IFI, antifungal agents, and mortality in: SOT & Hematological malignancies

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ESCMID Postgraduate Education Course
Sepsis & Immunocomprised Hosts: Challenges in 2024
Antalya, Türkiye 18 – 19 May 2024

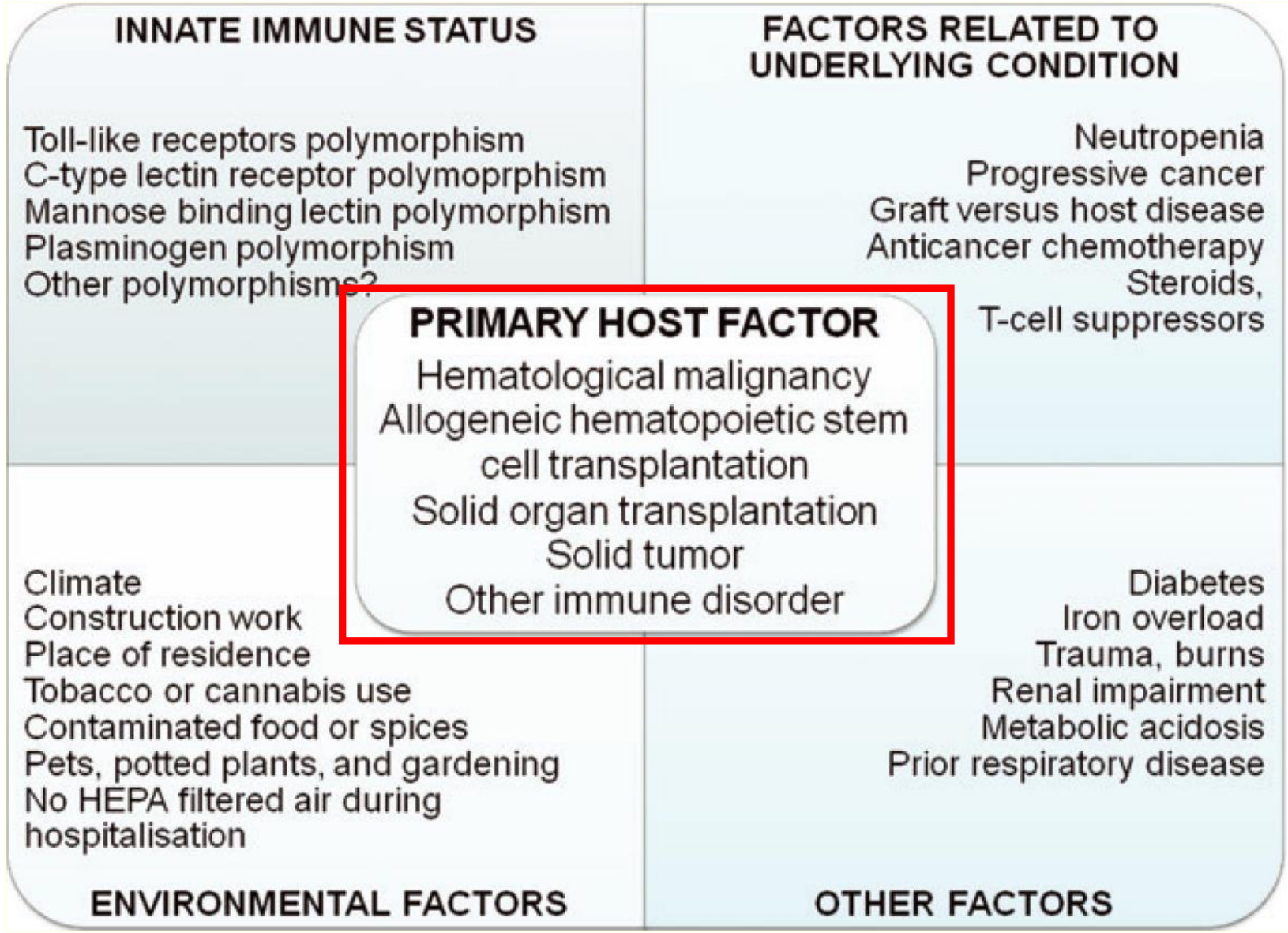
Global incidence and mortality of invasive fungal diseases

	Mean annual incidence (thousands)	Treated mortality (%)	Untreated mortality* (%)	Ratio of treated to untreated cases*	Mean estimated deaths (thousands)	Percentage of deaths attributable to fungal infection (%)	Attributable deaths (thousands)
Invasive aspergillosis in COPD	1513 (753–2272)	43–72%	>95%	1:5	1325	~80%	1060
Invasive aspergillosis in ICU	519 (208–1038)	50% (46–82)	>95%	1:3	416	~50%	208
Invasive aspergillosis in leukaemia and lymphoma, and allogeneic HSCT	27	45% (30–57)	>95%	10:1	14	~80%	11
Invasive aspergillosis (lung cancer)	57*	51%	>95%	1:4	49*	~40%	19*
Chronic pulmonary aspergillosis	1837	8%	20%	1:12	340*	60% (0–85·7)	204*
Candida bloodstream infection	626	35% (8·7–77·3)	~90%	9:1	254	~65% (21–100)	165
Invasive candidiasis without positive blood culture	939	35% (27–60)	~90%	1:5	742*	~65% (21–100)	482*
Pneumocystis pneumonia in AIDS	400	15% (0–71)	>95%	4:1	140	90%	126
Pneumocystis pneumonia not in AIDS	105	40% (8–58)	100%	1:1	74	35% (30–90)	49*
Cryptococcal meningitis	194	60% (20–70)	100%	3:2	147	80% (63–68)	118
Disseminated histoplasmosis in AIDS	71 (47–95)*	30%	100%	1:10	66*	80%	53*
Talaromycosis	19	28%	>95%	3:1	9	90%	8
Mucormycosis	211	25%	100%	4:1	84	70%	59
Coccidioidomycosis (95% USA and Mexico)	30	..	..	10:1	2	90%	2
Fungal asthma	..	..	..	1:20†	92*	50%	46*
Totals	6548	NA	NA	NA	3752	NA	2548

Data are mean (range), unless stated otherwise. COPD=chronic obstructive pulmonary disease. ICU=intensive care unit. HSCT=haematopoetic stem cell transplant. NA=not applicable. *Low-confidence estimates requiring additional study. †Refers to antifungal treatment, not standard asthma therapy.

Denning D. Lancet Infect Dis 2024 Published Online January 12, 2024

Factors influencing the risk of IFI



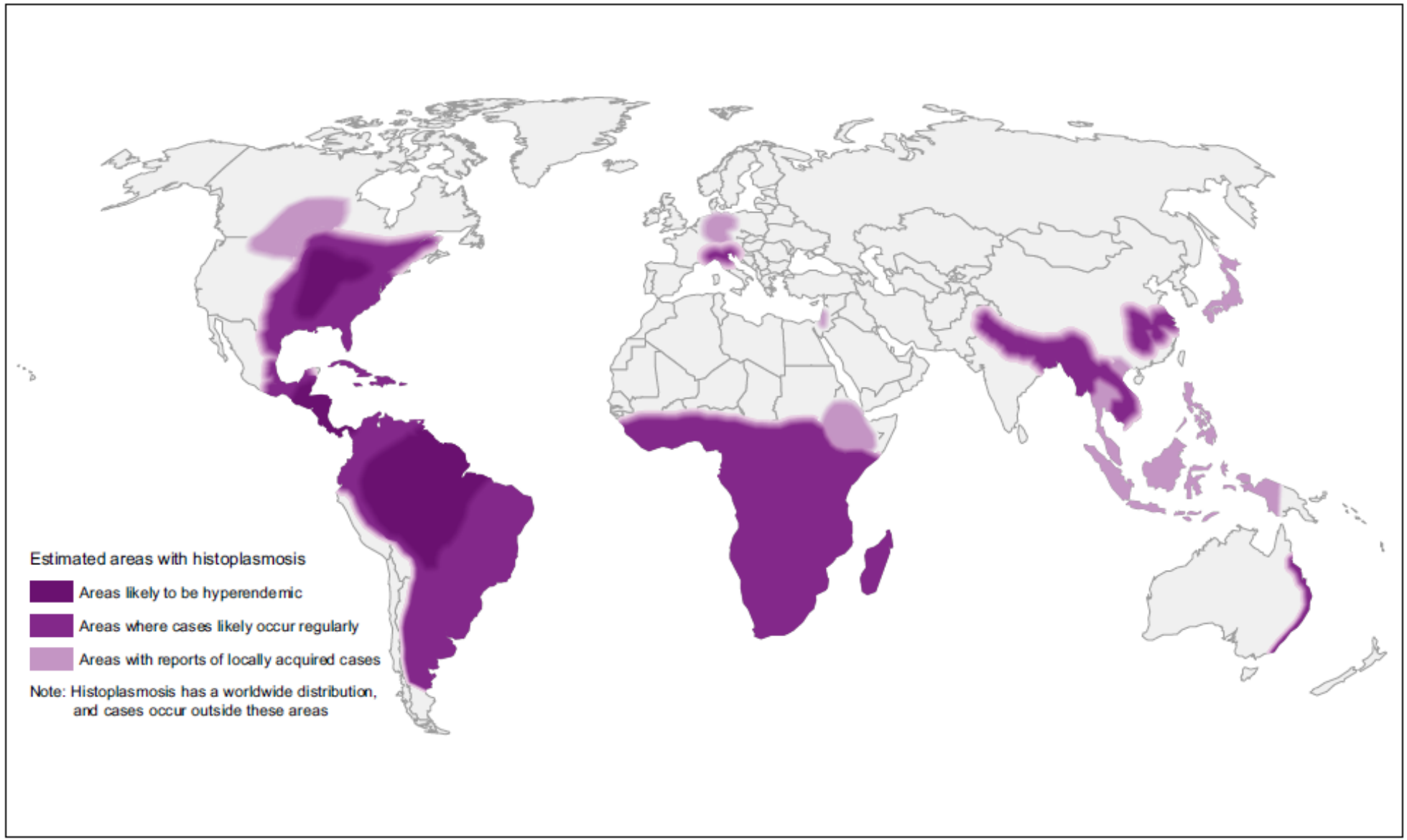
R.Herbrecht Ann N Y Acad Sci 1272 (2012;) 23-30

Re-drawing the Maps for Endemic Mycoses

- Endemic mycoses such as histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, and talaromycosis are well-known causes of focal and systemic disease within specific geographic areas of known endemicity.
- However, over the past few decades, there have been increasingly frequent reports of infections due to endemic fungi in areas previously thought to be ‘‘non-endemic.’’
- There are numerous potential reasons for this shift such as increased use of immune suppressive medications, improved diagnostic tests, increased disease recognition, and global factors such as migration, increased travel, and climate change.

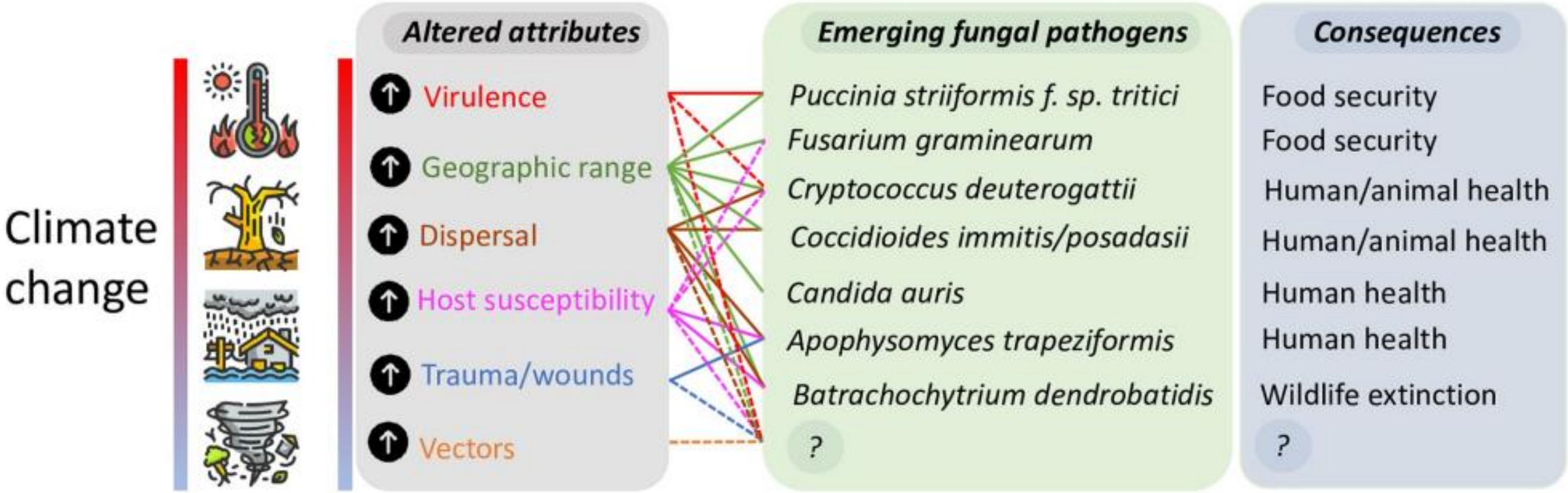
Ashraf N, et al. Mycopathologia. 2020 Oct;185(5):843-865.

World map estimating regions most likely to have histoplasmosis based on literature review



Ashraf N, et al. Mycopathologia. 2020 Oct;185(5):843-865.

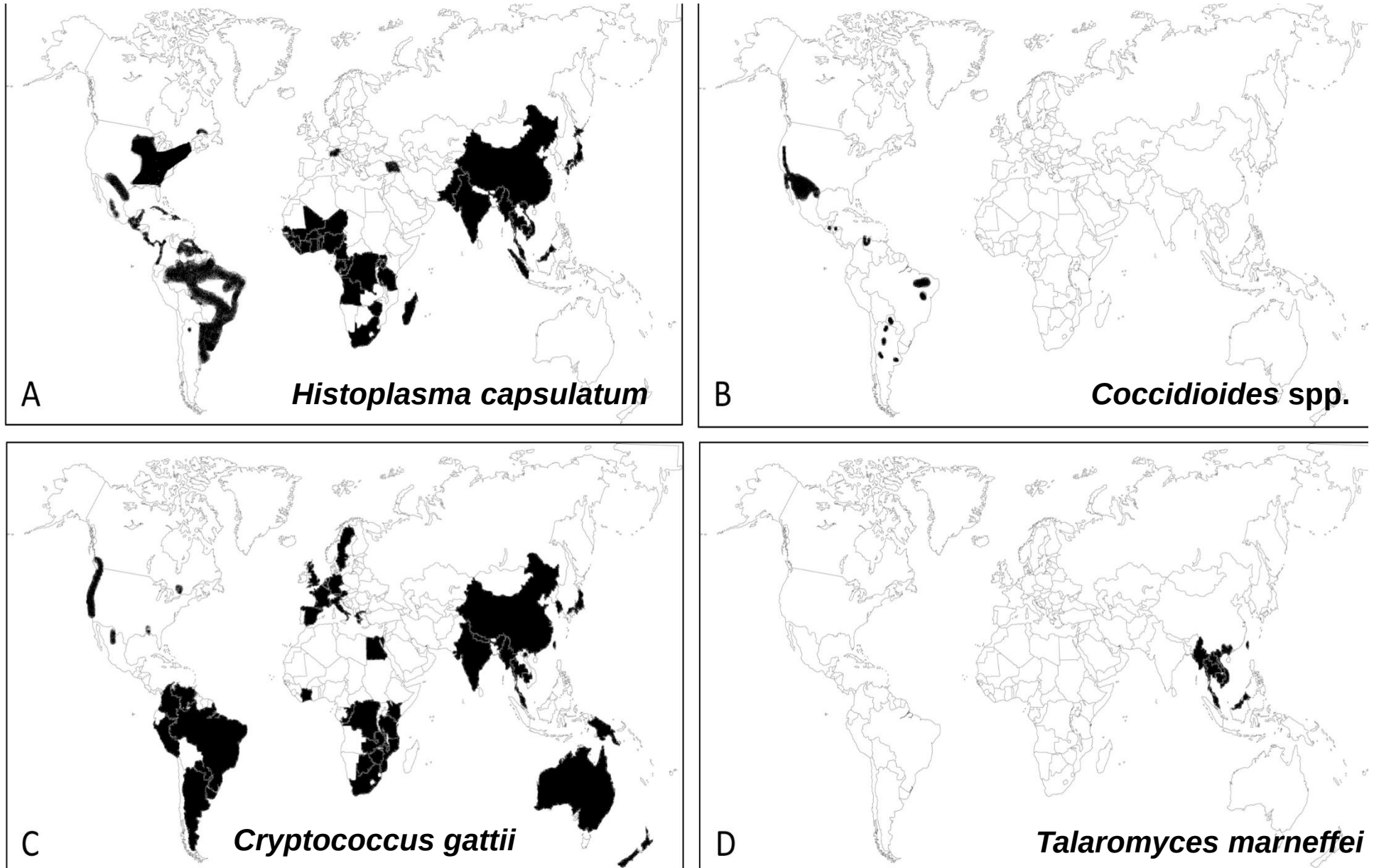
The effect of climate change on the emergence of fungal pathogens



Nnadi and Carter PLoS Pathogens., 2021

Immunocompromised SOT and worldwide fungal risk

Lortholary O *et al*. CID 2013



CASE REPORT

WILEY mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases

First-in-man observation of *Talaromyces marneffei*-transmission by organ transplantation

Frederik Hermans[1] | Sien Ombelet[2,3] | Karlien Degezelle[4] | Dries Testelmans[1] | Dirk E. Van Raemdonck[5,6] | Geert M. Verleden[1,7] | Eric K. Verbeken[8] | Pascal Van Bleyenbergh[1] | Katrien Lagrou[2,3] | Robin Vos[1,7]

***Mycoses* 2016; 1–5**

Candida auris

- *Candida auris*, an emerging fungus that can cause invasive infections, is associated with high mortality and is often resistant to multiple antifungal drugs.
- *C. auris* was first described in 2009 after being isolated from external ear canal discharge of a patient in Japan.
- Since then, reports of *C. auris* infections, including bloodstream infections, have been published from patients on 5 continents.

