# Antifungal Updates

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## Disclosures

No relevant financial disclosures.

There will be discussions of non-FDA-approved antifungals and indications, which are undergoing clinical trials.

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# Objectives

By the end of this lecture, you will be able to:

1) Identify current and future opportunities for antifungal stewardship (AFS)
2) Describe novel antifungal agents and their potential niches

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# Antifungal Stewardship (AFS)

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# The Need for AFS

**Antifungal use**

- 2.7% of inpatients
- 7.7% of ICU patients

**Up to 40% of antifungals used inappropriately**

**High-risk agents**

- Drug-related adverse events
- Drug-drug interactions
- High-risk patient populations
- Financial toxicity
- Rise in resistant fungi
  - *C. auris*, azole-resistant *Aspergillus*

**Opportunities for diagnostic stewardship**


Vallabhaneni S et al. Trends in antifungal use in US hospitals, 2006-12. *J Antimicrob Chemother*. 2018;73(10):2867-2875.
Nivoix Y et al. Adherence to recommendations for the use of antifungal agents in a tertiary care hospital. *J Antimicrob Chemother*. 2012;67(10):2506-2513.
Johnson MD et al. Core Recommendations for Antifungal Stewardship: A Statement of the MSERGC. J Infect Dis. 2020;222(Suppl 3):S175-S198.

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# MSGERC 7 Core Elements of AFS

- Engagement of senior hospital management leadership toward antimicrobial stewardship
- Accountability and responsibility
- Available expertise on infection management
- Education and practical training
- Actions aiming at responsible use
- Monitoring and surveillance
- Reporting and feedback

Johnson MD et al. Core Recommendations for Antifungal Stewardship: A Statement of the MSGERC. J Infect Dis. 2020;222(Suppl 3):S175-S198.

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# ID Consult (IDC) for Candidemia

**Meta-analysis of 13 studies**

- Half received IDC
- IDC associated with
  - Mortality reduction
  - Increased ophthalmology examination
  - Increased echocardiogram usage
  - Increased central line removal

**IDC associated with less untreated cases**

**Highly recommend IDC in candidemia**

Kobayashi T et al. Impact of Infectious Disease Consultation in Patients With Candidemia: A Retrospective Study, Systematic Literature Review, and Meta-analysis. *OFID*. 2020;7(9):ofaa270.
Mejia-Chew C et al. Effect of infectious disease consultation on mortality and treatment of patients with candida bloodstream infections: a retrospective, cohort study. *Lancet Infect Dis*. 2019;19(12):1336-1344.

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# Empiric Antifungals?

EMPIRICUS RCT

- 251 patients with ICU-acquired sepsis, *Candida* colonization, and multiple organ failure
  - 14d micafungin vs placebo
- 28d survival
  - 70.3% micafungin vs 69.9% placebo (HR 1.04, 95% CI: 0.64-1.67)
- Decreased number of ICU-acquired IFIs with micafungin
  - 3% vs 12% (p=0.008)

Timsit JF et al. 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. *JAMA*. 2016;316(15):1555-1564.

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# Empiric Antifungals?

CandiSep RCT (n=342)

- BDG-guided antifungals vs standard of care
  - BDG: 48.8% received antifungals
  - SOC: 6% received antifungals
- 28d mortality
  - 33.7% in BDG and 30.5% in control (p=0.53)
- BDG for invasive candidiasis:
  - Sensitivity: 54%
  - Specificity: 65%

Bloos F et al. (1 → 3)-β-D-Glucan-guided antifungal therapy in adults with sepsis: the CandiSep randomized clinical trial. *Intensive Care Med*. 2022;48(7):865-875.

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# *C. auris*

- First described in 2009
  - 4 clades
- Biofilm formation
  - Device colonization
- Multidrug resistance
- Large outbreaks
  - LTCFs
  - COVID-19
- Infection control
  - Isolation with enhanced precautions, hand hygiene, screening
  - Avoid quaternary ammonium disinfectants

Countries reporting *C. auris* as of February 2021

Desoubeaux G et al. Overview about Candida auris: What's up 12 years after its first description?. *J Mycol Med*. 2022;32(2):101248.

