Mercoledì 29 gennaio

10.30-13.15 **IX SESSIONE**

INFEZIONI BATTERICHE

Moderatori: *P. Blanc (Pistoia), A. Nerli (Prato)*

Infezioni fungine invasive: update sulla terapia.
M. Tumbarello (Siena)

Infezioni fungine invasive: update sulla terapia

Mario Tumbarello

Azienda ospedaliero-universitaria Senese

UNIVERSITÀ DI SIENA 1240

1. *Candida auris*

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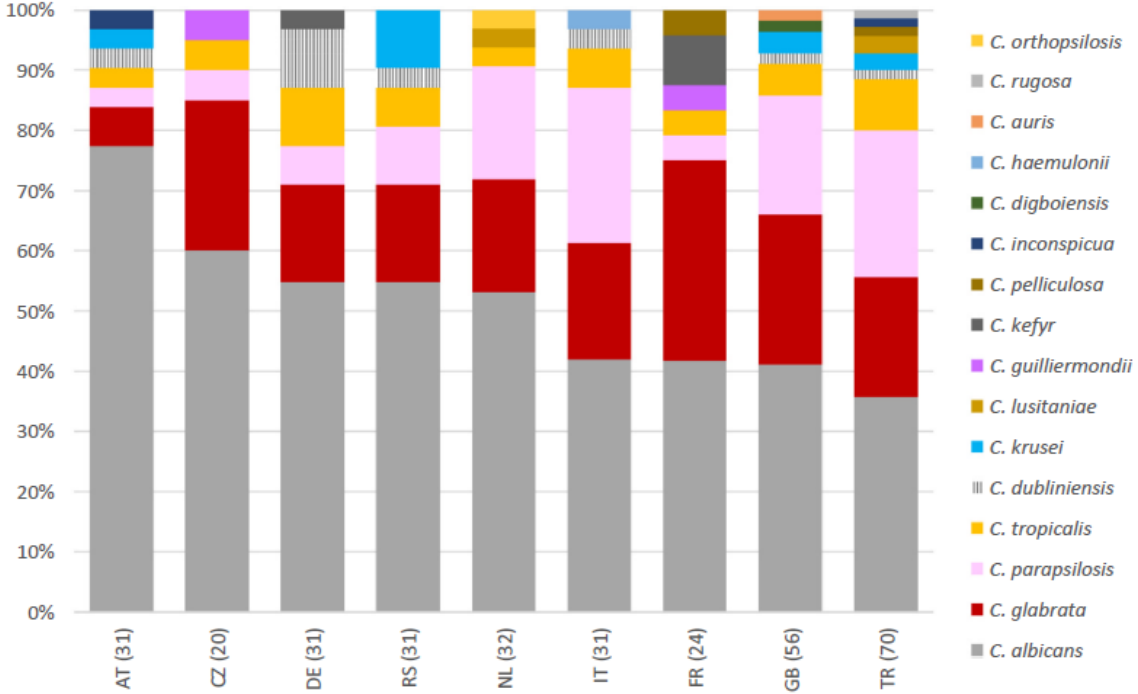
journal homepage: www.elsevier.com/locate/jinf

European candidaemia is characterised by notable differential epidemiology and susceptibility pattern: Results from the ECMM *Candida* III study



RAPID COMMUNICATION

Increasing number of cases and outbreaks caused by *Candida auris* in the EU/EEA, 2020 to 2021

Anke Kohlenberg[1] , Dominique L Monnet[1] , Diamantis Plachouras[1] , *Candida auris* survey collaborative group[2]
1. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
2. The members of the *Candida auris* survey collaborative group are listed under Collaborators and at the end of the article

Correspondence: Anke Kohlenberg (anke.kohlenberg@ecdc.europa.eu)

Collaborators: The collaborators are listed at the end of the article.

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Kohlenberg Anke, Monnet Dominique L, Plachouras Diamantis, Candida auris survey collaborative group. Increasing number of cases and outbreaks caused by Candida auris in the EU/EEA, 2020 to 2021. Euro Surveill. 2022;27(46):pii=2200846. https://doi.org/10.2807/1560-7917.ES.2022.27.46.2200846

Article submitted on 28 Oct 2022 / accepted on 14 Nov 2022 / published on 17 Nov 2022

- 5 countries (Denmark, France, Germany, Greece and Italy) reported 14 *C. auris* outbreaks, defined as ≥ 2 cases with an epidemiological link
- Total of 327 affected patients

Epidemiological stages of *C. auris:*

Stage 0: No cases of C. auris infection or colonisation have been detected.

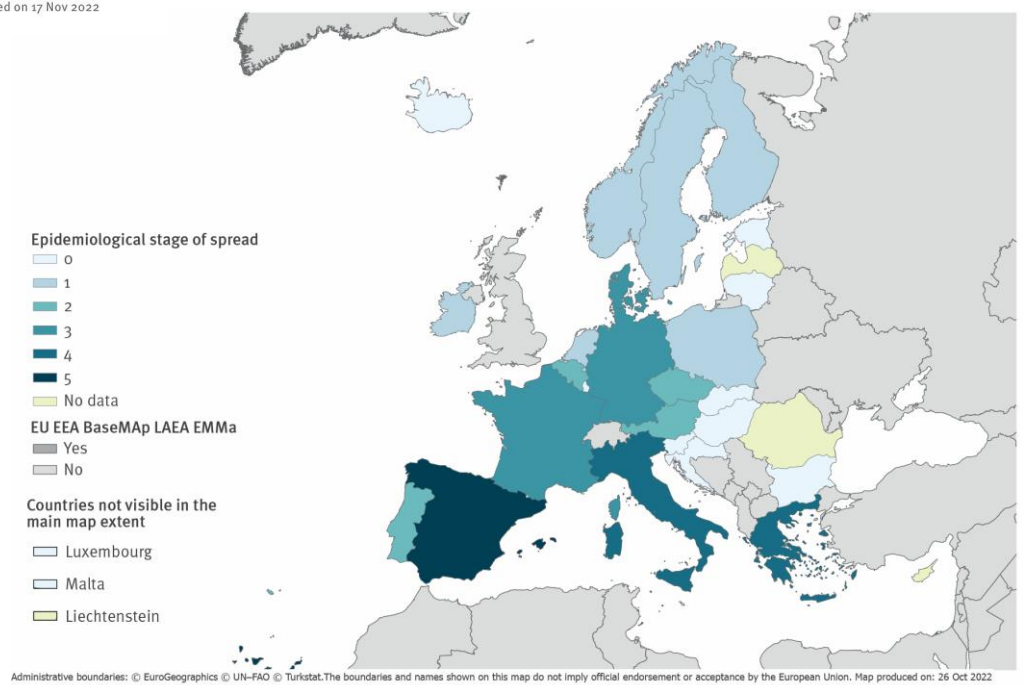
Stage 1: Only imported cases of C. auris have been detected.

Stage 2: Only sporadic cases of C. auris that were locally acquired or of unknown origin have been detected.

Stage 3: Sporadic outbreaks of C. auris have occurred without or with only limited inter-facility spread.

Stage 4: Multiple outbreaks of C*. auris* with verified or plausible inter-facility spread have occurred.

Stage 5: C. auris is endemic in parts of the country (regional spread).



