From genetics to treatment of fungal infections

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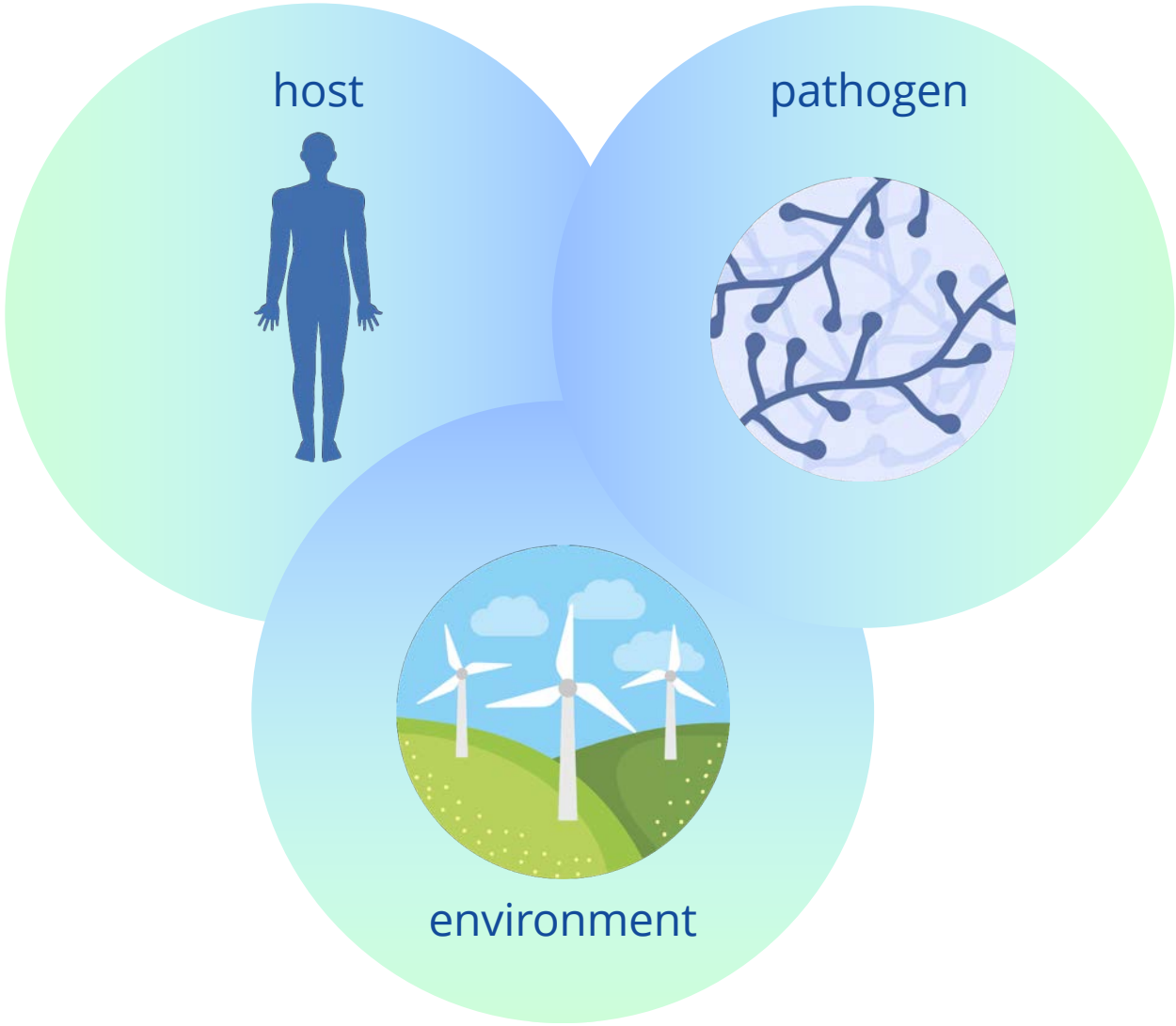
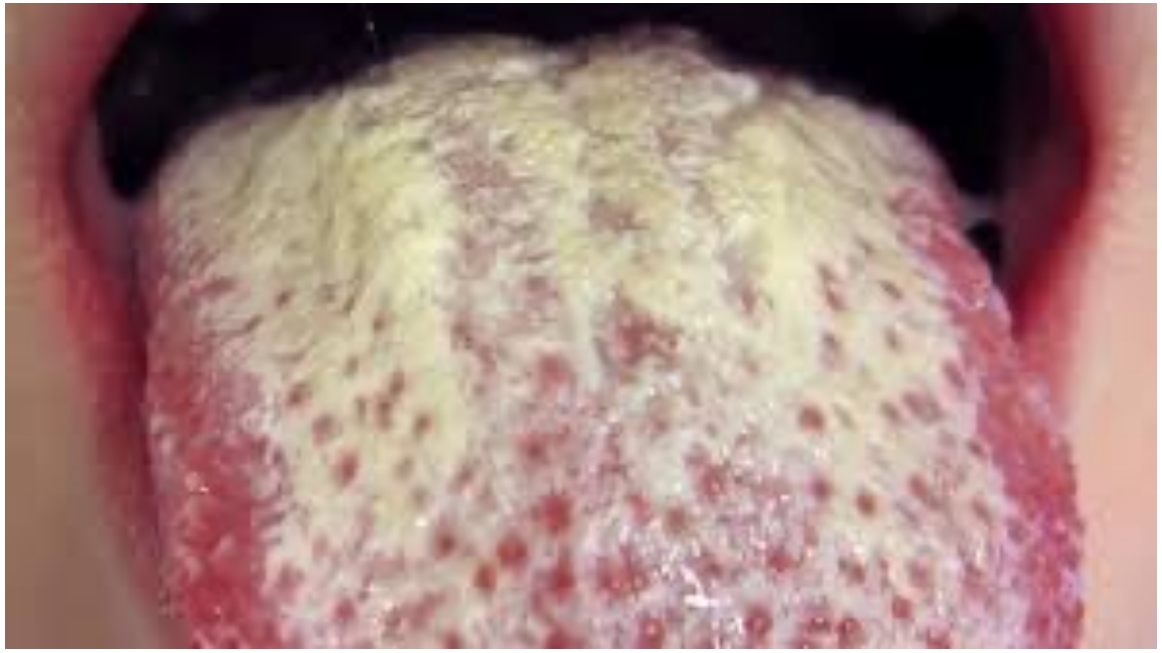
dcasip.medicine.duke.edu

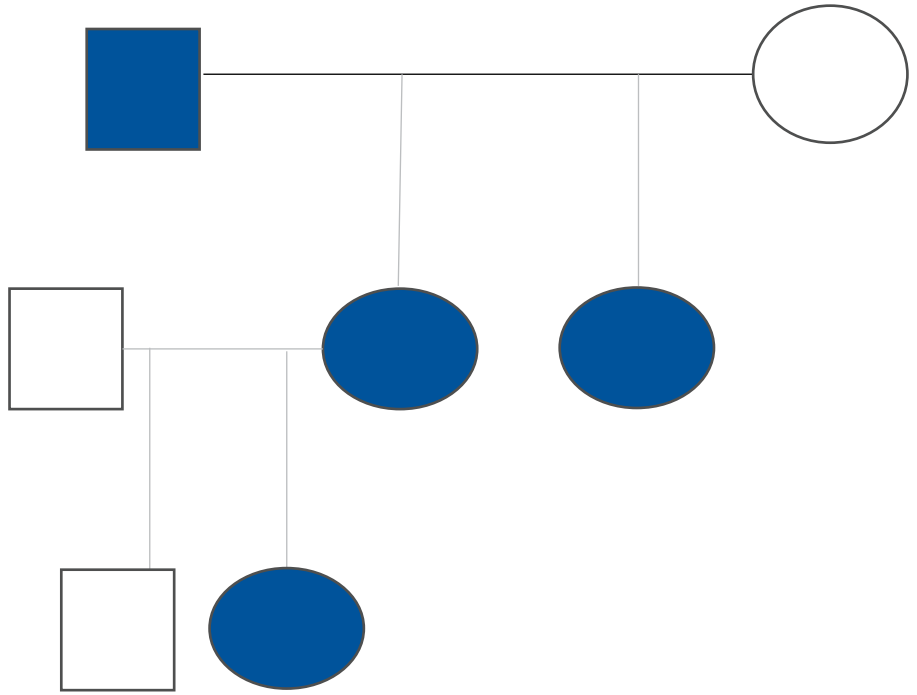
Duke Center for Antimicrobial Stewardship and Infection Prevention

Risk Factors/Risk Groups



Chronic Mucocutaneous Candidiasis





Liu L et al. Journal of Experimental Medicine. 2011: DOI: 10.1084/jem.20110958

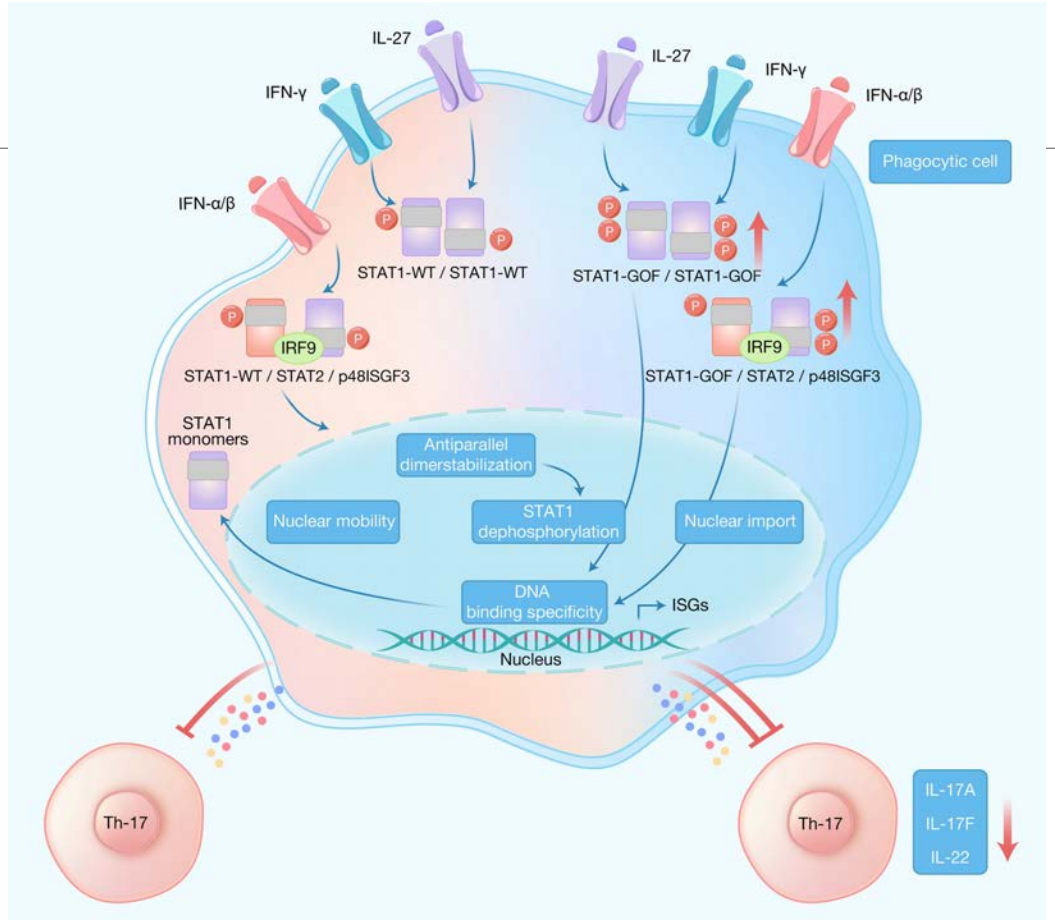
CMC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

