Fungal Infections in Hematology

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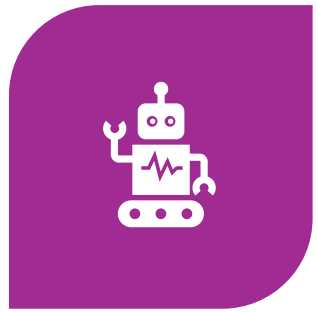
Disclosure

TRAVEL GRANT : SERVIER, ABBVIE, GILEAD, INCYTE

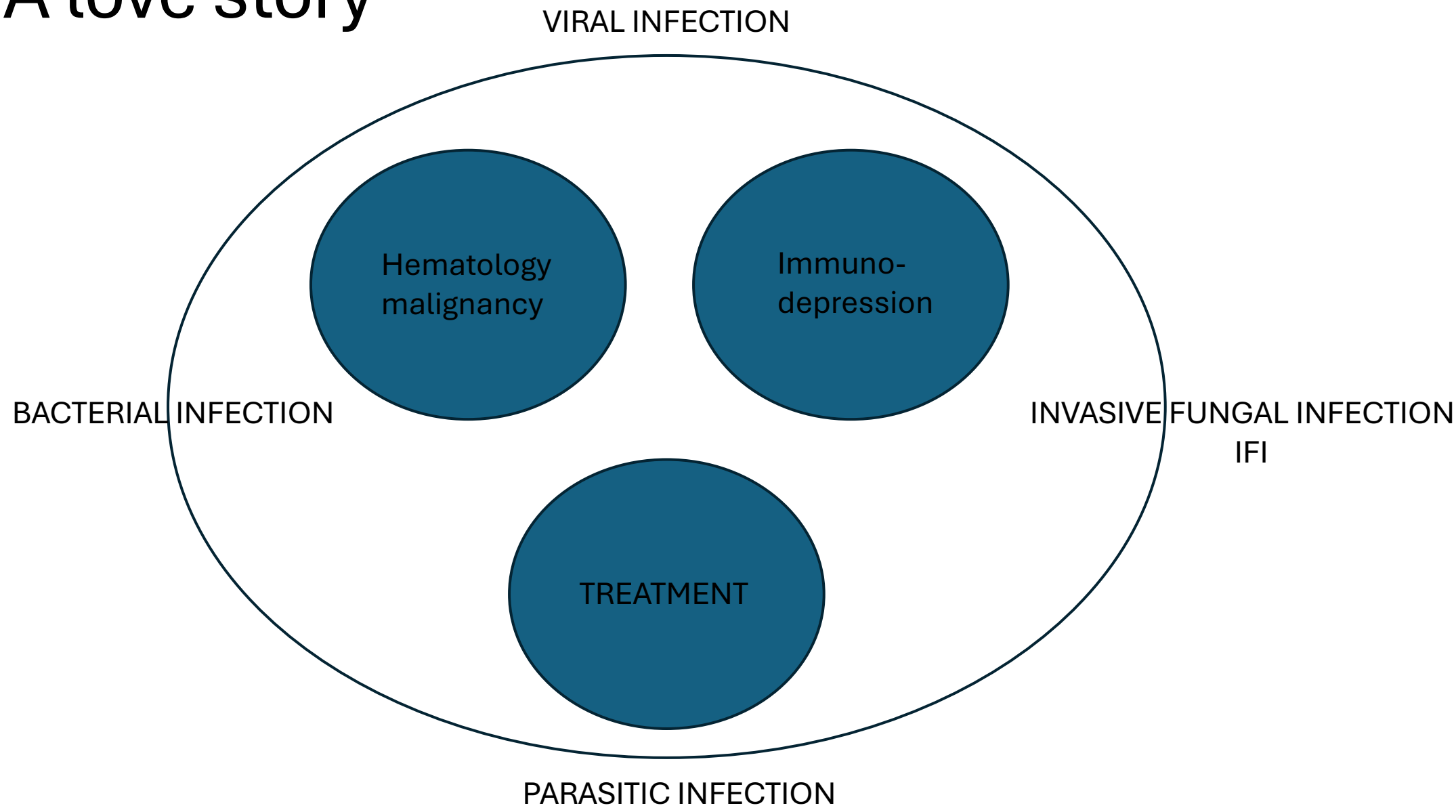
RESEARCH GRANT : GILEAD

CONSULTANCE: SERVIER, ABBVIE



I USED NO LLM MODEL TO GENERATE ANY PART OF THIS PRESENTATION.

A love story


VIRAL INFECTION
Hematology malignancy
Immuno-depression
BACTERIAL INFECTION
INVASIVE FUNGAL INFECTION
IFI
TREATMENT
PARASITIC INFECTION

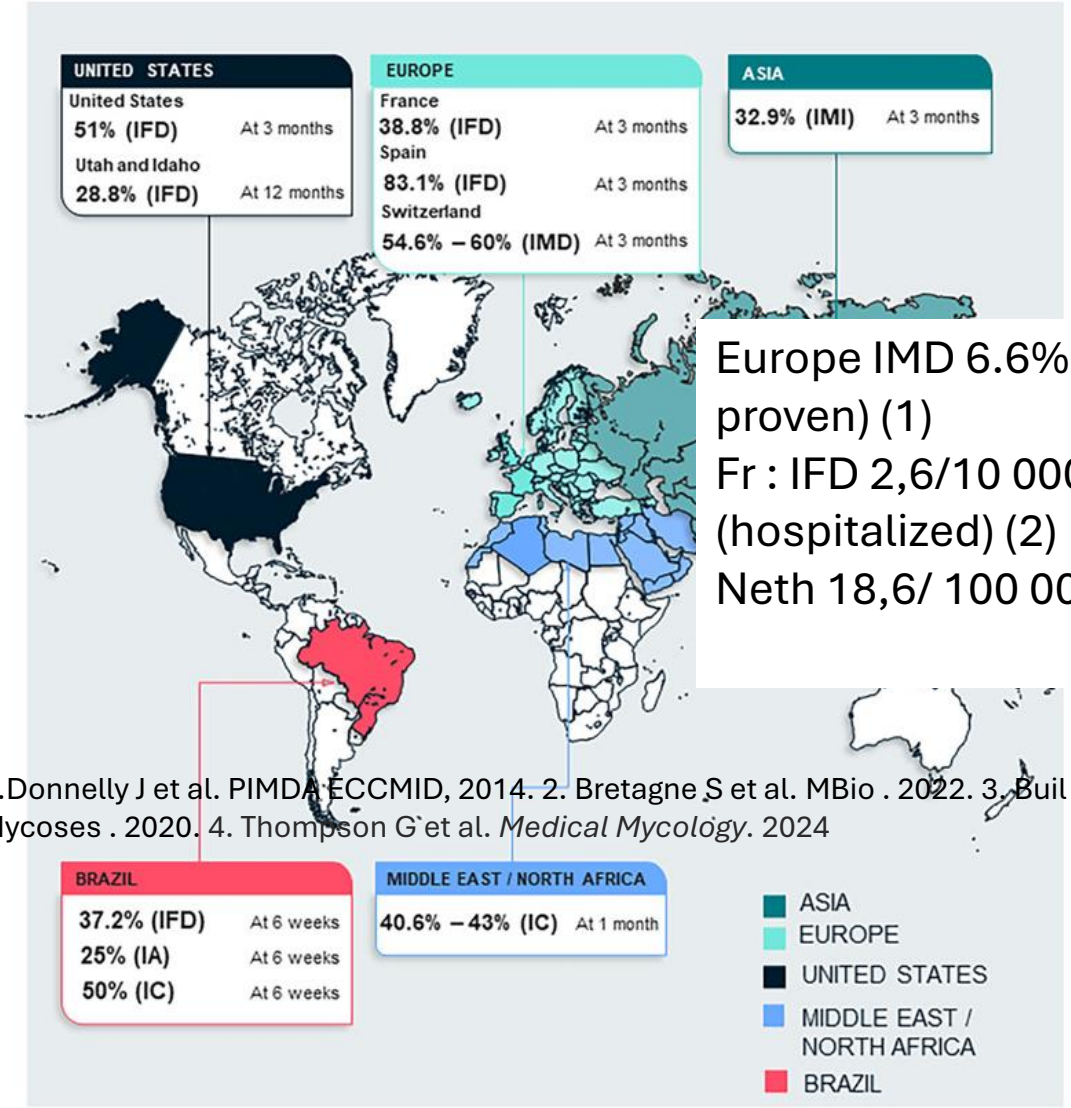
The bad – Hematology malignancies and IFI

- AML treated with invasive chemotherapy : up to 12% (1-2)
- (allo-)HSCT : 5 – 15% (3-4)
- Acute lymphoblastic leukemia : 6-10% (5-6)

- CLL : 0,5 – 8% (7)

1.Pagano L et al. Haematologica 2006
2. Ananda-Rajah MR et al. Haematologica 2012
3. Kontoyiannis DP et al.Clin Infect Dis 2010
4. Girmenia C et al. Biol Blood Marrow Transplant 2014
5. Mariette C al. Leuk Lymphoma 2017; 58: 586–93.
6. Doan TN et al. J Antimicrob Chemother 2016; 71: 497–505.
7. Teng JC et al. Haematologica 2015.

