Novità nella gestione di infezioni da *Candida*

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UNIVERSITÀ DEGLI STUDI DI GENOVA

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Istituto Nazionale per la Ricerca sul Cancro

Quiz TIME!

Prof. Antonio Vena
Dott.ssa Claudia Bartalucci

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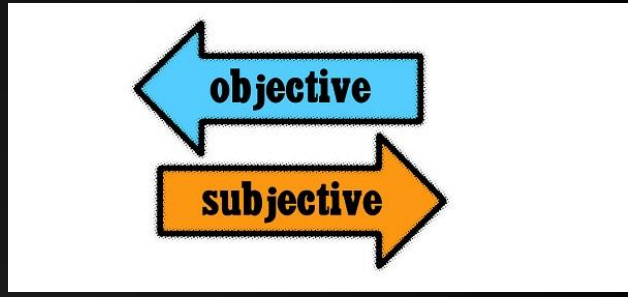
Disclosures
(past 5 years)

- Advisor/consultant/speaker bureau
  - Angelini, Gilead, Menarini, MSD, Pfizer, Shionogi, Mundipharma, Tillots, Advanz Pharma.

My selection

- PubMed
- June 2023- June 2025
- Published in English
- **Immediate practice impact**



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My selection

1. New nomenclature
2. Antifungal susceptibility testing
3. Clinical impact of antifungal resistance
4. Length of antifungal therapy
5. New antifungals

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Role of molecular-based techology in fungal nomenclature

Enhance our understanding of phylogenetic relationships both between and within species.

Correct taxonomical errors arising from the phenotypic classification

Discover more genetic differences within species, which has led to identifying and describing new genera.

Kidd S. OFID, 2023

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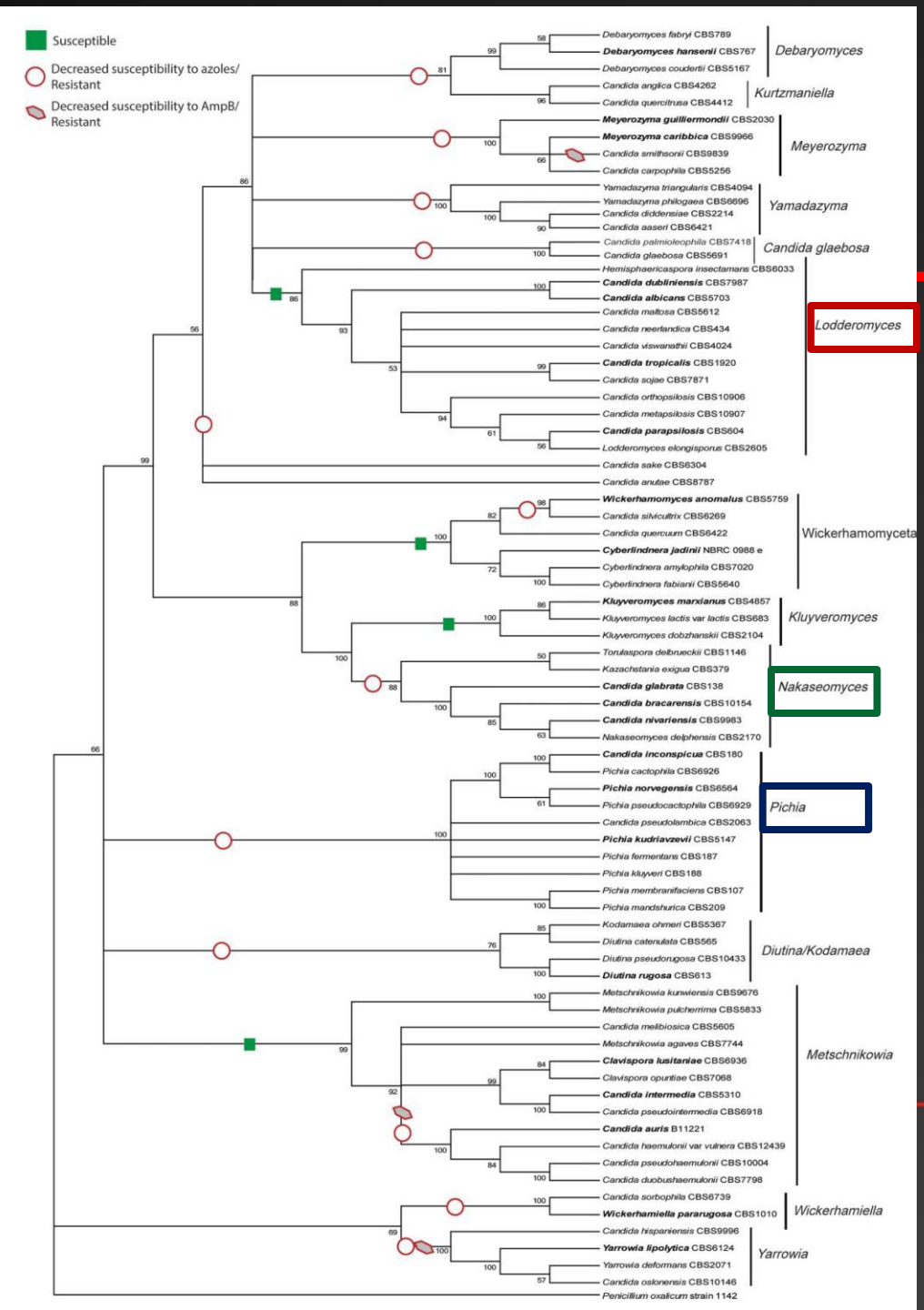

The problem of *Candida*

Highly polyphyletic group of yeasts

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New fungal nomenclature

OLD		NEW
Lodderomyces ***clade***	*Candida albicans* *Candida parapsilosis* *Candida tropicalis*	*Candida albicans* *Candida parapsilosis* *Candida tropicalis*
Pichia ***clade***	*Candida krusei*	***Pichia kudriavzevii***
Nakaseomyces ***clade***	*Candida glabrata* *Candida bracarensis* *Candida nivariensis*	***Nakaseomyces glabrata*** ***Nakaseomyces bracarensis*** ***Nakaseomyces nivariensis***
Meyerozyma ***clade***	*Candida guilliermondii*	***Meyerozyma guilliermondii***
Clavispora ***clade***	*Candida lusitaniae*	***Clavispora lusitaniae***
Diutina ***clade***	*Candida rugosa*	***Diutina rugosa***

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Antifungal susceptibility testing for intra-abdominal Candidiasis.

