Candidemia: diagnostica innovativa e nuovi approcci terapeutici

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Conflicts of interest

- Investigator-initiated grants (Pfizer, Gilead Italia, bioMérieux, Tillotts pharma, Shionogi, Menarini, Advanz Pharma)
- Personal fees for speaker/consultant (Pfizer, Tillotts Pharma, bioMérieux, Menarini, Advanz Pharma)

Empirical therapy of candidemia

- Why to treat empirically?
- Results from RCT?
- Who to treat empirically?
- Diagnostic-driven approach
- Pre-emptive approach

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Background

- Candidemia vs. deep-seated candidiasis vs. both
- Candidemia is the most common form of IC (~7 episodes per 1000 ICU patients), with 30-day mortality >40%
- Intra-abdominal candidiasis (IAC) accounts for most cases of deep-seated candidiasis

Bassetti M, et al. Crit Care. 2019;23(1):219.
Kett DH, et al. Crit Care Med. 2011;39(4):665–70.
Bassetti M, et al. Intensive Care Med. 2015;41(9):1601–10.
Bartalucci C, et al. Current Fungal Infection Reports (2024) 18:136–145

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Effect of delay in treatment (observational)

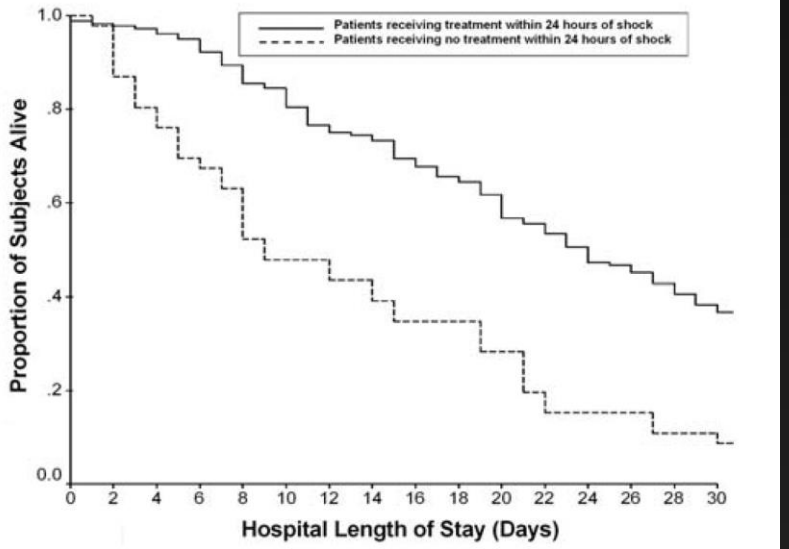

Figure 1. Kaplan-Meier curves comparing patients who received antifungal therapy within 24 hours of the onset of septic shock and those who received no antifungal therapy within 24 hours of the onset of septic shock ($P < .001$; log-rank test).

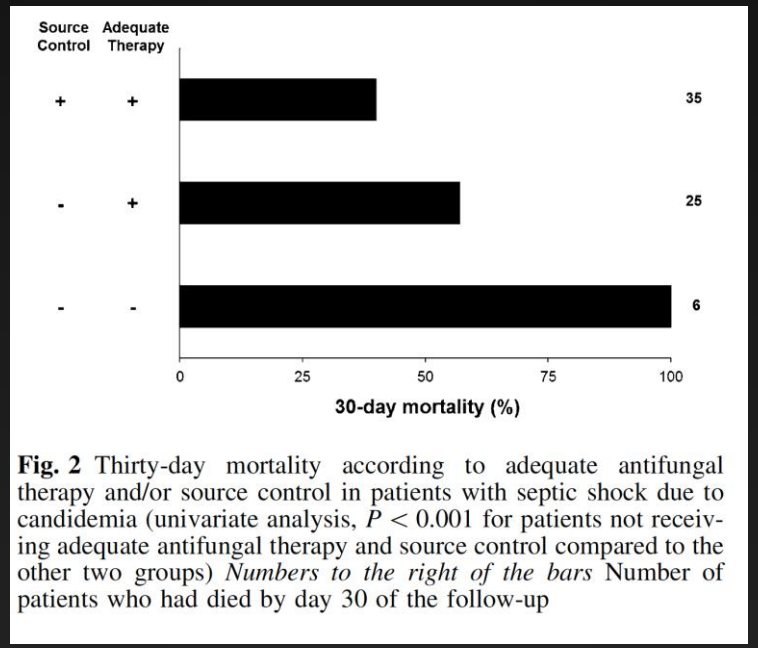

Fig. 2 Thirty-day mortality according to adequate antifungal therapy and/or source control in patients with septic shock due to candidemia (univariate analysis, $P < 0.001$ for patients not receiving adequate antifungal therapy and source control compared to the other two groups) *Numbers to the right of the bars* Number of patients who had died by day 30 of the follow-up

Kollef M, et al. Clin Infect Dis. 2012;54(12):1739–46..

Labelle AJ, et al. Crit Care Med. 2008;36(11):2967–72.

Bassetti M, et al. Intensive Care Med. 2014;40(6):839–45

Morrell M, et al. Antimicrob Agents Chemother. 2005;49(9):3640–5.

Garnacho-Montero et al. J Antimicrob Chemother. 2013;68(1):206–13.

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Brief (classical) diagnostic considerations

- Microscopic examination is rapid and can be helpful but a negative result does not exclude IC
- Cultures are the diagnostic gold standard but it can take several days before *Candida* is identified at species level and antifungal susceptibility test results are available
- Furthermore, are positive in only 50–70% of cases of candidemia, and even less frequently in IAC (5–20%)

Clancy CJ, et al. J Fungi. 2018;4:1.
Schelenz S, et al. Lancet Infect Dis. 2015;15(4):461–74.
Clancy CJ, et al. Clin Infect Dis. 2013;56(9):1284–92.
Bartalucci C, et al. Current Fungal Infection Reports (2024) 18:136–145

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Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, *Candida* Colonization, and Multiple Organ Failure

The EMPIRICUS Randomized Clinical Trial

- Design: Multicenter double-blind RCT in 260 nonneutropenic critically ill patients with ICU-acquired sepsis, multiple *Candida* colonization, multiple organ failure, and exposed to broad-spectrum antibacterial agents that compared empirical micafungin vs. placebo

- Primary endpoint: invasive fungal infection-free survival at day 28.

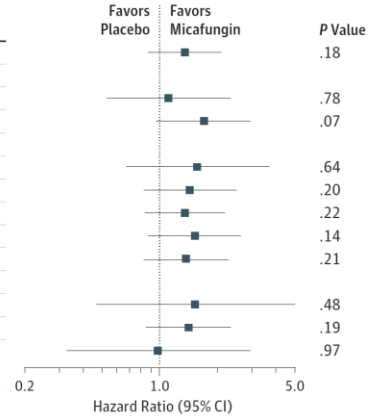
Timsit JF, et al. JAMA. 2016;316(15):1555–64.

Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, *Candida* Colonization, and Multiple Organ Failure

The EMPIRICUS Randomized Clinical Trial

Figure 2. Comparison of Fungal Infection–Free Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups

	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	*P* Value
All patients	87	128	74	123	1.35 (0.87-2.08)	.18
SOFA score						
≤8	51	66	52	68	1.11 (0.53-2.33)	.78
>8	36	62	22	55	1.69 (0.96-2.94)	.07
Admission category						
Surgical	22	34	16	31	1.56 (0.67-3.70)	.64
Medical	65	94	58	92	1.43 (0.83-2.50)	.20
Colonization index ≥0.5[a]	68	101	58	99	1.35 (0.84-2.17)	.22
Corrected colonization index ≥0.4[b]	52	76	45	80	1.52 (0.87-2.63)	.14
Candida score ≥3	64	96	47	85	1.37 (0.83-2.27)	.21
(1-3)-ß-D-glucan, pg/mL[c]						
>250	14	21	14	25	1.52 (0.47-5.00)	.48
>80	58	91	47	84	1.41 (0.85-2.33)	.19
≤80	29	37	27	39	0.98 (0.30-2.94)	.97



All analyses are stratified by center and adjusted on parameters imbalanced between groups (ie, diabetes and body mass index).

[a] Colonization index (range, 0-1) indicates the number of positive sites colonized with *Candida* divided by the number of sites sampled.

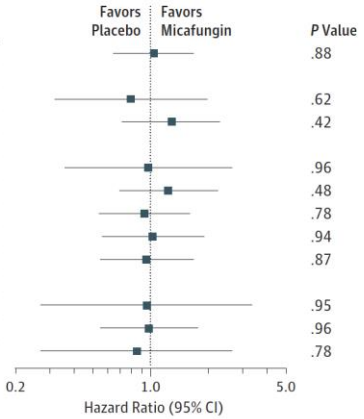
[b] Corrected colonization index (range, 0-1) indicates the number of heavily colonized sites divided by the number of sites sampled.

[c] Candida score (range, 0-5) items are surgical admission (1 point), severe sepsis (2 points), multiple sites positive with *Candida* species (1 point), and parenteral nutrition (1 point).

SOFA indicates Sequential Organ Failure Assessment.

Figure 3. Comparison of Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups

	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	*P* Value
All patients	90	128	86	123	1.04 (0.64-1.67)	.88
SOFA score						
≤8	53	66	58	68	0.79 (0.32-1.96)	.62
>8	37	62	28	55	1.28 (0.71-2.27)	.42
Admission category						
Surgical	23	34	23	31	0.97 (0.36-2.63)	.96
Medical	67	94	63	92	1.23 (0.69-2.22)	.48
Colonization index ≥0.5[a]	70	101	70	99	0.93 (0.54-1.59)	.78
Corrected colonization index ≥0.4[b]	54	76	56	80	1.02 (0.56-1.89)	.94
Candida score ≥3	66	96	58	85	0.95 (0.55-1.67)	.87
(1-3)-ß-D-glucan, pg/mL[c]						
>250	14	21	17	25	0.96 (0.27-3.33)	.95
>80	61	91	58	84	0.98 (0.55-1.75)	.96
≤80	29	37	28	39	0.85 (0.27-2.63)	.78



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Timsit JF, et al. JAMA. 2016;316(15):1555–64.

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Table 1 Primary results of randomized controlled trials evaluating the use of empirical antifungal therapy in critically ill patients with suspected invasive candidiasis

Study [ref]	Investigated strategy	Comparator/s	Primary endpoint Study population	Population of the primary analysis Study arms	No. patients achieving primary outcome/ Total (rates, %)	Effect size (% difference if not otherwise specified) (95% CI)
EMPIRICUS [49]	Empirical treatment with micafungin (100 mg q24h iv for 2 weeks)	Placebo	*Primary endpoint* Invasive fungal infection (IFI)–free survival at day 28 *Study population* Nonneutropenic, nontransplanted, critically ill patients with ICU-acquired sepsis, multiple *Candida* colonization, multiple organ failure, and exposed to broad-spectrum antibacterial agents	*Modified ITT population* Micafungin Placebo	 87/128 (68.0) 74/123 (60.2)	 HR 1.35 (0.87 to 2.08) Reference
INTENSE [50]	Empirical treatment* with micafungin (100 mg q24h iv for 6 weeks)	Placebo	*Primary endpoint* Incidence of IC *Study population* ICU patients requiring surgery for intra-abdominal infection	*Full analysis set* Micafungin Placebo	 13/117 (11.1) 11/124 (8.9)	 2.24 (– 5.52 to 10.20) Reference
Schuster et al. [51]	Empirical treatment with fluconazole (800 mg q24h iv for 2 weeks)	Placebo	*Primary endpoint* Successful outcome, defined as all of the following: resolution of fever; absence of invasive fungal infection; no discontinuation because of toxicity; and no need for a nonstudy, systemic antifungal medication *Study population* ICU patients with fever despite administration of broad-spectrum antibiotics. All patients had central venous catheters and an APACHE II score > 16	*Primary population*** Fluconazole Placebo	 44/122 (36.1) 48/127 (37.8)	 RR 0.95 (0.69–1.32)

Schuster MG, et al. Ann Intern Med. 2008;149(2):83–90.

