Nuovi Antifungini

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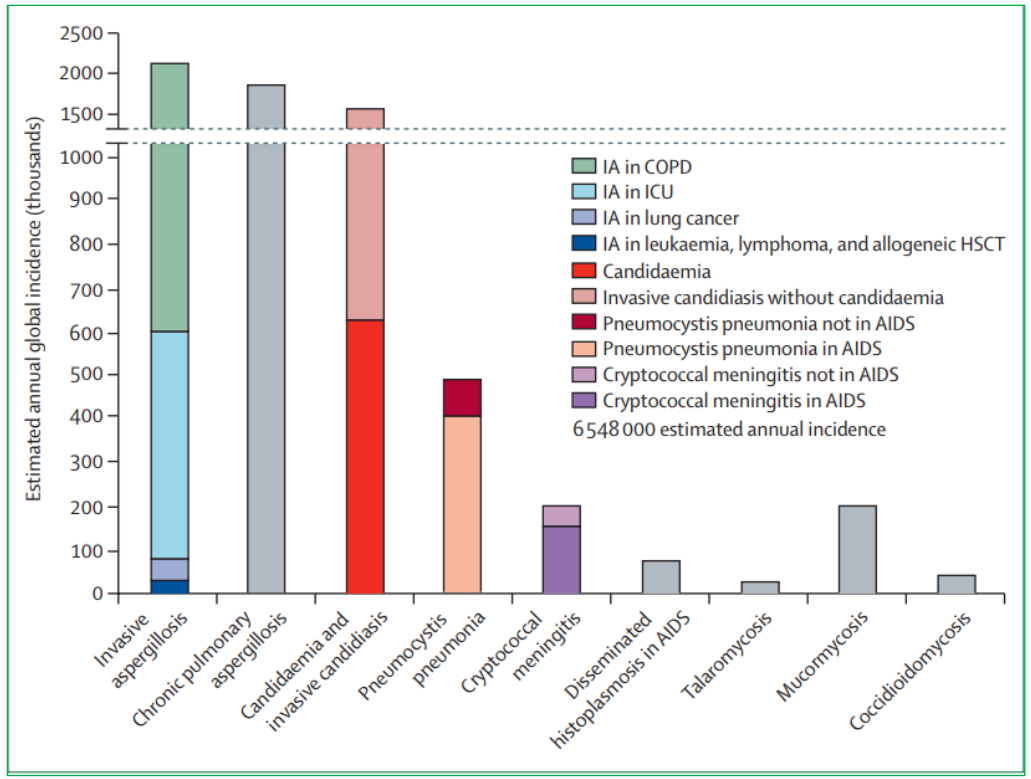
THE LANCET
Infectious Diseases

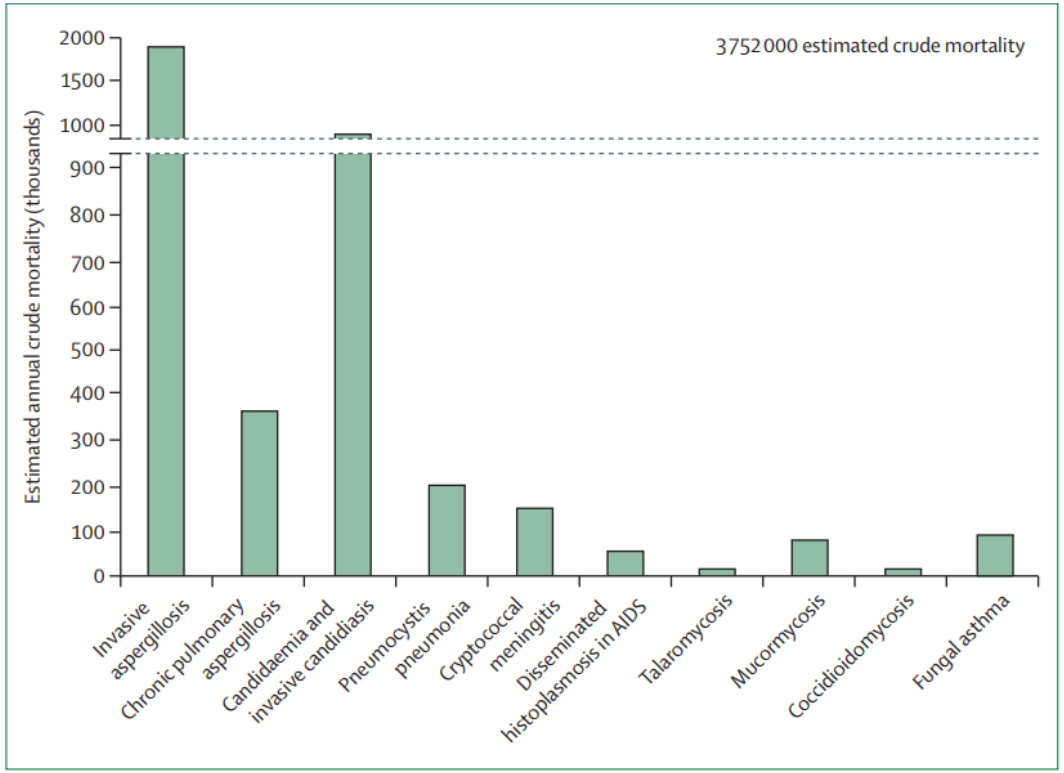
Global incidence and mortality of severe fungal disease

David W Denning

Estimated annual incidence of life-threatening invasive mycoses



Estimated crude mortality of severe fungal disease, worldwide



Lancet Infect Dis. 2024

Risk factors associated with death in ICU

	Prevalence or duration
Prevalence of infections	
CAPA*: pr/pb invasive aspergillosis	76 (15%)
pr/pb invasive fungal infection other than pr/pb CAPA (one or more)	38 (7%)
Candidemia	32 (6%)
Invasive mucormycosis	6 (1%)
Invasive fusariosis	1 (<1%)
Bacterial ventilator-associated pneumonia (n=509)†	374 (73%)
Cytomegalovirus infection (n=491)†	49 (10%)
Herpes simplex virus type 1 infection (n=491)†	76 (15%)

Gangneux, LRM, 2022

Risk factors associated with death in ICU

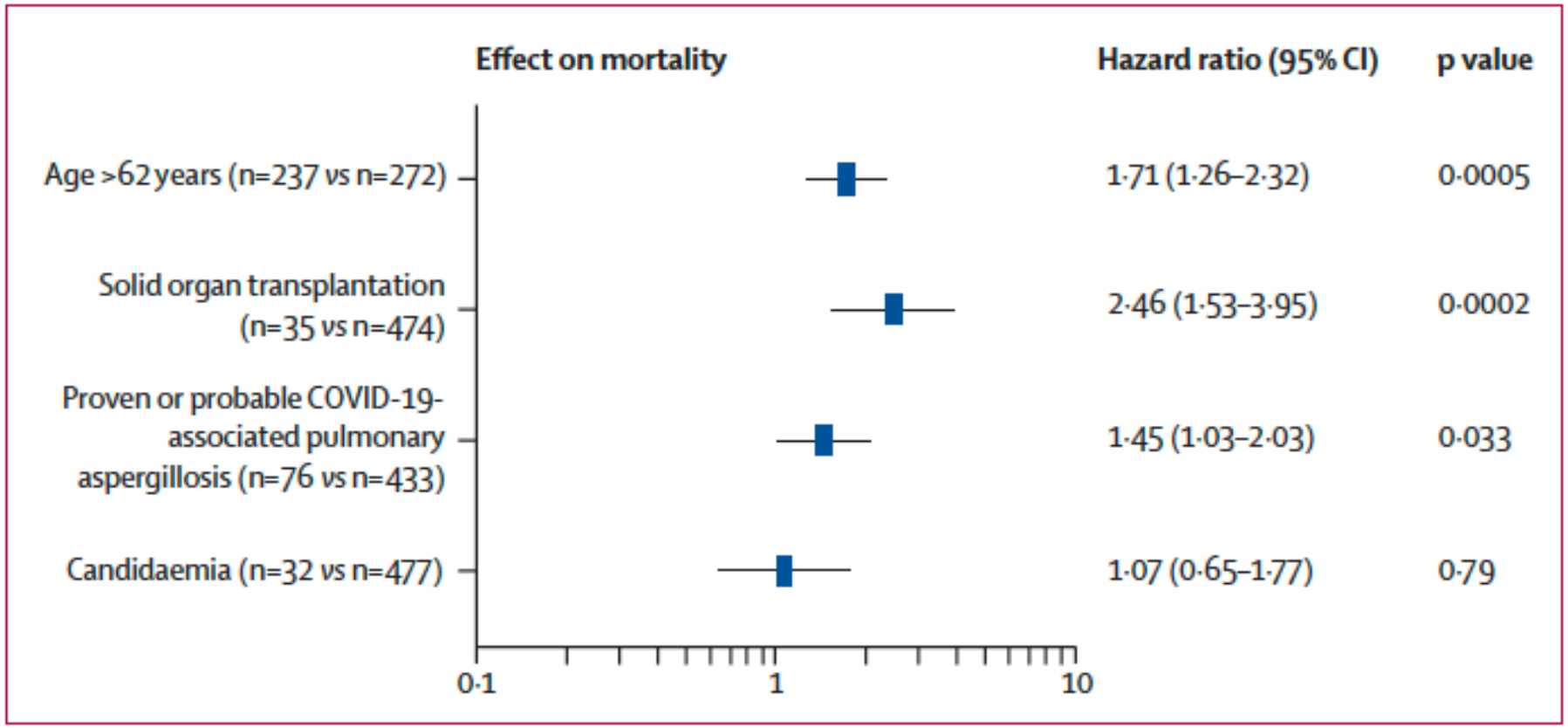


Figure 3: **Multivariate analysis of factors associated with death**

Gangneux, LRM, 2022

Candidemia and fluconazole resistance before and after pandemic

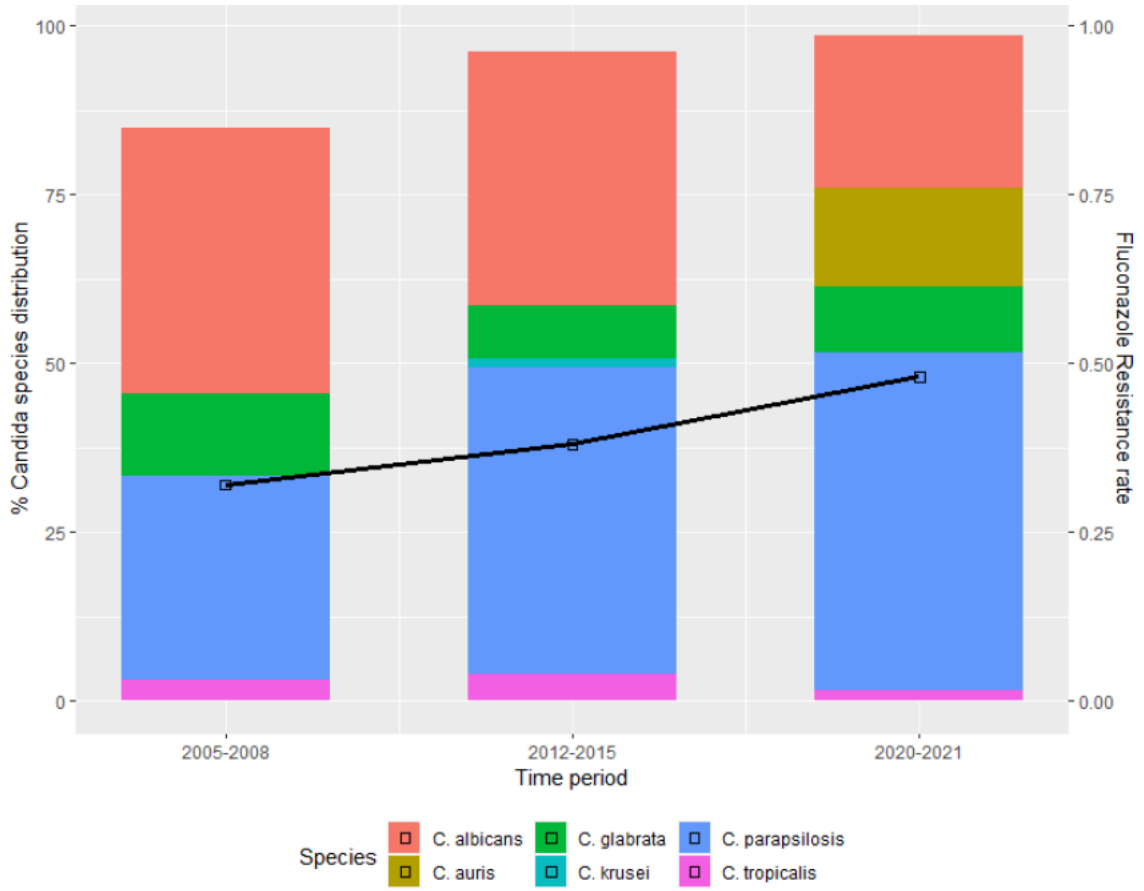


Figure 1. Species distribution of *Candida* bloodstream isolates and fluconazole resistance before and during the COVID-19 pandemic era.