- Antifungal susceptibility testing is mostly conducted on blood-cultured *Candida* spp isolates.

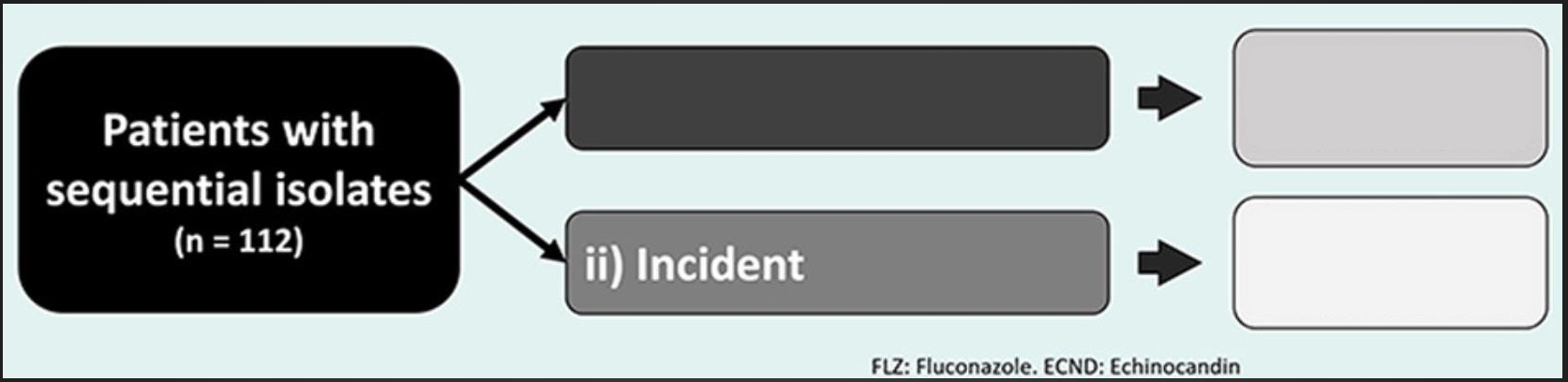
- However, the intra-abdominal cavity has been highlighted as a hidden echinocandin-resistant *C. glabrata* reservoir.

- When performed on intra-abdominal samples, it is generally common clinical practice to conduct AF susceptibility tests on the incident sample without repeating them in subsequent microbiological samples.

GAPS: no information whether testing sequential isolates from a given patients may increase the chance of detecting AF resistance

Antifungal resistance in *Candida* spp within the intra-abdominal cavity: study of resistance acquisition in patients with serial isolates

- To determine the accuracy of antifungal resistance testing, the susceptibility of **125 *initial isolates*** (the first sample of each species obtained per patient) were compared with **183 *sequential*** (obtained in subsequent sample) isolates in 112 pts with IAC.



AF was present in 18/112 (16%) patients and would have been missed in 11/18 (61%) if only initial isolates had been evaluated!

Diaz Garcia J et al. Clinical Microbiology and Infection 2023.

Take home message

As with candidemia, **follow-up specimens** of abdominal candidiasis should be sent for culture and resistance testing whenever possible.

Diaz Garcia J et al. Clinical Microbiology and Infection 2023.

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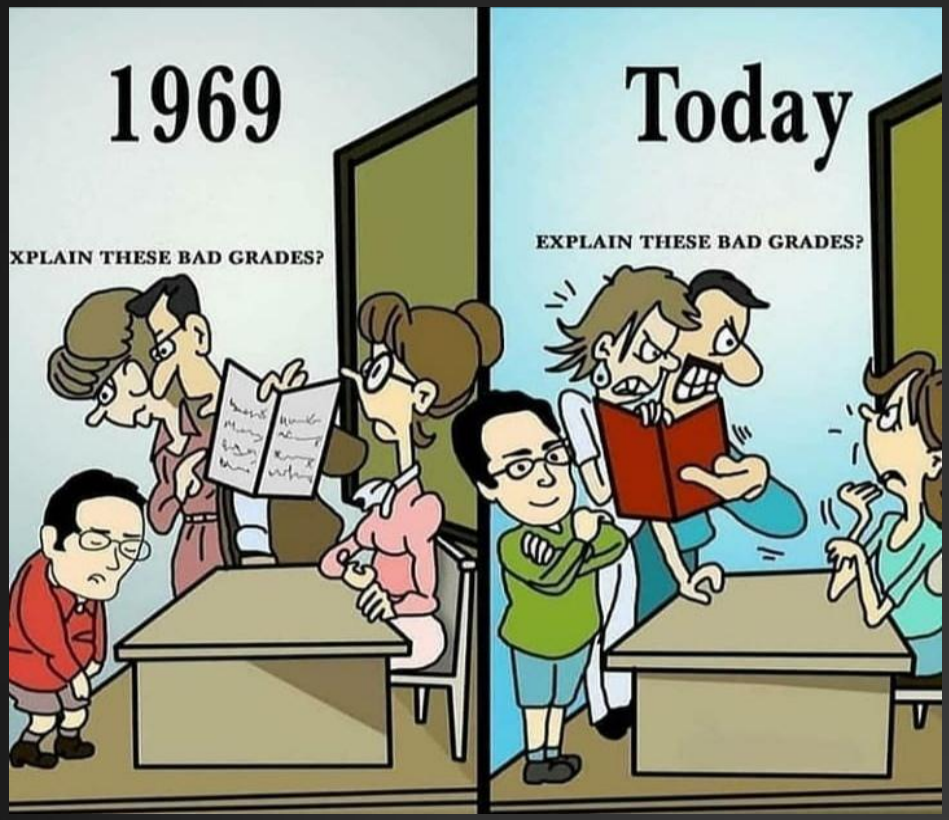
The world is changing…