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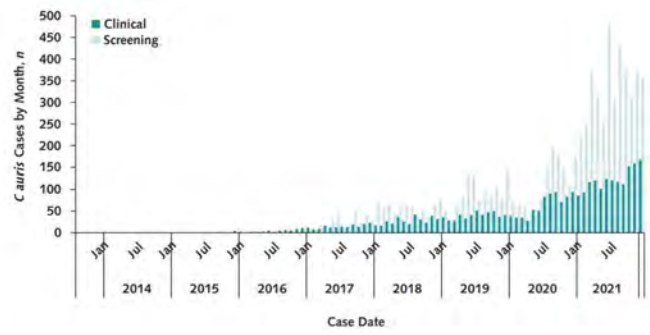
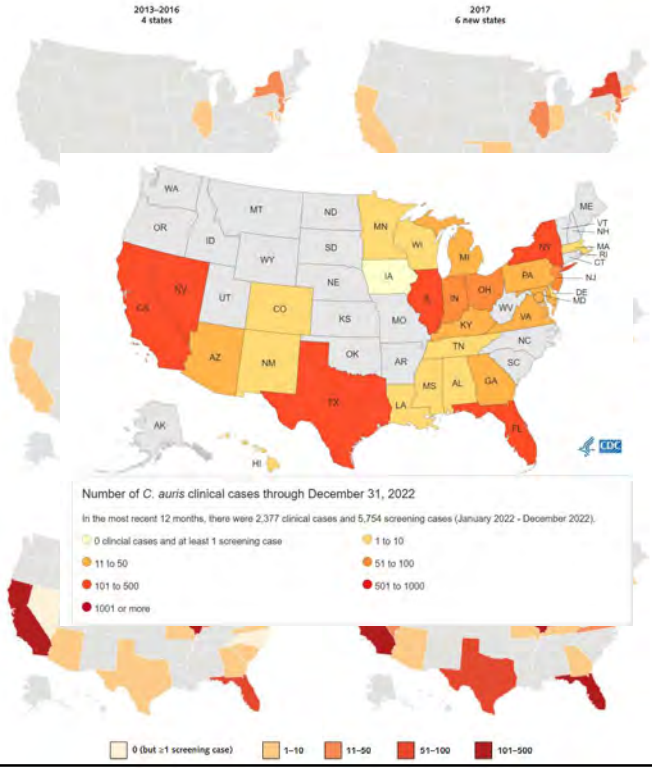



*Table.* Percentage Resistance of *Candida auris* Isolates Tested by the Antimicrobial Resistance Laboratory Network, 2018 to 2020*

| Year or Region | Azoles† | Amphotericin B‡ | Echinocandins§ |
|---|---|---|---|
| **Year** | | | |
| 2018 (*n* = 463) | 372 (80.3) | 151 (32.6) | 2 (0.4) |
| 2019 (*n* = 1006) | 787 (78.2) | 242 (24.1) | 14 (1.4) |
| 2020 (*n* = 1294) | 1109 (85.7) | 331 (25.6) | 15 (1.2) |
| **Region‖** | | | |
| Mid-Atlantic (*n* = 135) | 133 (98.5) | 115 (85.2) | 4 (3.0) |
| Midwest (*n* = 156) | 17 (10.9) | 2 (1.4) | 0 (0.0) |
| Mountain (*n* = 25) | 24 (96.0) | 1 (4.0) | 0 (0.0) |
| Northeast (*n* = 1051) | 1046 (99.5) | 468 (44.5) | 22 (2.1) |
| Southeast (*n* = 172) | 170 (99.4) | 9 (5.2) | 0 (0.0) |
| West (*n* = 556) | 553 (99.5) | 17 (3.1) | 1 (0.2) |




Lyman M, Forsberg K, Sexton DJ, et al. Worsening Spread of *Candida auris* in the United States, 2019 to 2021. *Ann Intern Med*. 2023;176(4):489-495.

