high-level evidence, the routine use of antifungal prophylaxis is not recommended for the majority of patients undergoing treatment with new haematological treatments
- Antifungal prophylaxis should be considered on an individual patient risk model

Table 1 Established risk groups for IFD and recommended antifungal prophylaxis coverage in adults

Risk level	Risk groups	Recommended prophylaxis†	SoR	QoE
High risk >10% incidence of IFD	Neutrophil <0.1 × 10^9/L for >3 weeks or <0.5 × 10^9/L for >5 weeks (e.g. allogeneic HSCT) Corticosteroids >1 mg/kg prednisolone equivalent and neutrophils <1 × 10^9/L for >1 week Corticosteroids >2 mg/kg prednisolone equivalent >2 weeks Unrelated, mismatched or cord blood allogeneic HSCT GVHD – extensive or severe AML – induction/reinduction ALL – induction/reinduction MDS	First line: Posaconazole Alternate agents: Voriconazole Itraconazole Micafungin Liposomal amphotericin Isavuconazole	A	I
Low risk Less than 5% incidence of IFD	Autologous HSCT (e.g. patients at high risk for mucositis) Allogeneic HSCT with expected neutropenia <14 days Lymphoma (e.g. intensive/dose-escalated therapy)	First line: Fluconazole Alternate agents: Echinocandins Itraconazole	B	II (context dependent; level I evidence in setting of alloHSCT)
Very low risk‡ Less than 5% incidence of IFD No mucositis	Other lymphoproliferative neoplasms (e.g. standard chemotherapy for lymphoma, induction therapy for myeloma, treatment-naïve CLL) Other myeloproliferative neoplasms Treatment for solid organ tumours	No prophylaxis	B	II

†Please refer to Table 4 for summary of recommendations and level of evidence supporting choice of antifungal prophylaxis agents.
‡Consider that low and/or sporadic occurrence is not equal to no risk and is dependent on underlying treatment regimen, previous and cumulative treatments.
ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; GVHD, graft versus host disease; HSCT, haemopoietic stem cell transplantation; IFD, invasive fungal disease; MDS, myelodysplastic syndrome; QoE, quality of evidence; SoR, strength of recommendation.

- For patients receiving new generation immunomodu-latory, monoclonal antibody therapy for relapsed and refractory myeloma, prophylaxis with fluconazole could be considered (Marginal recommendation, Level III evidence).
- or patients undergoing CAR T-cell therapy, prophy-laxis withfluconazole should be considered (Strong recommendation, Level II evidence).
- or patients deemed at higher risk of fungal infection(e.g. due to severe neutropenia or multiple lines of ther-apy, treatment of cytokine release syndrome (CRS)),mould-active azole prophylaxis could be considered(Moderate recommendation, Level II evidence)
- For patients with a prior history of IFD, secondaryprophylaxis should be administered (Marginal recom-mendation, Level III evidence)

- increasing number of targeted agents have become available as standard of care options for the treatment of haematology patients
- through their effects on immune function, they may increase the risk of IFD
- Reported rates of IFD accom-panying the use of these agents vary according to the patient group being treated

1. treatment naïve vs relapsed/refractory malignancy;

2. previous treatments used, including number of lines of therapy;

3. whether these agents are used in combination with other therapies, especially conventional chemotherapy that induces mucositis or prolonged neutropenia.

Agent specific evidence

- Ibrutinib

- a BTK inhibitor commonly used for the treatment of chronic lymphocytic leukaemia (CLL) and other B-cell lymphoproliferative disorders
- interrupts B-cell receptor signalling and also results in hypogammaglobulinaemia.
- A retrospective study of 378 patients receiving ibrutinib (monotherapy in 84% of cases) reported an IFD rate of **4.2%**, with the majority of IFD cases lacking classical risk factors such as **neutropenia or corticosteroid usage**
- real-world data suggests an IFD rate as high as 12.1% in patients treated with ibrutinib monotherapy in the setting of relapsed/refractory CLL

1. Varughese T, Taur Y, Cohen N,Palomba ML, Seo SK, Hohl TMet al.Serious infections in patients receivingibrutinib for treatment of lymphoidcancer.Clin Infect Dis2018;67: 687–91
2. Teh BW, Chui W, Handunnetti S,Tam C, Worth LJ, Thursky KAet al.High rates of proven invasive fungaldisease with the use of ibrutinibmonotherapy for relapsed or refractorychronic lymphocytic leukemia.LeukLymphoma2019;60: 1572–5

- The majority of fungal infections reported were invasive aspergillosis with a predilection for central nervous system (CNS) involvement (40%).Most patients developed IFD within 3–6 months of starting ibrutinib
- Substantially higher IFD rates of 38.9% (7/18) have been observed in the context of primary CNS lymphoma treated with ibrutinib, potentially due to the concomitant use of chemotherapy and corticosteroid agents

Lionakis MS, Dunleavy K,Roschewski M, Widemann BC,Butman JA, Schmitz Ret al. Inhibitionof B cell receptor signaling by ibrutinibin primary CNS lymphoma.Cancer Cell2017;31: 833–43.e5

Summary of IFD risks with newer therapeutic agents

Therapy	Population	IFD rates (%)	Comments
BTK inhibitor (e.g. ibrutinib)	Relapsed/refractory B-cell lymphoproliferative disorder	3–12	Rates of 1% reported in clinical trials of BTK inhibitors Invasive aspergillosis with CNS involvement up to 40% *Cryptococcus* spp. *Pneumocystis jirovecii* pneumonia
	Primary CNS lymphoma	5–44	In combination with corticosteroids and conventional chemotherapy
PI3K inhibitor (e.g. idelalisib)	Relapsed/refractory B-cell lymphoproliferative disorder	3	*Pneumocystis jirovecii* pneumonia
BCL-2 inhibitor (e.g. venetoclax)	CLL	1	*Aspergillus* spp., *Pneumocystis jirovecii* pneumonia
Hypomethylating agents (e.g. azacitadine)	MDS AML	5–13	Rates higher in relapsed/refractory disease versus its use as front-line therapy Rate of 13% when used in combination with BCL-2 inhibitor venetoclax *Aspergillus* spp., *Candida* spp.
FLT-3 inhibitors (e.g. midostaurin, gliteritinib)	AML	5	Limited data from clinical trial
Second generation IMiD, PI CD38 or SLAMF7 monoclonal antibodies	Relapsed/refractory myeloma	2–7	*Candida* spp., *Cryptococcus* spp.
CAR T-cell therapy	Relapsed/refractory ALL Relapsed/refractory NHL	5–8	In the setting of fluconazole or micafungin prophylaxis Rates up to 13% in patients with ALL *Aspergillus* spp., *Candida* spp., *Mucor* spp.
Bi-specific antibody therapies (e.g. blinatumomab)	Relapsed/refractory ALL Relapsed/refractory NHL	2	Limited clinical trial data

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BCL-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukaemia; CNS, central nervous system; FLT-3, fms-like tyrosine kinase; IFD, invasive fungal disease; IMiD, immunomodulatory drug therapy; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; PI, proteasome inhibitor; PI3K, phosphatidylinositol 3-kinase; SLAMF7, signalling lymphocytic activation molecule F7.

Evidence for prophylactic agents

- POSACONAZOLE:
- Preferred agent for AML and those undergoing HSCT
- Network meta-analyses of randomised controlled trials of triazole prophylaxis confirm posaconazole's efficacy for the prevention of proven or probable IFD and invasive aspergillosis, reducing the requirement for empiric anti-fungal therapy and all-cause mortality compared to fluconazole and itraconazole*
- When evaluated, its use appears to be cost-effective compared to voriconazole**

- Bow EJ, Vanness DJ, Slavin M,Cordonnier C, Cornely OA, Marks DIet al. Systematic review and mixed treatment comparison meta-analysis of randomized clinical trials of primary oral antifungal prophylaxis in allogeneic hematopoietic cell transplant recipients.BMC Infect Dis2015;15: 128
- **Zhao Yallogeneic J, Khoo AL, Tan G, Teng M,Tee C, Tan BHet al. Network meta-analysis and pharmacoeconomicevaluation offluconazole,itraconazole, posaconazole,and voriconazole in invasivefungal infection prophylaxis.Antimicrob Agents Chemother2016;60:376–86

RESEARCH ARTICLE Open Access

Systematic review and mixed treatment comparison meta-analysis of randomized clinical trials of primary oral antifungal prophylaxis in allogeneic hematopoietic cell transplant recipients

Eric J Bow[1*], David J Vanness[2], Monica Slavin[3], Catherine Cordonnier[4], Oliver A Cornely[5], David I Marks[6], Antonio Pagliuca[7], Carlos Solano[8], Lael Cragin[9], Alissa J Shaul[9], Sonja Sorensen[9], Richard Chambers[10], Michal Kantecki[11], David Weinstein[11] and Haran Schlamm[12]

- Systematic literature review in 2014 to identify and analyze all RCTs studying fluconazole, itraconazole, posaconazole and voriconazole for primary oral antifungal prophylaxis in alloHCT recipients post-transplant.
- Primary outcome evaluated: proven/probable Invasive fungal infection defined by criteria laid down by S. Ascioglu in his paper (2002) for EORTC/IFICG
- Other outcomes: all cause mortality, proven invasive candidiasis, administration of other licensed antifungal therapy
- Outcomes were evaluated at 180 days post-transplant (or the closest available time point) (data extracted from each RCT)

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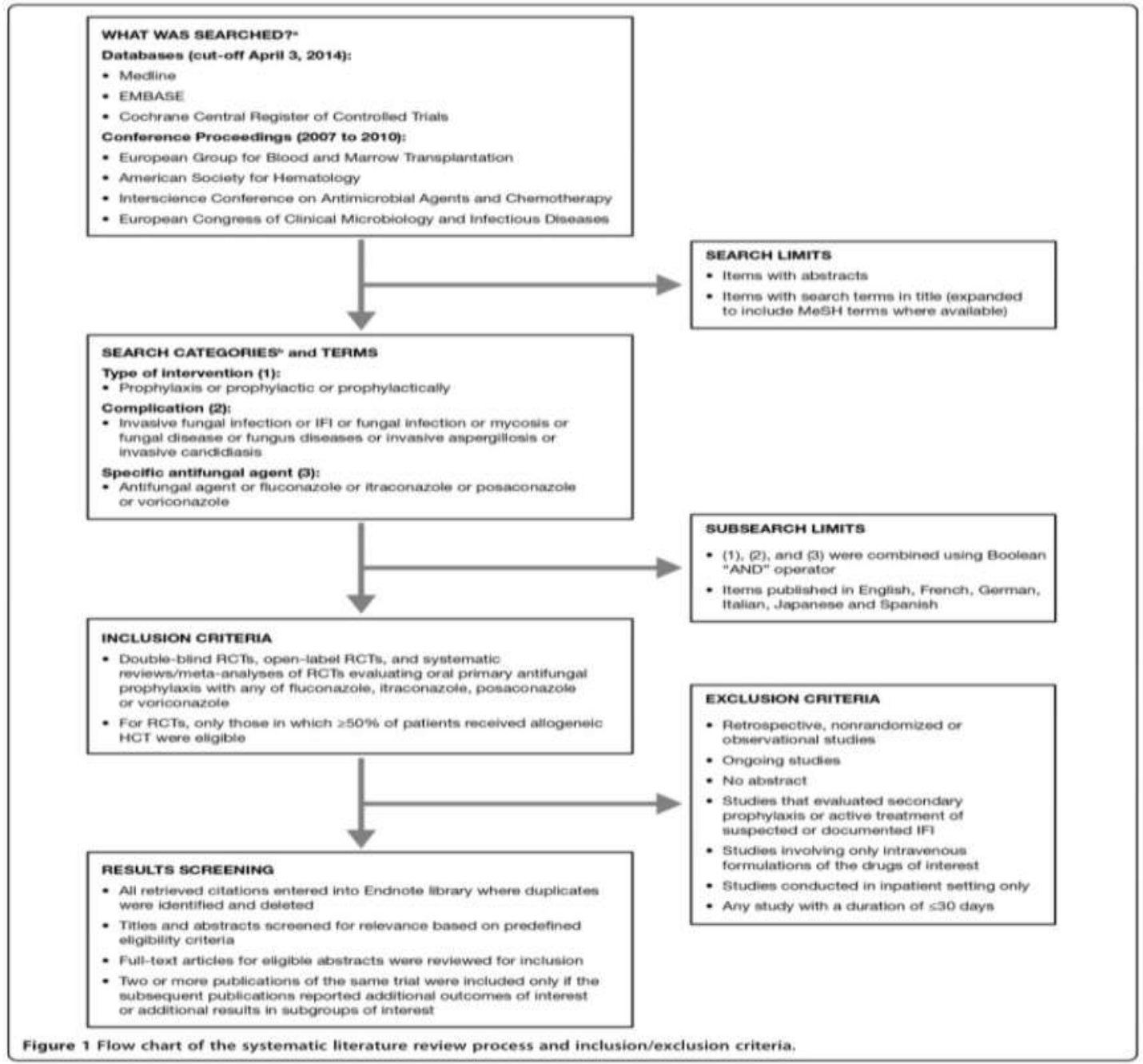

Figure 1 Flow chart of the systematic literature review process and inclusion/exclusion criteria.