Knitsch W, et al. Clin Infect Dis. 2015;61(11):1671–8.

Timsit JF, et al. JAMA. 2016;316(15):1555–64.

Bartalucci C, et al. Current Fungal Infection Reports (2024) 18:136–145

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Exploring European Consensus About the Remaining Treatment Challenges and Subsequent Opportunities to Improve the Management of Invasive Fungal Infection (IFI) in the Intensive Care Unit

Table 1 (continued)

No	Statement	Agreement (%)
Topic C: Initiation and change of treatment		
17	Where high clinical suspicion exists, treatment should start immediately and prior to receiving the results from any diagnostic test	94

Hoenigl M, et al. Mycopathologia. 2024 May 5;189(3):41.2025.

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- Why to treat empirically?
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Risk score based-approach

- Risk scores can be considered as early diagnostic tools when evaluating empirical antifungal therapy in ICU at the bedside of patients with signs and symptoms consistent with IC

- However, most risk factors for IC are also common among ICU patients without candidemia

- Risk scores usually have high NPV and low PPV

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Bartalucci C, et al. Current Fungal Infection Reports (2024) 18:136–145

Which risk factors to consider?

- High APACHE II score
- Diabetes mellitus
- Renal insufficiency
- Surgery (especially abdominal surgery)
- Pancreatitis
- Use of broad-spectrum antibiotics
- Parenteral nutrition
- Haemodialysis,
- Mechanical ventilation

- Presence of CVC
- Candida colonization
- Therapy with immunosuppressive agents
- …

Muskett H, et al. Crit Care. 2011;15(6):R287.
Jameran AS, et al. J Crit Care. 2021;65:216–20.
Thomas-Ruddel DO, et al. Chest. 2022;161(2):345–55.
Calandra T, et al. Crit Care. 2016;20(1):125.
Poissy J, et al. Crit Care. 2020;24(1):109.

Risk scores

- Leroy G, et al. Ann Intensive Care. 2011;1(1):50.
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- Pittet D, et al. Ann Surg. 1994;220(6):751–8.
- Paphitou ND, et al. Med Mycol. 2005;43(3):235–43.
- Ostrosky-Zeichner L, et al. Eur J Clin Microbiol Infect Dis. 2007;26(4):271–6.
- Leon C, et al. Crit Care Med. 2006;34(3):730–7.
- Ostrosky-Zeichner L. Crit Care. 2011;15(5):189.
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- Bassetti M, et al. Semin Respir Crit Care Med. 2019;40(4):524–39.
- Solomkin JS, et al. Arch Surg. 1982;117(10):1272–5.
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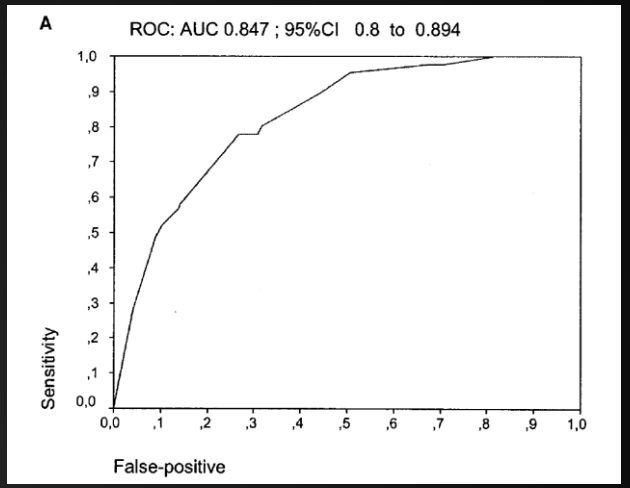
- Guillamet CV, et al. J Crit Care. 2015;30(4):715–20.
- Playford EG, et al. Clin Infect Dis. 2016;63(11):1463–9

Table 4. Calculation of the Candida score: Variables selected in the logistic regression model

Variable	Coefficient (β)	Standard Error	Wald χ^2	*p* Value
Multifocal *Candida* species colonization	1.112	.379	8.625	.003
Surgery on ICU admission	.997	.319	9.761	.002
Severe sepsis	2.038	.314	42.014	.000
Total parenteral nutrition	.908	.389	5.451	.020
Constant	−4.916	.485	102.732	.000



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Global guideline for the diagnosis and management of candidiasis: an initiative of the ECMM in cooperation with ISHAM and ASM

- The guideline group moderately recommends initiating empirical antifungal treatment for patients with septic shock or patients with deteriorating health with additional risk factors of candidaemia, such as prolonged stay at an intensive care unit, an indwelling vascular catheter, or *Candida* spp. colonisation.

Cornely OA, et al. Lancet Infect Dis 2025; 25: e280–93.

Role of AI

- Risk scores can be considered as early diagnostic tools
- AI-based models for risk: (usually) need for large dataset
- Ability to exploit complex interactions patters

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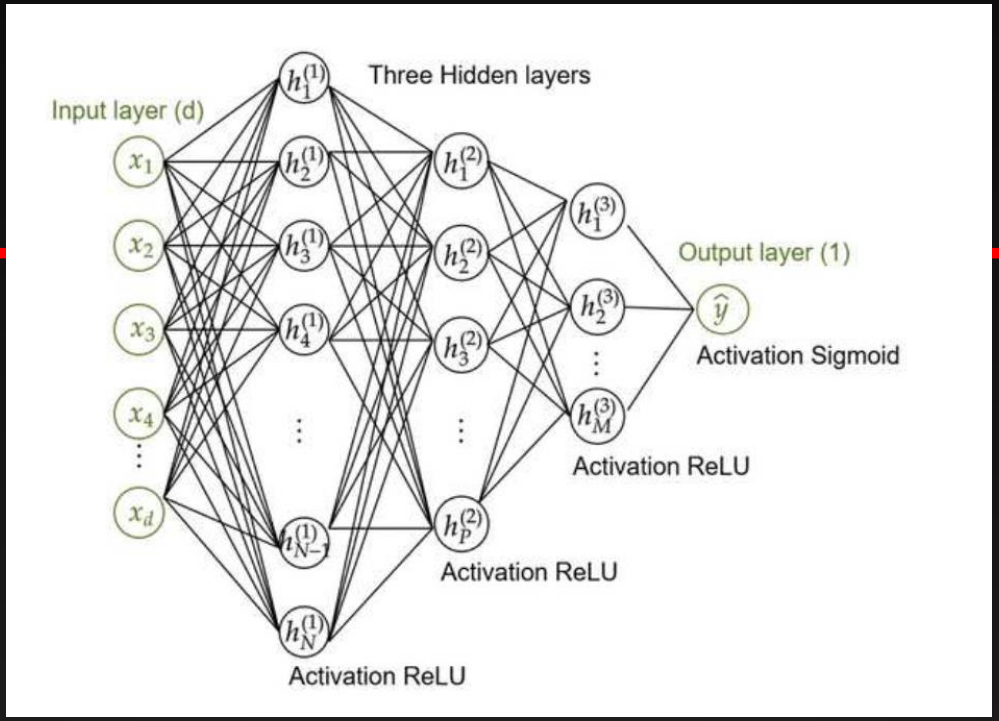
Giacobbe DR, et al. Ann Med. 2023;55(2):2285454



Model	*Sensitivity*	*Specificity*	*PPV*	*wPPV*	*NPV*	*TSS*	*AUC*
7 features	0.62 (±0.05)	0.59 (±0.04)	0.15 (±0.01)	0.85 (±0.00)	0.93 (±0.05)	0.22 (±0.02)	0.61 (±0.01)
12 features	0.62 (±0.06)	0.61 (±0.05)	0.15 (±0.01)	0.85 (±0.01)	0.93 (±0.01)	0.22 (±0.03)	0.61 (±0.01)
29 features	0.70 (±0.06)	0.58 (±0.06)	0.16 (±0.01)	0.87 (±0.00)	0.95 (±0.01)	0.29 (±0.03)	0.64 (±0.01)

Giacobbe DR, et al. Infect Dis Ther 2025. Accepted for publication.

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Fungal Ag and/or Ab based tests

- serum 1,3-β-D-glucan (BDG), combination of mannan antigen (Mn) and anti-mannan IgG antibodies (Anti-Mn), and *Candida albicans* germ tube antibody (CAGTA)

- Most studied in ICU is BDG

Giacobbe DR, et al. Mycoses. 2022 Dec;65(12):1073-1111.
Bartalucci C, et al. Current Fungal Infection Reports (2024) 18:136–145

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Theoretical gain (over empirical)

- They are expected to improve overall PPV for IC in patients with risk scores and to have a high NPV on their own

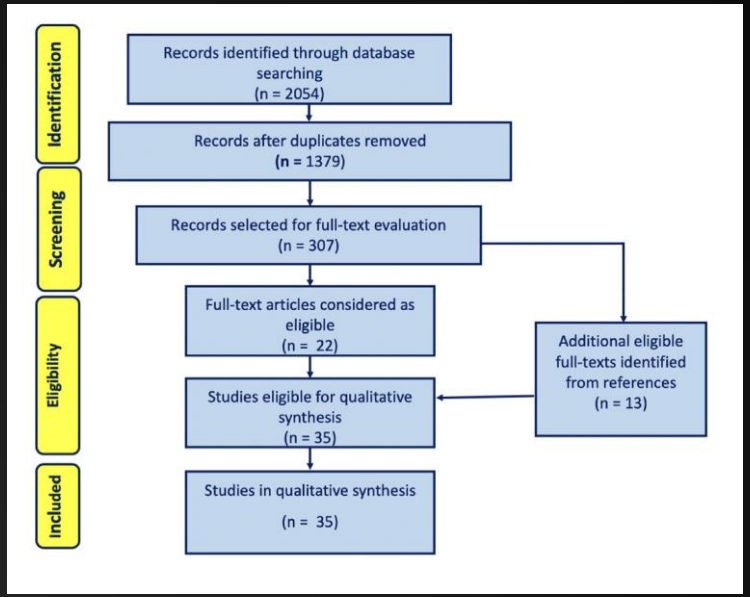
- Of importance, they confer a probability of infection and not a definitive diagnosis

Clancy CJ, et al. J Fungi. 2018;4:1.
Bartalucci C, et al. Current Fungal Infection Reports (2024) 18:136–145

Performance of existing clinical scores and laboratory tests for the diagnosis of invasive candidiasis in critically ill, nonneutropenic, adult patients: A systematic review with qualitative evidence synthesis

- Fungal antigen-based biomarkers (with most studies assessing serum BDG) showed a high NPV across studies

- The PPV of laboratory tests varies significantly according to the baseline patients' risk of IC.



Giacobbe DR, et al. Mycoses. 2022 Dec;65(12):1073-1111.