Candida auris

- The emergence of *C. auris* raises several serious concerns for public health.
- First, many isolates are multidrug-resistant, with some strains having elevated minimum inhibitory concentrations to drugs in all three major classes of antifungal medications, a feature not found in other clinically relevant Candida species.
- Second, *C. auris* is challenging to identify, requiring specialized methods such as matrix-assisted laser desorption/ionization time-of-flight or molecular identification based on sequencing the D1-D2 region of the 28s ribosomal DNA.
- When using common biochemical methods such as analytical profile index strips or the VITEK 2, *C. auris* is often misidentified as other yeasts (most commonly *Candida haemulonii*, but also *Candida famata*, *Saccharomyces cerevisiae*, and *Rhodotorula glutinis*)
- Finally, *C. auris* has caused outbreaks in health care settings.
- **Multidrug resistance and health care–associated transmission are often found with resistant bacteria, such as carbapenem-resistant Enterobacteriaceae, but have been uncommon among Candida spp.**

Scheme representing the hypothetical Candida auris evolutionary emergence, and the possible role of intermediate hosts in environmental dissemination and interspecies transmission

V. Garcia-Bustos et al. Clinical Microbiology and Infection 29 (2023) 858e862

Candida auris In Italy

- In 2019, the first case of invasive *C. auris* infection was identified, followed by an outbreak that affected the northern regions in the pandemic period 2020-2021.
- Since 2019, both imported and autochthonous cases have been described and/or notified for a total of about 300 cases in an epidemic outbreak that mainly involved Liguria and Emilia Romagna regions.
- The first case of *C. auris* in Liguria was reported in a hospital in July 2019, and cases continued to occur sporadically in the same hospital; in February 2020, *C. auris* was detected in an intensive care unit for the treatment of patients with severe COVID-19 in the same hospital, with a subsequent increase in the number of cases during 2020 and a decrease in the second half of 2021.

https://www.epicentro.iss.it/candida-auris/epidemiologia

WHO fungal priority pathogens list

Inspired by the bacterial priority pathogens list (WHO BPPL) developed in 2017, WHO has now developed the first fungal priority pathogens list (WHO FPPL).

The WHO FPPL is the first global effort to systematically prioritize fungal pathogens, considering their unmet R&D needs and perceived public health importance.

The WHO FPPL aims to focus and drive further research and policy interventions to strengthen the global response to fungal infections and antifungal resistance.

https://www.who.int/publications/i/item/9789240060241

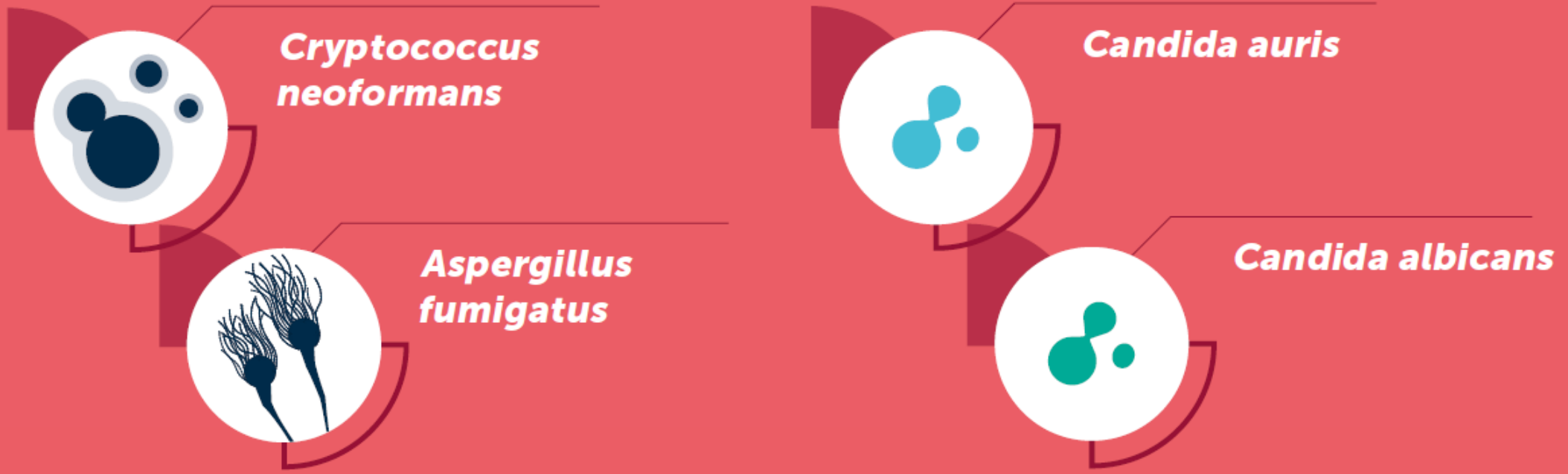
WHO fungal priority pathogens list

Critical group	High group	Medium group
Cryptococcus neoformans	*Nakaseomyces glabrata (Candida glabrata)*	*Scedosporium* spp.
Candida auris	*Histoplasma* spp.	*Lomentospora prolificans*
Aspergillus fumigatus	Eumycetoma causative agents	*Coccidioides* spp.
Candida albicans	Mucorales	*Pichia kudriavzeveii (Candida krusei)*
	Fusarium spp.	*Cryptococcus gattii*
	Candida tropicalis	*Talaromyces marneffei*
	Candida parapsilosis	*Pneumocystis jirovecii*
		Paracoccidioides spp.

https://www.who.int/publications/i/item/9789240060241

WHO fungal priority pathogens list

Critical Priority Group



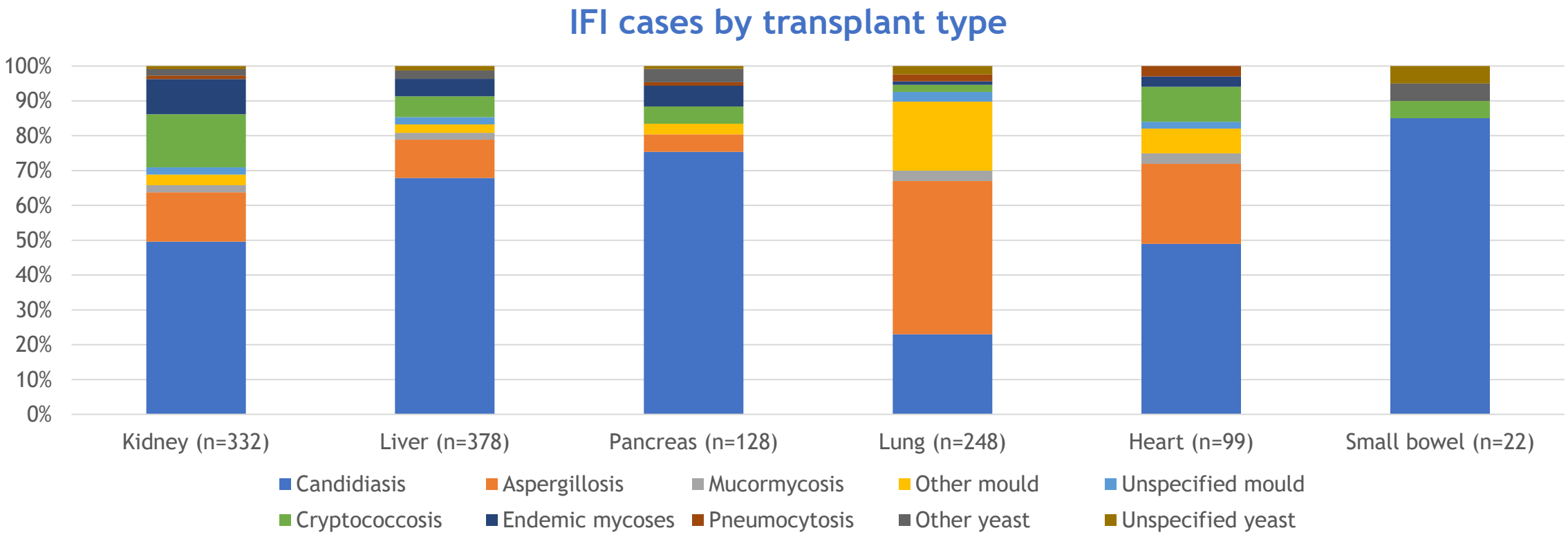
https://www.who.int/publications/i/item/9789240060241

Invasive fungal infections in transplant recipients TransNet Surveillance Program 2001-2006

Solid organ transplant [1] (1208 IFIs among 1063 organ transplant recipients)		HSCT [2] (983 IFIs among 875 HSCT recipients)	
Candidiasis	53%	Aspergillosis	43%
Aspergillosis	19%	Candidiasis	28%
Cryptococcosis	8%	Zygomycoses	8%
Other moulds	8%	Other moulds	7%
Endemics	5%	Fusariosis	3%
Zygomycoses	2%	Pneumocystis	2%

[1]Pappas P., et al. Clinical Infectious Diseases 2010;50:1101–1111
[2]Kontoyannis D., et al. Clinical Infectious Diseases 2010;50:1091–1100

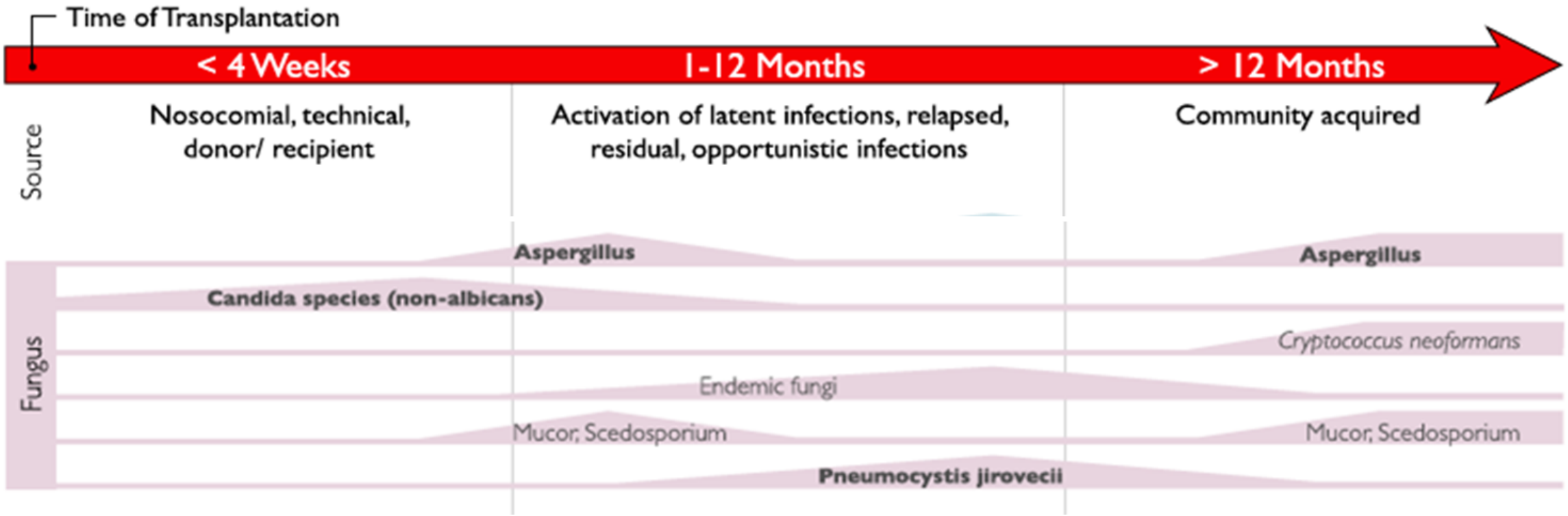
TRANSNET: IFIs among organ transplant recipients



- **Prevalence of IFIs varies depending on the type of organ transplant received**

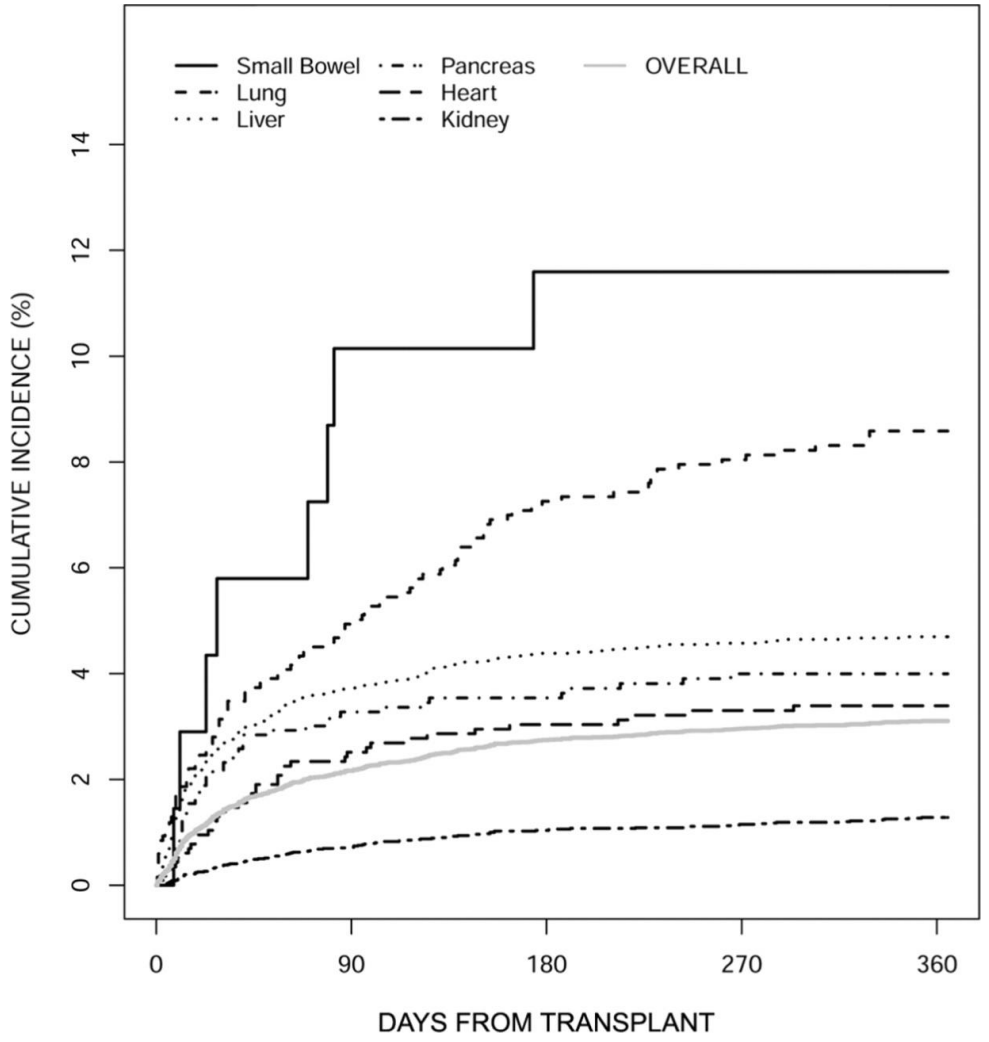
Pappas PG, et al. *Clin Infect Dis* 2010;50(8):1101–11.