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# *C. Auris* – Role of AFS

- Fast recognition of cases
  - Most MALDI-TOF-MS platforms identify accurately
- Minimize unnecessary antibiotic/ antifungal use
  - Western NY Case
- Ensure proper treatment
  - Rapid infection control measures
  - IDC
  - Echinocandins first line
  - Only treat symptomatic invasive infections
  - Remove medical devices

| Identification Method | Organisms *C. auris* can be misidentified as |
|---|---|
| Vitek 2 YST | *C. haemulonii*<br>*C. duobushaemulonii* |
| BD Phoenix | *C. haemulonii*<br>*C. catenulata* |
| Microscan | *C. famata*<br>*C. guilliermondii*<br>*C. lusitaniae*<br>*C. parapsilosis* |

Adapted from CDC: https://www.cdc.gov/fungal/candida-auris/identification.html

| Drug | Total DOT Before Isolation of *C. auris* |
|---|---|
| AZM | 3 |
| FEP | 7 |
| MEM | 16 |
| MFG | 15 |
| TZP | 8 |
| VAN | 17 |
| Total | 73 |

McGann P et al. The Emergence and Persistence of *Candida auris* in Western New York With No Epidemiologic Links: A Failure of Stewardship?. *Open Forum Infect Dis*. 2023;10(3):ofad123.

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# Is Shorter Better for Candidemia?

- Retrospective study in Italy, 2018-2020
- N=114 with uncomplicated candidemia
- Short (n=30) vs prolonged (n=79) course
- Short course: more likely to be in surgical ward or septic shock
- No difference in mortality or relapse
- Limitations:
  - Lacks generalizability (75% excluded)
  - Single-center
  - Unmeasured confounding
  - Small sample size


Warrants an RCT

Vena A et al. Short Course of Antifungal Therapy in Patients With Uncomplicated *Candida* Bloodstream Infection: Another Case of Less Is More in the Clinical Setting?. *OFID*. 2022;10(1):ofac656.

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# Asymptomatic Candiduria

- Does not warrant treatment unless neutropenic, neonate, or urologic manipulation
  - In one study, 43% of patients with asymptomatic candiduria were not managed per IDSA guidelines
- Use of a Microbiologic Nudge

| | |
|---|---|
| Culture growth | >100,000 CFU/mL Candida glabrata ! |
| | No susceptibility performed. |
| | In the absence of symptoms, Candida is generally considered normal flora. No therapy indicated unless high risk (pregnant, neonate or neutropenic) or undergoing urologic procedure. If Foley catheter present, remove or replace when able. |

  - After implementation, antifungal administration within 72 hours decreased (48.1% vs 34%; p=0.02)

Pappas PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):e1-e50.
Schartz WR et al. Templated microbiology comments with candiduria to enhance antimicrobial stewardship. *Antimicrob Steward Healthc Epidemiol*. 2022;2(1):e156.

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# New Terms, Old Germs

- On-going process
- Patient safety concerns
- Include prior name in reports for 5+ years
- Clinician, lab, and student education
- Importance of AFS

| Old Name | New Name |
|---|---|
| *Absidia corymbifera* | |
| *Candida famata* | |
| *Candida glabrata* | |
| *Candida guilliermondii* | |
| *Candida krusei* | |
| *Candida kefyr* | |
| *Candida lusitaniae* | |
| *Emmonsia helica* | |
| *Emmonsia pasteuriana* | |
| *Geotrichum capitatum* | |
| *Fusarium solani* | |
| *Penicillium marneffei* | |
| *Pseudallescheria boydii* | |
| *Scedosporium prolificans* | |


Kidd SE, Abdolrasouli A, Hagen F. Fungal Nomenclature: Managing Change is the Name of the Game. *Open Forum Infect Dis*. 2023;10(1):ofac559.

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# New Terms, Old Germs

- On-going process
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| Old Name | New Name |
|---|---|
| *Absidia corymbifera* | *Lichtheimia corymbifera* |
| *Candida famata* | *Debaryomyces hansenii* |
| *Candida glabrata* | *Nakaseomyces glabrata* |
| *Candida guilliermondii* | *Meyerozyma guillermondii* |
| *Candida krusei* | *Pichia kudriavzevii* |
| *Candida kefyr* | *Kluyveromyces marxianus* |
| *Candida lusitaniae* | *Clavispora lusitaniae* |
| *Emmonsia helica* | *Blastomyces helices* |
| *Emmonsia pasteuriana* | *Emergomyces pasteurianus* |
| *Geotrichum capitatum* | *Magnusiomyces capitatus* |
| *Fusarium solani* | *Neocosmospora solani* |
| *Penicillium marneffei* | *Talaromyces marneffei* |
| *Pseudallescheria boydii* | *Scedosporium boydii* |
| *Scedosporium prolificans* | *Lomentaspora prolificans* |

Kidd SE, Abdolrasouli A, Hagen F. Fungal Nomenclature: Managing Change is the Name of the Game. *Open Forum Infect Dis*. 2023;10(1):ofac559.