STAT1 Mutations in Autosomal Dominant Chronic Mucocutaneous Candidiasis

Frank L. van de Veerdonk, M.D., Ph.D., Theo S. Plantinga, Ph.D., Alexander Hoischen, Ph.D., Sanne P. Smeekens, M.Sc., Leo A.B. Joosten, Ph.D., Christian Gilissen, Ph.D., Peer Arts, Ph.D., Diana C. Rosentul, M.Sc., Andrew J. Carmichael, M.D., Chantal A.A. Smits-van der Graaf, M.D., Ph.D., Bart Jan Kullberg, M.D., Ph.D., Jos W.M. van der Meer, M.D., Ph.D., Desa Lilic, M.D., Ph.D., Joris A. Veltman, Ph.D., and Mihai G. Netea, M.D., Ph.D.



- >125 STAT1 GOF mutations now identified
  - CMC, other fungi

Van de Veerdonk FL et al. NEJM 2011. 365:1: 54-61.
Liu L et al. Journal of Experimental Medicine. 2011: DOI: 10.1084/jem.20110958
Guo L et al. hLife 2024. https://doi.org/10.1016/j.hlife.2024.03.002

Other genetic associations and fungal infections

Pathogen/Disease	Gene	Molecular Phenotype
Candida		
Candidemia, invasive candidiasis	CCL8	Defective type I IFN pathway
	CXCR1	Impaired neutrophil effector function
	IL-10	↑ Candida-induced IL-10 production
	IL-12B	↓ Candida-induced IFN-γ production
	PSMB8	Defective type I IFN pathway
	SP110	Defective type I IFN pathway
	STAT1	Defective type I IFN pathway
	TLR1	↓ IL-1β, IL-6, IL-8 after stimulation
	TLR2	↓ IFN-γ and IL-8
	TLR4	↑ IL-10 production
Candida colonization, *Candida* carriage	Dectin-1	↓ IL-1β and TH17 responses
	DEFB1	Unknown
CDC	IL-4	Unknown
CMC	PTPN22	Unknown
	TLR3	↓ IFN-γ levels
IAC	MBL	↓ MBL levels
RVVC	IL-4	↑ vaginal IL-4, ↓ NO and MBL levels
	MBL	↓ vaginal MBL levels
	NLPR3	Impaired IL-1β production

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and Infection Prevention

Maskarinec SA et al. Curr Clin Microbiol Rep 2016. 3(2): 81-91.

Other genetic associations and fungal infections

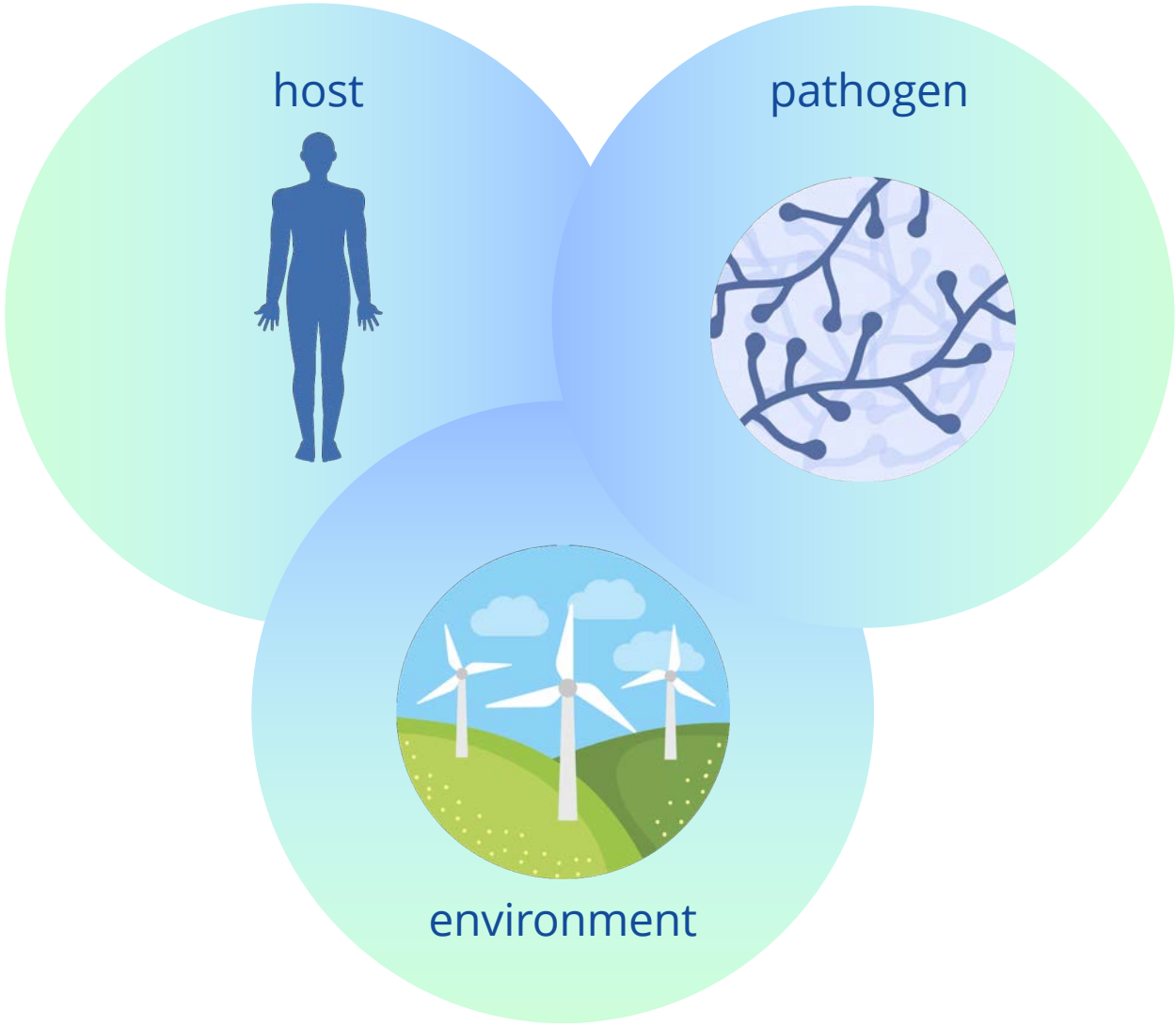
Pathogen/Disease	Gene	Molecular Phenotype
Aspergillus		
IA	AGER	Enhanced expression of RAGE
	CLEC7A	Defective cytokine production Defective expression of dectin-1
	CXCL-10	Impaired expression of CXCL-10
	Dectin-1	Unknown
	IL-10	Unknown
	MBL	Variable MBL levels
	PLG	Unknown
	PTX3	↓ PTX3 levels
	S100B	Enhanced secretion of S100B
	TLR1	Unknown
	TLR3	Defective antigen presentation and activation of CD8 T-cell responses
	TLR4	Unknown
	TLR6	Unknown
	TNFR1	Impaired expression of TNFR1 mRNA
	TNFR2	Unknown
Cryptococcus		
Cryptococcosis	FCGR(2A/3A)	Unknown
	IL12RB1	Defective IL-12 signaling ↓ IL-12Rβ1 expression on cell surface
	MBL	↓ MBL levels

New cancer therapeutics impacting risk

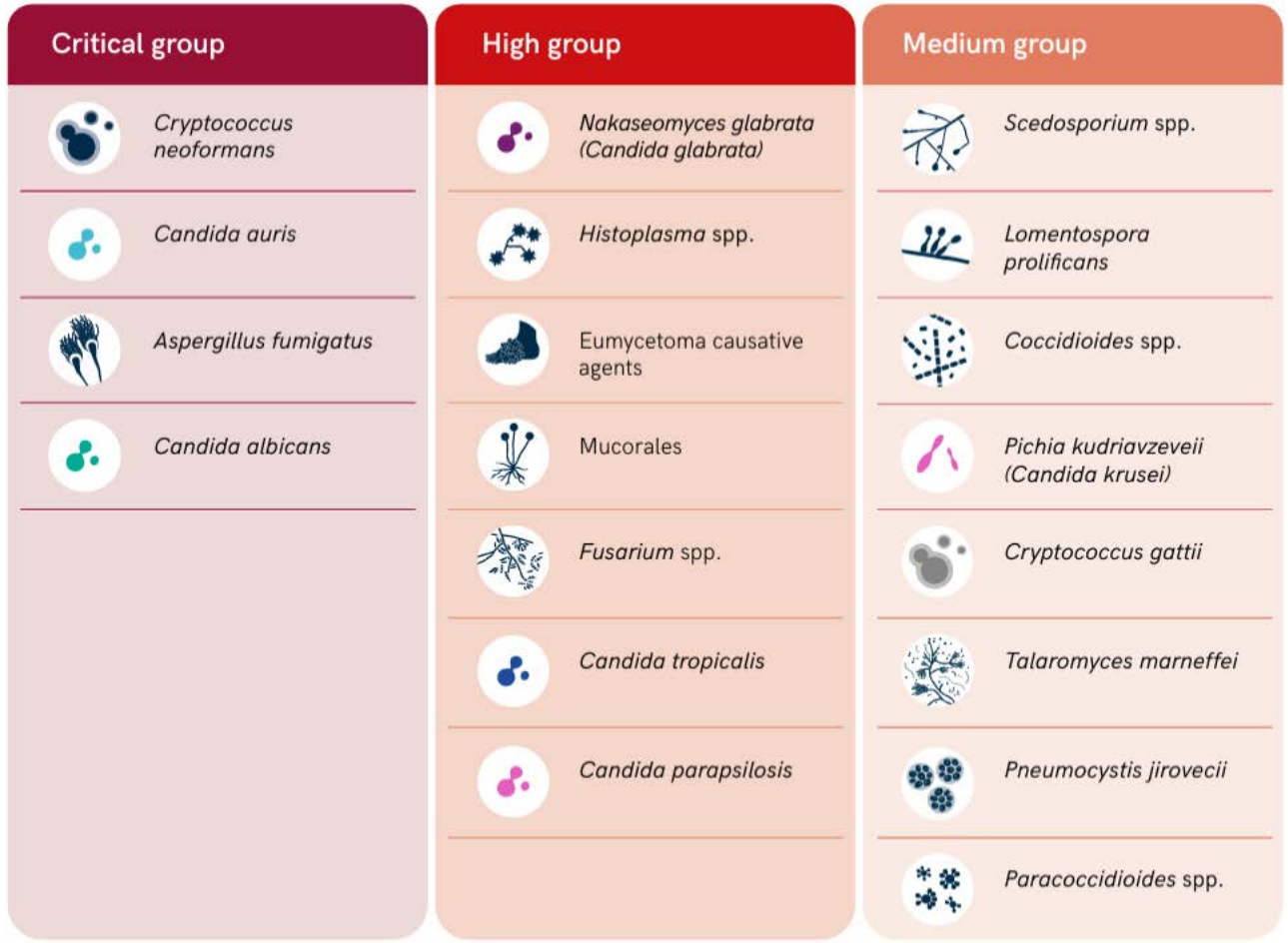
Class	Agent
BTK Inhibitors	ibrutinib acalbrutinib zanubrutinib
Multitargeted tyrosine kinase inhibitors	midostaurin
PI3K inhibitor	idelalisib copanlisib duvelisib
Anti-CD20 antibody	rituximab obinutuzumab
Anti-CD52 antibody	alemtuzumab
CAR T-cell therapy	ciltacabtagene autoleucel
Anti CD-30 antibody	brentuximab vedotin
Anti-CTLA-4 antibody	ipilimumab