- Identified six RCTs that compared directly or indirectly inform a comparison of fluconazole, itraconazole, voriconazole and posaconazole.
- 5 head to head studies randomized 2174 subjects (140-600 patients per study)
- 4 multicentre trials, 3 open-label designs, 2 double blind design
- Comparators- fluconazole in 4 RCTs, itraconazole in 3 RCTs, vori in 2 RCTs and posa in 1 RCT;

- Voriconazole most likely to reduce incidents of overall proven/probable IFI at 180 days post transplant relative to fluconazole
- Lowest posterior probability of IFIs among four agents (but not statistically significant)
- Posaconazole has highest reduction in incidence of IA in comparison to others
- Itraconazole has the higher preventive role against IC relative to fluconazole, voriconazole and posaconazole
- Voriconazole had the highest probability of avoiding use of OLAT in comparison to others
- There was no significant difference in all cause mortality among the agents

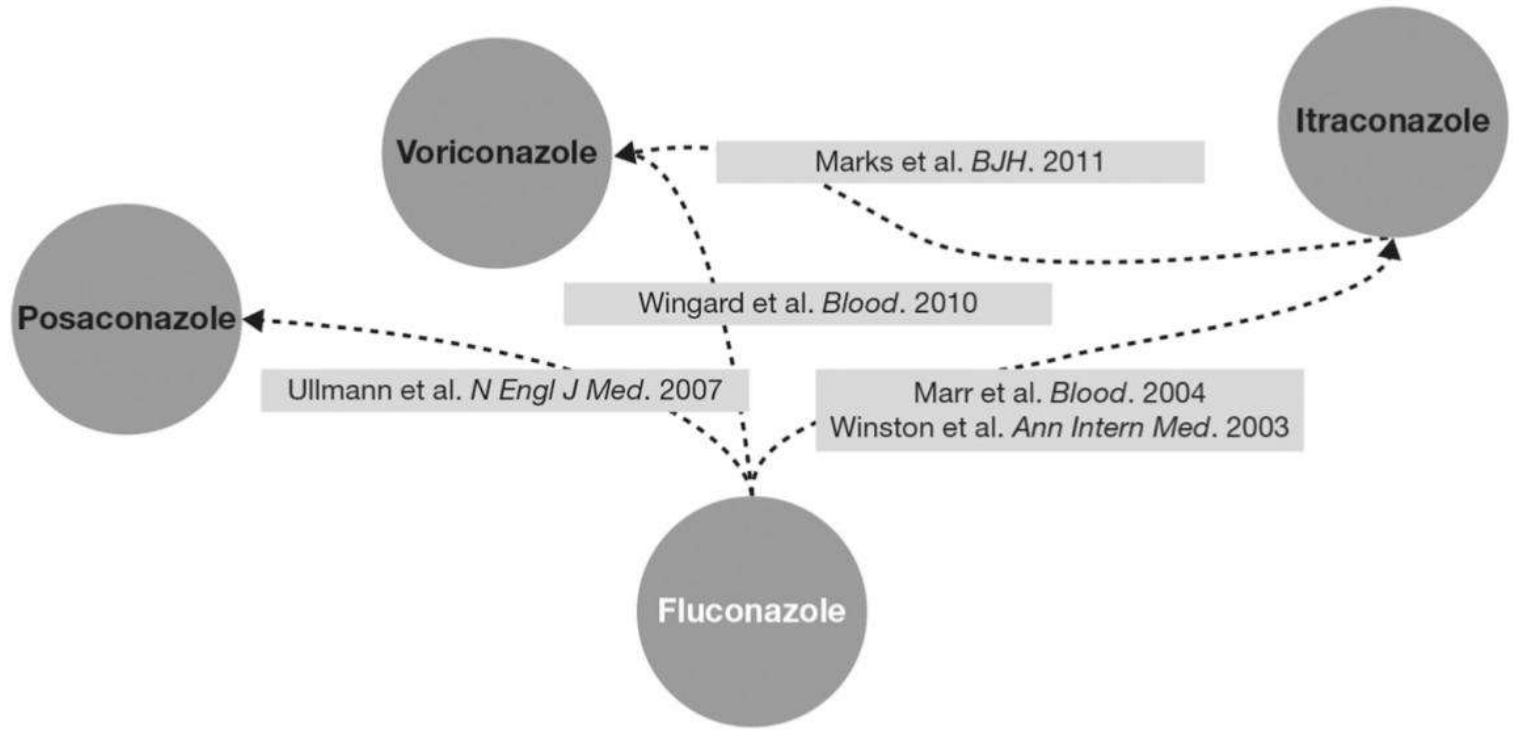

Figure 2 Evidence network of randomized controlled trials (RCTs) included into the mixed treatment comparison (MTC).

Table 1 Outcomes extracted from the randomized clinical trials and included into the mixed treatment comparison

Study	All-cause mortality	Incidence of proven/ probable IFI overall	Incidence of proven/ probable IA	Incidence of proven IC	Incidence of OLAT use
Winston 2003 [29]					
Fluconazole	28/67 (42%)	17/67 (25%)	8/67 (12%)	8/67 (12%)	Not reported
Itraconazole	32/71 (45%)	6/71 (8%)	3/71 (4%)	2/71 (3%)	Not reported
Marr 2004 [26]					
Fluconazole	44/148 (30%)	25/148 (17%)	20/148 (14%)	5/148 (3%)	25/148 (17%)
Itraconazole	55/151 (36%)	19/151 (13%)[a]	16/151 (11%)	4/151 (3%)	19/151 (13%)
Ullmann 2007 [27]					
Fluconazole	59/299 (20%)	27/299 (9%)	21/299 (7%)	4/299 (1%)	29/288 (10%)
Posaconazole	58/301 (19%)	16/301 (5%)	7/301 (2%)	4/301 (1%)	31/291 (11%)
Wingard 2010 [28]					
Fluconazole	59/295 (20%)	24/295 (8%)	17/295 (6%)	5/295 (2%)	89/295 (30%)
Voriconazole	57/305 (19%)	14/305 (5%)	9/305 (3%)	3/305 (1%)	73/305 (24%)
Marks 2011 [10]					
Itraconazole	44/241 (18%)	5/241 (2%)	5/241(2%)	0/241 (0%)	101/241 (42%)
Voriconazole	40/224 (18%)	3/224 (1%)	1/224 (0.4%)	2/224 (1%)	67/224 (30%)

IFI, invasive fungal infections; IA, invasive aspergillosis; IC, invasive candidiasis; OLAT, other licensed antifungal therapy.
[a]One patient developed both proven IC and probable IA, which was counted as a single IFI instead of 2 separate IFIs.

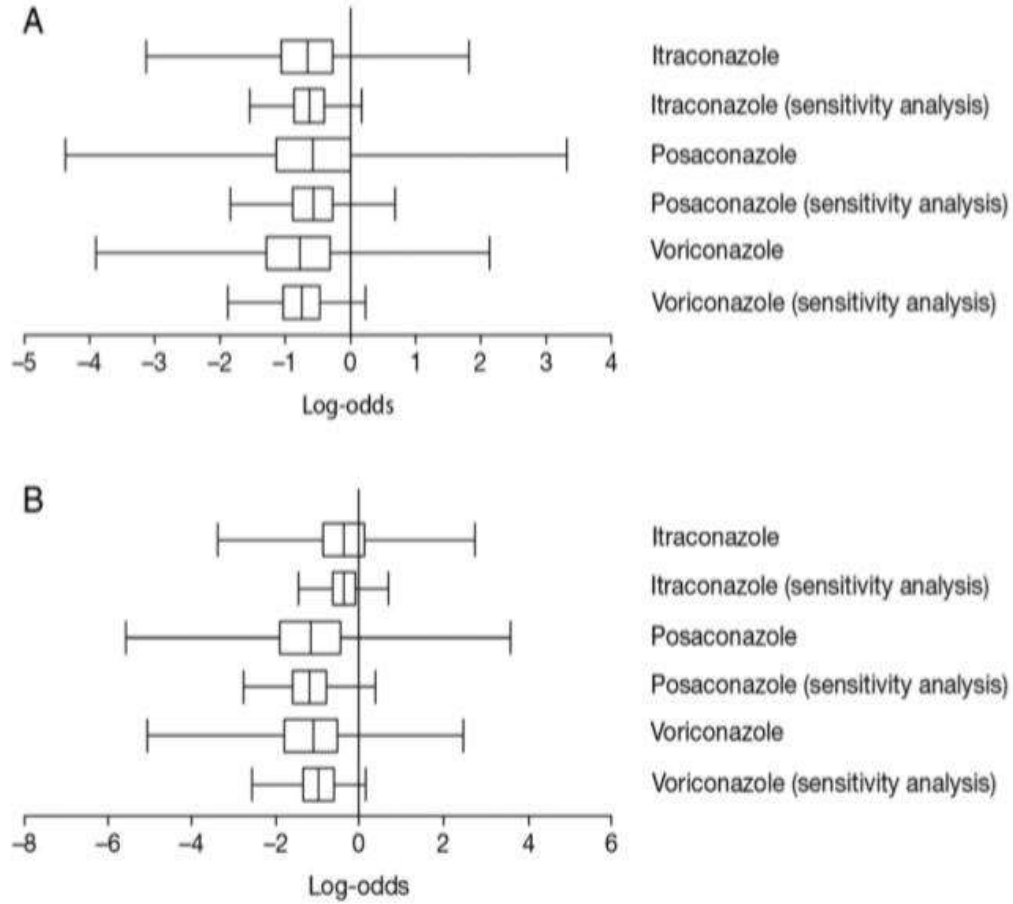

Figure 3 Treatment effect of antifungal agents on A) proven/probable invasive fungal infection (IFI) and B) proven/probable invasive aspergillosis (IA) at 180 days, compared between the base-case mixed treatment comparison (MTC) and the sensitivity analysis MTC using an empirical prior, expressed in log odds. Estimates less than zero indicate a reduced probability of IFI relative to fluconazole. The vertical bar of the box plot represents the posterior median value (probability <50%); the outer limits of the box plot represent the posterior interquartile range (probability 25%–75%); whiskers represent the most extreme Markov Chain Monte Carlo values of the posterior no more than 1.5 times the width of the interquartile range above or below the upper or lower bounds of the interquartile range.

- Conclusion of the analysis:

- Preferable to use mold active azoles over fluconazole to prevent IFIs in alloHCT recipients
- To prevent IA, Posaconazole and voriconazole may be preferred over other agents
- To prevent IC, itraconazole is preferred
- Voriconazole would reduce OLAT (other licensed antifungals) use

- Points of concern in the analysis:
- Many outcome comparisons do not meet traditional statistical significance criteria
- Confidence interval had to be wider in some of the comparisons to clearly show any statistical difference between two agents
- Studies had large heterogeneity in terms of the time of starting prophylaxis, the duration of continuation and the reasons for drug withdrawal

- Cohort studies evaluating posaconazole against voriconazole, itraconazole or micafungin consistently report lower rates of IFD with posaconazole ranging from 0 to 5% versus 5 to 11%
- For patientsundergoing HSCT, observational cohort studies haveshown that rates of breakthrough IFD during prophylaxis with posaconazole suspension remain low at between 3 and 8%
- Cohort studies of AML patients report similarly low rates of proven or probable break-through IFD (0–7%)

1. Epstein DJ, Seo SK, Huang YT,Park JH, Klimek VM, Berman Eet al.Micafungin versus posaconazoleprophylaxis in acute leukemia ormyelodysplastic syndrome: arandomized study.J Infect2018;77:227–34
2. Wang CH, Kan LP, Lin HA, Chang FY,Wang NC, Lin TYet al. Clinical efficacyand safety of primary antifungalprophylaxis with posaconazole versusfluconazole in allogeneic bloodhematopoietic stem celltransplantation recipients: aretrospective analysis of a singlemedical center in Taiwan.J MicrobiolImmunol Infect2016;49: 531–8.
3. Calmettes C, Gabriel F, Blanchard E,Servant V, Bouchet S, Kabore Net al.Breakthrough invasive aspergillosisand diagnostic accuracy of serumgalactomannan enzyme immune assayduring acute myeloid leukemiainduction chemotherapy withposaconazole prophylaxis.Oncotarget2018;9: 26724–36

- VORICONAZOLE
- Voriconazole is an alternate agent for IFD prophylaxis.
- Meta-analyses show no significant difference between posaconazole and voriconazole efficacy for the prevention of proven or probable IFD and invasive aspergillosis
- a significantly higher risk for treatment-relatedliver abnormalities was noted, compared to other azoles
- In cohort studies of AML patients, the use of voriconazole prophylaxis was associated with an IFD rate of 3–5%
- Due to vari-able metabolism, CYP2C19 testing prior to commence-ment could assist with dose selection

Bui V, Walker SA, Elligsen M, Vyas A,Kiss A, Palmay L. Voriconazoleprophylaxis in leukemic patients: aretrospective single-center study.J Oncol Pharm Pract2020;26: 873–81

- ITRACONAZOLE

- The only new data supporting the use of intravenous itraconazole or its solution are from a few cohort studies reporting IFD rates of 1–7% for HSCT patients and 5% for patients with AML.

Lin R, Xu X, Li Y, Sun J, Fan Z, Jiang Qet al. Comparison of long-term and short-term administration of itraconazole for primary antifungal prophylaxis in recipients of allogeneic hematopoietic stem cell transplantation: a multicenter,randomized, open-label trial. TransplInfect Dis2014;16: 286–94

- MICAFUNGIN

- In two trials, the rate of IFD was not significantly different when assessed against fluconazole and itraconazole at 7.3 and 4.4% respectively.
- Adverse event rates were significantly higher with itraconazole
- dosing with 100–150 mg intravenous (IV) daily followed byoral voriconazole or posaconazole on discharge, led to proven or probable IFD rates of between 1 and 4%
- Overall, the use of micafungin could be considered during the neutropenic period in high-risk patients if use of azoles is contraindicated or there are concerns about absorption

1. Huang X, Chen H, Han M, Zou P,Wu D, Lai Yet al. Multicenter,randomized, open-label studycomparing the efficacy and safety ofmicafungin versus itraconazole forprophylaxis of invasive fungalinfections in patients undergoinghematopoietic stem cell transplant.BiolBlood Marrow Transplant2012;18:1509–16
2. Rosillo C, Avila AM, Huang YT,Devlin S, Cho C, Montoro Jet al.Sequential systematic anti-moldprophylaxis with micafungin andvoriconazole results in very lowincidence of invasive mold infectionsin patients undergoing allogeneichematopoietic stem celltransplantation.Transpl Infect Dis2018;20: e12897.

- LIPOSOMAL AMB
- A recent randomised trial of L-AMB at 5 mg/kg twice a week compared to placebo for prophylaxis in ALL reported no difference in the rate of proven or probable IFD (7.9 vs 11.7%;P=0.24)
- a significantly higher rate of adverse events led to interruption of L-AMB in 20.3% of patients.
- Post hoc analysis did report a trend for lower IFD rates in patients who were administered L-AMB prophylaxis (7.6 vs14.4%;P=0.07)
- this agent could be considered in the setting of azole intolerance or contraindication
- Doses ranging from 50 to 200 mg, three times per week, have been used

Cornely OA, Leguay T, Maertens J,Vehreschild M, Anagnostopoulos A,Castagnola Cet al. Randomizedcomparison of liposomal amphotericinB versus placebo to prevent invasivemycoses in acute lymphoblasticleukaemia.J Antimicrob Chemother2017;72: 2359–67

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Network Meta-analysis and Pharmacoeconomic Evaluation of Fluconazole, Itraconazole, Posaconazole, and Voriconazole in Invasive Fungal Infection Prophylaxis

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Pharmacy and Therapeutics Office, Group Corporate Development, National Healthcare Group, Singapore[a]; Pharmacoeconomics and Drug Utilisation, Health Products Regulation Group, Health Sciences Authority, Singapore[b]; Department of Pharmacy, National University Health System, Singapore[c]; Department of General Internal Medicine and Infectious Diseases, Singapore General Hospital, Singapore[d]; Division of Infectious Diseases, University Medicine Cluster, National University Health System, Singapore[e]

- Objective- to examine the efficacy, tolerability and cost-effectiveness of all the triazoles in market in reducing bIFI in haematological malignancy patients and HSCT recipeients
- Study design: network meta-analysis

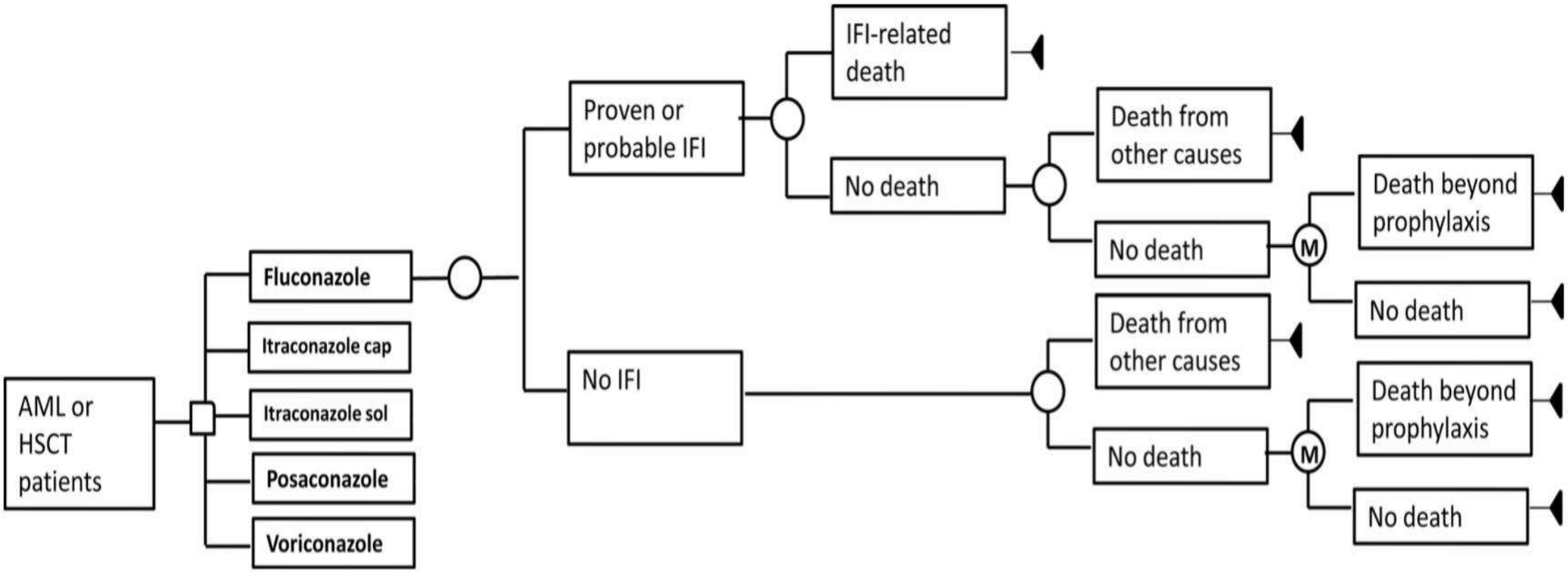


FIG 1 Schematic representation of the cost-effectiveness analysis model. AML, acute myeloid leukemia; HSCT, hematopoietic stem cell; cap, capsule; sol, solution; IFI, invasive fungal infection; M, Markov model.