When do infections occur after solid organ transplantation ?



Fishman J. AJT **2017**;17:856

Cumulative incidence curve of first invasive fungal infection (IFI) according to transplant type.



Pappas P G et al. Clin Infect Dis. 2010;50:1101-1111

Clinical Infectious Diseases

12 month survival after fungal infection in SOT TransNet Data

Invasive Aspergillosis	Non-Aspergillus molds	Invasive candidiasis	Cryptococcosis
59%	61%	66%	73%

Pappas P., et al. Clinical Infectious Diseases 2010;50:1101–1111

Unique Factors Contributing to the Risk of Infections in Lung Transplant Recipients

- Continuous contact with pathogens
- Higher state of immunosuppression
- Airways colonization
- Pulmonary stents
- The native lung
- Hypogammaglobulinemia
- CARV infections
- Denervation
- Impaired cough reflex
- Ischemic reperfusion injury
- Decreased mucociliary clearance

Husain S., et al. Clin Chest Med 2009; 30:307-13

Common Molds in lung transplantation and their usual clinical manifestations

Pathogen	Usual clinical manifestation
Aspergillus sp.	• Airway colonization • Tracheobronchitis • Pulmonary disease
Dematiaceous molds	• Skin and soft tissue infection • Brain abscess
Fusarium sp.	• Skin and soft tissue infection
Scedosporium sp. / Lomentospora prolificans	• Pulmonary disease • Disseminated disease
Zygomycete	• Pulmonary disease • Rhinocerebral infection • Disseminated disease

The clinical spectrum of pulmonary aspergillosis

- *Aspergillus fumigatus* is the most common species implicated in all pulmonary syndromes
- *Aspergillus flavus* is a more common cause of various forms of allergic rhinosinusitis, postoperative aspergillosis and fungal keratitis.
- *Aspergillus terreus* is a common cause of IA in some institutions and is amphotericin B resistant.
- *Aspergillus niger* is an occasional cause of IA or Aspergillus bronchitis, but is also a proportionately more common coloniser of the respiratory tract.

Frequency of isolation of filamentous fungi in 218 sputum specimens from 66 CF patients in Sydney

Organism	No. of specimens (%)
Aspergillus spp.	110/218 (50.5%)
A. fumigatus	99/218 (45.4%)
A. flavus	19/218 (8.7%)
Other *Aspergillus* spp.	9/218 (4.1%)
Scedosporium spp.	32/218 (14.7%)
S. aurantiacum	17/218 (7.8%)
S. prolificans	11/218 (5.0%)
S. apiospermum	4/218 (1.8%)
Penicillium spp.	18/218 (8.3%)
Paecilomyces spp.	7/218 (3.2%)
Other hyaline hyphomycetes	9/218 (4.1%)
Cladosporium spp.	4/218 (1.8%)
Curvularia spp.	3/218 (1.4%)
Alternaria spp.	3/218 (1.4%)
Other dematiaceous fungi	4/218 (1.8%)
Rhizopus spp.	2/218 (0.9%)
Other fungi	3/218 (1.4%)

Blyth CC, et al. J Clin Microbiol 2010; 48:314–316.

Perspectives on *Scedosporium* species and *Lomentospora prolificans* in lung transplantation: Results of an international practice survey from ESCMID fungal infection study group and study group for infections in compromised hosts, and European Confederation of Medical Mycology

Blandine Rammaert[1,2,3] | Mathieu Puyade[4] | Oliver A. Cornely[5] | Danila Seidel[5] | Paolo Grossi[6] | Shahid Husain[7] | Clément Picard[8] | Cornelia Lass-Flörl[9] | Oriol Manuel[10] | Jérôme Le Pavec[11,12,13] | Olivier Lortholary[14,15]the SCEDO-LUNG collaborative group

Transpl Infect Dis. 2019;21:e13141

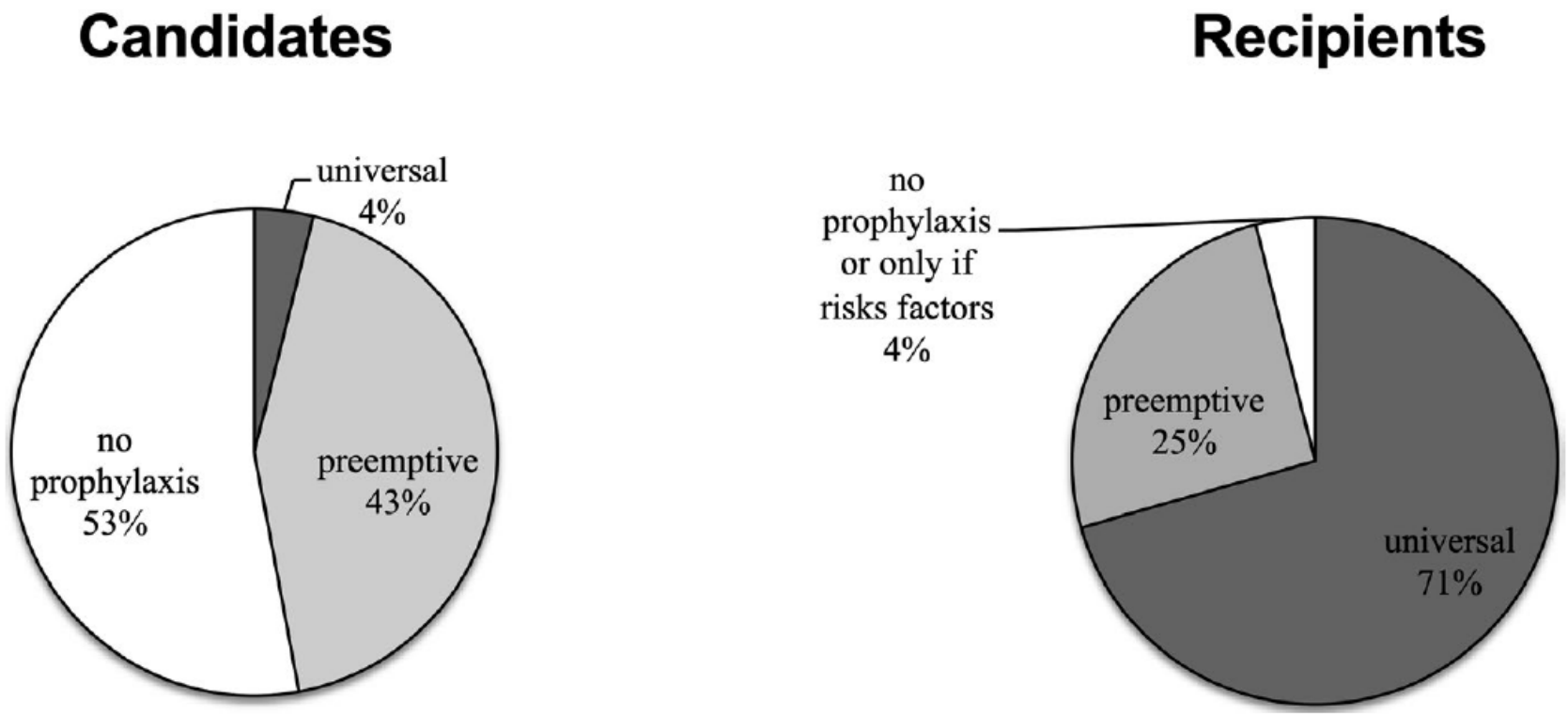


FIGURE 1 Preventive antifungal strategies against S/L for lung transplant candidates or recipients according to 51 respondents. Universal prophylaxis is given to every patient whatever the lower respiratory tract colonization. Preemptive strategy is administered only if the patient has lower respiratory tract fungal colonization

Rammaert B, et al. Transpl Infect Dis. 2019;21:e13141

Risk factors for Invasive Aspergillosis

Liver transplant recipients	
Early (0-3 mo)	• Re-transplantation • Renal failure, particularly requiring renal replacement therapy • Fulminant hepatic failure • MELD > 30 • Reoperation involving thoracic or intra-abdominal cavity
Late (>3 mo)	• Cytomegalovirus infection • Creatinine > 3.3 g/dL

Kidney transplant recipients
• Pre-transplant diagnosis of COPD • Acute rejection episode in last 3 mo • Graft failure • High and prolonged duration of corticosteroids

Husain S., Camargo J.F. *Clinical Transplantation.* 2019;33:e13544. https://doi.org/10.1111/ctr.13544

Risk factors for Invasive Aspergillosis

Lung transplant recipients

- Single-lung transplant
- Early airway ischemia
- Cytomegalovirus infection
- Rejection and augmented immunosuppression within last 3 mo, particularly in CF patients
- Pre-transplant *Aspergillus* colonization
- Post-transplant *Aspergillus* colonization within a year of transplant
- Positive intraoperative *Aspergillus* culture in CF patients
- Acquired hypogammaglobulinemia (IgG <400 mg/dL)

Heart transplant recipients

- *Aspergillus* colonization
- Airborne *Aspergillus* spores in ICU
- Reoperation (thoracic)
- CMV disease
- Post-transplant hemodialysis
- Existence of an episode of IA in the program 2 mo before or after heart transplant

Husain S., Camargo J.F. *Clinical Transplantation.* 2019;33:e13544. https://doi.org/10.1111/ctr.13544

Diagnosis of invasive fungal infections in the immunocompromised patient: what's new?

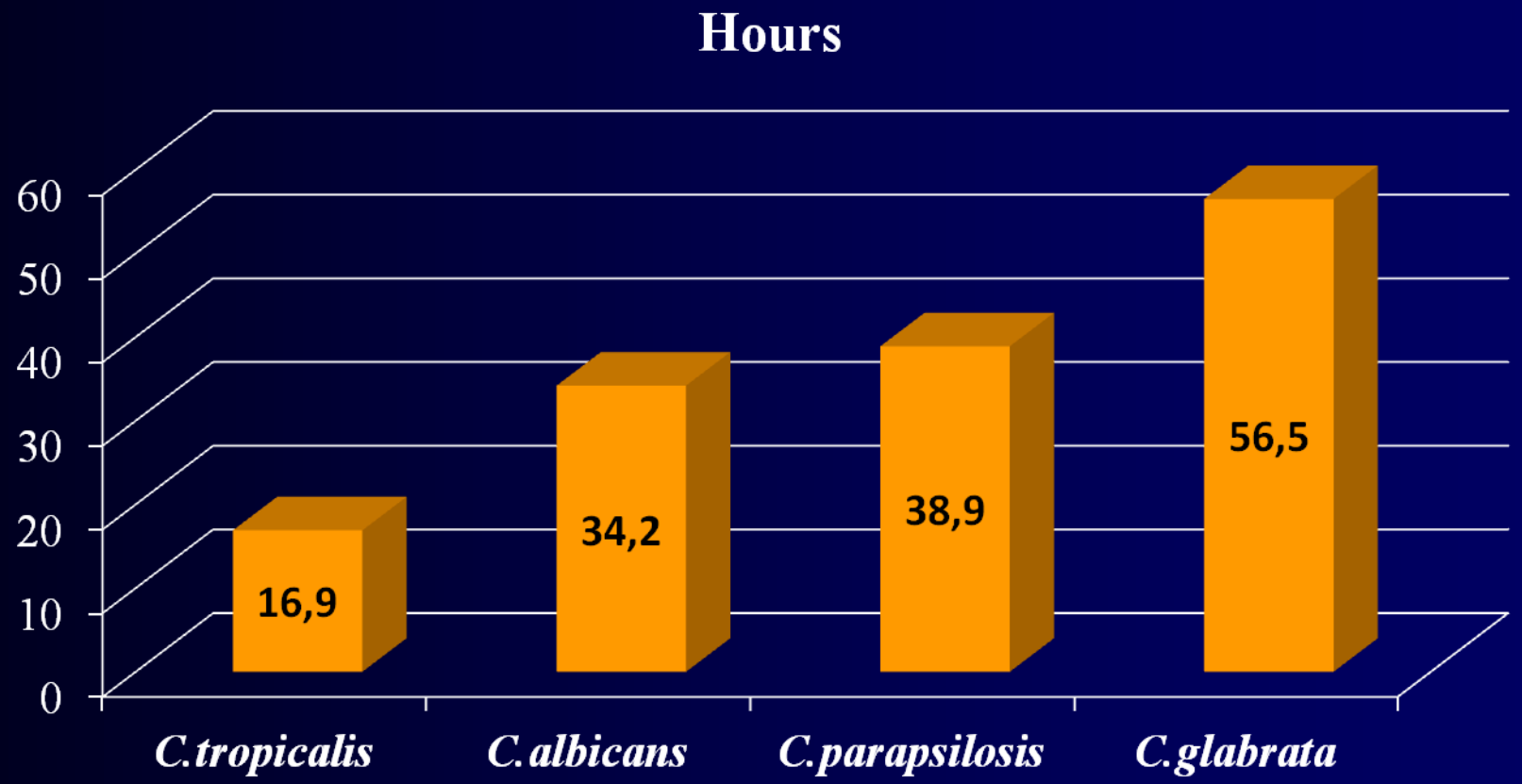
“Classical” cultures, still an important tool for fungal infections diagnosis

Culture approach for fungal infections diagnosis

- Important to use specific fungal media, bacteriological media are less efficient
- At least 3 sputum specimens should be submitted for fungal culture when fungal infections are suspected
- In Invasive Aspergillosis, BAL cultures are positive in ~30% of the samples
- Cultures take 1 to 10 days to grow, so please incubate accordingly in the Lab!
- Identification require time but the MALDI-TOF approach changed completely this scenario

From: Fraczek et al, Mycoses, 2014; Ullmann *et al.*, CMI, 2018

Time to positivity of blood cultures of different Candida species causing fungaemia



Lai CC, et al. J Med Microbiol. 2012;61:701-4

Commercially available culture-independent diagnostic modalities for detecting *Candida* sp.