The bad – Hematology malignancies and IFI



Europe IMD 6.6% (prb and proven) (1)
Fr : IFD 2,6/10 000 (hospitalized) (2)
Neth 18,6/ 100 000 (3)

Infection	Number of infections per underlying disorder per year: None	HIV/ AIDS	Respiratory disease	Cancer/ Tx	ICU	Total burden	Rate/ 100 000 inhabitants
Candidaemia				388	165	555	5.0
Intra-abdominal candidiasis					83	83	0.75
Recurrent *Candida* vaginitis (≥4×/year)	174 760					174 760	3149[1]
Invasive aspergillosis				402	273	675	6.08
Chronic pulmonary aspergillosis			662			662	22.7
ABPA			23 119			23 119	208.3
Severe asthma with fungal sensitisation			30 402			30 402	273.9
Cryptococcal meningitis						10	0.09
Pneumocystis pneumonia		15	105			120	1.1
Total burden estimated						233 000	2099

ABPA, allergic bronchopulmonary aspergillosis; Tx, transplant recipients.
[1]Rate of recurrent *Candida* vaginitis per 100 000 females, not per total population.

Lagrou K et al. Mycoses. 2015

1.Donnelly J et al. PIMDA ECCMID, 2014. 2. Bretagne S et al. MBio . 2022. 3. Buil JB et al. Mycoses . 2020. 4. Thompson G`et al. *Medical Mycology*. 2024

The Bad – not so simple

- AML patients unfit for intensive chemotherapy treated with venetoclax and azacitidine present serious IFI

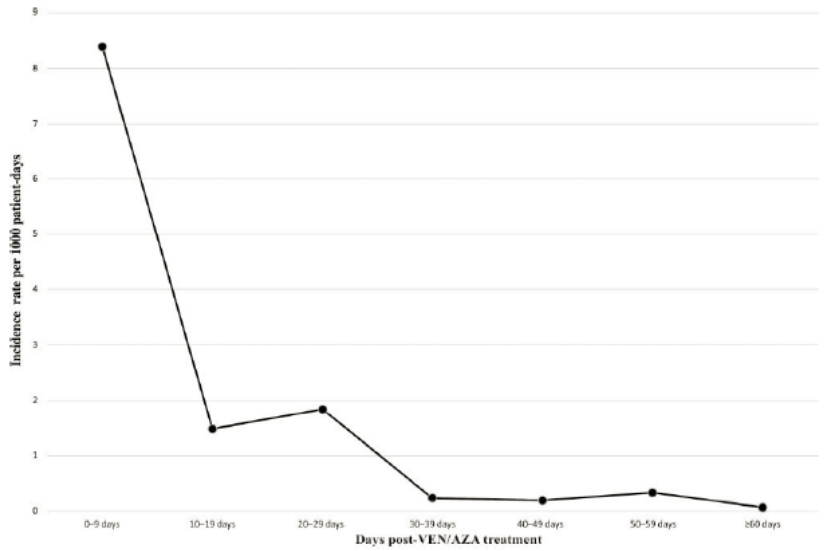
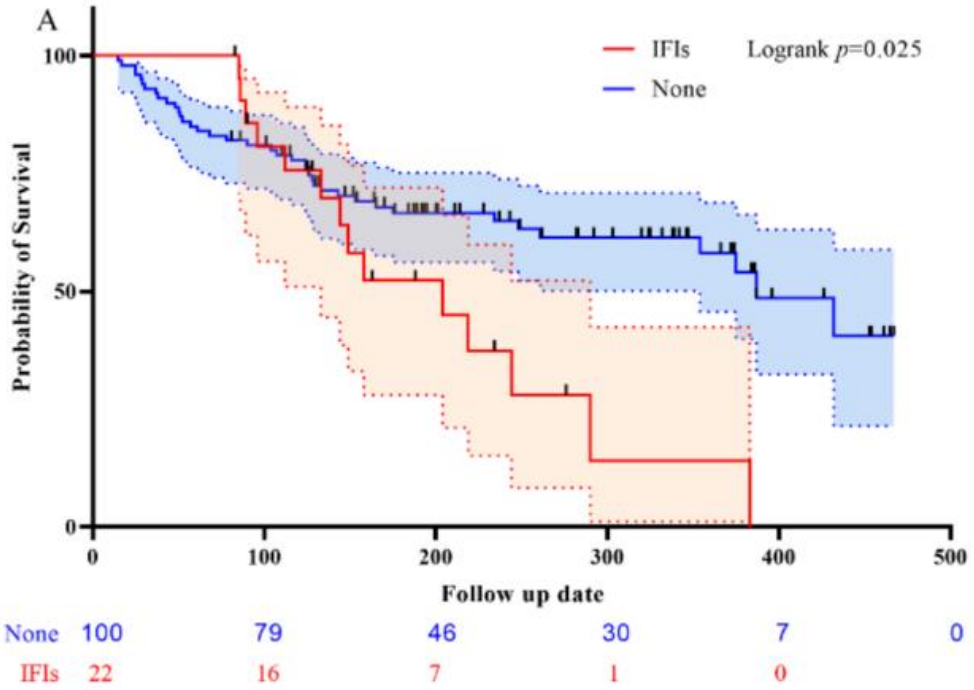


Figure 1. Incidence rate of invasive fungal infections (IFIs) after starting venetoclax/azacitidine (VEN/AZA) treatment. Patients diagnosed with proven, probable, and possible IFI were categorized by the number of days between starting VEN/AZA treatment and starting antifungal treatment.