Routsi et al, Antibiotics 2022

Incidence of Fungemia Due to Fluconazole-Resistant *Candida parapsilosis*

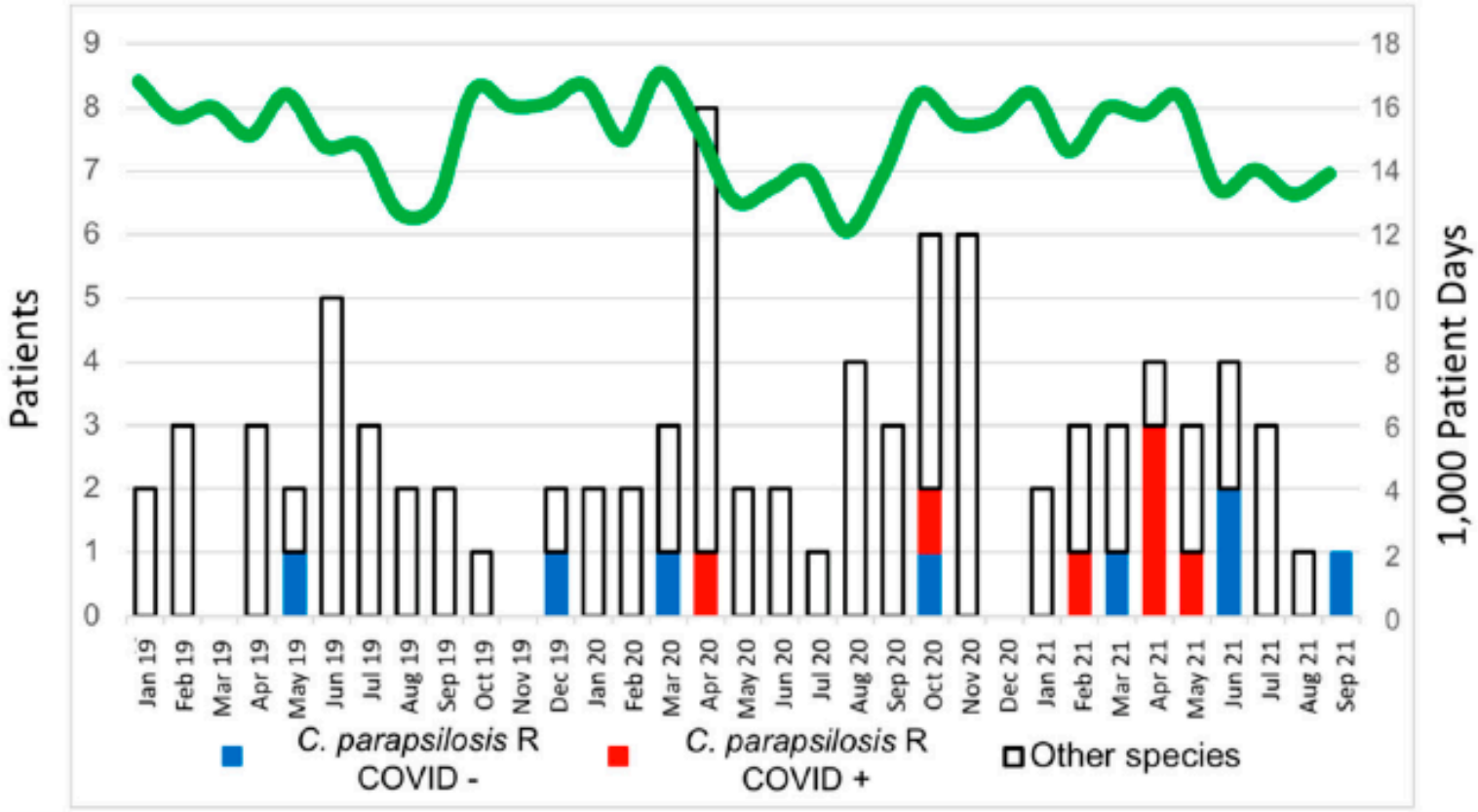
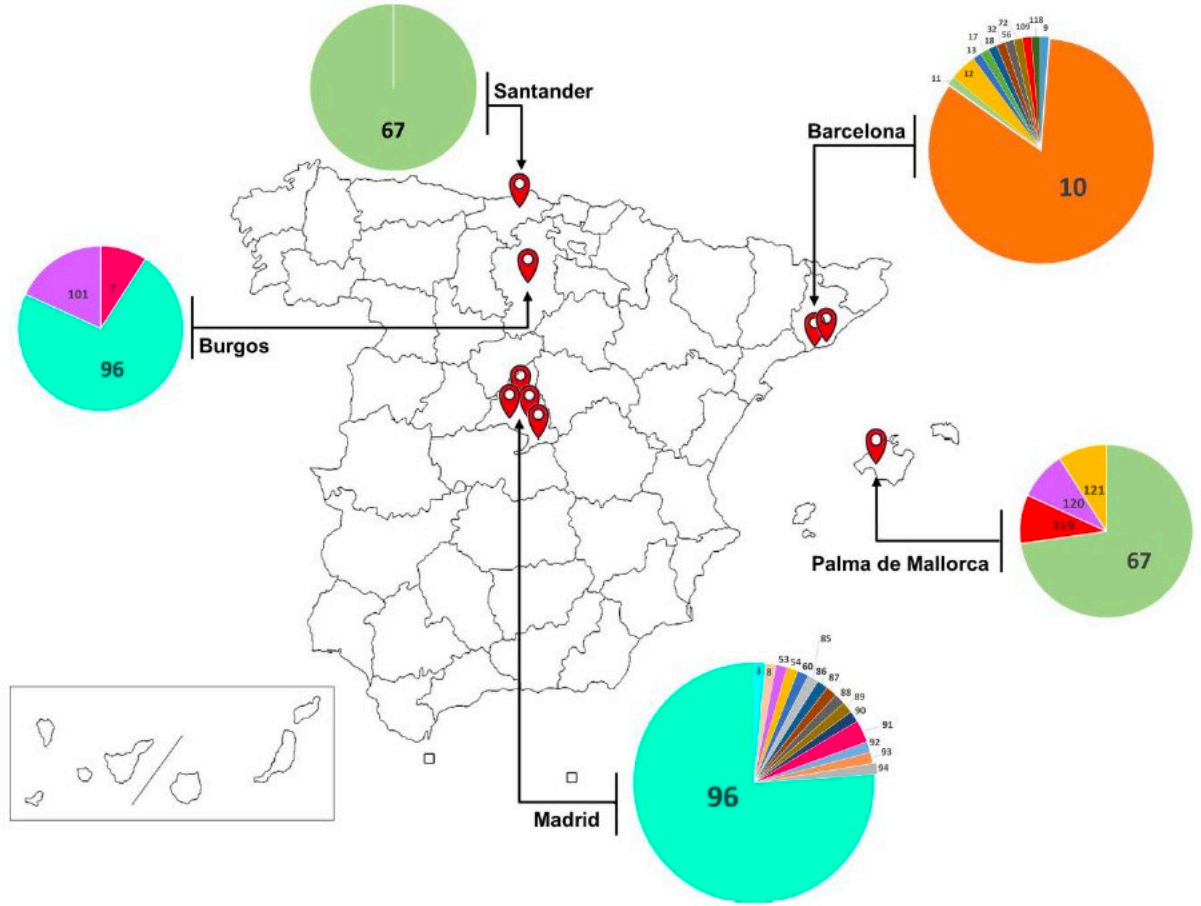


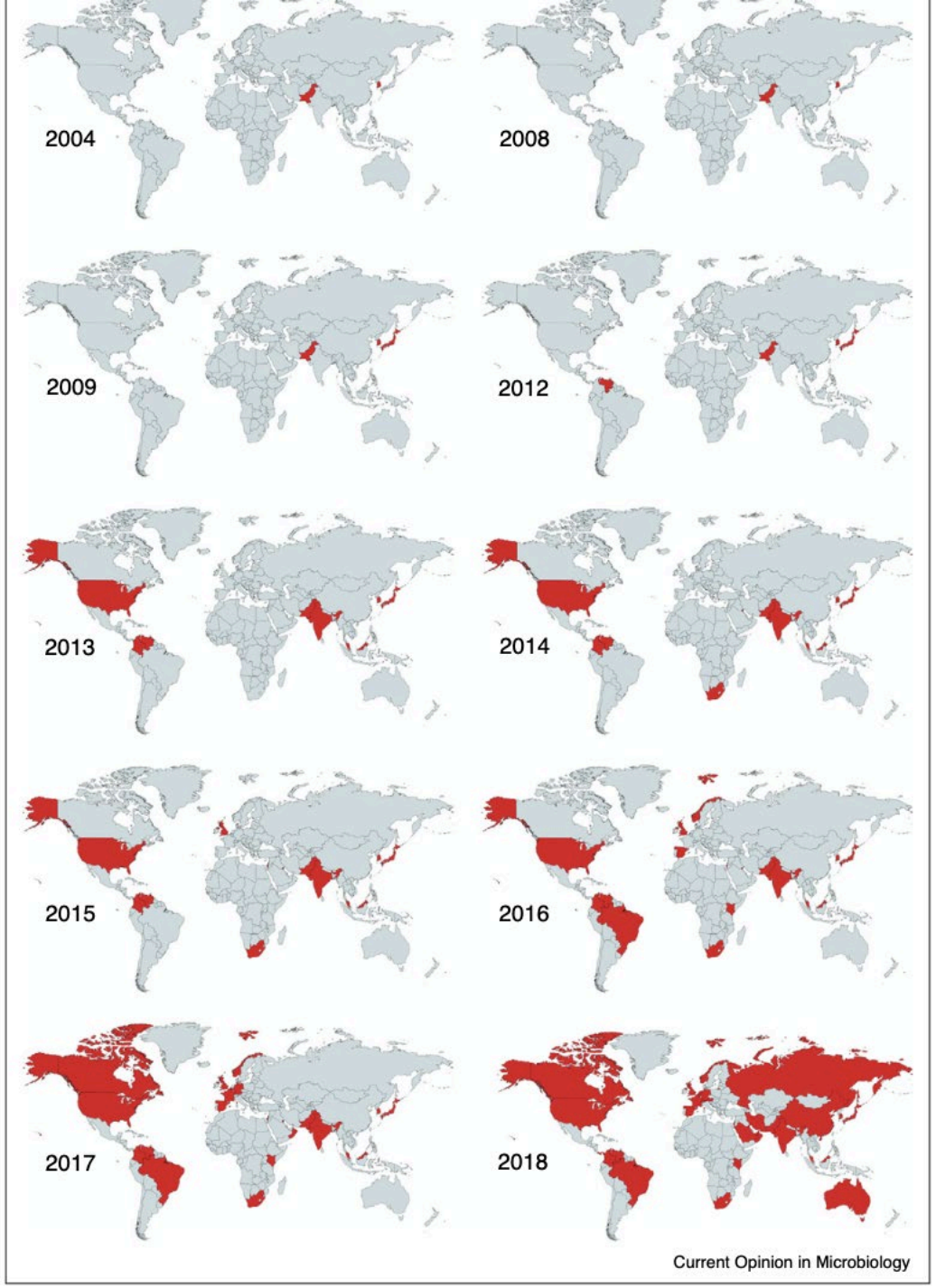
Figure 1. Incidence of candidemia from January 2019 to September 2021. R—resistant.

Ramos-Martinez et al, J of Fungi 2022

Global Emergence of Resistance to Fluconazole and Voriconazole in *Candida parapsilosis* in Tertiary Hospitals in Spain During the COVID-19 Pandemic



Trevijano-Contador et al, OFID 2022



Timeline showing the expanding worldwide detection of *C. auris*

Rhodes and Fisher Current Opinion in Microbiology 2019

Table 1 Clinical Conditions/Risk Factors Associated with Candidemia, Resistance Rates, Antifungal Treatment According to Different *Candida* Species

***Candida* spp.**	**Patients at Risk/Risk Factors**	**Rate of Resistance**	**Therapy**
C. albicans	All patients	Fluconazole: 0.1–0.4% Echinocandins: 0–0.1% Amphotericin B: rare	• Echinocandins (1) • Fluconazole, 800 mg then 400 mg (2) • Liposomal amphotericin B, 3–5 mg/kg/day (3)
C. parapsilosis	ICU patients Neonates Vascular catheter	Fluconazole: 0.6 up to 53% Echinocandins: 0–0.1% Amphotericin B: rare	• Echinocandins (1) • Fluconazole, 800 mg then 400 mg (2)
C. glabrata	Older age Diabetes Cancer Hematological malignancies Stem cell transplantation Azole prophylaxis	Fluconazole: 2.6–10.6% Echinocandins: 0%-2.8% Amphotericin B: rare	Fluconazole and voriconazole are not recommended for frequent azoles resistance • Echinocandins (1) • Liposomal amphotericin B, 3–5 mg/kg/day (3)
C. tropicalis	Corticosteroid therapy Hematological malignancies Stem cell transplantation	Fluconazole: 1.1–37.8% Echinocandins: 0–1.3% Amphotericin B: rare	• Echinocandins (1) • Fluconazole, 800 mg then 400 mg (2) • Liposomal amphotericin B, 3–5 mg/kg/day (3)
C. krusei	Corticosteroid therapy Hematological malignancies Stem cell transplantation Azole prophylaxis	Fluconazole: innately Echinocandins: 0–0.7% Amphotericin B: rare	Fluconazole is not recommended for frequent azoles resistance • Echinocandins (1) • Liposomal amphotericin B, 3–5 mg/kg/day (3) • Voriconazole (4)
C. auris	Diabetes Cancer Hematological malignancies ICU patients Invasive procedures	Fluconazole: 15.4–90% Voriconazole: 50% Echinocandins: 2–8% Amphotericin B: 15–30%	• Echinocandins (1)

Notes: (1) Caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily. (2) In stable patients without previous exposure to azoles. (3) If isolates are not susceptible to azoles and echinocandins or in the presence of organ involvement. (4) 6 mg/kg q12h × 2 doses (load) then 3–4 mg/kg q12h.

The paradigm of intraabdominal candidiasis

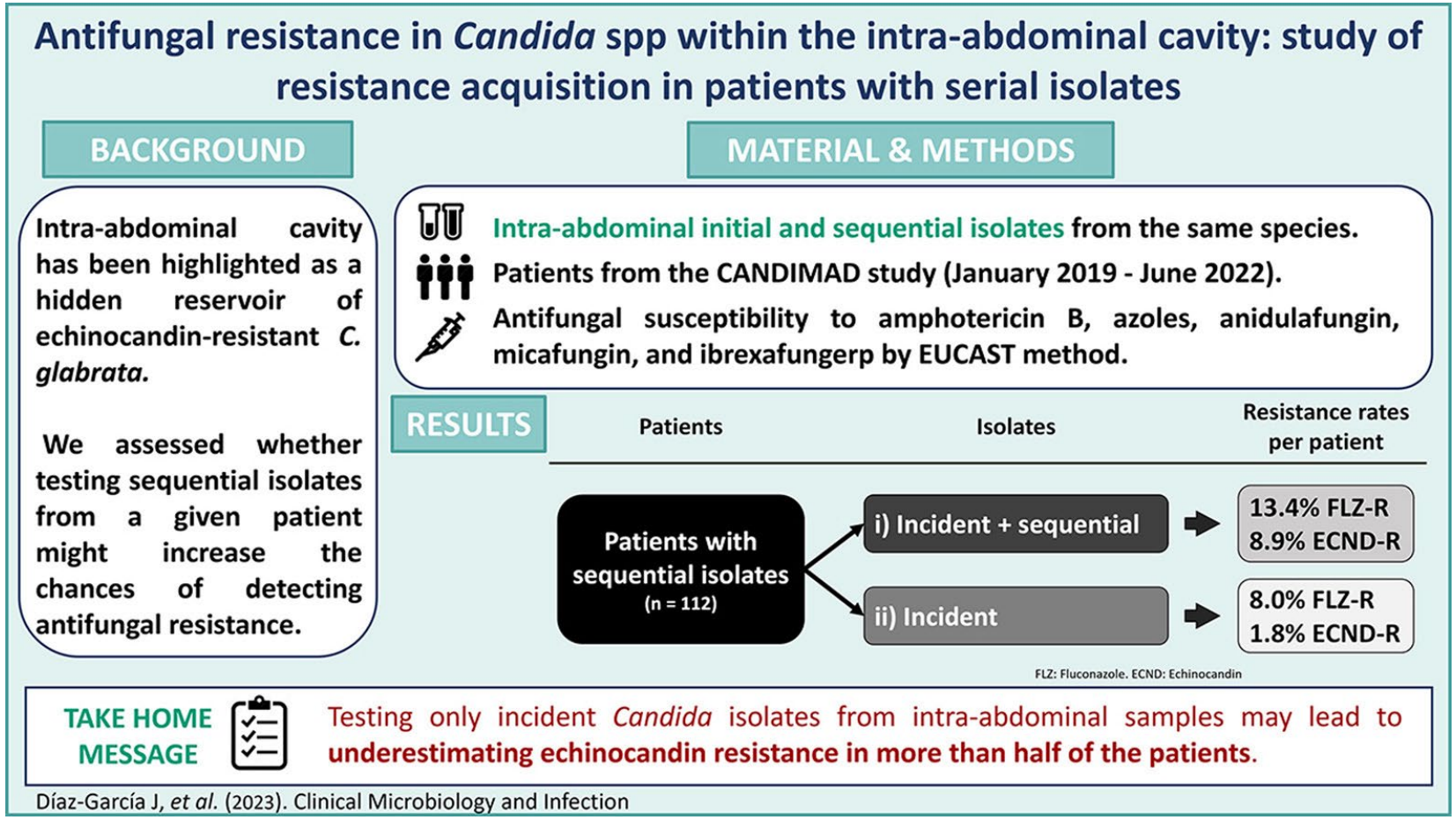


Table 4 Factors to be considered when choosing the most appropriate antifungal drug for ICU patients

Factor	Rationale
Clinical stability of patient	Fungicidal drug (e.g. echinocandin) preferred if clinically unstable
Previous antifungal exposure	Prior or prolonged use of azole and echinocandins associated with increased risk of resistance
Fungal colonization	Assess risk of infection with less susceptible/resistant-*Candida*
Local epidemiology	Assess risk of infection with less susceptible/resistant-*Candida* e.g *C. auris* outbreaks, echinocandin-resistant *C. glabrata*
Site of infection and dissemination	Echinocandins: poor penetration to aqueous sites (CSF, synovial fluid, anterior chamber of the eye, brain tissue, and urine) Amphotericin B: renal penetration of AmBd greater than L-AMB
Concurrent medications	Triazoles: inhibit various cytochrome P450 (CYP) isoenzymes; multiple drug-drug interactions. Caution with other hepato-toxic and cardio-toxic drugs Amphotericin: caution with other nephrotoxic drugs and drugs affecting electrolytes
Organ failure	Assess if drug and dose is appropriate in renal or liver impairment
Organ support	Assess if drug and dose is appropriate in RRT or ECMO
Therapeutic drug monitoring (TDM) requirement	essential for voriconazole and flucytosine to ensure effectiveness and prevent toxicity

AmBd **amphotericin deoxycholate,** ***ECMO*** **extracorporeal membrane oxygenation,** ***L-AMB*** **liposomal amphotericin,** ***RRT*** **renal replacement therapy**