RAPID COMMUNICATION

In vivo evolution to echinocandin resistance and increasing clonal heterogeneity in *Candida auris* during a difficult-to-control hospital outbreak, Italy, 2019 to 2022

Giulia Codda[1], Edward Willison[2], Laura Magnasco[3], Paola Morici[2], Daniele Roberto Giacobbe[3,4], Antonella Mencacci[5,6], Daniele Marini[5,6], Malgorzata Mikulska[3,4], Matteo Bassetti[3,4], Anna Marchese[1,2], Vincenzo Di Pilato[1]

- A difficult-to-control outbreak of *Candida auris* is ongoing in a large tertiary care hospital in Liguria, Italy
- July 2019 – December 2022: **503** cases of *C. auris* carriage or infection
- Genomic surveillance identified
  - putative cases that no longer occurred as part of one defined outbreak
  - the emergence of echinocandin (pandrug) resistance following independent selection of FKS1S639F and FKS1F635Y mutants upon prolonged exposure to caspofungin and/or anidulafungin

Annals of Internal Medicine ORIGINAL RESEARCH

Worsening Spread of *Candida auris* in the United States, 2019 to 2021

Meghan Lyman, MD; Kaitlin Forsberg, MPH; D. Joseph Sexton, PhD; Nancy A. Chow, PhD, MS; Shawn R. Lockhart, PhD; Brendan R. Jackson, MD, MPH; and Tom Chiller, MD, MPHTM

Figure 1. Number of clinical and screening *C auris* cases reported to the Centers for Disease Control and Prevention during 2013 to 2021.

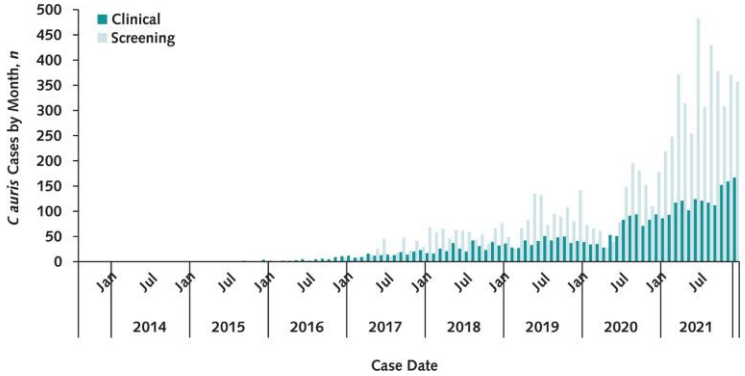


Figure 2. Volume of *C auris* screening through the Antimicrobial Resistance Laboratory Network, 2013 to 2021.

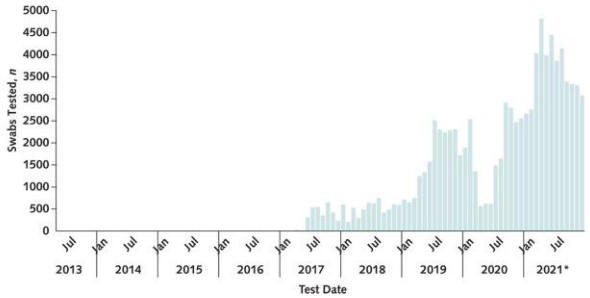
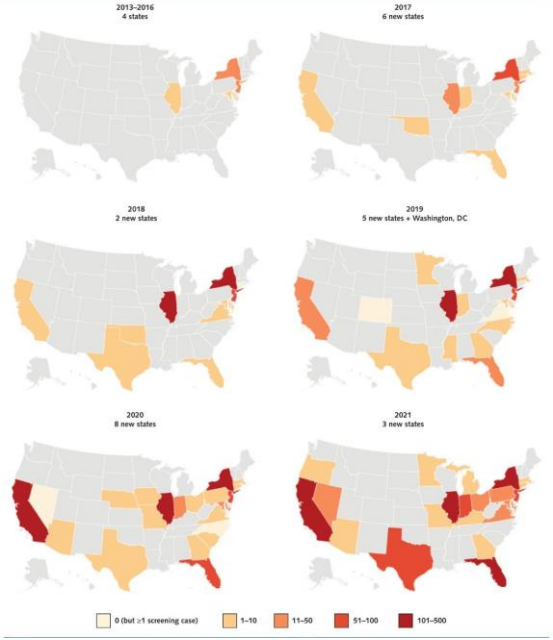


Figure 3. Geographic distribution of clinical *C auris* cases in the United States reported to the Centers for Disease Control and Prevention by state during 2013 to 2021.

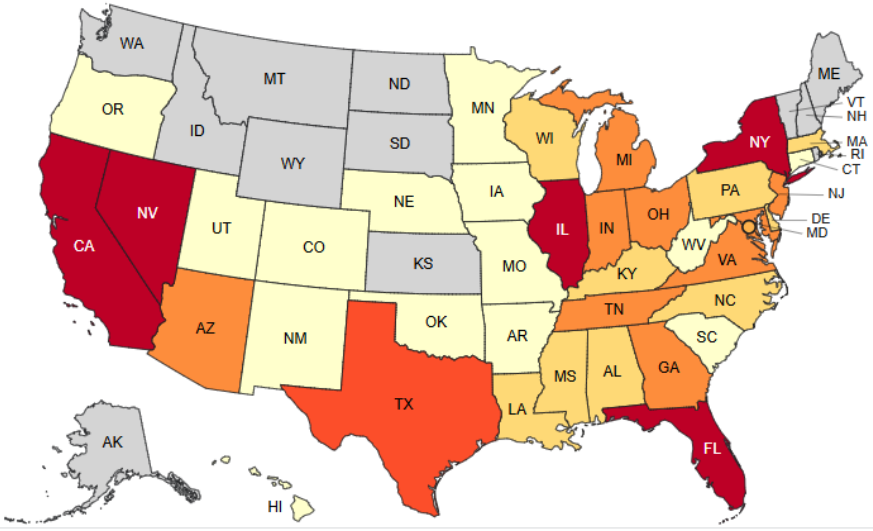


- 3270 clinical cases and 7413 screening cases of *C. auris* were reported in the US until 31/12/2021
- Colonization screening volume and screening cases increased
- The number of *C. auris* cases that were resistant to echinocandins in 2021 was about 3 times that in each of the previous 2 years (1.2% in 2020)

New Clinical Cases of *C. auris* Reported in the U.S.

