Fungal Infections

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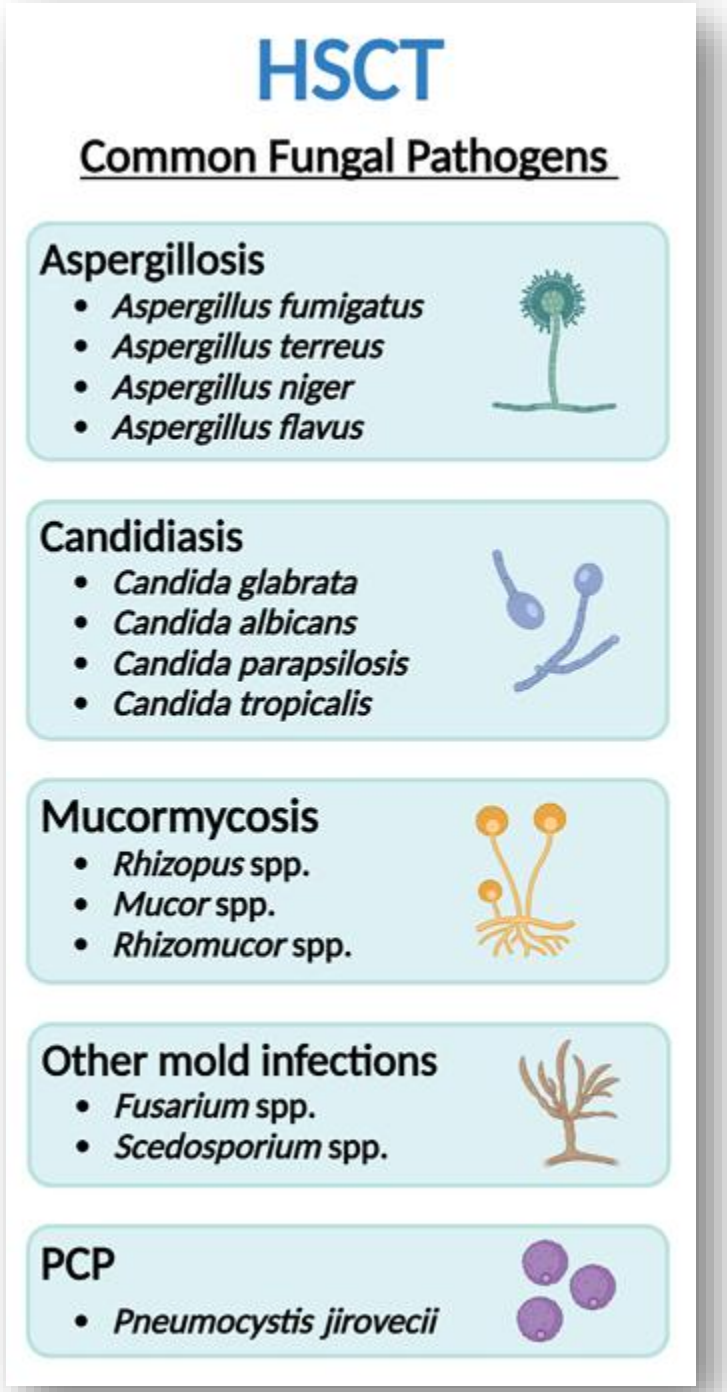


IFI/IFD in HSCT

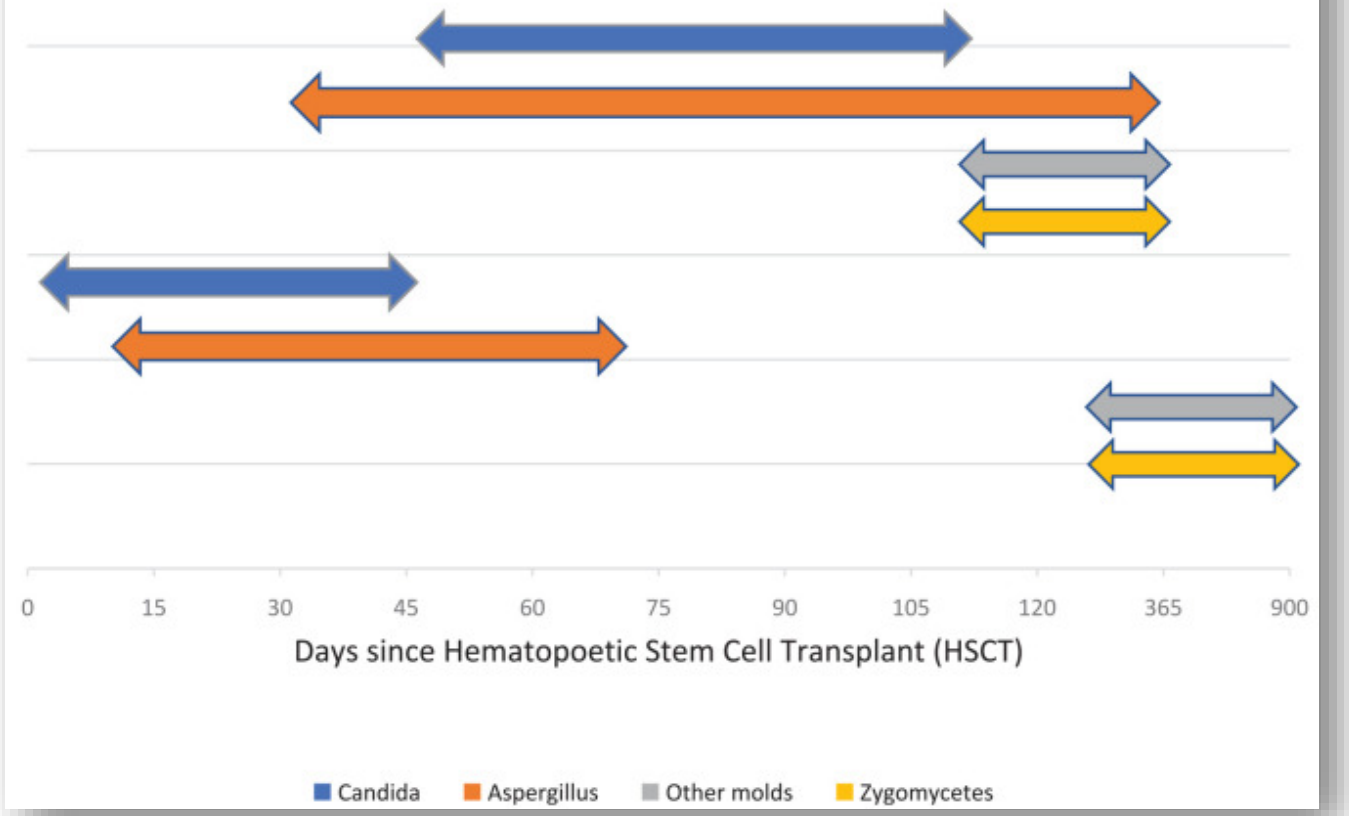
- The incidence ranges from 5% to 17% across studies,
- with a mortality rate of 35% to 50%

  (TRANSNET) Database 2010, SEIFEM B-2004 study,

- Non- Albicans candida – most common infection:
- Mucositis
- Multiple antibiotics – breakthrough C *Krusei*
- Nosocomial pathogens – C *tropicalis*
- TPN/Indwelling catheters – C *parapsilosis*
- Intrinsic resistance to fluconazole – C *glabrata*

BiomedicalJournal47(2024)100719

- Neutropenia - Mucositis - Myoablative conditioning regimen - Acute Graft-	- Chronic graft-*versus*-host disease requiring chronic immunosuppresion - CMV reactivation	- Severe graft-*versus*-host disease causing secondary neutropenia - Use of TNF alfa