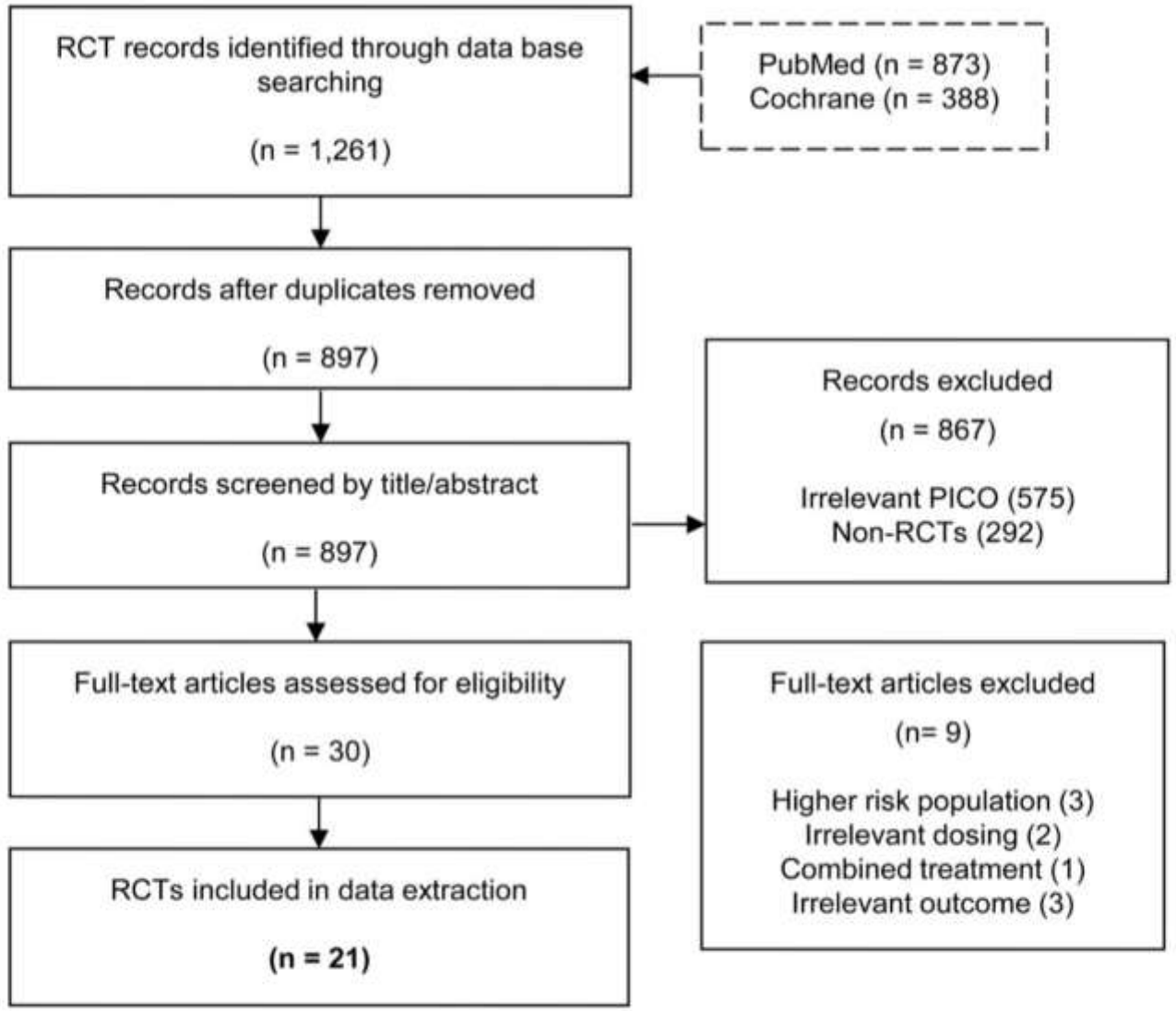


FIG 2 Study flow diagram. PICO, patient or population, intervention, comparison, or outcome(s).

- Results:
- 21 studies met inclusion criteria
- Published between 1992 and 2013
- Participants- 5505, mean age- 43 years, male 58%
- Median duration of anti-fungal prophylaxis- 70 days, mean follow up period- 100 days
- 61% received chemotherapy, 39% received HSCT
- Most common underlying disease- AML(56%)

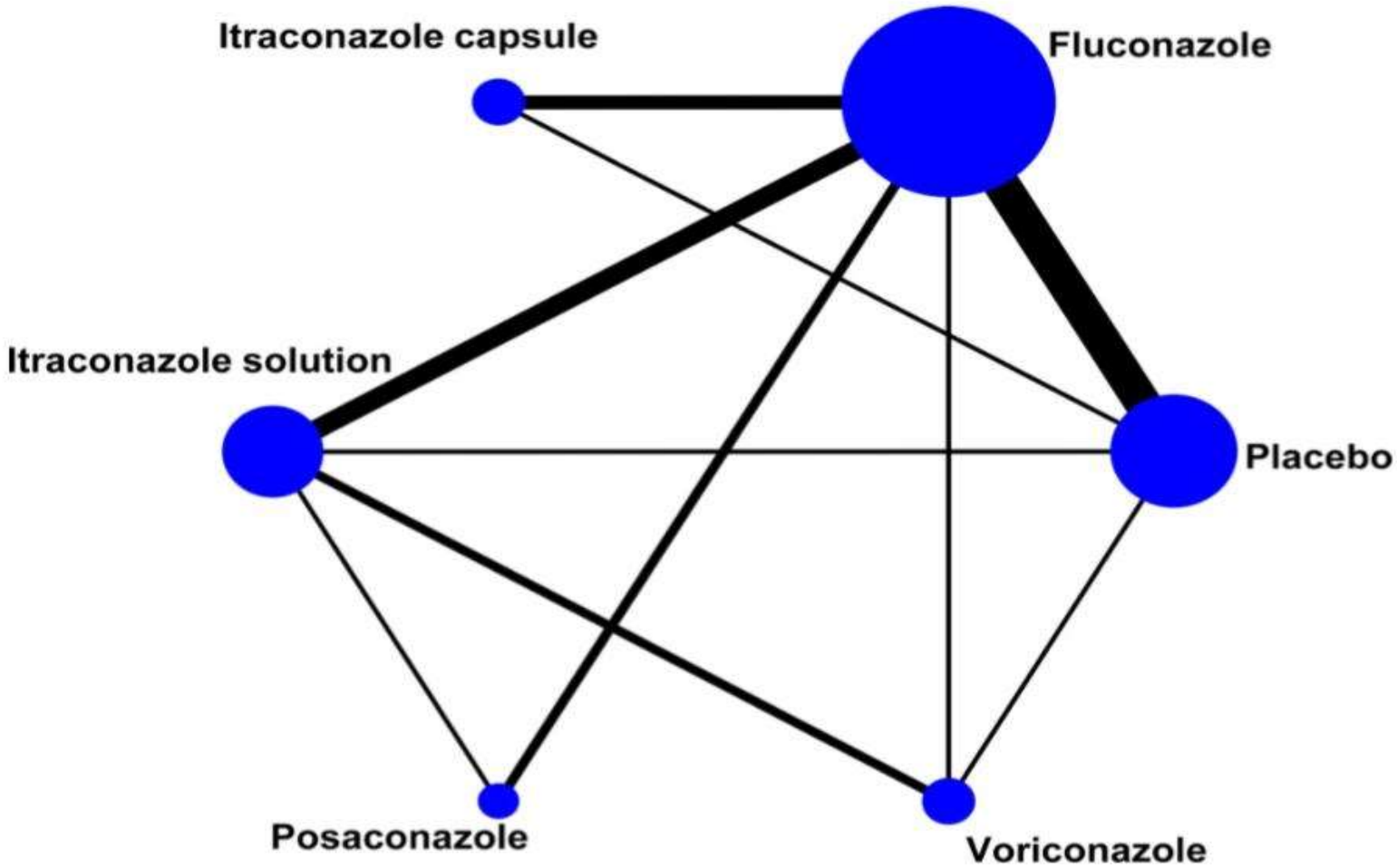


FIG 3 Network of all direct comparisons between triazole antifungal agents. The sizes of the nodes indicate the numbers of participants, and the widths of the lines indicate the numbers of included trials.

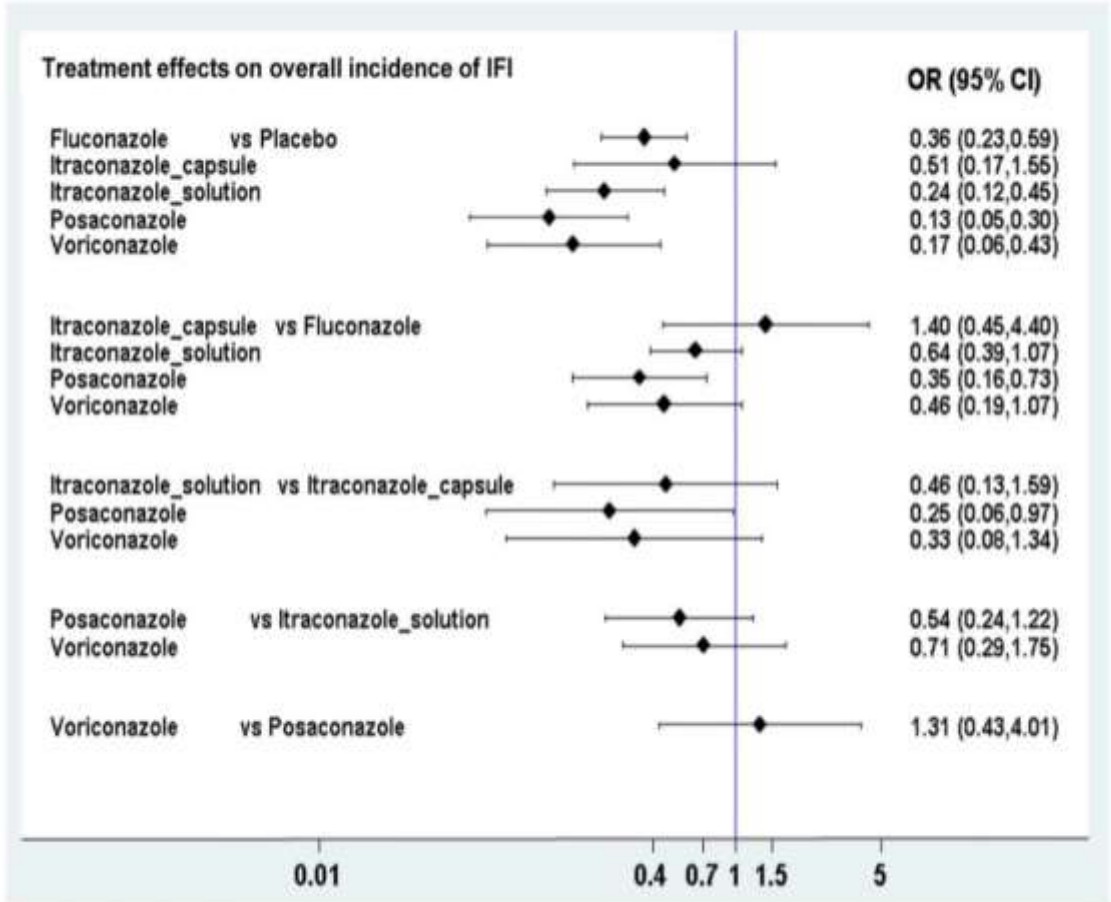
- Overall 5% IFI incidence (45% candida, 49% aspergillus)
- Quality of included studies- moderate
- All triazoles were better than placebo at preventing IFI (except itraconazole)
- Posa was superior to fluconazole (OR 0.35) and Itraconazole capsule (OR 0.25) but not to voriconazole (OR 1.3)
- Voriconazole superior to fluconazole and itraconazole (not statistically significant)