Antinfungal resistance is increasing…

- Geographical location
- Use of antifungals
- Spread of resistance clones

https://www.who.int/publications/i/item/97892400602

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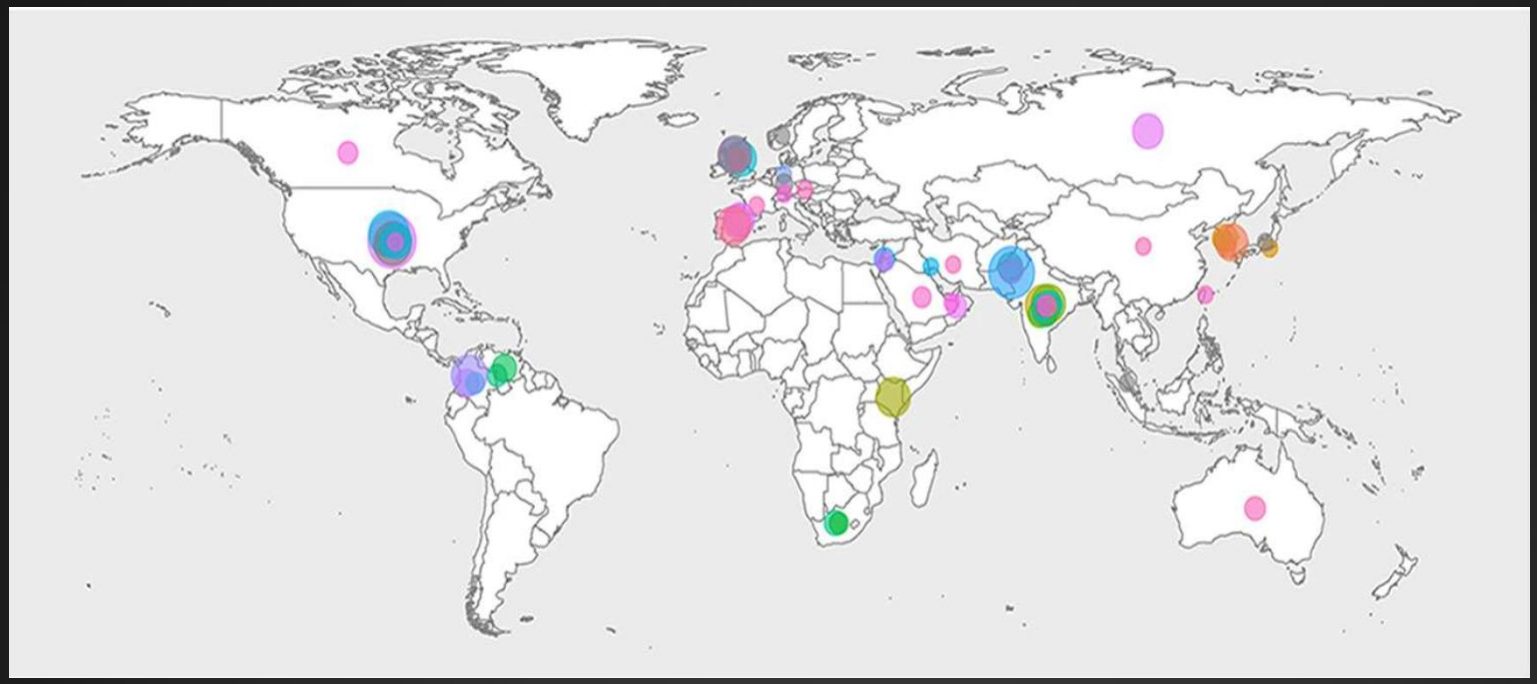
Antifungal Resistance in the Emerging Pathogen *Candida auris*



Traditionally associated with higher mortality rates

South Asian clade

San Martino hospital

- **Azoles R: 100%**
- **Amphotericin B-R: 57%**
- **Echinocandins-R: 2%**

- Two-point mutations in ERG11 and overexpression of the ABC transporter Cdr1: decreased fluconazole sensitivity.
- An amino acid substitution in FKS1: reduced sensitivity to echinocandins

Chaabane F. Front Microbiol 2019
Briano F et al. Infect Disease Therapy 2022

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Comparative Outcomes *of Candida auris* Bloodstream Infections: A Multicenter Retrospective Case-Control Study

Aim

- To compare clinical characteristics and outcomes between pts with BSIs caused by *C. auris* and those with BSIs due to other *Candida* spp. (All empirically treated with an echinocandin)

Results

- Overall, 196 pts; **83 *C. auris*** VS 113 other *Candida* species
- ***C. auris:*** ↑ ↑ ↑ admission from nursing home, length of hospital stay, COPD, dementia and prior antibiotics. ↓↓↓ prior surgery and total parenteral nutrition.

	Patients, No. (%)				
Outcome	*Candida auris* (n = 83)	Other *Candida* spp. (n = 113)	*P* Value	aOR (95% CI)	*P* Value
30-d mortality rate	25 (30.1)	44 (38.9)	.20	1.014 (.563–1.828)	.96
In-hospital mortality rate	37 (44.6)	48 (42.4)	.76	1.40 (.787–2.489)	.25
90-d mortality rate	37 (44.6)	53 (46.9)	.75	0.863 (.478–1.558)	.62
14-d clinical failure	21 (25.3)	36 (31.9)	.32	1.28 (.698–2.364)	.42
60-d microbiologic recurrence	8/67(11.9)	3/75 (4.0)	.08	4.461 (1.033–19.263)	.04
Sequelae of candidemia					
Endophthalmitis	0 (0)	2 (1.8)	.51	…	…
Persistently positive blood cultures	9 (10.8)	22 (19.5)	.10	…	…
Endocarditis (confirmed)	2 (2.4)	3 (2.7)	>.99	…	…
Endocarditis (probable)	4 (4.8)	2 (1.8)	.24	…	…

NS

Mortality due to *C. auris* fungemia IS NOT higher in comparison to other *Candida* spp

Journal of Fungi J.Fungi 2023 MDPI

Article

Mortality Caused by *Candida auris* Bloodstream Infections in Comparison with Other Candida Species, a Multicentre Retrospective Cohort

Cynthia Ortiz-Roa [1], Martha Carolina Valderrama-Rios [1], Sebastián Felipe Sierra-Umaña [2], José Yesid Rodríguez [3], Gerardo Antonio Muñetón-López [4], Carlos Augusto Solórzano-Ramos [4], Patricia Escandón [5], Carlos Arturo Alvarez-Moreno [1] and Jorge Alberto Cortés [1,6,*]

Journal of Fungi J.Fungi 2023 MDPI

Brief Report

The Mortality Attributable to Candidemia in *C. auris* Is Higher than That in Other *Candida* Species: Myth or Reality?