Zhang A et al. OFID. 2022



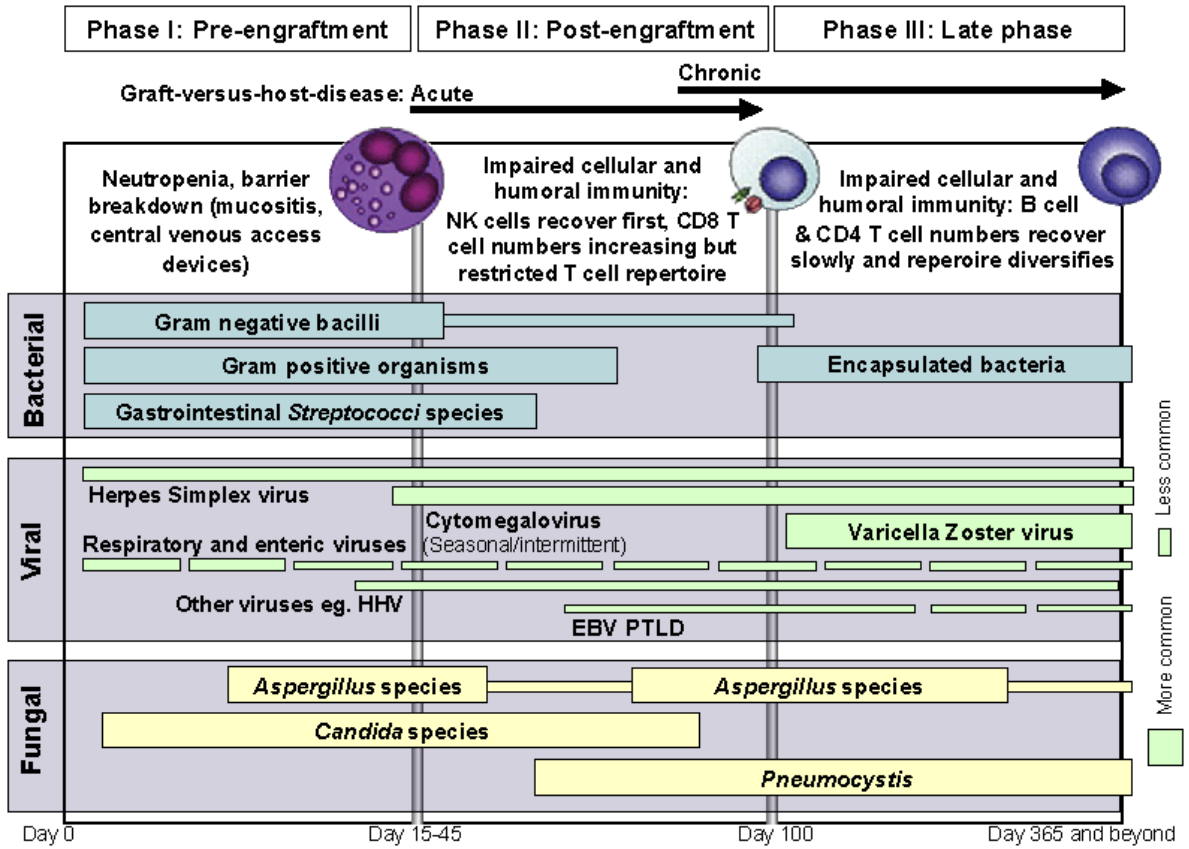
Lee R et al. Cancers. 2021

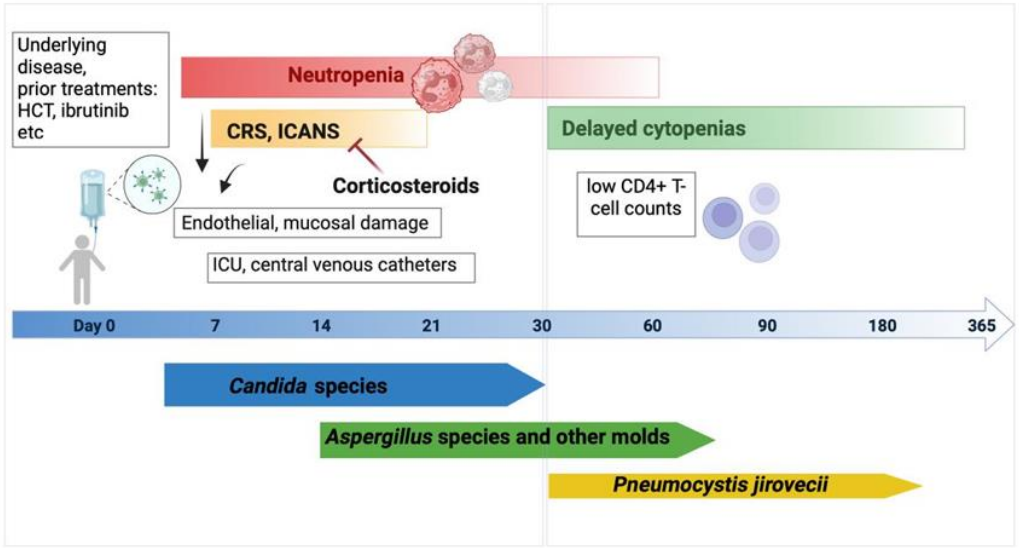
The good - treatment

- HSCT (age, underlying disease, iron overload, alternative donors, GVH prophylaxis, GVH, CMV infection, environment) (1)
- Intensive and non-intensive treatment for AML
- Bispecific and car-t Cell (3% of IFI reported) (2)
- Bruton tyrosine kinase inhibitors (with mention for cerebral aspergillosis) (3)

1. PAGANO L et al. Blood reviews. 2017
2. LITTLE J et al. *Open Forum Infectious Diseases. 2024*
3. Ruchlemer R et al. NEJM. 2016

The good - treatment

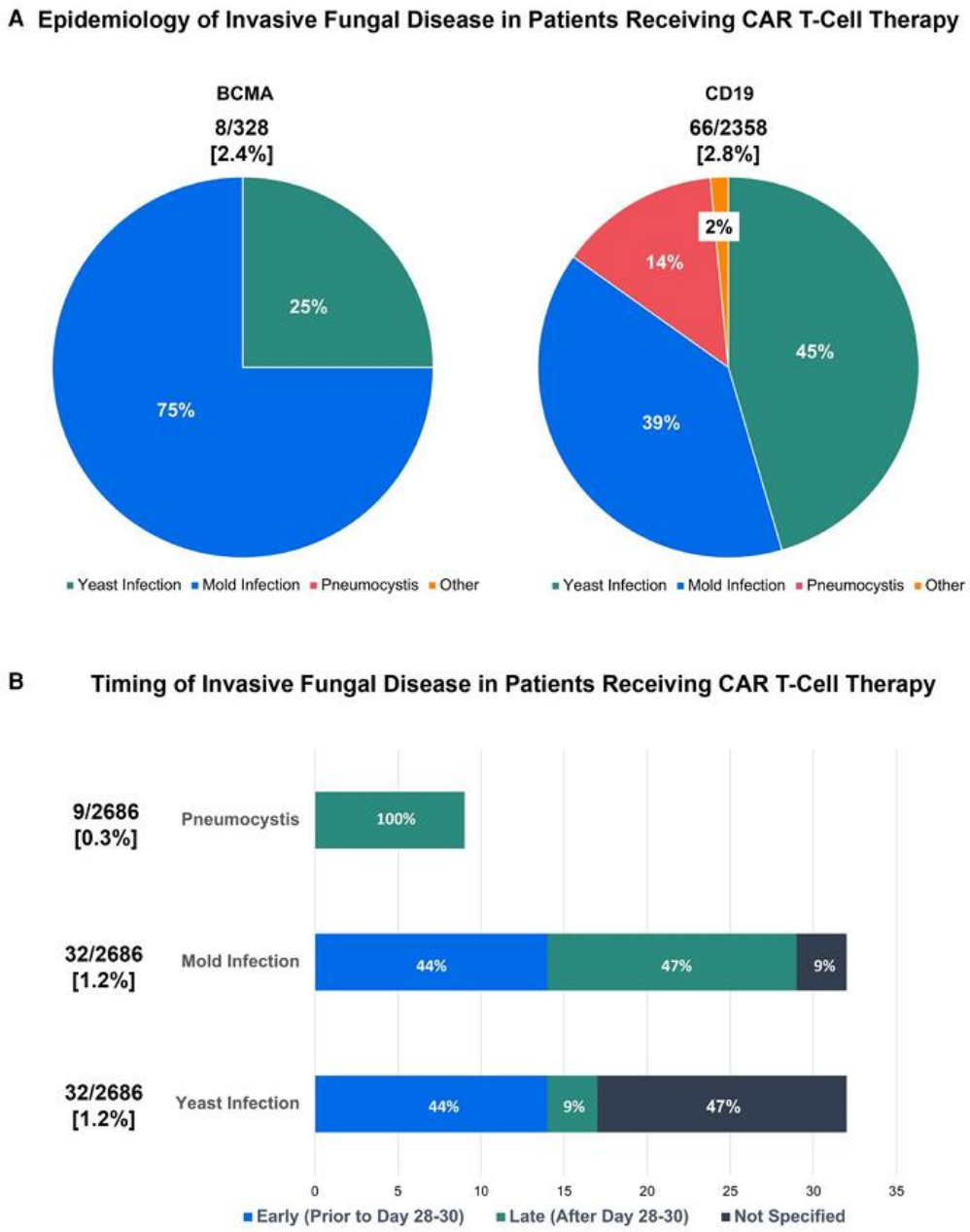




EBMT Handbook 2009

LITTLE J et al. *Open Forum Infectious Diseases. 2024*

The good - treatment



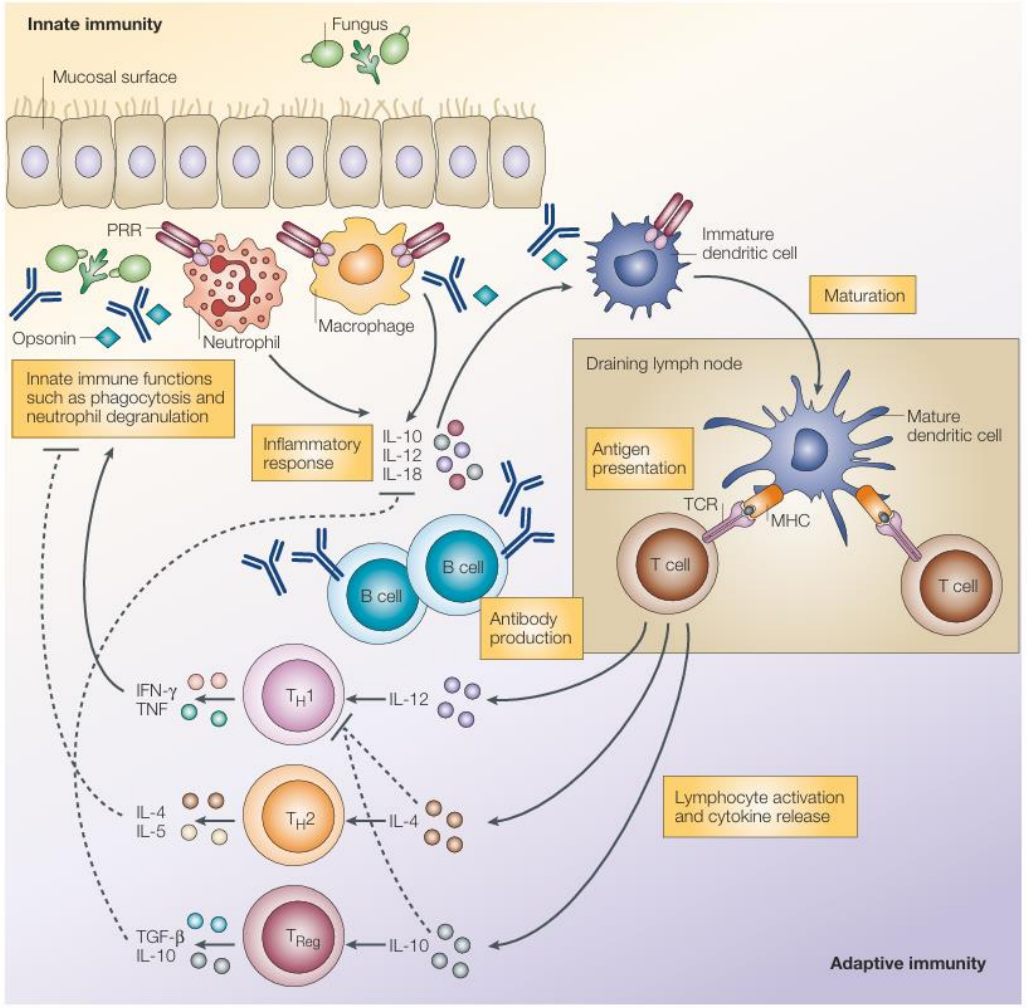
LITTLE J et al. *Open Forum Infectious Diseases. 2024*