C. Logan *Intensive Care Med 2020*

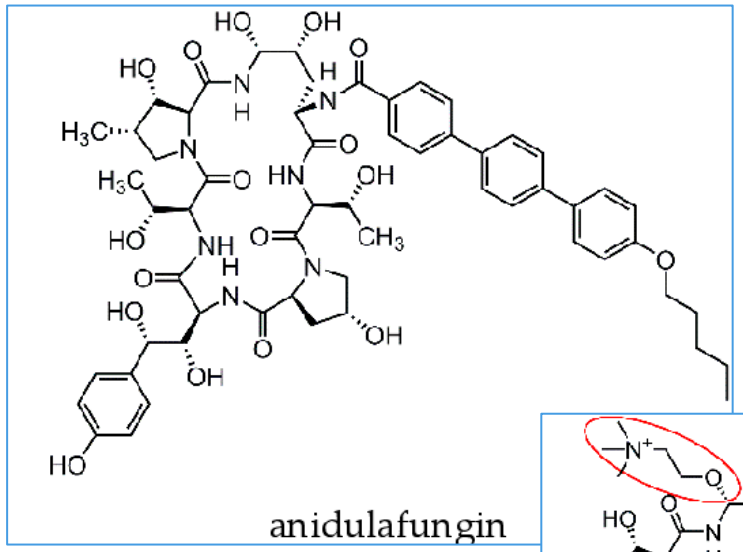
Invasive fungal diseases

- ✓Triazoles
- ✓Polyenes
- ✓Echinocandins

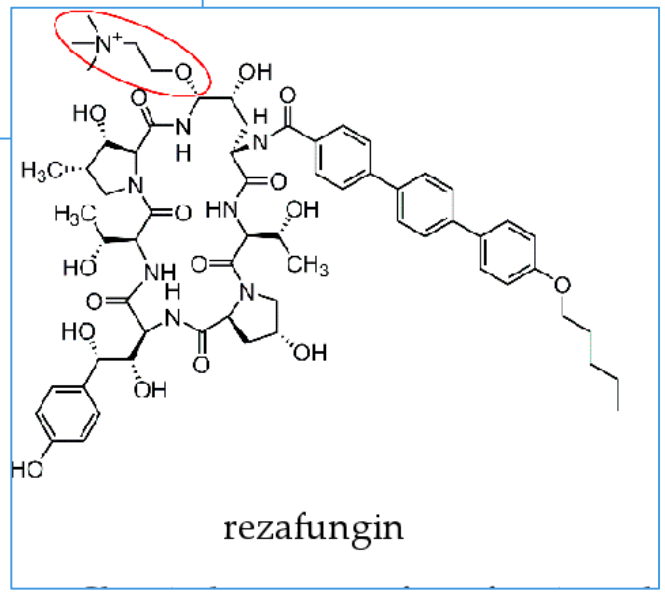
- ✓Drug toxicity
- ✓Drug-drug interactions
- ✓Lack of oral formulation

RESISTANCE

Rezafungin: mechanism of action

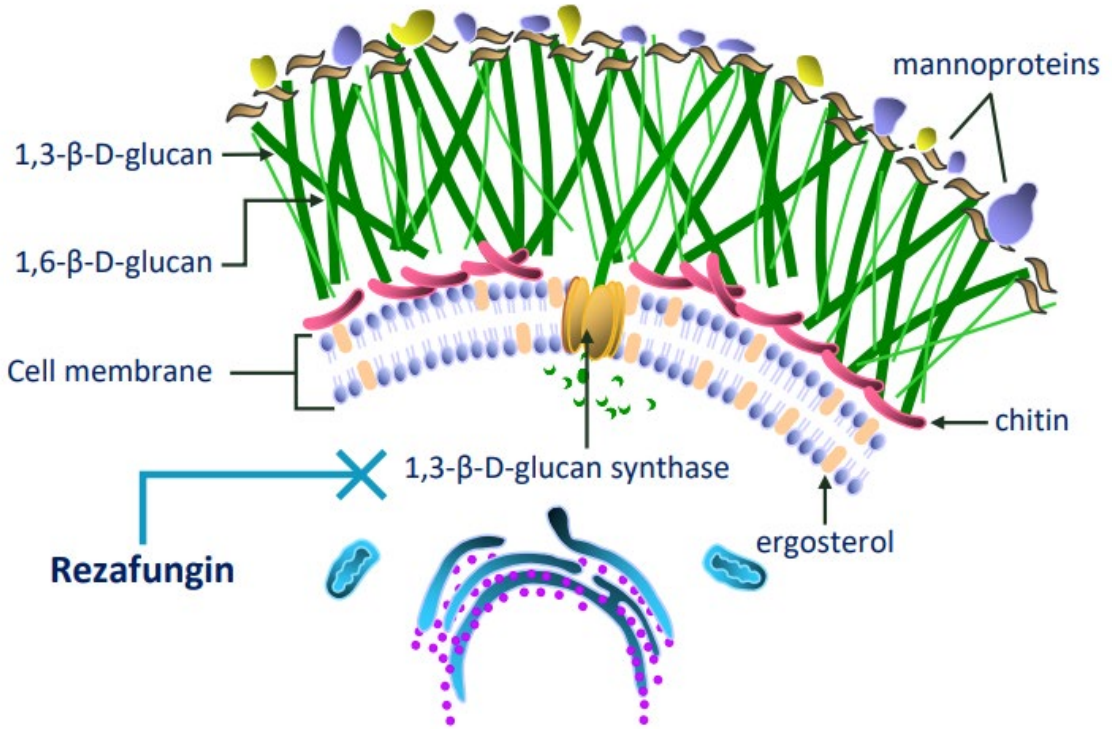


anidulafungin



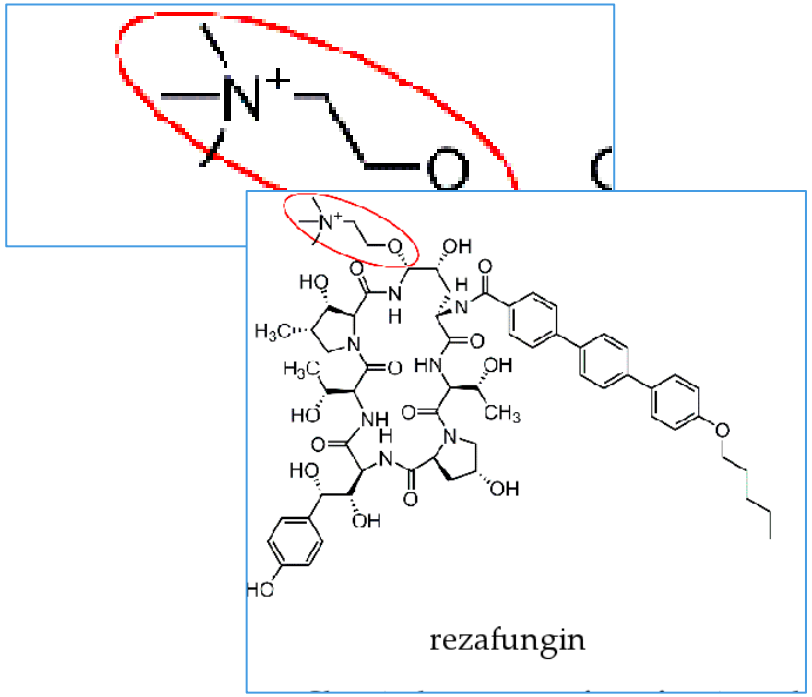
rezafungin

Rezafungin inhibits production of 1,3-β-D-glucan → **Fungal cell lysis**



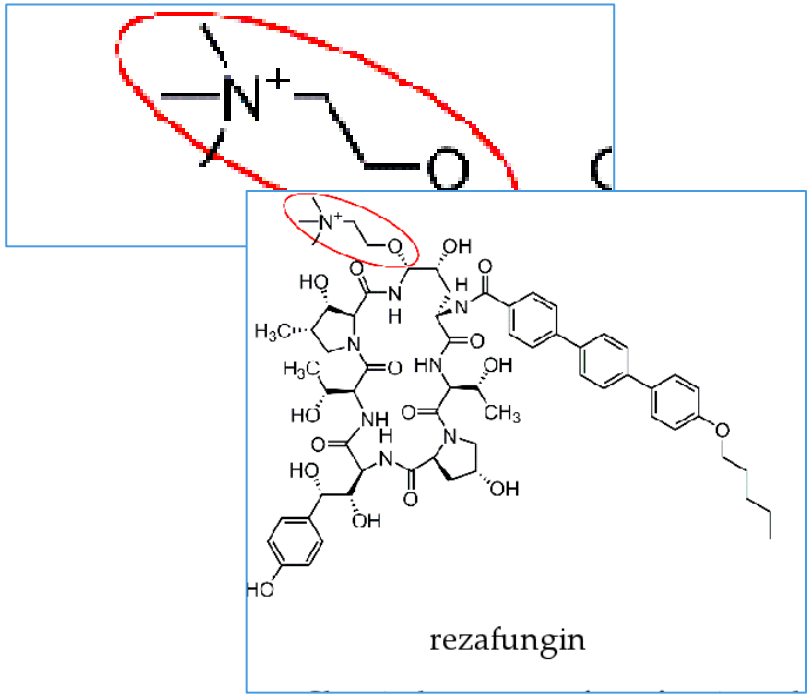
Diamond RD, ed. Atlas of Infectious Diseases: Fungal Infections. 1st ed. Current Medicine Group; 2020

Rezafungin: the “new” echinocandin



- Broad spectrum activity
  (look at new challenges *Candida parapsilosis*, *Candida auris*)
- Novel PK/PD
- Improverd safety/increased stability

Rezafungin: the “new” echinocandin



- ❑ **Broad spectrum activity**
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- ❑ Novel PK/PD
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Rezafungin spectrum of activity

***Candida* spp**

	MIC$_{90}$ (µg/mL)[1-3*]									
	C. albicans (n=835)[2†]	*C. glabrata* (n=374)[2†]	*C. tropicalis* (n=196)[2†]	*C. krusei* (n=77)[2†]	*C. parapsilosis* (n=329)[2†]	*C. kefyr* (n=52)[3‡]	*C. lusitaniae* (n=46)[3‡]	*C. guilliermondii* (n=27)[3‡]	*C. dubliniensis* (n=22)[3‡]	*C. auris* (n=19)[3‡]
Rezafungin	**0.06**	**0.12**	**0.06**	**0.06**	**2**	**0.12**	**0.25**	**1**	**0.06**	**0.25**
Anidulafungin	0.03	0.12	0.06	0.12	2	0.06	0.06	2	0.03	0.25
Caspofungin	0.03	0.06	0.06	0.25	0.5	0.5	1	1	0.25	1
Micafungin	0.03	0.03	0.06	0.12	1	0.12	0.25	2	0.03	0.5

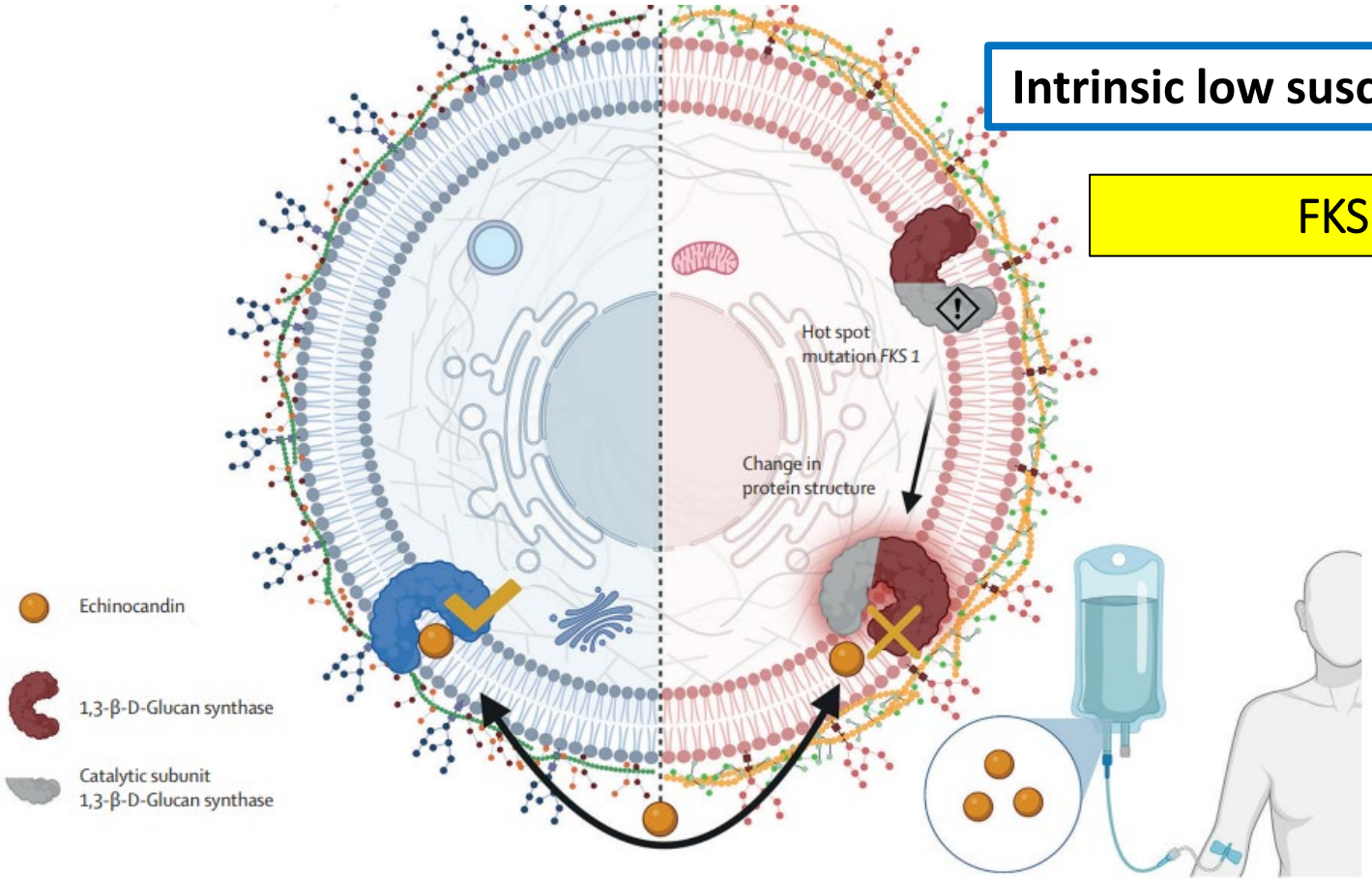
***Aspergillus* spp**

	MEC$_{90}$/MIC$_{90}$ (µg/mL)*	
	A. fumigatus (n=183)[1†]	*A. flavus* (n=45)[1†]
Rezafungin	**0.03**	**0.015**
Anidulafungin	0.03	0.015
Caspofungin	0.03	0.03
Micafungin	0.015	0.03

	MEC$_{90}$/MIC$_{90}$ (µg/mL)*		
	Azole-resistant *A. fumigatus* (n=31)[2‡]	*A. lentulus* (n=11)[2‡]	*A. calidoustus* (n=11)[2‡]
Rezafungin	**0.12**	**≤0.015**	**0.06**
Posaconazole	4	0.5	4
Voriconazole	>16	8	4
Micafungin	0.06	≤0.015	0.03

Pfaller MA, Antimicrob Agents Chemother. 2020

Worldwide emergence of fluconazole-resistant *Candida parapsilosis*: current framework and future research roadmap