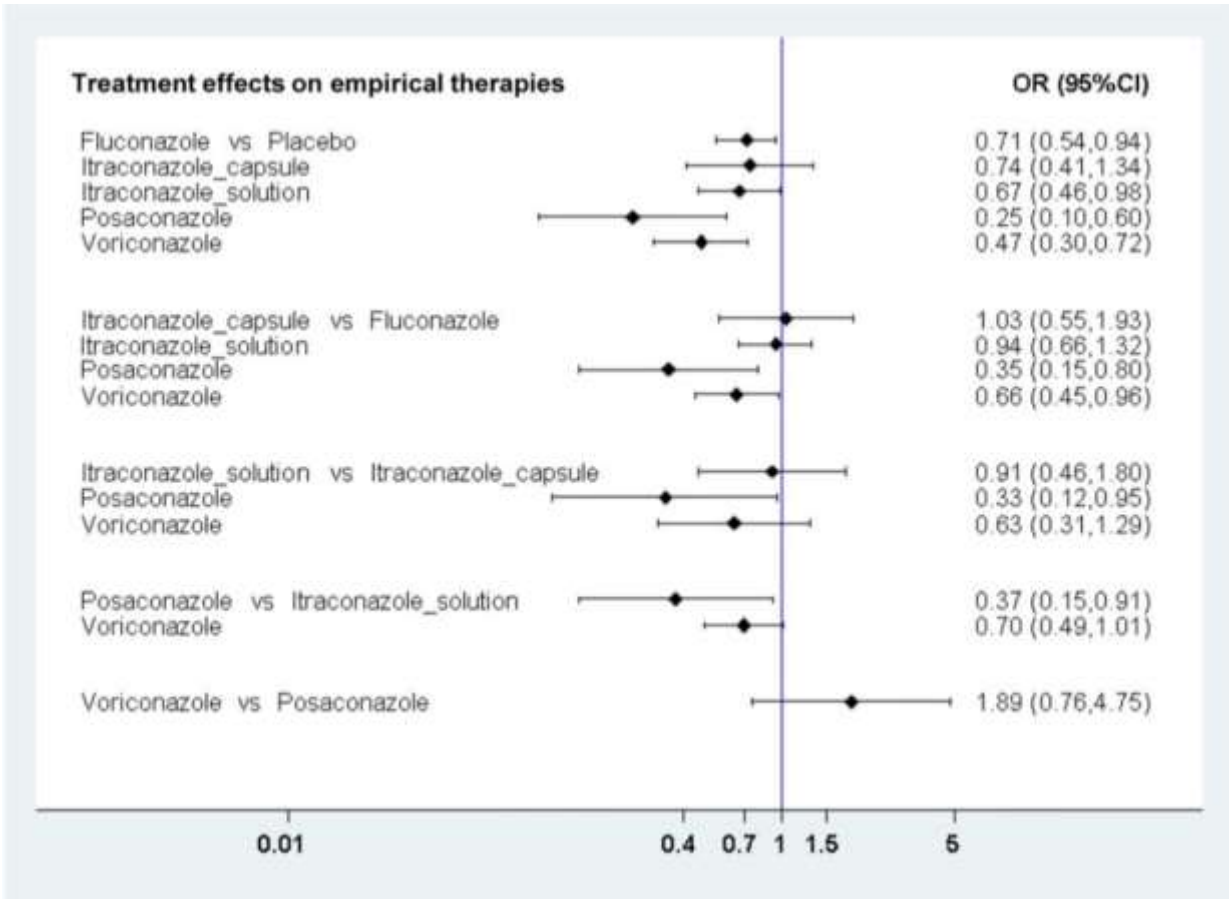
- In preventing invasive aspergillosis Posaconazole was superior to all other azoles
- Voriconazole was better than fluconazole in the same respect
- Apart from itraconazole capsule all triazoles were better than placebo at preventing invasive candidiasis

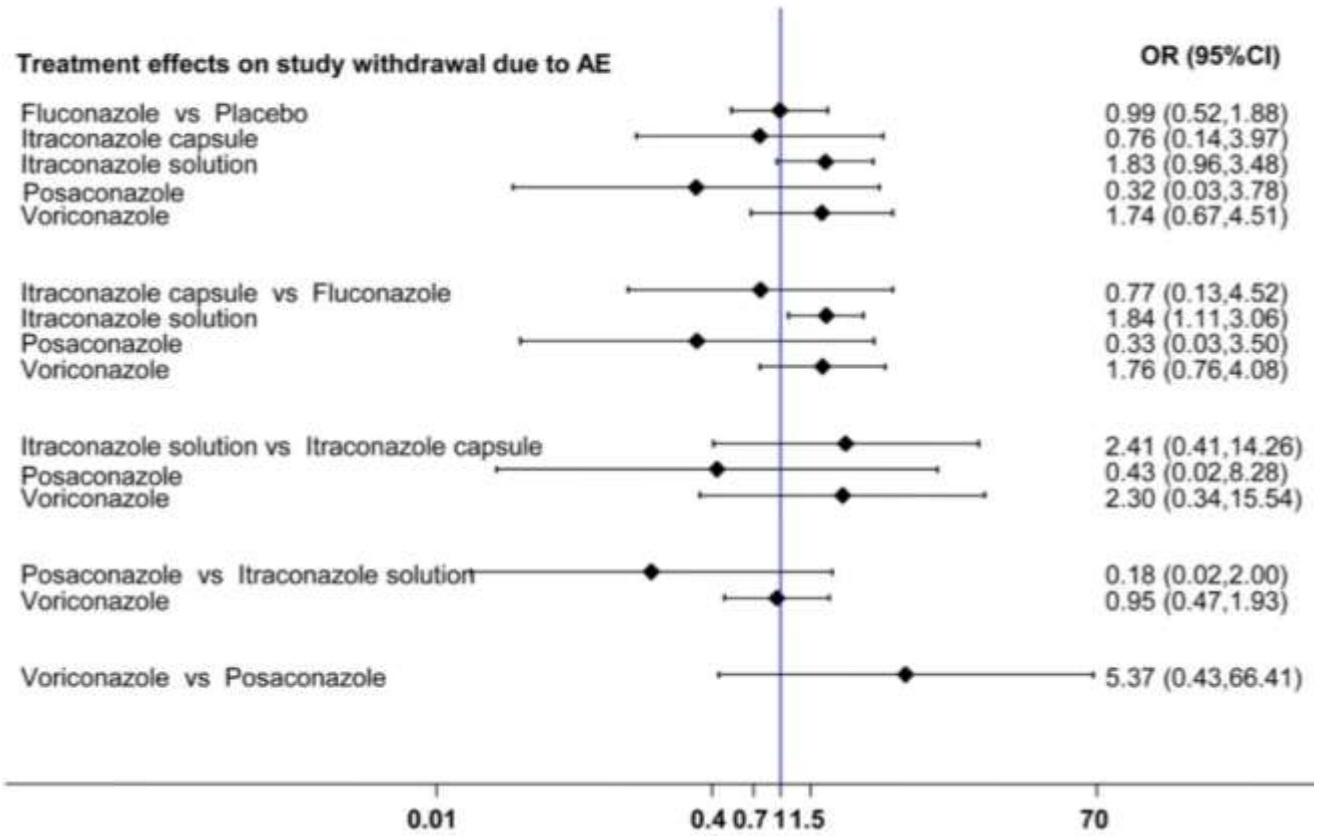
- Posaconazole was a/w significant reduction in all cause mortality in comparison with placebo, fluconazole and itraconazole solution
- Posaconazole, fluconazole and itraconazole were effective in reducing IFI-related death compared to placebo
- Posa and vori led to fewer requirement of empirical therapy in IFI patients
- Posaconazole had a higher Sucra value than all other antifungals for preventing IFI

- Itraconazole solution was a/w higher withdrawal due to intolerance
- All drugs had comparable tolerability
- Liver dysfunction was commoner with voriconazole
- Posaconazole was a/w greatest benefits in terms of numbers of IFIs avoided and LY saved

a)


Treatment effects on overall incidence of IFI
OR (95% CI)
Fluconazole vs Placebo
0.36 (0.23,0.59)
Itraconazole_capsule
0.51 (0.17,1.55)
Itraconazole_solution
0.24 (0.12,0.45)
Posaconazole
0.13 (0.05,0.30)
Voriconazole
0.17 (0.06,0.43)
Itraconazole_capsule vs Fluconazole
1.40 (0.45,4.40)
Itraconazole_solution
0.64 (0.39,1.07)
Posaconazole
0.35 (0.16,0.73)
Voriconazole
0.46 (0.19,1.07)
Itraconazole_solution vs Itraconazole_capsule
0.46 (0.13,1.59)
Posaconazole
0.25 (0.06,0.97)
Voriconazole
0.33 (0.08,1.34)
Posaconazole vs Itraconazole_solution
0.54 (0.24,1.22)
Voriconazole
0.71 (0.29,1.75)
Voriconazole vs Posaconazole
1.31 (0.43,4.01)
0.01
0.4
0.7
1
1.5
5


Treatment effects on empirical therapies
OR (95%CI)
Fluconazole vs Placebo
0.71 (0.54,0.94)
Itraconazole_capsule
0.74 (0.41,1.34)
Itraconazole_solution
0.67 (0.46,0.98)
Posaconazole
0.25 (0.10,0.60)
Voriconazole
0.47 (0.30,0.72)
Itraconazole_capsule vs Fluconazole
1.03 (0.55,1.93)
Itraconazole_solution
0.94 (0.66,1.32)
Posaconazole
0.35 (0.15,0.80)
Voriconazole
0.66 (0.45,0.96)
Itraconazole_solution vs Itraconazole_capsule
0.91 (0.46,1.80)
Posaconazole
0.33 (0.12,0.95)
Voriconazole
0.63 (0.31,1.29)
Posaconazole vs Itraconazole_solution
0.37 (0.15,0.91)
Voriconazole
0.70 (0.49,1.01)
Voriconazole vs Posaconazole
1.89 (0.76,4.75)
0.01
0.4
0.7
1
1.5
5


Treatment effects on study withdrawal due to AE
OR (95%CI)
Fluconazole vs Placebo
0.99 (0.52,1.88)
Itraconazole capsule
0.76 (0.14,3.97)
Itraconazole solution
1.83 (0.96,3.48)
Posaconazole
0.32 (0.03,3.78)
Voriconazole
1.74 (0.67,4.51)
Itraconazole capsule vs Fluconazole
0.77 (0.13,4.52)
Itraconazole solution
1.84 (1.11,3.06)
Posaconazole
0.33 (0.03,3.50)
Voriconazole
1.76 (0.76,4.08)
Itraconazole solution vs Itraconazole capsule
2.41 (0.41,14.26)
Posaconazole
0.43 (0.02,8.28)
Voriconazole
2.30 (0.34,15.54)
Posaconazole vs Itraconazole solution
0.18 (0.02,2.00)
Voriconazole
0.95 (0.47,1.93)
Voriconazole vs Posaconazole
5.37 (0.43,66.41)
0.01
0.4
0.7
1
1.5
70

b)

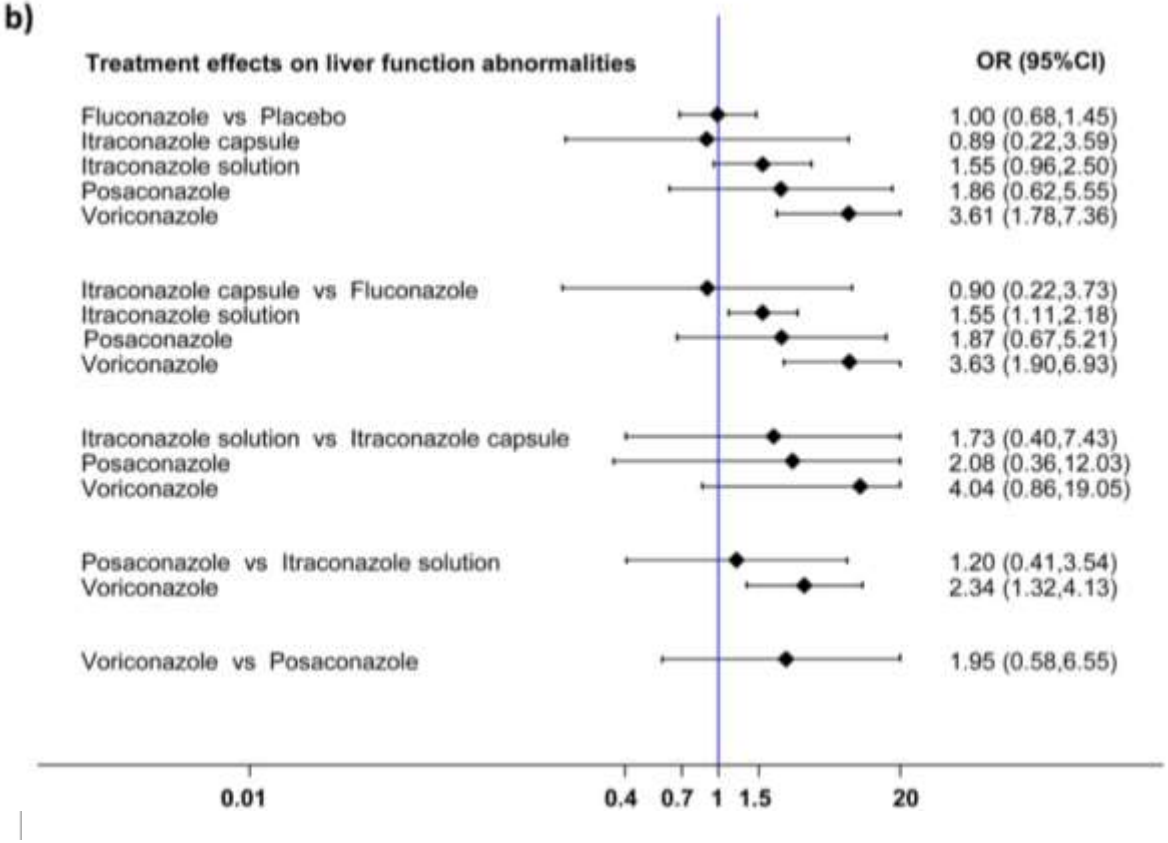

Treatment effects on liver function abnormalities
OR (95%CI)
Fluconazole vs Placebo
1.00 (0.68,1.45)
Itraconazole capsule
0.89 (0.22,3.59)
Itraconazole solution
1.55 (0.96,2.50)
Posaconazole
1.86 (0.62,5.55)
Voriconazole
3.61 (1.78,7.36)
Itraconazole capsule vs Fluconazole
0.90 (0.22,3.73)
Itraconazole solution
1.55 (1.11,2.18)
Posaconazole
1.87 (0.67,5.21)
Voriconazole
3.63 (1.90,6.93)
Itraconazole solution vs Itraconazole capsule
1.73 (0.40,7.43)
Posaconazole
2.08 (0.36,12.03)
Voriconazole
4.04 (0.86,19.05)
Posaconazole vs Itraconazole solution
1.20 (0.41,3.54)
Voriconazole
2.34 (1.32,4.13)
Voriconazole vs Posaconazole
1.95 (0.58,6.55)
0.01
0.4
0.7
1
1.5
20

TABLE 2 Costs and health outcomes for AML patients

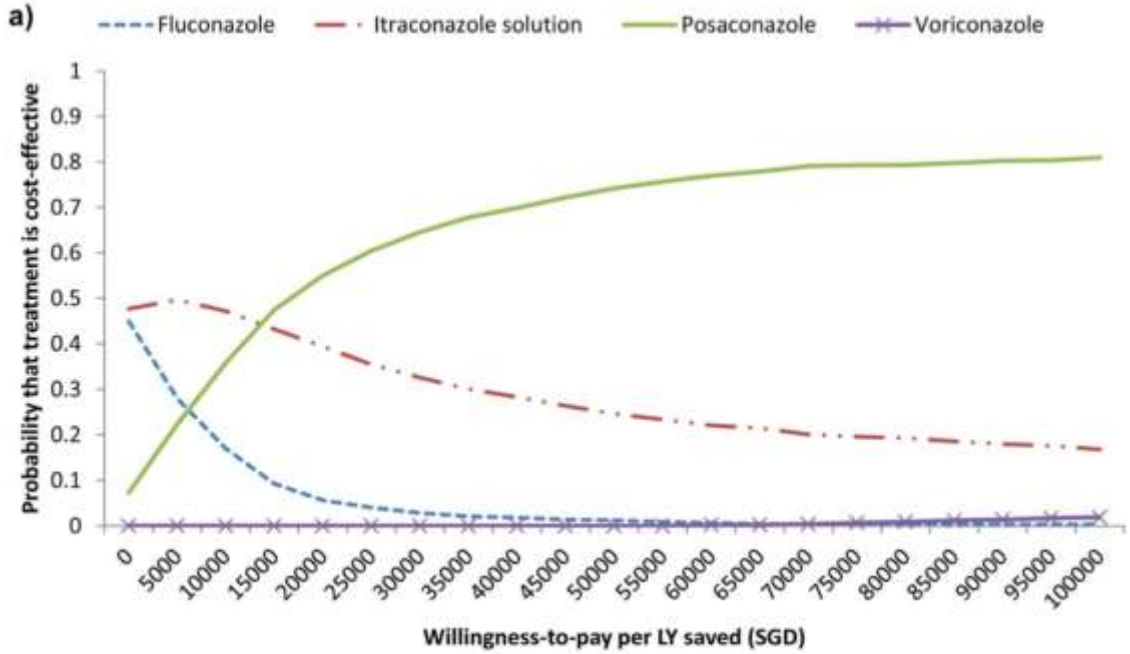
		Effectiveness[a]				ICER	
Treatment	Total cost (SGD)	No. of IFIs	No. of IFIs avoided	LY	LY saved	Per IFI avoided	Per LY saved
Fluconazole	4,186.91	0.100		5.197			
Itraconazole capsule	5,748.09	0.135	−0.035	5.134	−0.063	Dominated	Dominated
Itraconazole solution	4,172.47	0.066	0.034	5.258	0.061	Dominant	Dominant
Posaconazole	4,909.45	0.037	0.063	5.310	0.113	11,469	6,394
Voriconazole	14,095.61	0.049	0.051	5.288	0.091	194,288	108,887

[a] IFI, invasive fungal infection; LY, life-years; ICER, incremental cost-effectiveness ratio.