The Ugly - immunodepression

- Host barrier
- Neutropenia
- Drug (immune suppressive after HSCT)
- Anorexia and cachexia
- Hyperferritinemia

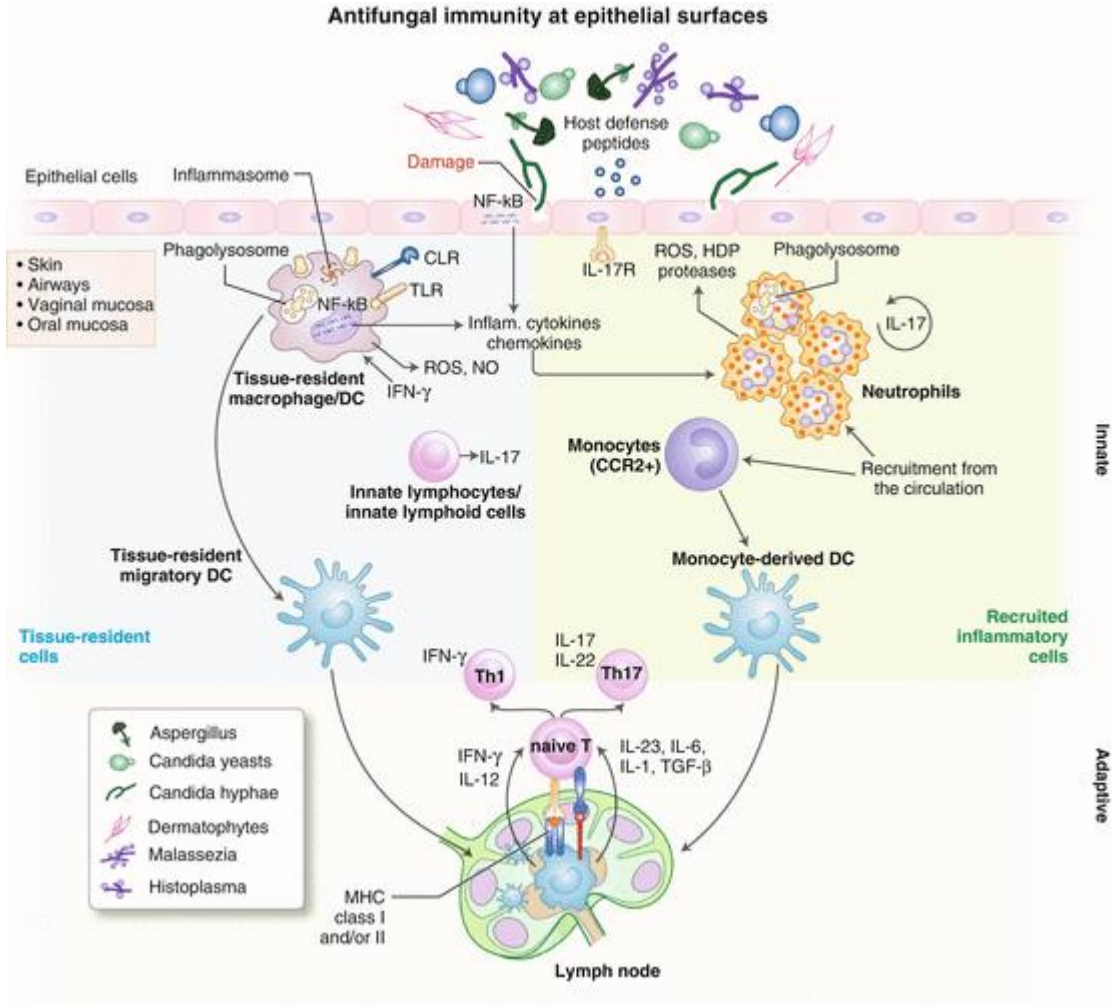
Girmenia C et al. Biol Blood Marrow Transplant 2014
Maertens JA et al. The EBMT Handbook (chp 37). 8th ed. 2024
Thompson G et al. *Medical Mycology*. 2024
Maschmeyer G et al. Leukemia 2019
Alqarihi Aet al. Front. Cell. Infect. Microbiol. 2023