Carlos A. Alvarez-Moreno [1,*], Soraya Morales-López [2], Gerson J. Rodriguez [3], Jose Y. Rodriguez [3], Estelle Robert [4], Carine Picot [4], Andrés Ceballos-Garzon [4,5], Claudia M. Parra-Giraldo [5] and Patrice Le Pape [4]

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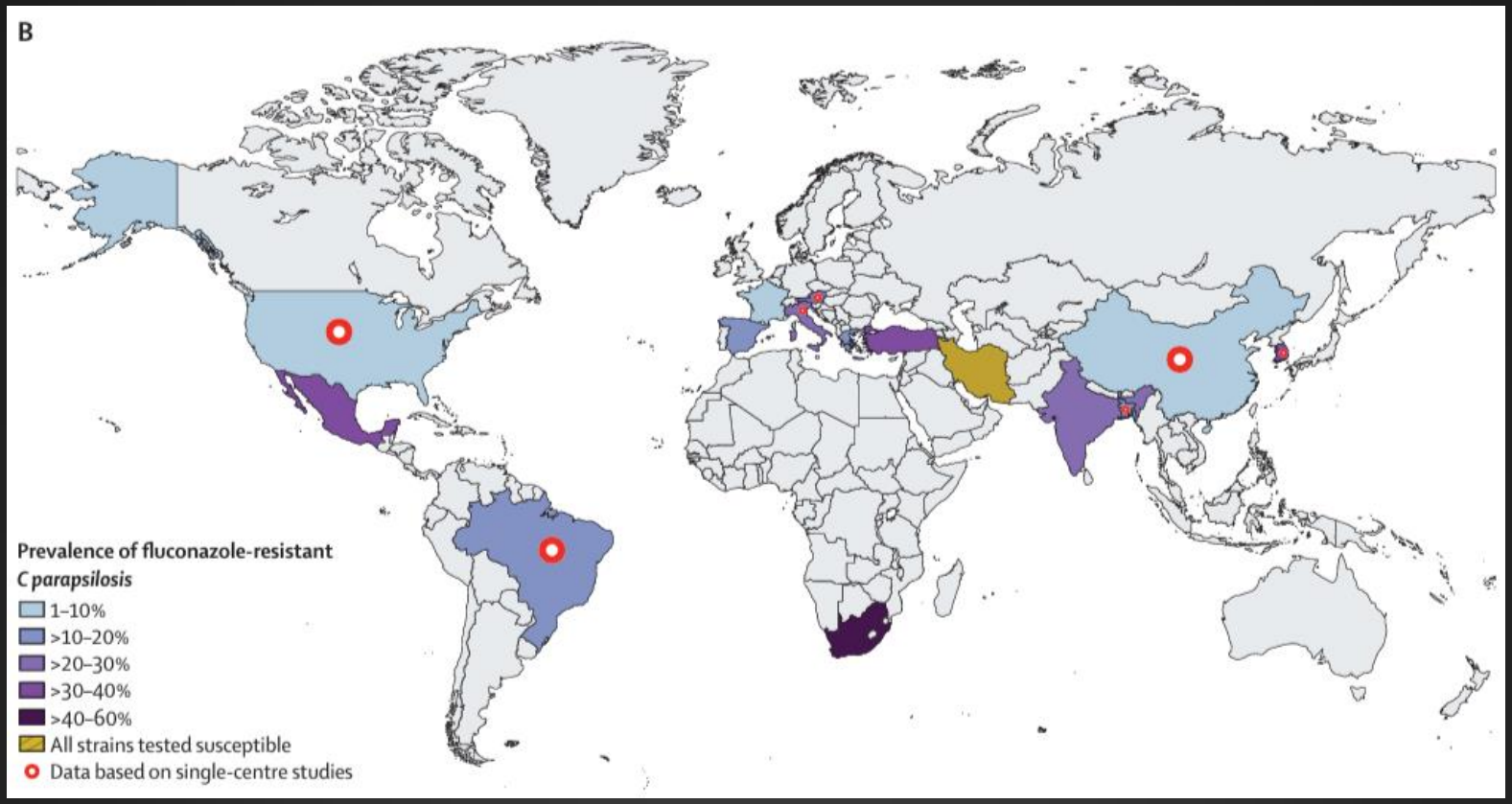
What about azole resistant *Candida parapsilosis?*



Higher mortality rates (50–63.8% vs 16.1–20%) than infection with fluconazole-susceptible strains