Ther Adv Infectious Dis 2021, Vol. 8: 1–26

Table 3
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		No. of studies[b]	No. of patients	HR (95% CI)	I^2%	p	No. of studies[b]	No. of patients	OR (95% CI)	I^2%	p
Age >40 y	9	5	24 489	1.98 (1.32–2.97)	38	<0.001					
Male recipients	12	5	3767	1.31 (0.80–2.14)	36	0.28					
Underlying disease: lymphoma	2	2	470	2.74 (0.30–24.76)	84	0.37					
Stem cell source: Cord blood	3	2	740	1.93 (0.85–4.41)	0	0.12					
Unrelated donor	9	3	2845	1.98 (1.01–3.87)	0	0.0469					
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Respiratory viral infection	2	2	1467	3.18 (1.91–5.30)	0	<0.001					
Secondary neutropenia	4	2	433	2.03 (0.70–5.92)	79	0.19	2	841	2.62 (0.83, 8.27)	72	0.1
Prolonged neutropenia	4	2	229	1.34 (1.05, 1.72)	0	0.02					
HCT-CI ≥ 3	3	2	21 812	1.78 (1.13–2.80)	34	0.01					
High-dose glucocorticoids	10	5	4396	3.37 (2.39–4.77)	0	<0.001					

ATG, anti-thymocyte globulin; CMV, cytomegalovirus; EBV, epstein-barr virus; GVHD, graft-versus-host disease; HCT-CI, haematopoietic cell transplantation comorbidity index; MAC, myeloablative conditioning.

[a] The number of studies where the risk factor was considered in the univariate analysis.

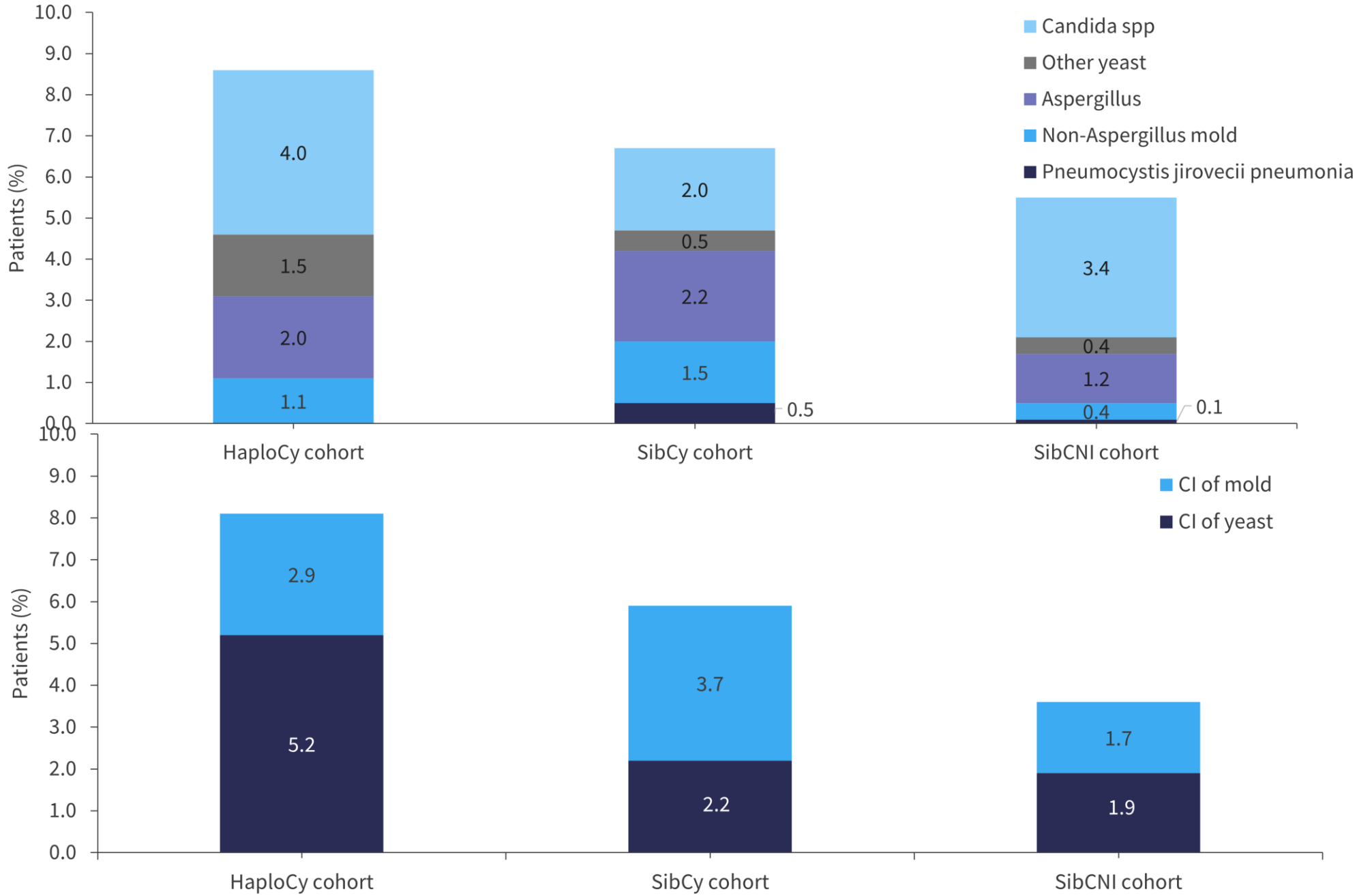
[b] The number of studies included in the meta-analysis.

Incidence and Impact of Fungal Infections in Post-Transplantation Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis and Haploidentical Hematopoietic Cell Transplantation: A Center for International Blood and Marrow Transplant Research Analysis

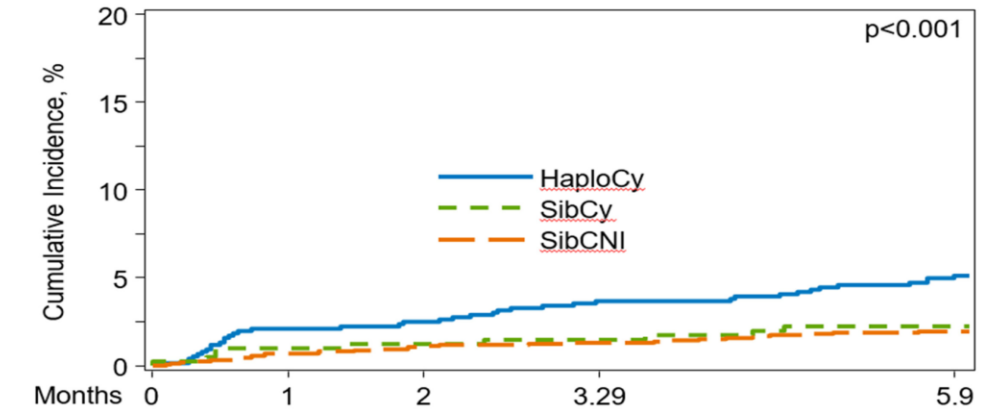
Genovefa A. Papanicolaou[1,2,*], Min Chen[3], Naya He[3], Michael J. Martens[3,4],

Transplantation and Cellular Therapy 30 (2024) 114.e1–114.e16

- CIBMTR registry cohort study comprising 11,964 patients aged ≥2 years
- first (HSCT) for AML ALL MDS (2012-17). The three cohorts included:
- haplo donor (≥2 antigen/allele mismatch) with PTCy (HaploCy cohort)
- human leukocyte antigen-identical sibling donor with PTCy (SibCy cohort)
- sibling donor with calcineurin inhibitor-based GvHD prophylaxis (SibCNI cohort)