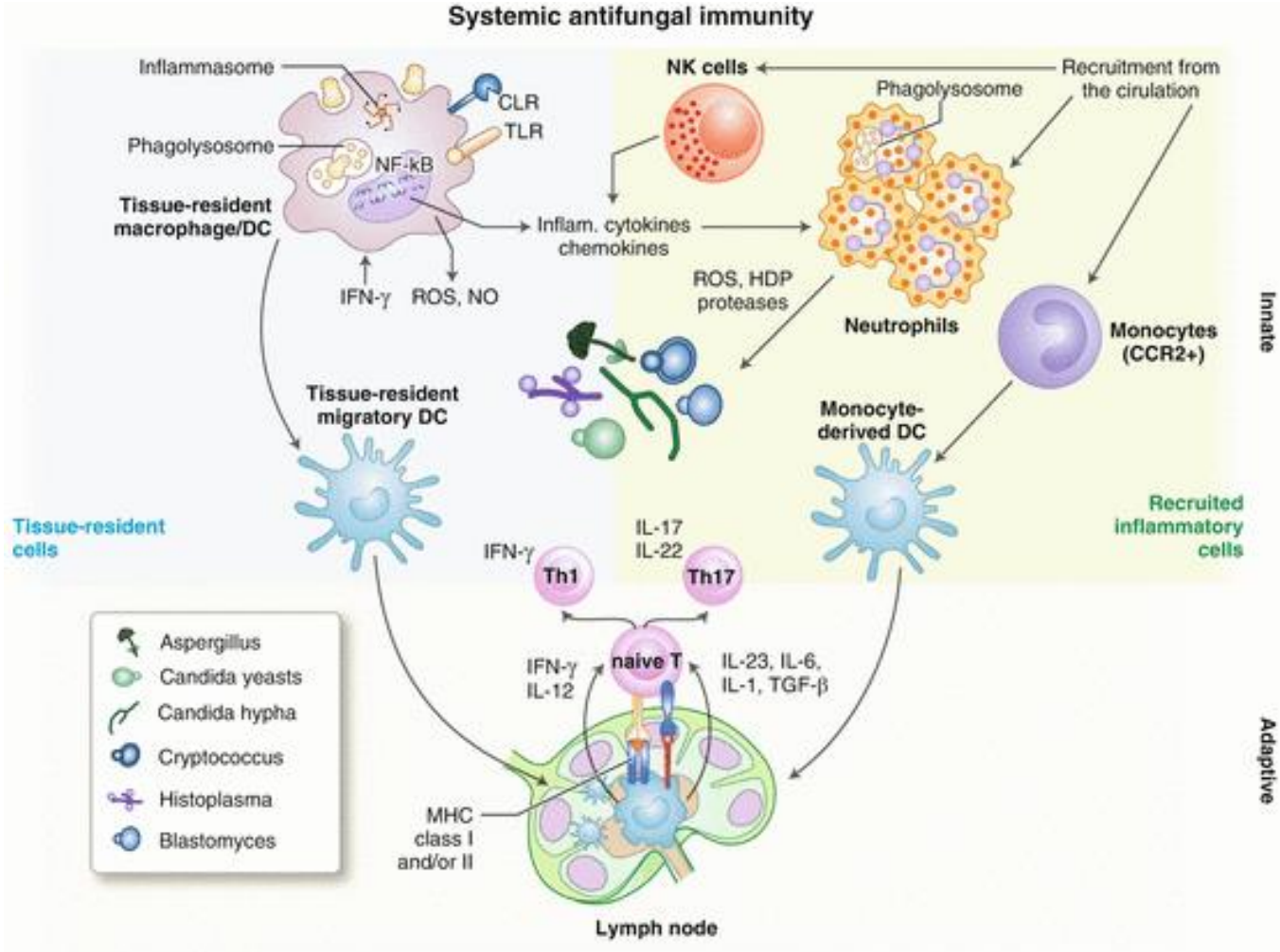
The Ugly - immunodepression



Romani L . *Nature Reviews Immunology.* 2004

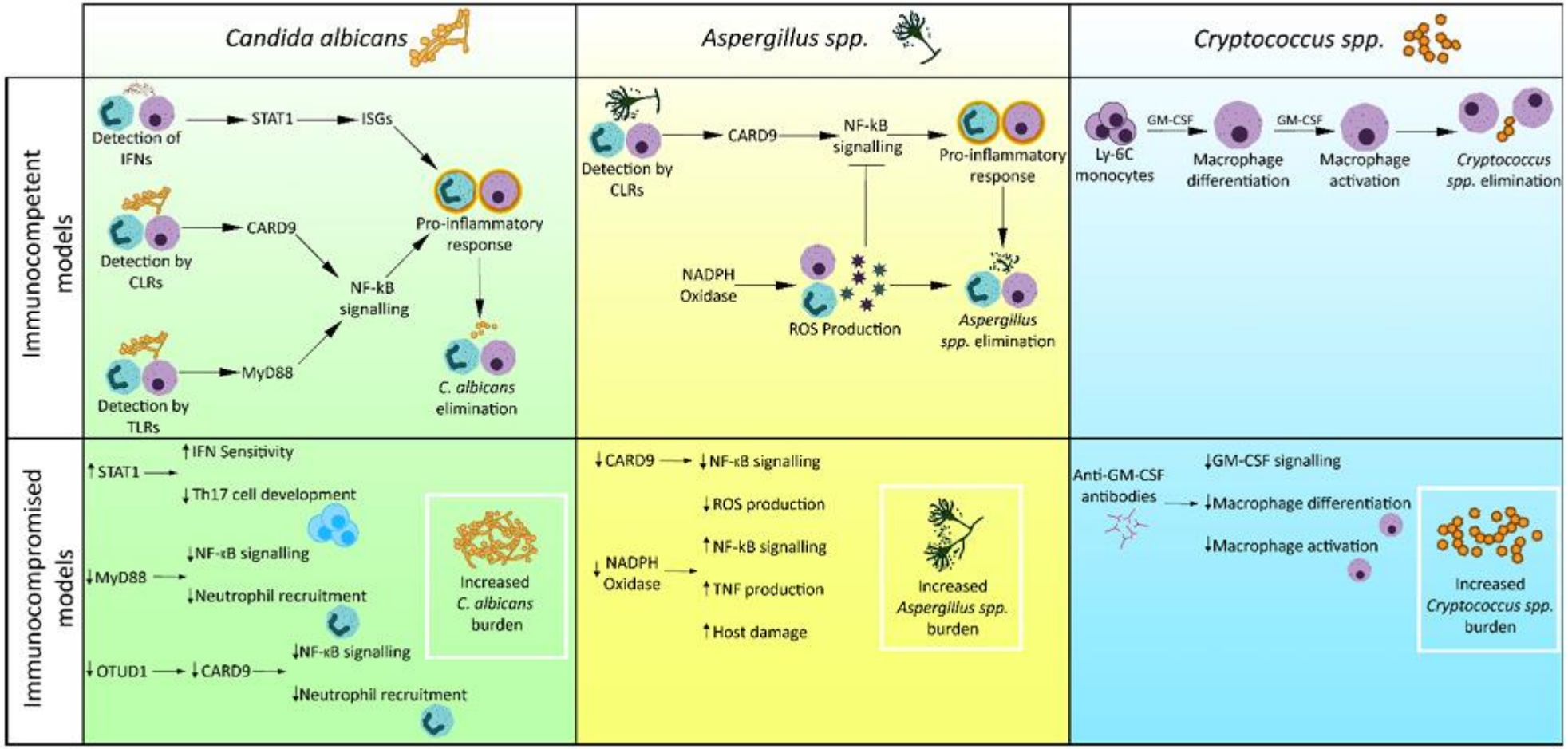
The Ugly - immunodepression





Altmeier, S et al. Immunogenetics of Fungal Diseases (book). 2017

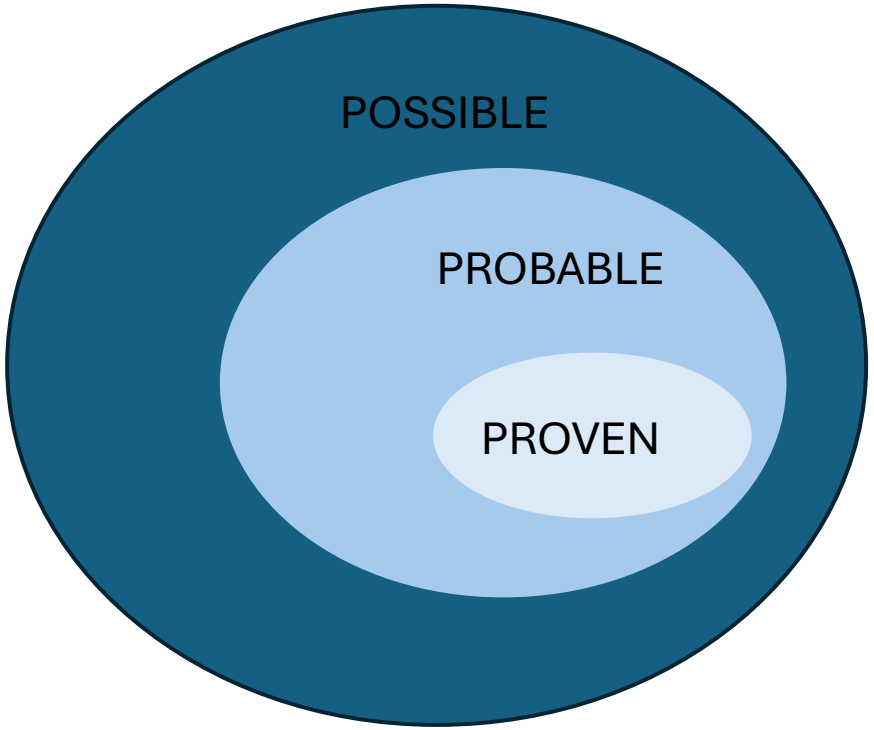
The Ugly - immunodepression



Burgess T et al. J. Fungi. 2022

Diagnosis

- Cf the talk of Dr Robina AERTS



Clinical finding (radiology)

Host factor (HSCT, long neutropenia, corticosteroid)

Microbiology (GM, bD Glucan)

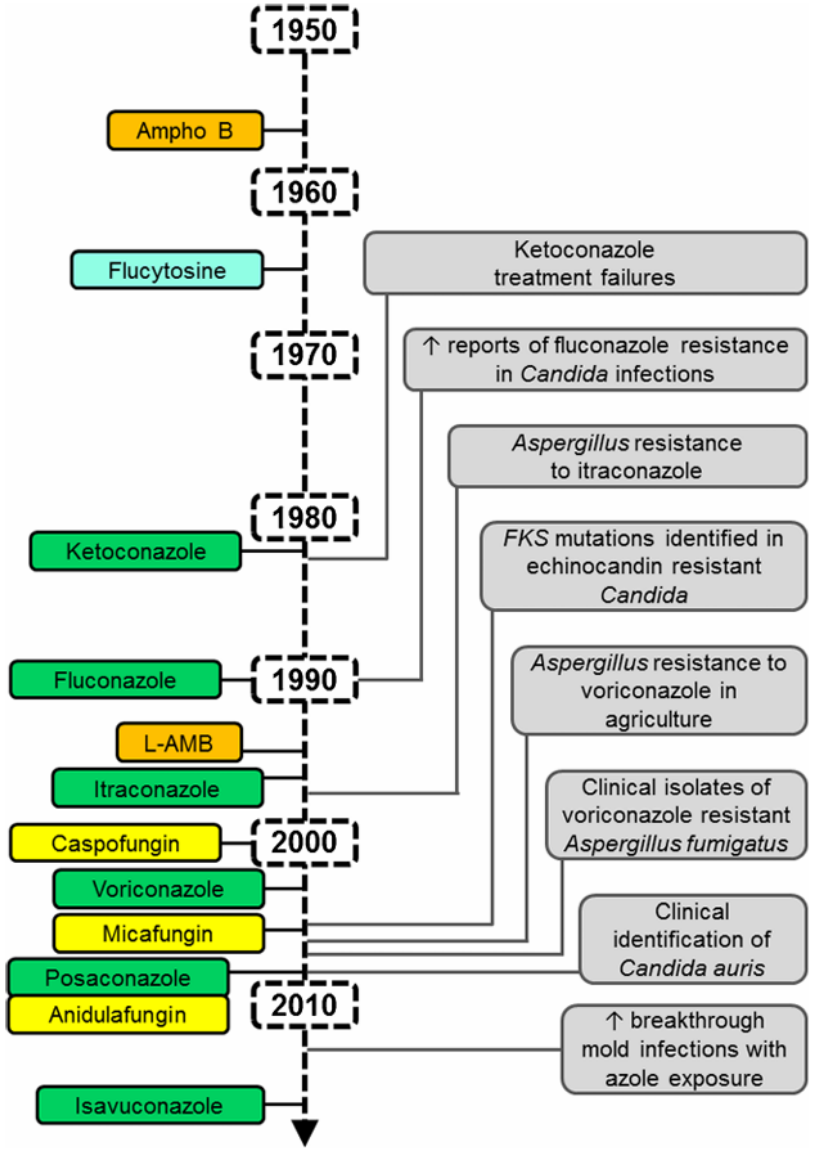
Donnelly J et al. *Clinical Infectious Diseases*, 2020.