Candidemia at my hospital

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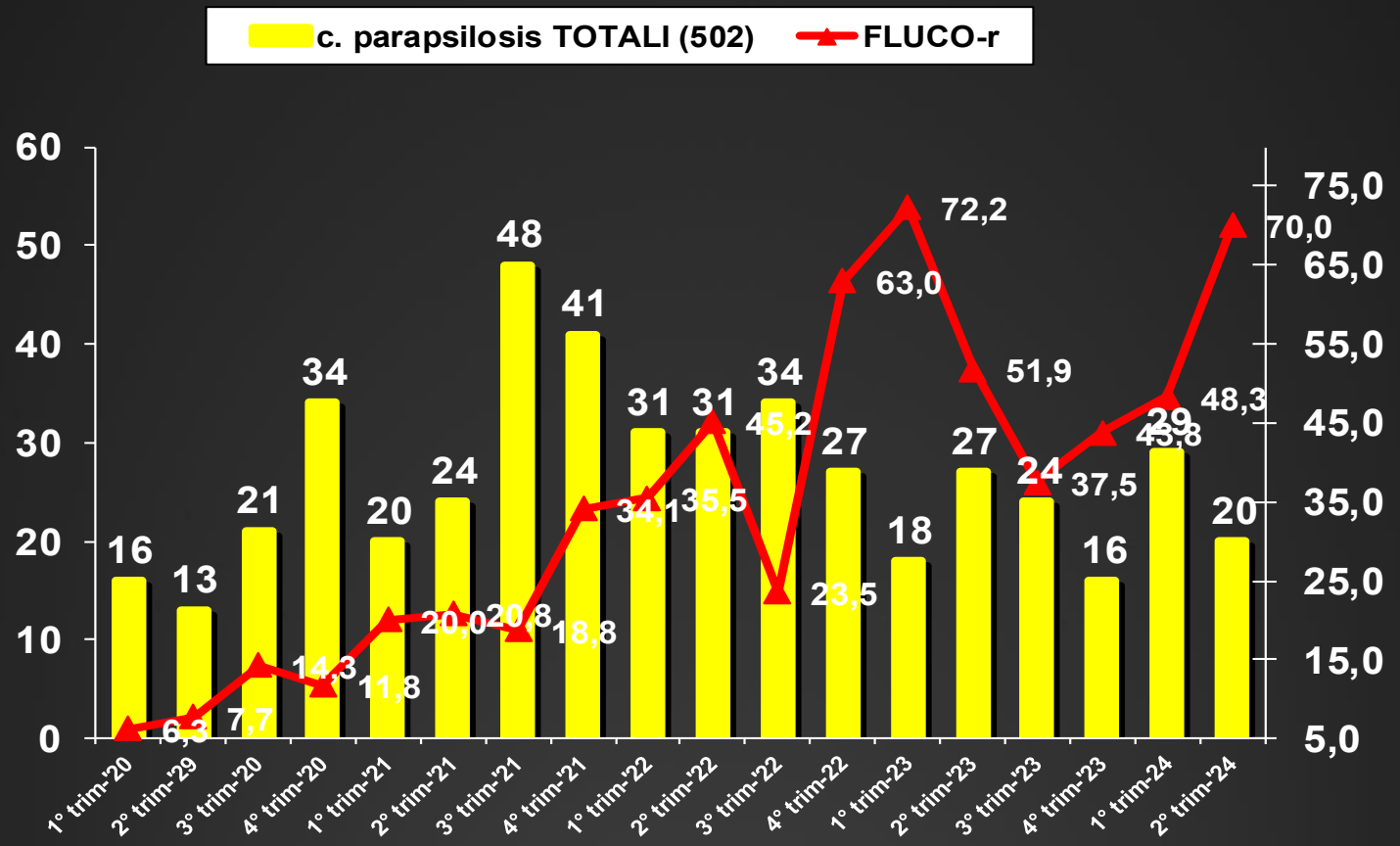
% of fluconazole-R *Candida parapsilosis*
San Martino Hospital



Vena A. personal data.

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Fluconazole resistance and mortality in candidemia due to *Candida parapsilosis*

Aim: To compare mortality in patients with FLUCO-S vs FLUCO-R *C.parapsilosis* fungemia (Madrid, Genova, Pisa)

457 pts with fungemia caused by *C. parapsilosis*

Fluco-R CP: 196/457 patients (42.8%)

All patients were adequately and definitively treated with echinocandins.

Fluco- S CP: 261/457 patients (57.2%)

Definitive treatment:
103/261 fluconazole vs
158/261 echinocandins

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Vena A, Tiseo G, Falcone M, Bassetti M.
Accepted in Clinical Infectious Disease 3 December 2024

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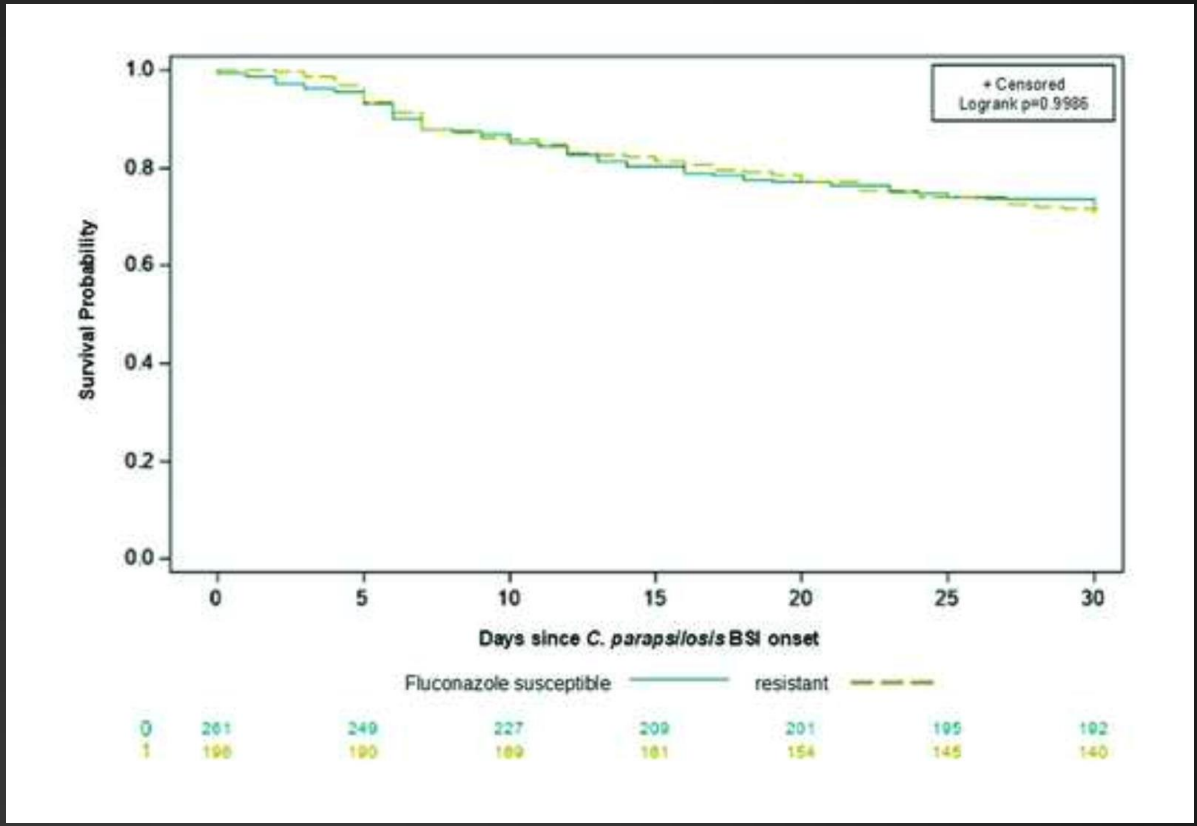
30-day survival rate

Survival rate 0.75 (95%CI: 0.69-0.80) Fluco-S vs 0.74 (95%CI: 0.67-0.79) for Fluco-R



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Adequate lenght of antifungal therapy

- A minimum of 14 days of antifungal therapy after the first negative blood cultures is recommended for patients with uncomplicated candidemia (eg, episodes w/o metastatic spread to other organs).