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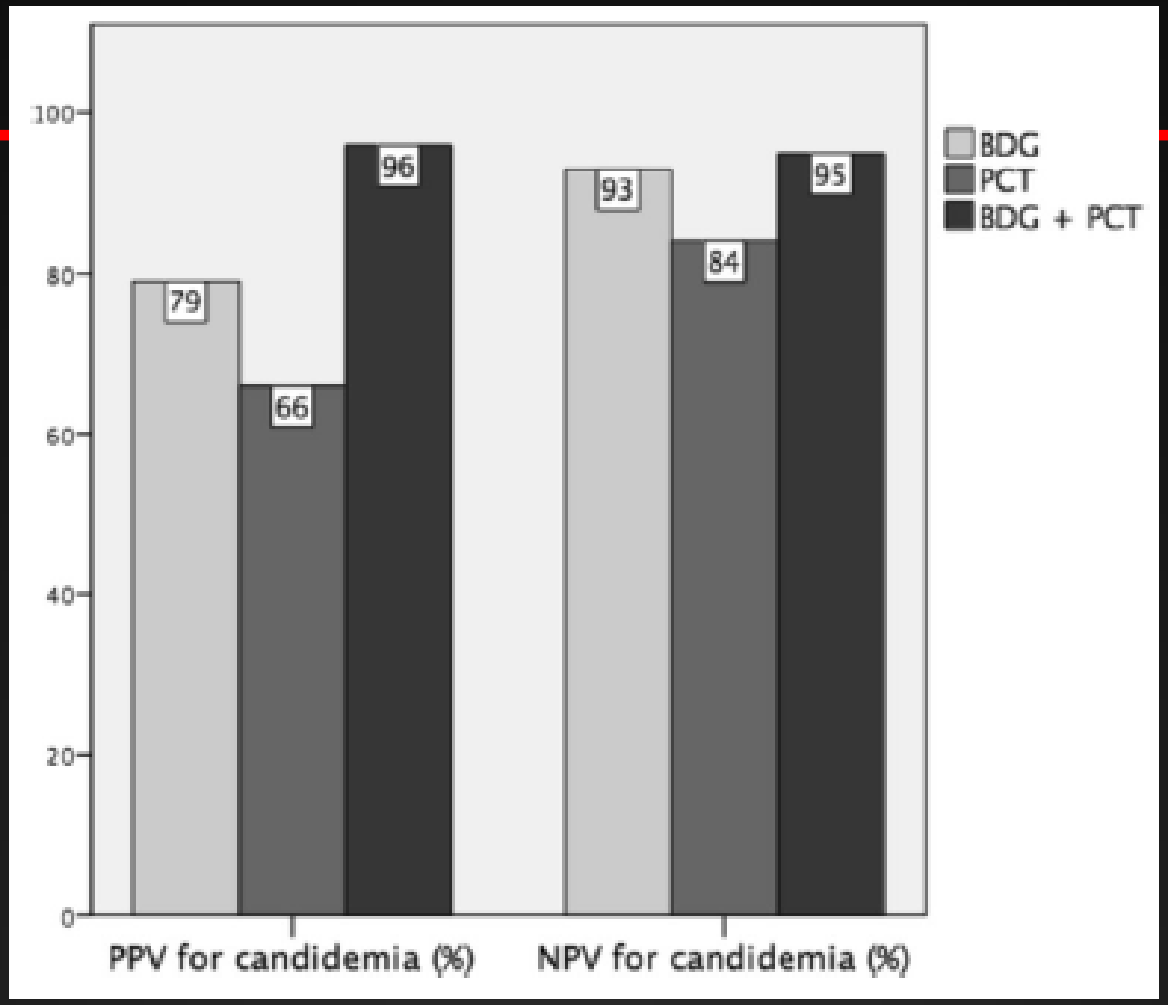
Intensive Care Med (2024) 50:502–515
https://doi.org/10.1007/s00134-024-07341-7

CONFERENCE REPORTS AND EXPERT PANEL

Invasive Fungal Diseases in Adult Patients in Intensive Care Unit (FUNDICU): 2024 consensus definitions from ESGCIP, EFISG, ESICM, ECMM, MSGERC, ISAC, and ISHAM

Matteo Bassetti[1,2*], Daniele R. Giacobbe[1,2], Christina Agvald-Ohman[3], Murat Akova[4], Ana Alastruey-Izquierdo[5,6], Sevtap Arikan-Akdagli[7], Elie Azoulay[8,9], Stijn Blot[10,11], Oliver A. Cornely[12,13,14,15], Manuel Cuenca-Estrella[5], Dylan W. de Lange[16], Francesco G. De Rosa[17], Jan J. De Waele[18], George Dimopoulos[19], Jose Garnacho-Montero[20], Martin Hoenigl[21,22,23], Souha S. Kanj[24], Philipp Koehler[12,25], Bart J. Kullberg[26], Frédéric Lamoth[27,28,29], Cornelia Lass-Flörl[30], Johan Maertens[31], Ignacio Martin-Loeches[32], Patricia Muñoz[33,34,35,36], Garyphallia Poulakou[37], Jordi Rello[38,39,40,41], Maurizio Sanguinetti[42,43], Fabio S. Taccone[44], Jean-François Timsit[45,46], Antoni Torres[47,48,49,50], Jose A. Vazquez[51], Joost Wauters[52], Erika Asperges[53], Andrea Cortegiani[54,55], Cecilia Grecchi[56], Ilias Karaiskos[57], Clément Le Bihan[58], Toine Mercier[59,60], Klaus L. Mortensen[61], Maddalena Peghin[62], Chiara Rebuffi[63], Sofia Tejada[38,41], Antonio Vena[1,2], Valentina Zuccaro[53], Luigia Scudeller[64] and Thierry Calandra[28,29] on behalf of the Study Group for Infections in Critically Ill Patients of the European Society of Clinical Microbiology and Infectious Diseases (ESGCIP), the Fungal Infection Study Group of the European Society of Clinical Microbiology and Infectious Diseases (EFISG), the European Society of Intensive Care Medicine (ESICM), the European Confederation of Medical Mycology (ECMM), the Mycoses Study Group Education and Research Consortium (MSGERC), the International Society of Antimicrobial Chemotherapy (ISAC), the International Society for Human and Animal Mycology (ISHAM), the Austrian Society for Medical Mycology (ÖGMM), the Italian Society of Anesthesia, Analgesia, Reanimation, and Intensive Care (SIAARTI), the Italian Society of Anti-Infective Therapy (SITA), and the FUNDICU Collaborators



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Giacobbe et al. Critical Care 2017

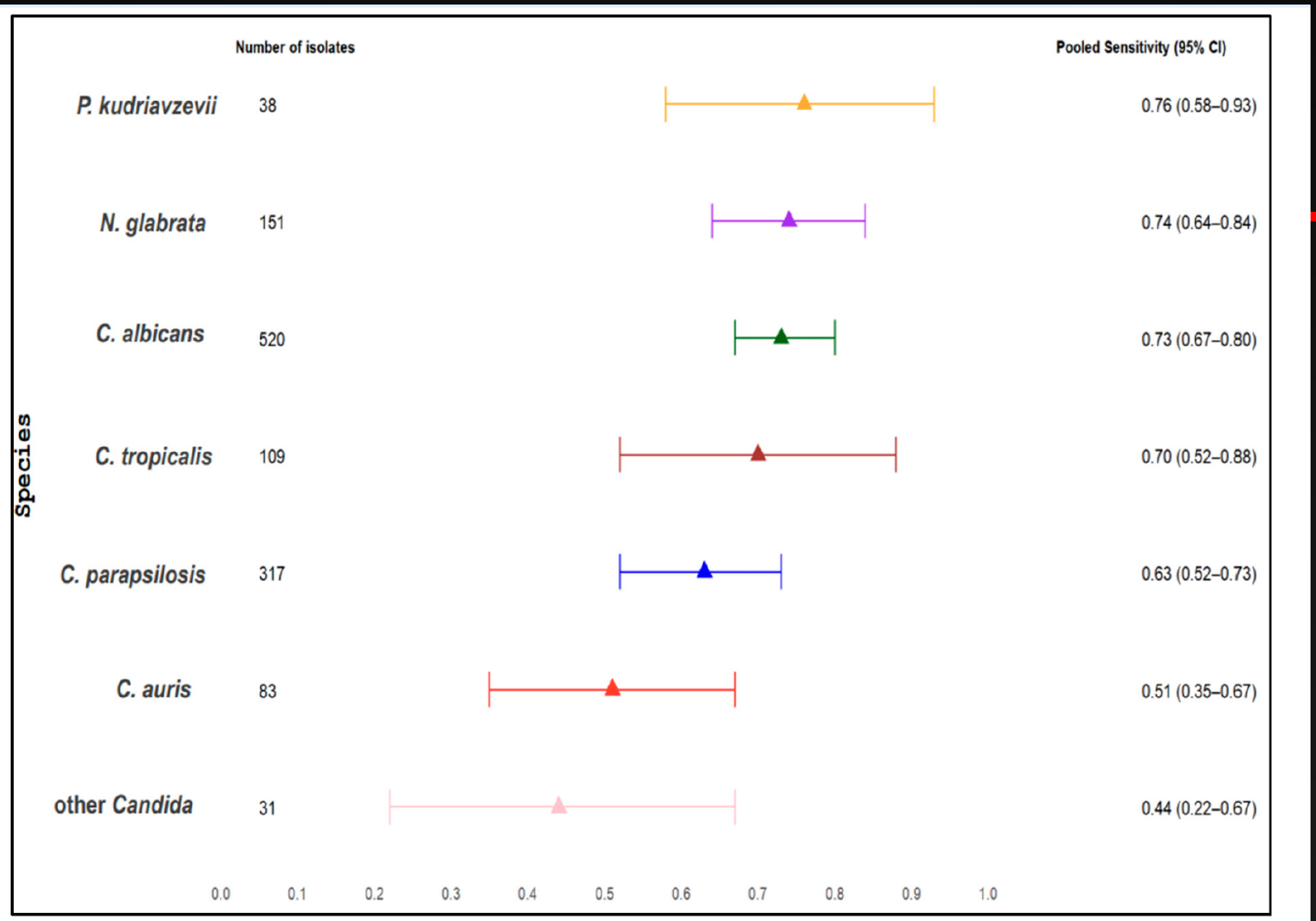
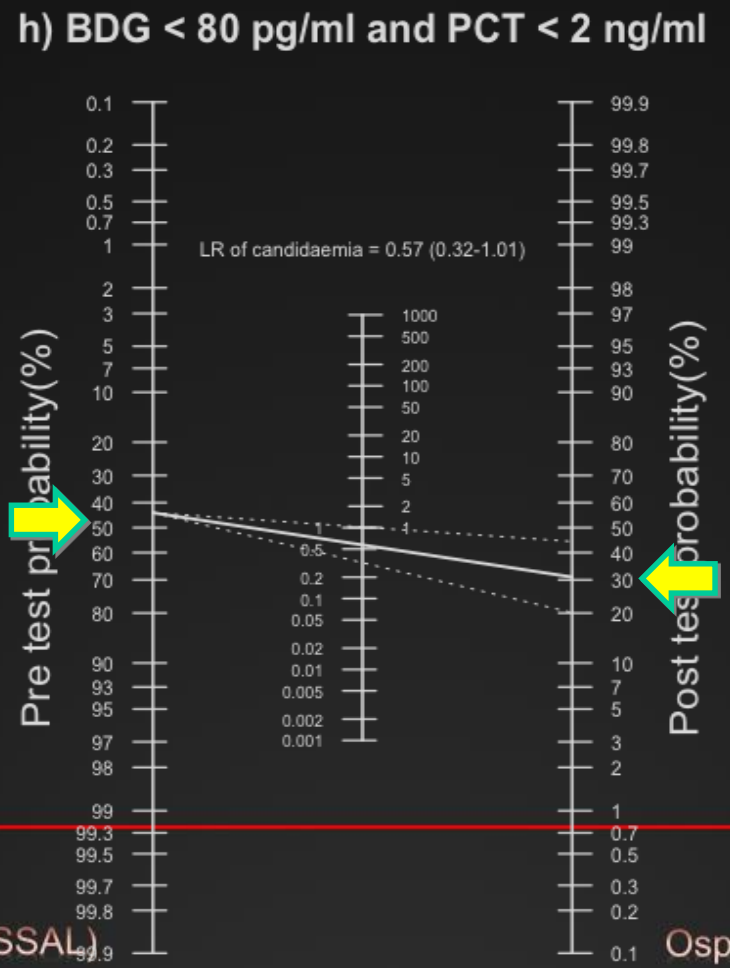


Figure 4. Pooled sensitivity of serum BDG for all *Candida* species and for all assays.