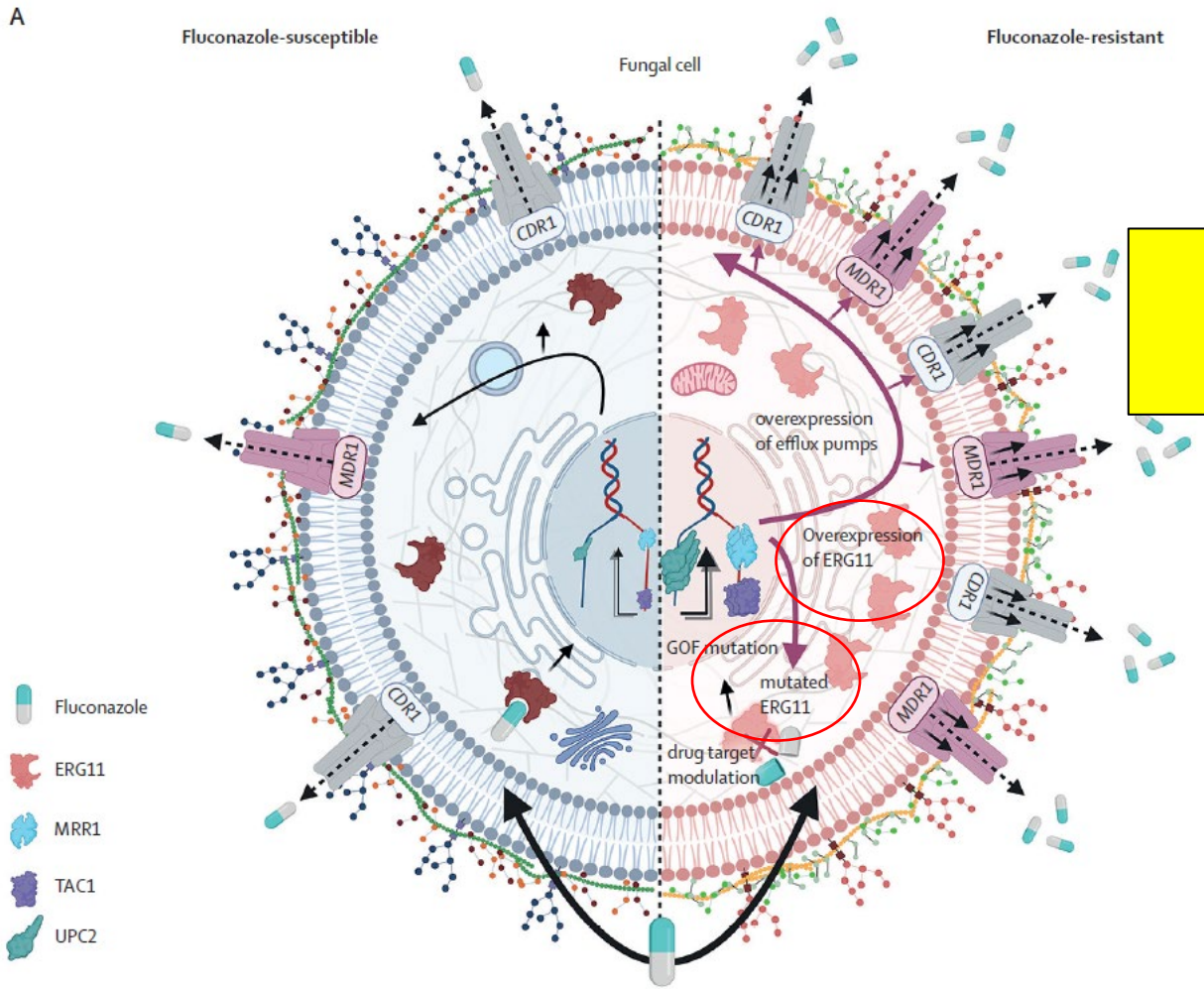


Intrinsic low susceptibility to echinocandins

FKS1 mutation

Daneshnia F, Lancet Microbe. 2023;4:e470-e480

Worldwide emergence of fluconazole-resistant *Candida parapsilosis*: current framework and future research roadmap



Fluconazole resistance

Overexpression and mutations in ERG11

a key enzyme involved in the ergosterol biosynthetic pathway

Daneshnia F, Lancet Microbe. 2023;4:e470-e480

Evaluation of Rezafungin Provisional CLSI Clinical Breakpoints and Epidemiological Cutoff Values Tested against a Worldwide Collection of Contemporaneous Invasive Fungal Isolates (2019 to 2020)

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

Cecilia G. Carvalhaes,[a] Abby L. Klauer,[a] Paul R. Rhomberg,[a] Michael A. Pfaller,[a] Mariana Castanheira[a]

Species and antimicrobial agent (no. of isolates)	MIC_{50}	MIC_{90}	Range	CLSI %S	ECV %S
Candida parapsilosis (239)					
Rezafungin	1	2	0.03 to >2	99.6	99.6
Anidulafungin	2	4	0.03 to>4	86.2	99.6
Caspofungin	0.25	0.5	0.03 to 0.5	100	100
Micafungin	1	1	0.25 to 2	100	100
Fluconazole	0.5	8	0.06 to 128	87.9	87.9
Voriconazole	0.008	0.12	<0.002 to 2	91.6	87
Amphotericin B	0.5	1	0.25 to 1	-	100

Carvalhaes CG, J Clin Microbiol. 2022

Rezafungin *In Vitro* Activity against Contemporary Nordic Clinical *Candida* Isolates and *Candida auris* Determined by the EUCAST Reference Method

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Rezafungin modal MIC for clinical *C. auris* is **0.25 mg/liter.**

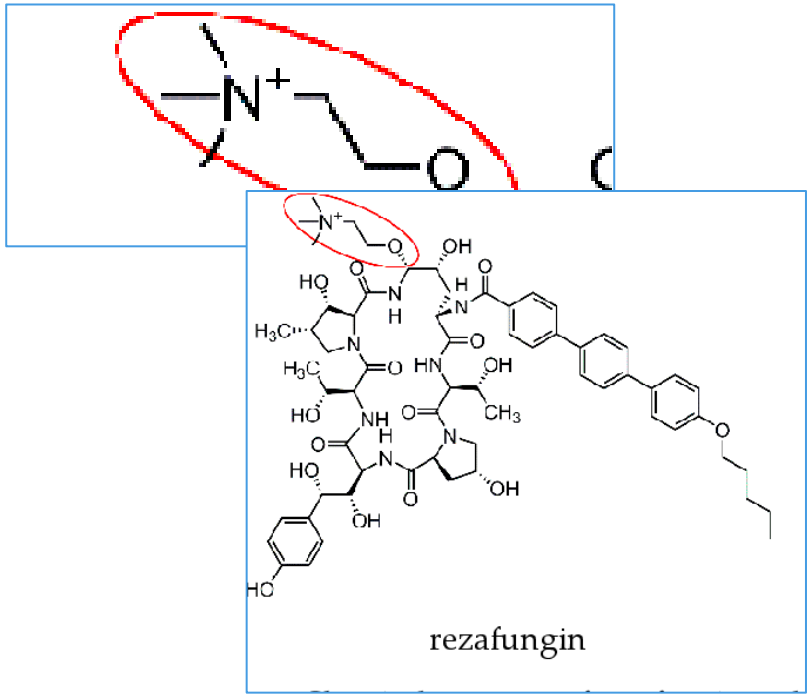
The *in vitro* activity of rezafungin is **similar** to those of anidulafungin and micafungin

fks hot spot mutations, MICs, and relative increases in MICs compared to modal MICs of rezafungin and comparators for *Candida* sp. isolates

Organism	Mutation[a]		MIC[b] (mg/liter)				
	Fks1	Fks2	RZF	ANF	MCF	AMB	FLU
C. auris	S639F	NT	**16**	**4**	**>32**	1	**>256**
	S639F	NT	**16**	**>32**	**>32**	1	**>256**
	S639F	NT	**8**	**>32**	**>32**	1	**>256**
	S639F	NT	**8**	**>32**	**>32**	1	**>256**
	S639F	NT	**8**	**>32**	**>32**	1	**>256**
	S639F	NT	**8**	**>32**	**>32**	1	**>256**
	S639F	NT	**8**	**>32**	**>32**	1	**>256**
	S639F	NT	**8**	**>32**	**>32**	1	**>256**
	WT	NT	**2**	**2**	0.25	1	**>256**
	WT	NT	**2**	**1**	0.25	1	**256**
	WT	NT	**2**	0.03	0.03	0.5	**256**

Helleberg M, Antimicrob Agents Chemother. 2020;64:e02438-19

Rezafungin: the “new” echinocandin



- ❑ Broad spectrum activity
  (look at new challenges *Candida parapsilosis*, *Candida auris*)
- ❑ **Novel PK/PD**
- ❑ Improved safety/increased stability

Distinctive pharmacokinetics of rezafungin

Prolonged half life….and more

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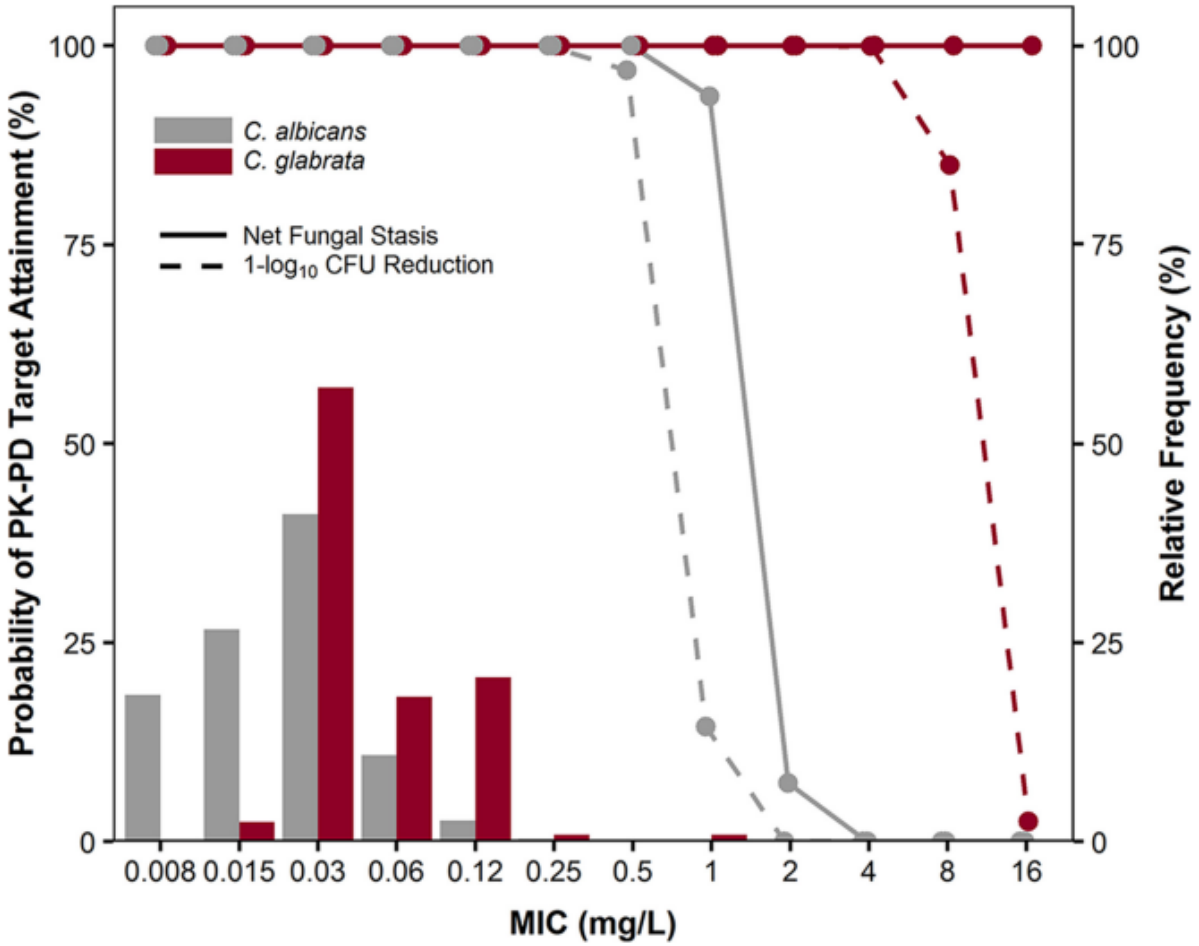


Prolonged half-life (~133 hours)

Week 1 percent probabilities of PK-PD target attainment for *Candida albicans* and *Candida glabrata* based on their respective AUC from time zero to 168 h – to MIC ratio

Bader JC. Antimicrob Agents Chemother. 2018

Rezafungin high probability of PK/PD target attainment against *C. albicans* and *C. glabrata* in Monte Carlo simulations

Maximized PK drivers of efficacy

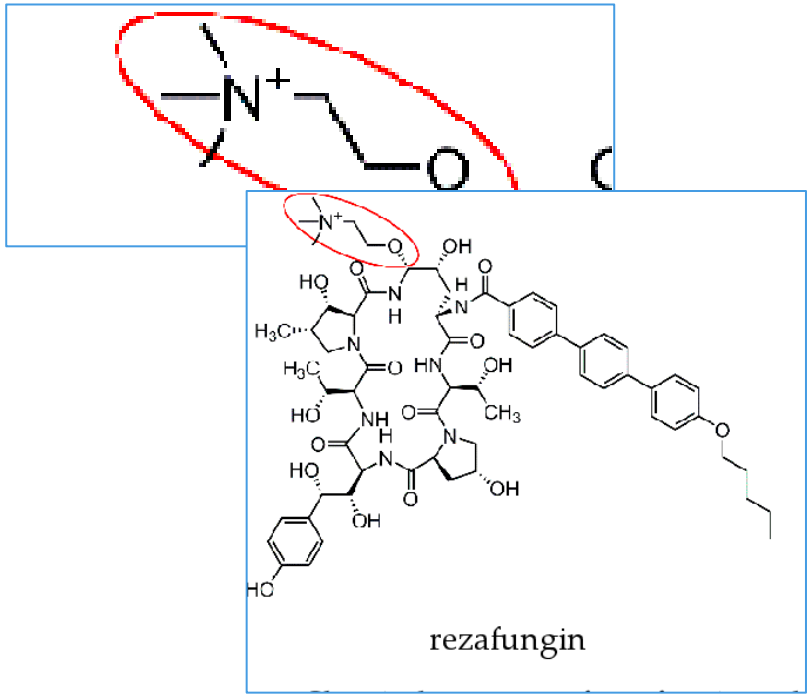
MIC (µg/mL)	*C. albicans*[1,2]			
	Micafungin	Anidulafungin	Caspofungin	Rezafungin
0.008	99.4	100	100	100
0.015	71.2	99.1	100	100
0.03	10.1	52.7	100	100
0.06	0.1	0.90	97.9	100
0.12	0	0	76.7	100
0.25	0	0	35.7	100
0.5	0	0	12.1	100
1	0	0	4.4	76.5
2	0	0	1.35	1.00
4	0	0	0.25	0
8	0	0	0.05	0

MIC (µg/mL)	*C. glabrata*[1,2]			
	Micafungin	Anidulafungin	Caspofungin	Rezafungin
0.008	100	100	100	100
0.015	100	100	100	100
0.03	97.5	99.2	100	100
0.06	49.9	54.3	100	100
0.12	3.40	0.95	100	100
0.25	0	0	100	100
0.5	0	0	97.0	100
1	0	0	73.2	100
2	0	0	33.9	100
4	0	0	11.3	100
8	0	0	4.35	100