- However, adequate duration of antifungal therapy in *Candida* BSI is a neglected topic in the medical literature.

- **Limitations of available evidence:**
  - Old studies
  - Mainly related to randomized controlled trials not specifically designed to address this issue

Results (I)

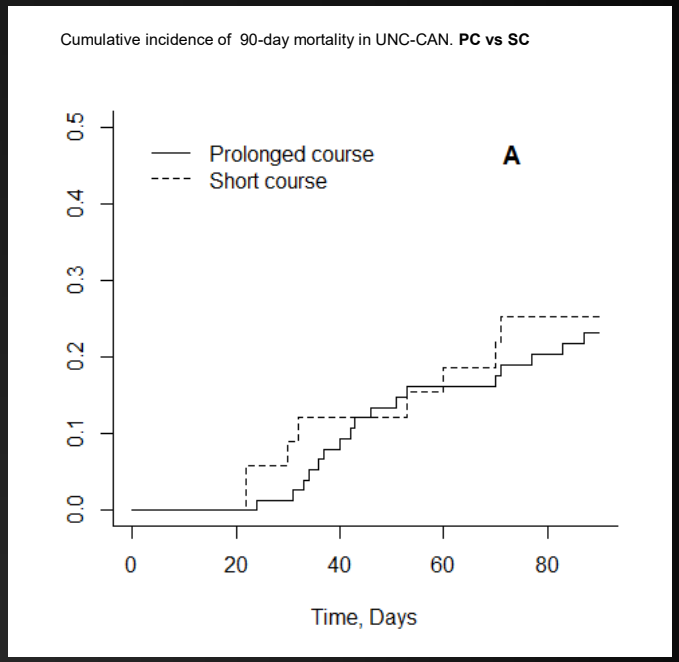
Clinical characteristics and Primary endpoint

- **Study design**: Retrospective single-center study including adult patients with UNC-CAN (2018-20).
- **Variable exposure :** duration of AF therapy dichotomized as Short (5-11 days) or prolonged (12-24 days).
- **Primary endpoint**: 90-day mortality

	Univariable analysis		Multivariable analysis		IPTW-adjusted HR	
Primary Endpoint	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
All cause 90-day mortality	0.87 (0.38-2.02)	0.75	0.45 (0.14-1.46)	0.18	0.60 (0.28-1.30)	0.20

Primary endpoint: 90-day mortality

All-cause 90-day mortality: **21.5%** (17/79) patients in the PC-group VS **22.9%** (8/39) in the SC group.



Secondary endpoints

1-year recurrent *Candida* BSI

1-year all cause mortality

We need a randomized controlled trial!

Vena. A. et al. OFID 2023

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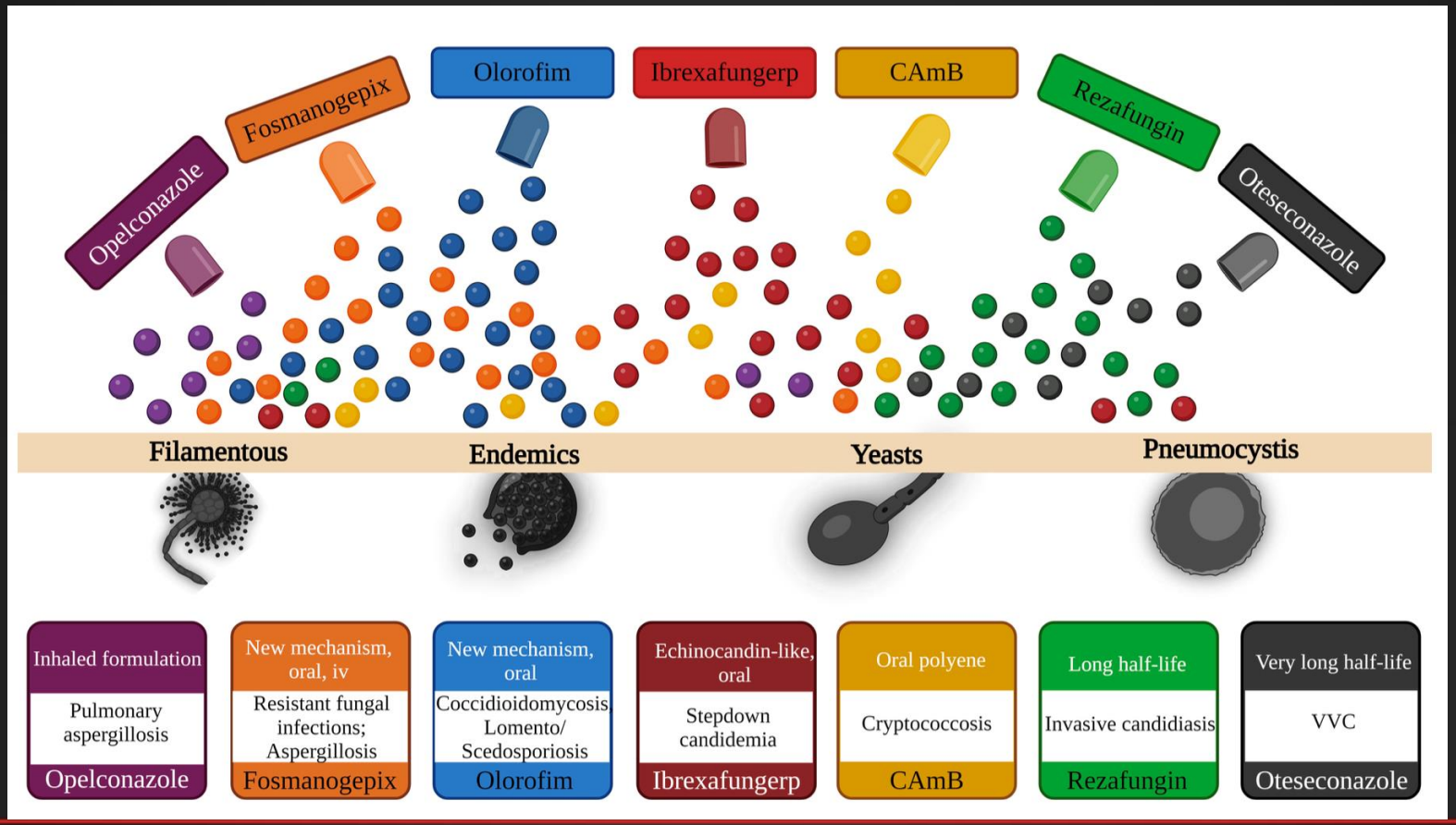
New antifungals per pathogens