BDG + PCT

- Discordanza: BDG < 80 pg/ml e PCT < 2 ng/ml



Giacobbe et al. Critical Care 2017

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Pre-emptive approach

- Different from diagnostic-driven approach
- Conflicting observational evidence in reducing incidence of IC
- Low PPV of non-culture-based test (role of denominator)

Azoulay E, et al. Crit Care Med. 2012;40(3):813–22.

Pang YK, et al. Eur J Clin Microbiol Infect Dis. 2017;36(1):187–94

Piarroux R, et al. Crit Care Med. 2004;32(12):2443–9.

Wissing H, et al. Infect Drug Resist. 2013;6:15–25.

Bartalucci C, et al. Current Fungal Infection Reports (2024) 18:136–145

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β-D-glucan Surveillance with Preemptive Anidulafungin for Invasive Candidiasis in Intensive Care Unit Patients: A Randomized Pilot Study

- 21/45 and 5/17 evaluable patients received antifungal therapy in the pre-emptive therapy and empirical therapy arms, respectively.

- Not designed to assess relevant clinical outcomes

- Survival at ICU discharge, length of ICU stay, proportion of febrile ICU days, and days on broad spectrum antibiotics were similar in the pre-emptive and empirical therapy arms (85% vs. 81%, median 19 vs. 15 days, 8% vs. 12%, and median 3 vs. 4 days, respectively)

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Exploring European Consensus About the Remaining Treatment Challenges and Subsequent Opportunities to Improve the Management of Invasive Fungal Infection (IFI) in the Intensive Care Unit

Table 1 (continued)

No	Statement	Agreement (%)
Topic C: Initiation and change of treatment		
17	Where high clinical suspicion exists, treatment should start immediately and prior to receiving the results from any diagnostic test	94
18	Where resistance is known to be > 10% for azoles generally in the local centre, alternative choice of treatment should be considered	90

.Hoenigl M, et al. Mycopathologia. 2024 May 5;189(3):41.2025.

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Global guideline for the diagnosis and management of candidiasis: an initiative of the ECMM in cooperation with ISHAM and ASM

- There are no comparative data to support the use of specific antifungal drugs for empirical fever-driven treatment.
- An echinocandin should be used as empirical treatment of patients with septic shock, given the superiority of this class over fluconazole as a primary treatment for candidaemia

Cornely OA, et al. Lancet Infect Dis 2025; 25: e280–93.

Conclusions (diagnosis)

- Empirical therapy burdened by low PPV (i.e., difficult to restrict to the group of patients for whom it may be essential)
- Role of diagnostic-driven therapy in reducing the time window of empirical therapy
- Future AI-based approaches more on anticipating diagnosis than improving empirical therapy?

Giacobbe DR, personal opinion.

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Current scenario

- Polyenes → safety, lack of oral formulation
- Azoles → safety, drug-drug interactions, variable PK
- Echinocandins → lack of oral formulation

- Other issues → resistance, daily administration

Personal opinion

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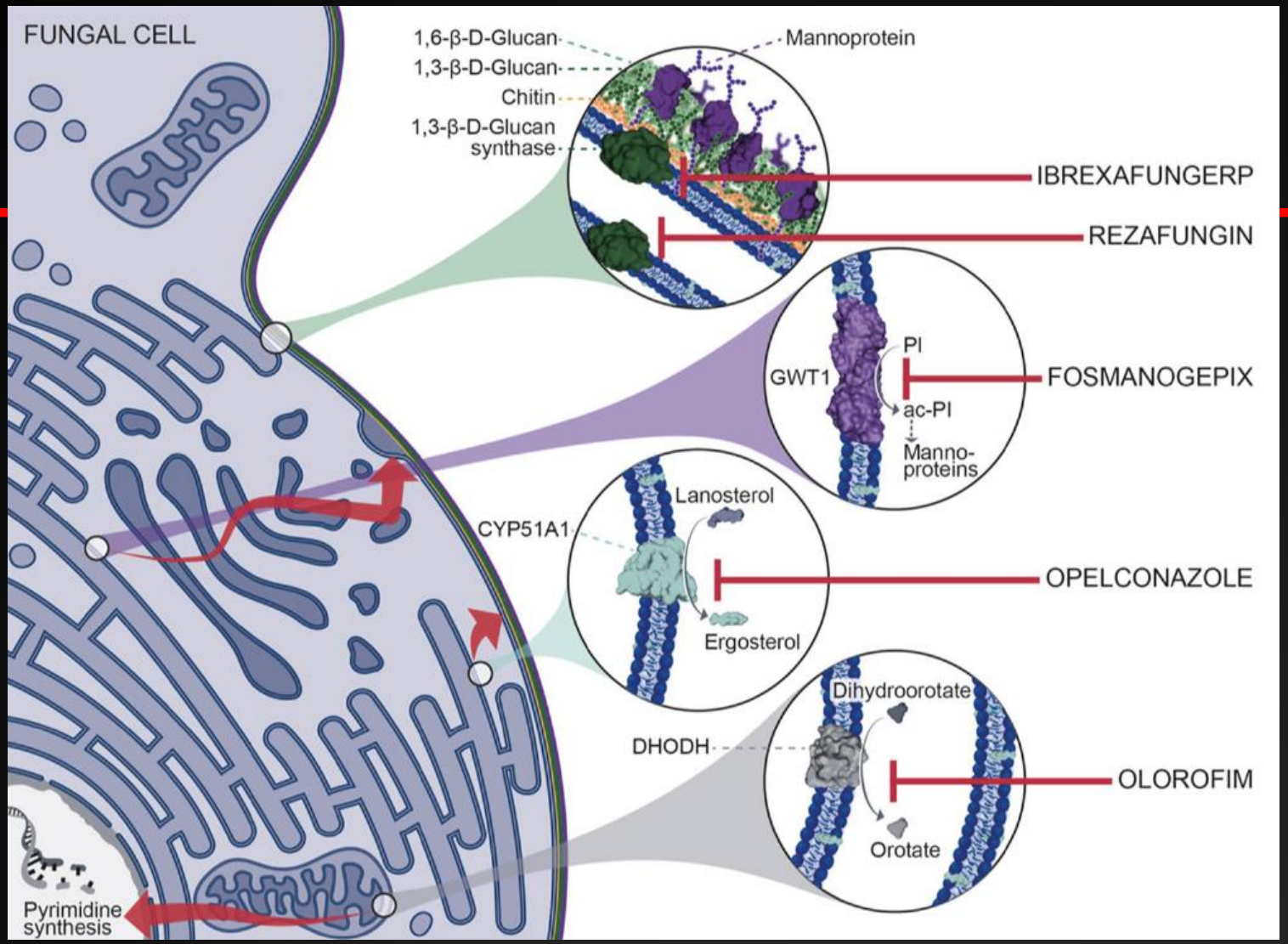
Novel antifungal agents

- Fosmanogepix
- Rezafungin
- Ibrexafungerp
- Opelconazole
- Encochleated AmB deoxycholate
- Olorofim



Novel targets

Hoenigl M, et al. Drugs 2021; 81:1703–1729

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Fosmanogepix (APX001)

- Glycosylphosphatidyl inositol anchor pathway inhibitor
- Converted to its active moiety (manogepix) by systemic phosphatases

Miyazaki M, et al. Antimicrob Agents Chemother 2011; 55:4652-4658
Watanabe NA, et al. Antimicrob Agents Chemother 2012; 56:960-971
Neoh CF, et al. Expert Rev Anti Infect Ther 2023; 21:577-594

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Fosmanogepix (APX001)

- High oral bioavailability (>90%)
- Good distribution to CNS, eye, liver, kidney, lung
- Elimination by bile/feces, minimally excreted in urine
- Weak/moderate inducer CYP2B6, CYP1A2, CYP2C19, CYP3A4
- Weak inhibitor CYP2C9, CYP2D6

Hodges MR, et al. Open Forum Infect Dis 2017; 4:S534
Mansbach R, et al. Open Forum Infect Dis 2017; 4:S472
Lee A, et al. Antimicrob Agents Chemother 2021; 65:e02476
Petraitiene R, et al. Antimicrob Agents Chemother 2021; 65:e01795
Shaw KJ, et al. J Fungi (Basel) 2020; 6:239

Fosmanogepix (APX001)

- *In vitro* activity against *Candida* spp.
  - Including *C. auris* and excluding *C. krusei*
  - Possible reduced susceptibility *C. albicans* and *C. parapsilosis* due to efflux pumps
- *In vitro* activity against other yeasts
  - *Cryptococcus* spp., *Saprochaete clavata*, *Magnusiomyces capitatus*, other
  - *Trichosporon* spp. and *Pichia norvegensis* less susceptible to manogepix
- *In vitro* activity against *Coccidioides* spp.