Palmucci J et al. PLOS Pathogens 2023; 19(12):e1011845

Risk Factors/Risk Groups



WHO Fungal Priority Pathogens



WHO fungal priority pathogens list to guide research, development and public health action. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

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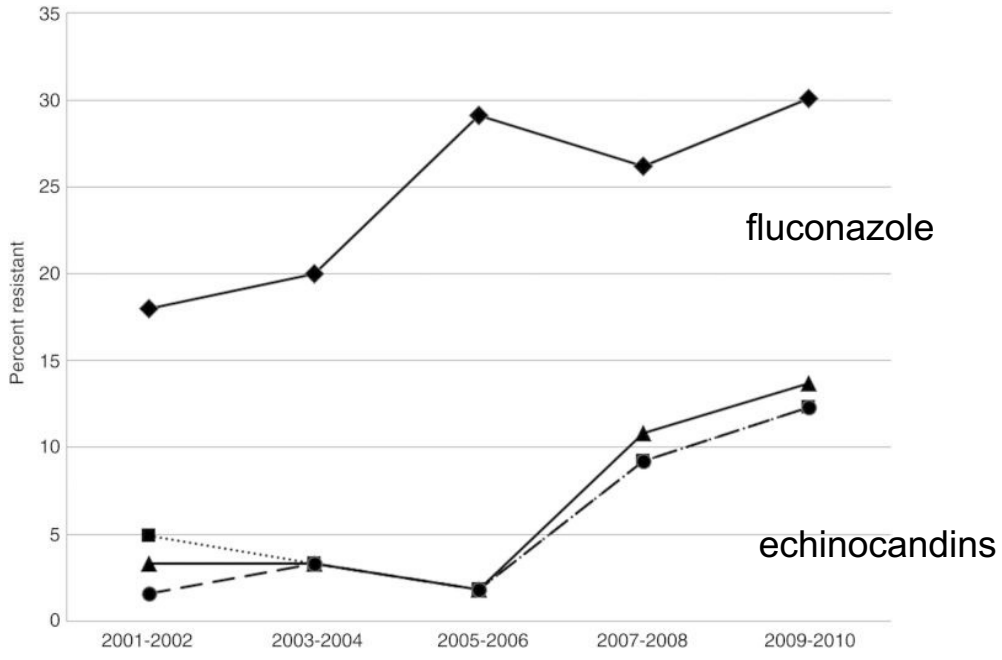
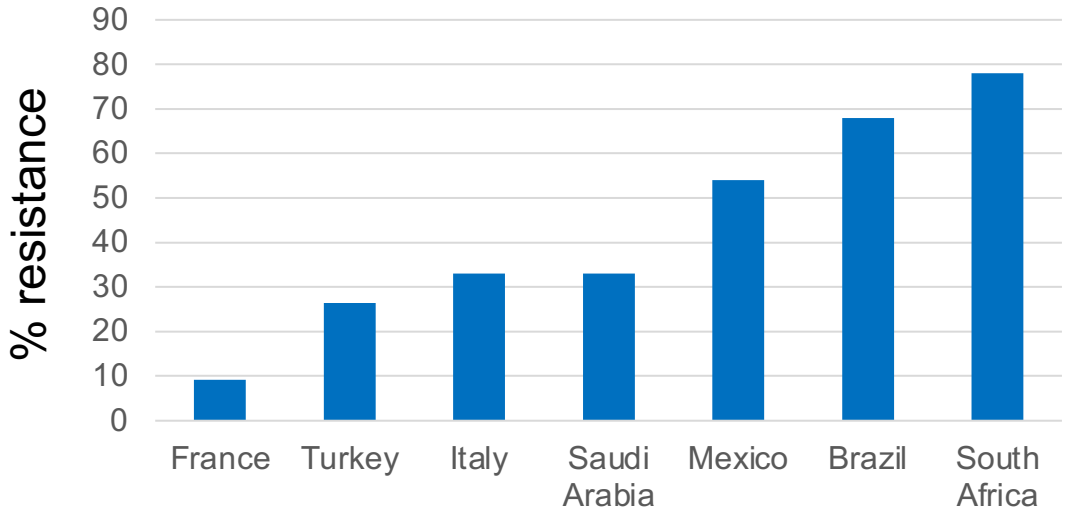
Recent trends in fungal epidemiology & resistance

C. glabrata resistance Duke



Fluconazole-resistant *C. parapsilosis*

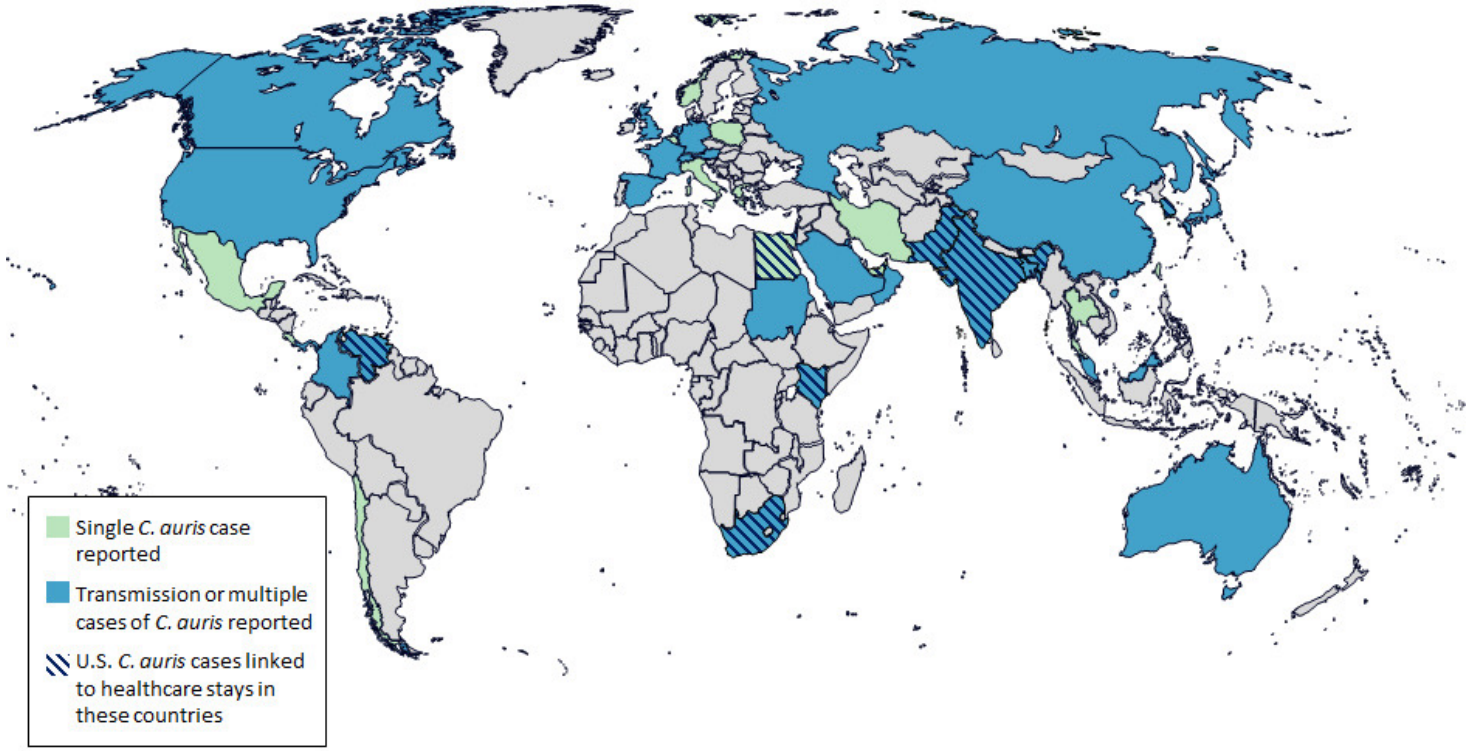


"rampant clonal spreading of C. parapsilosis fluconazole-resistant genotypes is taking place in Madrid" (Diaz Garcia J, et al. Antimicrob Agents Chemother 2023; 67(11): e0098623.)

Alexander BD et al. Clin Infect Dis 2013 ; 56(12): 1724-32. doi: 10.1093/cid/cit136
Escribano P. Front Fungal Biol. 2022. 3: https://doi.org/10.3389/ffunb.2022.1010782
Witt LS et al. IDWeek 2023: 2885.