Briano F et al. Infect Disease Therapy 2022

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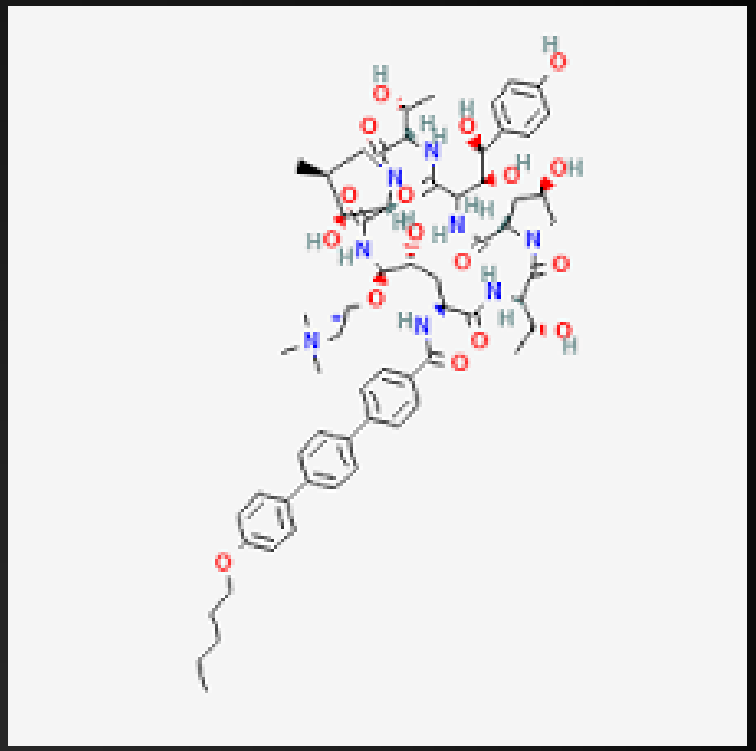
Rezafungin

- Long-acting new generation echinocandin
- **IV once weekly** (half-life>150 h)
- Allows high exposure > better treatment of less susceptible pathogens/ Sites that are more difficult to treat (e.g. IAC?)
- No evidence of serious adverse effects
- No clinically relevant DDI in in a pharmacokinetic study with nine drugs

Chemically related to anidulafungin



Ham Yy et al. Future Microbiol. 2021

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Cornely O.A et al. 2025 the Lancet Infectious Diseases 2025

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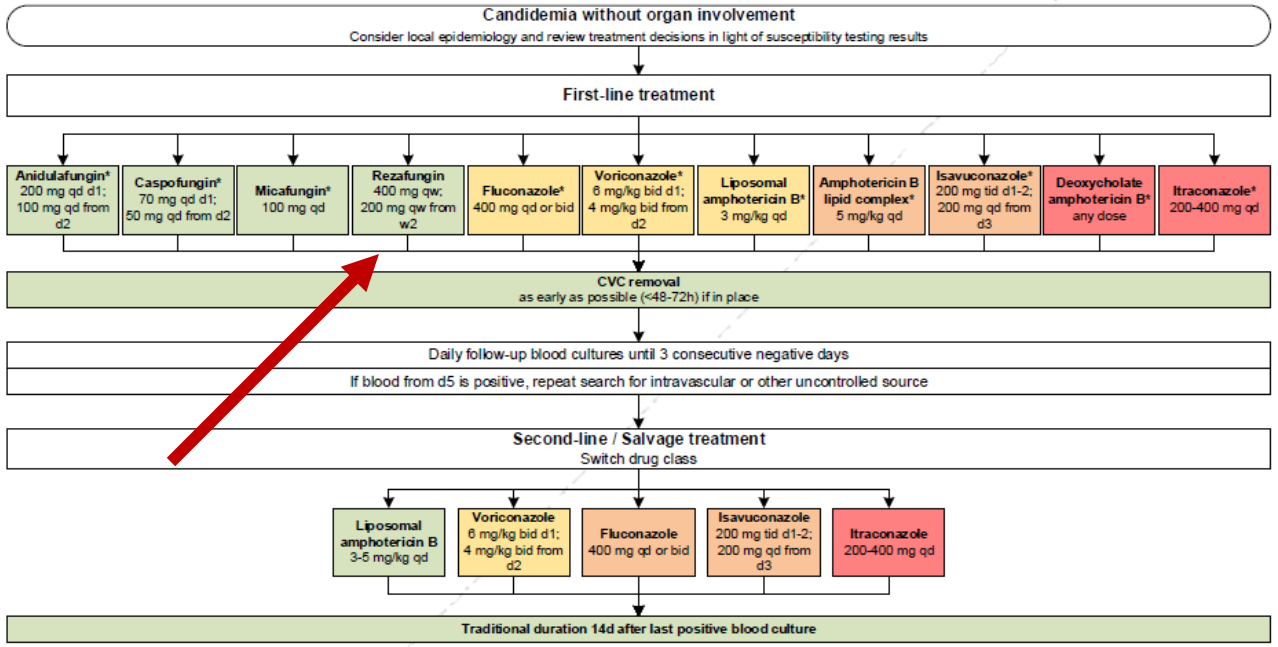
Candidemia 1° line treatment: all drugs available

‡

Echinocandins (including REZA) are strongly recommended as **first-line treatment of candidaemia**.

Cornely O.A et al. 2025 the Lancet Infectious Diseases 2025

Figure 11. Optimal treatment pathway for candidaemia without organ involvement in adults when all treatment modalities and antifungal drugs are available.



The recommended duration of treatment of uncomplicated candidaemia is 14 days from the first day of persistently negative blood cultures.