Test Name	Example Commercial Products	Sample Source	TAT	Disadvantages	Sensitivity	Specificity	Notes	Citations
1,3-β-D-glucan (BDG)	Fungitell, Fungitell STAT (Associates of Cape Cod, Inc.) and Fungitec G-MK. (Seikagaku). Wako β-glucan (Fujifilm Wako Chemicals)	Serum	Fungitell STAT (qualitative)40–60 min Fungitell: 24–72 h 120 min	Not specific for Candida (e.g., can be + with invasive aspergillosis, fusariosis, *Pneumocystis jirovecii* infection) High false positives Often run in reference labs Lower sensitivity	IC: 75–80% IA/DS: 56–77%	IC: ~80% IA/DS: 57–83%	FDA approved in 2004, better performance with two consecutive results Available in Europe, does not require batch testing	[8,22,23]
Candida mannan	Pastorex Candida (Bio-Rad) Platelia Candida Ag Plus (Bio-Rad)	Serum or plasma	2 h	May form immune complexes and be rapidly cleared	IC: 58%	IC: 93%	Available in Europe	[8]
Combined mannan/antimannan	Platelia Candida Ag-Plus and Ab-Plus (Bio-Rad) Serion Mannan Kit (Serio GmbH)	Serum or plasma	2 $\frac{1}{2}$ h	Low sensitivity due to rapid clearance and complex formation with antibodies	IC: 83% IA/DS: 40%	IC: 86% IA/DS: 25%	Available in Europe	[8,24,25]
T2 Candida nanodiagnostic panel	T2 Candida (T2 Biosystems)	Whole blood	4.4 +/− 1 h	Identifies limited number of Candida species (only 5 most common) High cost. Needs further validation in IA/DS	IC: 91% IA/DS: 33%	IC: 94% IA/DS: 93%	FDA approved	[26,27]
C. albicans germ tube antibody assays (CAGTA)	CAGTA; Vircell Kit and VirClia IgG Monotest	Serum	~3 h	Lower sensitivity for *C. tropicalis*	IC: 42–96% IA/DS: 53–73%	IC: 54–100% IA/DS: 54–80%	Not FDA approved (used in Europe) Increased accuracy when combined with BDG	[28]
Candida PCR performed directly on clinical specimens	LightCycler. SeptiFast (Roche Diagnostics), SepsiTest (Molzym), Magicplex system (Seegene), or VYOO. (SIRS-Lab),	Whole blood, serum, plasma	Minutes to hours (real-time PCR). Multiplex PCR: 4–12 h	Not standardized or validated in multicenter trials. False negatives (low burden of fungal cells in blood, difficulties with sample preparation and DNA extraction) and false positives (similarities with human DNA, sample contamination)	IC: 73–95% IA/DS: 86–91%	IC: 92–95% IA/DS: 33–97%	None FDA approved Variety of DNA targets including Candida-specific genes or broad range pan-fungal genes	[24,29]

IC: invasive candidiasis. IA: intra-abdominal. DS: deep seated

From: Weiss *et al.*, J. Fungi, 2021

Journal of *Fungi*

MDPI

Brief Report

Sensitivity of Serum Beta-D-Glucan in Candidemia According to *Candida* Species Epidemiology in Critically Ill Patients Admitted to the Intensive Care Unit

Malgorzata Mikulska [1,2,†], Laura Magnasco [2,†], Alessio Signori [3], Chiara Sepulcri [1,2], Silvia Dettori [1,2], Stefania Tutino [1,2], Antonio Vena [1,2], Franca Miletich [1,2], Nadir Ullah [1], Paola Morici [4], Lorenzo Ball [5,6], Paolo Pelosi [5,6], Anna Marchese [4,5], Daniele Roberto Giacobbe [1,2,*] and Matteo Bassetti [1,2]

Table 1. Serum BDG values, overall sensitivity, and sensitivity stratified according to *Candida* species.

Candida Species (Total Number of Episodes = 146; Total Number of BDG Samples = 187) §	Median BDG Value (IQR), in pg/mL §§	Median Time from Candidemia Onset to First BDG Determination (IQR), in Days	Sensitivity (95% CI)
For all samples (n = 187) For all episodes (n = 146)	84 (21–314)	−0.06 (−1.28, 0.83)	51.3% (44.1–58.5%) 47.3% (39.0–55.0%)
For *C. albicans* (n = 40) samples For *C. albicans* (n = 29) episodes	182 (30.5–523)	0 (−1.16–0.78)	65.0% (48.7–78.4%) 62.1% (42.8–78.2%)
For *C. parapsilosis* (n = 105) samples For *C. parapsilosis* (n = 84) episodes	78 (19–290)	−0.08 (−1.29–1.00)	48.6% (39.1–58.2%) 44.0% (33.7–54.9%)
For *C. auris* (n = 26) samples For *C. auris* (n = 21) episodes	48 (15–159)	0 (−1.99–0.83)	42.3% (24.5–62.4%) 42.9% (23.0–65.3%)
For other species (n = 16) samples * For other species (n = 12) episodes **	81 (29–195)	−0.62 (−1.99–0.53)	50.0% (25.6–74.4%) 41.7% (16.4–72.2%)

§ Number of episodes refers to the number of candidemia episodes; §§ Referred to total number of BDG samples; * *C. glabrata* n = 11, *C. tropicalis* n = 4, *C. lusitaniae* n = 1; ** *C. glabrata* n = 7, *C. tropicalis* n = 4, *C. lusitaniae* n = 1; BDG: b-D-glucan, 95% CI: 95% confidence interval; IQR: interquartile range.

Recommendations for BDG testing for IFI diagnosis in hematologic cancer patients

Objective	Grading	Comment
To screen for IFI (serial monitoring, e.g. 2/week)	D II	Limited sensitivity [1] Concern for specificity (e.g. concomitant IVIG administration) [2, 3]
To diagnose IFI	C II	Lack of specificity of type of fungal species Limited sensitivity [1, 4] No plus values compared to galactomannan (IA) and culture (IC) No detection of mucormycosis

BDG testing for the detection of IFI (except for PcP) in hematologic cancer patients is marginally recommended (**CII**) because of its limited sensitivity and specificity, and limited added value compared to other fungal diagnostic tests (GM, qPCR).
According to the clinical context, local epidemiology and other mycological evidence, BDG testing might be useful to aid in the diagnosis of chronic disseminated candidiasis or non-Aspergillus non-Mucorales invasive mold infections (e.g., invasive fusariosis or scedosporiosis/lomentosporosis) (**BIII**).

IFI: invasive fungal infection, IVIG: intravenous immunoglobulins

1. Lamoth et al. Clin Infect Dis 2012; 54:633-43 2. Tschopp et al. Clin Infect Dis 2022 (in press) 3. Bougnoux et al. Clin Microbiol Infect 2020; 26:1101-2 4. Angebault et al. Open Forum Infect Dis 2016; 3:ofw128

ECIL-9: Serum beta-D-glucan in HIV-negative patients

- We recommend the use of b-D-glucan in serum as a contributively laboratory diagnostic tool for the diagnosis of PCP, but confirmation should be performed with another test (BAL or non-invasive respiratory sample qPCR) when serum BDG is positive (specificity 83% - false positive results): **AII**
- Consider a significant rate of false positivity with low correlation between BDG titre and qPCR loads (good correlation in HIV patients)
- Despite the high negative predictive value, a negative serum BDG does not exclude PCP in at risk non-HIV patients with unexplained or refractory radiological findings compatible with pulmonary infection: **B-II**

Commercially available non-culture-based testing for Aspergillosis and *Mucorales*

Test Name	Example Commercial Product	Sample Source	TAT	Disadvantages	Sensitivity	Specificity	Notes	Citations
1,3-β-D-glucan (BDG)	Fungitell (Associates of Cape Cod, Inc.) and Fungitec G-MK. (Seikagaku).	Serum	Fungitell STAT (qualitative): 40–60 min Regular Fungitell: 24–72 h (d)	Cross-reactive with other fungi, False positives frequent. Often run in reference labs.	Fungitell: 33–100% Fungitec: 67–88%	Fungitell: 36–94% Fungitec: 84–85%	FDA approved.	[116]
Galactomannan	Platelia *Aspergillus* EIA/Ag (Bio-Rad)	Serum, BAL (also CSF, pleural fluid)	1–7 days	Cross-reactive with other fungi. False positives frequent.	**Neutropenic/heme malignancy** Serum: 61–79% BALF: 58–90% **Non-neutropenic:** Serum: 38–41% BALF: 65–76%	**Neutropenic/heme malignancy** Serum: 81–95% BALF: 84–96% **Non-neutropenic:** Serum: 87–89% BALF: 81–90%	FDA approved. Serially monitoring can assess treatment response.	[117–121]
Lateral flow devices	AspLFD (OLM Diagnostics) and the Aspergillus galactomannan LFA (IMMY)	Serum, BAL, urine	15–30 min	Serum LFD requires additional preparation steps/pre-treatment. Sensitivity decreased with antifungals.	**AspLFD: Neutropenic/heme malignancy:** Serum: 56–68% BAL: 71–89% **Non-neutropenic:** BAL: 46–69% **LFA: Neutropenic/heme malignancy:** 89–97% **Non-neutropenic:** BALF: 65–69%	**AspLFD: Neutropenic/heme malignancy:** Serum: 87–90% BAL: 88–100% **Non-neutropenic:** BAL: 46–58% **LFA: Neutropenic/heme malignancy:** 88–98% **Non-neutropenic:** BALF: 62–68%	Available in Europe. Urinary GM-like antigen-based test also exists but needs further validation.	[103–107,109]
Aspergillus PCR	MycAssay Aspergillus (real-time PCR) AsperGenius assay (multiplex real-time PCR)	Serum, BAL	12–24 h	Sensitivity decreased by antifungal treatment. Many commercially available assays. Standardization efforts ongoing. Small clinical studies.	**Serum:** 60–79% **BALF:** 77%	**Serum:** 80–95% **BALF:** 94%	Some detect azole-resistant mutations. Independent validation still needed for most.	[90,110–112]
Mucorales PCR	MucorGenius (Pathonostics)	BAL, biopsy fluid	3 h		90–100%	90–99%		[122,123]

IC: invasive candidiasis. IA: intra-abdominal. DS: deep seated

From: Weiss *et al.*, J. Fungi, 2021

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journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

Galactomannan testing in blood samples

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Patients with prolonged neutropenia or allogeneic stem cell transplantation recipients **not on mould-active prophylaxis**	Prospective screening for IA	GM in blood[a] Draw samples every 3–4 days	A C	I III	Highest test accuracy requiring two consecutive samples with an ODI ≥0.5 or retesting the same sample Prospective monitoring should be combined with HRCT and clinical evaluation	[82,94,390–394]
Patients with prolonged neutropenic or allogeneic stem cell transplantation recipients **on mould active prophylaxis**	Prospective screening for IA	GM in blood[a]	D	II	Low prevalence of IA in this setting with consequently low PPV of blood GM test Prophylaxis may have a negative impact on sensitivity of the test or the low yield may be due to decreased incidence of IA	[395,396]
Patients with a haematological malignancy	To diagnose IA	GM in blood[a]			Significantly lower sensitivity in non-neutropenic patients	[319,391,397,398]
• Neutropenic patients			A	II		
• Non-neutropenic patients			B	II		
ICU patients	To diagnose IA	GM in blood[a]	C	II	Better performance in neutropenic than in non-neutropenic patients	[89,399]
Solid organ recipients	To diagnose IA	GM in blood[a]	C	II	Low sensitivity, good specificity Most data for lung SOT	[319,400,401]
Any other patient	To diagnose IA	GM in blood[a]	C	II	Piperacillin/tazobactam may no longer be responsible for false-positive results according to recent studies Cross-reactivity in case of histoplasmosis, fusariosis, talaromycosis (formerly: penicilliosis) False-positive results reported due to ingestion of ice-pops, transfusions, antibiotics, Plasmalyt® infusion	[398,402–409]
Cancer patients	To monitor treatment	GM in blood[a]	A	II		[85,353,410]

Abbreviations: GM, galactomannan; IA, invasive aspergillosis; ICU, intensive care unit; ODI, optical density index; PPV, positive predictive value; QoE, Quality of evidence; SoR, Strength of recommendation; SOT, solid organ transplantation.

[a] Serum or plasma.

IDSA Guidelines for the diagnosis and management of aspergillosis

- **If PCR assays are used, results should be considered with other diagnostic tests and the clinical context** **(strong recommendation; moderate-quality evidence)**
- **Serum and BAL galactomannan (GM) is recommended as an accurate marker for the diagnosis of IA in adult and paediatric patients** when used in certain patient subpopulations (haematologic malignancy, HSCT) **(strong recommendation; high-quality evidence)**
- **GM is not recommended for routine blood screening in patients receiving mould-active antifungal therapy or prophylaxis**, but can be applied to bronchoscopy specimens from those patients **(strong recommendation; high-quality evidence)**
- Serum assays for **(1->3)-β-D-glucan** are recommended for diagnosing IA in high-risk patients (haematologic malignancy, allogeneic HSCT), but are not specific for *Aspergillus* **(strong recommendation; moderate-quality evidence)**
- **We recommend performing BAL** in patients with a suspicion of IPA **(strong recommendation; moderate quality evidence)**

BAL: bronchoalveolar lavage; HSCT: haematopoietic stem cell transplant; IA: invasive aspergillosis; IPA: invasive pulmonary aspergillosis; PCR: polymerase chain reaction;
Slide courtesy of A. Busca; Patterson TF, et al. *CID* 2016;63:433-42.

ECIL-9: suggested changes for GM

- There is good evidence to support the use of serum/plasma* or BAL GM (Platelia assay) for the diagnosis of IA in high-risk hemato-oncological patients
  - AII for BAL in all patients (neutropenic and non-neutropenic)
  - AII for serum/plasma in (prolonged = more than 7 days) neutropenic (less than 500 neutrophils/microliter) patients; BII for non-neutropenic patients
  - Confirmed positivity in blood (≥ 2 ODI above 0.5) and use of a higher threshold (≥ 1.0) in BAL improves specificity with an acceptable loss in sensitivity (AII)
  - * Plasma has not been validated by the manufacturer
- A diagnosis-driven strategy that incorporates serum GM monitoring (combined with appropriate clinical and microbiological evaluation, including other biomarkers as appropriate, and high-resolution CT imaging) every 3-4 days (twice weekly) is proposed in prolonged neutropenic patients not receiving mold-active prophylaxis (AI; kids AII_t)
- Prospective monitoring of serum GM in the presence of mold-active prophylaxis: DII.
  - However, a positive sample may still be diagnostic for a breakthrough Aspergillus infection (AII).
- The course of the serum GM index during antifungal therapy is predictive of outcome (AII)
  - ≥2 serum galactomannan measurements elevated compared with baseline after 2 weeks of therapy or rising GM antigenemia after 7 days of therapy is a poor prognostic sign and should prompt clinical reassessment: AII
- GM in CSF* with an ODI > 0.5 is an adjunctive method for the diagnosis of central nervous system aspergillosis (AII)
  - * CSF has not been validated by the manufacturer
- The combined use of blood GM and PCR for screening is highly recommended: AI
- Recommendations for pediatric use have been proposed in ECIL-8 (Groll et al. Lancet Oncol 2016); the performance appears to be similar in children and adults

ECIL-9 recommendations

- *Aspergillus*-specific lateral flow assays (IMMY and OLM), used as an alternative to GM to diagnose IA on serum samples or BAL fluid are useful (BII)

Aspergillus PCR Recommendations

- Aspergillus PCR alone (screening and diagnosis): **AII**
- Combined Aspergillus PCR and GM
  - Screening of blood (**AI**) – Multiple RCT including PCR
  - Diagnostic confirmation (**AII**): needs to be supported by additional evidence (clinical and/or imaging)
  - Prognostic marker (no grade)
    - Limited data, Strong positive = poor prognosis, persistent PCR positivity despite antifungal therapy = poor sign)
- High-risk hosts – AML, allogeneic SCT
- Genetic Markers of resistance – (no grade - further evaluation required – comment on Dutch/Belgian study demonstrating link with resistance/mortality Chong et al JAC 2016) vary
- CT values vary between centres and assays

Important Definitions - ISHLT 2015

Colonization

- Presence of fungus in the respiratory secretions (sputum or BAL) detected by the culture, PCR or biomarker (GM/cryptococcal antigen) in the absence of symptoms, radiologic, and endobronchial changes.

Invasive fungal disease (IFD)

- Presence of fungus in the respiratory secretions (sputum or BAL) detected by the culture, PCR, or biomarker (GM/cryptococcal antigen) in the presence of symptoms, radiologic, and endobronchial changes, or presence of histologic changes consistent with fungal invasion of the tissue

Husain S, et al. JHLT 2016;35:261-282

Important Definitions Used in the ISHLT 2015 Document

Universal anti-fungal prophylaxis

- Refers to an anti-fungal medication started in the post-operative period in all patients,before any post-transplant isolation of a fungal pathogen.