TABLE 3 Costs and health outcomes for HSCT patients

		Effectiveness[a]				ICER	
Treatment	Total cost (SGD)	No. of IFIs	No. of IFIs avoided	LY	LY saved	Per IFI avoided	Per LY saved
Fluconazole	4,271.27	0.100		6.247			
Itraconazole capsule	5,893.90	0.135	−0.035	6.172	−0.075	Dominated	Dominated
Itraconazole solution	4,697.85	0.066	0.034	6.320	0.073	12,546	5,844
Posaconazole	5,960.76	0.037	0.063	6.383	0.136	26,817	12,423
Voriconazole	17,442.68	0.049	0.051	6.357	0.110	258,263	119,740

[a] IFI, invasive fungal infection; LY, life-years; ICER, incremental cost-effectiveness ratio.



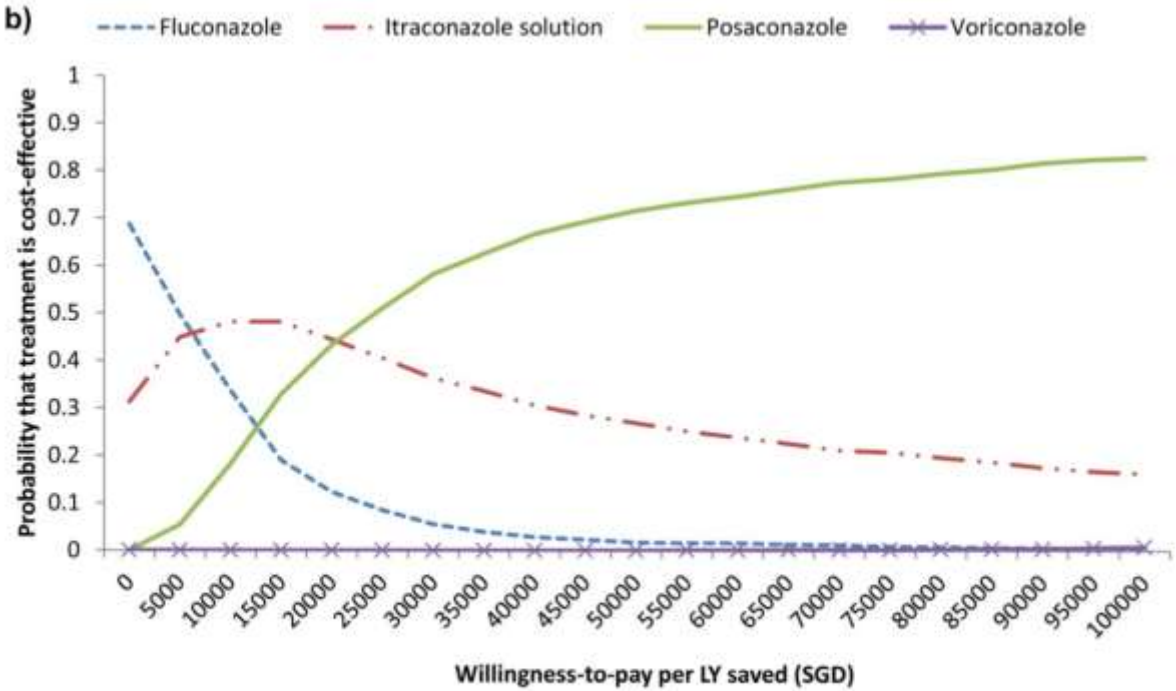


FIG 6 Cost-effectiveness acceptability curves for AML (a) and HSCT (b) cohorts. LY, life-year.

JAMA Network Open™

Original Investigation | Infectious Diseases

Comparison of Antifungal Prophylaxis Drugs in Patients With Hematological Disease or Undergoing Hematopoietic Stem Cell Transplantation

A Systematic Review and Network Meta-analysis

Jing Wang, MD, PhD; Min Zhou, MD, PhD; Jing-Yan Xu, MD, PhD; Rong-Fu Zhou, MD, PhD; Bing Chen, MD, PhD; Yuan Wan, PhD

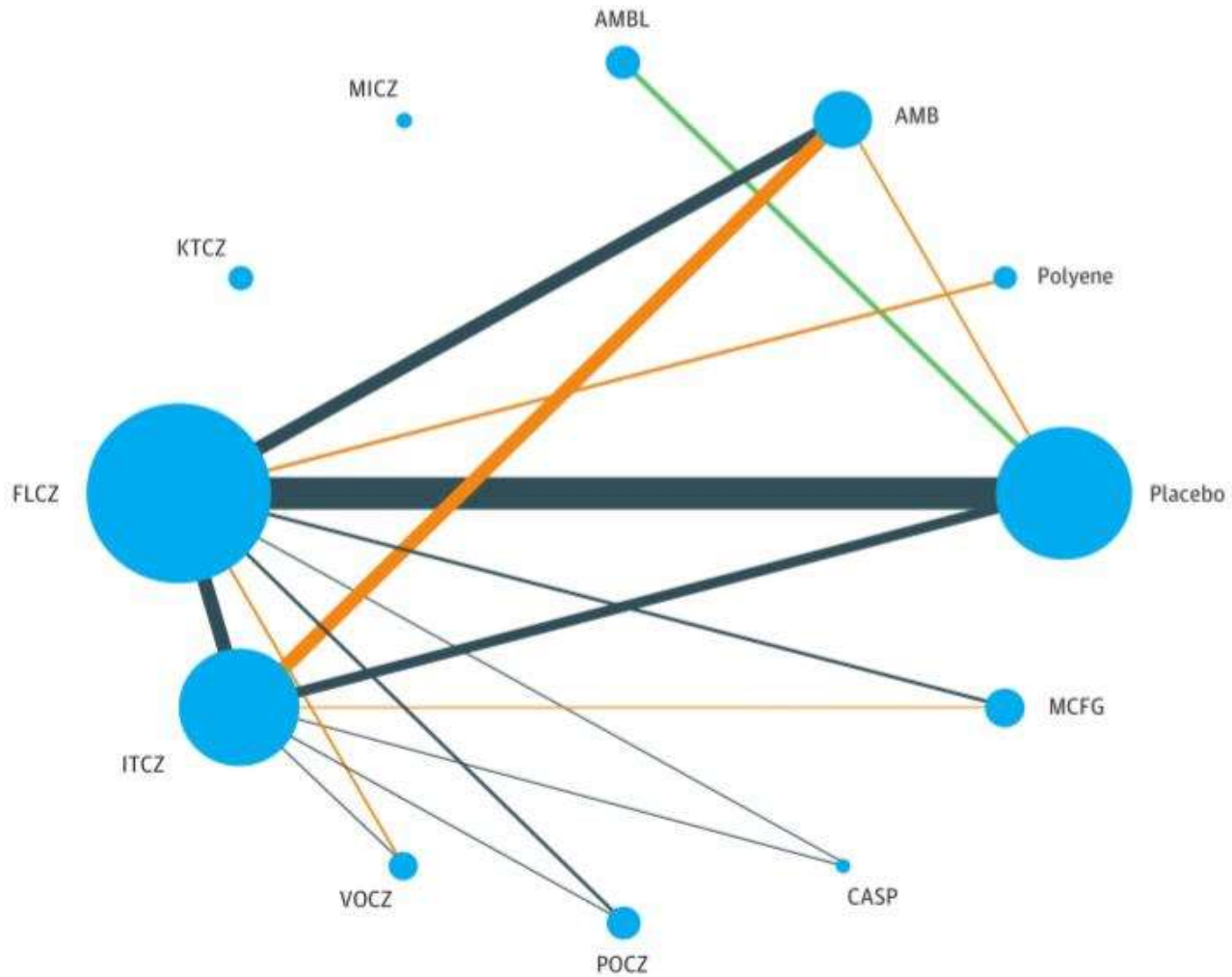
- 69 studies that compared efficacy of different antifungals against other antifungals/placebo in reducing incidence of IFIs in haematological malignancies and HSCT recipients
- Primary outcome: IFI and mortality
- Secondary outcome: fungal infections, proven IFI, invasive candidiasis, invasive aspergillosis, fungi-related deaths, withdrawal related to adverse effects of drugs
-

- Results:

- Posaconazole had the highest SUCRA values (surface under the cumulative ranking curve) (86.7%) followed by capsofungin and micafungin in reducing risk of IFIs (RR 0.57; 95% CI, 0.42-0.79) compared to placebo
- Regarding mortality reduction, Micafungin had the highest SUCRA values (90%, mean rank 2.1) followed by voriconazole and posaconazole
- For reducing fungal infections, capsofungin was the best agent (SUCRA 84.9%); Posaconazole (SUCRA 87.8%) in reducing IA, capsofungin (88.5%) in preventing IC, LAMB (SUCRA 78.8%) in reducing fungi-related death

- Voriconazole had significant reduction in IC incidence (RR 0.15, 95% CI, 0.09-0.26)
- Voriconazole had the highest tolerability (lowest withdrawal rate due to adverse events) while Posaconazole had the highest incidence of withdrwal due to adverse reactions (SUCRA 17.5%)
- In subgroup analysis, voriconazole was ranked the best choice for preventing IFIs in HSCT recipients and Posaconazole was the better choice for patients with AML and MDS;

Figure 1. Schematic of the Network of Evidence Used in Network Meta-analysis for Invasive Fungal Infections



AMB indicates conventional amphotericin B; AMBL, liposomal amphotericin B; KTCZ, ketoconazole; FLCZ, fluconazole; ITCZ, itraconazole; VOCZ, voriconazole; POCZ, posaconazole; CASP, caspofungin; and MCFG, micafungin.

Table 2. SUCRA Values and Mean Rank for All Outcomes

Measure	Fungal infections	IFIs	Proven IFIs	Invasive candidiasis	Invasive aspergillosis	Mortality	Fungi-related death	Withdrawal
Overall								
Placebo								
SUCRA, %	6.2	19.2	25.3	11.6	40.9	38.0	33.7	45.2
Mean rank	11.3	9.9	8.5	10.7	7.5	7.8	8.3	6.5
Polyene								
SUCRA, %	27.5	12.6	37.0	31.0	18.0	15.0	22.6	72.0
Mean rank	9.0	10.6	7.3	8.6	10.0	10.4	9.5	3.8
Amphotericin B								
SUCRA, %	37.5	41.0	14.1	3.6	69.3	42.7	28.3	50.5
Mean rank	7.9	7.5	9.6	11.6	4.4	7.1	8.9	5.9
Liposomal amphotericin B								
SUCRA, %	46.8	61.5	59.7	44.2	37.8	61.8	78.8	4.3
Mean rank	6.8	5.2	5.0	7.1	7.8	5.2	3.3	10.6
Miconazole								
SUCRA, %	76.6	55.2	NA	60.7	42.3	44.5	58.5	NA
Mean rank	3.6	5.9	NA	5.3	7.3	7.1	5.6	NA
Ketoconazole								
SUCRA, %	58.4	17.1	6.3	26.6	63.4	15.4	7.5	63.0
Mean rank	5.6	10.1	10.4	9.1	5.0	10.3	11.2	4.7
Fluconazole								
SUCRA, %	48.8	45.8	60.5	67.1	24.2	49.0	51.6	41.0
Mean rank	6.6	7.0	4.9	4.6	9.3	6.6	6.3	6.9
Itraconazole								
SUCRA, %	28.4	64.6	75.4	80.5	22.4	47.1	64.3	38.0
Mean rank	8.9	4.9	3.5	3.1	9.5	6.8	4.9	7.2
Voriconazole								
SUCRA, %	30.5	36.9	81.5*	67.1	51.2	73.8	75.0	78.1*
Mean rank	8.6	8.4	2.9	4.6	6.4	3.9	3.8	3.2
Posaconazole								
SUCRA, %	82.9	86.7*	78.6	62.6	87.8*	68.5	76.2*	17.5
Mean rank	2.9	2.5	3.1	5.1	2.3	4.5	3.6	9.2
Caspofungin								
SUCRA, %	84.9*	84.2	35.1	88.5*	78.6	54.2	36.9	67.6
Mean rank	2.7	2.7	7.5	2.3	3.4	6.0	7.9	4.2
Micafungin								
SUCRA, %	71.4	75.0	76.4	56.6	64.0	90.0*	66.6	72.7
Mean rank	4.1	3.7	3.4	5.8	5.0	2.1	4.7	3.7
Transplantation								
Placebo								
SUCRA, %	8.5	7.4	4.5	2.3	41.8	25.7	25.6	45.8
Mean rank	8.3	7.5	7.7	6.9	4.5	5.5	4.7	4.8
Polyene								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Amphotericin B								
SUCRA, %	44.1	48.2	44.5	75.9	22.6	94.2*	23.4	48.0
Mean rank	5.5	4.6	4.9	2.4	5.6	1.3	4.8	4.6
Liposomal amphotericin B								
SUCRA, %	14.3	25.2	40.7	30.7	40.7	36.3	32.7	6.4
Mean rank	7.9	6.2	5.1	5.2	4.6	4.8	4.4	7.6

Table 2. SUCRA Values and Mean Rank for All Outcomes (continued)