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# New Old

- On-
- Pati
  con
- Inclu
  in re
  year
- Clin
  stud
- Imp

| Very Old Name | Old Name | New Name |
|---|---|---|
| *Mucor corymbifer* | *Absidia corymbifera* | *Lichtheimia corymbifera* |
| | *Candida famata* | *Debaryomyces hansenii* |
| *Torulopsis glabrata* | *Candida glabrata* | *Nakaseomyces glabrata* |
| *Pichia guilliermondii* | *Candida guilliermondii* | *Meyerozyma guillermondii* |
| *Issatchenckia orientalis* | *Candida krusei* | *Pichia kudriavzevii* |
| *Candida pseudotropicalis* | *Candida kefyr* | *Kluyveromyces marxianus* |
| | *Candida lusitaniae* | *Clavispora lusitaniae* |
| | *Emmonsia helica* | *Blastomyces helices* |
| | *Emmonsia pasteuriana* | *Emergomyces pasteurianus* |
| *Blastoschizomyces capitatum* | *Geotrichum capitatum* | *Magnusiomyces capitatus* |
| | *Fusarium solani* | *Neocosmospora solani* |
| | *Penicillium marneffei* | *Talaromyces marneffei* |
| *Allescheria boydii* | *Pseudallescheria boydii* | *Scedosporium boydii* |
| *Scedosporium inflatum* | *Scedosporium prolificans* | *Lomentaspora prolificans* |

Kidd SE, Abdolrasouli A, Hagen F. Fungal Nomenclature: Managing Change is the Name of the Game. *Open Forum Infect Dis*. 2023;10(1):ofac559.

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# Novel Antifungals

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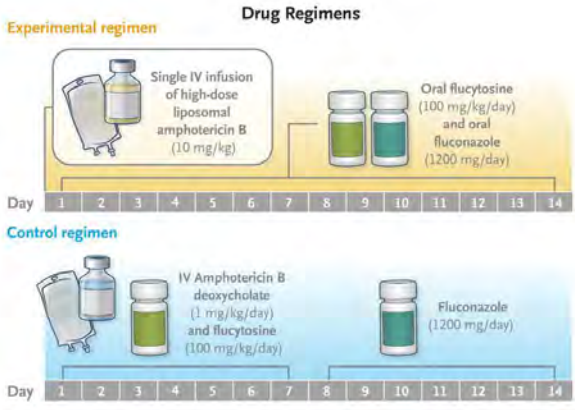
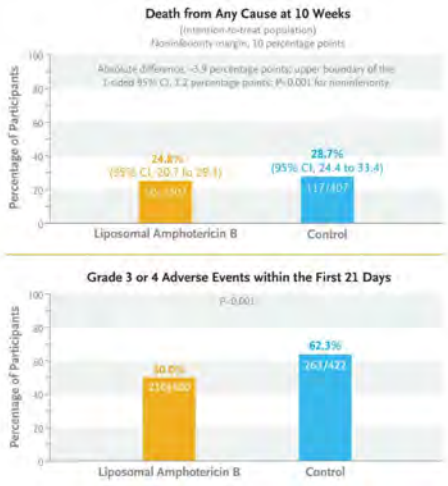
# What's New with AmphoB?

## AMBITION Trial




Jarvis JN et al. Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis. *N Engl J Med*. 2022;386(12):1109-1120.

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# What's Next for AmphoB?