Select a year

All Years

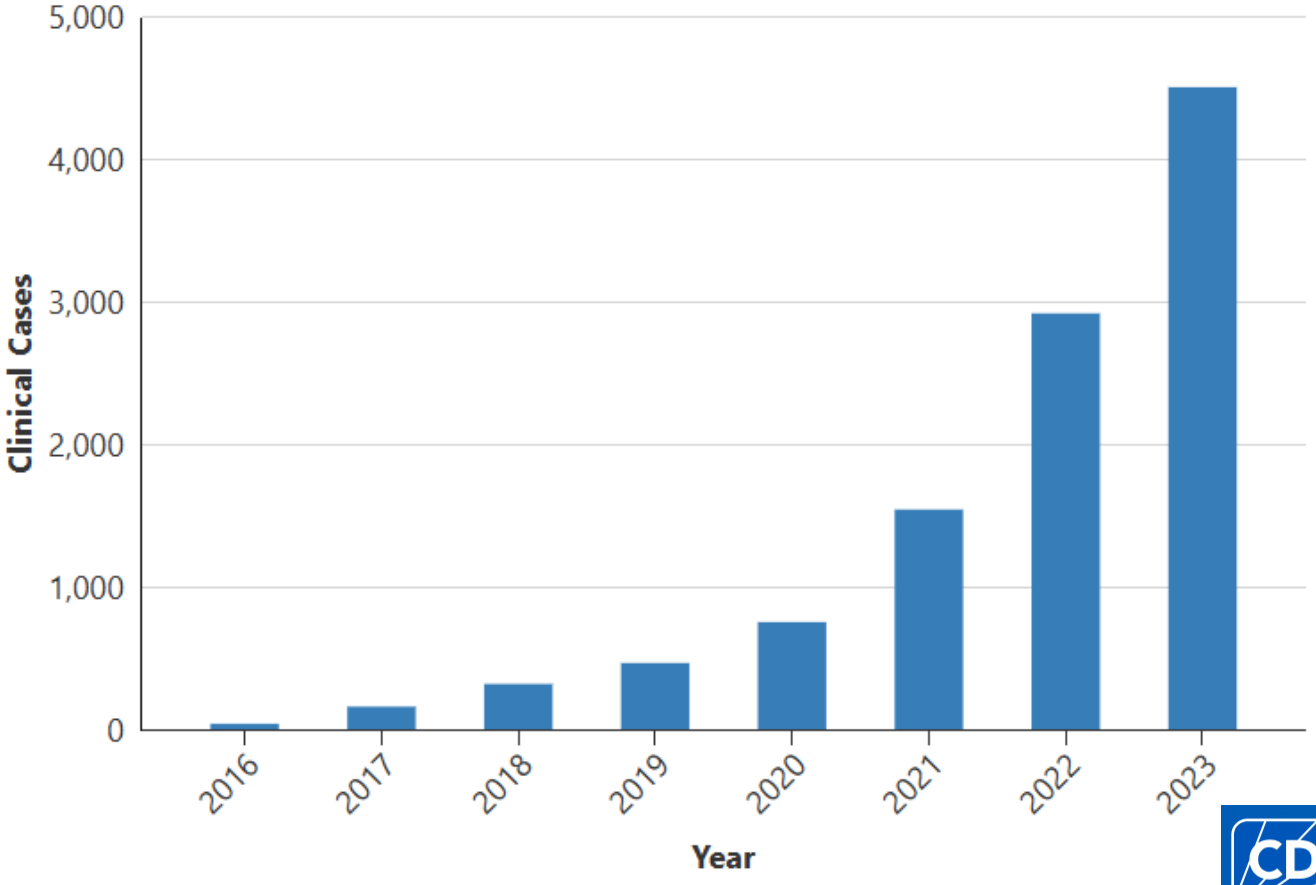


Legend

From 2016-2023, there have been 10,788 clinical cases. There were an additional 22,931 screening cases not shown on the map. There were 9 clinical cases from 2013-2015 that were reported retrospectively.

- No new clinical cases
- 1 to 10
- 11 to 50
- 51 to 100

National Clinical Cases Reported Over Time



Risk of *C. auris* candidemia in colonised patients

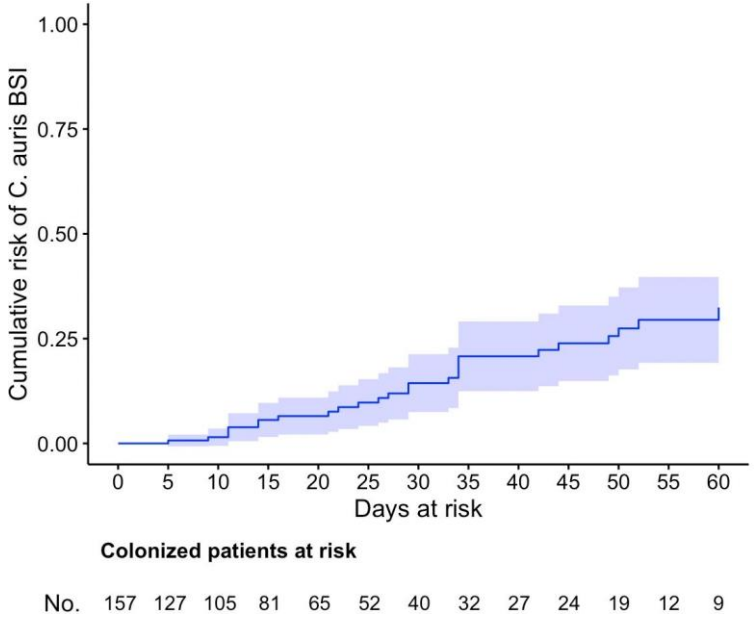


Figure 1 legend. Cumulative risk of *Candida auris* candidemia in colonized ICU patients. The risk was estimated by means of the Aalen-Johansen method, with the first occurring *C. auris* candidemia as the event of interest, death as a competing event, and discharge from the ICU as a right-censoring event. ICU, intensive care unit.

27/157 (17%) patients developed at least one episode of *C. auris* candidemia, after a median of 29 days (IQR 15–38) from the first detection of colonization

Independent risk factors:

- Previous ICU stay in days
- CRRT
- Multisite colonisation

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Antifungal Resistance Trends of *Candida auris* Clinical Isolates in New York and New Jersey from 2016 to 2020

Shannon Kilburn,[a] Gabriel Innes,[b] Monica Quinn,[a] Karen Southwick,[c] Belinda Ostrowsky,[d] Jane A. Greenko,[e] Emily Lutterloh,[a,f] Rebecca Greeley,[b] Reed Magleby,[b] Vishnu Chaturvedi,[a] Sudha Chaturvedi[a,f]

TABLE 1 Resistance and non-wild-type antifungals pattern of New York *C. auris* clinical isolates from 2016 through 2020

Year and total no. of isolates			2016 (28)	2017 (141)	2018 (231)	2019 (300)	2020 (448)	
Antifungal	CDC BP	ECV UL-WT	% (n) resistance/non-wild-type					*P* value
FLC	≥ 32	-	100% (28)	100% (141)	100% (231)	100% (300)	99.6% (446)	0.6393
ITC	-	2	0	0	0	0.7% (2)	0.2% (1)	0.666
ISA	-	2	0	7.1% (10)	0.9 (2)	0	9.2% (41)	$4.42e^{-12}$
POS	-	0.5	0	23.4% (33)	13.4% (31)	33% (99)	42.6% (191)	$2.2e^{-16}$
VRC	-	4	7.4% (2)	14.2% (20)	0.9% (2)	4.3% (13)	4.9% (22)	$3.94e^{-6}$
AFG	≥ 4	-	0	1.4% (2)	0.4% (1)	2.3% (7)	4% (18)	0.05707
CAS	≥ 2	-	0	1.4% (2)	0.4% (1)	2.3% (7)	4% (18)	0.05707
MFG	≥ 4	-	0	1.4% (2)	0.9% (2)	1.7% (5)	3.8% (17)	0.1549
AMB	≥ 2	-	82.1% (23)	75.9% (107)	48.1% (111)	45.3% (136)	51.3% (230)	$1.019e^{-9}$
5-FC	-	0.125	7.1% (2)	11.3% (16)	19.4% (31)[a]	-	-	0.0793

[a]160 of 231 *C. auris* isolates were part of testing due to discontinuation of 5-FC Etest strips in 2018.