Viriyakosol S, et al. Antimicrob Agents Chemother 2019; 63:e01715-18
Liston SD, et al. Antimicrob Agents Chemother 2020; 64:e00220-00261
Huband MD, et al. ECCMID 2021
Pfaller MA, et al. Antimicrob Agents Chemother 2022; 66:e0102822
Pfaller MA, et al. Antimicrob Agents Chemother 2019; 63:e00840
Pfaller MA, et al. J Glob Antimicrob Resist 2021; 26:117-127
Hager CL, et al. Antimicrob Agents Chemother 2018; 62:e02319
Shaw KJ, et al. Antimicrob Agents Chemother 2018; 62:e00518-00523

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Fosmanogepix (APX001)

- *In vitro* activity against *Aspergillus* spp.
  - Including cryptic or azole-resistant
- *In vitro* activity against *Fusarium* spp.
  - *With the exception of F. verticillioides*
- Inactive against Mucorales
  - Effective in murine models of *Rhizopus* spp. infection
- *In vitro* activity against other molds
  - Including *Lomentospora prolificans*, *Scedosporium* spp., other

Gebremariam T, et al. Open Forum Infect Dis 2019; 6:S235-326
Gebremariam T, et al. Antimicrob Agents Chemother 2020; 64:e00178
Gebremariam T, et al. Open Forum Infect Dis 2017; 4:S475
Huband MD, et al. ID Week 2022; Huband MD, et al. ECCMID 2021
Pfaller MA, et al. Antimicrob Agents Chemother 2022; 66:e0102822
Pfaller MA, et al. Antimicrob Agents Chemother 2019; 63:e00840
Pfaller MA, et al. J Glob Antimicrob Resist 2021; 26:117-127
Alkhazraji S, et al. Antimicrob Agents Chemother 2020; 64:e01719-01735
Badali H, et al. Antimicrob Agents Chemother 2021; 65:e02320-02343
Jorgensen KM, et al. Antimicrob Agents Chemother 2020; 64:e00720-00730
Rivero-Menendez O, et al. J Antimicrob Chemother 2019; 74:1295-1299

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Fosmanogepix (APX001)

- Efficacy in *in vivo* models of invasive candidiasis
  - Endophthalmitis, HME, IAC, disseminated *C. auris* candidiasis
- Efficacy in *in vivo* models of cryptococcal meningitis
- Efficacy in *in vivo* models of other IFD
  - Aspergillosis, coccidioidomycosis, disseminated fusariosis

Lee A, et al. Antimicrob Agents Chemother 2021; 65:e02476
Petraitiene R, et al. Antimicrob Agents Chemother 2021; 65:e01795
Hager CL, et al. Antimicrob Agents Chemother 2018; 62:e02319
Shaw KJ, et al. Antimicrob Agents Chemother 2018; 62:e00518-00523
Viriyakosol S, et al. Antimicrob Agents Chemother 2019; 63:e01715-18
Alkhazraji S, et al. Antimicrob Agents Chemother 2020; 64:e01719-01735
Gebremarianm T, et al. Antimicrob Agents Chemother 2019; 63:e01713-18
Wiederhold NP, et al. Antimicrob Agents Chemother 2019; 63;e01120

Clinical safety and efficacy of novel antifungal, fosmanogepix, for the treatment of candidaemia: results from a Phase 2 trial

Journal of Antimicrobial Chemotherapy

- Population: 20 adults with candidemia
- Design: single-arm
- Intervention: FMGX IV 1 g BID on day one, then 600 mg IV QD
- Possible switch to oral FMGX 700 mg QD by day 4
- Primary endpoint: treatment success (survival and clearance of *Candida* from blood cultures without additional antifungals)
- Safety: No treatment-related serious adverse events/discontinuations

Pappas PG, et al. J Antimicrob Chemother 2023; 78:2471-2480

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Clinical safety and efficacy of novel antifungal, fosmanogepix, for the treatment of candidaemia: results from a Phase 2 trial

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Table 2. Efficacy endpoints: treatment success and survival

	mITT *n/N* (%) (95%CI)
Response at EOST	
Success[a]	16/20 (80) (56.3–94.3)
Failure	4/20 (20) (5.7–43.7)
Reasons for failure at EOST	
Persistent *Candida* spp. in blood cultures[b]	3/20
Death[c]	1/20
Response at EOT	
Success	15 (75.0) (50.9–91.3)
Failure[d]	5 (25.0) (8.7–49.1)
Response at 2 weeks after EOT	
Treatment success sustained	12 (60.0) (36.1–80.9)
Clinical relapse	2 (10.0) (1.2–31.7)
Death	1
Response at 4 weeks after EOT	
Treatment success sustained	11 (55.0) (31.5–76.9)
Death	1
Survival at D30	
Participant survival at D30	17/20 (85)
Median time to death (days)	15
Reasons for mortality through D30:	
Gram-negative (*Acinetobacter)* sepsis (D12)	1/20
Progression of underlying cancers (D15)	1/20
Worsening of interstitial pneumonia (D30)	1/20

Pappas PG, et al. J Antimicrob Chemother 2023; 78:2471-2480

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Clinical Efficacy and Safety of a Novel Antifungal, Fosmanogepix, in Patients with Candidemia Caused by *Candida auris:* Results from a Phase 2 Trial

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

- Population: 9 adults with candidemia by *C. auris*
- Design: single-arm
- Intervention: FMGX IV 1 g BID on day one, then 600 mg IV QD
- Possible switch to oral FMGX 800 mg QD by day 4
- Primary endpoint: treatment success (survival and clearance of *C. auris* from blood/tissue cultures without additional antifungals)
- Safety: No treatment related adverse events or study drug discontinuations were reported

Vazquez JA, et al. Antimicrob Agents Chemother 2023; 67:e0141922

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TABLE 2 Efficacy endpoints: treatment success and survival

Endpoint	Fosmanogepix *N* = 9
Response at EOST[a]	
Treatment Success[b], *n* (%) [95% CI[c]][d]	8 (88.9) [51.8, 99.7]
Treatment Failure, *n* (%)	1 (11.1)
Reasons for failure at EOST	
Death, *n* (%)	1 (11.1)
Response at 2 wks after EOST	
Treatment Success Sustained, *n* (%) [95% CI][d]	6 (66.7) [29.9, 92.5]
Clinical Relapse (Positive culture), *n* (%)	1 (11.1)
Death, *n* (%)	1 (11.1)
Response at 4 wks after EOST	
Treatment Success Sustained, *n* (%)	6 (66.7)
Survival at Day 30, *n* (%)	8 (88.9)

[a]EOST, end of study treatment.

[b]Treatment Success was defined as meeting all of the following criteria: 2 consecutive blood cultures negative for *Candida* spp. and/or for participants with a deep-seated site of infection, at least 1 negative tissue culture or aspirate/fluid culture; alive at EOST; and no concomitant use of any other systemic antifungals through EOST.

[c]CI, confidence interval.

[d]95% CIs were two-sided exact binomial CIs.

Vazquez JA, et al. Antimicrob Agents Chemother 2023; 67:e0141922

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TABLE 4 Activity of manogepix and comparators against *C. auris* baseline isolates (CLSI and EUCAST methods)[a]

	MIC (CLSI[b]/EUCAST[c]; μg/mL)					
Participant	Amphotericin	Anidulafungin	Micafungin	Fluconazole	Manogepix	Voriconazole
1	1/0.5	0.5/1	0.25/0.25	>128/>128	0.015/0.015	2/2
2	1/0.5	0.5/0.06	0.12/0.03	>128/128	0.015/0.008	2/0.5
3	1/0.5	1/2	0.25/2	128/>128	0.015/0.03	2/8
4	1/0.5	1/0.25	0.25/0.25	>128/128	0.015/0.004	2/0.5
5	1/0.5	1/0.06	0.25/0.12	>128/>128	0.008/0.008	1/1
6	1/0.5	1/0.06	0.25/0.5	>128/>128	0.015/0.008	2/1
7	1/0.5	0.5/0.12	0.25/0.25	>128/>128	0.015/0.008	2/1
8	1/0.5	0.5/0.03	0.25/0.06	>128/>128	0.008/0.004	2/4
9	1/0.5	1/0.06	0.25/0.12	>128/>128	0.015/0.008	2/1

[a]MICs of isolates collected at baseline shown for all participants.
[b]CLSI, Clinical & Laboratory Standards Institute.
[c]EUCAST, European Committee on Antimicrobial Susceptibility Testing.

Vazquez JA, et al. Antimicrob Agents Chemother 2023; 67:e0141922

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Fosmanogepix (APX001)

NCT05421858 Recruiting

A Phase 3 Efficacy and Safety Study of Fosmanogepix for the Treatment of Adult Participants With Candidemia and/or Invasive Candidiasis.

- Design: Phase 3 RCT
- Intervention: Fosmanogepix IV followed by oral fosmanogepix
- Comparator: Caspofungin IV followed by oral fluconazole

https://clinicaltrials.gov/study/NCT05421858

Ibrexafungerp (SCY-078)

- Triterpenoid
- Derivative of enfumafungin
- Inhibition of beta-(1,3)-D-glucan synthesis

Hoenigl M, et al. Drugs 2021; 81:1703–1729
Neoh CF, et al. Expert Rev Anti Infect Ther 2023; 21:577-594

Ibrexafungerp (SCY-078)

- Bioavailability from 35% to >51%
- Enhanced absorption with food
- Good distribution to kidney, lung, liver, spleen, vaginal tissue, bone marrow, skin, and skeletal muscle
- Limited distribution to SNC
- Elimination by bile/feces, minimally excreted in urine
- Low risk of DDI

Wring S, et al. Antimicrob Agents Chemother 2017; 61:e02068
Wring S, et al. Antimicrob Agents Chemother 2019; 63:e02119
Wring S, et al. Clin Pharmacol Drug Dev 2019; 8:60-69
Wring S, et al. J Clin Pharmacol 2018; 58:1305-1313
Neoh CF, et al. Expert Rev Anti Infect Ther 2023; 21:577-594

Ibrexafungerp (SCY-078)

- *In vitro* activity against *Candida* spp.
  - Including fluconazole-resistant or echinocandin-resistant *C. glabrata* and *C. auris*
  - Decreased susceptibility of *C. glabrata* with FKS2 gene substitution
  - Descreased susceptibility of *C. pararugosa*
  - Potent anti-biofilm activity against *C. auris*
- Decreased susceptibility of *Cryptococcus* spp.
- Variable activity against rare yeasts
  - Active against *P. jirovecii*

Jorgensen KM, et al. J Fungi (Basel) 2022; 8:1106
Mesquida A, et al. Clin Microbiol Infect 2022; 28:e140
Larkin E, et al. Antimicrob Agents Chemother 2017; 61:e02396
Borroto-Esoda K, et al. Open Forum Infect Dis 2020; 7:S643

Quindos G, et al. Front Celll Infect Microbiol 2022; 12:906563
Arendrup MC, et al. Antimicrob Agents Chemother 2020; 64:e02136
Pfaller MA, et al. Antimicrob Agents Chemother 2017; 61:e00161
Mesquida A, et al. Clin Microbiol Infect 2022; 28:e1154

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Ibrexafungerp (SCY-078)

- *In vitro* activity against *Aspergillus* spp.
  - Including azole-susceptible and azole-resistant *A. fumigatus*
  - Limited/reduced activity against *A. ustus* complex and *A. alliaceus*
- Inactive against *Fusarium* spp.
- Inactive against Mucorales
- *In vitro* activity against other molds
  - Only marginal activity against *Lomentospora prolificans*, *Scedosporium* spp., *Scopulariopsis* spp.

Pfaller MA, et al. Antimicrob Agents Chemother 2013; 57:1065-1068
Rivero-Menendez O, et al. J Fungi (Basel) 2021; 7:232
Lamoth F, et al. Antimicrob Agents Chemother 2015; 59:4308-4311
Ghannoum M, et al. ASM Microbe 2020

MSG-10: a Phase 2 study of oral ibrexafungerp (SCY-078) following initial echinocandin therapy in non-neutropenic patients with invasive candidiasis

Journal of Antimicrobial Chemotherapy

- Population: 27 adults with invasive candidiasis
- Design: initial IV echinocandin and then step-down to oral therapy
- Study arms: ibrexafungerp 500 mg/die (after 1 g loading dose); ibrexafungerp 750 mg/die (after 1250 mg loading dose); fluconazole (SOC)
- Safety and PK/PD: The oral ibrexafungerp dose estimated to achieve the target exposure in subjects with invasive candidiasis is 750 mg daily. This dose was well tolerated and achieved a favourable global response rate, similar to the SOC.