- Single, High-dose L-AmB for Induction in Disseminated Histoplasmosis in HIV
  - Phase II open-label RCT
- Oral Encochleated Formulation in Cryptococcal Meningitis in HIV
  - Phase II RCT
  - Not FDA approved

| Trial Arms | Day 14 Overall Survival |
|---|---|
| **1)** Single dose 10mg/kg L-AmB | 34/38 (89.5%) |
| **2)** 10mg/kg L-AmB on D1, 5mg/kg L-AmB on D3 | 29/37 (78.4%) |
| **3)** 3mg/kg L-Amb for 2 weeks (control) | 35/38 (92.1%) |

| Trial Arms | 18-week survival |
|---|---|
| **1)** 2 doses IV AmphoB then 1.8g PO cAMB QD with PO flucytosine for 2 weeks, then 1.2g QD cAMB until 6 weeks | 36/40 (90%) |
| **2)** 7 days IV amphoB with flucytosine, then 7 days fluconazole 1200mg QD | 26/30 (87%) |

Pasqualotto AC et al. Single high-dose of liposomal amphotericin B in HIV/AIDS-related disseminated histoplasmosis: a randomized trial. *Clinical Infectious Diseases*. 2023;ciad313. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9752325/

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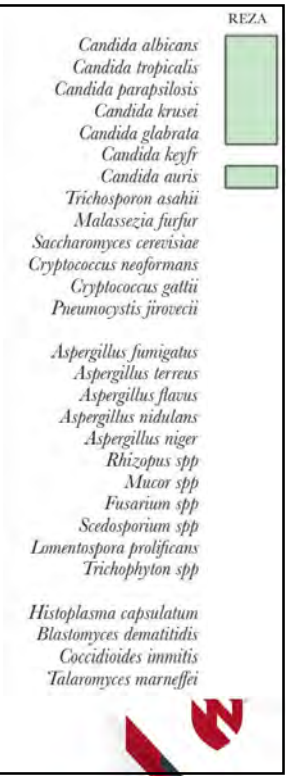
# Rezafungin

- Class: Echinocandin
- Dosing:
  - IV 400mg on D1, then 200mg once weekly starting D8
- RESTORE Phase 3 trial
  - Non-inferior to caspofungin for 30-day all-cause mortality
- Development Status
  - FDA approved 2023 for candidemia and invasive candidiasis in patients with limited or no alternative treatment options
  - Phase 3 ReSPECT trial on-going
    - 90-day prophylaxis for *Candida, Aspergillus* & PJP in allo-HSCT




Rauseo AM et al. Hope on the Horizon: Novel Fungal Treatments in Development. *OFID*. 2020;7(2):ofaa016.
Thompson GR 3rd et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. *Lancet*. 2023;401(10370):49-59.
https://clinicaltrials.gov/ct2/show/NCT04368559

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# Ibrexafungerp

- Class: Triterpenoid
- Dosing:
  - Acute vulvovaginal candiasis (VVC)
    - PO 300mg Q12 for 1 day
  - Recurrent VVC prevention
    - PO 300mg Q12 for 1 day, once per month up to 6 months
- Trial data
  - VANISH: higher clinical cure and mycological eradication compared to placebo for acute VVC
  - CANDLE: not yet published for recurrent VVC
  - Phase 2 for invasive candidiasis: similar response rate to standard of care
- Development Status
  - FDA approved 2021 for treatment of VVC and prevention of recurrent VVC
  - Multiple on-going studies, including phase 3 for invasive candidiasis


https://clinicaltrials.gov/ct2/show/NCT05178862
https://clinicaltrials.gov/ct2/show/NCT04029116
Rauseo AM et al. Hope on the Horizon: Novel Fungal Treatments in Development. *OFID*. 2020;7(2):ofaa016.
Schwebke JR et al. Ibrexafungerp Versus Placebo for Vulvovaginal Candidiasis Treatment: A Phase 3, Randomized, Controlled Superiority Trial (VANISH 303). *Clin Infect Dis*. 2022;74(11):1979-1985.