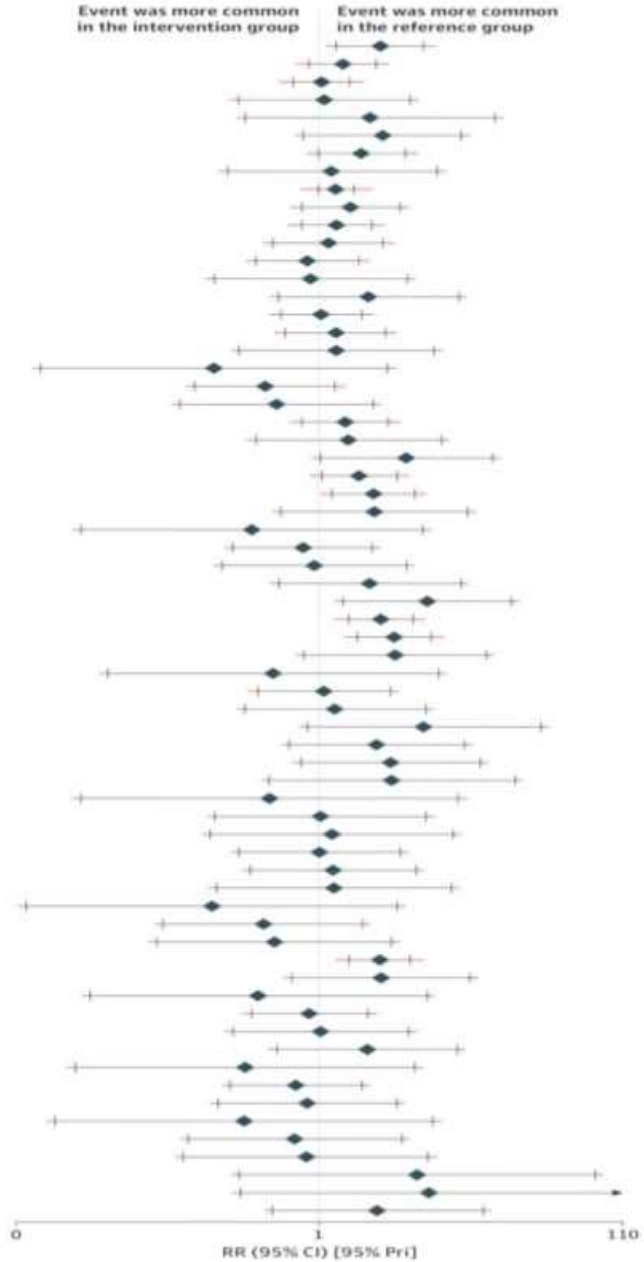
Measure	Fungal infections	IFIs	Proven IFIs	Invasive candidiasis	Invasive aspergillosis	Mortality	Fungi-related death	Withdrawal
Miconazole								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Ketoconazole								
SUCRA, %	42.8	NA	NA	NA	NA	NA	NA	NA
Mean rank	5.6	NA	NA	NA	NA	NA	NA	NA
Fluconazole								
SUCRA, %	48.3	44.2	44.2	56.8	37.8	44.5	59.0	62.3
Mean rank	5.1	4.9	4.9	3.6	4.7	4.3	3.0	3.6
Itraconazole								
SUCRA, %	69.7	66.9	59.5	77.8*	54.2	32.3	72.7	35.0
Mean rank	3.4	3.3	3.8	2.3	3.7	5.1	2.4	5.6
Voriconazole								
SUCRA, %	75.1*	68.4	71.6*	60.9	70.5	49.2	NA	89.4*
Mean rank	3.0	3.2	3.0	3.3	2.8	4.0	NA	1.7
Posaconazole								
SUCRA, %	73.0	76.3*	69.5	NA	NA	NA	NA	28.2
Mean rank	3.2	2.7	3.1	NA	NA	NA	NA	6.0
Caspofungin								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Micafungin								
SUCRA, %	74.2	63.4	65.5	45.6	82.3*	67.7	86.6*	84.9
Mean rank	3.1	3.6	3.4	4.3	2.1	2.9	1.7	2.1
AML or MDS								
Placebo								
SUCRA, %	73.5	74.0	NA	NA	NA	22.5	NA	NA
Mean rank	2.9	2.8	NA	NA	NA	6.4	NA	NA
Polyene								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Amphotericin B								
SUCRA, %	11.9	14.3	54.2*	45.8	43.5	66.7	55.9	NA
Mean rank	7.2	7.0	2.4	3.7	3.8	3.3	3.6	NA
Liposomal amphotericin B								
SUCRA, %	18.0	11.5	NA	21.0	55.4	44.4	59.4	44.6
Mean rank	6.7	7.2	NA	4.9	3.2	4.9	3.4	3.8
Miconazole								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Ketoconazole								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Fluconazole								
SUCRA, %	52.0	53.1	49.0	50.0	26.5	56.1	59.8	71.9
Mean rank	4.4	4.3	2.5	3.5	4.7	4.1	3.4	2.4
Itraconazole								
SUCRA, %	42.4	43.5	53.4	55.7	14.6	28.5	18.2	28.5
Mean rank	5.0	5.0	2.4	3.2	5.3	6.0	5.9	4.6
Voriconazole								

Micafungin								
SUCRA, %	74.2	63.4	65.5	45.6	82.3[a]	67.7	86.6[a]	84.9
Mean rank	3.1	3.6	3.4	4.3	2.1	2.9	1.7	2.1
AML or MDS								
Placebo								
SUCRA, %	73.5	74.0	NA	NA	NA	22.5	NA	NA
Mean rank	2.9	2.8	NA	NA	NA	6.4	NA	NA
Polyene								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Amphotericin B								
SUCRA, %	11.9	14.3	54.2[a]	45.8	43.5	66.7	55.9	NA
Mean rank	7.2	7.0	2.4	3.7	3.8	3.3	3.6	NA
Liposomal amphotericin B								
SUCRA, %	18.0	11.5	NA	21.0	55.4	44.4	59.4	44.6
Mean rank	6.7	7.2	NA	4.9	3.2	4.9	3.4	3.8
Miconazole								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Ketoconazole								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Fluconazole								
SUCRA, %	52.0	53.1	49.0	50.0	26.5	56.1	59.8	71.9
Mean rank	4.4	4.3	2.5	3.5	4.7	4.1	3.4	2.4
Itraconazole								
SUCRA, %	42.4	43.5	53.4	55.7	14.6	28.5	18.2	28.5
Mean rank	5.0	5.0	2.4	3.2	5.3	6.0	5.9	4.6
Voriconazole								

Measure	Fungal infections	IFIs	Proven IFIs	Invasive candidiasis	Invasive aspergillosis	Mortality	Fungi-related death	Withdrawal
SUCRA, %	82.7	83.1	NA	NA	NA	55.8	58.5	6.8
Mean rank	2.2	2.2	NA	NA	NA	4.1	3.5	5.7
Posaconazole								
SUCRA, %	83.4[a]	83.3[a]	NA	46.4	84.0[a]	80.1[a]	83.0[a]	89.5[a]
Mean rank	2.2	2.2	NA	3.7	1.8	2.4	2.0	1.5
Caspofungin								
SUCRA, %	35.9	37.2	43.4	81.1[a]	76.0	45.8	15.4	58.7
Mean rank	5.5	5.4	2.7	1.9	2.2	11.0	6.1	3.1
Micafungin								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Allo-HSCT								
Placebo								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Polyene								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Amphotericin B								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Liposomal amphotericin B								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Miconazole								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Ketoconazole								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Fluconazole								
SUCRA, %	4.4	4.7	10.3	27.9	15.9	60.1	22.4	50.8
Mean rank	2.9	2.9	2.8	2.4	2.7	1.8	1.8	2.0
Itraconazole								
SUCRA, %	65.3	66.0	64.6	85.8[a]	40.9	14.5	77.6[a]	0.0
Mean rank	1.7	1.7	1.7	1.3	2.2	2.7	1.2	3.0
Voriconazole								
SUCRA, %	80.3[a]	79.3[a]	75.1[a]	36.3	93.3[a]	75.4[a]	NA	99.2[a]
Mean rank	1.4	1.4	1.5	2.3	1.1	1.5	NA	1.0
Posaconazole								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Caspofungin								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA
Micafungin								
SUCRA, %	NA	NA	NA	NA	NA	NA	NA	NA
Mean rank	NA	NA	NA	NA	NA	NA	NA	NA

Figure 2. Forest Plot of Invasive Fungal Infections

Treatment effect	RR (95% CI) [95% PrI]
Polyene vs placebo	1.30 (0.58-2.89) [0.48-3.51]
AMB vs placebo	0.65 (0.35-1.20) [0.28-1.51]
AMBL vs placebo	0.44 (0.26-0.74) [0.20-0.95]
MICZ vs placebo	0.47 (0.10-2.28) [0.08-2.63]
KTCZ vs placebo	1.08 (0.11-10.58) [0.10-12.16]
FLCZ vs placebo	1.35 (0.32-5.73) [0.27-6.64]
ITCZ vs placebo	0.92 (0.41-2.07) [0.34-2.52]
VOCZ vs placebo	0.54 (0.08-3.70) [0.07-4.25]
POCZ vs placebo	0.57 (0.41-0.79) [0.30-1.10]
CASP vs placebo	0.74 (0.30-1.83) [0.25-2.19]
MCFG vs placebo	0.58 (0.30-1.10) [0.24-1.38]
AMB vs placebo	0.50 (0.18-1.37) [0.15-1.63]
AMBL vs placebo	0.34 (0.13-0.87) [0.11-1.04]
MICZ vs placebo	0.36 (0.06-2.13) [0.05-2.45]
KTCZ vs placebo	1.04 (0.20-5.44) [0.17-6.27]
FLCZ vs placebo	0.44 (0.21-0.92) [0.17-1.13]
ITCZ vs placebo	0.57 (0.23-1.42) [0.19-1.70]
VOCZ vs placebo	0.58 (0.10-3.44) [0.08-3.96]
POCZ vs placebo	0.06 (0.00-1.47) [0.00-1.70]
CASP vs placebo	0.16 (0.04-0.57) [0.04-0.67]
MCFG vs placebo	0.19 (0.03-1.13) [0.03-1.30]
AMBL vs AMB	0.68 (0.31-1.51) [0.25-1.84]
MICZ vs AMB	0.72 (0.13-3.94) [0.12-4.54]
KTCZ vs AMB	2.08 (0.43-10.01) [0.37-11.56]
FLAC vs AMB	0.88 (0.44-1.76) [0.36-2.18]
ITCZ vs AMB	1.14 (0.53-2.42) [0.43-2.97]
VOCZ vs AMB	1.16 (0.21-6.37) [0.18-7.33]
POCZ vs AMB	0.12 (0.01-2.82) [0.00-3.27]
CASP vs AMB	0.31 (0.09-1.11) [0.08-1.30]
MCFG vs AMB	0.39 (0.07-2.09) [0.06-2.40]
MICZ vs AMML	1.06 (0.20-5.61) [0.18-6.47]
KTCZ vs AMBL	3.06 (0.66-14.21) [0.57-16.43]
FLCZ vs AMBL	1.30 (0.72-2.33) [0.57-2.96]
ITCZ vs AMBL	1.67 (0.85-3.30) [0.68-4.10]
VOCZ vs AMBL	1.70 (0.32-9.06) [0.28-10.45]
POCZ vs AMBL	0.18 (0.01-3.74) [0.01-4.33]
CASP vs AMBL	0.46 (0.14-1.55) [0.12-1.82]
MCFG vs AMBL	0.57 (0.11-2.97) [0.09-3.42]
KTCZ vs MICZ	2.87 (0.34-24.48) [0.29-28.11]
FLCZ vs MICZ	1.22 (0.24-6.12) [0.21-7.07]
ITCZ vs MICZ	1.57 (0.30-8.10) [0.26-9.34]
VOCZ vs MICZ	1.60 (0.17-15.06) [0.15-17.30]
POCZ vs MICZ	0.17 (0.01-5.39) [0.00-6.28]
CASP vs MICZ	0.43 (0.06-3.00) [0.05-3.44]
MCFG vs MICZ	0.53 (0.06-4.95) [0.05-5.69]
FLCZ vs KTCZ	0.42 (0.10-1.87) [0.08-2.17]
ITCZ vs KTCZ	0.55 (0.12-2.49) [0.10-2.88]
VOCZ vs KTCZ	0.56 (0.06-4.79) [0.06-5.50]
POCZ vs KTCZ	0.06 (0.00-1.77) [0.00-2.06]
CASP vs KTCZ	0.15 (0.02-0.94) [0.02-1.08]
MCFG vs KTCZ	0.19 (0.02-1.58) [0.02-1.81]
ITCZ vs FLCZ	1.29 (0.72-2.23) [0.58-2.86]
VOCZ vs FLCZ	1.31 (0.26-6.65) [0.22-7.67]
POCZ vs FLCZ	0.14 (0.01-3.05) [0.01-3.53]
CASP vs FLCZ	0.36 (0.12-1.03) [0.10-1.22]
MCFG vs FLCZ	0.44 (0.09-2.18) [0.08-2.51]
VOCZ vs ITCZ	1.02 (0.20-5.31) [0.17-6.12]
POCZ vs ITCZ	0.11 (0.00-2.41) [0.00-2.80]
CASP vs ITCZ	0.28 (0.08-0.91) [0.07-1.07]
MCFG vs ITCZ	0.34 (0.07-1.74) [0.06-2.01]
POCZ vs VOCZ	0.11 (0.00-3.39) [0.00-3.95]
CASP vs VOCZ	0.27 (0.04-1.89) [0.03-2.17]
MCFG vs VOCZ	0.33 (0.04-3.13) [0.03-3.59]
CASP vs POCZ	2.54 (0.10-66.10) [0.08-76.84]
MCFG vs POCZ	3.12 (0.10-98.03) [0.09-114.37]
MCFG vs CASP	1.23 (0.18-8.43) [0.16-9.68]



The dotted line indicates null effect; diamonds, relative risk (RR); and black whiskers, 95% CI; red whiskers, 95% predicted interval (PrI); AMB, conventional amphotericin B; AMBL, liposomal amphotericin B; KTCZ, ketoconazole; FLCZ, fluconazole; ITCZ, itraconazole; VOCZ, voriconazole; POCZ, posaconazole; CASP, caspofungin; and MCFG, micafungin.

- Limitations:
- No therapeutic drug monitoring
- Short follow up time- survival benefit not clear
- Limited studies on posaconazole vs voriconazole
- Heterogeneity in study parameters
- Inability to analyze difference in outcome based upon variations of age, race/ethnicity

Newer options of anti-fungal prophylaxis

- ISAVUCONAZOLE
- In a mixed population of relapsed refractory and HSCT patients, a breakthrough rate of 5.8% was reported.
- the use of isavuconazole as prophylaxis in newly diagnosed AML was associated with a rate of 7.9% (higher than the rate reported with posaconazole (2.7%), but not statistically significant(P=0.06))
- Use of isavuconazole as prophylaxis in the setting of relapsed or refractory AML has been associated with break-through rates of between 12 and 18.5% (higher than that reported with posaconazole and voriconazole(5.5%))
- In the majority of cases, breakthrough infections were due to Aspergillus spp. And Mucor spp

1. Fontana L, Perlin DS, Zhao Y,Noble BN, Lewis JS, Strasfeld Let al.Isavuconazole prophylaxis in patients with hematologic malignancies and hematopoietic-cell transplantrecipients.Clin Infect Dis2020;70:723–30
2. Bose P, McCue D, Wurster S,Wiederhold NP, Konopleva M,Kadia TMet al. Isavuconazole as primary anti-fungal prophylaxis in patients with acute myeloid leukaemia myelodysplastic syndrome: an open-label, prospective, phase II study.Clin Infect Dis2021;72: 1755–63.