Spec A, et al. J Antimicrob Chemother 2019; 74:3056–3062

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MSG-10: a Phase 2 study of oral ibrexafungerp (SCY-078) following initial echinocandin therapy in non-neutropenic patients with invasive candidiasis

Journal of Antimicrobial Chemotherapy

Table 2. Global response in the ITT population of 22 patients with invasive candidiasis

	Ibrexafungerp 500 mg (*N*=7), *n* (%)	Ibrexafungerp 750 mg (*N*=7), *n* (%)	SOC		All patients (*N*=22), *n* (%)
			fluconazole (*N*=7), *n* (%)	micafungin (*N*=1), *n* (%)	
EOT					
global response	5 (71)	6 (86)	5 (71)	1 (100)	17 (77)
clinical response	5 (71)	6 (86)	5 (71)	1 (100)	17 (77)
microbiological response	6 (86)	6 (86)	6 (86)	1 (100)	19 (86)
missing	1 (14)	1 (14)	0 (0)	0 (0)	2 (9)
Week 2 post-treatment					
global response	4 (57)	4 (57)	5 (71)	0 (0)	13 (59)
clinical response	4 (57)	4 (57)	5 (71)	0 (0)	13 (59)
microbiological response	4 (57)	4 (57)	5 (71)	0 (0)	13 (59)
missing	2 (29)	3 (43)	2 (29)	1 (100)	8 (36)
Week 6 post-treatment					
global response	3 (43)	2 (29)	4 (57)	0 (0)	9 (41)
clinical response	3 (43)	2 (29)	4 (57)	0 (0)	9 (41)
microbiological response	3 (43)	2 (29)	4 (57)	0 (0)	9 (41)
missing	3 (43)	5 (71)	3 (43)	1 (100)	12 (55)

Spec A, et al. J Antimicrob Chemother 2019; 74:3056–3062

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O0514

An open-label study of ibrexafungerp in patients with refractory fungal infections (FURI)

06. Fungal infection & disease

06e. Antifungal drugs & treatment (incl pre-clinical studies and clinical trials)

O.A. Cornely[1], B.D. Alexander[2], P.G. Pappas[3], T.F. Patterson[4], M. Hoenigl[5], M.H. Miceli[6], P. Vergidis[7], A. Spec[8], G.R. Thompson[9], L. Ostrosky-Zeichner[10], R.S. Siebert[11], M. Middle[12], E. McKie[13], F. Lewis[13], D. Angulo[12].

[1]CECAD Institute of the University of Cologne - Cologne (Germany), [2]Duke University - Durham (United States), [3]University of Alabama at Birmingham - Birmingham (United States), [4]University of Texas Health San Antonio - San Antonio (United States), [5]ECMM Excellence Center for Medical Mycology, Medical University of Graz - Graz (Austria), [6]University of Michigan - Ann Arbor (United States), [7]Mayo Clinic - Rochester (United States), [8]Washington University in St. Louis School of Medicine - St. Louis (United States), [9]University of California-Davis - Sacramento (United States), [10]The University of Texas Health Science Center - Houston (United States), [11]Life Groenkloof Hospital - Pretoria (South Africa), [12]SCYNEXIS, Inc. - Jersey City (United States), [13]GSK - Stevenage (United Kingdom)

Table 2: Global response by fungal disease as determined by DRC–ITT population

Parameter	Acute IC*	Candidaemia only†	Chronic IC	OC	OPC	CMC	VVC	DF	CPA	ABPA	IPA	Other	Overall
N	61	20	43	16	14	13	32	3	6	5	29	11	233
Combination therapy used,‡ %	0	0	0	0	0	0	0	0	0	0	22 (75.9)	2 (18.2)	24 (10.3)
Response timepoint§	EOT	EOT	EOT	EOT	EOT	EOT or day 84	TOC (day 17)	EOT	EOT or day 90	EOT or day 90	EOT	EOT	–
Response,¶ n (%)													
Success	40 (65.6)	13 (65.0)	30 (69.8)	9 (56.3)	9 (64.3)	8 (61.5)	26 (81.3)	1 (33.3)	0	0	12 (41.4)	7 (63.6)	142 (60.9)
Complete/Yes**	34 (55.7)	13 (65.0)	16 (37.2)	6 (37.5)	5 (35.7)	1 (7.7)	26 (81.3)	1 (33.3)	0	0	3 (10.3)	4 (36.4)	96 (41.2)
Partial/No**	6 (9.8)	0	14 (32.6)	3 (18.8)	4 (28.6)	7 (53.8)	4 (12.5)	0	6 (100.0)	3 (60.0)	9 (31.0)	3 (27.3)	59 (25.3)
Failure	13 (21.3)	3 (15.0)	9 (20.9)	5 (31.3)	5 (35.7)	5 (38.5)	4 (12.5)	2 (66.7)	6 (100.0)	3 (60.0)	14 (48.3)	3 (27.3)	69 (29.6)
Stable	6 (9.8)	0	5 (11.6)	5 (31.3)	3 (21.4)	4 (30.8)	0	1 (33.3)	0	0	6 (20.7)	2 (18.2)	32 (13.7)
Progressive	5 (8.2)	2 (10.0)	4 (9.3)	0	2 (14.3)	1 (7.7)	0	1 (33.3)	0	0	7 (24.1)	1 (9.1)	21 (9.0)
Death	2 (3.3)	1 (5.0)	0	0	0	0	0	0	0	0	1 (3.4)	0	3 (1.3)
Unable to determine	7 (11.5)	4 (20.0)	3 (7.0)	1 (6.3)	0	0	0	0	0	2 (40.0)	3 (10.3)	0	16 (6.9)
Not evaluable	8 (13.1)	4 (20.0)	4 (9.3)	2 (12.5)	0	0	2 (6.3)	0	0	2 (40.0)	3 (10.3)	1 (9.1)	22 (9.4)

*Including candidaemia. †Candidaemia only is a subset of acute IC disease category. ‡The following combination options were allowed: addition of ibrexafungerp to any ongoing antifungal therapy; replacement of one (toxic/ineffective) element of a two-antifungal combination therapy with ibrexafungerp; replacement of current monotherapy with a new combination: replacement of AMB monotherapy with an azole plus ibrexafungerp combination, or replacement of an azole monotherapy with an AMB plus ibrexafungerp combination; continuation of an azole plus echinocandin combination where the subject could go home on an oral regimen by replacing the parenteral echinocandin with ibrexafungerp. §EOT or day specified, whichever came first. ¶Global response success (complete, partial) or failure (stable, progressive, death) were determined by DRC. Global outcome was scored as global success, global failure or not evaluable (unable to determine due to missing data). **Yes/No responses are for VVC, CPA and ABPA patients; complete, partial, stable, progressive, death and unable to determine are for all other patients. Efficacy evaluations consisted of clinical evaluations of the signs and symptoms of infection, mycological testing (including, but not limited to, fungal culture, KOH and other fungal stains, and T2 testing), imaging (e.g. CT, MRI, X-ray or ultrasound) and serological testing (including, among others, β-D-glucan levels, GM and fungal antibody titres) as applicable for each fungal disease.

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Table 1: Mycological findings at baseline*

Fungal species	N†	MIC/MEC range for ibrexafungerp (µg/mL)
***Candida* spp.**		
Candida albicans	52	0.03–1
Candida glabrata	51	0.12–4
Candida krusei‡	10	0.03–1
Candida parapsilosis	5	0.12–0.5
Candida auris	3	0.5–1
Candida dubliniensis	2	0.25
Candida tropicalis	2	0.06–0.5
Candida metapsilosis	1	0.12

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E0054

Ibrexafungerp is effective in treatment of patients with candidiasis, including candidaemia, caused by *Candida auris*: a multicentre, open-label study (CARES)

Table 2: **Global success rates per site of infection**

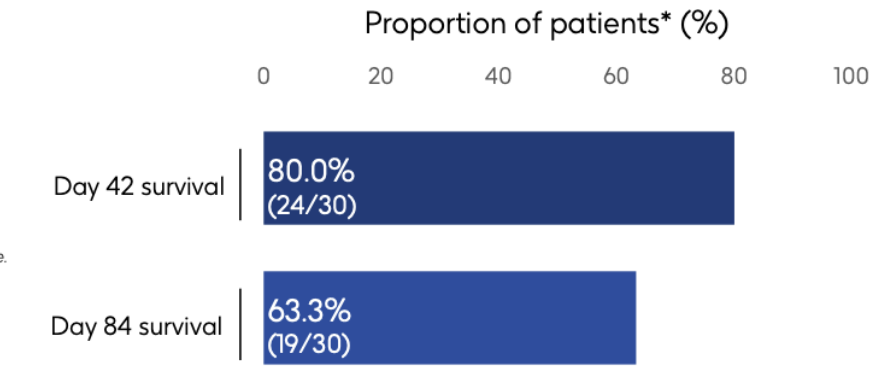
Response, n (%)	Candidaemia (n=19)	Intra-abdominal/ pelvic (n=1)	Urinary tract (n=9)	Other* (n=2)
Success	13 (68.4)	1 (100.0)	7 (77.8)	0
Failure	4 (21.1)	0	2 (22.2)	2 (100.0)
Not evaluable	2 (10.5)	0	0	0

**Otomycosis, n=1; discitis plus candidaemia, n=1.*

Recurrence at 6-week follow-up and survival

- Recurrence at 6 weeks post-EOT was reported for one patient
- Survival rates are shown in **Figure 2**

Figure 2: **Survival**



**A response of 'not evaluable' was not included in the analysis.*

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Patterson TF, et al. 2025

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Recruiting

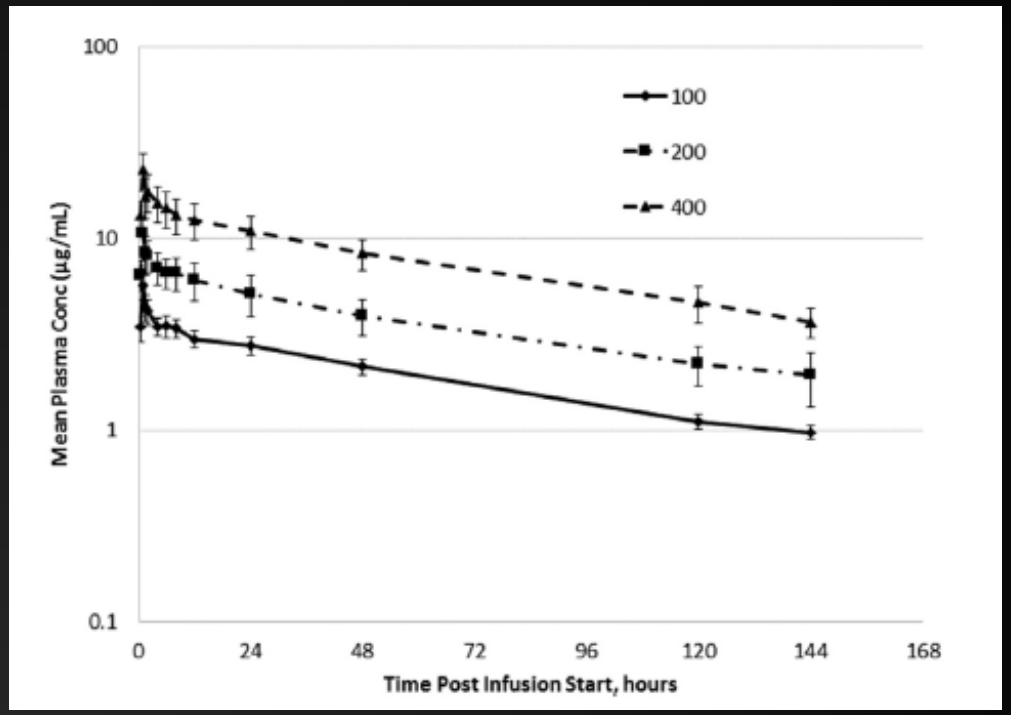
A Phase 3, Randomized, Double-blind Study for Patients With Invasive Candidiasis Treated With IV Echinocandin Followed by Either Oral Ibrexafungerp or Oral Fluconazole (MARIO)