Emerging Pathogen: *C. auris*

- Often mis-identified
- Colonizes skin
- Rapidly transmitted
- Serious infections
- Often multi-drug resistant



C. auris world map
(Sept 2020)

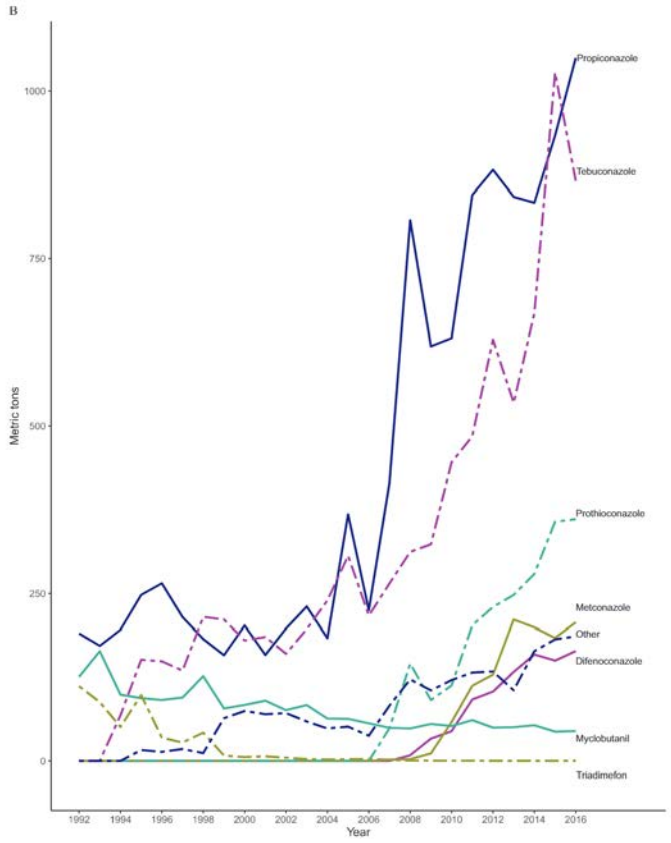
https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html#world

Antifungal resistant Aspergillus

- 2022: first reported US patient death with fungicide-associated triazole-resistant Invasive Aspergillosis
- *A. fumigatus* with environmentally acquired TR_{34}/L98 mutation

- Europe *A. fumigatus* :
  - Amphotericin B resistance ~11% Greece, 3% Denmark
  - Triazole resistance <1%-13%

Agricultural Fungicide Use, US 1992-2016



With permission,Toda M et al. Env Health Persp 2021.129(5):https://doi.org/10.1289/EHP7484

Lestrade PPA et al. Clin Microbiol Infect 2019; 25(7): 799-806.
Bradley K et al. Emerg Infect Dis 2022; 28(9):1904-1905.
DeFrancesco MA. Pathogens 2023; 12(11): 1305.

Others!

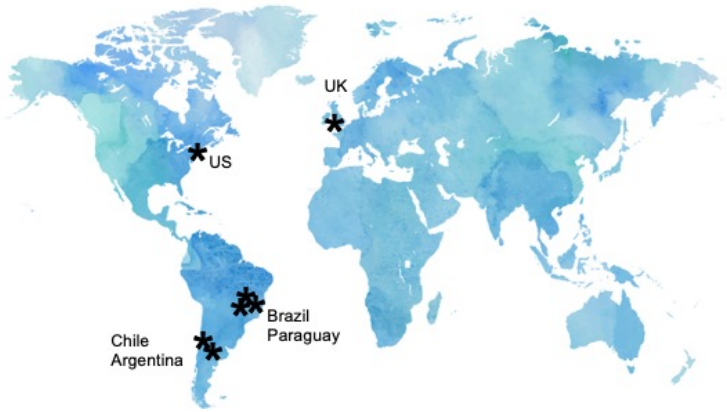
Journal of *Fungi*

MDPI

Review

Sporothrix brasiliensis: Epidemiology, Therapy, and Recent Developments

Melissa Orzechowski Xavier [1,2,†], Vanice Rodrigues Poester [1,2,†], Mariana Rodrigues Trápaga [1,2] and David A. Stevens [3,4,*]



The New York Times

1 Dead and Nearly 100 Sickened in Fungal Outbreak at Paper Mill

Local and federal investigators are investigating the source of a rare outbreak of blastomycosis at a paper mill in Escanaba, Mich.

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

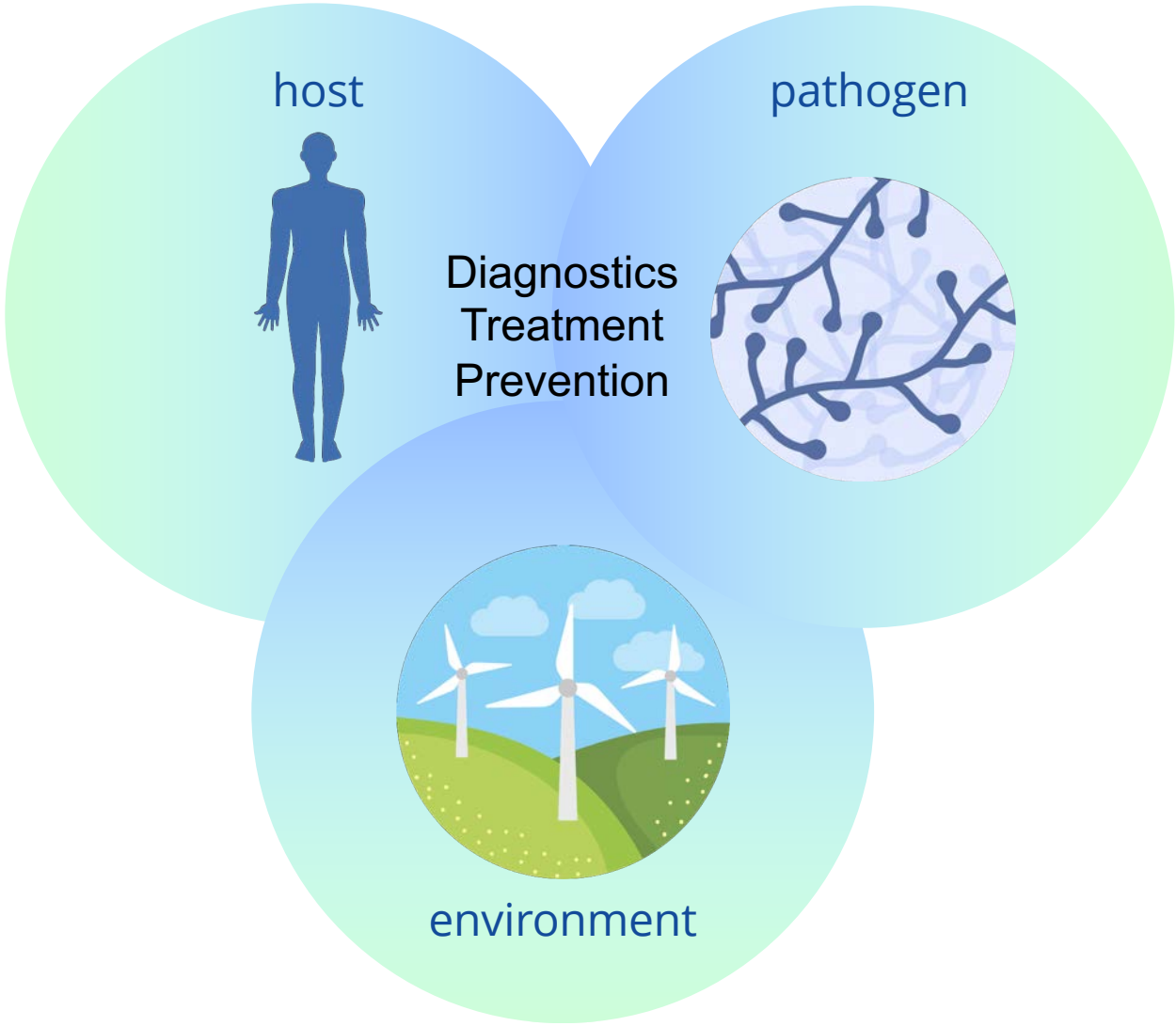
Update on Outbreak of Fungal Meningitis Among US Residents Who Received Epidural Anesthesia at Two Clinics in Matamoros, Mexico

Dallas J. Smith,[1,@] Jeremy A. W. Gold,[1] Tom Chiller,[1] Nirma D. Bustamante,[2] Maria Julia Marinissen,[3,4] Gabriel Garcia Rodriquez,[5] Vladimir Brian Gonzalez Cortes,[5] Celida Duque Molina,[6] Samantha Williams,[1] Axel A. Vazquez Deida,[7,8] Katrina Byrd,[2,7] Peter G. Pappas,[9] Thomas F. Patterson,[10] Nathan P. Wiederhold,[11] George R. Thompson III,[12,13] and Luis Ostrosky-Zeichner;[14,@] Fungal Meningitis Response Team

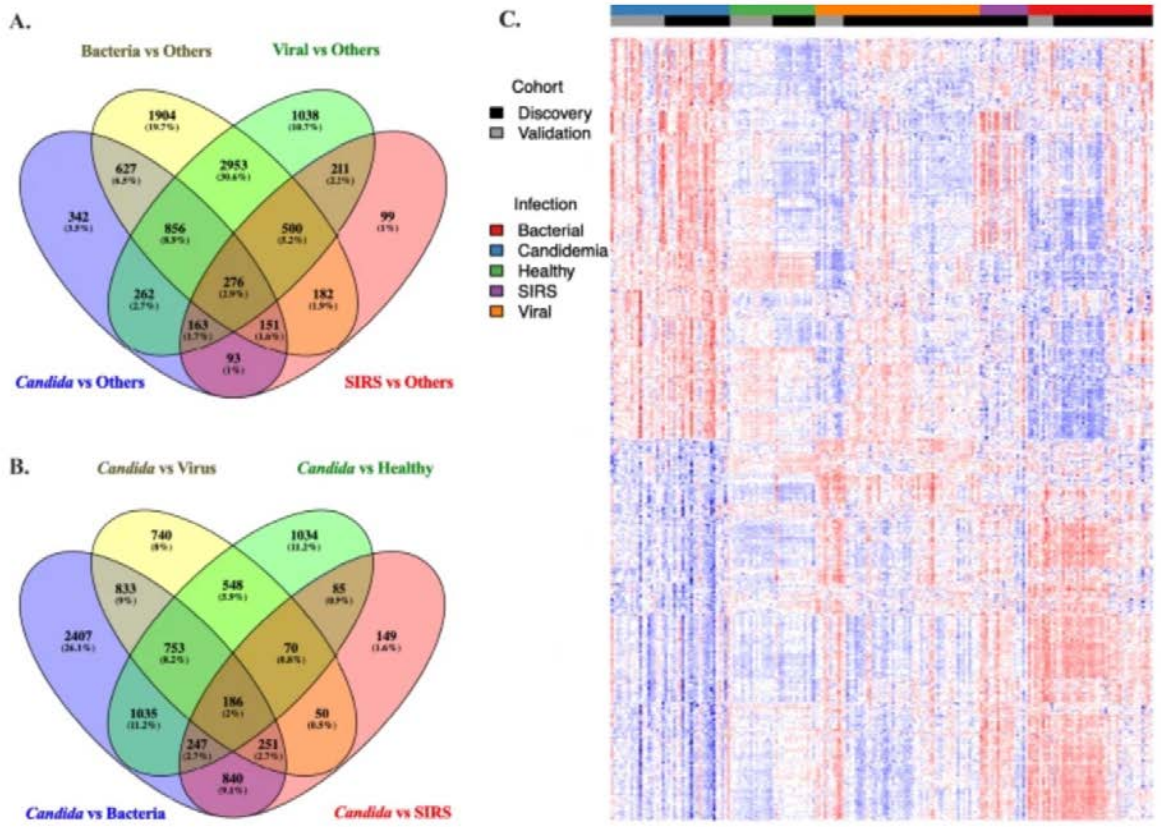
https://www.cdc.gov/fungal/diseases/sporotrichosis

Xavier MO et al. J Fungi 2023; 9(9): 921. https://doi.org/10.3390/jof9090921; Van Howe RS. Med Mycol 2023; myad123. doi: 10.1093/mmy/myad123; https://www.cdc.gov/hai/outbreaks/meningitis-epidural-anesthesia.html Smith DJ et al. IDWeek 2023: 969: Outbreak of Fungal Meningitis in US Patients who Received Surgical Procedures under Epidural Anesthesia in Matamoros, Mexico.