Table 1. Criteria for Proven Invasive Fungal Disease

Fungus	Microscopic Analysis: Sterile Material	Culture: Sterile Material	Blood	Serology	Tissue Nucleic Acid Diagnosis
Molds[a]	Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage	Recovery of a hyaline or pigmented mold by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding BAL fluid, a paranasal or mastoid sinus cavity specimen, and urine	Blood culture that yields a mold[c] (eg, *Fusarium* species) in the context of a compatible infectious disease process	Not applicable	Amplification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue
Yeasts[a]	Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast cells, for example, *Cryptococcus* species indicating encapsulated budding yeasts or *Candida* species showing pseudohyphae or true hyphae[d]	Recovery of a yeast by culture of a sample obtained by a sterile procedure (including a freshly placed [<24 hours ago] drain) from a normally sterile site showing a clinical or radiological abnormality consistent with an infectious disease process	Blood culture that yields yeast (eg, *Cryptococcus* or *Candida* species) or yeast-like fungi (eg, *Trichosporon* species)	Cryptococcal antigen in cerebrospinal fluid or blood confirms cryptococcosis	Amplification of fungal DNA by PCR combined with DNA sequencing when yeasts are seen in formalin-fixed paraffin-embedded tissue
Pneumocystis	Detection of the organism microscopically in tissue, BAL fluid, expectorated sputum using conventional or immunofluorescence staining	Not applicable	Not applicable	Not applicable	Not applicable
Endemic mycoses	Histopathology or direct microscopy of specimens obtained from an affected site showing the distinctive form of the fungus	Recovery by culture of the fungus from specimens from an affected site	Blood culture that yields the fungus	Not applicable	Not applicable

Donnelly J et al. *Clinical Infectious Diseases*, 2020.

The history of the friendship between fungal infections and hematologist



Miller R et al. *Curr Fungal Infect Rep. 2018*

Prophylaxis

- ECIL 5-6 in favor for high-risk patients (AML, allo-HSCT) with some difference amongst the different groups
- An update (ECIL 10) is awaited with novelty for unfit AML patients and CLL patients under BTK inhibitor

- Posaconazole remains the drug of choice when the incidence of invasive mould diseases exceeds 8% (especially in AML and patients with severe GVH).

Maertens J et al . J Antimicrob Chemother. 2018
Cornely O et al. NEJM. 2007
Ullman A et al. NEJM. 2007

Pre-emptive

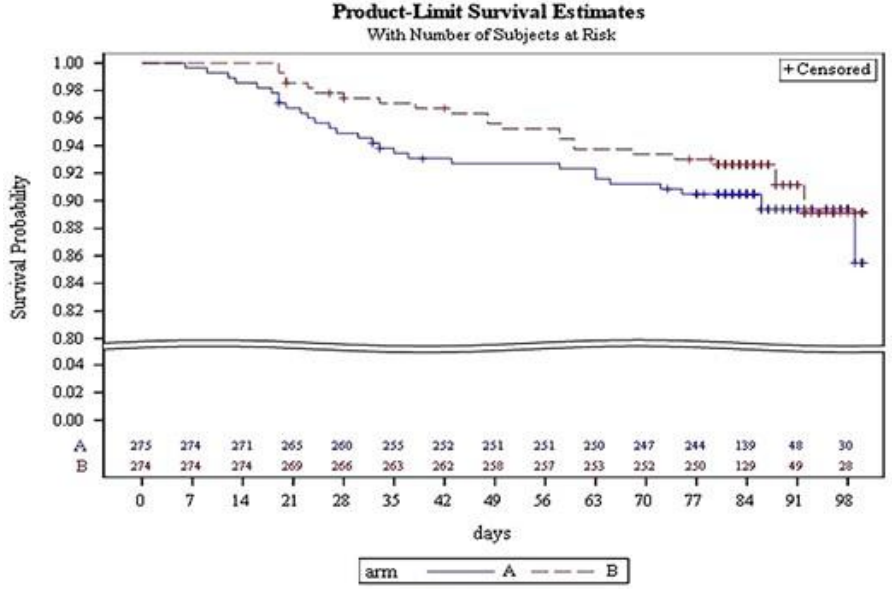
- 2 RCTs :

- **PREVERT trial**

Failed to show no inferiority for prolonged neutropenia patient but same OS

- **EORTC trial**

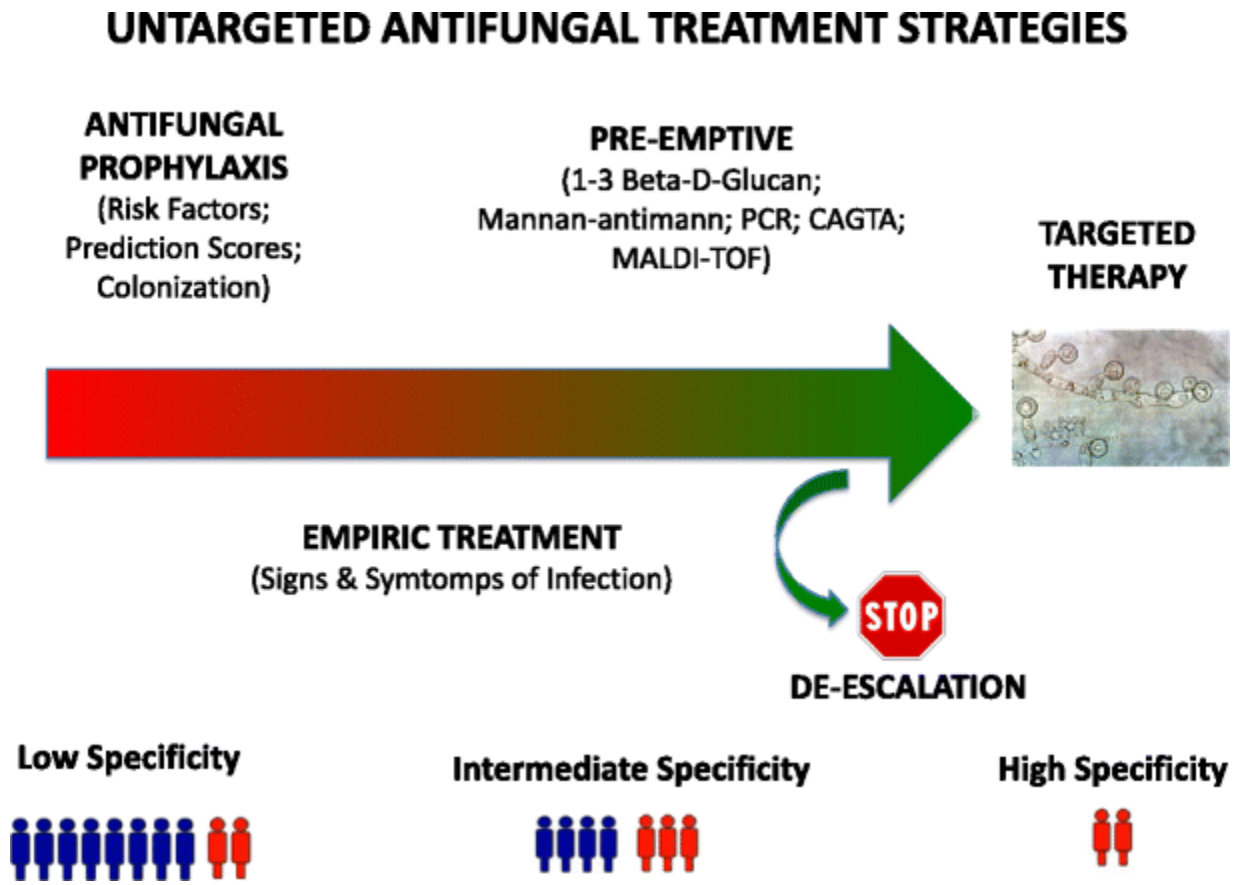
Same OS and non-inferiority



Overall survival at day 42: Arm A: 93.1% (95% CI, 89.3-95.5%) and Arm B: 96.7% (95% CI, 93.8-98.3%)