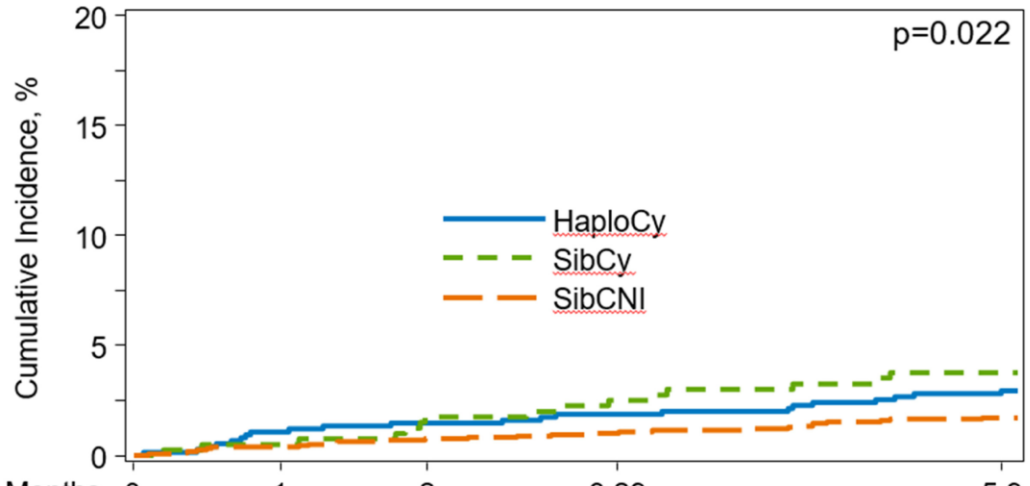

Patients (%)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Candida spp
Other yeast
Aspergillus
Non-Aspergillus mold
Pneumocystis jirovecii pneumonia
4.0
1.5
2.0
1.1
2.0
0.5
2.2
1.5
0.5
3.4
0.4
1.2
0.4
0.1
HaploCy cohort
SibCy cohort
SibCNI cohort
Patients (%)
CI of mold
CI of yeast
2.9
5.2
3.7
2.2
1.7
1.9
HaploCy cohort
SibCy cohort
SibCNI cohort

A. **Cumulative Incidence of yeast FI by Day 180.**

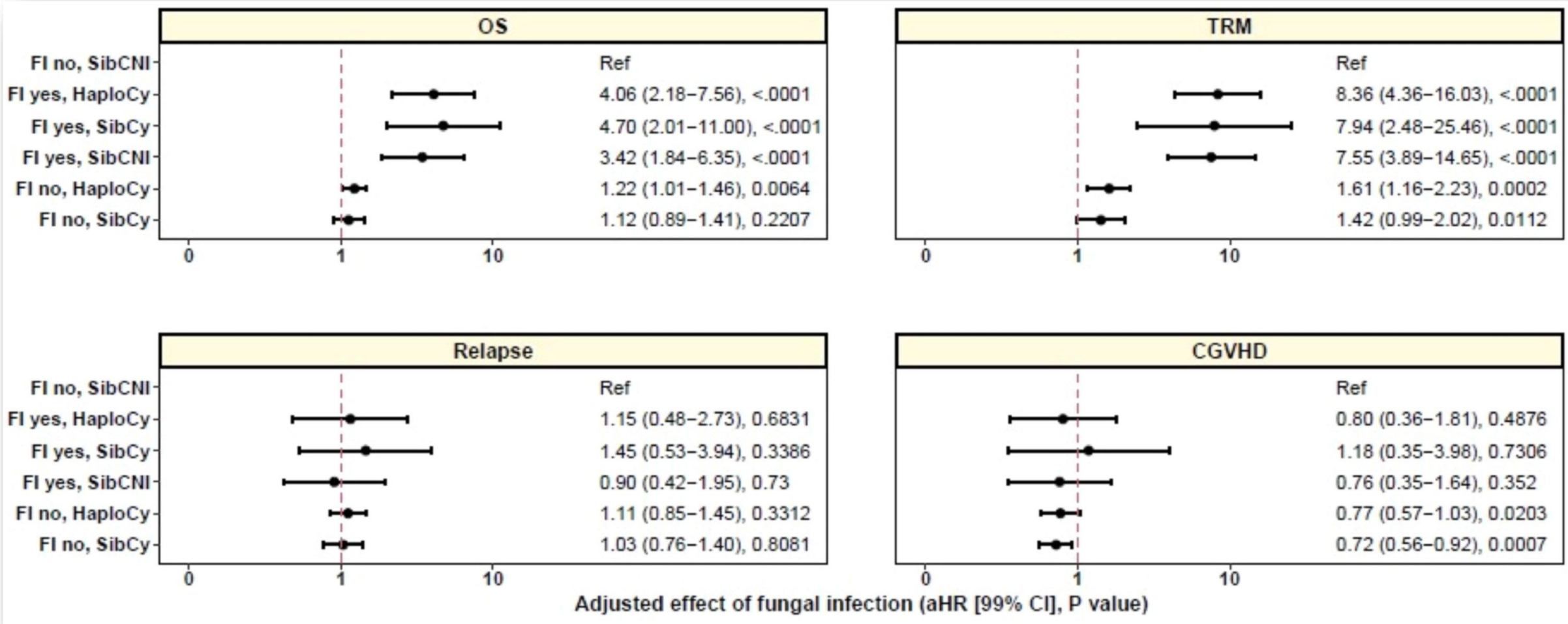


# at Risk					
HaploCy	757	710	683	633	561
SibCy	402	390	371	355	314
SibCNI	1605	1575	1536	1459	1319

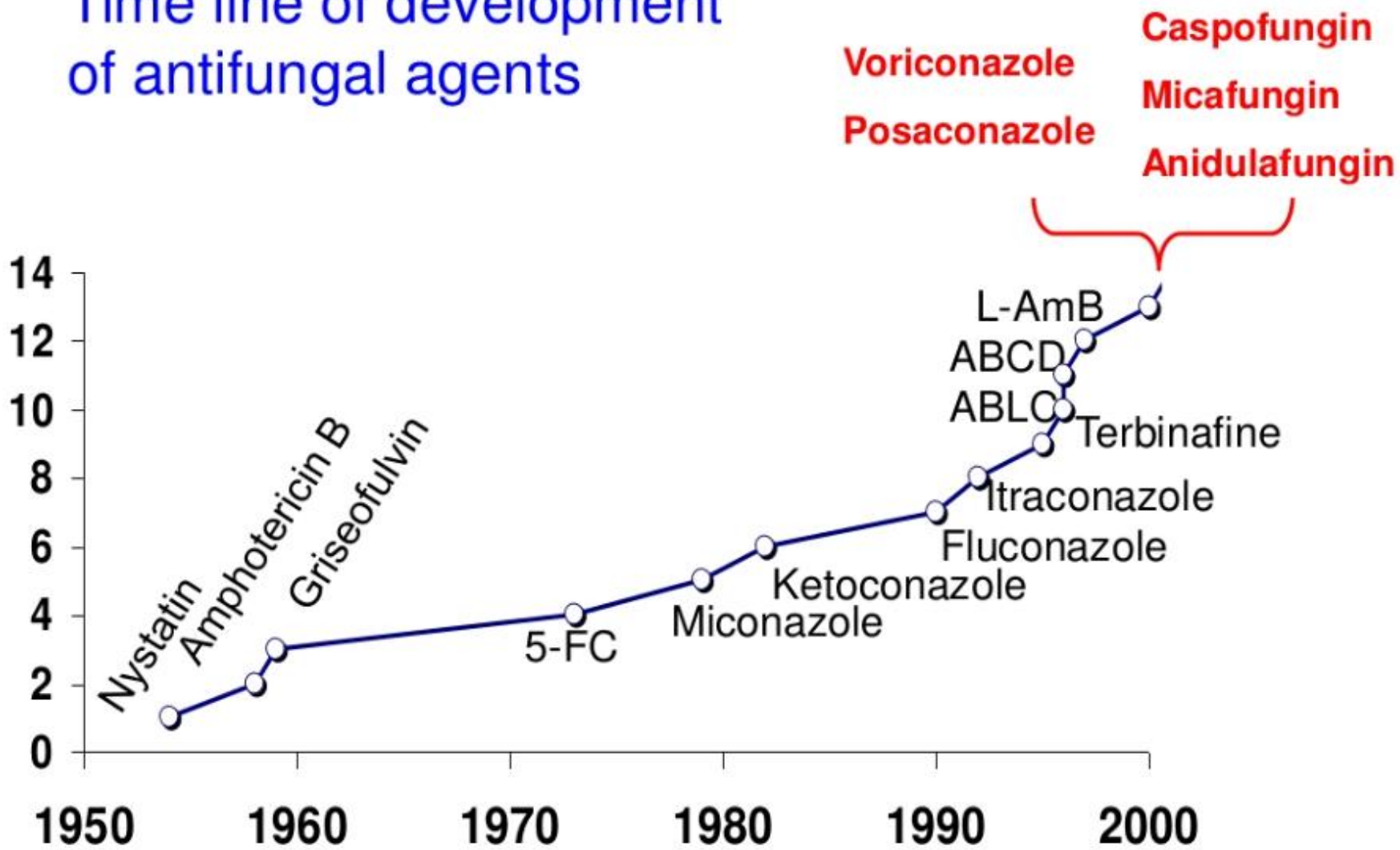
B. **Cumulative Incidence of mold FI by Day 180.**