MIC, minimal inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic

Bader JC. Antimicrob Agents Chemother. 2018

Rezafungin: the “new” echinocandin



- Broad spectrum activity
  (look at new challenges *Candida parapsilosis*, *Candida auris*)
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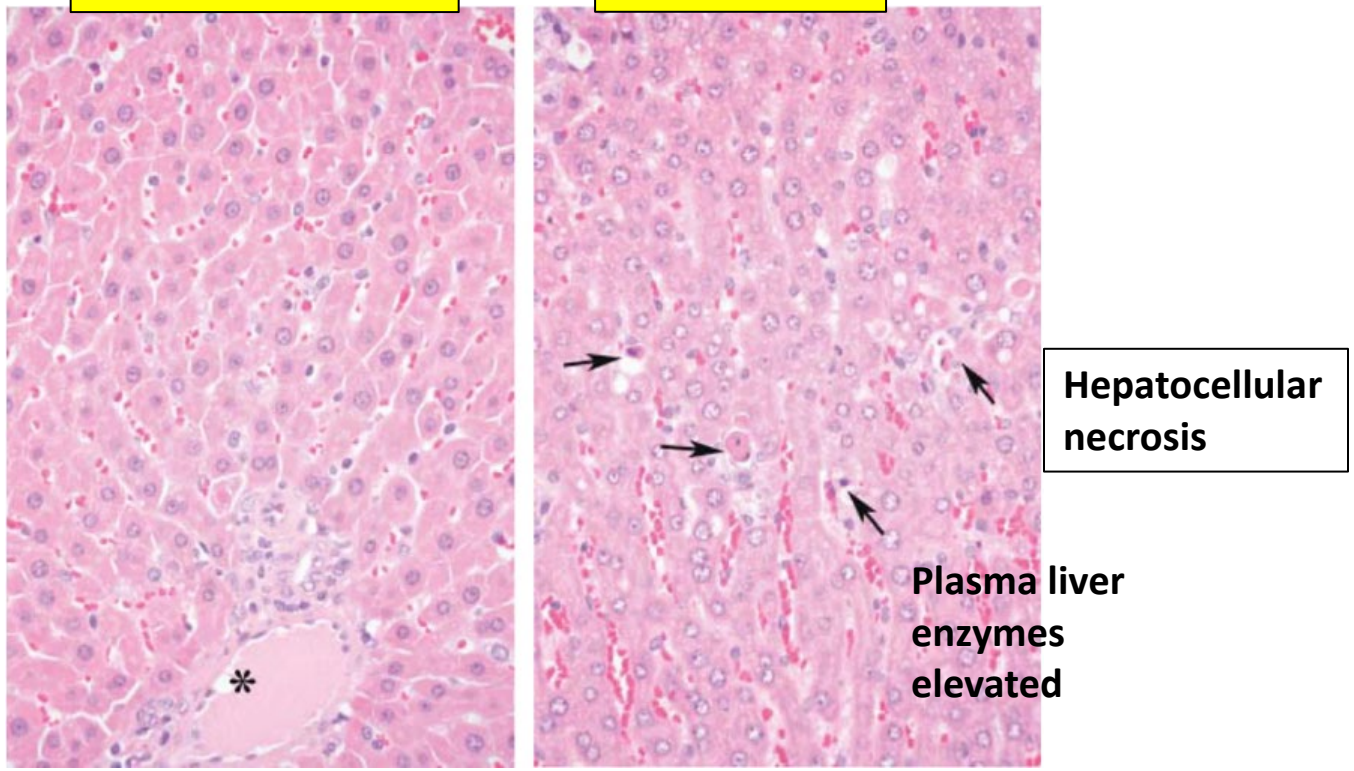
Preclinical Evaluation of the Stability, Safety, and Efficacy of CD101, a Novel Echinocandin

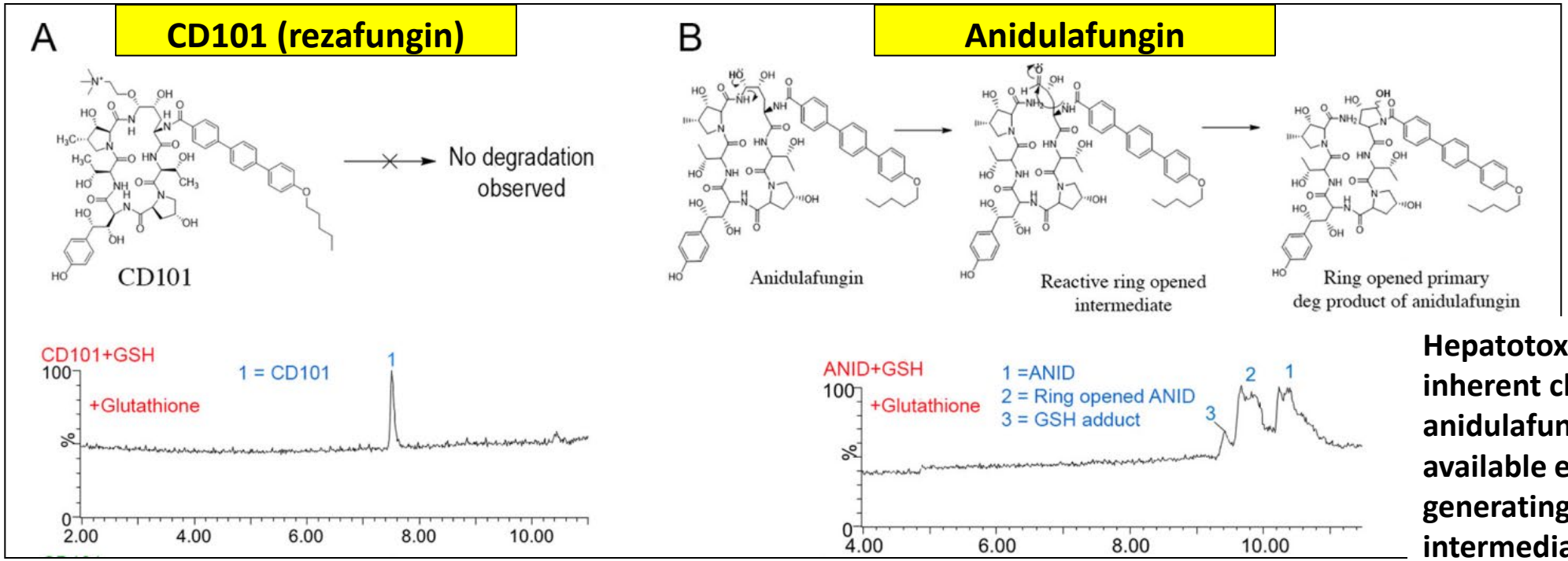
An asterisk shows the portal tract, while black arrows point to hepatocellular necrosis in the case of anidulafungin.



Ong V, Antimicrob Agents Chemother. 2016

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Preclinical Evaluation of the Stability, Safety, and Efficacy of CD101, a Novel Echinocandin



Hepatotoxicity may be due to the inherent chemical lability of anidulafungin (or other currently available echinocandins) generating potentially reactive intermediates

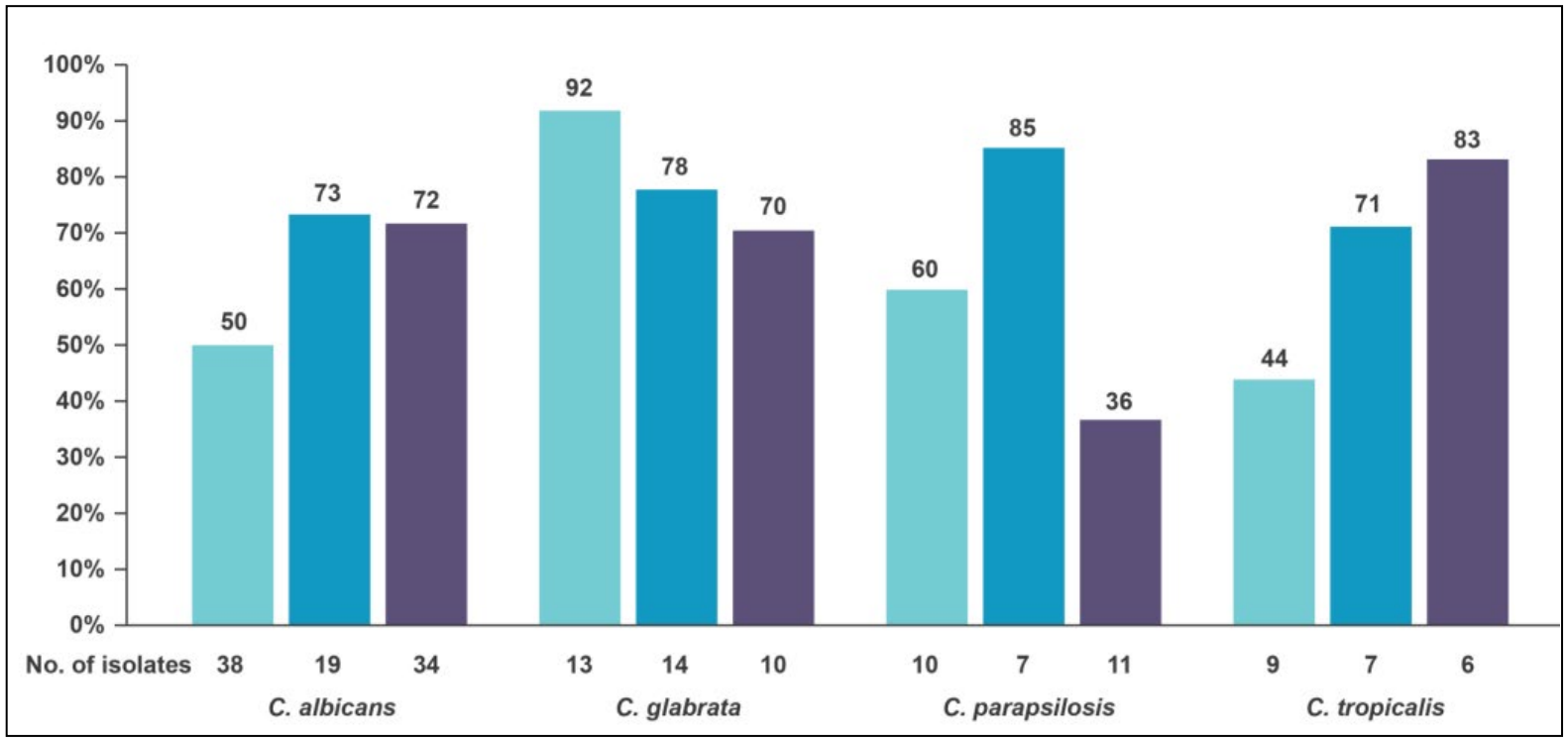
Ong V, Antimicrob Agents Chemother. 2016

Clinical Infectious Diseases
MAJOR ARTICLE

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

Overall Response by *Candida* Species at Day 14 (mITT Population)

- Rezafungin 400 mg/400 mg weekly (N=76)
- Rezafungin 400 mg/200 mg weekly (N=46)
- Caspofungin 70 mg/50 mg daily (N=61)



Thompson GR, Clin Infect Dis. 2021

Efficacy and safety of rezafungin and caspofungin in candidaemia and invasive candidiasis: pooled data from two prospective randomised controlled trials

Pooled data from phase 2 STRIVE and phase 3 ReSTORE rezafungin trials

Efficacy

	Rezafungin (n=139)	Caspofungin (n=155)	Treatment difference (95% CI)
Primary pooled efficacy endpoint: day 30 all-cause mortality			
Deceased or unknown survival status	26 (19%)	30 (19%)	..
Known deceased	21 (15%)	25 (16%)	..
Unknown survival status	5 (4%)	5 (3%)	..
Alive	113 (81%)	125 (81%)	..

Thompson GR 3rd, et al. Lancet Infect Dis. 2024

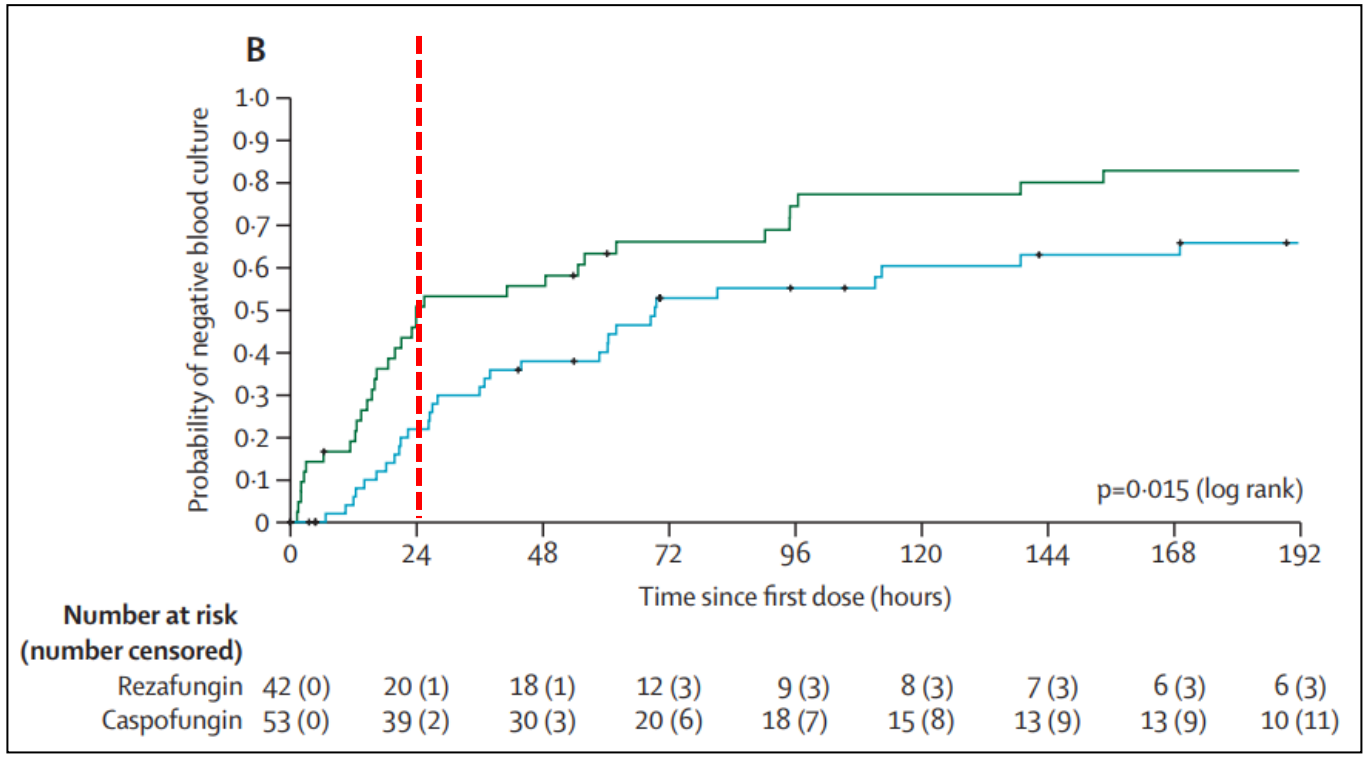
Efficacy and safety of rezafungin and caspofungin in candidaemia and invasive candidiasis: pooled data from two prospective randomised controlled trials

Pooled data from phase 2 STRIVE and phase 3 ReSTORE rezafungin trials

Time to negative BC

Rapid infection clearance

Time to first negative blood culture in patients with a positive blood culture at randomisation



BC blood cultures

Thompson GR 3rd, et al. Lancet Infect Dis. 2024

JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlae042

JAC-Antimicrobial Resistance

Treatment of *Candida glabrata* native valve endocarditis with rezafungin: a case report

Giovanni Mori [1,2]*, Martina Gottardi[1], Monica Guffanti[3], Antonella Castagna[2,3] and Massimiliano Lanzafame[1]

Open Forum Infectious Diseases

NOVEL ID CASES

Expanded Access Use of Rezafungin for Salvage Therapy of Invasive *Candida glabrata* Infection: A Case Report

Alina Adeel,[1] Ming D. Qu,[1] Efaza Siddiqui,[2] Stuart M. Levitz,[1] and Richard T. Ellison III[1]

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

CHALLENGING CLINICAL CASE
August 2024 Volume 68 Issue 8 e00750-24
https://doi.org/10.1128/aac.00750-24

Safety of rezafungin as a long-term treatment option in two patients with complicated fungal infections: two cases from Lecco Hospital (Italy)

Giacomo Ponta [1,2], Valentina Morena[1], Martina Strano[1,2], Chiara Molteni[1], Silvia Pontiggia [1], Erica Michela Cavalli[3], Anna Grancini[4], Carola Mauri[5], Antonella Castagna[2], Andrea Galanti[6], Stefania Piconi [1]

Extended-Interval Dosing of Rezafungin against Azole-Resistant *Aspergillus fumigatus*

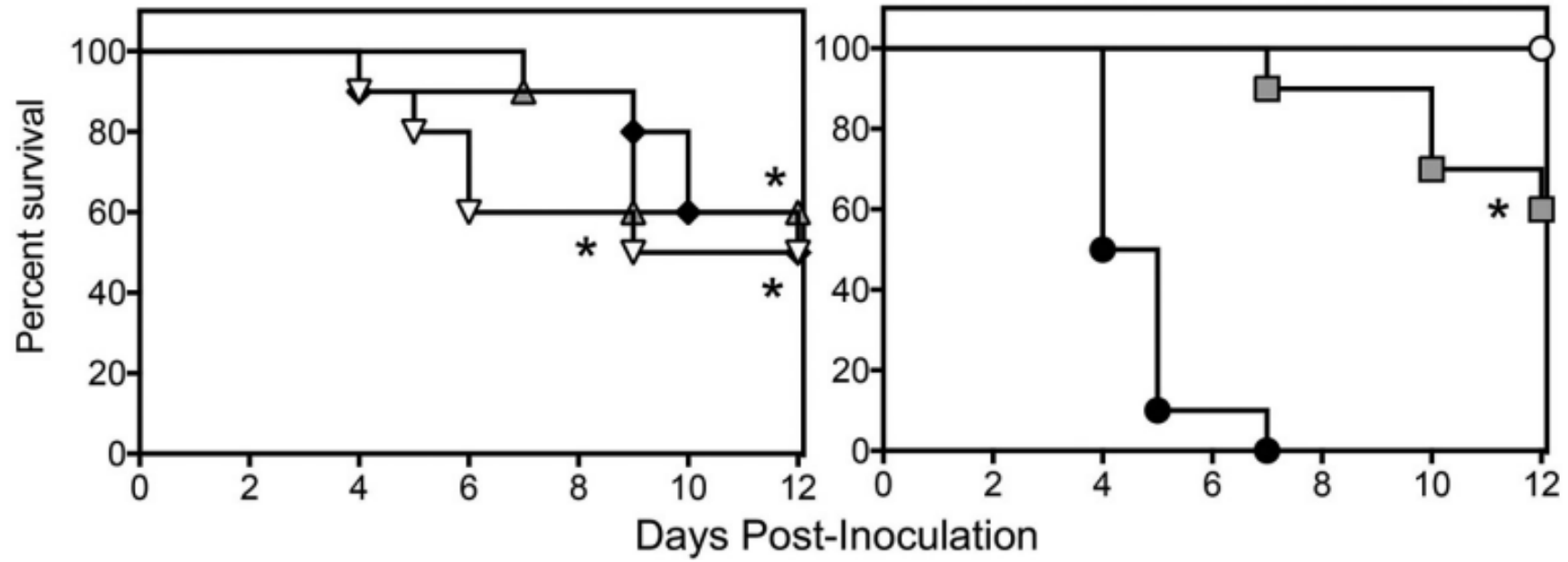
AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Nathan P. Wiederhold,[a] Laura K. Najvar,[b,d] Rosie Jaramillo,[b,d] Marcos Olivo,[b,d] Brian L. Wickes,[c] Gabriel Catano,[b,d] Thomas F. Patterson[b,d]

Survival curves in a neutropenic murine model of invasive aspergillosis caused by an azole-resistant *A. fumigatus* isolate harboring a TR34/L98H mutations.