Preemptive anti-fungal therapy

- Refers to an anti-fungal medication started after post-transplant isolation of a fungal pathogen or serologic marker of fungus in the absence of any evidence for IFD

Targeted anti-fungal prophylaxis

- Refers to an anti-fungal medication started in the post-operative period, before any post-transplant isolation of a fungal pathogen or serologic marker of fungus, which is prescribed only to patients deemed at higher risk for IFD (e.g., cystic fibrosis patients and those with pre-transplant fungal colonization/infection or on augmented immunosuppression)

Husain S, et al. JHLT 2016;35:261-282

Universal Prophylaxis

- At present, universal prophylaxis against IA is not routinely recommended in kidney, liver and heart transplant recipients.
- Like it is the case for other organs, the optimal *Aspergillus* prevention strategy in lung transplant recipients remains to be defined.
- Current practices of antifungal prophylaxis in lung transplant recipients are derived from non-randomized clinical trials of small sample size, single-center non-comparative case series, or case-control studies

AST recommendations for Prevention of IA Liver Transplantation

- Targeted prophylaxis in patients with any of the following high-risk factors is recommended (*Strong; moderate)*.
  - Re-transplantation (second or third liver transplant).
  - Renal replacement therapy (hemodialysis or continuous venovenous dialysis) at the time of or within 7 days of transplantation.
  - Reoperation involving thoracic or intra-abdominal cavity, for example, exploratory laparotomy or any intrathoracic surgery.
  - Anidulafungin, micafungin or caspofungin in standard dose, or voriconazole is recommended for the use of targeted prophylaxis against IA in liver transplant recipients (*Strong; high)*
  - Targeted prophylaxis with a lipid formulation of amphotericin B in dosages ranging 3-5 mg/kg may be considered (*Weak; moderate)*
  - Targeted prophylaxis should be continued for 14-21 days (*Strong; high)*
  - Screening with serum GM and β-D-Glucan is not recommended for preemptive therapy (*Weak; low*)

Husain S., Camargo J.F. *Clinical Transplantation.* 2019;33:e13544. https://doi.org/10.1111/ctr.13544

AST recommendations for Prevention of IA Lung Transplantation

- Either universal prophylaxis or preemptive therapy can be employed as a strategy to prevent IA in lung transplant recipients, depending on the availability of the diagnostic tests (*Strong; moderate*).
- No randomized trials comparing the two strategies have been performed to date.
- In cases where a preemptive therapy strategy is employed, both BAL culture and BAL GM should be incorporated into the protocol (Strong; low).
- A BAL GM index value of 1.0 is preferred as a threshold for the initiation of preemptive therapy (Strong; low).

Husain S., Camargo J.F. *Clinical Transplantation.* 2019;33:e13544. https://doi.org/10.1111/ctr.13544

Invasive Aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

It is recommended to initiate targeted antifungal prophylaxis if any one of the following risk factors is present in lung transplant recipients (*Strong; moderate)*	**Targeted antifungal prophylaxis against IA may be considered if more than one of these risk factors are present in lung transplant recipients (*Weak; low*)**
Pre-transplant Aspergillus colonization	Early airway ischemia
Post-transplant *Aspergillus* colonization within a year of transplant	Induction with alemtuzumab or anti-thymocyte globulin
Single-lung transplant	Cytomegalovirus infection
Positive intraoperative Aspergillus culture in CF patient	Rejection and augmented immunosuppression (particularly the use of T cell-depleting monoclonal antibodies post-transplant)
	Acquired hypogammaglobulinemia (IgG level <400 mg/dL)
The use of **serum** GM for the screening of IA **is not recommended** in lung transplant recipients (*Strong; moderate*).	
In cases of universal and targeted antifungal prophylaxis, the recommended duration is **4-6 months**. However, when using a preemptive strategy, the duration of antifungal therapy should be **3-4 months** (*Strong; moderate*).	

***Husain S, et al. Clinical Transplantation.* 2019;33:e13544.**

Antifungal agents for invasive mycoses

- **Amphotericin B**
  - **Lipid associated polyenes**
  - Ambisome, ABLC, ABCD
- **Echinocandins**
  - Caspofungin
  - Micafungin
  - Anidulafungin
  - *Rezafungin (Phase 3 trial)*

- **Azoles**
  - Fluconazole (oral and i.v.)
  - Itraconazole (oral and i.v.)
  - Voriconazole (oral and i.v.)
  - Posaconazole (oral – new tablet formulation)
  - Isavuconazole (oral and i.v.)

Use of antifungal drugs

Limited evidence of optimal strategies for utilizing the available antifungal armamentarium

Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

Population	Intention	Intervention	SoR	QoE	Comment
HIV	To treat IA	Voriconazole	A	III	Consider drug–drug interactions with antiretroviral drugs.
SOT Heart	To treat IA	Itraconazole	C	III	6 patients cured with itraconazole 200–400 mg/day Erratic absorption and interaction with calcineurin inhibitors and other agents
SOT, any	To treat IA	Voriconazole	A	III	e.g. Herbrecht study 11 SOT; voriconazole increases the levels of anti-calcineurin immunesuppressors, TDM; monitor liver function tests especially in liver transplant recipients.
OT, any	To treat IA	L-AmB	A	II	
SOT, any	To treat IA	Voriconazole & caspofungin	B	II	40 SOT voriconazole & caspofungin ($n = 40$) vs amphotericin B ($n = 47$). Survival benefit in patients with *A. fumigatus* or renal insufficiency
SOT, if voriconazole contraindicated	To treat IA	Caspofungin	B	III	Complete response 83%; response 7/9 monotherapy and 7/10 combination

Ullmann AJ, et al. Clin Microbiol Infect. 2018 May;24 Suppl 1:e1-e38.

Azole Antifungal Drugs and Potential for Drug Interactions

Drug	CYP3A4		CYP2C8/9		CYP2C19		P-glycoprotein	
	Inhibitor	substrate	Inhibitor	substrate	Inhibitor	substrate	Inhibitor	substrate
Fluconazole	++		++		+		No	Yes
Itraconazole	+++	+++	+				Yes	Yes
Voriconazole	+	+	++	+	++	+++	No	No
Posaconazole	++						Yes	Yes

Dodds-Ashley E. Pharmacotherapy 2010;30:842-854

Recommendations for Percent Dose Reduction of Immunosuppressants During Concomitant Administration of Azole Antifungal Agents

Azole	Cyclosporine Dose	Tacrolimus Dose	Sirolimus Dose
Fluconazole ≥ 200 mg/day	↓ 21-50%	↓ 40%	↓ 50-70%
Itraconazole	↓ 50-60%	↓ 50-60%	No data
Voriconazole	↓ 50% ↓ dose to one half at start of voriconazole	↓ 66% ↓ dose to one third at start of voriconazole	↓ 90% Coadministration contraindicated
Posaconazole	↓ 0-30% ↓ dose to three fourths at start of posaconazole	↓ 75-80% ↓ dose to one third at start of posaconazole	Substantial dose reduction required Coadministration contraindicated

Dodds-Ashley E. Pharmacotherapy 2010;30:842-854

Journal of
Clinical Pharmacy and Therapeutics

Journal of Clinical Pharmacy and Therapeutics, 2015, **40**, 609–611 doi: 10.1111/jcpt.12308

Case Report

Drug–drug interaction between isavuconazole and tacrolimus: a case report indicating the need for tacrolimus drug-level monitoring

T. Kim* PharmD, BCPS, T. Jancel† PharmD, BCPS, P. Kumar* PharmD and A. F. Freeman‡ MD

**Pharmacy Department, National Institutes of Health Clinical Center, Bethesda, †Office of Safety and Epidemiology, US Food and Drug Administration, Silver Spring, and ‡Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA*

- Based on our experience of this case and the increased tacrolimus exposure seen in one reported drug–drug interaction study, we would suggest **an initial 50% reduction in dose of tacrolimus** and recommend close weekly monitoring of tacrolimus concentration.
- Further dose decreases of 25–50% may be required over an 8-week period.

Isavuconazole prophylaxis among solid organ transplant recipients: effectiveness and drug interaction with tacrolimus

- 187 patients were enrolled: 60 lung, 51 kidney, 53 liver, 16 heart, 4 small bowel and 3 pancreas.
- ISA was prematurely stopped due to side effects in 5%; in all except one instance, premature discontinuation occurred in lung transplant recpients. GI intolerance predominated.
- 3% developed breakthrough infections: 3 due to Candida (1 candidemia; 2 intra-abdominal infections), and 2 due to Aspergillus fumigatus (1 was colonized before transplant; 1 with unsuspected pulmonary aspergillus found in the explanted lungs).
- For TAC interaction with ISA, we focused on 59 patients who had TAC levels performed while on (total levels n=641) and off (n=459) ISA prophylaxis, respectively.
- **TAC concentration/dose (C/D) were highest on day 4**, then decreased and stabilized day 8, reflecting the effect of **ISA loading doses**. While on ISA, TAC C/D was higher among liver recipients (median, 192) than kidney (124), lung (106) and heart (105, p=0.002). **There was considerable inter-patient variability** of TAC C/D.
- ISA exerts significant drug interaction with TAC in SOT recipients, resulting in decreased TAC concentration after ISA is discontinued.
- Given considerable inter-patient variability in the magnitude of drug interaction, **TAC dose reductions should be individualized.**
- ISA exerts interaction on TAC for a **median of 4 weeks**. reflecting its long half-life and large volume of distribution.

Ryan Rivosecchi, et al. Antimicrob Agents Chemother. 2017 Aug 24;61(9)

Clinical Practice Guidelines for the Management of Candidiasis: 2016 Update by the IDSA - Candidemia in Nonneutropenic Patients

Primary	Alternative	Comments
An **echinocandin** (caspofungin: loading dose of 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose of 200 mg, then 100 mg daily) (**strong recommendation; high-quality evidence**).	**Fluconazole, intravenous or oral, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily** is an acceptable alternative to an echinocandin as initial therapy in selected patients, including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant Candida species **(strong recommendation; high-quality evidence)**. **LFAmB** (3–5 mg/kg daily or **AmB-d** 0.5-1.0 mg/kg/daily or **voriconazole** 400 mg (6 mg/kg) bid for 2 doses then 200 mg (3 mg/kg) bid (A-I)	**Choose an echinocandin for moderately severe to severe illness and for patients with recent azole exposure.** Transition to fluconazole after initial echinocandin is appropriate in many cases. **Remove all intravascular catheters, if possible.** Treat 14 days after first negative blood culture result and resolution of signs and symptoms associated with candidemia. Ophthalmological examination recommended for all patients.

Pappas PG, et al. Clin Infect Dis. 2016;62:e1-e50.

General susceptibility patterns of *Candida* species

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole	5FC	AmB	Echinocandins
Candida albicans	S	S	S	S	S	S	S	S
Candida tropicalis	S	S	S	S	S	S	S	S
Candida parapsilosis	S	S	S	S	S	S	S	S to R[a]
Candida glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I	S to R
Candida krusei	R	S-DD to R	S	S	S	I to R	S to I	S
Candida lusitaniae	S	S	S	S	S	S	S to R	S
Candida auris	R	R	R	R	-	S	S to R	S to R
						Aren't most *C auris*		
						resistant to AmB		

Aslam S, Rotstein C. Clinical Transplantation. 2019;00:e13623.

Treatment of *Candida auris*

- Regarding antifungal therapy, there are no Clinical and Laboratory Standards Institute (CLSI) or European Committee for Antimicrobial Susceptibility Testing (EUCAST) defined breakpoints for *C. auris* susceptibility.
- CDC recommends that all *C. auris* isolates undergo susceptibility testing and provides guidance for MIC breakpoints based on related Candida species and expert opinion.

Infection Prevention and Control for Candida auris | Candida auris | Fungal Diseases | CDC

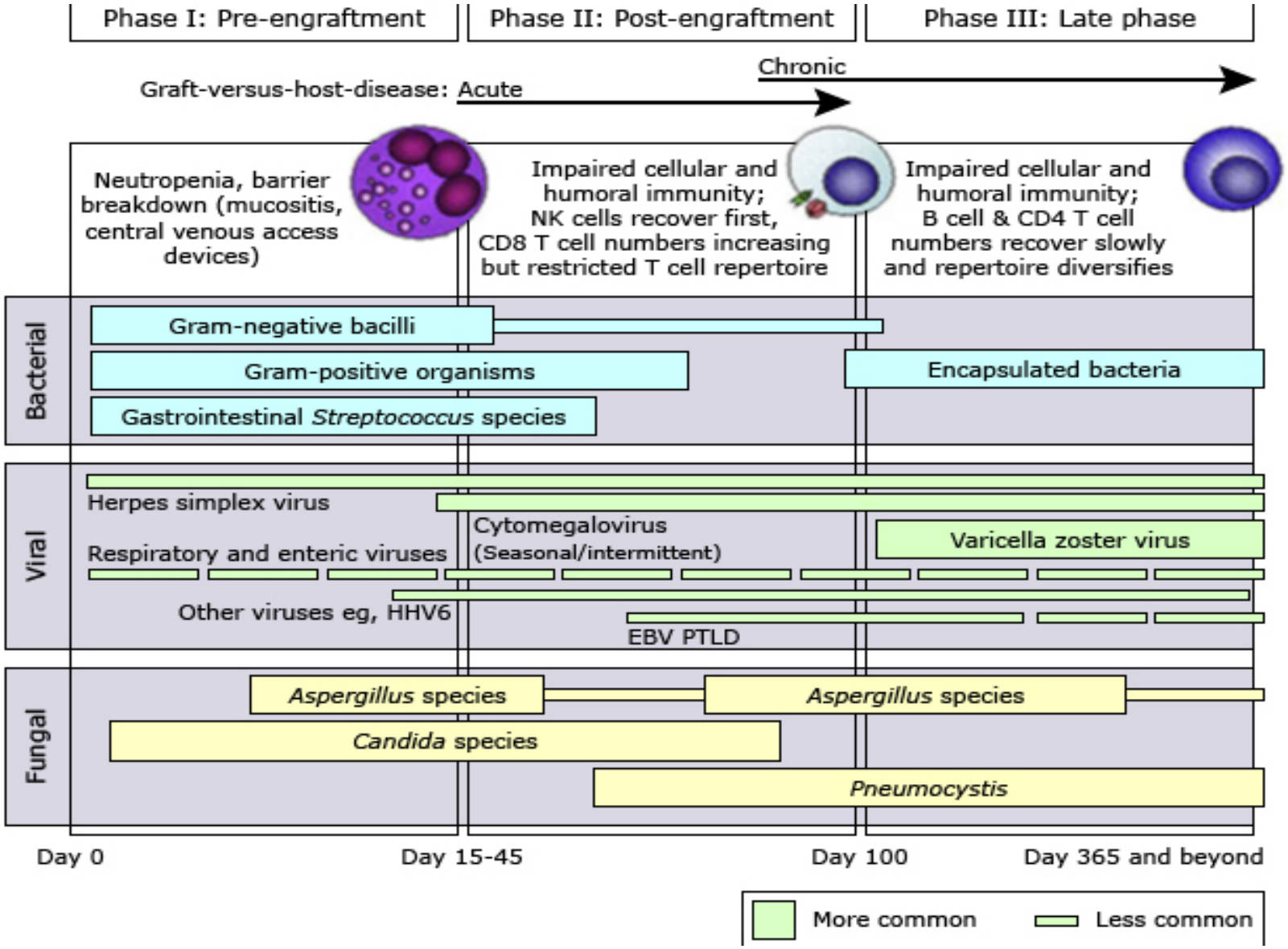
In vivo evolution to echinocandin resistance and increasing clonal heterogeneity in *Candida auris* during a difficult-to-control hospital outbreak, Italy, 2019 to 2022

Giulia Codda[1], Edward Willison[2], Laura Magnasco[3], Paola Morici[2], Daniele Roberto Giacobbe[3,4], Antonella Mencacci[5,6], Daniele Marini[5,6], Malgorzata Mikulska[3,4], Matteo Bassetti[3,4], Anna Marchese[1,2], Vincenzo Di Pilato[1]

- The evolution towards PDR phenotypes calls for close monitoring of antifungal resistance in patients with prolonged exposure to echinocandins.
- Prompt implementation of genomic surveillance and antifungal stewardship programmes is critical to contain the selection and spread of PDR *C. auris*.

Codda G, et al. Euro Surveill. 2023 Apr;28(14):2300161.