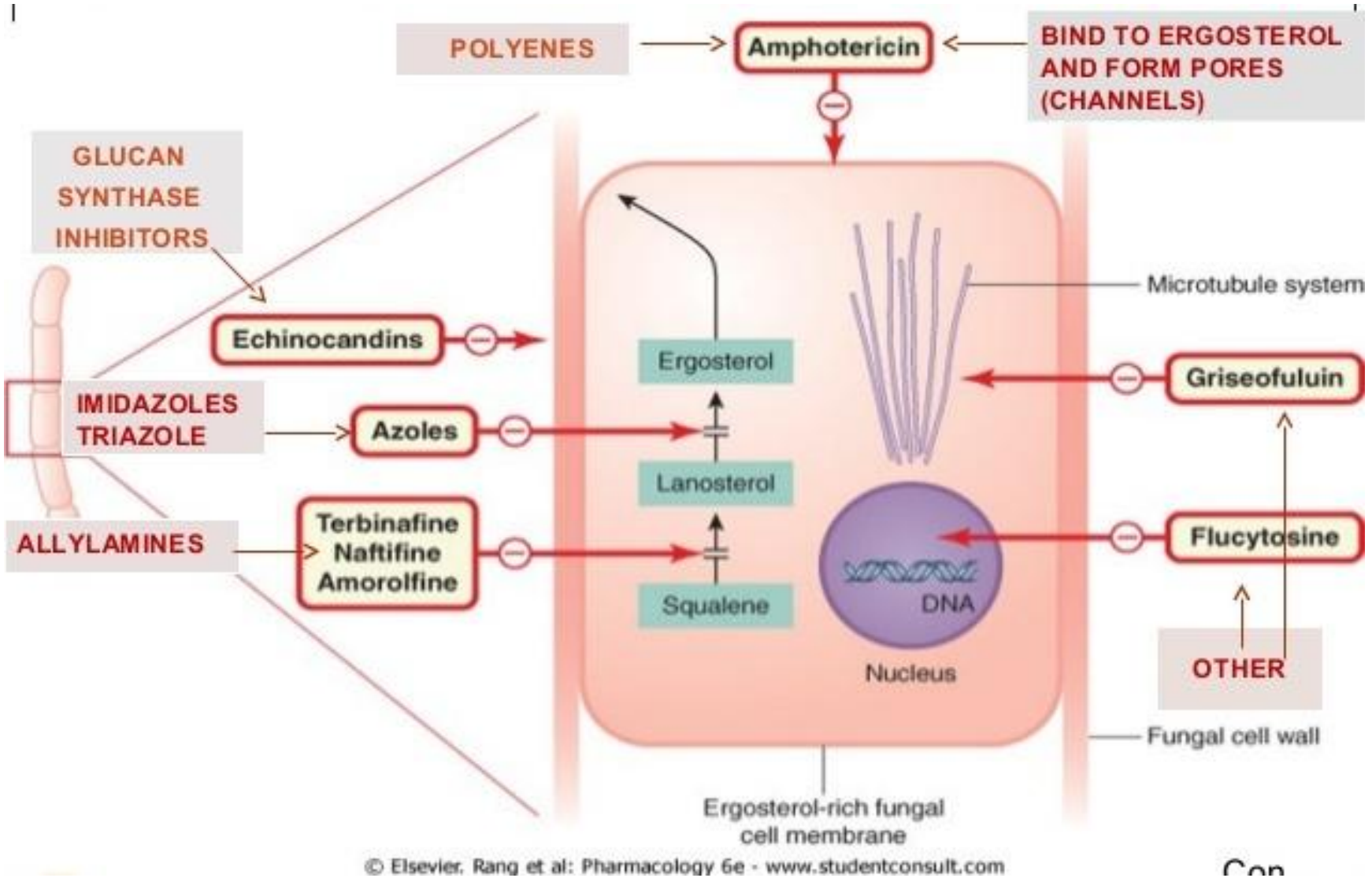
# at Risk					
HaploCy	757	715	688	643	568
SibCy	401	390	368	353	310
SibCNI	1604	1577	1540	1462	1325


OS
FI no, SibCNI
FI yes, HaploCy
FI yes, SibCy
FI yes, SibCNI
FI no, HaploCy
FI no, SibCy
Ref
4.06 (2.18–7.56), <.0001
4.70 (2.01–11.00), <.0001
3.42 (1.84–6.35), <.0001
1.22 (1.01–1.46), 0.0064
1.12 (0.89–1.41), 0.2207
0
1
10
TRM
Ref
8.36 (4.36–16.03), <.0001
7.94 (2.48–25.46), <.0001
7.55 (3.89–14.65), <.0001
1.61 (1.16–2.23), 0.0002
1.42 (0.99–2.02), 0.0112
0
1
10
Relapse
FI no, SibCNI
FI yes, HaploCy
FI yes, SibCy
FI yes, SibCNI
FI no, HaploCy
FI no, SibCy
Ref
1.15 (0.48–2.73), 0.6831
1.45 (0.53–3.94), 0.3386
0.90 (0.42–1.95), 0.73
1.11 (0.85–1.45), 0.3312
1.03 (0.76–1.40), 0.8081
0
1
10
CGVHD
Ref
0.80 (0.36–1.81), 0.4876
1.18 (0.35–3.98), 0.7306
0.76 (0.35–1.64), 0.352
0.77 (0.57–1.03), 0.0203
0.72 (0.56–0.92), 0.0007
0
1
10
Adjusted effect of fungal infection (aHR [99% CI], P value)

Time line of development of antifungal agents



Mechanism of action



Spectrum of Antifungal agents

Table 2 - Microbiologic spectrum of the different antifungal agents

	AMB	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Echinocandins
Candida albicans	+++	+++	+++	+++	+++	+++
Candida tropicalis	+++	+++	+++	+++	+++	+++
Candida parapsilosis	+++	+++	+++	+++	+++	+++
Candida glabrata	++	+/-	+/=	+	+	+++
Candida krusei	+++	-	+/-	+++	+++	+++
*Aspergillus fumigatus**	+++	-	+++	+++	+++	++**
Aspergillus flavus	+++	-	+++	+++	+++	++**
Aspergillus terreus	-	-	+++	+++	+++	++**
Fusarium species	+	-	-	-/+	-/+	-
Agents of mucormycosis	++	-	-	-	+	-

* Molecular studies show that *Aspergillus fumigates* comprises a complex of various species, some of which may be less susceptible to antifungal agents; ** ++ because the echinocandins have fungistatic effect against *Aspergillus* species

HSCT Antifungal Prophylaxis

Autologous HSCT (ECIL Low Risk)

- Primary antifungal prophylaxis is not recommended,
- although fluconazole (400 mg q24h) should be considered to prevent mucosal *Candida* infection during the neutropenic phase (B-III) [4].