Different doses of Rezafungin (1, 4, 16 mg/kg)

Vehicle control, or supratherapeutic posaconazole (20 mg/kg BID)



Antimicrob Agents Chemother. 2019

Recruiting

Study of Rezafungin Compared to Standard Antimicrobial Regimen for Prevention of Invasive Fungal Diseases in Adults Undergoing Allogeneic Blood and Marrow Transplantation (ReSPECT)

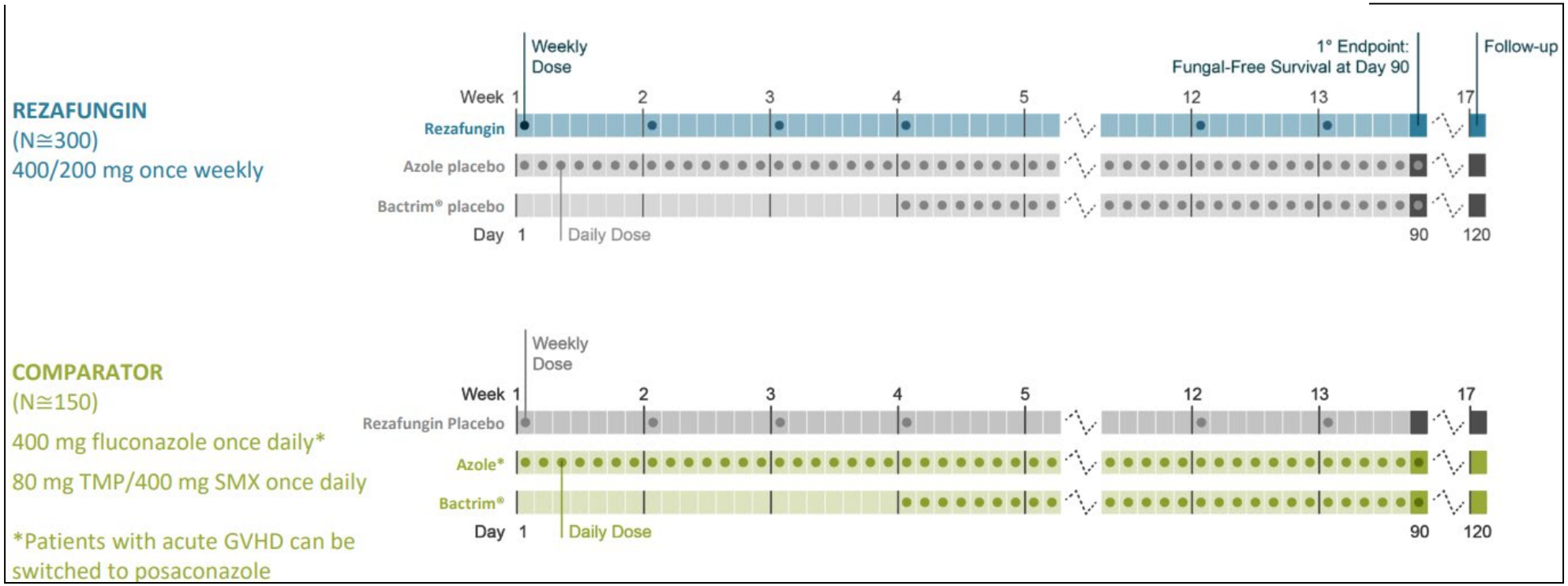
ClinicalTrials.gov ID NCT04368559

Sponsor Mundipharma Research Limited

Information provided by Mundipharma Research Limited (Responsible Party)

Last Update Posted 2024-07-26

Prophylaxis in HSCT

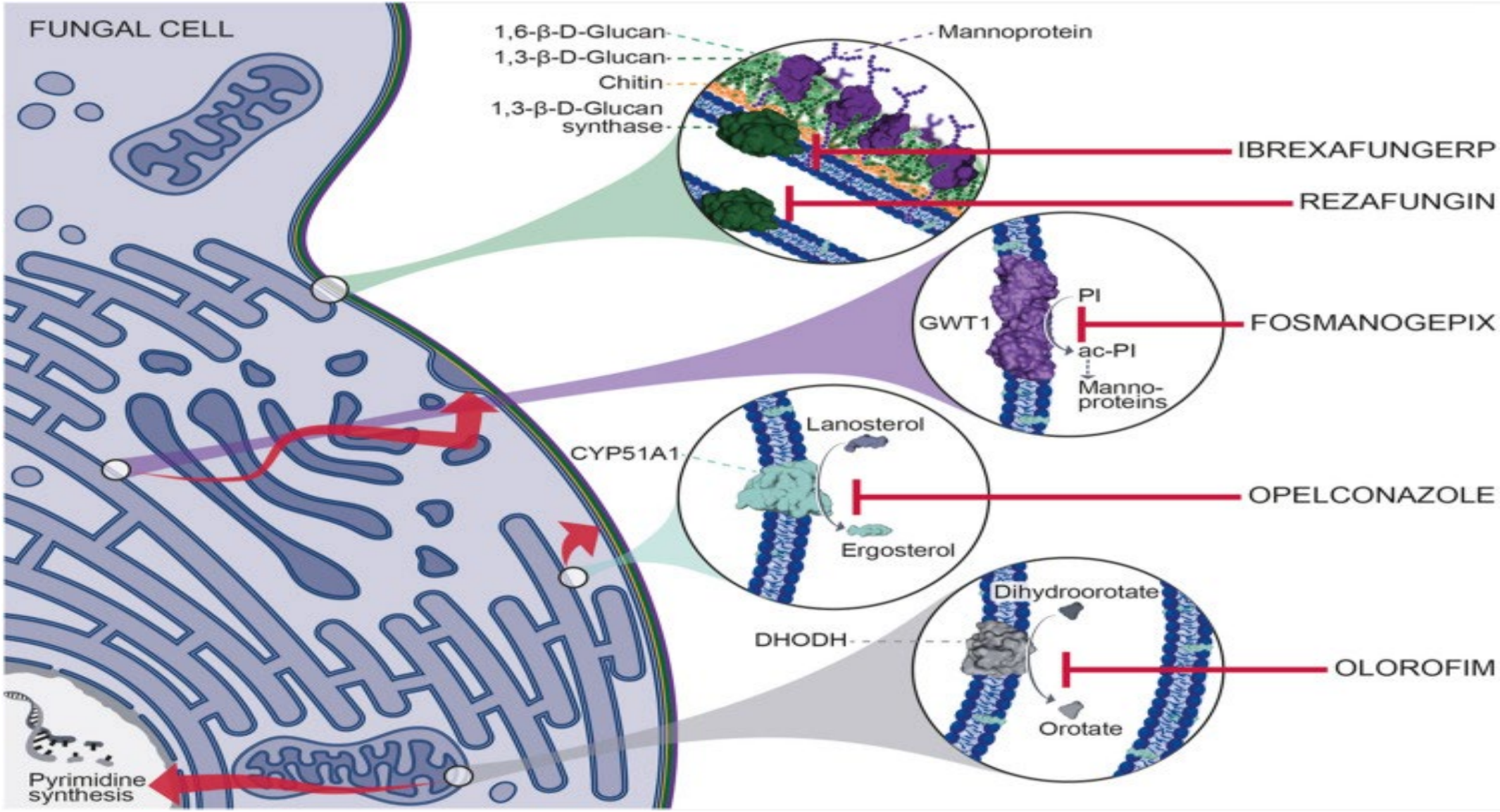


https://www.clinicaltrials.gov/study/NCT04368559. Accessed 19 NOV 2024

Hot points for Rezafungin

- **Long half-life, improved PK**
- **Broad spectrum activity (activity against *Candida* spp, including *Candida parapsilosis* and *Candida auris*, but pay attention to FKS mutations).**
- **Early discharge.**
- **Management of difficult-to-treat subacute/chronic Candida infections (endocarditis).**
- **Future use as prophylaxis (candidemia, aspergillosis, pneumocystosis)**

Mechanism of action of novel antifungal drugs



The Antifungal Pipeline: Fosmanogepix, Ibrexafungerp, Olorofim, Opelconazole, and Rezafungin. Martin Hoenigl, Rosanne Sprute, Matthias Egger. Drugs. 2021

Antifungal drug	*Candida* spp.		*Aspergillus* spp.		*Mucorales*	*Fusarium* spp.	*Scedosporium / Lomentospora* spp.
	Wild-type[1]	Echinocandin-resistant[2]	Wild-type[3]	Azole-resistant[4]			
Rezafungin	Except *C. parapsilosis* (higher MIC)						
Ibrexafungerp							
Olorofim						Activity against *F. oxysporum* >> *F. solani*	
Manogepix	Except *C. krusei* (higher MIC)					Some resistant isolates (*F. oxysporum*, *F. verticilloides*)	Few resistant isolates (*S. apiospermum*)

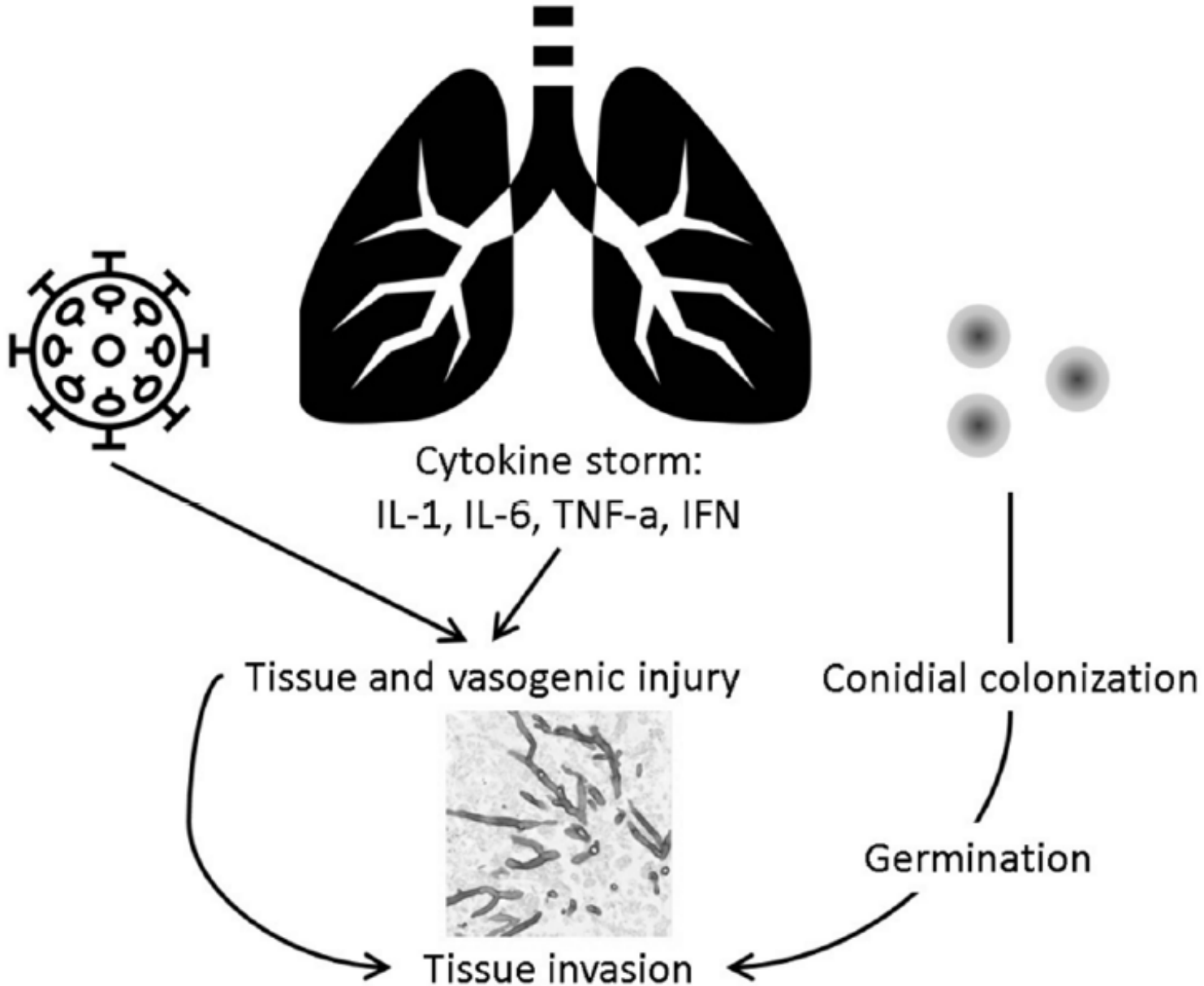
Activity against most isolates

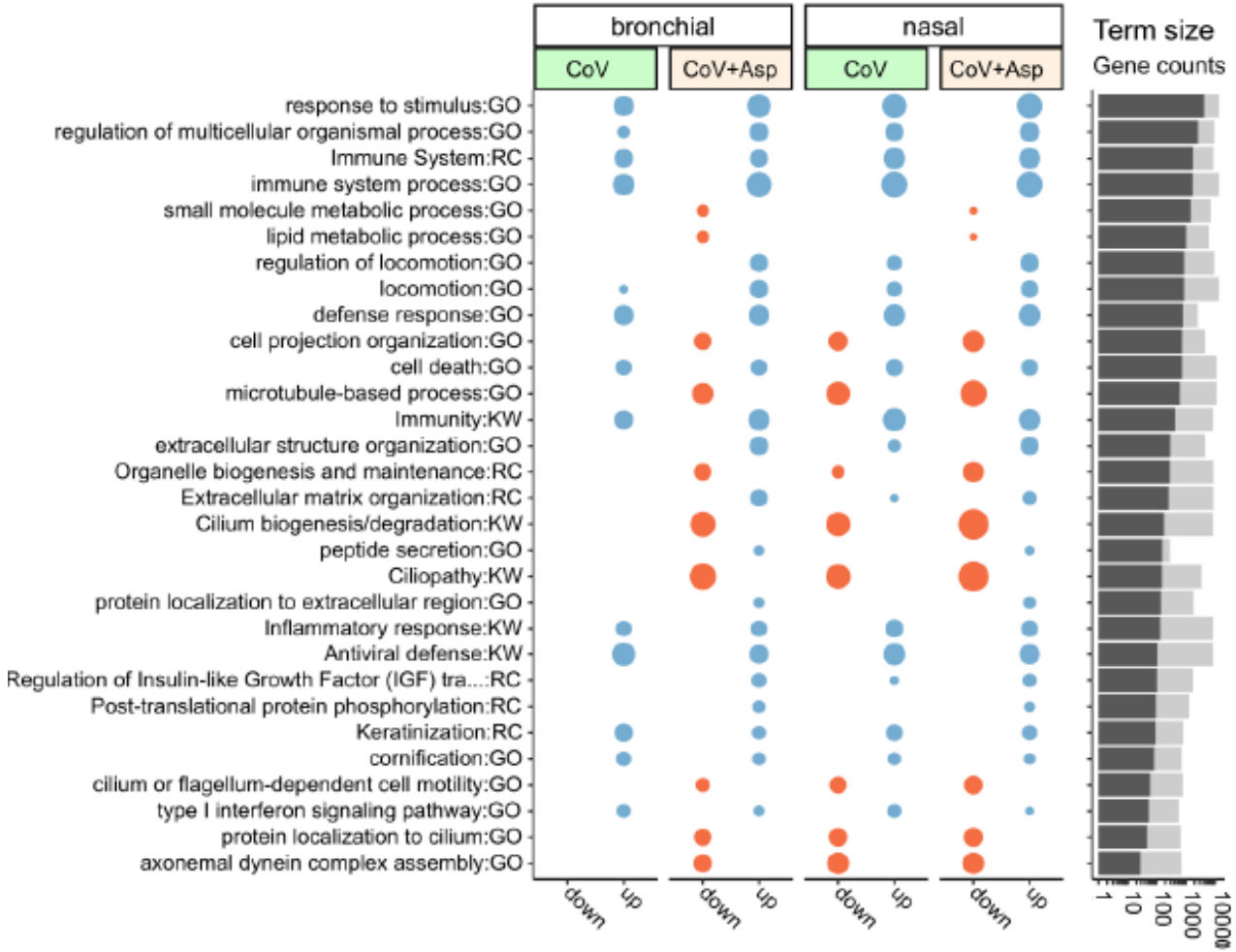
Variable activity (species-specific or isolate-specific)

Marginal activity (few susceptible isolates or relatively high MIC

No significant activity

The Antifungal Pipeline: Fosmanogepix, Ibrexafungerp, Olorofim, Opelconazole, and Rezafungin. Martin Hoenigl,Rosanne Sprute, Matthias Egger. Drugs.2021 Oct;81(15):1703-1729. doi: 10.1007/s40265-021-01611-0. Epub 2021 Oct 9.