Phases of opportunistic infections among allogeneic hematopoietic cell transplant recipients

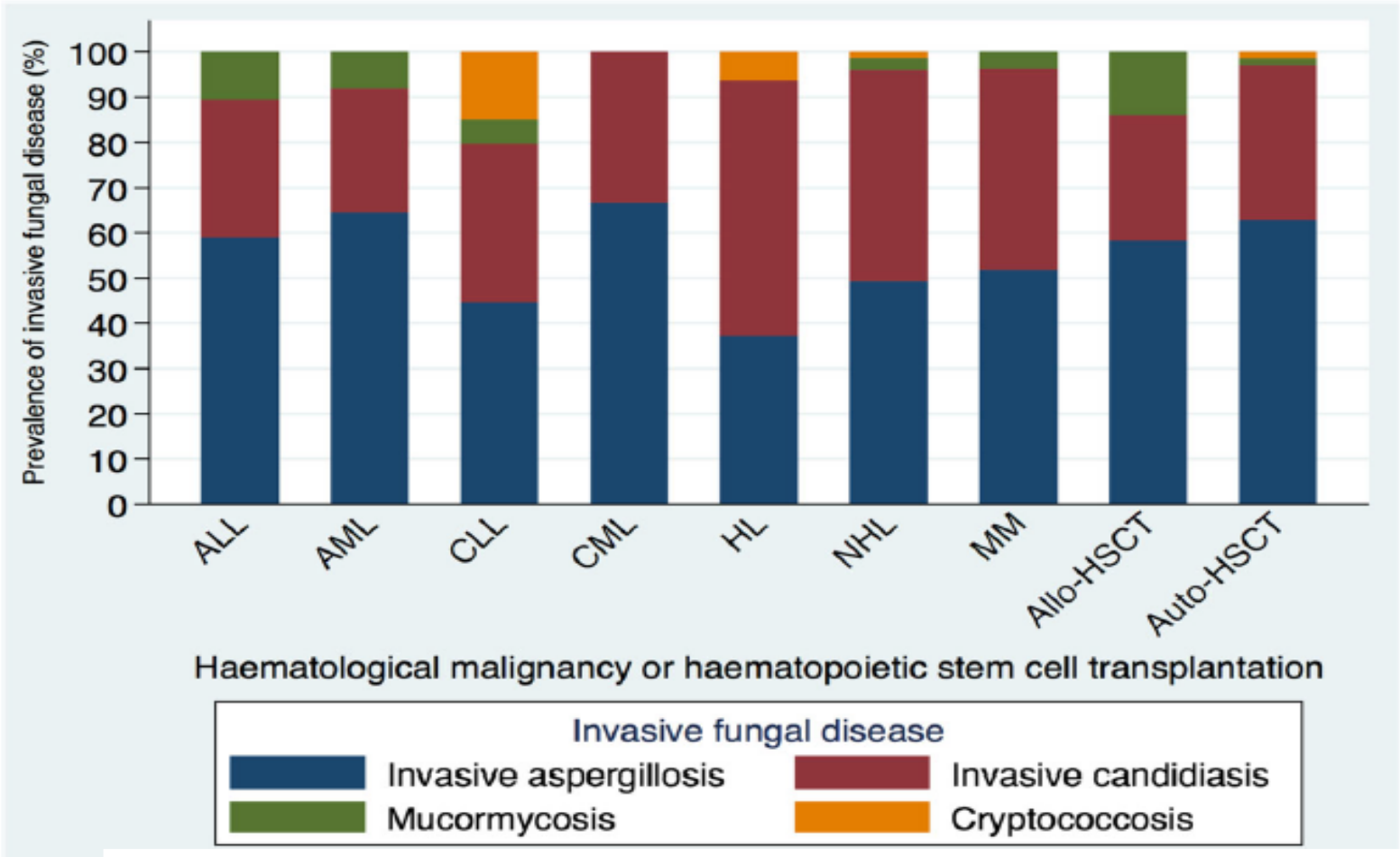


MacKall C *et al. Bone Marrow Transplant* 2009;44:457–462

A population-based analysis of IFI in haematology-oncology patients using data linkage of state-wide registries and administrative databases: 2005 -2016

- **Population-based** analysis including
  - 32,815 hematological-malignancies
  - 1,765 HSCT.

- **Incidence IFI:**
  - 669 **(2.04%)** hematological malignancies
  - 111 **(6.29%)** HSCT-recipients



Valentine et al. BMC Infectious Diseases (2019) 19:274

- **Infections and ibrutinib**

Clinical Infectious Diseases

VIEWPOINTS

Call for Action: Invasive Fungal Infections Associated With Ibrutinib and Other Small Molecule Kinase Inhibitors Targeting Immune Signaling Pathways

Chamilos G et al. Clin Infect Dis. 2018 Jan 6;66(1):140-148

Frequency of Reported IFIs in Clinical Studies of Ibrutinib Treatment for Hematological Cancer

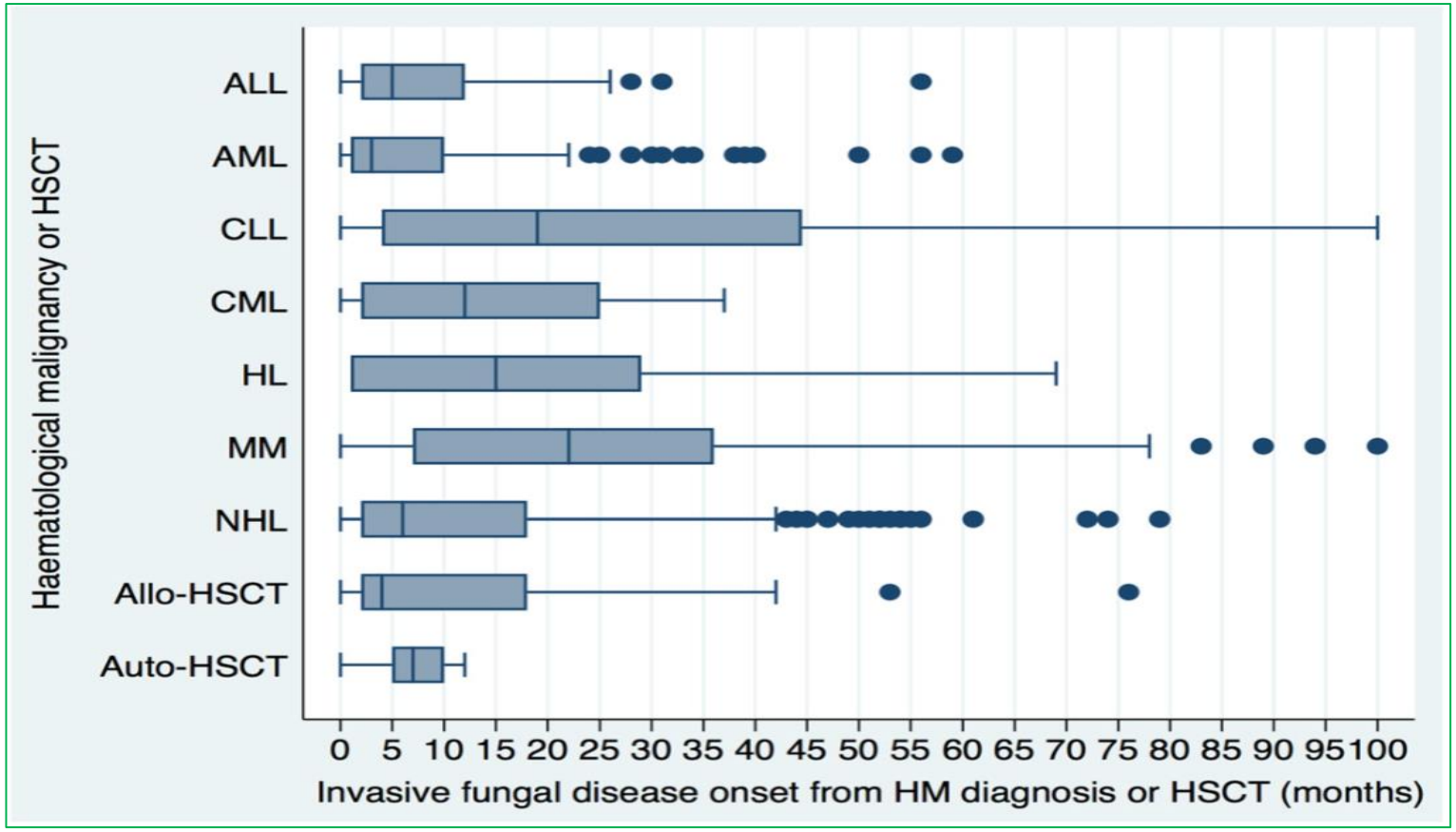
Type and Status of Cancer	Type of IFI (No. of Cases)	Frequency of IFI, %	Patients, No.	Median Follow-up, mo	Study Timing, Month/ Year	Reference
Relapsed CLL	Cryptococcosis (1)	1.2	85	20.9	5/2010–2/2013	Byrd et al [11]
Relapsed CLL/SLL	IA (2)	0.5	391	9.4	6/2012–11/2013	Byrd et al [10]
Relapsed WM	IA (1)	3.2	31	18.1	8/2014–2/2015	Dimopoulos et al [9]
Relapsed MCL	Cryptococcosis (1), PJP (1), histoplasmosis (1)	2.7	111	26.7	2/2011–1/2014	Wang et al [7]
CLL	1 multifocal IA, 1 fungal pneumonia	1.6	127	13	7/2010–5/2014	Jain et al [6]
Relapsed/refractory DLBCL	None	0	80	11.5	5/2012–5/2013	Wilson et al [8]
Refractory CLL/SLL	PJP (1)	0.7	145	27.6	1/2013–6/2013	O'Brien et al [21]
Refractory PCNSL[a]	IA (7), PJP (1)	44	18	15.5	8/2014–3/2016	Lionakis et al 12]
Refractory PCNSL	IA (2)	11	18	NA	9/2015–8/2016	Choquet et al [24]
Refractory PCNSL	IA (1)	5	20	NA	NA	Grommes et al [25]

Abbreviations: CLL, chronic lymphocytic leukemia; CNS, central nervous system; DLBCL, diffuse large B cell lymphoma; IA, invasive aspergillosis; IFI, invasive fungal infection; MCL, mantle cell lymphoma; NA, not available; PCNSL, primary central nervous system lymphoma; PJP, *Pneumocystis jirovecii* pneumonia; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

[a]Of enrolled patients, 28% were previously untreated.

Chamilos G et al. Clin Infect Dis. 2018 Jan 6;66(1):140-148

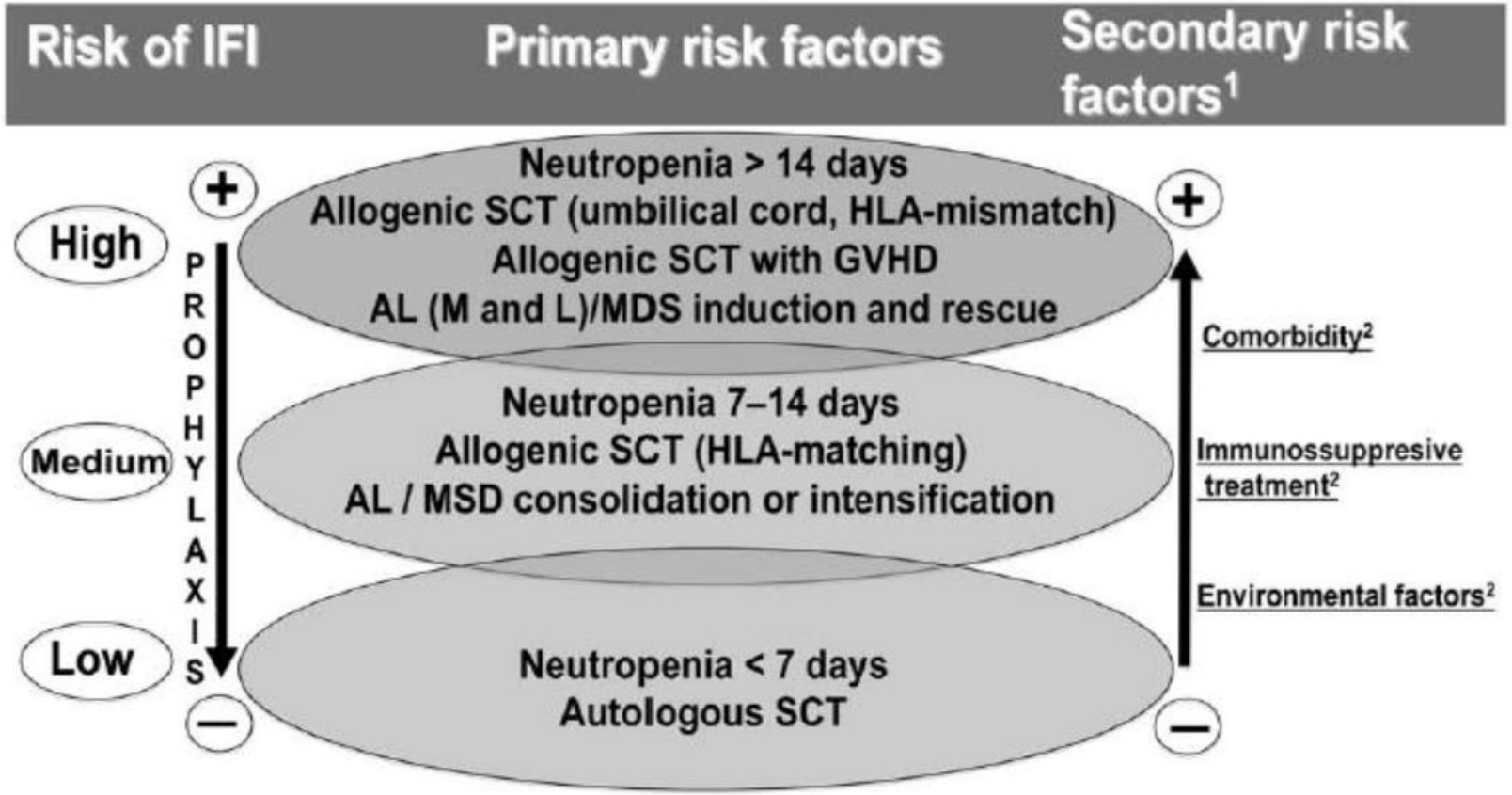
Time at risk after HM diagnosis
Australian cohort 2005-2016



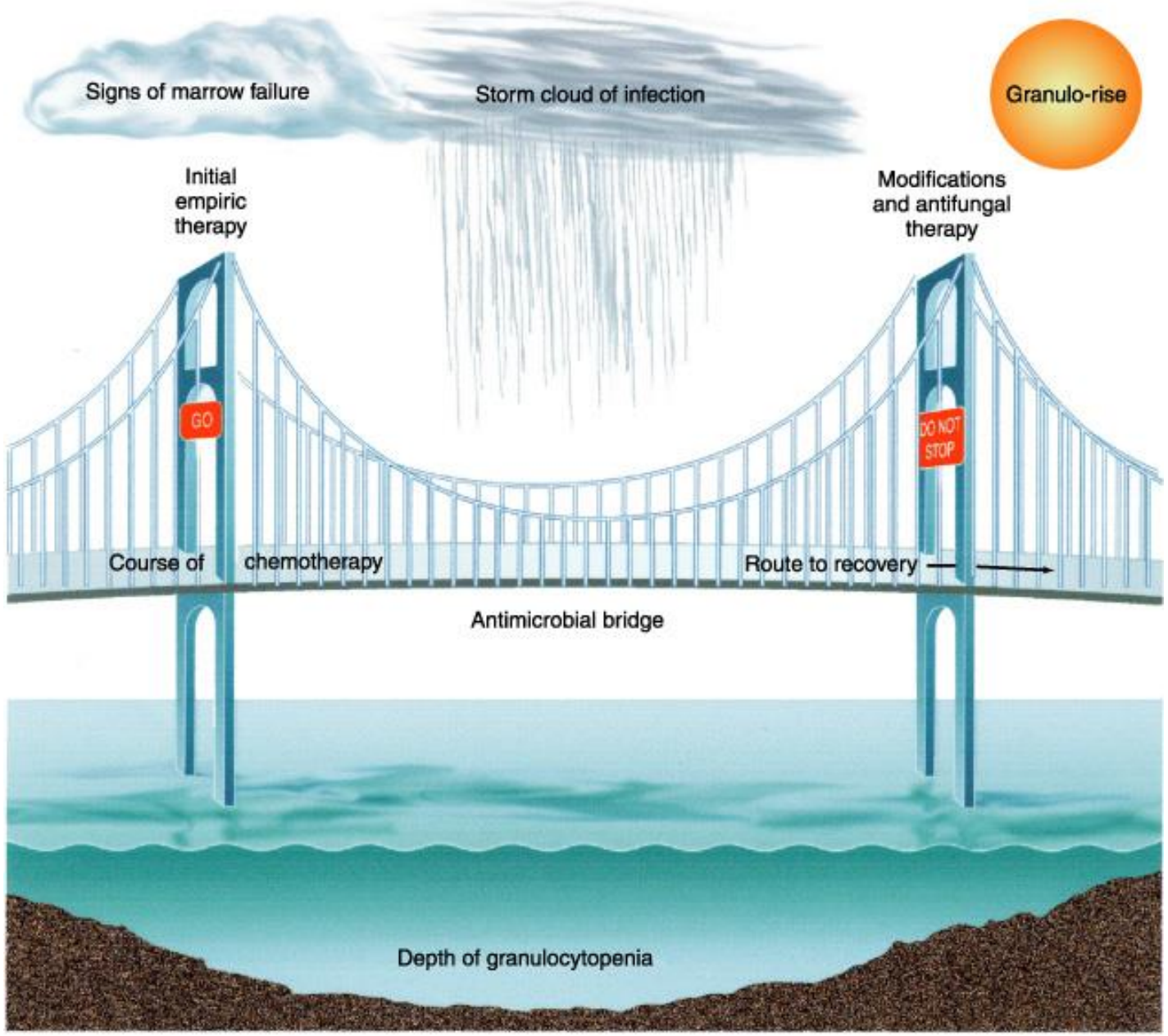
Total number of episodes of IFI
331 in high risk vs 392 in intermediate/low risk!!!