Risk Factors/Risk Groups

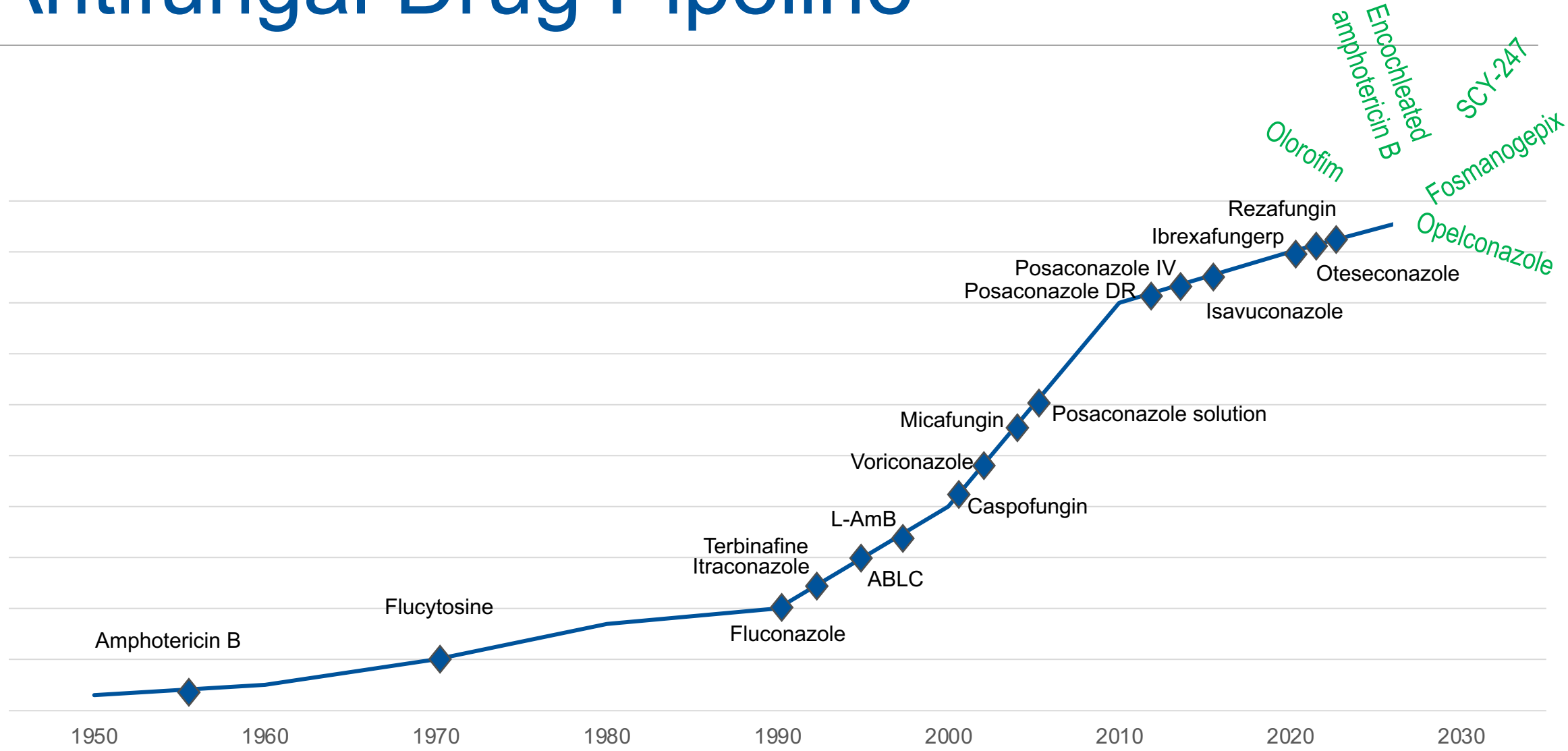


Diagnostics



Steinbrink JM. Genome Medicine 13: 108 (2021).

Antifungal Drug Pipeline



Adapted from Ostrosky-Zeichner L. *Nature Reviews Drug Discovery*. 2010;9:719-727.

Antifungal Activity of Newer Agents vs. Yeasts

	Rezafungin	Ibrexafungerp	Isavuconazole	Oteseconazole	Opelconazole	Fosmanogepix	Olorofim	Encochleated Amphotericin B
C. albicans	+	+	+	+	+	+	-	+
C. parapsilosis	+	+	+	+	+	+	-	+
C. krusei	+	+	+	+	+	-	-	+
C. glabrata	+	+	+/-	+	+	+	-	+
C. lusitaniae	+	+/-	+	+	+	+	-	+/-
C. auris	+/-	+	+/-	?	+	+	-	+/-
Cryptococcus neoformans	-	-	+	+	+	+	-	+

Hsu AJ et al. J Ped Infect Dis Soc 2024; 13(S1): S68-S77; Hoenigl M. Drugs 2021; 81(15): 1703-1729.
Hoenigl M. Clin Microbiol Reviews 2024. e0007423.doi: 10.1128/cmr.00074-23

Antifungal Activity of Newer Agents vs. Molds and Dimorphic Fungi

	Rezafungin	Ibrexafungerp	Isavuconazole	Oteseconazole	Opelconazole	Fosmanogepix	Olorofim	Encochleated Amphotericin B
Aspergillus spp.	+	+	+	?	+	+	+	+
Azole-resistant Aspergillus spp.	+	+	+/-	?	+/-	+	+	+
Fusarium spp.	-	-	-	?	?	+	+/-	+/-
Scedosporium apiospermum	-	+/-	-	?	?	+	+	-
Lomentospora prolificans	-	+/-	-	?	?	+/-	+	-
Mucorales	-	-	+/-	+/-	+/-	+/-	-	+/-
Histoplasma capsulatum	-	+	+	+	?	+	+	+
Blastomyces dermatitidis	-	+	+	+	?	+	+	+
Coccidioides immitis	-	+	+	+	?	+	+	+

Hsu AJ et al. J Ped Infect Dis Soc 2024; 13(S1): S68-S77;Hoenigl M. Drugs 2021; 81(15): 1703-1729.
Hoenigl M. Clin Microbiol Reviews 2024. e0007423.doi: 10.1128/cmr.00074-23

Rezafungin

- FDA approved 2023 (Cidara/Melinta, Brand Name: Rezzayo)
- Echinocandin, structural analog of anidulafungin
  - improved stability & solubility
- Long $T_{1/2}$ >150 hours, highly protein bound (97.4%)
- C_{max} 16.4 mg/L
- Dose-proportional pharmacokinetics
  - Metabolized by hydroxylation of terphenyl, pentyl ether side chain
- Well-tolerated
- IV administration
- 200 mg vials for administration
  - 400 mg loading dose, followed by 200 mg once weekly

Prescribing information, Rezzayo. 2023. Melinta Therapeutics. Rubino CM, Antimicrob Agents Chemother 2021. 65(11): e00842-21. Johnson MD Infect Dis Clin North Amer 2021; 35(2): 341-71. Oong V et al. Antimicrob Agents Chemother 2022; 66(1):e0139021.

Rezafungin Clinical Use

- Invasive Candidiasis & Candidemia
- Multicenter, randomized double-blind, double-dummy clinical trials in adults
- STRIVE: Phase II, 2016-2019
- RESTORE: Phase III, 2018-2021
  - Rezafungin 400 mg IV X1, followed by 200 mg IV weekly (up to 4 doses total)
  - Caspofungin 70 mg LD, followed by 50 mg IV daily (up to 28 days)
  - Could transition to fluconazole after ≥ 3 days *(rezafungin group received placebo along with IV rezafungin)*

Thompson GR et al. The Lancet, 2023. 401(10370): 49-59.
Thompson GR et al. Lancet Infect Dis 2024. 24(3): 319-328.

Pooled Analysis: RESTORE & STRIVE

Outcome	Rezafungin	Caspofungin	Difference (95% CI)
Day 5 Mycological Response			
Eradication Failure or indeterminate	73% (102/139) 27% (37/139)	65% (100/155) 35% (55/155)	10.0% (-0.3 to 20.4)
Day 14 Mycological Response			
Eradication Failure or indeterminate	72% (100/139) 28% (39/139)	68% (106/155) 32% (49/155)	4.3% (-6.2 to 14.7)
Negative Blood Culture			
At 24 h At 48 h	60% (63/105) 78% (80/103)	49% (57/116) 64% (73/115)	Exploratory*

*Log Rank p=0.0051 in Kaplan-Meier analysis of those with positive blood culture at screening & p=0.015 in mITT population of those with positive blood culture at screening

Early Treatment Benefit ?

Thompson GR et al. Lancet Infect Dis 2024; 24(3): 319-328.