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Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial

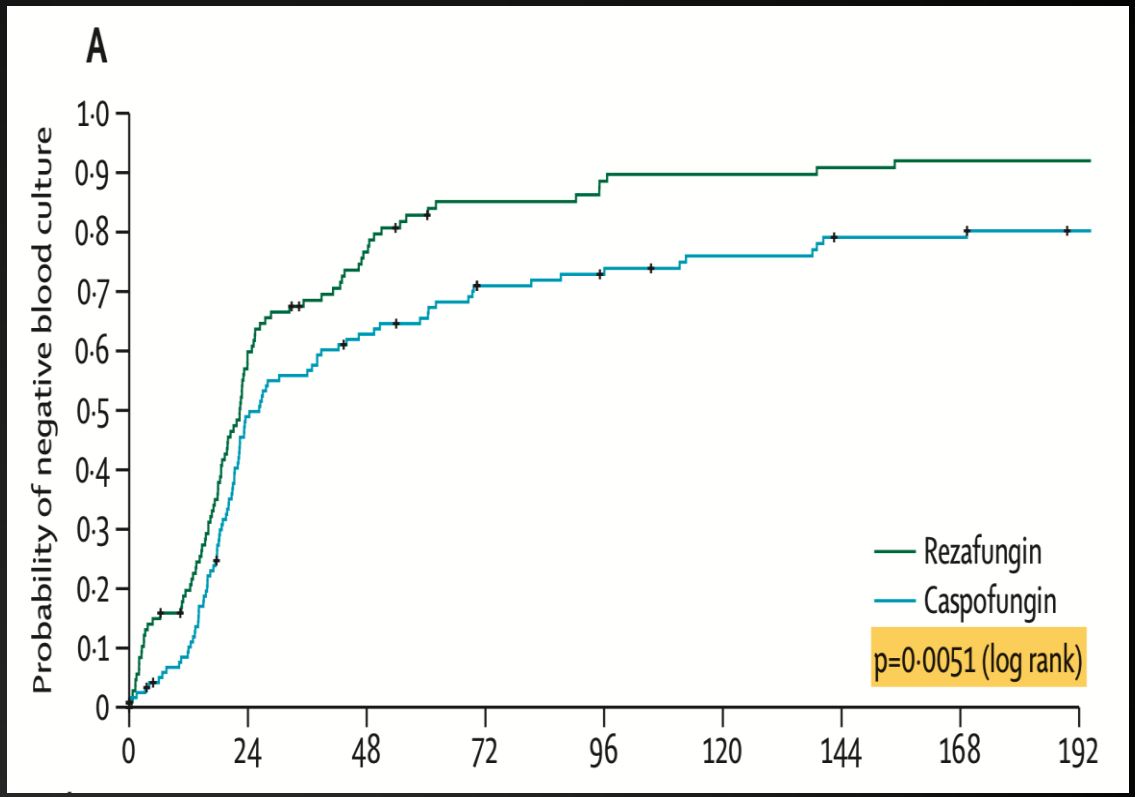
EMA endpoint: Clinical cure+ radiological cure for those with IC + mycological eradication

	Rezafungin group (n=93)	Caspofungin group (n=94)	Treatment difference (95% CI)
All-cause mortality at day 30 (US FDA primary outcome)			
Died	22 (24%)	20 (21%)	2·4 (−9·7 to 14·4)*
Known to have died	19 (20%)	17 (18%)	..
Unknown survival	3 (3%)	3 (3%)	..
All-cause mortality at day 30 by diagnosis			
Candidaemia only	18/64 (28%)	17/67 (25%)	2·8 (−12·5 to 18·0)*
Invasive candidiasis	4/29 (14%)	3/27 (11%)	2·7 (−16·7 to 21·7)*
Global response at day 14 as assessed by DRC (EMA primary outcome)			
Cure	55 (59%)	57 (61%)	−1·1 (−14·9 to 12·7)†
Failure	28 (30%)	29 (31%)	..
Indeterminate	10 (11%)	8 (9%)	..

Rezafungin: Front-Loaded Dosing for Optimized Therapeutic Efficacy

Pooled Analysis STRIVE+ RESTORE

- Mycological eradication at day 5 was significantly higher in rezafungin group (73% vs 65%)
- FU- BC suggested that REZ may be associated with a shorter time to negative BC than
- Safety were similar across group (<3%)



Thompson III G. et al. Lancet Infectious Disease 2023

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Lenght of hospital and ICU stay in pts with IC and Candida BSI treated with rezafungin vs Caspofungin

Post hoc pooled exploratory analysis of LOS for hospital and intensive care unit stays in ReSTORE and STRIVE trial.

- 294 patients (rezafungin 139, caspofungin 155); 126 (43%) ICU admission

	REZA	CASPO	Absolute difference	Relative risk
Hospital LOS unadjasted (SD), days	25.2 (19.26)	28.3 (20.16)	**3.1**	1.12 (95% CI 0.94–1.33)
Unadjasted Mean ICU (SD)	16.1 (15.2)	21.6 (18.0)	**5.5**	1.34 (95% CI 0.96, 1.86)
Adjusted mean ICU (95% CI), days	17.3 (13.4–20.6)	21.4 (17.3–26.8)	**4.1**	1.24 (95% CI 0.89–1.72)

Physicians would have considered earlier discharge for 16% of patients (30/187) with weekly rezafungin, an average of 5–6 days earlier.

Costs

- Cost of hospitalization: €700 /day in an ID ward
- Average length of stay: 5–6 d per patient
- Potential cost savings per patient: €3,500–€4,200
- Annual savings estimate: €168,000 per year (based on 40 cases/year→ 16% of 250)
- Equivalent savings: Salary of 2,3 ID physicians annually!

Thank you

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New fungal nomenclature

Managing Change is the Name of the Game

***Candida* is the most frequent IFI, worldwide.**

- No current guidelines for micro lab on implementing changes
- Will clinicians disregard the 'familiar nomenclature'?
- What about the potential for misinterpretation of lab reports when unfamiliar species names are used?

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Conclusions

- When patients receive proper antifungal therapy active *in vitro*, IFI due to antifungal-resistant strains do not appear to be associated with increased risk of mortality.

- Nevertheless, resistance could have a significant impact in terms of:
  - Recurrence of infection
  - Empirical therapeutic choices in a given hospital setting.
  - Increased costs
  - Side effects/drug drug interactions
  - Length of hospital stay (lack of oral medications)