Valentine et al. BMC Infectious Diseases (2019) 19:274

Patient at risk for IA-hematological patients

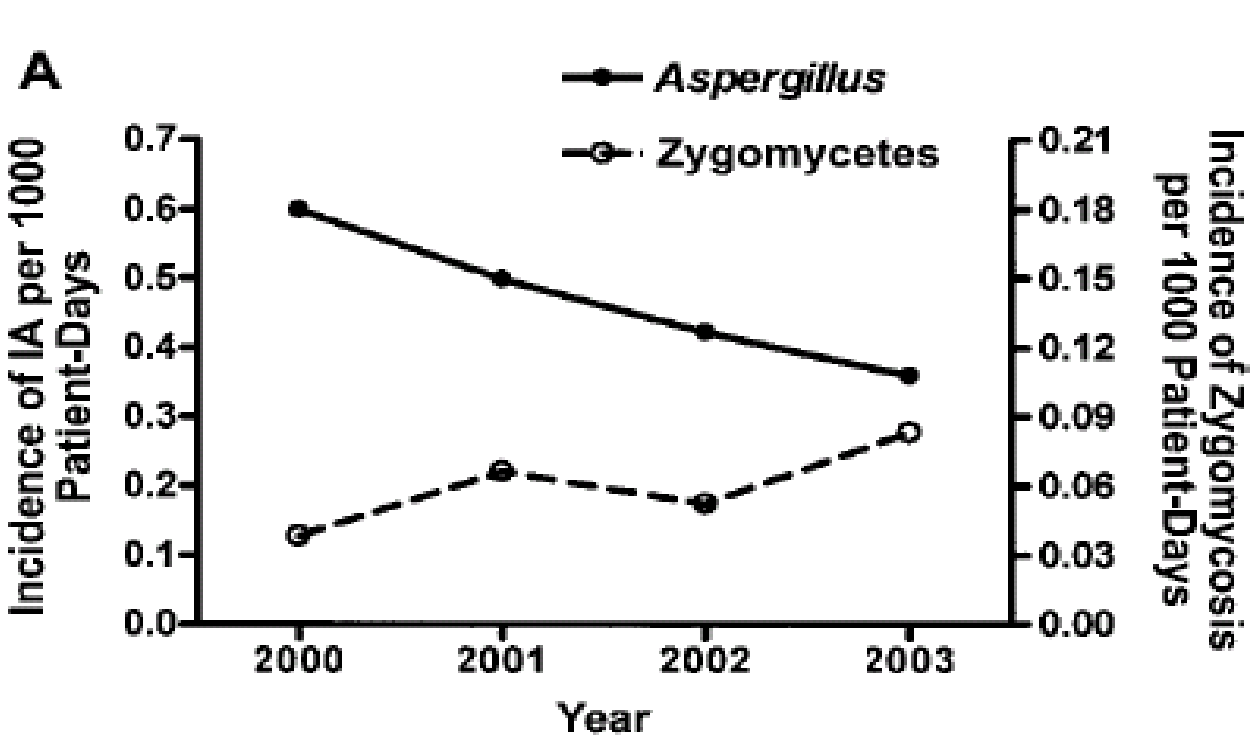


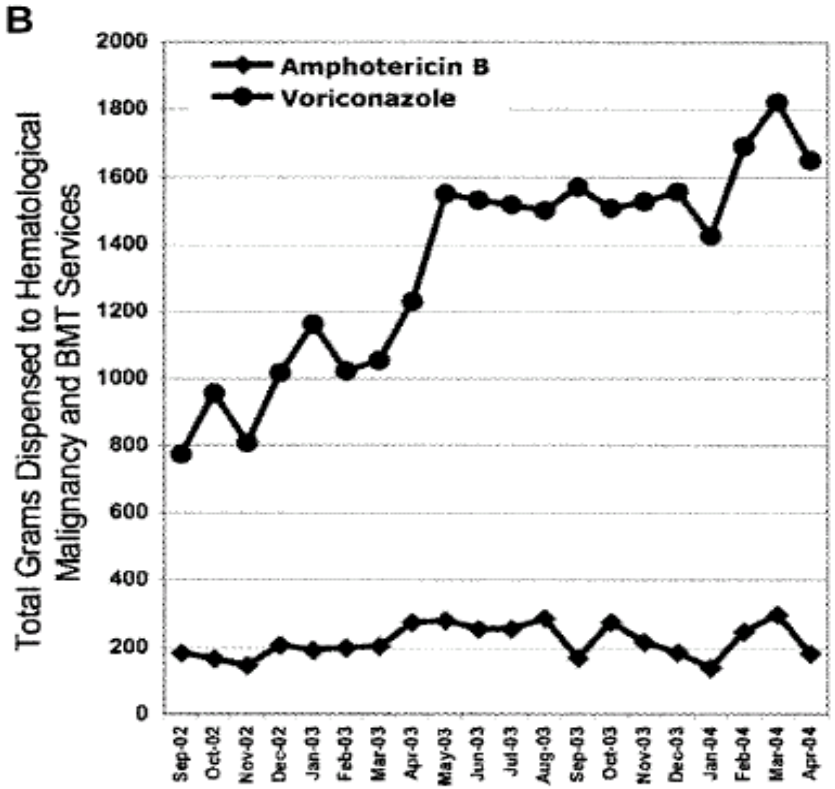
Fleming S, Intern Med J. 2014;44:1283-97.



Pizzo PA. J Pediatr. 1981;98:513-523

Incidence of invasive aspergillosis and zygomycosis at the M.D. Anderson Cancer Center in Houston, TX, 2000–2003.



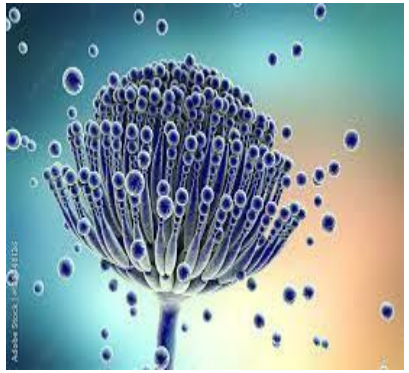


Conclusions. Zygomycosis should be considered in immunosuppressed patients who develop sinusitis while receiving VRC prophylaxis, especially those with diabetes and malnutrition.

Kontoyiannis DP, et al. JID 2005; 191:1350–60

Aspergillus-GVHD

- *Aspergillus* is the most common mold pathogen and the second most common fungal pathogen in HCT recipients, occurring most commonly during the postengraftment period in patients with severe graft-versus-host disease (GVHD).



Wingard JR, Hsu J, Hiemenz JW. Hematol Oncol Clin North Am. 2011 Feb;25(1):101-16.

Update: ECIL 5, 2013

Recommendations for allogeneic HSCT recipients (2013)

Antifungal prophylaxis*	Pre-engraftment Low risk for moulds	Pre-engraftment High risk for moulds	GvHD
Fluconazole	A-I	A-III - against	A-III against
Itraconazole	B-I	B-I	B-I
Voriconazole	B-I	B-I	B-I
Posaconazole OS/Tablet	B-II	B-II	A-I
Micafungin	B-I	C-I	C-II
Caspofungin /anidulafungin	No data	No data	No data
Liposomal Amphotericin B	C-II	C-II	C-II
Aerosolized amphotericin B plus fluconazole	C-III	B-II	No data

*For doses & need for Therapeutic Drug Monitoring: please refer to slides 21 and 22

Serious drug interactions and prophylaxis

- Administration of extended-spectrum triazole-based (posaconazole, voriconazole, itraconazole) prophylaxis should be delayed until after completion of the transplant conditioning regimen. An echinocandin can be given safely during the conditioning regimen if a gap in antifungal coverage is unadvisable, such as in a patient with prior aspergillosis.
- Caution is advised for concomitant use of the extended-spectrum triazoles with chemotherapy drugs metabolized by the liver, especially those metabolized by cytochrome **P450 isoenzymes.**
- Interactions between the anti-mold azoles and immunosuppressive drugs are substantial; reductions of cyclosporine and tacrolimus doses by 50 percent are important, and monitoring of levels of these drugs is necessary to avoid toxicity. Coadministration with sirolimus should be avoided due to extreme potentiation of sirolimus levels

Gubbins PO, Heldenbrand S. Mycoses. 2010;53(2):95.

The duration of antifungal prophylaxis

- The duration of antifungal prophylaxis should be individualized based on the patient's clinical status and history of prior fungal infections.

Tomblyn M, et al. Biol Blood Marrow Transplant. 2009;15(10):1143.

Allogeneic HCT recipients who do not have GVHD

- Prophylaxis against *Candida* spp is continued either until engraftment or for up to 75 days following transplantation, which in one trial was associated with continued benefit after engraftment

Marr et al Blood. 2000;96(6):2055.

Allogeneic HCT recipients with GVHD

- The optimal duration of antifungal prophylaxis in allogeneic HCT recipients with GVHD has not been defined
- In general, prophylaxis should be continued during the period of peak immunosuppression (eg, glucocorticoid equivalent of ≥1 mg/kg per day of prednisone for more than two weeks or addition of other anti-GVHD therapies for refractory GVHD)
- Continue anti-mold prophylaxis until substantial doses of immunosuppressants (especially glucocorticoids) are no longer required.

John R Wingard, MD https://www.uptodate.com/contents/prophylaxis-of-invasive-fungal-infections-in-adult-hematopoietic-cell-transplant-recipients?csi=019b57a7-bf0e-44f7-94ca-822cc0930da0&source=contentShare

Patients who have a history of a prior invasive fungal infection who are receiving secondary prophylaxis following HCT

- Prophylaxis is usually continued until discontinuation of immunosuppressive therapy
- Follow-up imaging (CT scan of the organ involved in prior infection) and fungal markers (eg, *Aspergillus* galactomannan antigen, beta-D-glucan) are often obtained two to four weeks after antifungal prophylaxis has been discontinued to ensure that reactivation has not occurred.

Patterson et al Clin Infect Dis. 2016;63(4):e1. Epub 2016 Jun 29

Targeted therapy Invasive Candidiasis

Table 4. ECIL-6 recommendations for initial first-line treatment of candidemia.

	Overall population	Hematologic patients
Antifungal therapy		
Micafungin[a]	A I	A II
Anidulafungin	A I	A II[b]
Caspofungin	A I	A II
Liposomal amphotericin B	A I	A II
Amphotericin B lipid complex	B II	B II
Amphotericin B colloidal dispersion	B II	B II
Amphotericin B deoxycholate[c]	C I	C II
Fluconazole[d,e]	A I	C III
Voriconazole[d]	A I	B II

Tissot F. Heaematologica 2017; 102 (3)

Targeted therapy- Invasive aspergillosis

Table 7. ECIL-6 recommendations for first-line treatment of invasive aspergillosis.

	Grade	Comments
Voriconazole[a]	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole[a] + anidulafungin	C I	
Other combinations	C III	
Recommendation against use Amphotericin B deoxycholate	A I	Less effective and more toxic

[a]Monitoring of serum levels is indicated. In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have not been graded.

Tissot F. Heaematologica 2017; 102 (3)

Cryptococcosis: Treatment recommendations – AST Guidelines 2019

Induction	Duration
CNS disease, disseminated disease, or moderate-to-severe pulmonary disease	
Preferred therapy	
Liposomal amphotericin B 3-4 mg/kg/d or amphotericin B lipid complex 5 mg/kg/d plus 5-flucytosine 100 mg/kg/d[a]	Minimum of 2 wk
Alternative therapy	
Liposomal amphotericin B 3-4 mg/kg/d or amphotericin B lipid complex 5 mg/kg/d	Minimum of 4-6 wk
Consolidation	
Fluconazole 400-800 mg/d	8 wk
Maintenance	
Fluconazole 200-400 mg/d	Minimum of 6-12 mo
Pulmonary disease	
Asymptomatic or mild-to-moderate disease[b]	
Fluconazole 400 mg/d	6-12 mo
Severe pulmonary disease, or azole use not an option	
Same as for CNS disease	

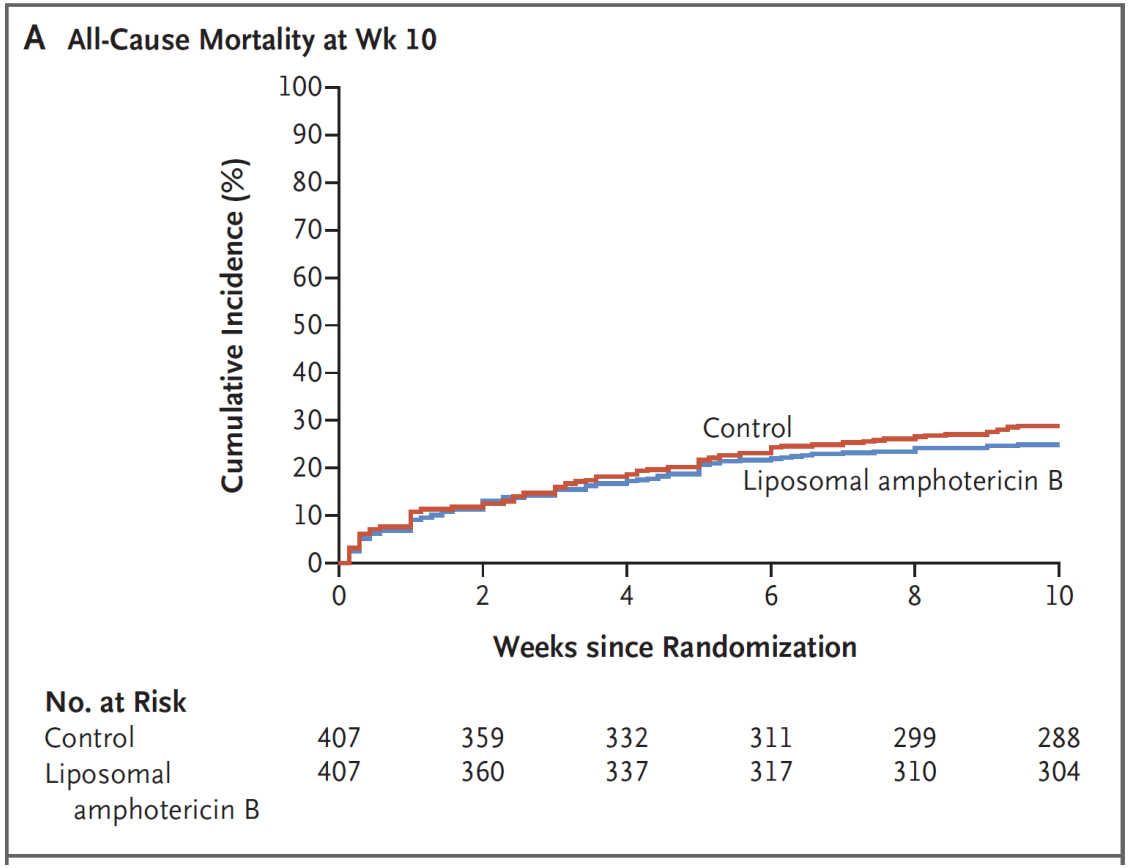
Baddley JW, Forrest GN; Clin Transplant. 2019 Sep;33(9):e13543.