Rezafungin Role

Advantages	Potential Role/Remaining Questions

• Once weekly dosing, lack of DDIs
• Discharge transitions
  • Patients lacking IV access with difficult-to-treat infections
• Activity against echinocandin non-wildtype clinical *Candida* strains (*C. glabrata*)?
	• IV only
	• Endocarditis/Deep Seated-infections- excluded from trials
	• Pediatrics- not approved in pediatrics
	• Cost? WAC: $1950/vial (loading dose = 2 vials)
	• Reduce Length of Stay / ICU Length of Stay?
	  • German analysis, median cost-saving potential of 7175 Euro per hospital case

Castanheira M et al. ESCMID Global 2024, E0542; Jeck J et al. JAC Antimicrob Resist 2023. 5(3): dlad079; Muszbek N et al.l ISPOR 2023. Poster 132702; www.clinicaltrials.gov

Rezafungin Future Directions- Open Trials

- ReSPECT trial: (Phase 3) Prophylaxis in Adults Undergoing Allogeneic Blood and Marrow Transplantation
  - Comparators: fluconazole + sulfamethoxazole/trimethoprim
    - Posaconazole + sulfamethoxazole/trimethoprim in patients with GVHD
- Treatment of Pneumocystis Pneumonia in HIV Adults
- Pediatric PK Study in Pediatric Subjects From Birth to <18 Years of Age
- Pharmacokinetics in ECMO

www.clinicaltrials.gov

Ibrexafungerp

- Triterpinoid antifungal (Scynexis, Brand name: Brexafemme, now with GSK)
- Inhibits glucan synthesis at a site distinct but partially shared with echinocandins
  - Retains activity against many echinocandin-resistant *Candida* isolates, including *C. auris*
- FDA-approved for treatment of vulvovaginal candidiasis (VVC) (2021) & reducing incidence of recurrent VVC (2022) in adult and post-menarchal pediatric females
  - VANQUISH2 trial completed- complicated VVC patients with fluconazole failure
- Oral formulation
- >99% protein bound, $T_{1/2}$= 20-30h

Davis MR et al. Medical Mycology, 2020. 58(5): 579-592; Prescribing information, Brexafemme, 2024.

Ibrexafungerp dosing

Infection	Status	Dose
VVC	FDA-approved	300 mg (two 150 mg tablets) q12 h x 2 doses
RVVC	FDA-approved	300 mg q12H for two doses each month, for 6 months
Candidemia/IC	Investigational	750 mg BID for 2 days, then 750 mg daily
Combination therapy Invasive Aspergillosis	Investigational	500 mg BID for 2 days, then 500 mg QD (plus voriconazole)

Davis MR et al. Medical Mycology, 2020. 58(5): 579-592; Prescribing information, Brexafemme, 2024.

Ibrexafungerp

- Cautions:
  - Some drug-drug interactions
    - CYP3A4 & P-glycoprotein substrate
    - Inhibitor of CYP3A4, P-glycoprotein, and OATP1B3 transporter, CYP2C8
    - Avoid strong & moderate CYP450 3A4 inducers
    - Reduce dose to 150 mg twice daily with strong CYP450 3A4 inhibitors
  - Potential for embryo-fetal toxicity based on animal studies, therefore not used in pregnancy & females of reproductive potential must be screened before initiating therapy, use effective contraception, and be reassessed monthly on treatment (for RVVC)
- Most common adverse events
  - Diarrhea, nausea, abdominal pain

Davis MR et al. Medical Mycology, 2020. 58(5): 579-592; Prescribing information, Brexafemme, 2024.

Ibrexafungerp

September 27, 2023

COMPANY ANNOUNCEMENT

SCYNEXIS Issues a Voluntary Nationwide Recall of BREXAFEMME® (ibrexafungerp tablets) Due to Potential for Cross Contamination with a Non-Antibacterial ßlactam Drug Substance

" Risk Statement: The potential cross contamination with a non-antibacterial beta-lactam drug substance could lead to hypersensitivity reactions such as swelling, rash, urticaria and anaphylaxis, a potentially life-threatening adverse reaction. To date, SCYNEXIS has not received any reports of adverse events established to be due to the possible beta-lactam cross contamination."

https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/scynexis-issues-voluntary-nationwide-recall-brexafemmer-ibrexafungerp-tablets-due-potential-cross

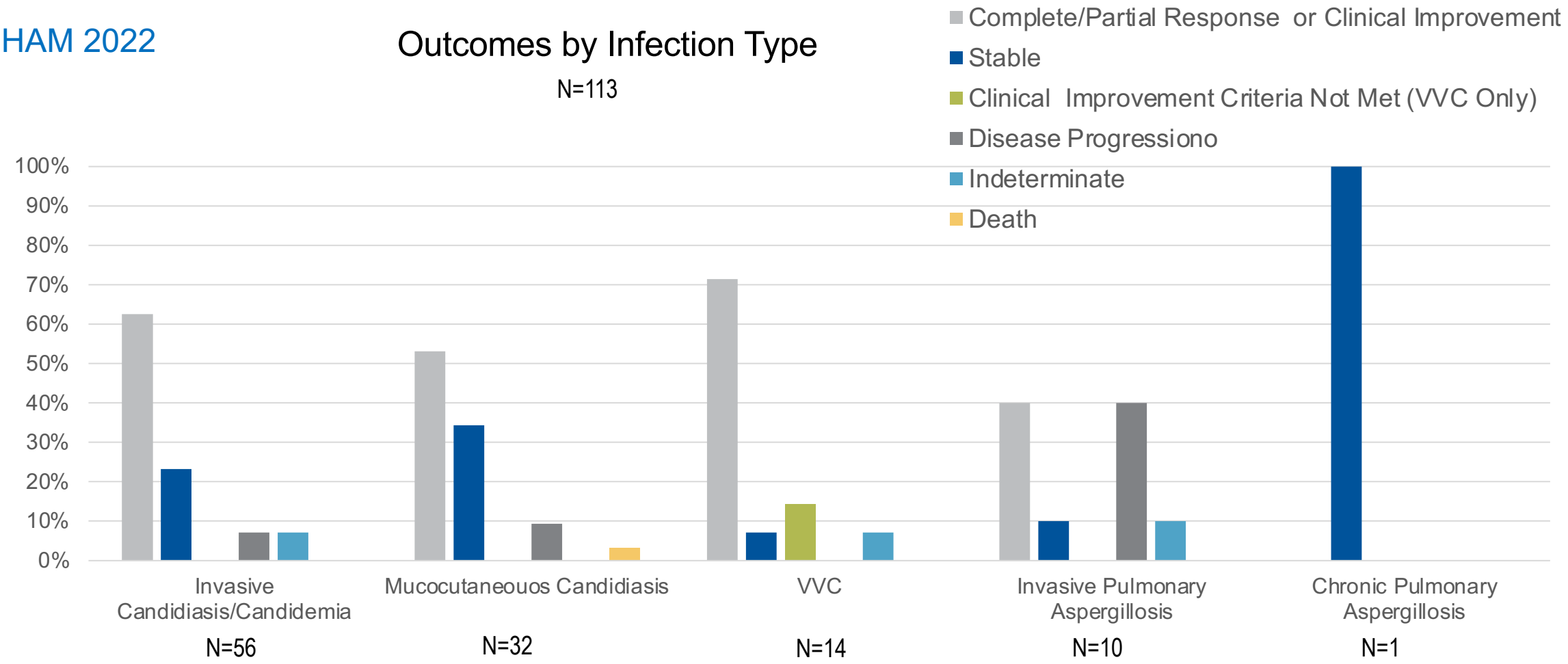
Ibrexafungerp Clinical Studies Underway

Study	Details	Status
FURI	Efficacy and safety of ibrexafungerp in patients with fungal diseases that are refractory or intolerant of standard antifungal treatment	Enrollment completed 233 patients
MARIO	Phase 3 randomized, double-blind study for patients with invasive candidiasis treated with IV echinocandin followed by either oral ibrexafungerp or oral fluconazole	On hold
CARES	Open label, emergency treatment use for C. auris candidemia/candidiasis	Enrollment completed 30 patients
SCYNERGIA	Phase 2, Safety and efficacy of ibrexafungerp plus voriconazole in patients with invasive pulmonary aspergillosis	Enrollment completed 22 patients
	Safety of pregnant subjects exposed to ibrexafungerp including infant outcomes	Open

www.clinicaltrials.gov

Ibrexafungerp open label experience (FURI)

ISHAM 2022



Prattes J et al. *Medical Mycology*, 2022. 60(1) myac072P056. https://doi.org/10.1093/mmy/myac072.P056

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Ibrexafungerp clinical data- UTIs

Ibrexafungerp urine penetration is 1-2% but it has high tissue penetration in kidney and bladder

- 7 patients with difficult -to- treat UTIs
  - 2 from the FURI Study
    - *Candida glabrata* resistant to oral fluconazole and caspofungin
    - Refractory *Candida* spp. infection
  - 5 from the CARES Study with *Candida auris* UTI
    - all had prior fluconazole treatment, 3 had prior echinocandin treatment
  - 2 men, 5 women
  - All responded to ibrexafungerp treatment
    - Mean duration of therapy 31 days (range 4-76 days)
    - Complete response 6/7 (86%)
      - 3 *C. auris*, 1 *C. auris* & *C. parapsilosis*, 1 *C. glabrata*, *1 C. lusitaniae*
    - Partial response 1/7 (14%) - *C. auris*

Siebert RS, et al. 2023. 33rd ECCMID. MEM0404.

Ibrexafungerp Role/Future Directions

- VVC and prevention of recurrent VVC
- Advantages
  - Oral option
  - Activity in resistant/refractory *Candida* spp. infections including *C. auris*
- Remaining Questions/Considerations
  - Combination therapy for invasive pulmonary aspergillosis
    - Rabbit model: Synergistic with isavuconazole
    - SYNERGIA results pending
  - Clinical activity in IFDs- FURI, MARIO data pending
  - Safety in pregnancy & lactation
  - Cost- current ~$550 via GoodRx for 4 x150 mg tablets
- Next-generation compound: SCY-247 (Mucormycosis activity)

Petraitis V et al. Antimicrob Agents Chemother 2020. 21(64): e02429-19.