ClinicalTrials.gov ID NCT05178862

- Design: Phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled, comparative study to evaluate the efficacy, safety and tolerability of oral IBX compared to oral fluconazole (FLU) step-down treatment following IV echinocandin in the treatment of adult subjects (≥18 years old) with invasive candidiasis and/or candidemia
- Arms: Eligible subjects receive initial treatment with IV echinocandin. Treatment will then be switched to double-blind, double-dummy oral therapy (either IBX or FLU)

Rezafungin (CD101)

- Long-acting echinocandin



Sandison et al. Antimicrob Agents Chemother 2017

Rezafungin (CD101)

- Improved stability, solubility, and reduced rate of elimination
- Long half-life (125-146 hours)
- Good distribution to various tissues, with the exception of SNC
- Primary excreted unchanged in bile/feces
- Low risk of DDI

James KD, et al. Antimicrob Agents Chemother 2017; 61:e01541
Sandison T, et al. Antimicrob Agents Chemother 2017; 61:e01627
Ong V, et al. Antimicrob Agents Chemother 2016; 60:6872-6879
Ong V, et al. Antimicrob Agents Chemother 2017; 61:e01626

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Rezafungin (CD101)

- *In vitro* activity against *Candida* spp.
  - Including also *C. auris*, although reported reduced susceptibility with FKS gene mutations
- Limited activity against *Cryptococcus* spp.
- Activity against *Pneumocystis jirovecii*
- *In vitro* activity against *Aspergillus* spp.
  - Comparable to that of other echinocandins
  - Activity against cryptic species with reduced susceptibility to posaconazole or voriconazole

Carvalhaes CG, et al. J Clin Microbiol 2022; 60:e02449
Wiederhold NP, et al. J Antimicrob Chemother 2018; 73:3063-3067
Pfaller MA, et al. Int J Antimicrob Agents 2017; 50:352-358
Pfaller MA, et al. J Antimicrob Chemother 2016; 71:2868-2873
Hager CL, et al. J Antimicrob Chemother 2018; 73:2085-2088
Berkov EL, et al. Diagn Microbiol Infect Dis 2018; 90:196-197
Helleberg M, et al. Antimicrob Agents Chemother 2020; 64:e02438
Pfaller MA, et al. Antimicrob Agents Chemother 2020; 64:e00099
Toth Z, et al. J Antimicrob Chemother 2019; 74:3505-3510
Miesel L, et al. Antimicrob Agents Chemother 2021; 65:e01992

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Rezafungin Versus Caspofungin in a Phase 2, Randomized, Double-blind Study for the Treatment of Candidemia and Invasive Candidiasis: The STRIVE Trial

Clinical Infectious Diseases
MAJOR ARTICLE

- Population: 183 adults with candidemia/IC
- Study arms: RZF 400 mg Qwk; RZF 400/200 mg Qwk; caspofungin
- Primary endpoint: overall cure (resolution of signs of candidemia/IC plus mycological eradication) at day 14
- Safety: No concerning safety trends were observed

Thompson GR, et al. Clin Infect Dis 2021; 73:e3647-e3655

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Clinical Infectious Diseases

MAJOR ARTICLE

Table 3. Primary Efficacy Endpoint: Overall Response at Day 14 (Microbiological Intent-to-Treat [mITT] Population)—Part A, Part B, and Combined

Overall Response, n (%)	Rezafungin Once Weekly 400 mg	Rezafungin Once Weekly 400 mg/200 mg	Caspofungin Once Daily 70 mg/50 mg
		Part A	
	N = 33	N = 31	N = 28
Overall cure [95% CI[a]]	19 (57.6) [39.2–74.5]	22 (71.0) [52.0–85.8]	18 (64.3) [44.1–81.4]
Failure/indeterminate	14 (42.4)	9 (29.0)	10 (35.7)
Failure	8 (24.2)	6 (19.4)	8 (28.6)
Indeterminate	6 (18.2)	3 (9.7)	2 (7.1)
		Part B	
	N = 43	N = 15	N = 33
Overall cure [95% CI[a]]	27 (62.8) [46.7–77.0]	13 (86.7) [59.5–98.3]	23 (69.7) [51.3–84.4]
Failure/indeterminate	16 (37.2)	2 (13.3)	10 (30.3)
Failure	12 (27.9)	2 (13.3)	9 (27.3)
Indeterminate	4 (9.3)	0	1 (3.0)
		Combined (Part A + Part B)	
	N = 76	N = 46	N = 61
Overall cure [95% CI[a]]	46 (60.5) [48.6–71.6]	35 (76.1) [61.2–87.4]	41 (67.2) [54.0–78.7]
Failure/indeterminate	30 (39.5)	11 (23.9)	20 (32.8)
Failure	20 (26.3)	8 (17.4)	17 (27.9)
Indeterminate	10 (13.2)	3 (6.5)	3 (4.9)

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Rezafungin Versus Caspofungin in a Phase 2, Randomized, Double-blind Study for the Treatment of Candidemia and Invasive Candidiasis: The STRIVE Trial

Clinical Infectious Diseases

MAJOR ARTICLE

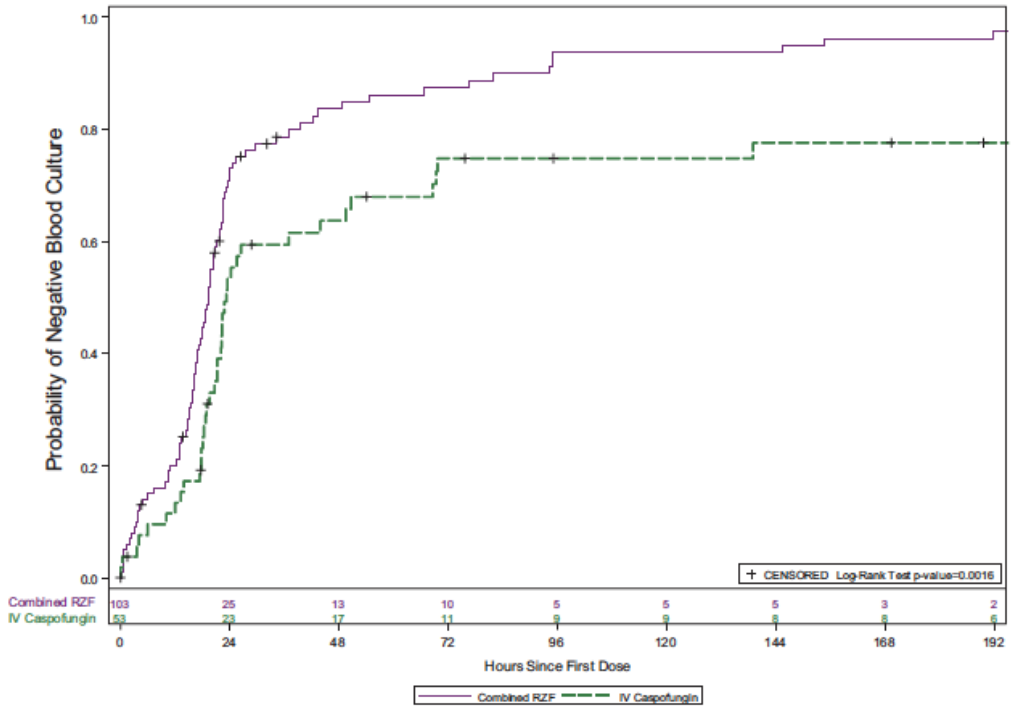

Figure 2. Time to negative blood culture following treatment with RZF versus caspofungin in patients with candidemia from the mITT population ($P = .0016$; log-rank test, post hoc analysis). Abbreviations: mITT, microbiological intent to treat; RZF, rezafungin. The first of two required negative cultures was used as the time of culture clearance, with the first negative blood culture drawn at least 1 hour after the last positive blood culture. The overall trend is unchanged, with significant differences between treatments observed as soon as ~24 hours after the first dose.

Thompson GR, et al. Clin Infect Dis 2021; 73:e3647-e3655
Erratum. Clin Infect Dis 2021; 73:561-562

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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

THE LANCET

- Population: 199 adults with candidemia/IC
- Study arms: RZF 400/200 mg Qwk; caspofungin
- Primary endpoint: global cure (consisting of clinical cure, radiological cure, and mycological eradication) at day 14 for the EMA and 30-day all-cause mortality for the FDA
- Safety: no concerning trends in treatment-emergent or SAE

Thompson GR, et al. Lancet 2023; 401:49-59

	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%)	..
Global response at day 14 as assessed by DRC by diagnosis			
Candidaemia only			
Cure	39/64 (61%)	43/67 (64%)	−3·2 (−19·6 to 13·3)*
Failure	21/64 (33%)	19/67 (28%)	..
Indeterminate	4/64 (6%)	5/67 (7%	..
Invasive candidiasis			
Cure	16/29 (55%)	14/27 (52%)	3·3 (−22·4 to 28·6)*
Failure	7/29 (24%)	10/27 (37%)	..
Indeterminate	6/29 (21%)	3/27 (11%)	..

Data are n (%) or n/N (%). ANC=absolute neutrophil count. APACHE II=Acute Physiology and Chronic Health Evaluation II score. DRC=data review committee. EMA=European Medical Agency. FDA=Food and Drug Administration. *Two-sided 95% CI for the observed difference (%), rezafungin group minus caspofungin group. †Two-sided 95% CI for the weighted difference (%), rezafungin group minus caspofungin group adjusted for the two randomisation strata of diagnosis (candidaemia vs invasive candidiasis) and high risk (APACHE II score ≥20 or ANC <500 cells per µL) versus low risk (APACHE II score <20 and ANC ≥500 cells per µL).