Cytokine storm:
IL-1, IL-6, TNF-a, IFN
Tissue and vasogenic injury
Conidial colonization
Germination
Tissue invasion



De Lamballerie et al, Microorganisms, 2020

Imbalanced type I/type III IFN

Induction of several monocyte and neutrophil associated chemokines

Polymorphisms in Toll-Like Receptor Genes and Susceptibility to Pulmonary Aspergillosis

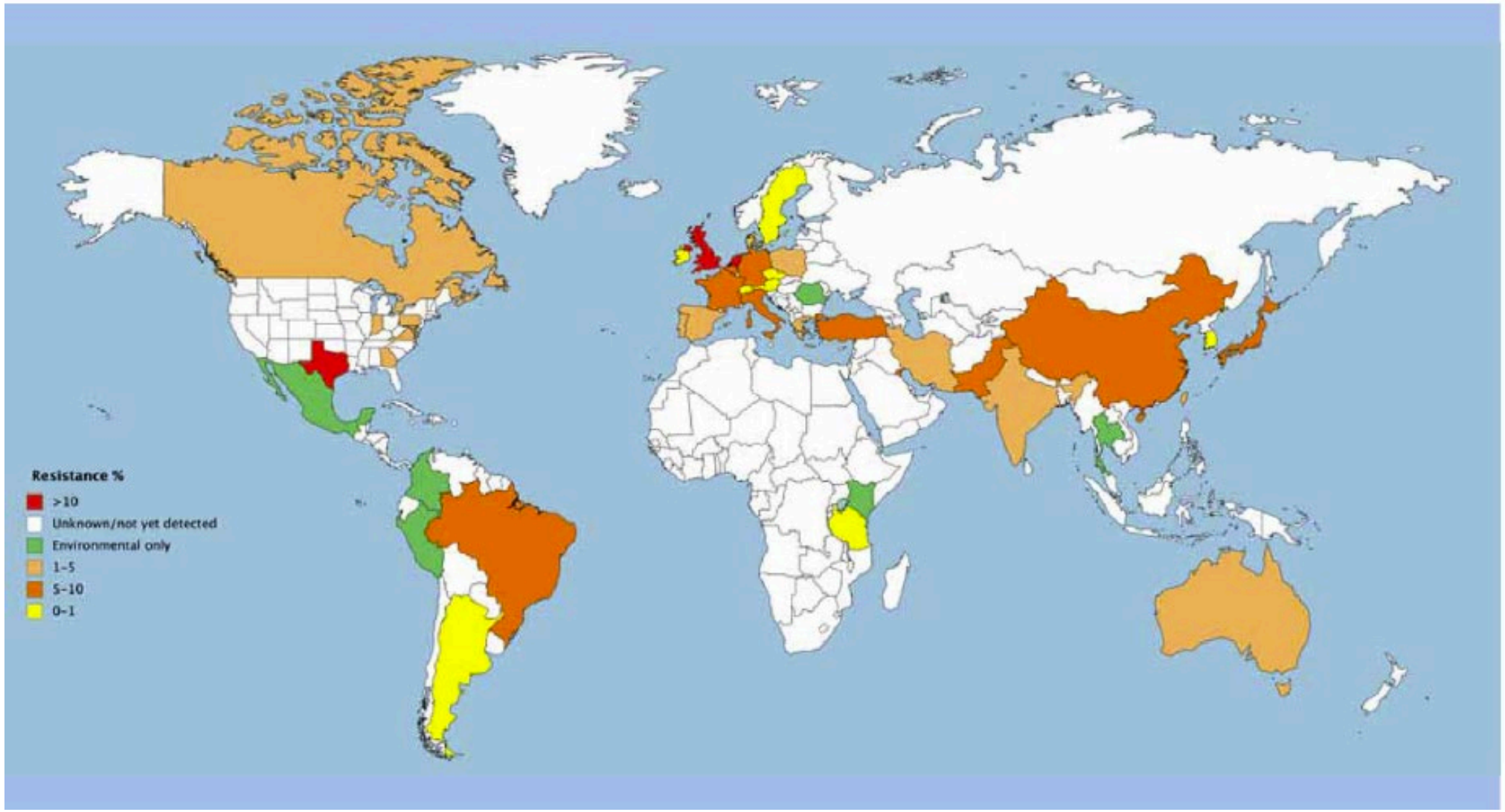
A significant association was observed between allele G on Asp299Gly (TLR4) and chronic cavitary pulmonary aspergillosis

Susceptibility to allergic bronchopulmonary aspergillosis was associated with allele C on T-1237C (TLR9)

Importance of innate immunity in the pathogenesis of different forms of aspergillosis.

Carvalho, JID, 2008

Can triazole resistance in *Aspergillus fumigatus* explain high mortality rates?

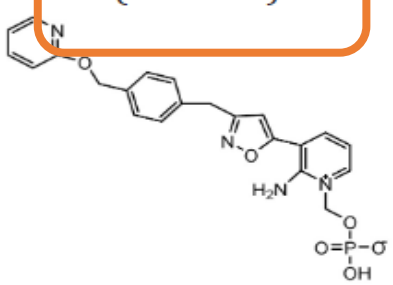


Lestrade et al, CMI 2019

Novel antifungal agents

Agents targeting the cell wall

Novel investigational antifungal agents in clinical trials.

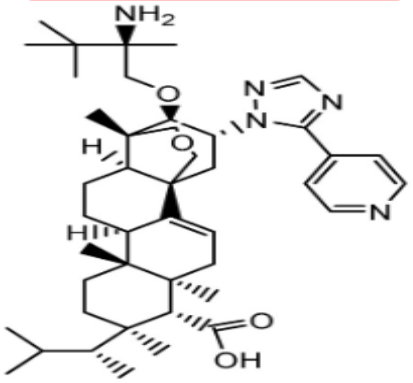
Class	Novel agent	Mechanism of action	Spectrum of activity	Completed/ongoing phase 2 and 3 clinical trials	Potential advantages
Glycosylphos-phatidylinositol (GPI) inhibitors	Fosmanogepix (APX001) 	Inhibits the fungal enzyme Gwt1 to disrupt GPI-anchor post-translational protein modification	*Candida* spp. except *C. krusei* *Cryptococcus* spp. *Aspergillus* spp. *Fusarium* spp. *Scedosporium* spp. *Lomentospora prolificans* *Purpureocillium lilacinum* *Rhizopus arrhizus* *Coccidioides* spp.	Ongoing • Treatment of IFIs due to *Aspergillus* spp or rare moulds (NCT04240886) • Treatment of candidemia or invasive candidiasis due to *C. auris* (NCT04148287) • Treatment of candidemia in non-neutropenic patients (NCT03604705)	Broad spectrum and active against highly resistant fungi

Novel antifungal agents in clinical trials. Samantha E Jacobs, Panagiotis Zagaliotis,Thomas J Walsh. 2021 Jun 28;10:507.doi: 10.12688/f1000research.28327.2

- ✓Rapid and extensive absorption to most tissues including lung, brain, liver, kidney, and eye. The elimination was primarily biliary (rats) and fecal (monkeys). There was no dose-limiting toxicity.

- ✓Fosmanogepix also shows *in vitro* activity against fluconazole-resistant *Candida* species, including *C. auris,* as well as echinocandin-resistant *C. albicans* and *C. glabrata* with *fks* mutations.

- ✓Clinical development of fosmanogepix has thus far focused on its role in the treatment of infections due to *Candida* spp., *Aspergillus* spp., and rare moulds. The U.S. Food and Drug Association (FDA) has granted Fast Track, Qualified Infectious Disease Product (QIDP), and orphan drug designation to fosmanogepix for the following indications: treatment of invasive candidiasis, invasive aspergillosis, scedosporiosis, fusariosis, mucormycosis, cryptococcosis, and coccidioidomycosis.

Triterpenoids	Ibrexafungerp (SCY-078) 	Inhibits (1(3)-β-D-glucan synthase	*Candida* spp. including echinocandin-resistant *C. glabrata* and *C. auris* *Aspergillus* spp. *Paecilomyces variotii* *Pneumocystis jirovecii*	Completed • Step-down therapy for candidemia and/or invasive candidiasis (NCT02244606) • Treatment of acute VVC (DOVE, NCT03253094; VANISH-303, NCT03734991; NCT02679456) Ongoing • Treatment in patients with refractory or intolerant fungal diseases (FURI, NCT03059992) • Ibrexafungerp and voriconazole combination for treatment of invasive pulmonary aspergillosis (NCT03672292) • Treatment of *Candida auris* infection (CARES, NCT03363841) • Prevention of recurrent VVC (CANDLE, NCT04029116) • Treatment of acute VVC (Vanish 306, NCT03987620)	• Active against resistant *Candida* species • First orally bioavailable inhibitor of (1(3)- β-D-glucan synthase • Combination therapy against invasive aspergillosis • Oral fungicidal therapy against *Candida* spp., including step-down for candidemia

Novel antifungal agents in clinical trials. Samantha E Jacobs, Panagiotis Zagaliotis,Thomas J Walsh. 2021 Jun 28;10:507

- ✓Ibrexafungerp retains *in vitro* activity against most echinocandin-resistant *C. glabrata* with *fks* mutations.

- ✓Ibrexafungerp has fungistatic activity against *Aspergillus* species (MEC range <0.06µg/mL to 4µg/mL). The combination of ibrexafungerp with voriconazole, amphotericin B, or isavuconazole demonstrates *in vitro* synergy against wild-type (WT) *Aspergillus* species but not against azole-resistant strains. Little *in vitro* activity is observed with ibrexafungerp against the Mucorales and non- *Aspergillus* hyaline moulds (*Fusarium* spp, *Scopulariopsis* spp, *Lomentospora prolificans*) with the exception of *Paecilomyces variotii* (MEC <0.02µg/mL to 0.03µg/mL).

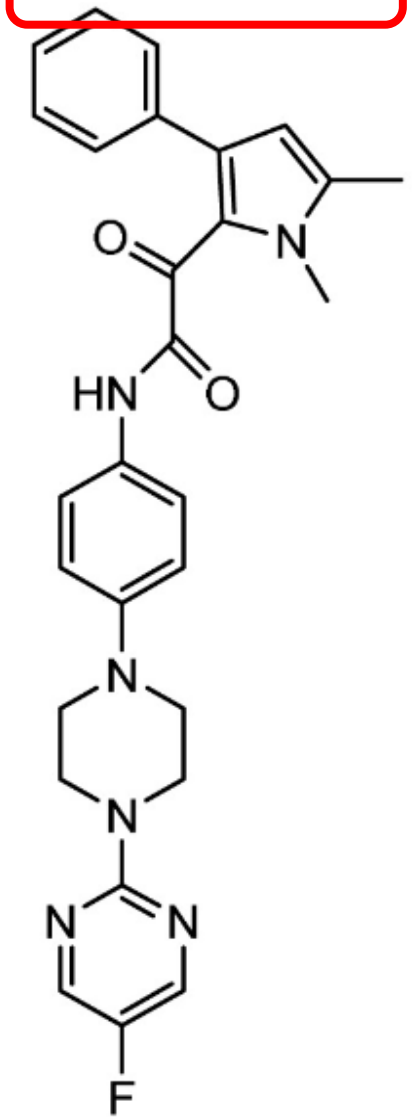
- ✓ Concentration in multiple tissues including liver, spleen, lungs, bone marrow, kidney, and skin exceeds that of plasma. However, there is low distribution to central nervous system (CNS) tissue. In rats, approximately 90% of drug is eliminated in feces and bile, and 1.5% eliminated in urine.

- ✓ Ibrexafungerp will likely play an important role in management of invasive candidiasis due to WT and resistant *Candida* species and invasive aspergillosis; the drug has received QIDP and orphan drug designations for both indications.

- ✓brexafungerp has also been studied for the treatment of vulvovaginal candidiasis (VVC). Day 10 and day 25 clinical cure and mycological eradication rates were similar or improved with ibrexafungerp 300mg twice daily × 2 doses compared to fluconazole 150mg × 1 dose.

- ✓Ibrexafungerp may develop a key role in combination antifungal therapy with an antifungal triazole in treatment of invasive aspergillosis. Simultaneous administration of an orally administered triazole and ibrexafungerp may allow patients to receive the potential therapeutic benefit of combination therapy in treatment of invasive pulmonary aspergillosis on an ambulatory basis.

Agents targeting nucleic acid metabolism

Orotomides	Olorofim (F901318) 	Inhibits the pyrimidine biosynthesis enzyme dihydroorotate dehydrogenase	*Aspergillus* spp. *Scedosporium* spp. *Lomentospora prolificans* *Fusarium* spp. *Histoplasma capsulatum* *Blastomyces dermatitidis* *Coccidioides* spp.	Ongoing • Treatment of IFIs due to resistant fungi (FORMULA-OLS, NCT03583164)	• Active against highly-resistant moulds

Novel antifungal agents in clinical trials. Samantha E Jacobs, Panagiotis Zagaliotis,Thomas J Walsh. 2021 Jun 28;10:507.doi: 10.12688/f1000research.28327.2

- ✓ Olorofim is available in oral and IV formulations and demonstrates time-dependent antifungal activity. Olorofim initially has a fungistatic effect on *Aspergillus* isolates but prolonged exposure is fungicidal.

- ✓Pharmacokinetic studies in mice have identified good distribution of olorofim to tissues including the kidney, liver, and lung, with lower levels of detection in the brain.

- ✓Olorofim exhibits time-dependent antifungal activity.

- ✓The European Medicines Agency Committee for Orphan Medicinal Products also granted orphan drug status to olorofim for the treatment of invasive aspergillosis and scedosporiosis.

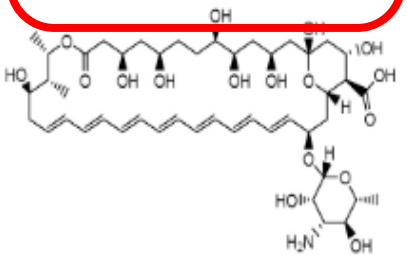
Table 1.