Clinical Infectious Diseases

MAJOR ARTICLE

Isavuconazole Prophylaxis in Patients With Hematologic Malignancies and Hematopoietic Cell Transplant Recipients

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- Retrospective study of adult (>18 years of age) heamatological malignancy patients and allogenic HSCT recipients who received >7 days of uninterrupted mold-active primary prophylaxis (sept 2016-sept2018)
- The participants received either Isavuconazole or voriconazole/posaconazole
- Therapeutic drug monitoring was not routinely performed
- Outcome observed was break-through invasive fungal infection (bIFI) on any particular antifungal
- By oct 2017, Posaconazole replaced Isavuconazole due to an unexpectedly high incidence of bIFI in Isavuconazole group

- Outcome specification: as per EORTC guidelines only proven and probable IFIs were considered
- bIFI was defined as onset of IFI after >7 days of antifungal prophylaxis
- Death was recorded if it occured within 42 days of IFI onset
- Number of participants: 145
- 12 patients (representing 8.3% of patients and 6.1% of courses of prophylaxis) developed bIFI on Isavuconazole (11 undergoing chemo for AML/ALL and 1 post-HSCT patientreceiving prophylaxis for prolonged pre-HSCT neutropenia)
- Isavuconazole suspectibility in bIFI cases could be performed in only 1 case (poor culture yield) and its trough level was detected in all cases (3.3-6.3 microgram/mL)

- Rate of bIFI in Isavuconazole patients was higher than expected based upon previous historical data
- Institutional protocol mandated that patients with relapsed/refractory AML received Posa/Isavu (85/68) and de novo AML patients predominantly received voriconazole (88)
- bIFI in de Novo AML occured in 7.9% courses of Isavu, 2.7% courses of Posa (p=0.6) and 0% courses of vori (p=0.04) (worth noting that neutropenia was more prolonged in patients receiving Isavu)
- bIFI in relapsed/refractory AML- 12% in Isavu vs 5.5% in Posa and 5.5% in voriconazole courses (duration of neutropenia was comparable) (difference not statistically significant)

Table 2. Breakthrough Invasive Fungal Infections During Isavuconazole Prophylaxis

Patient	Date of Onset	Age/Sex	Underlying Malignancy	HCT	Prophylaxis Indication	Chemotherapy	Pathogen	Mycological Diagnosis	EORTC/MSG Classification	Duration of Neutropenia, d[a]	Duration Prophylaxis, d[a]	Trough Level, μg/mL[b]	ISA MIC, μg/mL	Therapy	Outcome[c]
1	30 Oct 2016	74/F	AML	N	Induction	FLAG-IDA	*Aspergillus* spp	Serum GM	Probable	26	10	6.3	ND	ISA	Death (34)
2	30 Nov 2016	71/M	AML	N	Induction	Study	*Aspergillus* spp	Serum GM	Probable	18	15	ND	ND	ISA	Alive
3	27 Mar 2017	30/M	R/R AML	N	Reinduction	Decitabine	*Aspergillus fumigatus*	BALF GM, BALF PCR	Probable	180	125	3.3	ND[d]	Amb	Alive
4	5 Apr 2017	57/M	R/R AML	N	Reinduction	FLAG-IDA	*Fusarium dimerum*	BALF culture	Probable	25	8	ND	ND[e]	ISA	Death (8)
5	29 Apr 2017	45/F	R/R AML	Y	Reinduction	FLAG-IDA	*Fusarium* spp	Blood culture	Proven	9	9	ND	ND[f]	Amb	Alive
6	5 May 2017	64/F	R/R AML	N	Reinduction	7 + 3	*A. fumigatus*	BALF GM, BALF PCR	Probable	38	13	3.7	ND[d]	VOR	Alive
7	28 May 2017	65/M	R/R AML	N	Reinduction	FLAG-IDA	*A. fumigatus*	BALF GM, BALF PCR	Probable	38	40	4.3	ND[d]	VOR	Death (19)
8	5 Jul 2017	60/M	R/R AML	N	Reinduction	MEC	*Rhizopus microsporus* or *azygosporus*	Histopathology, Lung tissue PCR	Proven	11	14	ND	ND	Amb, POS	Alive
9	13 Aug 2017	64/F	MF	Y	Pre-HCT neutropenia	NA	*A. fumigatus*	Sputum culture	Probable	16	12	ND	0.5	Mica	Death (12)
10	3 Sept 2017	67/M	R/R ALL	Y	Reinduction	FLAG-IDA	*Syncephalastrum monosporum* or *racemosum*	BALF culture, BALF PCR	Probable	27	22	ND	2	POS	Death (14)
11	8 Sept 2017	53/F	AML	N	Induction	7 + 3	*A. fumigatus*	BALF PCR	Possible w/ PCR+	21	20	3.4	ND	Mica	Death (27)
12	30 Jul 2018	25/M	R/R ALL	N	Targeted therapy	CAR-T	*Candida glabrata*	Blood culture	Proven	82	14	ND	ND[g]	Mica	Death (7)

Abbreviations: 7 + 3, cytarabine, anthracycline; ALL, acute lymphocytic leukemia; Amb, AmBisome; AML, acute myeloid leukemia; BALF, bronchoalveolar lavage fluid; CAR-T, chimeric antigen receptor T-cell therapy; EORTC/MSG, European Organization for Research and Treatment of Cancer/Invasive Fungal Infection Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group; F, female; FLAG-IDA, fludarabine, cytarabine, idarubicin; GM, galactomannan; HCT, hematopoietic cell transplant; ISA, isavuconazole; M, male; MEC, mitoxantrone, etoposide, cytarabine; MF, myelofibrosis; MIC, minimum inhibitory concentration; Mica, micafungin; N, no; NA, not applicable; ND, not determined; PCR, polymerase chain reaction; POS, posaconazole; R/R, relapsed/refractory; VOR, voriconazole; Y, yes.

[a]Prior to breakthrough invasive fungal infection (bIFI).

[b]Performed within 72 hours of bIFI.

[c]Defined as occurring within 42 days of date of onset of bIFI, with interval (days) from date of onset to date of death provided when applicable.

[d]*CYP51A* gene sequencing performed (refer to text and Supplementary Table 1).

[e]MICs: itraconazole (ITRA) ≥16, POS ≥16, VOR = 8.

[f]MIC ≥16 for ITRA, POS, and VOR.

[g]MICs: fluconazole = 16, POS = 2, ITRA = 1.

Table 3. Comparison of Courses of Isavuconazole, Posaconazole, and Voriconazole Primary Prophylaxis in Patients Undergoing Treatment for Acute Myeloid Leukemia

Characteristic	ISA	POS	*P* Value[a]	VOR	*P* Value[b]
Total patients, No.	85	68		88	
Total courses, No.	88	73		90	
Indication					
De novo AML, induction chemotherapy					
Patients, No. (% of total patients)	38 (45)	37 (54)	.25	72 (82)	< .0001
Courses, No. (% of total courses)	38 (43)	37 (51)	.4	72 (80)	< .0001
Duration of neutropenia, days, median (IQR)	24.5 (21–44)	31 (23–76)	.07	26 (19–42)	.9
Duration of prophylaxis, days, median (IQR)	20 (16–24)	28 (16–62)	.09	19 (15–25)	.6
Anthracycline chemotherapy, No. (% of courses per indication)	29 (76.3)	27 (73)	.8	61 (84.7)	.3
R/R AML, reinduction/salvage chemotherapy					
Patients, No. (% of total patients)	47 (55)	31 (46)		16 (18)	
Courses, No. (% of total courses)	50 (57)	36 (49)		18 (20)	
Duration of neutropenia, days, median (IQR)	28.5 (15–64)	35 (16–57)	.9	38 (27–56)	.5
Duration of prophylaxis, days, median (IQR)	19.5 (16–32)	22 (15–50)	.8	27 (16–43)	.4
Anthracycline chemotherapy, No. (% of courses per indication)	38 (75.3)	27 (75)	1	15 (83)	.7

Abbreviations: AML, acute myeloid leukemia; IQR, interquartile range; ISA, isavuconazole; POS, posaconazole; R/R, relapsed/refractory; VOR, voriconazole.

[a]ISA vs POS.

[b]ISA vs VOR.

Table 4. Breakthrough Invasive Fungal Infections During Isavuconazole, Posaconazole, and Voriconazole Primary Prophylaxis in Patients Undergoing Treatment for Acute Myeloid Leukemia

Characteristic	ISA	POS	*P* Value	VOR	*P* Value[a]
Indication					
De novo AML induction chemotherapy					
bIFI, No.	3	1		0	
Organism, No.					
Aspergillus fumigatus	1[b]	0		0	
Aspergillus spp	2	0		0	
Candida glabrata	0	1		0	
Courses, No.	38	37		72	
bIFI, % of courses	7.9	2.7	.6	0	.04
R/R AML salvage/reinduction chemotherapy					
bIFI, No.	6	2		1	
Organism, No.					
Aspergillus fumigatus	3	1		0	
Rhizopus microsporus/azygosporus	1	0		0	
Fusarium spp	2	1		0	
Scedosporium apiospermum	0	0		1	
Courses, No.	50	36		18	
bIFI, % of courses	12	5.5	.4	5.5	.7
Total courses, No.	88	73		90	
Total bIFI, No. (% total courses)	9 (10.2)	3 (4.1)	.2	1 (1.1)	ND
Breakthrough IPA, No. (% total courses)	6 (6.8)	1 (1.3)	.1	0	ND
bIFI, non-IPA, No. (% total courses)	3 (3.4)	2 (2.8)	1	1 (1.1)	ND

Abbreviations: AML, acute myeloid leukemia; bIFI, breakthrough invasive fungal infection; IPA, invasive pulmonary aspergillosis; ISA, isavuconazole; ND, not determined; POS, posaconazole; R/R, relapsed/refractory; VOR, voriconazole.

[a]ISA vs VOR.

[b]Possible with positive polymerase chain reaction.

- Possible causes discussed for higher bIFI in Isavuconazole group-
- resistance- poor culture yield precluded evaluation; circumstantially if azole resistance had been the cause Vori and Posa groups should have shown higher bIFI as well
- Seasonal clustering- ruled out; bIFIs occurred across seasons
- Reduced fungicidal activity of Isavu in presence of neutropenia- could not be ruled out

- Conclusion drawn-

- Higher rate of bIFIs (especially IPA) in haematological malignancy patients with Isavu
- Despite its proven therapeutic benefit in treating such cases, as a prophylaxis its role needs to be farther evaluated if recommendations are to be made in favour of its use as prophylactic agent in such cases

- Limitations:
- Single centre study
- Drug trough level examined in <50% cases
- Evaluation of resistance minimal- poor culture yield
- No comment on safety and tolerability was made

- The use of isavuconazole following micafungin prophylaxis in HSCT patients has been associated with an IFD rate of 3.1%.
- In this study, all IFD were bloodstream infections with Candida parapsilosis and Candida glabrata.
- Tolerability appears to be good with a low risk of QTc prolongation in the setting of potential drug–drug interactions
- Its use could be considered in the setting of intolerance or if use of other azoles is contraindicated.

Stern A, Su Y, Lee YJ, Seo S, Shaffer B,Tamari Ret al. A single-center, open-label trial of isavuconazole prophylaxis against invasive fungal infection in patients undergoing allogeneic hematopoietic cell transplantation.BiolBlood Marrow Transplant2020;26:1195–202.

- New formulation of ITRACONAZOLE:
- A novel formulation of itraconazole (SUper BioAvailabil-ity (SUBA)-itraconazole has been introduced
- recently several small cohort studies have demonstrated good tolerability and levels in the therapeutic range using SUBA-itraconazole in haematology and HSCT recipients
- One small prospective cohort (n=57) comparing SUBA-itraconazole for primary prophylaxis in an allogeneic HSCT cohort to itraconazole oral solution showed that therapeutic concentrations were achieved significantly more quickly in the SUBA-itraconazole group (median of 6 vs 14 days) with therapeutic concentrations achieved in 69 versus 21% of patients ($P < 0.01$) (no intolerance due to GI disturbances)

Lindsay J, Sandaradura I, Wong K,Arthur C, Stevenson W, Kerridge Iet al. Serum levels, safety and tolerability of new formulation SUBA-itraconazole prophylaxis in patients with haematological malignancy or undergoing allogeneic stem celltransplantation.J Antimicrobials Chemother2017;72: 3414–19

Open Forum Infectious Diseases

MAJOR ARTICLE

SUBA-Itraconazole for Primary Antifungal Prophylaxis After Allogeneic Hematopoietic Cell Transplantation

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- Study performed over two hospitals in australia
- All patients undergoing HSCT w/o a prior documented IFD/exposure to SUBA-itra (patients with GVHD II-IV excluded)
- Given initial dose of S-Itz 200 mg BID
- Followed for 180 days post-HCT/death
- Incidence of proven/probable/possible IFI noted
- Trough levels checked twice weekly and kept between 500-2000 ng/mL
- Adverse reactions/intolerance leading to discontinuation noted

- Primary outcome- IFI during the course or within 7 days of last dose
- Secondary outcome- overall incidence of IFI, survival analysis (overall fungal free survival), early permanent S-itz discontinuation (due to adverse effects, IFI, failure to achieve trough level or others)
- Result- overall incidence of bIFI 1% (95% CI) (at day 180 post-HCT)
- Proven/peobable IFI- 3% (no significant difference between cohorts)
- FFS at day 180 82.9% (only the incidence of grade II-IV IFI was a/w poorer FFS)

- Early discontinuation and starting of alternative antifungal in 3.4% patients (in absence of GVHD)
- 1 patient developed grade III DILIN liver injury due to S-itz
- 31% required temporary discontinuation (causes- usually malignancy/therapy related mucositis, non-drug-related liver injury
- By day 14 and day 21 75.8% and 94% patients achieved trough levels

- Conclusion: SUBA itraconazole is an effective and well-tolerated drug for antifungal prophylaxis in post-HSCT patients
- It also attains an effective concentration in serum at doses with less risk of adverse events

- However, this study included only two centres, had a short follow-up time, did not have any comparator drug

- Farther studies are required to comment on comparative efficacy of SUBA itraconazole in preventing bIFI