Opelconazole

- Investigational triazole: Nebulizer suspension
  - Inhibits 14-α-demethylase
- Pulmocide (PC945)
- Broad spectrum of activity, *in vitro* potency against Aspergillus >> voriconazole, similar to posaconazole
  - Reduced activity against azole-resistant Aspergillus strains (?)
- Persistent effects after dosing in epithelial cells and in hyphal fungal body
- Synergy between inhaled opelconazole and oral posaconazole in murine models of Aspergillosis

Colley T et al. Scientific Reports 2019; 9:9482. https://doi.org/10.1038/s41598-019-45890-w
Ito K. Expert Opin Drug Deliv 2022. 19:7, 755-769. doi: 10.1080/17425247.2022.2084530

Opelconazole clinical trials: Phase 2

- OPERA-T: Refractory invasive pulmonary aspergillosis, combination therapy (ongoing)

- OPERA-S: prophylaxis or pre-emptive therapy for pulmonary aspergillosis lung transplant recipients (recently completed)
  - 102 participants, open-label, randomized 2:1 vs standard of care (SOC)
  - Safety & tolerability: cough 6.2%, nausea 4.6%
  - Similar breakthrough fungal infections (4% opelconazole, 3% SOC)
    - Eradication of fungal colonization in many patients colonized at baseline

https://pulmocide.com/press-release/pulmocide-announces-successful-results-from-the-opera-s-study-a-phase-2-safety-study-with-inhaled-opelconazole/

Opelconazole Role/Future Directions

Advantages	Potential Role/Remaining Questions
• Novel delivery - may avoid some DDIs/adverse events in this complex patient population • Activity against *Candida* spp. and *Aspergillus* spp.	• Prophylaxis in at-risk patient groups (eg lung transplant) • Potentially treatment of refractory invasive aspergillosis in combination with systemic antifungal therapy
Other Comments: Other inhaled antifungals in use/in development	

Ito K. Expert Opin Drug Deliv 2022. 19:7, 755-769. doi: 10.1080/17425247.2022.2084530
Hoenigl M. Clin Microbiol Reviews 2024. e0007423.doi: 10.1128/cmr.00074-23

Olorofim

- Investigational Orotomide (F2G, F901318)
- Interferes with de novo pyrimidine biosynthesis by inhibiting the enzyme dihydroorotate dehydrogenase (DHODH)
  - Disrupts synthesis of cell wall components, leading to cell cycle arrest and cell lysis
  - Fungicides ipflufenoquin (approved in US 2022) and quinofumelin (in development) share mechanism of action – cross resistance?
- Mold activity- many difficult-to-treat molds
  - *Aspergillus*, *Scedosporium*, *Lomentospora*, *Scopulariopsis* spp. & dimorphic fungi
    - When compared to other agents, olorofim had the lowest MICs against *Aspergillus terreus*
  - Not *Mucor, Cunninghamella, Alternaria, Candida, Cryptococcus* spp.
- Oral formulation
- >99% protein bound, wide distribution with some CNS penetration
- $T_{1/2}$ ~20-30h
- CYP3A4 substrate, Weak CYP3A4 inhibitor- some DDIs (↑ midazolam 30%)
- Dosing: 150mg BID on day 1, followed by 90mg BID

Hoenigl M. Clin Microbiol Reviews 2024. e0007423.doi: 10.1128/cmr.00074-23;
Johnson MD Infect Dis Clin North Amer 2021; 35(2): 341-71; Vahedi- Shahndashti R et al. TIMM. 2023. S07/6.

Olorofim clinical trials

- FORMULA: Phase 2b: open label, proven/probable difficult to treat mold infections
- Submitted results of first 100 patients to FDA; FDA issued a "Complete Response Letter" requesting additional data and analysis
  - Study now complete, 203 patients
  - Presented at TIMM
  - Submitted to FDA
  - Generally well-tolerated, GI intolerance (~10%), some hepatic enzyme elevations (led to discontinuation in 2.5%)

www.clinicaltrials.gov; F2G.com/news ; Maertens J et al. TIMM 2023. S08.5; Hoenigl M. Clin Microbiol Reviews 2024. e0007423.doi: 10.1128/cmr.00074-23; Johnson MD Infect Dis Clin North Amer 2021; 35(2): 341-71

Olorofim FORMULA results

- Olorofim for 84 days +/- 6 days (main phase), with extended therapy beyond day 90 allowed; median treatment 308 days
- Difficult to treat invasive mold infections
  - *Aspergillus* spp. (101), including 22 cases with azole-resistant strains
  - *L. prolificans* (n=26), *Scedosporium* spp. (n=22), *Coccidioides* spp. (n=41), *Scopulariopsis* spp. (n=6) and other fungi (n=8)

Outcomes (mITT population, n=202)	Day 42	Day 84
Overall Success CR/PR	28.7%	27.2%
CR/PR/Stable	75.2%	63.4%
Excluding coccidioidomycosis CR/PR	36.0%	34.2%
Coccidioidomycosis CR/PR	75.6%	73.2%
All Cause Mortality- Overall All Cause Mortality- Invasive Aspergillosis	11.4% 17.8%	15.8% 25.7%

Maertens J et al. TIMM 2023. S08.5.

Olorofim Role/Future Directions

Advantages	Potential Role/Remaining Questions
• Unique mechanism of action • Activity for several molds where treatment options are limited, with an oral formulation	• Difficult to treat mold infections: *Lomentospora prolificans*, *Scedosporium* spp., *Scopulariopsis* & some *Fusarium* spp. that are resistant to other antifungals • Option for step-down or salvage treatment • Coccidioidomycosis option • Other endemic mycoses ? • Antagonism with azoles/olorofim (?) / role in combination therapy • Role in first-line therapy for aspergillosis when other agents are available (?)
Ongoing Studies: OASIS: Phase 3 aspergillosis, vs Liposomal Amphotericin B followed by standard of care	

Hoenigl M. Clin Microbiol Reviews 2024. e0007423.doi: 10.1128/cmr.00074-23

Fosmanogepix

- Prodrug of manogepix (APX001, Amplyx/Pfizer/Basilea)
- Inhibits glucosylphosphatidylinositol-anchored wall transfer protein (Gwt1), which mediates crosslinking of cell wall mannoproteins to ß-1,6-glucan and is necessary for biofilm & germ-tube formation
  - Pyridine antifungal pesticides targeting Gwt1 are in development (aminopyrifen)
- $T_{1/2}$ ~52h , bioavailability >90%
- IV and oral formulations
- Broad spectrum of antifungal activity including yeasts & molds
  - (potentially not *C. krusei*?)

Hodges MR et al. Antimicrob Agents Chemother 2023. 67(4): e01623-22.

Fosmanogepix Clinical trials

- Two small Phase II studies for invasive candidiasis/candidemia
  - 30 patients total
- Phase II open-label study, invasive aspergillosis & other rare mold infections
  - 21 patients enrolled, 11 completed
    - 20 Evaluable: 8/20 (40%) had treatment success by day 42 (complete/partial response)
  - Terminated to prioritize Phase III study

- Planned:
  - Phase III study invasive candidiasis
  - Phase III study invasive mold infections

Hoenigl M et al. Clin Microbiol Reviews 2024. e0007423.doi: 10.1128/cmr.00074-23; https://www.basilea.com/news#news_1471

Fosmanogepix Role/Future Directions

Advantages	Potential Role/Remaining Questions
• Unique mechanism of action • Extended spectrum of activity with oral/IV formulations • CNS activity 	• Potential important role in *Fusarium spp., Scedosporium spp., Lomentospora prolificans* infections • Combination therapy (?) • Potential first-line and/or salvage therapy for invasive aspergillosis • Attractive for Mucor coverage as well (early empiric coverage when diagnosis unknown?) in combination with liposomal amphotericin B • Emergency Treatment Use Program (?)

Planned Studies:

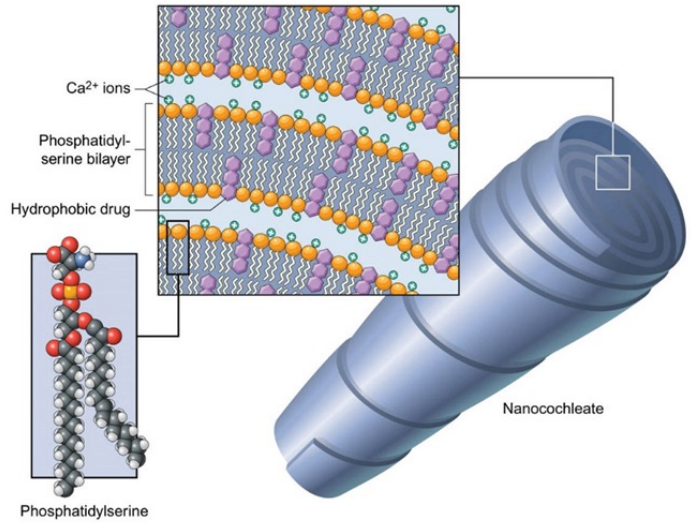
Phase III study invasive candidiasis

Phase III study invasive mold infections

Hoenigl M et al. Clin Microbiol Reviews 2024. e0007423.doi: 10.1128/cmr.00074-23

Encochleated Amphotericin B

- Investigational polyene formulation
  - Matinas Biopharma, MAT2203
- Oral formulation of amphotericin B
  - “lipid nanocrystal”



- Lipid bilayer rolled into a spiral, fuses with target cell membranes in the body releasing amphotericin B into the cytoplasm
  - Readily taken up by monocytes/macrophages
  - Distributes widely including target organs such as lungs, liver, kidneys, spleen; may also penetrate brain tissue

Hoenigl M et al. Clin Microbiol Reviews 2024. e0007423.doi: 10.1128/cmr.00074-23; Boulware DR et al. Clin infect Dis 2023. 77(12): 1659-1667, https://doi.org/10.1093/cid/ciad440; Skipper CP et al. Antimicrob Agents Chemother 2020. 64(10): e00838-20. Graphic license: https://creativecommons.org/licenses/by/4.0/