TABLE 2 Resistance and non-wild-type antifungals pattern of New Jersey *C. auris* clinical isolates from 2017 through 2020

Year and total no. of isolates			2017 (12)	2018 (13)	2019 (48)	2020 (61)	
Antifungal	CDC BP	ECV UL-WT	% (n) resistance/non-wild-type				*P* value
FLC	≥ 32	-	100% (12)	100% (13)	100% (48)	100% (61)	1
ITC	-	2	0	7.7% (1)	0	0	0.1852
ISA	-	2	0	7.7% (1)	0	14.8% (9)	0.01613
POS	-	0.5	0	15.4% (2)	18.7% (9)	47.5% (29)	0.0002489
VRC	-	4	8.3% (1)	7.7% (1)	2.1% (1)	4.9% (3)	0.3546
AFG	≥ 4	-	0	0	0	0	1
CAS	≥ 2	-	0	0	0	0	1
MFG	≥ 4	-	0	0	0	0	1
AMB	≥ 2	-	66.7% (8)	46.2% (6)	43.7% (21)	31.1% (19)	0.1108

Infection control interventions

1. screening for skin carriage (combined axilla and groin skin swab) at admission to ICU for early identification of possible community-acquired cases;
2. repeated weekly screening for carriage at skin, respiratory (whenever mechanically ventilated) and urine level during the ICU stay until first detection of *C. auris*;
3. implementation of strict contact precautions for colonized patients
4. screening for skin carriage upon when a *C. auris*-negative patient was discharged from the ICU and admitted to a different ward, with preventive contact precautions pending culture results;
5. Patients who are colonized or infected with *C. auris* should be isolated until discharge and flagged for at least 1 year after the first negative screening culture
6. Readmission of a previous C. auris -positive patient:
    - place in contact isolation and screened on 3 consecutive days
    - if all 3 screens negative, discontinue isolation but screen weekly as *C. auris* may resurface after antibiotic therapy

0019076-19/06/2023-DGPRE-DGPRE-P

Ministero della Salute

DIREZIONE GENERALE DELLA PREVENZIONE SANITARIA
UFFICIO 5 PREVENZIONE DELLE MALATTIE TRASMISSIBILI E PROFILASSI INTERNAZIONALE

In Italia, nel periodo 1° luglio 2019 - 22 dicembre 2022 sono stati notificati allo scrivente Ministero 361 casi di infezione/colonizzazione (età mediana circa 64 anni, range 0–91, soprattutto maschi) da 17 strutture sanitarie in quattro regioni (Liguria 82%, Piemonte 13%, Emilia-Romagna 4%, Veneto 1 caso), di cui almeno 146 (40%) deceduti. Oltre il 90% dei casi erano colonizzati, almeno la metà presentavano comorbidità e almeno un terzo era SARS-CoV-2 positivo. Nello stesso periodo, altri casi di infezione/colonizzazione (almeno 206 casi) non sono stati notificati[5,6,7,8]. Successivamente, sono stati notificati altri casi (circa 40), con l'interessamento anche di due Regioni che non avevano notificato casi in precedenza (Liguria, Piemonte, Lazio, Toscana). Si rappresenta, pertanto, **un crescente rischio di trasmissione intraospedaliera, di possibile sviluppo di candidemia soprattutto in caso di colonizzazione simultanea multipla, e di diffusione comunitaria.**

Considerato quindi il crescente rischio di trasmissione intraospedaliera, il Ministero della Salute e la Regione Toscana **raccomandano l'esecuzione di screening per *C.Auris* al momento del ricovero nei soggetti con storia di degenza ospedaliera (almeno una notte) o attività di riabilitazione nei precedenti 12 mesi in strutture di assistenza sanitaria situate nelle regioni maggiormente interessate e cioè Liguria, Piemonte ed Emilia Romagna.**

SST Servizio Sanitario della Toscana

Oggetto: indicazioni regionali per lo screening per *Candida auris*

In Regione Toscana, nel 2024, sono stati identificati n. 4 casi di colonizzazione da *Candida auris* presso l'Azienda Ospedaliero Universitaria Pisana. Il paziente n. 1 non presentava i criteri epidemiologici definiti dal Ministero per lo screening in ammissione. Questa situazione, unita all'interessamento di ulteriori regioni (Lazio, Lombardia, Marche) che hanno notificato nuovi casi nel corso del 2023 e 2024, indica un crescente rischio di trasmissione intraospedaliera e di diffusione comunitaria di tali ceppi.

Al fine di monitorare la situazione nella nostra regione e meglio definire le dimensioni del problema, riteniamo opportuno porre indicazione per lo **screening in ammissione** mediante tampone cutaneo eseguito in sede ascellare e inguinale bilateralmente, come suggerito dai CDC americani.

Lo screening dovrà essere eseguito, indipendentemente dai fattori di rischio o presenza dei criteri epidemiologici, dal 1° febbraio al 30 aprile c.a., a tutti i pazienti alla prima ammissione nei seguenti reparti di degenza:

a) Terapia Intensiva/Subintensiva
b) Cardiochirurgia
c) Chirurgia dei Trapianti
e) Ematologia/Trapianti di midollo

Resta attiva l'indicazione ministeriale del tampone nei soggetti con storia di degenza ospedaliera (di almeno una notte) o attività di riabilitazione, nei precedenti 12 mesi, in strutture di assistenza situate nelle regioni maggiormente interessate (Liguria, Piemonte e Emilia-Romagna), come riportato nella Circolare Ministeriale n. 19076 del 19 giugno 2023.

2. Nuove terapie per neoplasie ematologiche & infezioni fungine

New targeted agents approved in HMs

AML

1. FLT3 inhibitors (quizartinib, midostaurin, sorafenib, gilteritinib)
2. Monoclonal antibodies (gemtuzumab ozogamicin, magrolimab)
3. Hh pathway inhibitor (glasgegib)
4. IDH1-2 inhibitors (ivosidenib, enasidenib)
5. Combined liposomal cytarabine and daunorubicin (CPX-351)

ALL

1. Monoclonal antibodies
    a. Anti-CD19 (blinatumomab)
    b. Anti-CD22 (inotuzumab ozogamicin)
2. TK inhibitors (imatinib, nilotinib, dasatinib, ponatinib)

Lymphomas (low and high grade)

1. BTK inhibitors (ibrutinib)
2. Monoclonal antibodies anti-CD20 (rituximab, ofatumumab)
3. PI3Kδ signalling inhibitor (idelalisib)

Multiple myeloma

1. IMiDs (thalidomide, lenalidomide pomalidomide)
2. Proteosome inhibitors (bortezomib, carfilzomib)
3. Monoclonal antibodies
    a. Anti-CD38 (daratumumab)
    b. Anti-CD319 (elotuzumab)
    c. Anti-BCMA (belantamab)

Hodgkin lymphoma

1. Monoclonal antibodies anti-CD30 (brentuximab)
2. IgG4 anti-PD-1 (nivolumab)

CLL

1. BTK inhibitors (ibrutinib)
2. Monoclonal antibodies anti-CD20 (ofatumumab)
3. PI3Kδ signalling inhibitor (idelalisib)
4. Anti-apoptotic BCL-2 (venetoclax)

CAR-T

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BCL-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukaemia; FLT3, fms-like tyrosine kinase 3; IDH, isocitrate dehydrogenase; IMiD, immunomodulary drug; PI3Kδ, phosphatidylinositol-4,5-bisphosphate 3-kinase subunit delta; TK, tyrosine kinase.