Recommendations in alloHSCT recipients: pre-engraftment

Antifungal agent	Pre-engraftment risk of mould infection	
	low	high
Fluconazole 400 mg q24h	A-I [a]	D-III
Posaconazole tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1 or oral solution 200 mg q8h	B-II	B-II
Itraconazole oral solution 2.5mg/kg q12h	B-I	B-I
Voriconazole 200mg q12h	B-I	B-I
Micafungin 50 mg q24h	B-I	C-I
Caspofungin and anidulafungin	no data	no data
Liposomal amphotericin B	C-II	
Aerosolized liposomal amphotericin B (10 mg twice weekly) associated with Fluconazole 400 mg q24h	C-III	
Isavuconazole 200 mg q24h following a loading dose of 200 mg q8h on days 1 and 2 [b]	no data	no data

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

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

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

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

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

Recommendations in alloHSCT recipients: post-engraftment

Antifungal agent	Steroids-treated acute GVHD
Posaconazole tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1 or oral solution 200 mg q8h	**A-I [a, b]**
Itraconazole oral solution 2.5mg/kg q12h	**B-I [b]**
Voriconazole 200mg q12h	**B-I [b]**
Micafungin 50 mg q24h	**C-II**
Caspofungin and anidulafungin	**no data**
Liposomal amphotericin B	**C-II**
Aerosolized liposomal amphotericin B (10 mg twice weekly) associated with Fluconazole 400 mg q24h	**no data**
Isavuconazole 200 mg q24h following a loading dose of 200 mg q8h on days 1 and 2 [c]	**no data**
Fluconazole 400 mg q24h	**D-III**

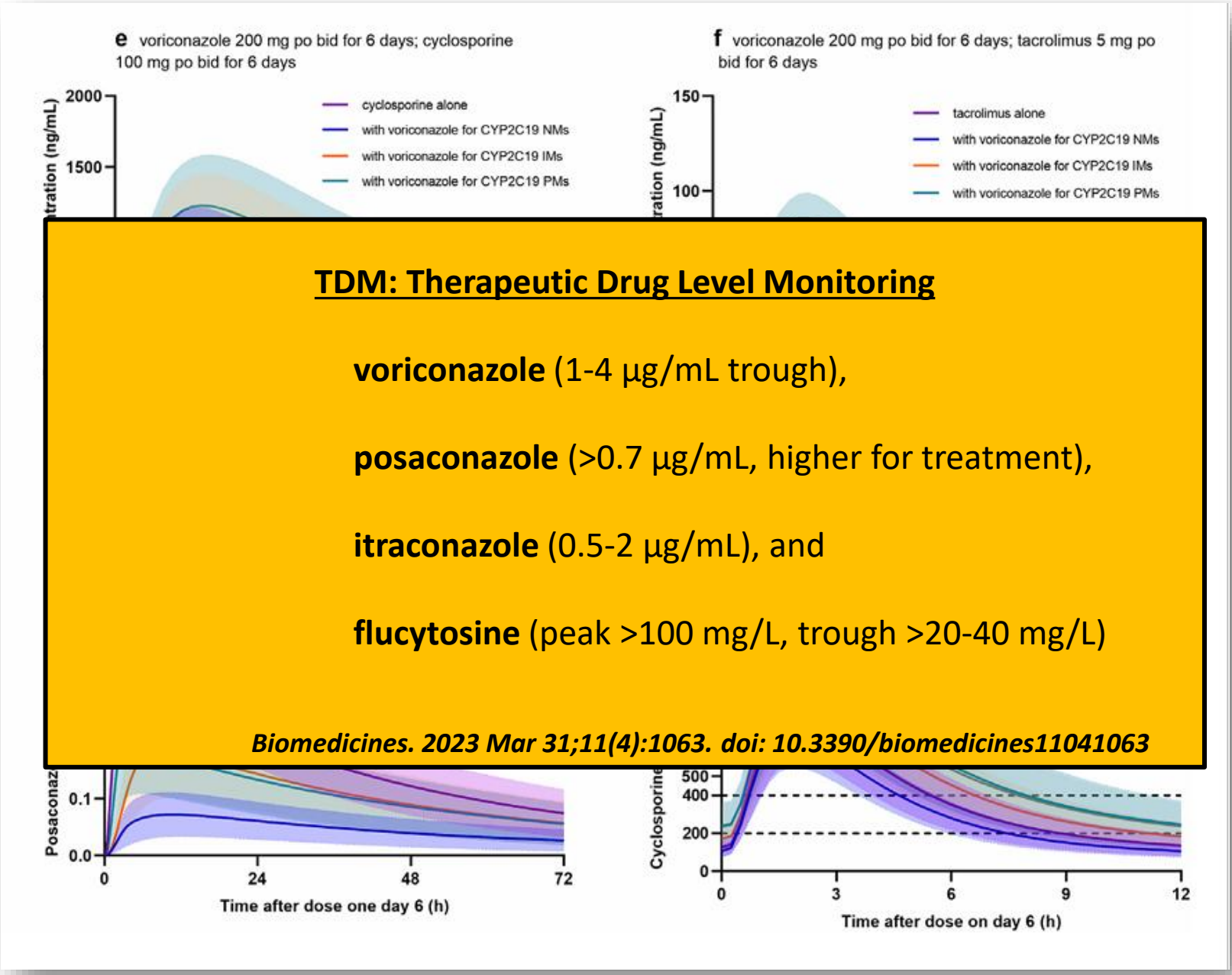
After engraftment, in patients without GVHD, fluconazole can be continued until D+75

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

[b] It is recommended to monitor serum drug concentration

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

Azole-CNI interaction and influence of food



TDM: Therapeutic Drug Level Monitoring

voriconazole (1-4 µg/mL trough),

posaconazole (>0.7 µg/mL, higher for treatment),

itraconazole (0.5-2 µg/mL), and

flucytosine (peak >100 mg/L, trough >20-40 mg/L)

Biomedicines. 2023 Mar 31;11(4):1063. doi: 10.3390/biomedicines11041063

Fungal Infection in HSCT: Management

Diagnostic -Therapeutic Rubric

	Prophylaxis	Empirical	Diagnostics-driven (pre-emptive)				Directed
			I	II	III	IV	
Radiological signs & clinical symptoms	No	Persistent febrile neutropenia	No	Clinical (any new infiltrate not fulfilling the EORTC/ MSG criteria)		Radiological signs on CT (dense, well-circumscribed lesions with or without a halo sign, air-crescent sign, or cavity)	
Mycology results	Negative	Negative	Positive biomarker or culture	Negative	Positive biomarker or culture	Negative	Positive biomarker or micrososcopy or culture
Evidence of IFD	No	No	No	No	No	Yes	Yes
Evidence of IFI	No	No	Yes	No	Yes	No	Yes
EORTC/MSG	-	-	-	-	-	Possible	Probable
Final diagnosis	No IFD		IFD cannot be excluded			IFD	

Figure 1. Patterns of IFD. (Adapted with permission from Maertens *et al.*[6]) EORTC/MSG, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group;[5] IFI, invasive fungal infection; IFD, invasive fungal disease.