Pharmacologic Properties of Novel Antifungal Drugs

Antifungal Drug	Type of Molecule and Mechanism of Action	PK/PD	Therapeutic Considerations
Rezafungin (CD 101; Cidara Therapeutics)	Echinocandin; inhibition of β-glucan synthase	Long half-life (130 h)[a]; low clearance; protein binding, 97%–99%; large volume of distribution; poor CNS penetration; prolonged accumulation in tissues at high concentrations; minimal cytochrome P450 metabolism; biliary elimination; PK/PD index, AUC/MIC	Intravenous formulation only; once-weekly administration; good safety profile
Ibrexafungerp (SCY-078, MK-3118; Scynexis)	Triterpenoid; inhibition of β-glucan synthase	Oral bioavailability, 35%–50%; half-life, 20–30 h; protein binding, >99%; large volume of distribution; poor CNS penetration; hepatic metabolism (cytochrome P450); biliary elimination; PK/PD index, AUC/MIC	Oral formulation (intravenous under investigation); good safety profile; no significant drug interactions (notably regarding anticalcineurin inhibitors)
Olorofim (F901318; F2G)	Orotomide; inhibition of fungal dihydroorotate dehydrogenase	Oral bioavailability: 45%–82%; half-life, 20–30 h; protein binding, >99%; high volume of distribution including CNS; hepatic metabolism (cytochrome P450); biliary elimination; PK/PD index, C_{min}/MIC	Oral or intravenous formulations; no relevant issues about drug-drug interactions to date (under investigation); possible role for TDM (under investigation)
Fosmanogepix (APX001; Amplyx Pharmaceuticals, now a Pfizer subsidiary)[b]	N-phosphonooxymethylene; inhibition of Gwt1 (GPI biosynthesis pathway)	Oral bioavailability, >90%; half-life, 2–2.5 d; large volume of distribution, including CNS; hepatic metabolism (cytochrome P450); biliary elimination; PK/PD index, AUC/MIC	Oral or intravenous formulations; no relevant issues about drug-drug interactions to date (under investigation)

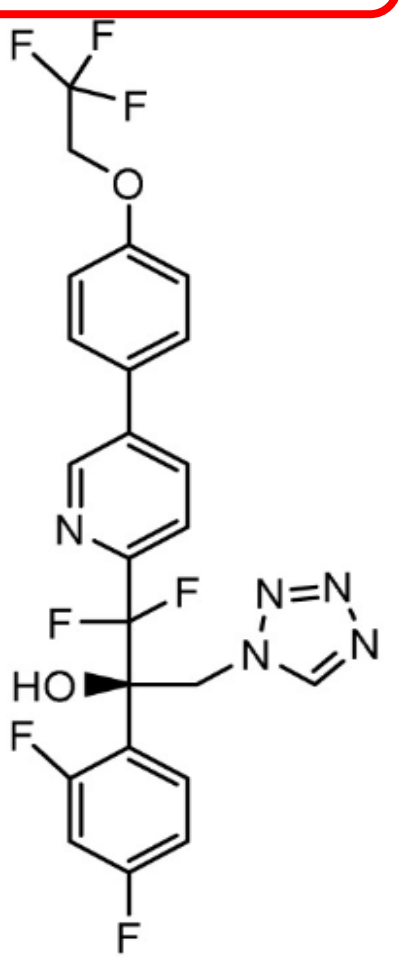
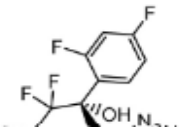
Investigational Antifungal Agents for Invasive Mycoses: A Clinical Perspective. Frederic Lamoth, Russell E Lewis, Dimitrios P Kontoyiannis. *Clinical Infectious Diseases*, Volume 75, Issue 3, 1 August 2022.

Agents targeting the cell membrane

Polyenes	Encochleated amphotericin B (MAT2203) 	Binds to ergosterol to form pores in fungal cell membrane	*Candida* spp. *Aspergillus* spp. *Cryptococcus* spp.	Completed • Treatment of VVC (NCT02971007) Ongoing • Treatment of refractory mucocutaneous candidiasis (NCT02629419) • Treatment of cryptococcal meningitis in HIV-infected patients (EnACT, NCT04031833)	• Oral formulation • Less toxicity than deoxycholate and lipid formulations of amphotericin B

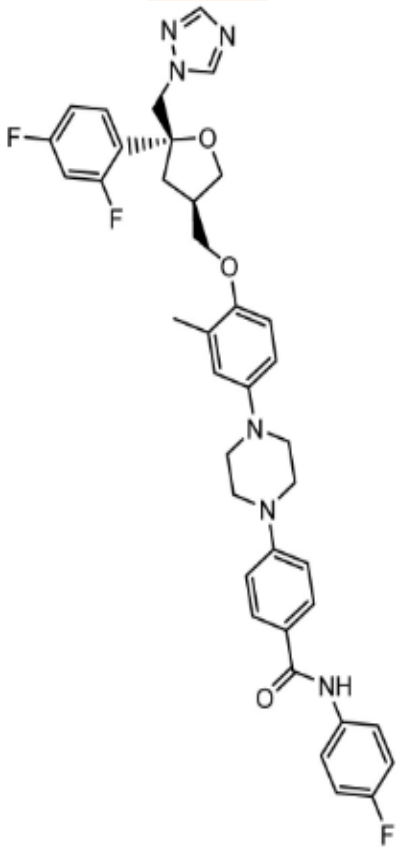
✓Comparable *in vitro* activity against *Candida* spp. and *Aspergillus* spp. are observed with CAmB and deoxycholate AmB.

✓A single dose of CAmB demonstrates extensive tissue distribution and penetration into target tissues in animal models. In a phase 1 study in healthy adults evaluating escalating doses of 200, 400, and 800mg, CAmB was well tolerated at doses of 200mg and 400mg. The most common adverse events were gastrointestinal.

Tetrazoles	Oteseconazole (VT-1161), VT-1598  Oteseconazole 	Inhibition of lanosterol 14-alpha-demethylase enzyme to disrupt ergosterol synthesis	*Candida* spp. including fluconazole- and echinocandin-resistant *C. glabrata* *Cryptococcus* spp. *Coccidioides* spp. *Histoplasma capsulatum* *Blastomyces dermatitidis* *Aspergillus* spp. *Rhizopus arrhizus*	Completed (Oteseconazole) • Treatment of toenail onychomycosis (NCT02267356) • Treatment of recurrent VVC (NCT02267382) • Treatment of acute vaginal candidiasis (NCT01891331) Ongoing (Oteseconazole) • Treatment of recurrent VVC (NCT02267382, NCT03562156, NCT03561701, NCT03840616) • Treatment of tinea pedis (NCT01891305)	• Fungal-specific enzyme target leads to fewer drug-drug interactions • Broad spectrum against yeasts, endemic fungi, and moulds (VT-1598)

✓In murine models of CNS coccidioidomycosis, VT-1598 treatment leads to improved survival and reduced fungal burden in brain tissue as compared to fluconazole.

✓In murine models of CNS coccidioidomycosis, VT-1598 treatment leads to improved survival and reduced fungal burden in brain tissue as compared to fluconazole.

Triazoles	PC945 	Inhibition of lanosterol 14-alpha-demethylase enzyme to disrupt ergosterol synthesis	*Candida* spp. including fluconazole-resistant *C. glabrata, C. krusei* and *C. auris* *Cryptococcus* spp. *Trichophyton rubrum* *Aspergillus fumigatus* and *A. terreus*	None	• Inhaled delivery • Activity against azole-resistant *Aspergillus fumigatus*

- ✓PC945 is a novel triazole antifungal agent that is being developed specifically for inhaled administration for treatment and prevention of invasive fungal infections of the sinopulmonary.

- ✓The therapeutic potential of intranasal PC945 has been investigated in transiently neutropenic mice with invasive pulmonary aspergillosis. Intranasal PC945 leads to reduced concentrations of GM in bronchoalveolar lavage fluid (BALF) and serum and improved survival as compared to controls, and reduced GM concentration and similar survival as compared to intranasal posaconazole.

- ✓Combination therapy with intranasal PC945 and oral posaconazole was also evaluated in immunocompromised neutropenic mice with azole-susceptible *A. fumigatus* infection.

Table 3.

Other Novel Antifungal Drugs in Ongoing Clinical Trials for Invasive Fungal Infections

Antifungal Drug	Type of Molecule and Mechanism of Action	PK/PD Properties	Antifungal Spectrum	FDA Designation and Clinical Research Stage[a]
Tetrazoles (VT-1161, VT-1129, and VT-1598)	Azoles; inhibition of ergosterol biosynthesis	Similar to azoles; decreased affinity for human P450 cytochrome enzymes (less toxicity and less drug-drug interactions)	Comparable to triazoles; active against *Candida* spp. including *C. auris* and some azole-resistant species;only VT-1598 active against *Aspergillus* spp. (except azole-resistant *Cyp51A* mutant strains); marginal activity against Mucorales (only *Rhizopus arrhizus* var. *arrhizus*)	VT-1161: QIDP, fast track; VT-1129: orphan drug, QIDP; VT-1598: orphan drug, QIDP, fast track; phase I (coccidioidomycosis; ongoing)
Encochleated amphotericin B	Polyenes; drug conditioned in a cochleate; targeted delivery to reticulo-endothelial cells	Similar to amphotericin B (less toxicity)	Comparable to amphotericin B	Orphan drug, QIDP, fast track; phase I (patients with HIV and prior cryptococcosis; completed) [83]; phase II (patients with HIV and cryptococcal meningitis; ongoing)
PC945	Triazoles; inhibition of ergosterol biosynthesis	Similar to triazoles; inhaled route of administration	Comparable to other triazoles, but improved activity against azole-resistant *Aspergillus fumigates*	Phase I (healthy subjects and mild asthma; completed) [84]; phase II (preemptive treatment of IPA in lung transplant recipients; interrupted)
T-2307	Arylamidine Inhibition of mitochondrial respiratory chain complexes III and IV	Under investigation	Broad antifungal activity against *Candida* spp., *Cryptococcus* spp. and *Aspergillus* spp., including azole- and echinocandin-resistant strains	Phase I (ongoing)
MGCD290	Inhibitor of histone deacetylase	Under investigation	Modest antifungal activity per se; synergism with azoles against *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp., Mucorales, *Fusarium* spp. and *Scedosporium* spp.	None

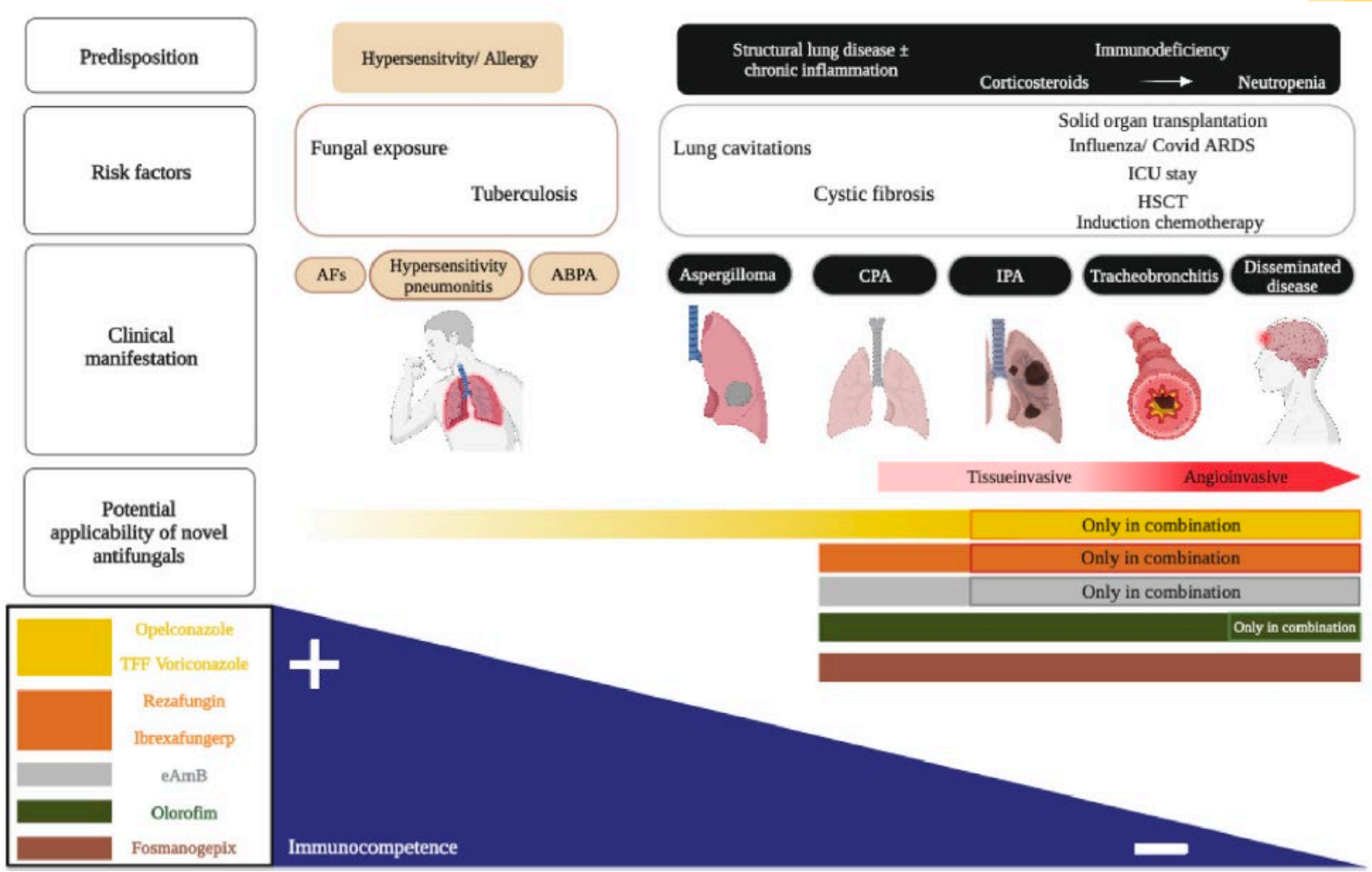
Investigational Antifungal Agents for Invasive Mycoses: A Clinical Perspective. Frederic Lamoth, Russell E Lewis, Dimitrios P Kontoyiannis. *Clinical Infectious Diseases*, Volume 75, Issue 3, 1 August 2022.

Table 4.

Challenges/Unmet Needs in Preclinical and Clinical Research for New Antifungal Agents

Stage	Issues
Study design	• Rarity of IFIs (in particular refractory IFIs) • Multiple types of IFIs (IC, IA, other IFIs) • Different sites of involvement • Different hosts at risk (hematologic cancer patients, ICU patients, transplant recipients, patients with COVID-19) • Different scenarios of use (eg, monotherapy and prophylactic, preemptive, empiric, targeted, combination, and step-down therapy) • Choice of the comparator antifungal drug • Combination therapy with conventional or new antifungal agents • Assessment of response to therapy) in view of multiple confounding factors affecting outcome (underlying diseases, prior antifungal exposure, comorbid conditions, degree of immunosuppression, surgical interventions), and low autopsy rates
Efficacy/toxicity analyses	• Establishment of clinically relevant in vitro susceptibility break points • Longitudinal assessment for propensity for tolerance or resistance • Efficacy in IFIs associated with biofilm formation • More studies on the activity against rare opportunistic fungi (eg, cryptic *Aspergillus* species) • More studies on the penetration and efficacy in anatomically privileged sites (eg, bone, eyes, and brain) • Efficacy of escalating doses/need for TDM in selected scenarios • Degree of cross-resistance with currently licensed antifungals (eg, rezafungin and ibrexafungerp with conventional echinocandins, fosmanogepix with azoles) • Potential drug interactions (eg, new anticancer chemotherapies, immunosuppressive therapies) • Toxicity ceiling when used in acute infection • Long-term tolerability and toxicity • Pharmacoeconomics and cost-effectiveness analysis (eg, cost saving from early discharge, no need for or less use of OPAT)

Investigational Antifungal Agents for Invasive Mycoses: A Clinical Perspective. Frederic Lamoth, Russell E Lewis, Dimitrios P Kontoyiannis. Clinical Infectious Diseases, Volume 75, Issue 3, 1 August 2022.



Kriegl et al, CMI 2024