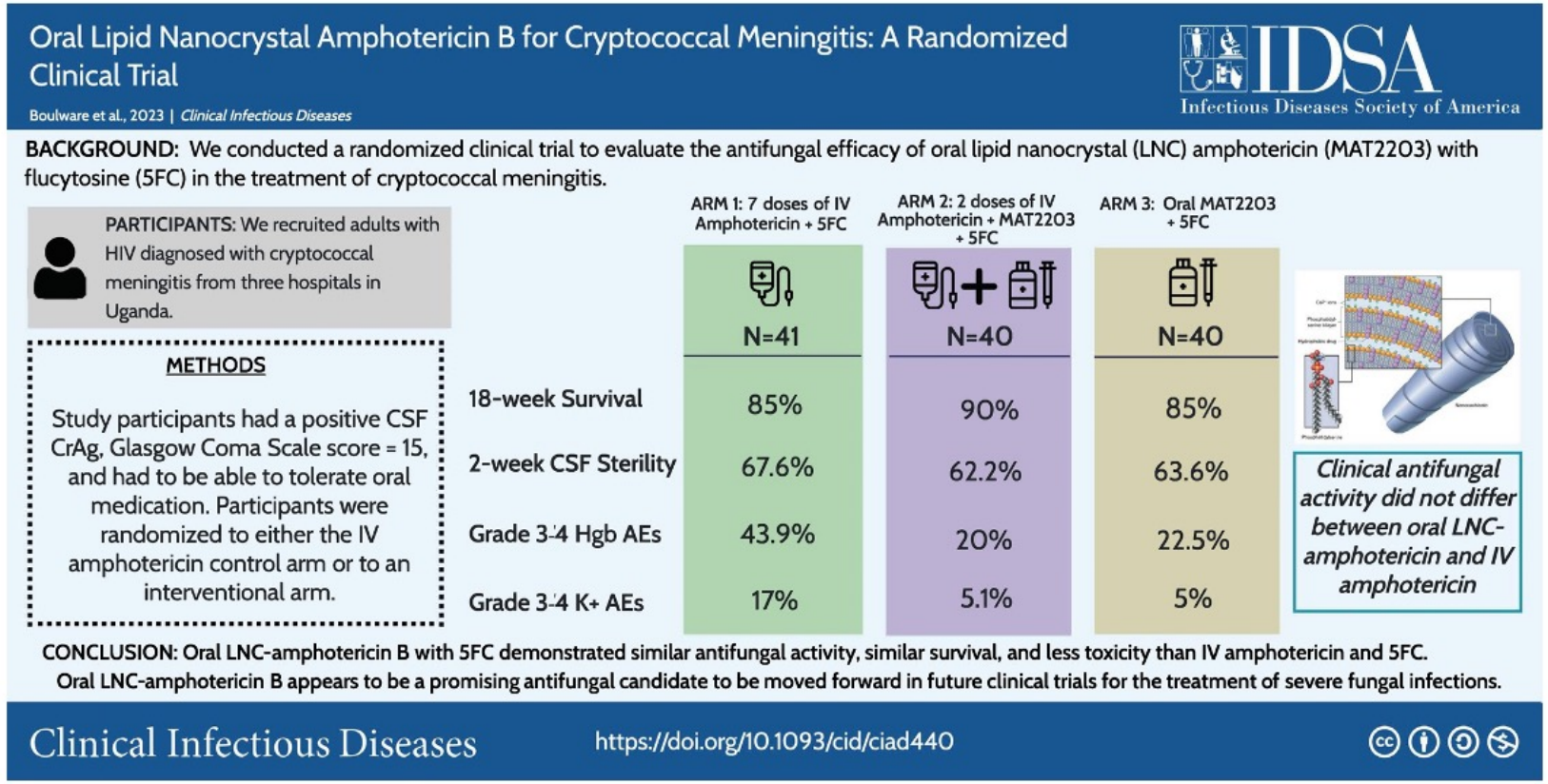
Encochleated Amphotericin B

- Broad spectrum of activity like amphotericin B deoxycholate (AmBd)
- Formulation stable at room temperature
- Dose-limiting toxicity = gastrointestinal
  - Induction dosing in cryptococcal meningitis 6x daily
- Less frequent electrolyte disturbances, kidney toxicity than AmBd

Hoenigl M et al. Clin Microbiol Reviews 2024. e0007423.doi: 10.1128/cmr.00074-23; Boulware DR et al. Clin infect Dis 2023. 77(12): 1659-1667, https://doi.org/10.1093/cid/ciad440

Encochleated Amphotericin B Clinical Trials

- Phase 2: Chronic Mucocutaneous Candidiasis, Vulvovaginal Candidiasis
- Phase 1/2: Cryptococcal Meningitis



Oral Lipid Nanocrystal Amphotericin B for Cryptococcal Meningitis: A Randomized Clinical Trial

Boulware et al., 2023 | *Clinical Infectious Diseases*

IDSA Infectious Diseases Society of America

BACKGROUND: We conducted a randomized clinical trial to evaluate the antifungal efficacy of oral lipid nanocrystal (LNC) amphotericin (MAT2203) with flucytosine (5FC) in the treatment of cryptococcal meningitis.

PARTICIPANTS: We recruited adults with HIV diagnosed with cryptococcal meningitis from three hospitals in Uganda.

METHODS

Study participants had a positive CSF CrAg, Glasgow Coma Scale score = 15, and had to be able to tolerate oral medication. Participants were randomized to either the IV amphotericin control arm or to an interventional arm.

	ARM 1: 7 doses of IV Amphotericin + 5FC	ARM 2: 2 doses of IV Amphotericin + MAT2203 + 5FC	ARM 3: Oral MAT2203 + 5FC
	N=41	N=40	N=40
18-week Survival	85%	90%	85%
2-week CSF Sterility	67.6%	62.2%	63.6%
Grade 3-4 Hgb AEs	43.9%	20%	22.5%
Grade 3-4 K+ AEs	17%	5.1%	5%

Clinical antifungal activity did not differ between oral LNC-amphotericin and IV amphotericin

CONCLUSION: Oral LNC-amphotericin B with 5FC demonstrated similar antifungal activity, similar survival, and less toxicity than IV amphotericin and 5FC. Oral LNC-amphotericin B appears to be a promising antifungal candidate to be moved forward in future clinical trials for the treatment of severe fungal infections.

Clinical Infectious Diseases https://doi.org/10.1093/cid/ciad440

Encochleated Amphotericin B Role/Future Directions

Advantages	Potential Role/Remaining Questions
• Oral delivery with improved tolerability • Broad spectrum of activity	• Would facilitate outpatient therapy for cryptococcal meningitis in limited resource settings • Potential clinical utility in many other scenarios given spectrum of activity

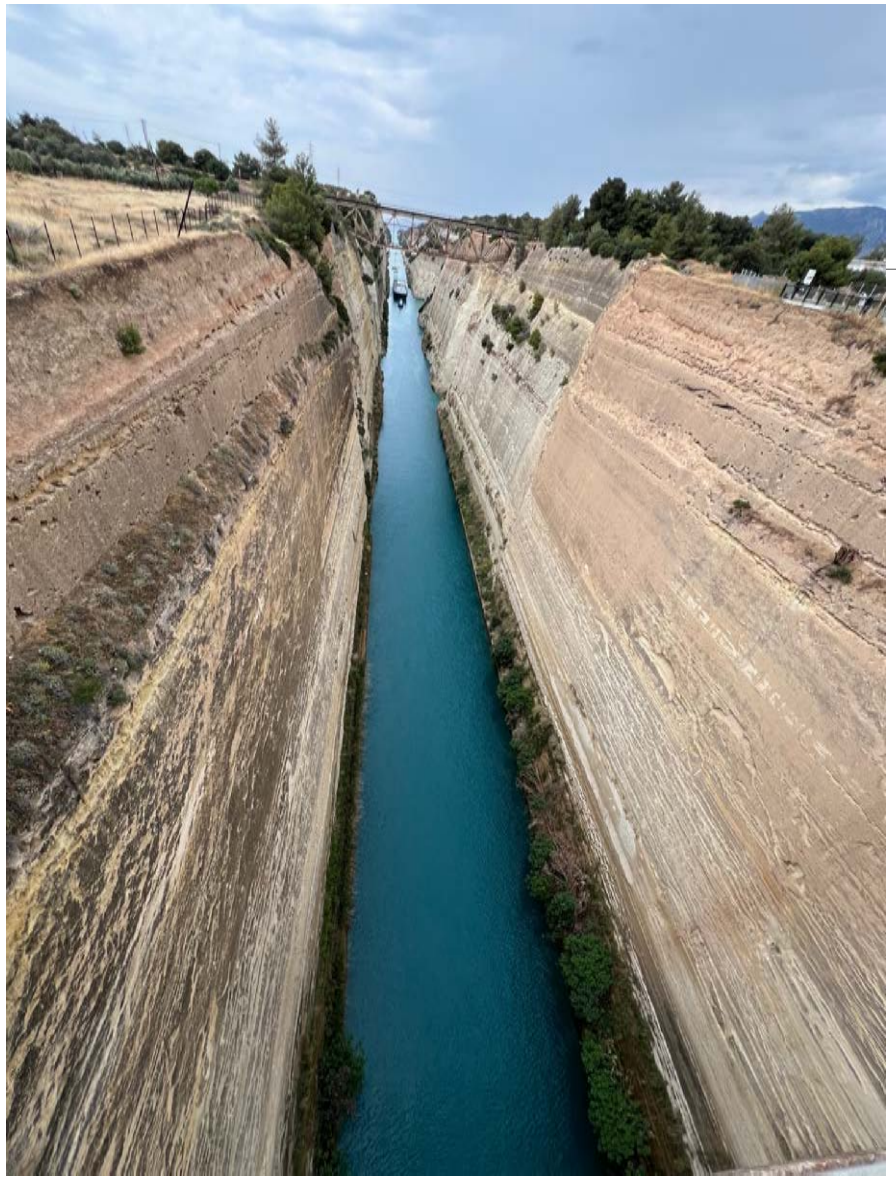
Planned Studies:

- Phase III study for invasive aspergillosis in patients with limited/no treatment options

Hoenigl M et al. Clin Microbiol Reviews 2024. e0007423.doi: 10.1128/cmr.00074-23;
https://www.matinasbiopharma.com/

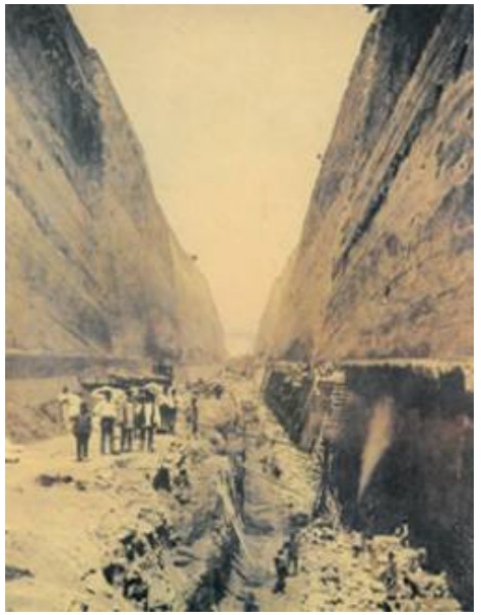
Summary of activity and (potential) roles

Agent	Advantages	Role
Rezafungin	High concentrations Long $T_{1/2}$	IC/Candidemia (Future: prophylaxis?)
Ibrexafungerp	Oral formulation *C. auris* activity	VVC/RVVC Potential: oral transition for IC/Candidemia, in combination for other difficult to treat fungi
Opelconazole	Nebulized delivery to lungs	Potential: pulmonary aspergillosis
Fosmanogepix	Broadest spectrum of newer agents, CNS penetration	Potential: resistant fungal infections, aspergillosis (higher MICs vs Mucorales)
Olorofim	Mold activity, some CNS penetration	Potential: coccidioidomycosis, lomentospora/scedosporium infections
Encochleated Amphotericin B	Broad spectrum of activity with reduced toxicity than AmBd, CNS activity	Potential: Cryptococcosis/Cryptococcal meningitis



Corinth Canal

- 602 B.C.: the tyrant of Corinth Periander decided to connect the Gulf of Corinth with the Saronic Gulf
  - Technical difficulties & prophecies
- 307 B.C.: plans taken up by Demetrius Poliorcetes
- 44 B.C.: Julius Caesar
- 37 A.D.: Caligula
- 66-67 A.D.: Nero (pickaxe)
- 1687 Venetians
- Opened in 1893



Thank you!

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School of Medicine

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Antimicrobial Stewardship
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