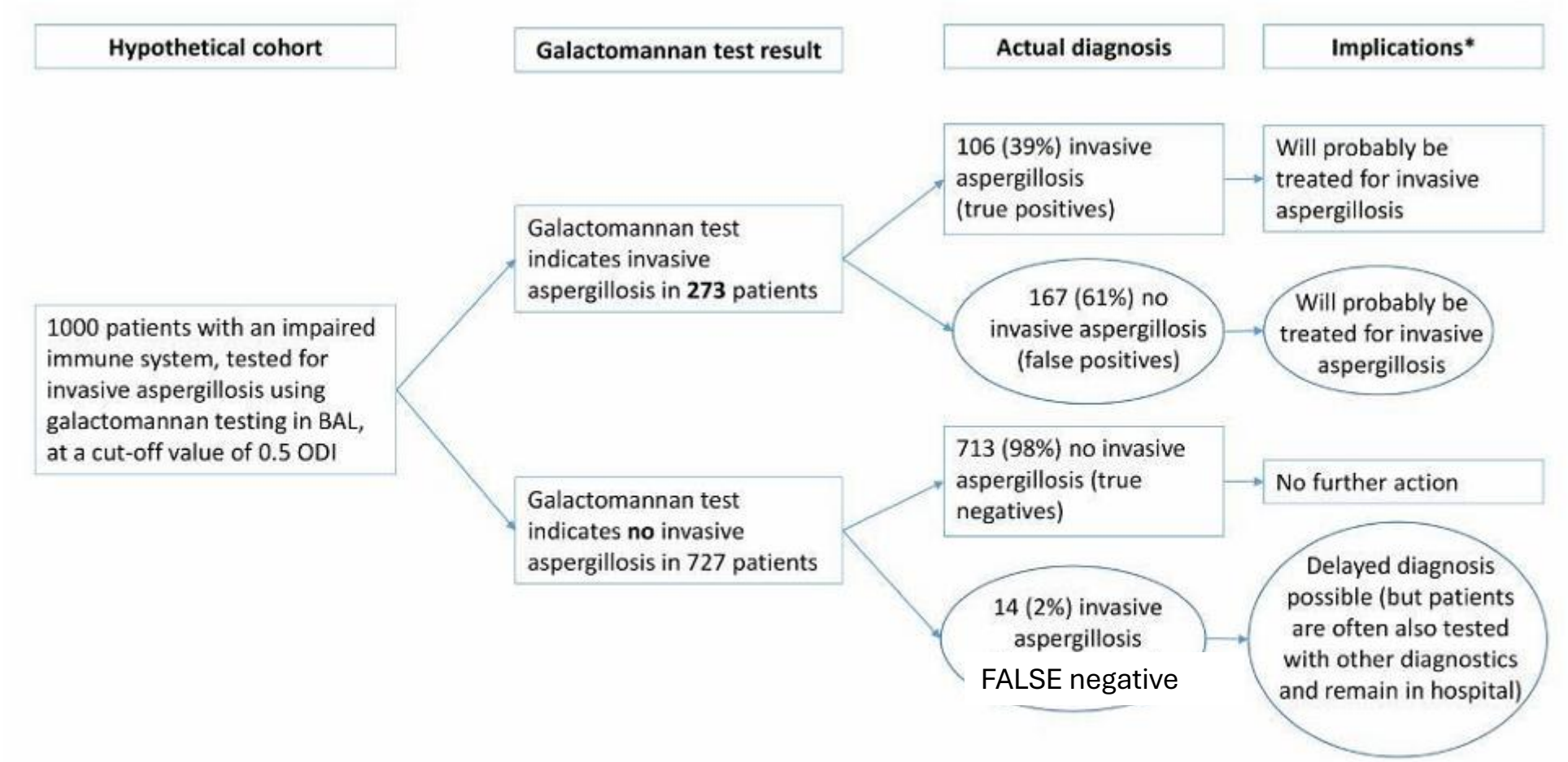
Cordonnier C et al. *Clin Infect Dis. 2009*
Maertens J et al. , *Clin Infect Dis.* 2023

Pre-emptive



Cortegiani, A*et al. Curr Fungal Infect Rep.* 2017

Pre-emptive



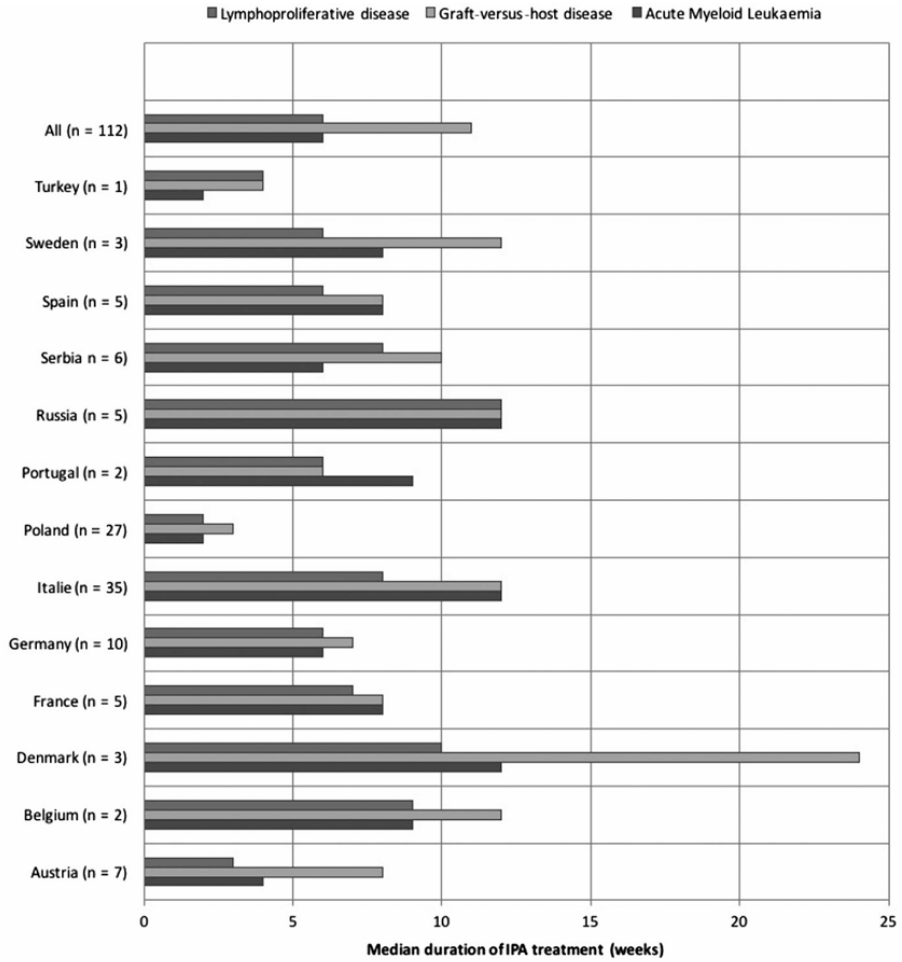
de Heer K et al. Cochrane Database of Systematic Reviews. 2019

Treatment

- Aspergillosis : Ullmann et al. Clin Microbiol Infect. 2018
- Candida : Pappas et al. Clin Infect dis. 2016
- Mucor : Cornelly O et al. Lancet Infect Dis. 2019
- Rare mold : Hoenigl M et al. Lancet infect dis. 2021

Frederic Tissot et al. Haematologica. 2017.