Gemtuzumab ozogamicin for *de novo* AML: ALFA-0701 trial

Preferred Term,† n (%)	GO n=131	Control n=137
Any SAE	88 (67.2)	76 (55.5)
Thrombocytopenia	34 (26.0)	6(4.4)
Bronchopulmonary aspergillosis	14 (10.7)	10 (7.3)
Septic shock	12 (9.2)	9 (6.6)
Febrile bone marrow aplasia	12 (9.2)	8 (5.8)
Bacterial sepsis	7 (5.3)	0
Acute kidney injury	6 (4.6)	4 (2.9)
Pneumonia	5 (3.8)	6 (4.4)
Sepsis	5 (3.8)	4 (2.9)
Acute respiratory distress syndrome	5 (3.8)	3 (2.2)
Escherichia sepsis	5 (3.8)	1 (0.7)
Veno-occlusive liver disease	5 (3.8)	0
Acute myeloid leukemia	5 (3.8)	0
Hepatocellular injury	4 (3.1)	2 (1.5)
Cholestatic liver injury	3 (2.3)	2 (1.5)
Febrile neutropenia	3 (2.3)	1 (0.7)
Mucosal inflammation	3 (2.3)	1 (0.7)
Disease progression	3 (2.3)	0
Enterococcal sepsis	3 (2.3)	0
Staphylococcal sepsis	2 (1.5)	5 (3.6)
Toxic skin eruption	1 (0.8)	3 (2.2)

AFP, antifungal prophylaxis; AML, acute myeloid leukaemia; GO, gemtuzumab ozogamicin; IA, invasive aspergillosis; SAE, serious adverse event.
Lambert, et al. Haematologica. 2019;104:113–119.

SAE	GO (n = 131)	Control (n = 137)
Bronchopulmonary aspergillosis	14 (10.7%)	10 (7.3%)
Septic shock	12 (9.2%)	9 (6.6%)
Bacterial sepsis	7 (5.3%)	0
Pneumonia	5 (3.8%)	6 (4.4%)
Sepsis	5 (3.8%)	4 (2.9%)
Escherichia sepsis	5 (3.8%)	1 (0.7%)
Enterococcal sepsis	3 (2.3%)	0
Staphylococcal sepsis	2 (1.5%)	5 (3.6%)
Febrile neutropenia	3 (2.3%)	1 (0.7%)

Liposomal daunorubicin plus Cytarabine (Vyxeos): Infections in induction

- Longer neutropenia
- Better outcome

authors		N° patients	Febrile neutropenia	Pneumonia	Bacteremia	Fungal	Viral
Cortes et al, Cancer 2015	CPX 351	81	44 (54%)	18 (22%)	24 (30%)	In pneumonia groups	0
	Comparator	44	14 (34%)	4 (9%)	19 (43%)		0
Lancet et al, Blood 2014	CPX 351	85	54 (63.5%)	13 (15%)	30 (35%)	12 (14%)	0
	3+7	41	21 (51.2%)	8 (19%)	8 (20%)	1 (2.4%)	0
Lancet et al, J Clin Oncol 2018	CPX 351	153	68%	20%	nr	nr	0
	3+7	156	70.9%	15%	nr	nr	
Issa et al. Leukemia 2020	Phase 2	65	19 (34%)	13 (23%)	9 (16%)	nr	0
Guolo et al, Blood Cancer J 2020	Phase 4	71	20 (28%)	8 (11%)	20 (28%)	2 PjP 3 (4%) IA	0
Roboz et al, Leuk & Lymph 2020	Phase 4	52	40 (77%)	7 (13%)	3 (6%)	nr	0
Chiche et al, Blood Adv 2021	Phase 4	103	94 (91%)	30 (30%)	25 (24%)	10 (10%) IA 1 (1%) CDC	0

AFP, antifungal prophylaxis.

1. Cortes, et al. Cancer. 2015;121:234-242; 2. Lancet, et al. Blood. 2014;123:3239–3246; 3. Chiche, et al. Blood Adv. 2021;5:176–184.

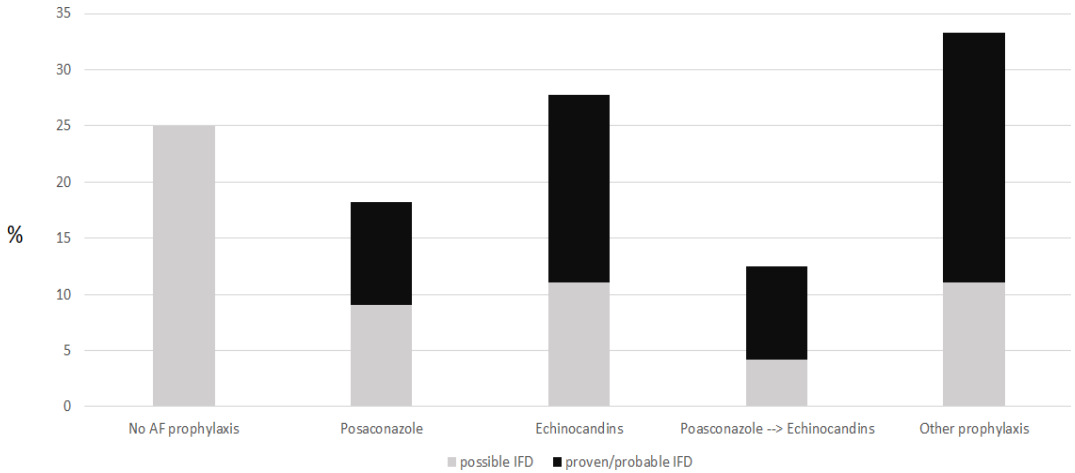
AML

High incidence of invasive fungal diseases in patients with FLT3- mutated AML treated with Midostaurin: results of a multicenter observational SEIFEM Study

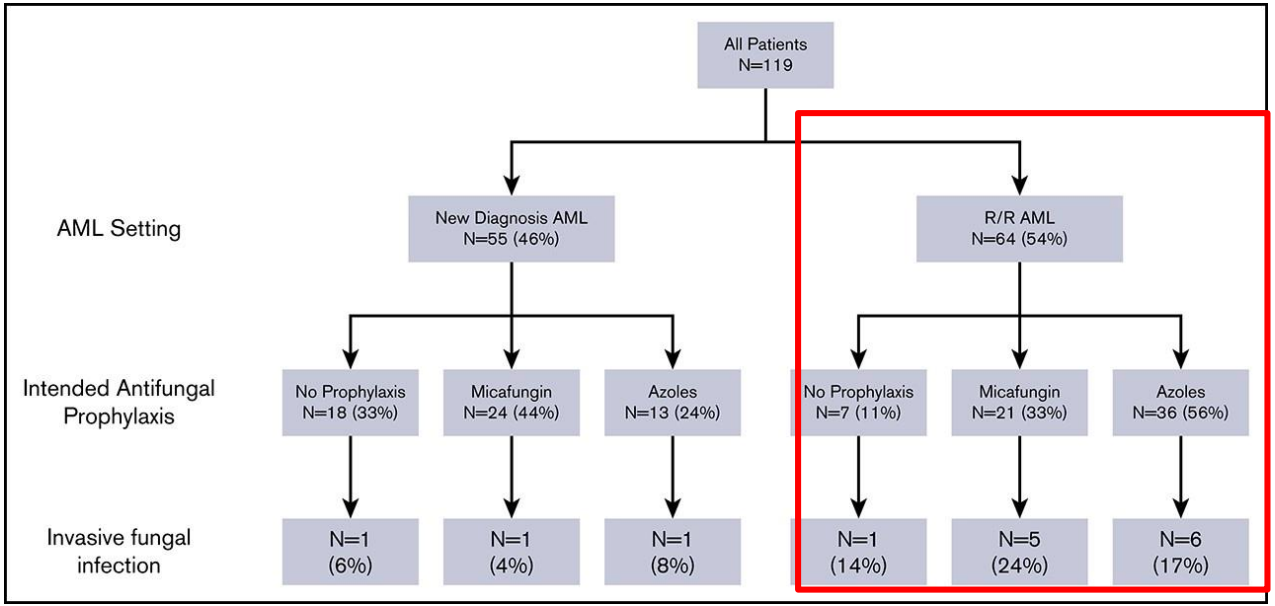
From June 1st, 2019, to December 31st, 2021, 119 patients treated with chemotherapy+midostaurin as induction/reinduction, consolidation. Only 114 were evaluable