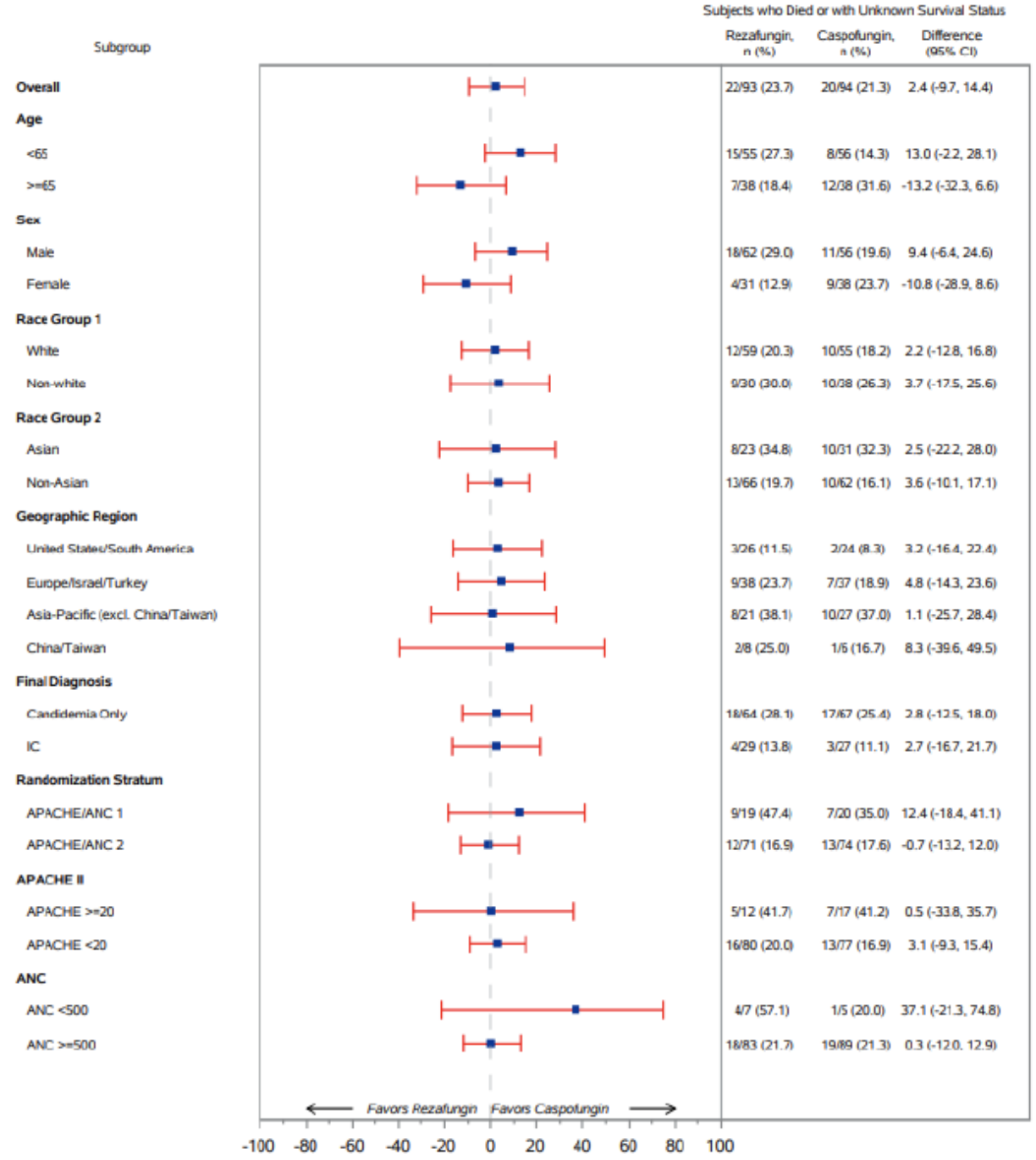
Table 2: **All-cause mortality at day 30 and global response at day 14 in the modified intention-to-treat population**

THE LANCET

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

Thompson GR, et al. Lancet 2023; 401:49-59

Figure S1: **Difference in all-cause mortality rates at day 30 by subgroups in the mITT population**



THE LANCET

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Thompson GR, et al. Lancet 2023; 401:49-59

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	Rezafungin group (n=93)	Caspofungin group (n=94)	Treatment difference (95% CI)*
Patients with negative blood culture†			
24 h	36/67 (54%)	30/65 (46%)	..
48 h	49/66 (74%)	41/64 (64%)	..
Outcomes at the day 5 visit			
Global cure as assessed by DRC	52 (56%)	49 (52%)	3·8 (−10·5 to 17·9)
Mycological eradication‡	64 (69%)	58 (62%)	7·1 (−6·6 to 20·6)
Patients with candidaemia only	50/64 (78%)	46/67 (69%)	9·5 (−5·8 to 24·4)
Investigator assessment of clinical cure	59 (63%)	70 (74%)	−11·0 (−24·0 to 2·3)
Outcomes at the day 14 visit			
Global cure as assessed by DRC§	55 (59%)	57 (61%)	−1·1 (−14·9 to 12·7)¶
Mycological eradication	63 (68%)	62 (66%)	1·8 (−11·7 to 15·2)
Patients with candidaemia only	46/64 (72%)	47/67 (70%)	1·7 (−13·9 to 17·2)
Investigator assessment of clinical cure	62 (67%)	63 (67%)	−0·4 (−13·8 to 13·1)

Data are n (%) or n/N (%). ANC=absolute neutrophil count. APACHE=Acute Physiology and Chronic Health Evaluation. DRC=data review committee. *Two-sided 95% CI for the observed difference (%), rezafungin group minus caspofungin group. †Exploratory endpoint. ‡Programmatically derived from the outcome definition described in the methods. §Primary endpoint for the European Medicines Agency (secondary endpoint for the US Food and Drug Administration). ¶Two-sided 95% CI for the weighted difference (%), rezafungin group minus caspofungin group adjusted for the two randomisation strata of diagnosis and APACHE II score and ANC.

Table 3: **Secondary and exploratory endpoints of efficacy in the modified intention-to-treat population**

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

Thompson GR, et al. Lancet 2023; 401:49-59

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Opelconazole (PC945)

- Novel triazole developed for administration via nebulizer
- Inhibition of 14-alpha-demethylase

Cass L, et al. Pharmacol Res Perspect 2021; 9:e00690
Hoenigl M, et al. Drugs 2021; 81:1703–1729
Neoh CF, et al. Expert Rev Anti Infect Ther 2023; 21:577-594

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Opelconazole (PC945)

- High concentration in the lung
- Prolonged retention
- Slow systemic absorption
- Minimal systemic exposure
- Low potential for DDI

Cass L, et al. Pharmacol Res Perspect 2021; 9:e00690
Neoh CF, et al. Expert Rev Anti Infect Ther 2023; 21:577-594

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Opelconazole (PC945)

- *In vitro* activity against *Aspergillus* spp.
  - Reduced activity against *A. niger* and *A. flavus*
- *In vitro* activity against *Candida* spp.
  - Activity against *C. auris*
- Inactive against Mucorales
  - However, active against *R. arrhizus*

Colley T, et al. Antimicrob Agents Chemother 2017; 61:e02280
Rudramurthy SM, et al. J Antimicrob Chemother 2019; 74:29432949

Safety and nonclinical and clinical pharmacokinetics of PC945, a novel inhaled triazole antifungal agent

What is already known about this subject

- The high plasma drug concentrations required to treat pulmonary fungal infections with current systemic antifungal therapies are commonly associated with side effects and drug-drug interactions.
- PC945, a novel triazole, inhibits planktonic growth and bronchial epithelial cell infection by *Aspergillus* species in vitro.

What this study adds

- Findings from clinical and nonclinical studies demonstrated that repeat daily doses of inhaled PC945 led to prolonged absorption from the lung and minimal systemic exposure.
- PC945 was well tolerated in healthy subjects and subjects with mild asthma.
- Inhaled PC945 should have a wider therapeutic index than systemic antifungal agents.

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Cass L, et al. Pharmacol Res Perspect 2021; 9:e00690

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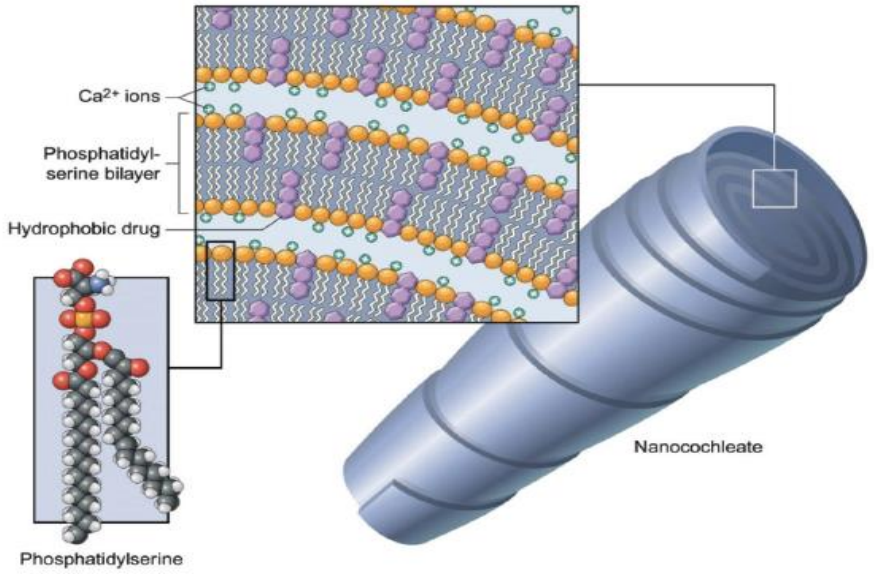
Encochleated amphotericin B deoxycholate (MAT023)

- Oral formulation of AMB



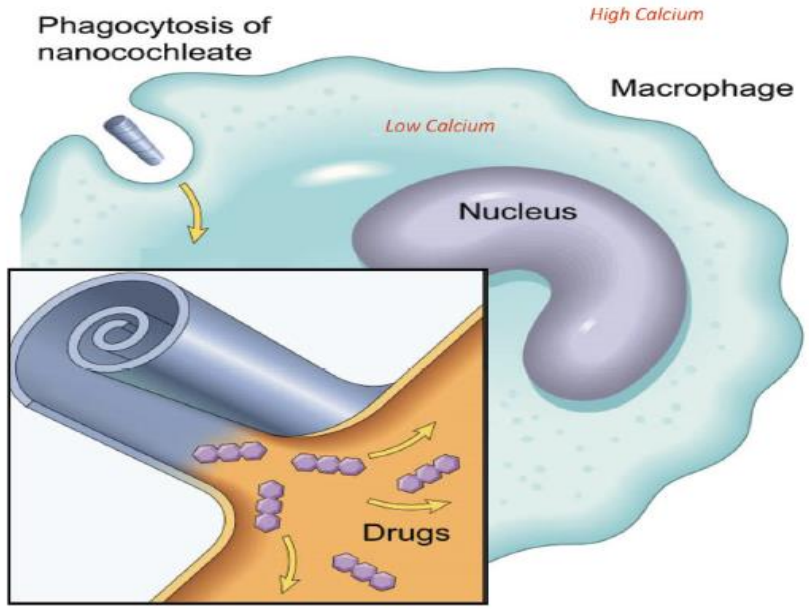


FIG 1 Illustration of cochleate technology. Amphotericin B is embedded within the phosphatidylserine bilayers of the cochleate, along with calcium ions. The cochleate protects the cAMB from digestive processes in the gastrointestinal tract until absorbed. Once absorbed, the cochleate is phagocytosed by macrophages. Due to the higher calcium concentration in the cochleate than in the cytoplasm of the macrophage, the cochleate is pulled open as calcium ions rush out, allowing intracellular delivery of the amphotericin B.

Gonzalez-Lar MF, et al. Drugs 2017; 77:1505-1518
Skipper CP, et al. Antimicrob Agents Chemother 2020; 64:e00838-20

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Encochleated amphotericin B deoxycholate (MAT023)

- Protection against degradation in unfavorable environments
- Targeted intracellular delivery into macrophages and reticuloendothelial cells
- High intracellular concentration for killing of intracellular organisms
- Low plasma concentrations with reduced toxicity

Gonzalez-Lar MF, et al. Drugs 2017; 77:1505-1518
Skipper CP, et al. Antimicrob Agents Chemother 2020; 64:e00838-20

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Encochleated amphotericin B deoxycholate (MAT023)

- *In vitro* activity against *Aspergillus* spp.
- *In vitro* activity against *Candida* spp.
- *In vitro* activity against *Cryptococcus* spp.

Skipper CP, et al. Antimicrob Agents Chemother 2020; 64:e00838-20

Thank you

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