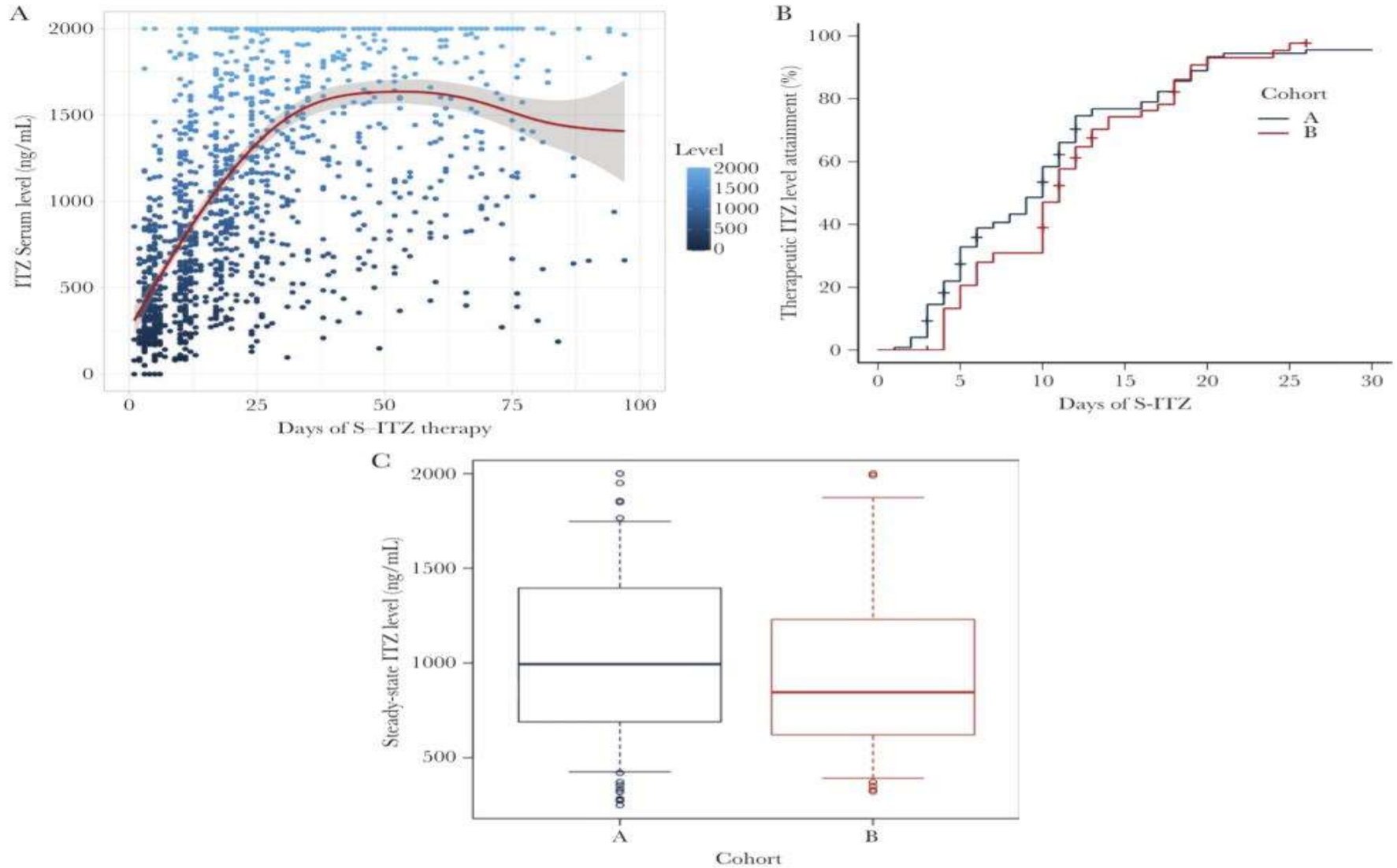

Figure 5. SUBA-itraconazole (S-ITZ) levels among study cohorts. *A*, Total S-ITZ levels with mean and 95% confidence interval indicated (n = 1414). *B*, Proportion of patients to attain therapeutic itraconazole (ITZ) levels (defined by >500 ng/mL; cohort A, n = 124; cohort B, n = 69). *C*, Steady-state levels (defined by first level taken >14 days of S-ITZ; cohort A, n = 99; cohort B, n = 33).

Table 6. Early Permanent SUBA-Itraconazole Discontinuation and/or Initiation of Alternative Antifungal Agent for Any Reason in the Absence of Graft-vs-Host Disease by Numbers of Patients

Cohort	Preengraftment[a]	Postengraftment[b]
Total	204	197
Cohort A	129	125
Cohort B	75	72
Proven/probable IFD		
Total	2 (1.0)	3 (1.5)
Cohort A	2 (1.6)	0
Cohort B	0	3 (2.4)
Possible/suspected IFD		
Total	2 (1.0)	3 (1.5)
Cohort A	0	1 (0.8)
Cohort B	2 (2.7)	2 (2.8)
Failure to achieve therapeutic serum ITZ concentrations after 14 d of therapy		
Total	1 (0.5)	0
Cohort A	1 (0.8)	0
Cohort B	0	NA
Adverse drug reactions attributed to S-ITZ		
Total	1 (0.5)	0
Cohort A	0	0
Cohort B	1 (1.3)	NA
Intolerance to S-ITZ		
Total	0	0
Cohort A	0	0
Cohort B	0	NA
Any other reason		
Total	1 (0.5)	0
Cohort A	1 (0.8)	0
Cohort B	0	NA

Data are presented as No. (%).

Abbreviations: IFD, invasive fungal disease; ITZ, itraconazole; NA, not applicable; S-ITZ, SUBA-itraconazole.

[a]Early permanent S-ITZ discontinuation and initiation of alternative antifungal.

[b]Early permanent S-ITZ discontinuation and initiation of alternative antifungal in cohort A and initiation of an antifungal agent in cohort B.

Table 4 Recommendations for choice and dose of antifungal prophylaxis agent in adults

Risk group		Antifungal agent	SoR	QoE	Comments
High risk	First line	Posaconazole Oral (tablets) Loading with 300 mg twice daily on Day 1, followed by 300 mg daily	A	I	Intravenous formulation can be used to continue prophylaxis if poor oral intake/absorption
	Alternate agents	Voriconazole Oral or intravenous 4 mg/kg twice daily†	A	II	High rates of adverse events (liver function abnormalities); variable CYP metabolism
		Micafungin Intravenous 100–150 mg daily	B	II	Could be used during periods of neutropenia if azoles contraindicated, poor oral intake/absorption
		Itraconazole Oral 200 mg twice daily	B	II	Less new data supporting its use compared to other azoles
		Liposomal amphotericin Intravenous 50–200 mg three times per week	B	II	Could be used if azoles contraindicated due to drug–drug interactions, adverse events, poor oral intake/absorption
		Isavuconazole Oral 200 mg three times per day for 48 h followed by 200 mg daily	C	II	Higher rates of IFD in cohort studies; could be used if other azoles contraindicated due to adverse events such as QTc prolongation
Low risk	First line	Fluconazole Oral 200–400 mg daily	A	I	
	Alternate agents	Echinocandin Intravenous Dosing dependent on agent	A	II	
		Itraconazole Oral 200 mg twice daily	A	II	
Very low risk		No prophylaxis	B	II	

†Dose used in prophylaxis studies have been 200 mg twice daily; measure voriconazole levels to ensure achievement of target level (refer to accompanying optimising antifungal therapy and TDM guidelines by Chau *et al.* 2021[182], which can be found elsewhere in this supplement).

Comparison: 2014 vs 2021

Table 1 Invasive fungal disease risk groups (adapted from multiple sources[8,11,13–15])

High risk: >10% incidence IFD	Neutrophils <0.1 x 10^9/L for >3 weeks[16] or <0.5 x 10^9/L for >5 weeks
	Unrelated, mismatched or cord blood donor HSCT
	GVHD
	Corticosteroids >1 mg/kg prednisolone equivalent and neutrophils <1 x 10^9/L for >1 week
	Corticosteroids >2 mg/kg prednisolone equivalent >2 weeks†
	High-dose cytarabine‡
	Fludarabine use in highly treatment-refractory patients with CLL or low-grade lymphoma§
	Alemtuzumab use, especially in highly treatment-refractory patients with CLL or lymphoma§[17]
	ALL
	AML
Intermediate risk: ~10% incidence of IFD	Neutropenia 0.1–0.5 x 10^9/L for 3–5 weeks
	Neutropenia 0.1–0.5 x 10^9/L for <3 weeks with lymphopenia (lymphocytes <0.5 x 10^9/L)
Low risk: ~2% incidence of IFD	PBSC autologous HSCT
	Lymphoma

†Other authors have described prednisolone equivalent of >1 mg/kg/day for 2 weeks or 0.25–1 mg/kg/day for 4 weeks in allogeneic HSCT[2]. ‡Some authors question whether the high rates of IFDs seen with high-dose cytarabine may be contributed to by concurrent fludarabine. §Represent additions to 2008 table. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukemia; GVHD, graft versus host disease; HSCT, haemopoietic stem cell transplant; IFD, invasive fungal disease; PBSC, peripheral blood stem cell; TBI, total body irradiation.

Table 1 Established risk groups for IFD and recommended antifungal prophylax

Risk level	Risk groups
High risk >10% incidence of IFD	Neutrophil <0.1 × 10^9/L for >3 weeks or <0.5 × 10^9/L for >5 weeks (e.g. allogeneic HSCT)
	Corticosteroids >1 mg/kg prednisolone equivalent and neutrophils <1 × 10^9/L for >1 week
	Corticosteroids >2 mg/kg prednisolone equivalent >2 weeks
	Unrelated, mismatched or cord blood allogeneic HSCT
	GVHD – extensive or severe
	AML – induction/reinduction
	ALL – induction/reinduction
	MDS
Low risk Less than 5% incidence of IFD	Autologous HSCT (e.g. patients at high risk for mucositis)
	Allogeneic HSCT with expected neutropenia <14 days
	Lymphoma (e.g. intensive/dose-escalated therapy)
Very low risk‡ Less than 5% incidence of IFD No mucositis	Other lymphoproliferative neoplasms (e.g. standard chemotherapy for lymphoma, induction therapy for myeloma, treatment-naive CLL)
	Other myeloproliferative neoplasms
	Treatment for solid organ tumours

†Please refer to Table 4 for summary of recommendations and level of evidence
‡Consider that low and/or sporadic occurrence is not equal to no risk and is c
treatments.
ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, ch
haemopoietic stem cell transplantation; IFD, invasive fungal disease; MDS, m
recommendation.

Table 4 Recommendations for the use and dosing of specific antifungal agents for prophylaxis (grade of evidence)

Risk group	Agent	Alternative agents
High risk	Posaconazole (A)	Voriconazole (B) Itraconazole (B) Liposomal amphotericin B (C) Micafungin† (B) Caspofungin (C)
Low risk	Fluconazole (B)	Itraconazole (B) Echinocandins (B)

Agent	Recommended dose for adult patients	Recommended dose for paediatric patients
Posaconazole	200 mg orally, 8-hourly	>13 years: 200 mg orally, 8-hourly plus TDM
Voriconazole	200 mg orally or IV, 12-hourly	2 years to <12 years or 12–14 years and weighing <50 kg: 8 mg/kg (day 1, 9 mg/kg) IV, 12-hourly or 9 mg/kg orally, 12-hourly plus TDM ≥15 years or aged 12–14 years and weighing ≥50 kg: 4 mg/kg (day 1, 6 mg/kg) IV, 12-hourly or 200 mg orally, 12-hourly plus TDM
Fluconazole	200–400 mg orally or IV, daily	6–12 mg/kg (max 400 mg) orally or IV, daily
Itraconazole	200 mg orally, 12-hourly	2.5 mg/kg orally, 12-hourly plus TDM
Liposomal amphotericin B	See text (adult section) for dosing recommendations	See text (paediatric section) for dosing recommendations
Echinocandins	See text (adult section) for dosing recommendations	See text (paediatric section) for dosing recommendations

Table 4 Recommendations for choice and dose of antifungal prophylaxis agent in adults

Risk group		Antifungal agent	SoR	QoE	Comments
High risk	First line	Posaconazole Oral (tablets) Loading with 300 mg twice daily on Day 1, followed by 300 mg daily	A	I	Intravenous formulation can be used to continue prophylaxis if poor oral intake/absorption
	Alternate agents	Voriconazole Oral or intravenous 4 mg/kg twice daily†	A	II	High rates of adverse events (liver function abnormalities); variable CYP metabolism
		Micafungin Intravenous 100–150 mg daily	B	II	Could be used during periods of neutropenia if azoles contraindicated, poor oral intake/absorption
		Itraconazole Oral 200 mg twice daily	B	II	Less new data supporting its use compared to other azoles
		Liposomal amphotericin Intravenous 50–200 mg three times per week	B	II	Could be used if azoles contraindicated due to drug–drug interactions, adverse events, poor oral intake/absorption
		Isavuconazole Oral 200 mg three times per day for 48 h followed by 200 mg daily	C	II	Higher rates of IFD in cohort studies; could be used if other azoles contraindicated due to adverse events such as QTc prolongation
Low risk	First line	Fluconazole Oral 200–400 mg daily	A	I	
	Alternate agents	Echinocandin Intravenous Dosing dependent on agent	A	II	
		Itraconazole Oral 200 mg twice daily	A	II	
Very low risk		No prophylaxis	B	II	

†Dose used in prophylaxis studies have been 200 mg twice daily; measure voriconazole levels to ensure achievement of target level (refer to accompanying optimising antifungal therapy and TDM guidelines by Chau *et al.* 2021[182], which can be found elsewhere in this supplement).

Recommending authority	2014 consensus guideline	2018 (ECIL)	2021 consensus guideline
High risk	Neutrophils <0.1 × 10^9/L for >3 weeks or <0.5 × 10^9/L for >5 weeks Unrelated, mismatched or cord blood donor HSCT GVHD Corticosteroids >1 mg/kg prednisolone equivalent and neutrophils <1 × 10^9/L for >1 week Corticosteroids >2 mg/kg prednisolone equivalent >2 weeks High-dose cytarabine Fludarabine use in highly treatment-refractory patients with CLL or low-grade lymphoma Alemtuzumab use, especially in highly treatment-refractory patients with CLL or lymphoma ALL AML	for AML 1. advanced age 2. prolonged and profound neutropenia and monocytopenia 3. use of purine analogues (e.g. fludarabine) 4. the presence of indwelling catheters, alimentary mucositis and individual genetic susceptibilities For CLL 1. the disease-associated humoral immunodeficiency (related to stage and duration of disease) 2. additional immunosuppression resulting from therapy with corticosteroids, cytotoxic drugs (alkylating agents and purine analogues) 3. monoclonal antibodies (rituximab, alemtuzumab, ofatumumab and obinutuzumab) 4. lenalidomide 5. kinase inhibitors (ibrutinib and idelalisib).	Neutrophil <0.1109/L for >3 weeks or<0.5109/L for >5 weeks (e.g. allogeneicHSCT) Corticosteroids >1 mg/kg prednisoloneequivalent and neutrophils <1109/L for>1 week Corticosteroids >2 mg/kg prednisolone equivalent >2 weeks Unrelated, mismatched or cord bloodallogeneic HSCT GVHD–extensive or severeAML–induction/reinductionALL–induction/reinductionMDS
low risk	Neutropenia 0.1–0.5 × 10^9/L for 3–5 weeks Neutropenia 0.1–0.5 × 10^9/L for <3 weeks with lymphopenia (lymphocytes <0.5 × 10^9/L)		Autologous HSCT (e.g. patients at high riskfor mucositis) Allogeneic HSCT with expected neutropenia <14 days Lymphoma (e.g. intensive/dose-escalated therapy)
Very low risk	PBSC autologous HSCT Lymphoma		Other lymphoproliferative neoplasms (e.g.standard chemotherapy for lymphoma,induction therapy for myeloma,treatment-naïve CLL) Other myeloproliferative neoplasmsTreatment for solid organ tumours
Addition			Added risk stratification for newer

Recommending authority	2014 consensus guideline	2018 (ECIL)	2021 consensus guideline
Prophylactic agents for high risk	Mould active prophylaxis (posaconazole>voriconazole)	For AML- posaconazole >> fluconazole HSCT Pre-engraftment – Fluconazole preferred (AI) Post-engraftment- Posaconazole preferred (AI) In other conditions, individualisation is needed	Posaconazole>voriconazole>micafungin New consideration- Isavuconazole
For low risk	Anti-candida prophylaxis		Fluconazole> echinocandins>intravenous
For very low risk	No prophylaxis		No prophylaxis
Addition			

Take home message

- Antifungal prophylaxis is not recommended in every patient of haematological malignancy
- Depending upon the state of secondary immunosuppression due to disease process or the therapy (risk stratification group an individual belongs to), prophylactic antifungal needs are to be determined
- Newer therapeutic modalities have raised new concerns about fungal infections in haematological disorders
- Posaconazole remains the preferred agent in almost all conditions
- Studies evaluating LAMB and echinocandins for prophylactic use are lacking in number
- Isavuconazole and new formulation of Itraconazole require farther study to be recommended in such situations