Definitions: Invasive Fungal Infection

- **Probable:** Presence of Host factor, Clinical criterion and mycological criterion

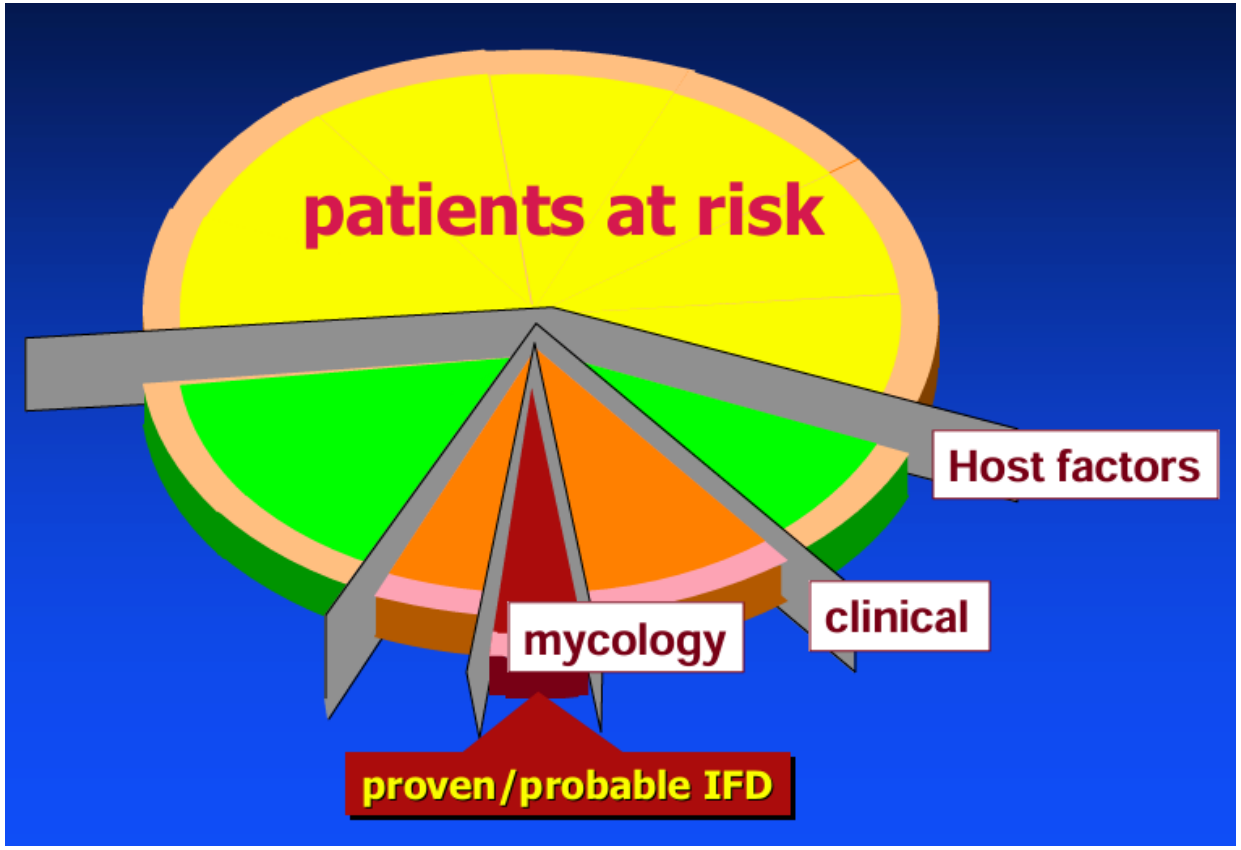
- **Possible:** Presence of Host factor + Clinical Criteria without Mycological Criteria

- **Definitive:**

Culture (candida)

And or

histopathological confirmation - molds



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[a] The number of studies where the risk factor was considered in the univariate analysis.

[b] The number of studies included in the meta-analysis.

Clinical criteria[b]

Clin Infect Dis. 2008 June 15; 46(12): 1813–1821. doi:10.1086/588660.

Lower respiratory tract fungal disease[c]

The presence of 1 of the following 3 signs on CT:

Dense, well-circumscribed lesions(s) with or without a halo sign

Air-crescent sign & for other pulmonary moulds – "Reverse Halo sign"

Cavity

Tracheobronchitis

Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis

Sinonasal infection

Imaging showing sinusitis plus at least 1 of the following 3 signs:

Acute localized pain (including pain radiating to the eye)

Nasal ulcer with black eschar

Extension from the paranasal sinus across bony barriers, including into the orbit

CNS infection

1 of the following 2 signs:

Focal lesions on imaging

Meningeal enhancement on MRI or CT

Disseminated candidiasis[d]

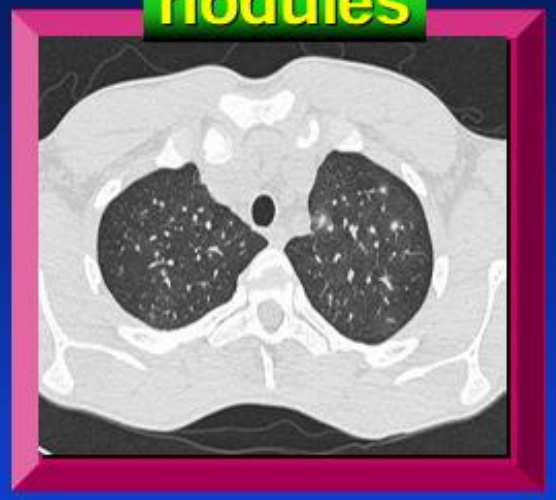
At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks:

Small, target-like abscesses (bull's-eye lesions) in liver or spleen

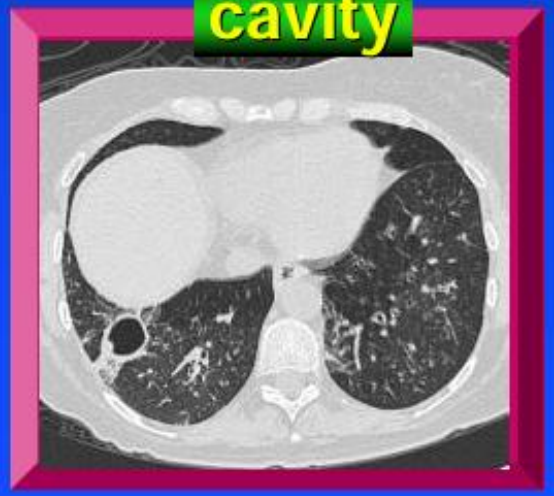
Progressive retinal exudates on ophthalmologic examination

Specific pulmonary infiltrates on CT scan

nodules



cavity



2008 EORTC	2020 updated EORTC
Mycological criteria (Direct test) Mold in sputum, bronchoalveolar lavage fluid, or bronchial brush, indicated by 1 of the following: - Presence of fungal elements indicating a mold - Recovery by culture of a mold (*e.g.*, *Aspergillus*, *Fusarium*, Zygomycetes, or *Scedosporium* species) (Indirect test) Galactomannan antigen detected in plasma, serum, or BAL fluid (Aspergillosis)	**Mycological criteria** (Direct test) Any mold, for example, *Aspergillus*, *Fusarium*, *Scedosporium* species or Mucorales recovered by culture from sputum, BAL, bronchial brush, or aspirate Microscopical detection of fungal elements in sputum, BAL, bronchial brush, or aspirate indicating a mold (Indirect test) Galactomannan antigen in plasma, serum, or BAL (Aspergillosis) Any 1 of the following: - Single serum or plasma: ≥1.0 - BAL fluid: ≥1.0 - Single serum or plasma: ≥0.7 and BAL fluid ≥0.8 *Aspergillus* PCR Any 1 of the following: - Plasma, serum, or whole blood 2 or more consecutive PCR tests positive - BAL fluid 2 or more duplicate PCR tests positive - At least 1 PCR test positive in plasma, serum, or whole blood and 1 PCR test positive in BAL fluid

Serum galactomannan in the setting of hematology and oncology

Studies	Cases of proven IA			
	TP/(TP + FP)	Pooled sensitivity (95% CI)	TN/(TN + FP)	Pooled specificity (95% CI)
Studies limited to patients with hematological malignancy	106/152	0.70 (0.62–0.77)	2570/2808	0.92 (0.90–0.93)
Studies limited to patients undergoing BMT	49/60	0.82 (0.70–0.90)	722/843	0.86 (0.83–0.88)
Studies limited to solid-organ transplant recipients	2/9	0.22 (0.03–0.60)	180/215	0.84 (0.78–0.88)

Ref: Christopher D. Pfeiffer, Jason P. Fine, Nasia Safdar, Diagnosis of Invasive Aspergillosis Using a Galactomannan Assay: A Meta-Analysis, *Clinical Infectious Diseases*, Volume 42, Issue 10, 15 May 2006

Index cut off value	Sensitivity, % (95% CI) (when not receiving mold active therapy)	Sensitivity, % (95% CI) (when receiving mold active therapy)
0.5	89 (65–97)	52 (32–71)
1.0	72 (37–92)	30 (16–49)
1.5	56 (13–91)	23 (12–41)

Receipt of mold-active antifungal drugs on the day of testing decreased sensitivity in this study

BAL galactomannan may be more sensitive in patients who are on mold active anti fungals !