Proven/probable and possible IFD incidence was 23/114 (20.2%) during induction and 7/167 (4.2%) during different consolidation courses

AF prophylaxis (induction cht, n=119)	
• No	8
• Fluconazole	3
• Posaconazole	60
• Posaconazole → Echinocandin	24
• Echinocandin	18
• L-AmB	4
• Isavuconazole	2
AF prophylaxis (consolidation cht, n=167)	
• No	91
• Fluconazole	8
• Posaconazole	20
• Posaconazole → Echinocandin	6
• Echinocandin	27
• L-AmB	1
• Isavuconazole	6
• Itraconazole	3
• Voriconazole	5



IFIs in AML treated with venetoclax and hypomethylating agents



- The authors concluded that the overall risk of IFIs during VEN+HMA therapy **is low**
- The risk of IFIs is higher in non-responders and in the R/R setting
- These patients need re-evaluation of their antifungal prophylaxis to minimise the risk of IFIs during therapy

AML, acute myeloid leukaemia; HMA, hypomethylating agent; IFI, invasive fungal infection; R/R, relapsed/refractory; VEN, venetoclax. Aldoss, et al. Blood Adv. 2019;3:4043–4049.

	Hill et al (2018)[13]		Park et al (2018)[14]		Logue et al (2020)[15]		Vora et al (2020)[16]		Strati et al (2020)[17]	Cordeiro et al (2020)[18]
	Early (≤28 days)	Late (>28 days)	Early (≤30 days)	Late (>30 days)	Early (≤30 days)	Late (>30 days)	Early (≤28 days)	Late (>28 days)	Any	Late (>90 days)
Number of patients	133	119	53	32	85	70	83	48	31	86 (data for late infections were available for 54 [63%] patients, who were mostly outpatients not diagnosed microbiologically)
All infections	43 in 30 (23%) patients	23 in 17 (14%) patients	26 in 22 (42%) patients	15 in 10 (31%) patients	38 in 31 (37%) patients	32 in 31 (44%) patients	37 in 33 (40%) patients	12 in 11 (23%) patients	71 in 24* (77%) patients	153 in 33 (61%) patients
Fungal infections	6 in 4 (3%) patients	2 in 2 (2%) patients	4 in 4 (8%) patients	1 in 1 (3%) patients	2	0	1	0	4	4
Invasive candidiasis	4¶¶	1	0	0	1‖‖	0	0	0	0	1***
Invasive pulmonary aspergillosis	1†††	1	2	1	0	0	0	0	0	2
Other‡‡‡	1	0	2	0	1	0	1	0	4	1

IFIs are really rare in patients undergoing CAR T therapy!

CAR-T therapy, chimeric antigen receptor T-cell therapy; IFI, invasive fungal infection. Gudiol, et al. Lancet Infect Dis. 2021; S2352–3026:30376–8.

3. Nuovi antifungini

Infection and Drug Resistance

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REVIEW

Novel Therapeutic Approaches to Invasive Candidiasis: Considerations for the Clinician

Frederic Lamoth[1,2]

Table 2 Advantages and Limitations of Novel Antifungal Drugs for IC

Antifungal Drug	Advantages	Limitations
Rezafungin	Fungicidal Prolonged half-life (once weekly administration)	Intravenous only Lack of penetration in CNS and eye Not appropriate for short-course or initial empirical therapy (potential risk of resistance because of prolonged effect)
Ibrexafungerp	Fungicidal Oral mode of administration Compared to echinocandins, extended spectrum against a majority of echinocandin-resistant *Candida* isolates	Oral bioavailability may be affected in some patients (e.g., proton pump inhibitors, gastro-intestinal disorders) Lack of penetration in CNS and eye
Fosmanogepix	Oral and intravenous mode of administration Efficient against most azole and echinocandin resistant *Candida* isolates Acceptable penetration in CNS and eye	Fungistatic effect Poor or limited efficacy against some *Candida* spp. (*C. krusei, C. kefyr*)

In vitro spectrum of activity of antifungals currently under late-stage clinical development

Antifungal	Manogepix	Olorofim	Ibrexafungerp	Rezafungin	Oteseconazole
			Yeasts		
C. albicans	+	–	+	+	+
C. auris	+	–	+	+	+
C. glabrata	+	–	+	+	+
C. krusei	–	–	+	+	+
C. parapsilosis	+	–	+	+	+
C. tropicalis	+	–	+	+	+
C. gattii	+	–	–	–	+
C. neoformans	+	–	–	–	+
Rhodotorula	+	–	–	–	
Trichosporon	+/–	–	–	–	
			Aspergillus		
A. flavus	+	+	+	+	–
A. fumigatus	+	+	+	+	–
A. niger	+	+	+	+	–
A. terreus	+	+	+	+	–
			Fusarium		
F. oxysporum	+	+/–	–		
F. solani	+	–	–		
			Scedosporium		
Scedosporium	+	+	–		
L. prolificans	+	+	–		
			Mucorales		
Mucor	–	–	–	–	
Rhizopus	+/–	–	–	–	+/–
Other Mucorales	–	–	–	–	
			Endemic Fungi		
Blastomyces		+	+		+
Coccidioides	+	+	+		+
Histoplasma		+	+		+
			Dermatophytes		
Trichophyton		+			+

J. Fungi 2022, 8, 857

Rezafungin

Semisynthetic, long-acting echinocandin with broad-spectrum activity against many *Candida* species and *Aspergillus* species

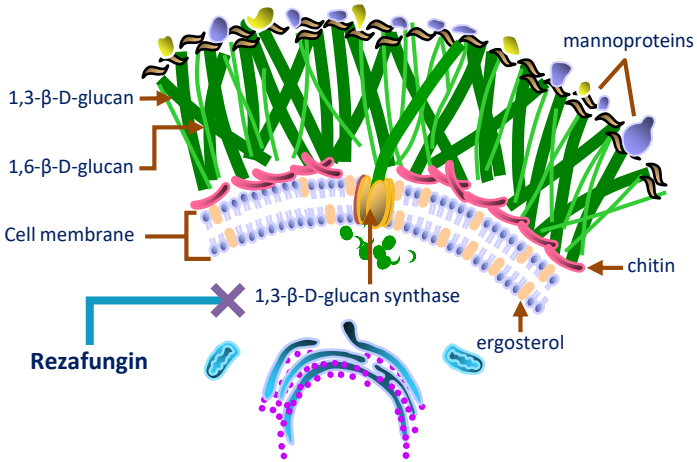


Image adapted from Diamond RD, ed. Atlas of Infectious Diseases: Fungal Infections. Copyright 2000 Springer Science+Business Media New York.