Treatment



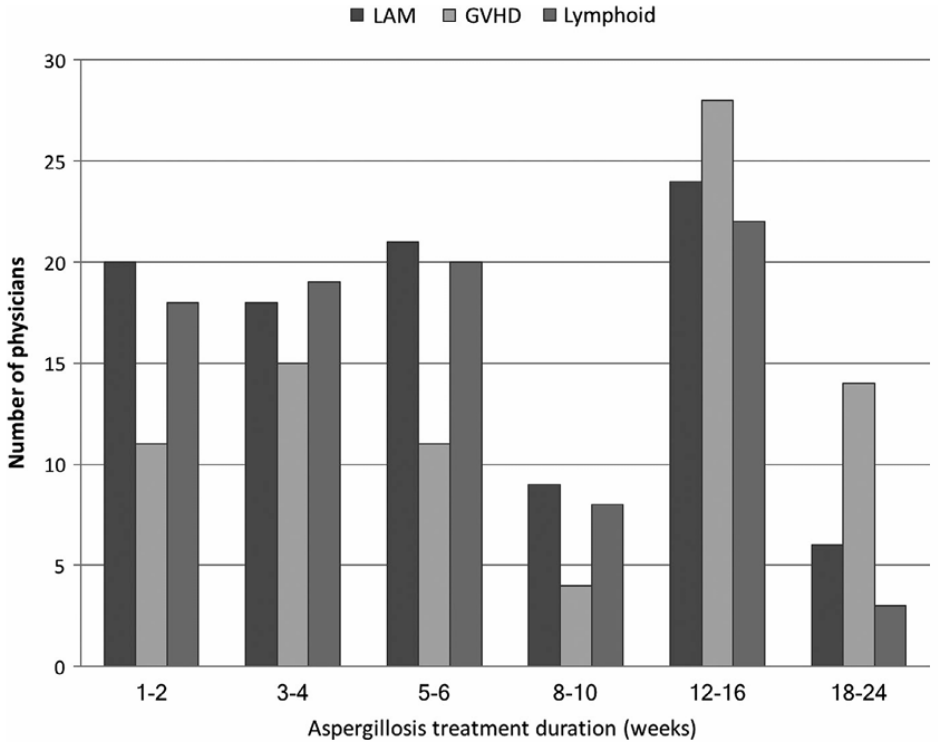


FIGURE 2 Aspergillosis treatment duration according to centres

Lanternier, F et al. Mycoses . 2020

Secondary prophylaxis

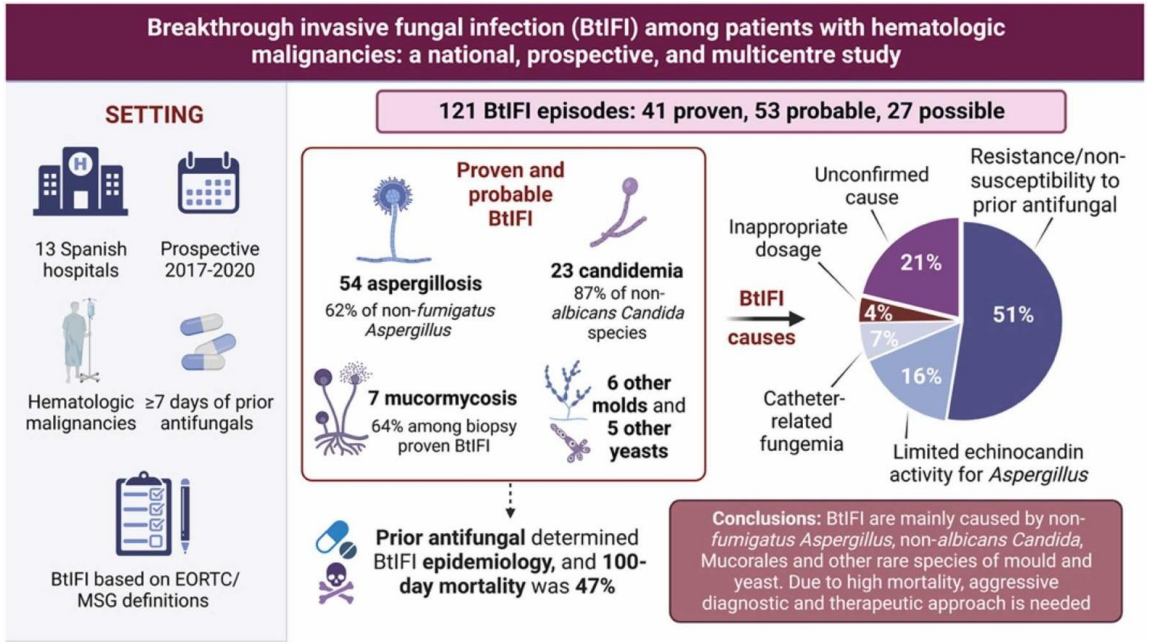
Table 36
Secondary prophylaxis

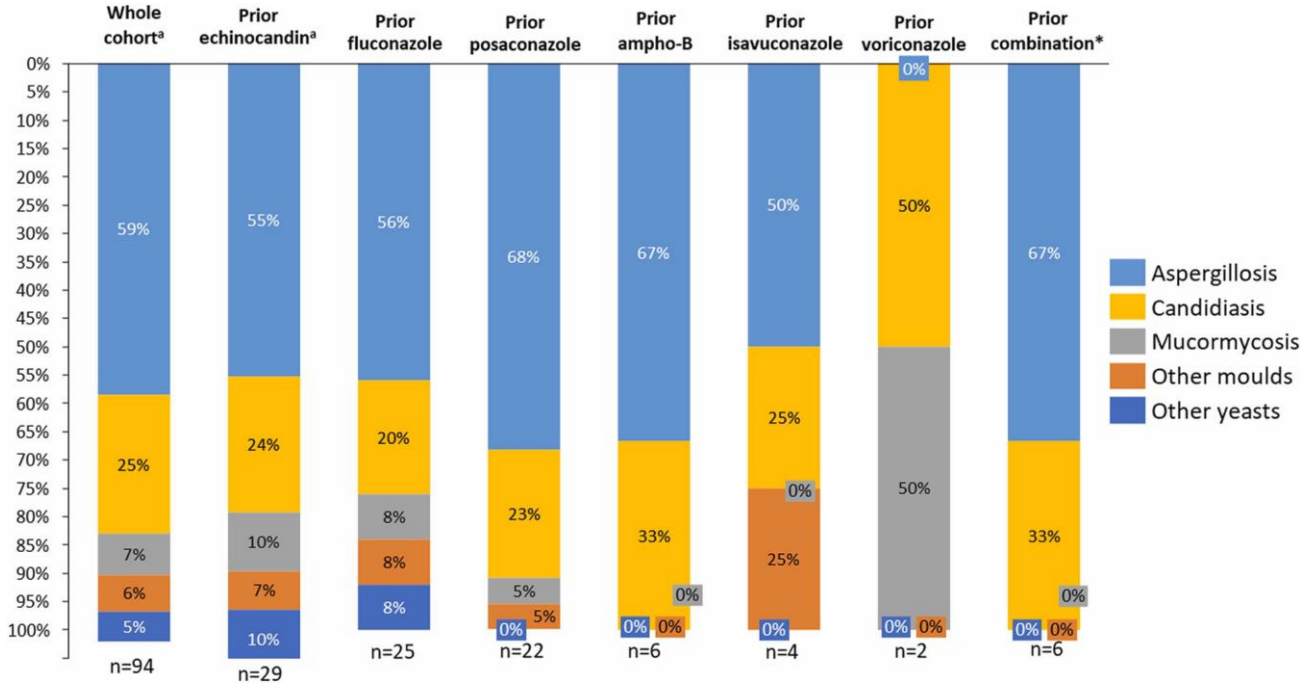
Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Previous IA and undergoing allogeneic HSCT or entering risk period with non-resectable foci of *Aspergillus* disease	To reduce risk of IA recurrence	Secondary prophylaxis with an *Aspergillus* active antifungal proven to be effective in the actual patient	A	II	Results compared to historical data, mostly in allogeneic HSCT setting	[703–708]
		Voriconazole	A	II_h	IA: 31/45 patients, 1 year cumulative incidence of IFD 6.7 ± 3.6%, TDM	[703]
		Caspofungin 70 mg day 1, followed by 50 mg/day IV until stable engraftment, followed by 400 mg itraconazole suspension PO	B	II_h		[707]
		L-AmB followed by voriconazole	C	II	Fungal infection related mortality 28% despite lipid-based AmB	[706,709]
Previous IA and with resectable foci of *Aspergillus* disease before entering risk period	To reduce risk of IA recurrence	Surgical resection following by secondary prophylaxis	B	III	Timing and methods of surgery important. Concomitant administration of appropriate antifungal compound justified Indication for surgical intervention by appropriate specialist. Interdisciplinary consensus needed	[710–714]

Abbreviations: HSCT, haematopoietic stem cell transplantation; IA, invasive aspergillosis, IFD, invasive fungal disease; L-AmB, liposomal amphotericin B; PO, *per os*; QoE, Quality of evidence; SoR, Strength of recommendation; TDM, therapeutic drug monitoring.

Ullmann et al. Clin Microbiol Infect. 2018

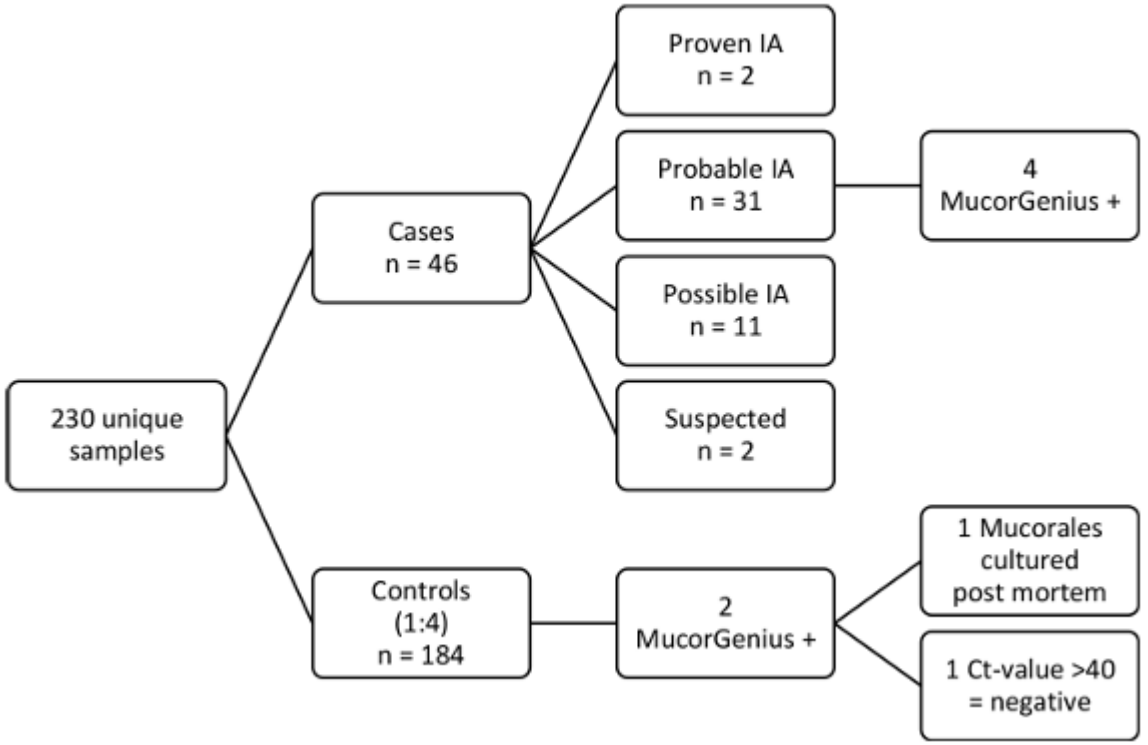
Breakthrough invasive fungal infection





Pedro et al. Journal of Infection. 2023

Dual infections



Aerts R et al. Front. Cell. Infect. Microbiol. 2022.

What’s next for the future?

- Cf the talk of Pr Maertens

Conclusion

- Hematology disorders are associated with invasive fungal infection
- Evolution of the treatments changes the epidemiology and population at risk
- Prophylaxis and pre-emptive should be discussed
- Aggressive and quick treatment is important
- Resistance is increasing ! So stay tune