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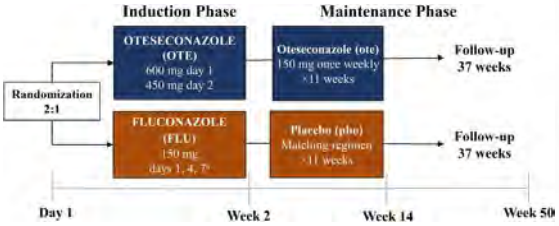
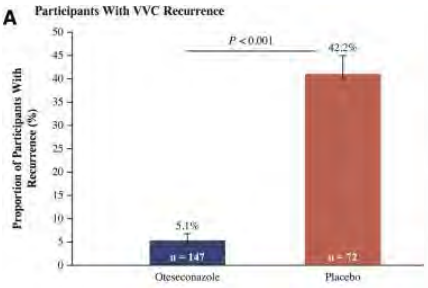
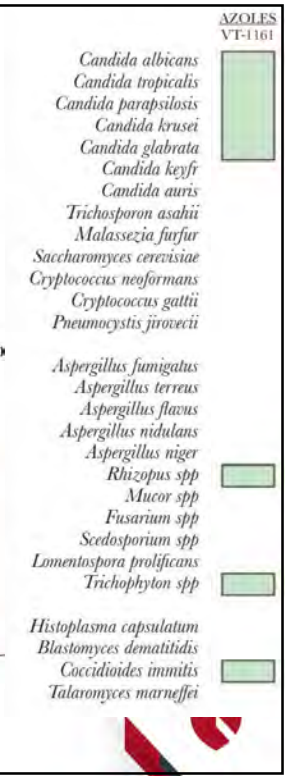
# Oteseconazole

- Class: Tetrazole
- Half-life: 138 days!
- Trial data:
  - Phase 3 RCT ultraVIOLET
- Development Status:
  - FDA approved in 2022 for females with recurrent VVC who are <u>not of reproductive potential</u>




Rauseo AM et al. Hope on the Horizon: Novel Fungal Treatments in Development. *OFID*. 2020;7(2):ofaa016.
Martens MG et al. Phase 3 study evaluating the safety and efficacy of oteseconazole in the treatment of recurrent vulvovaginal candidiasis and acute vulvovaginal candidiasis infections. *Am J Obstet Gynecol*. 2022;227(6):880.e1-880.e11.

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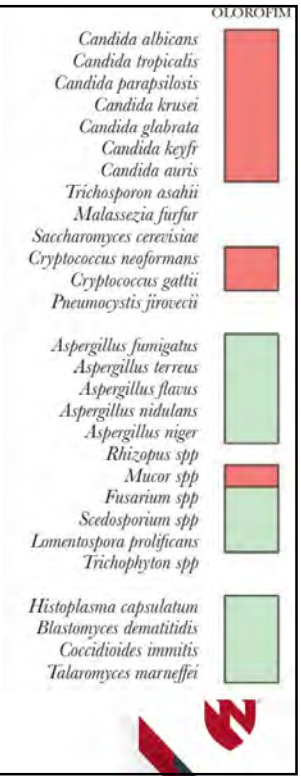
# Olorofim

- Class: Orotomide
- Dosing
  - IV/PO 150mg BID x1, then 90mg BID
- Interim FORMULA-OLS data
  - 3-month mortality: 32% vs 87% in historical controls
- Development Status:
  - Phase 3 RCT vs L-Amb for *Aspergillus* IFI
  - Phase IIb for *Lomentospora, Scedosporium, Aspergillus,* other resistant IFIs without other options
  - Not FDA approved




Rauseo AM et al. Hope on the Horizon: Novel Fungal Treatments in Development. *OFID*. 2020;7(2):ofaa016.
https://clinicaltrials.gov/ct2/show/NCT05101187
https://clinicaltrials.gov/ct2/show/NCT03583164?term=olorofim&draw=2&rank=9
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9752288/

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# Fosmanogepix

- Class: Glycosylphosphatidylinositol (GPI) inhibitor
- Phase 2 open-label, single arm study for candidemia due to *C. auris*
  - n=9, 89% 30-day survival
- Development Status:
  - Phase 3 trial comparing to caspofungin/ fluconazole for candidemia/invasive candidiasis
  - Not FDA approved


https://clinicaltrials.gov/ct2/show/NCT05421858?term=fosmanogepix&draw=2&rank=2
Rauseo AM et al. Hope on the Horizon: Novel Fungal Treatments in Development. *OFID*. 2020;7(2):ofaa016.
Vazquez JA et al. Clinical Efficacy and Safety of a Novel Antifungal, Fosmanogepix, in Patients with Candidemia Caused by Candida auris: Results from a Phase 2 Trial. *AAC*. 2023;67(5):e0141922.

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# Summary

- Incorporate AFS into routine AMS activities
- Start by targeting high-yield conditions
- Prepare for taxonomic changes if adopted
- Numerous novel antifungals recently approved or being studied

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# Questions?

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