Rezafungin inhibits production of 1,3-β-D-glucan[2]

Increased permeability of the cell wall causes osmotic imbalance[2]

Fungal cell lysis occurs[2]

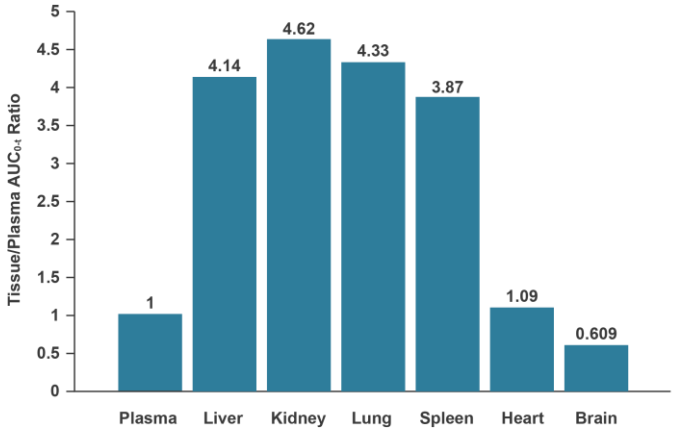
- **Fungicidal against *Candida* spp.**
- **Fungistatic against *Aspergillus* spp.[2]**
- **Active against *Pneumocystis* spp.[3,4]**

1. Diamond RD, ed. *Atlas of Infectious Diseases: Fungal Infections*. 1st ed. Current Medicine Group; 2000. **2.** Patil, et al. *J Pharm Pharmacol*. 2017 Dec;69(12):1635-1660. **3.** Cushion, et al. ASH 2019; Orlando, Florida. **4.** Sandison, et al. ICHS 2021.

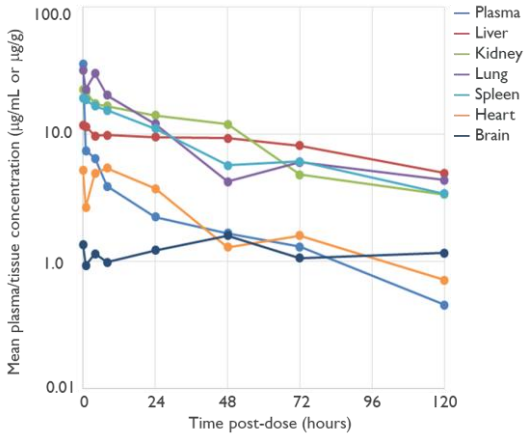
Tissue Distribution *In Vivo*

Rat PK Models

Uniform tissue distribution across liver, kidney, lungs, and spleen[1]



Similar half-life/elimination in organs[2]



AUC, area under the curve.

1. Ong, et al. *Antimicrob Agents Chemother*. 2017;61:e01626-16. **2.** Ong, et al. *Biol Blood Marrow Transplant*. 2018;24:S291–S459.

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

George R Thompson III, Alex Soriano, Oliver A Cornely, Bart Jan Kullberg, Marin Kollef, Jose Vazquez, Patrick M Honore, Matteo Bassetti, John Pullman, Methee Chayakulkeeree, Ivan Poromanski, Cecilia Dignani, Anita F Das, Taylor Sandison, Peter G Pappas, on behalf of the ReSTORE trial investigators

www.thelancet.com Vol 401 January 7, 2023

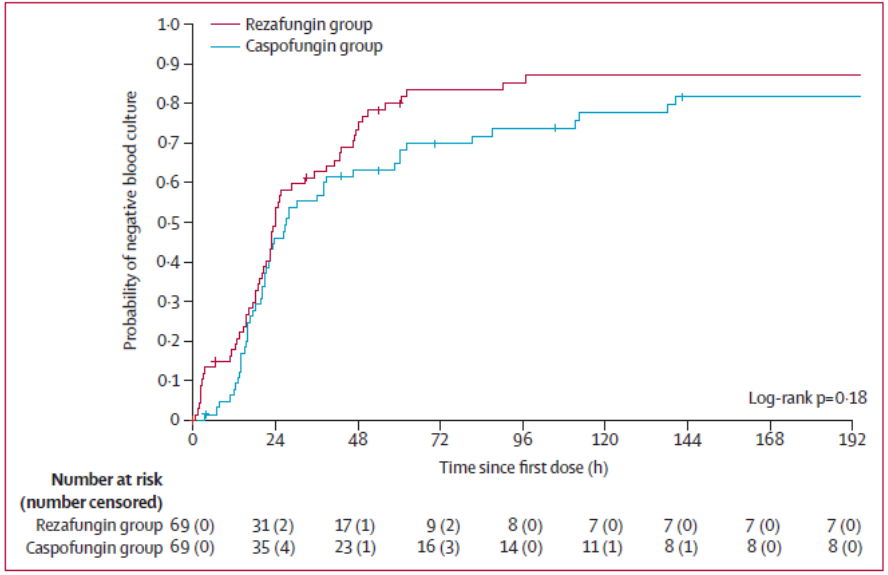


Figure 2: Time to negative blood culture after treatment with rezafungin versus caspofungin in the modified intention-to-treat population

	Rezafungin group (n=93)	Caspofungin group (n=94)	Treatment difference (95% CI)
All-cause mortality at day 30 (US FDA primary outcome)			
Died	22 (24%)	20 (21%)	2·4 (−9·7 to 14·4)*
Known to have died	19 (20%)	17 (18%)	..
Unknown survival	3 (3%)	3 (3%)	..
All-cause mortality at day 30 by diagnosis			
Candidaemia only	18/64 (28%)	17/67 (25%)	2·8 (−12·5 to 18·0)*
Invasive candidiasis	4/29 (14%)	3/27 (11%)	2·7 (−16·7 to 21·7)*
Global response at day 14 as assessed by DRC (EMA primary outcome)			
Cure	55 (59%)	57 (61%)	−1·1 (−14·9 to 12·7)†
Failure	28 (30%)	29 (31%)	..
Indeterminate	10 (11%)	8 (9%)	..
Global response at day 14 as assessed by DRC by diagnosis			
Candidaemia only			
Cure	39/64 (61%)	43/67 (64%)	−3·2 (−19·6 to 13·3)*
Failure	21/64 (33%)	19/67 (28%)	..
Indeterminate	4/64 (6%)	5/67 (7%	..
Invasive candidiasis			
Cure	16/29 (55%)	14/27 (52%)	3·3 (−22·4 to 28·6)*
Failure	7/29 (24%)	10/27 (37%)	..
Indeterminate	6/29 (21%)	3/27 (11%)	..

Rezafungin was non-inferior to caspofungin for the primary endpoints of day-14 global cure (EMA) and 30-day all-cause mortality (FDA). There were no concerning trends in treatment-emergent or serious adverse events.