Ref: Marr et. al. Antifungal Therapy Decreases Sensitivity of the *Aspergillus* Galactomannan Enzyme Immunoassay, *Clinical Infectious Diseases*, 2005

Diagnosis of Invasive Fungal Disease Using Serum (1→3)-β-D-Glucan: A Bivariate Meta-Analysis

Yuan Lu[1], Yi-Qiang Chen[2], Ya-Ling Guo[3], Shou-Ming Qin[2], Cong Wu[2] and Ke Wang[2]

Again the host matters !

Patient population	Sensitivity	Specificity
SOT recipients	0.66	0.45
ICU patients	0.82	0.67
Hematological patients	**0.76**	**0.95**
Two positive samples	0.65	0.93
Single positive sample	0.81	0.78

Ref: Lu Y et. al.. 2011. Diagnosis of invasive fungal disease using serum (1–>3)-beta-D-glucan: a bivariate meta-analysis. *Intern Med*

False positivity in hematology patients

False positive BDG	Reference
IVIG	BDG peak levels within 3 days after IVIG - median 201.4) pg/ml (Egger M et. al. J Infect, 2018)
Albumin	Administration of albumin within 2 days prior to BDG testing was was found to significantly confound the diagnostic performance (Cascio et. al. , Eur J Clin Microbiol Infect Dis., 2015 Feb)
Blood products	In patients receiving PRBC transfusions, BDG values increased from 13 and 17 pg/ml to 183 and 361 pg/ml (Liss B et. al.Mycoses. 2016)
Excessive sample manipulation	2/3 of initially negative specimens became positive after the 3rd or 4th successive transfer of samples to new transport tubes (Pickering, et al. JCM 2005).
PEG-asparaginase	Patients who received PEG-asparaginase had a mean BDG value of 118 pg/mL vs. 65.7 pg/mL in patients who did not receive the drug (Hammarström H, et al. Eur J Clin Microbiol Infect Dis 2015)
Defibrotide	Median peak BDG level post Defibrotide : 103 pg/mL (range 72–244 pg/mL). (Alosaimy S, et al. Bone Marrow Transplant 2020)

BDG in patients with febrile neutropenia

NEGATIVE

POSITIVE

- If possible, confirm with repeat testing - increases specificity
- Proceed to look for IFI

Look at the pretest probability, clinical and radiographic picture - Which fungus ? Site of infection ?

Does not exclude IFI

Aspergillus PCR

- Blood PCR: High sensitivity and NPV in severely neutropenic patients where antifungal prophylaxis is not used.
- In patients with high pretest probability, two positive PCRs provide high specificity
- Higher potential to diagnose IA earlier compared to GM
- BAL PCR may perform better in patients on mold active ppx, but may imply colonization
- GM plus PCR : Combination has high NPV in this setting

Treatment of Fungal infections

Table 1. Examples of common antifungal dosing regimens for adults used in clinical practice

Intermittent (phased dosing)	Cryptococcosis (meningitis)	• Induction (AmB 1 mg/kg/day + 5-FC for 14 days) • Consolidation/maintenance (fluconazole 400 mg/day for maintenance therapy in immunocompromised patients)	Reduces toxicity by limiting exposure duration; ensures high peak concentrations	Requires careful monitoring during induction phase due to potential toxicity of amphotericin B and 5-FC	Resistance development is unlikely but may occur in rare cases with prolonged or suboptimal therapy	4, 67–69
Weight-based dosing	Mucormycosis	• Targeted (L-AmB 5–10 mg/kg/day for 2–4 weeks, depending on infection severity; consider surgical debridement where feasible)	Personalized therapy, ensuring adequate drug exposure in diverse patient populations	Complex calculation; potential for overdose or underdose in rapidly changing weight conditions; drug penetration into necrotic areas is often limited, highlighting the importance of surgical intervention	Resistance risk is lower if properly dosed but may still develop if insufficient concentrations are achieved	27, 70, 71
High-dose dosing	*C. auris* infections	• Targeted (micafungin 150 mg IV daily for 14 days or until clearance is confirmed; alternative dosing includes anidulafungin)	High doses may overcome innate drug resistance in some fungal species	Associated with increased toxicity (e.g. hepatotoxicity)	Resistance may still develop despite high drug pressure	72, 73

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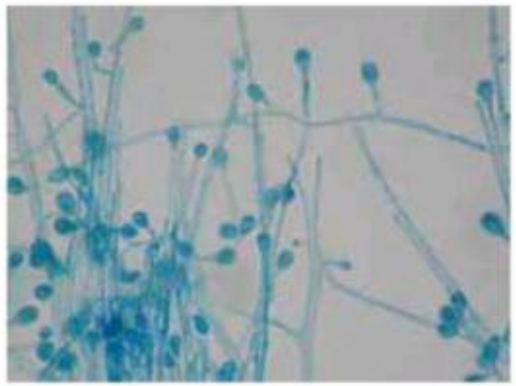
Management of Breakthrough Infections

Table 3 - Antifungal agents used as empiric/preemptive therapy based on the prophylactic strategy

Prophylaxis	Etiology of breakthrough IFD	Antifungal agent for empiric / preemptive therapy	Comments
No	*Candida*>>>*Aspergillus*>>> Other moulds*	Fluconazole, caspofungin	Risk of aspergillosis depends on duration of neutropenia and T-cell immune status
Fluconazole	Aspergillus >>> Other moulds* ≥ *Candida*	Caspofungin, L-AMB**, voriconazole	In preemptive strategy, voriconazole (or L-AMB) is preferred if clinical parameters suggest a diagnosis of invasive aspergillosis
Posaconazole or voriconazole	Other moulds* ≥ *Aspergillus* ≥ *Candida*	L-AMB**	Breakthrough infection may be due to non-susceptible agent or low serum levels of the azole

IFD = invasive fungal disease; L-AMB = liposomal amphotericin B
* Other moulds: Fusarium, agents of mucormycosis;
** Other lipid formulations of amphotericin B may be used, but L-AMB has been more extensively studied

Antifungal treatment of other invasive mould infections



Fusarium and Scedosporium spp:

Voriconazole and lipid formulations of amphotericin B
+/-surgical debridement of necrotic tissue

Posaconazole can be used as salvage therapy for these infections

Invasive mucormycosis:

Lipid-based formulation of amphotericin B as first-line therapy

Nucci M, Anaissie E. Fusarium infections in immunocompromised patients. Clin Microbiol Rev 2007; 20: 695–704.
Troke P, et al. Treatment of scedosporiosis with voriconazole: clinical experience with 107 patients. Antimicrob Agents Chemother 2008; 52: 1743–50.
Spellberg B, et al. Clinical practice: recent advances in the management of mucormycosis: from bench to bedside. Clin Infect Dis 2009; 48: 1743–51.

Antifungal Combinations

Table 2. Commonly Used CAF Therapy [9-11, 33-35, 41, 43]

	Commonly used CAF therapy	
Invasive candidiasis	AmB + flucytosine	Pappas et al [10], 2016 IDSA guidelines*
	AmB + azole	Rex et al [33]
	Echinocandin + azole	Cui et al [34] Chen et al [35]
Invasive aspergillosis	Azole or AmB + echinocandin	Patterson et al [9], 2016 IDSA guidelines **Panackal et al [41]
	Voriconazole + anidulafungin	Marr et al [43]
Mucormycosis	AmB + posaconazole or caspofungin	Cornely et al [11]***

*Amphotericin B with or without flucytosine for initial therapy for candida native valve endocarditis, candida CNS infection, azole-resistant *Candida glabrata*, ascending pyelonephritis and fluconazole-resistant candida endophthalmitis. **Salvage therapy with echinocandin either alone or in combination against invasive aspergillosis. Uncertainty of the CAF still exists. ***Intent to cure therapy for refractory disease or in case of intolerance to prior antifungal therapy.