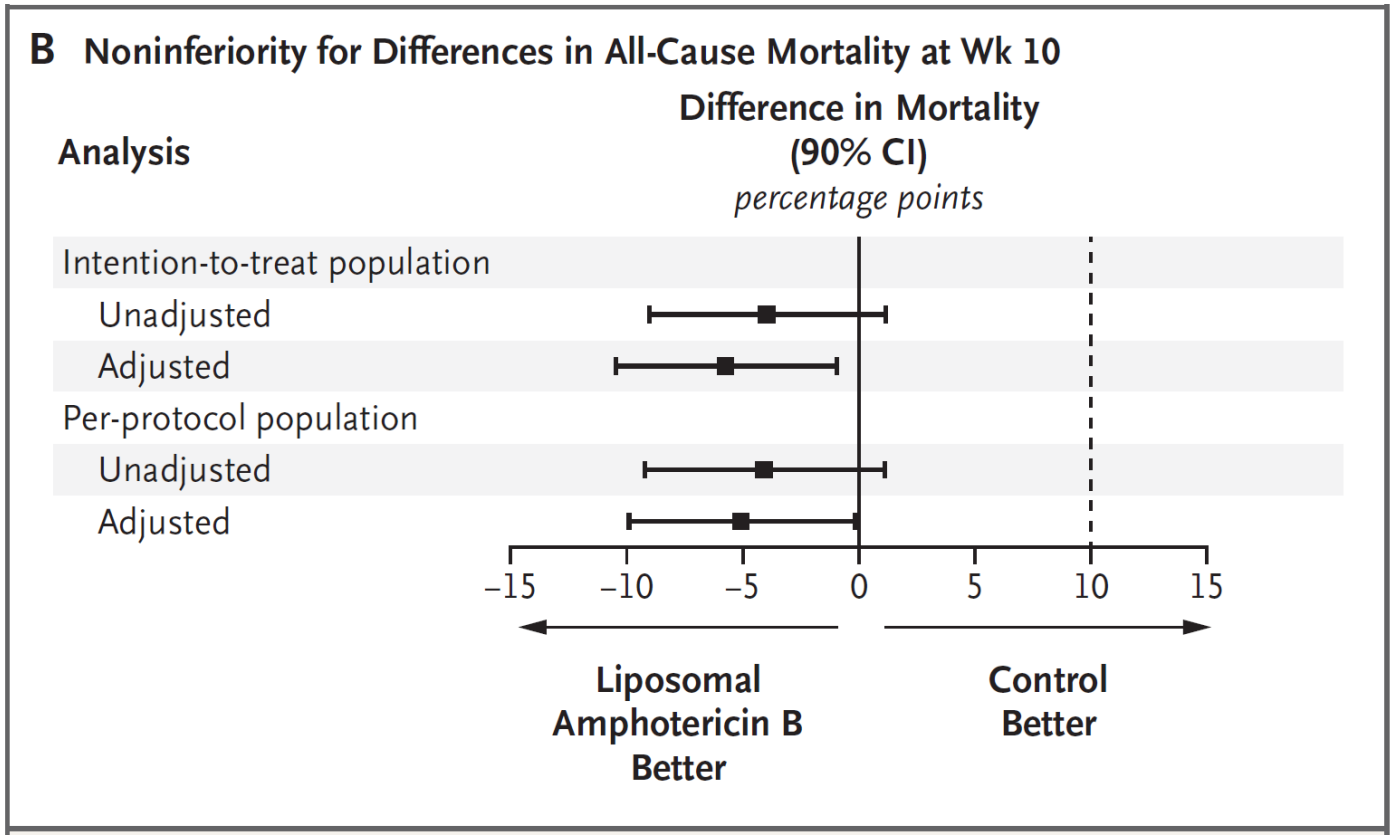
Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis

- In this phase 3 randomized, controlled, noninferiority trial conducted in five African countries, we assigned HIV-positive adults with cryptococcal meningitis in a 1:1 ratio to receive either a **single high dose of liposomal amphotericin B (10 mg per kilogram of body weight) on day 1** plus 14 days of flucytosine (100 mg per kilogram per day) and fluconazole (1200 mg per day) or the current World Health Organization–recommended treatment, which includes amphotericin B deoxycholate (1 mg per kilogram per day) plus flucytosine (100 mg per kilogram per day) for 7 days, followed by fluconazole (1200 mg per day) for 7 days (control). The primary end point was death from any cause at 10 weeks; the trial was powered to show noninferiority at a 10-percentage-point margin.
- This trial showed that a single high dose of liposomal amphotericin B given with flucytosine and fluconazole was non inferior to the current WHO recommended standard of care for cryptococcal meningitis and offers a practical treatment for the management for HIV-associated cryptococcal meningitis that is easier to administer and associated with fewer drug-related adverse effects.

Jarvis Jnet al. N Engl J Med. 2022 Mar 24;386(12):1109-1120.

Cumulative All-Cause Mortality Up to Week 10 and Noninferiority Analysis



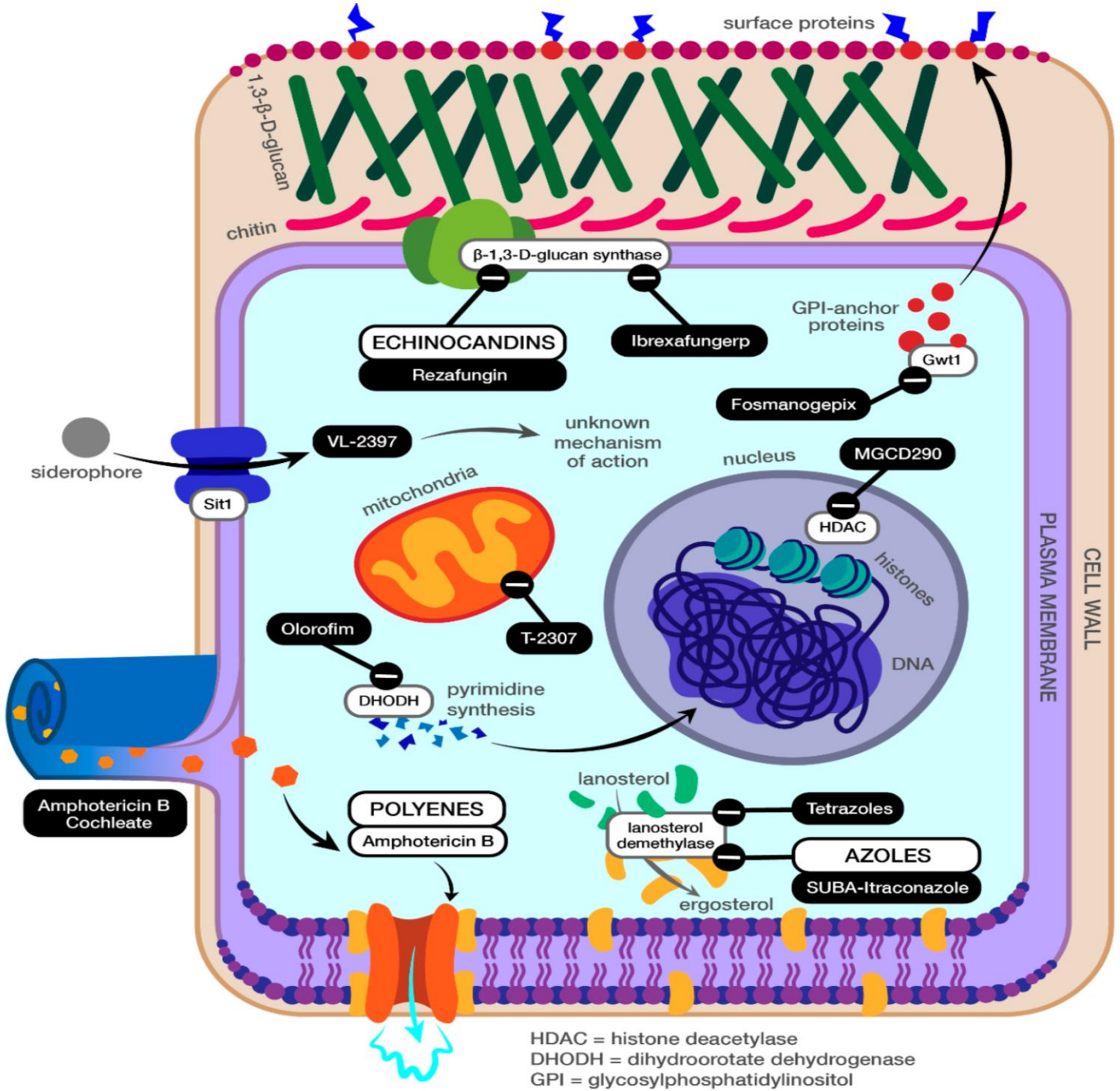


Jarvis J, et al. N Engl J Med. 2022 Mar 24;386(12):1109-1120.

New antifungal drugs in the clinical pipeline

Agent	Phase 1	Phase 2	Phase 3	Types of Fungal Infections for Enrollment in Clinical Trials
Olorofim (F901318)	NCT05101187			Invasive aspergillosis
	NCT03583164			Invasive infections due to *Lomentospora prolificans*, *Scedosporium* spp., *Aspergillus*, and other resistant fungi
Rezafungin (CD101)	NCT03667690			Candidemia and/or invasive candidiasis (Completed)
	NCT04368559 (ReSPECT)			Antifungal prophylaxis in adults with allogeneic blood or bone marrow transplant
Oteseconazole (VT-1161)	NCT03562156 & NCT03561701 (VIOLET)			Recurrent vulvovaginal candidiasis (Completed)
Fosmanogepix (APX001)	NCT05421858			Candidemia and/or invasive candidiasis
	NCT04240886			Invasive infections due to *Aspergillus* or rare molds
Opelconazole (PC945)	NCT05037851			Antifungal prophylaxis or pre-emptive therapy against pulmonary aspergillosis in lung transplant
Encochleate Amphotericin B (MAT2203 or CAMB)	NCT02971007			Moderate to severe vulvovaginal candidiasis (Completed)
	NCT04031833 (EnACT)			Cryptococcal meningitis in HIV+ patients
	NCT02629419			Mucocutaneous candidiasis in patients who are refractory or intolerant to standard non-intravenous therapies
Ibrexafungerp (SCY-078) *approved for vulvovaginal candidiasis in U.S.	NCT05399641			Complicated vulvovaginal candidiasis
	NCT03672292 (SCYNERGIA)			Invasive pulmonary aspergillosis combined with voriconazole
	NCT03363841 (CARES)			Candidiasis caused by *Candida auris*
	NCT03059992 (FURI)			Invasive fungal infections in patients who are refractory or intolerant to standard therapies

Neil A. R. Gow, et al. Nat Commun. 2022 Sep 12;13(1):5352.



New antifungals

In existing antifungal classes

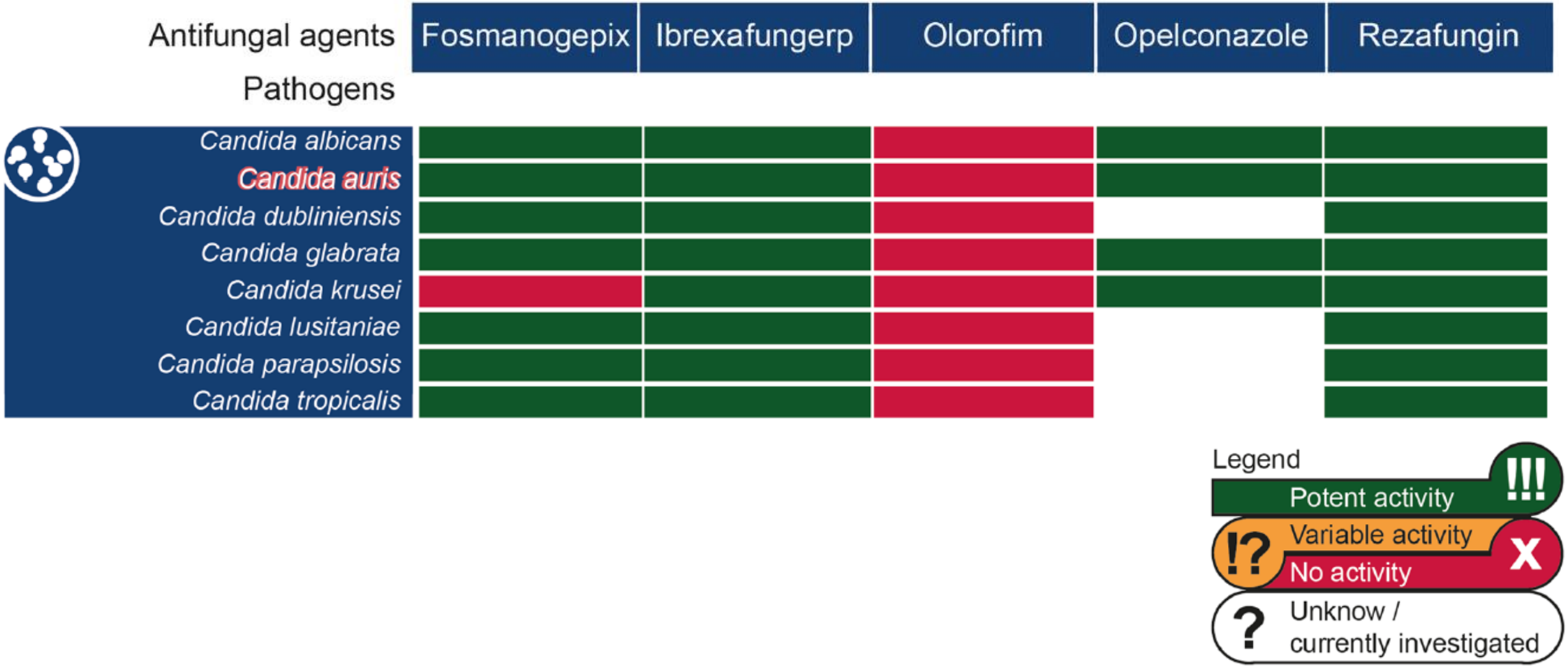
1. Rezafungin - once-weekly administered echinocandin
2. Triazole and tetrazole
3. SUBA-itraconazole - a highly bioavailable azole
4. oral formulation of amphotericin B

Novel classes (> phase 2 trials)

1. Olorofim – oral pyrimidine synthesis inhibitor with a broad spectrum of activity
2. Ibrexafungerp - oral glucan synthase inhibitor
3. (Fos)manogepix – affects cell wall stability

Gintjee et al. J Fungi 2020

The Antifungal Pipeline:
Fosmanogepix, Ibrexafungerp, Olorofim, Opelconazole, and Rezafungin.



Hoenigl M, et al. Drugs. 2021 Oct;81(15):1703-1729.

Conclusions

- Invasive fungal infections continue to be a major problem in patients with SOT or hematological malignancies and causes high mortality.
- Although we know many of the risk factors for IA in these patients, other new factors have appeared that we must consider when deciding to start antifungal prophylaxis.
- At this time, we should reconsider the strategy to follow in the use of antifungal prophylaxis, including its duration, and the possibility of using azoles with low toxicity and reduced interference with immunosuppressive drugs.
- Voriconazole remains the drug of choice to treat IA, but isavuconazole is an excellent alternative for its greater safety and less interactions with immunosuppressive drugs.
- Interesting new entries approved and in advanced phases
- Many oral, few drug interactions, Active against (difficult) moulds