To conclude

IFIs in HSCT recipients in India

- The burden of fungal infections is high, but elaborate epidemiological data in this setting are lacking
- Access to diagnostic tools may be limited
- For autologous HSCT anti-candida prophylaxis is reasonable; while mold active prophylaxis is needed for allogeneic HSCT recipients as well as those patients being treated for GVHD
- Therapy must take into account the etiological agent, as well as the site of infection, and whether it is a breakthrough infection
- Outcomes of IFIs are better with neutrophil recovery
- Interactions of azoles with other agents and the importance of TDM must be borne in mind

IFIs: Invasive fungal infections, HSCT: Hematopoietic stem cell transplantation, TDM: Therapeutic drug monitoring, GVHD: Graft versus host disease

Questions

- 30 year old AML FLU MEL (140) SibCNI transplant
- post bmt day +8 on Posaconazole prophylaxis TLC 100
- Fever + Non healing painful patch in the palate

Next Step ?

1. Imaging of sinuses and orbit
2. Scraping of lesion
3. Biopsy of lesion
4. PCR/ Galactomanan assay

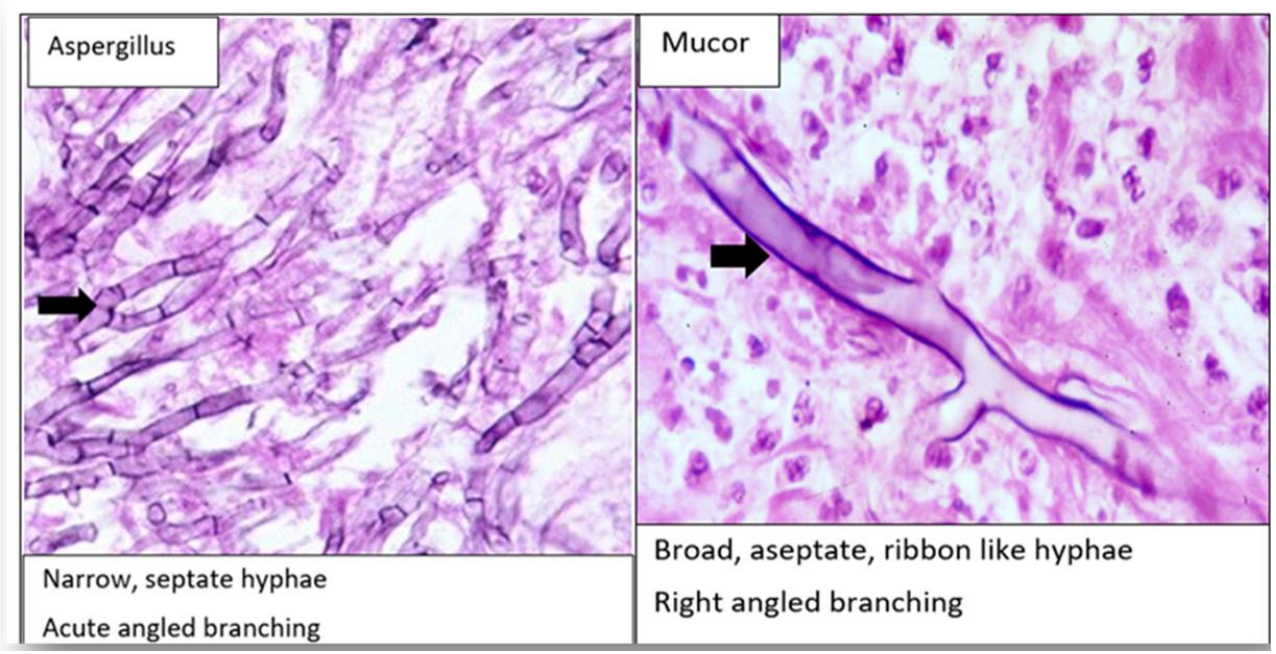
Question 2 and 3

Scraping shows –

- Non septate broad hyphae with right angled branching

- Diagnosis ?

- Therapy ?



Question –

credit Dr.Punit Jain

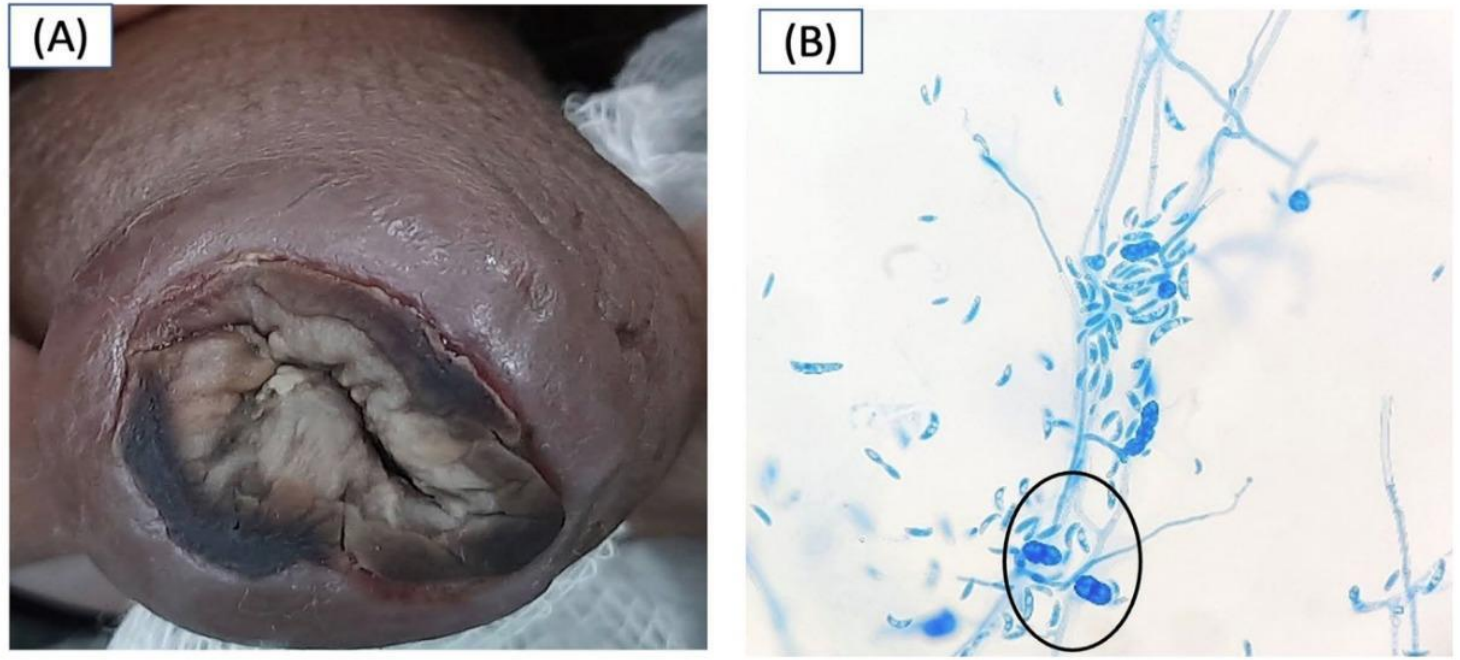


Fig. 1 **A** Central whitish discoloration surrounded by black necrotic margin at tip of penile prepuce. **B** Day 7 Lactophenol Cotton Blue (LPCB) mount on microscopy showed long branched as well as unbranched conidiophores with sickle shaped, 2–3 septa, fusiform macroconidia and small oval micro-conidia (Single/Clusters). Single chlamydospores or in pairs also seen on short lateral branches of conidiophores