Potent Activity Against *Aspergillus* Species

In Vitro Activity Includes Azole-Resistant Strains and Cryptic Species

	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

*CLSI broth microdilution methodology was employed for MEC and MIC determination (M38-A2).[2]

†Clinical isolates collected internationally in the JMI Laboratories SENTRY Antimicrobial Surveillance Program (2016-2018).[1]

‡Clinical isolates collected in the US and resistance genotypes confirmed by DNA sequence analysis (CYP51A only, n=13; TR_{34}/L98H, n=2; TR_{46}/Y121F/T289A, n=2; resistant/no CYP51A mutation, n=6; resistant/CYP51A status unknown, n=8).[3]

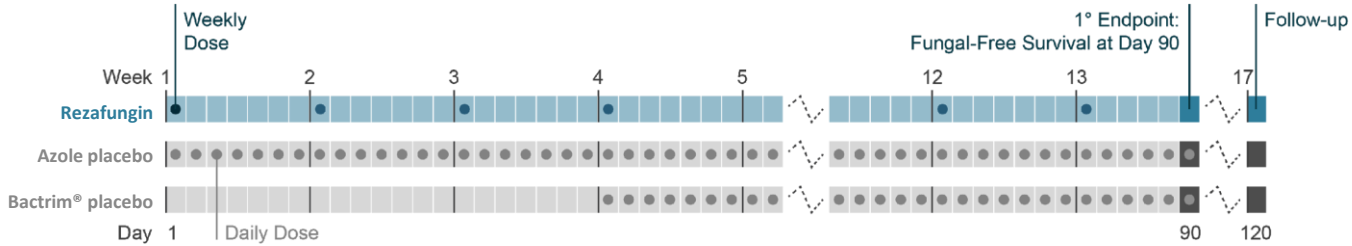
CLSI, Clinical and Laboratory Standards Institute; CYP, cytochrome P450; MEC, minimal effective concentration; MIC, minimal inhibitory concentration.

1. Pfaller, et al. *Antimicrob Agents Chemother*. 2020;pii: AAC.00099-20. **2.** Wiederhold, et al. *J Antimicrob Chemother*. 2018b;73:3063-3067.

The ReSPECT Trial

Prophylaxis in HSCT

REZAFUNGIN
(N≅300)
400/200 mg once weekly

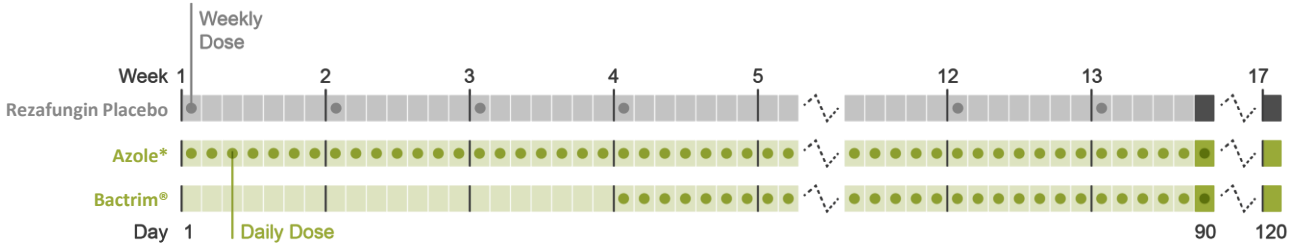


COMPARATOR
(N≅150)

400 mg fluconazole once daily*

80 mg TMP/400 mg SMX once daily

*Patients with acute GVHD can be switched to posaconazole



BMT, blood and marrow transplantation; GVHD, graft-versus-host disease; IFD, invasive fungal disease; SMX, sulfamethoxazole; TMP, trimethoprim.

1. Clinicaltrials.gov NCT04368559 accessed 4 Feb 2021.

Rezafungin and invasive candida infections: a new game changing antifungal?

The STRIVE[7] and ReSTORE studies have identified rezafungin as an antifungal drug for the management of invasive candidiasis.

However, rezafugin is not a new-in-class antifungal and a careful consideration of advantages and disadvantages of the drug compared with approved echinocandins will dramatically affect its future use.

The main advantages of rezafungin depend on its pharmacokinetic peculiarities that allow once-a-week administration, enhance its penetration to difficult-to-reach anatomical sites (eg, liver abscess and the peritoneal cavity), and lower the probability of resistance promotion. Such traits would help its use in outpatients, avoid catheter overuse, and improve the management of patients with intra-abdominal candida infections.

Future studies must assess the prospect of rezafungin for the treatment of invasive candida infections.

The cost of a newly marketed drug compared with already approved echinocandins might be

Fosmanogepix: First-in-Class, Potent and Selective Gwt1 Inhibitor

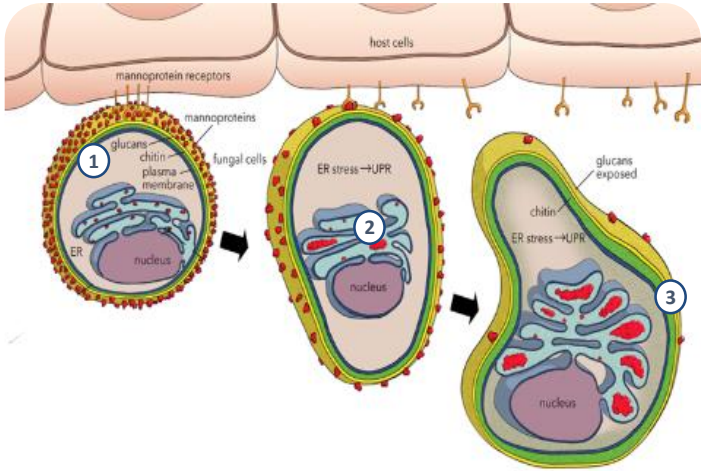
- ✓ **Novel Targeted Mechanism:** Inhibits Gwt1, a target specific to fungal cells that triggers two distinct cell vulnerabilities
- ✓ **Broad Spectrum:** Preclinical antifungal efficacy in yeasts and molds, including rare and resistant strains
- ✓ **Wide Tissue Distribution:** Reaches important compartments in brain, lung, kidney, and eye
- ✓ **Favorable Safety Profile:** Minimizes additional toxicity burden for seriously ill patients
- ✓ **Favorable DDI Profile:** Low potential for CYP3A4 inhibition, simplifies co-administration
- ✓ **IV and Oral Formulations:** Supports continuation of care outside of the hospital

Fosmanogepix Inhibits Gwt1

Gwt1 protein exists only in fungal cells

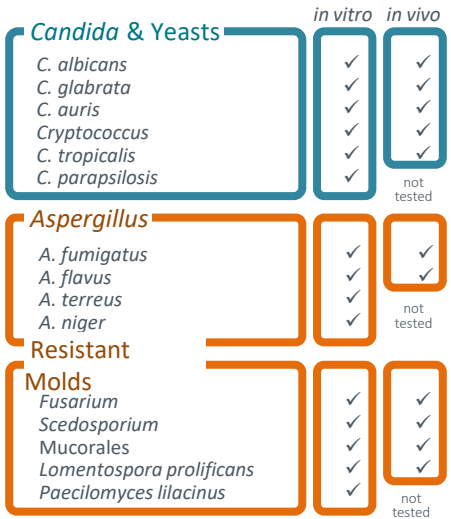
Gwt1 inhibition blocks mannoprotein transport

Lack of mannoproteins on cell wall and stress response lead to fungal cell death



Fosmanogepix: current available and emerging data

Preclinical Proof-of-Concept



Additional preclinical activity against pathogens that cause endemic mycoses (e.g. Cocci, Blasto, Histo) diamorphic fungi (e.g. Talormyces and Sporothrix) and Phaeohyphomycetes black molds and Hyalohyphomycetes

Phase 2 Clinical Trials

201: Complete
Candidemia

203: Complete
Resistant *C. auris*

202: Enrolling
Invasive Mold Infections

Expanded Access
(available only in USA)

Miyazaki, AAC 2011; Viriyakasol, AAC 2019; Pfaller, AAC 2019

Antimicrobial Agents and Chemotherapy®

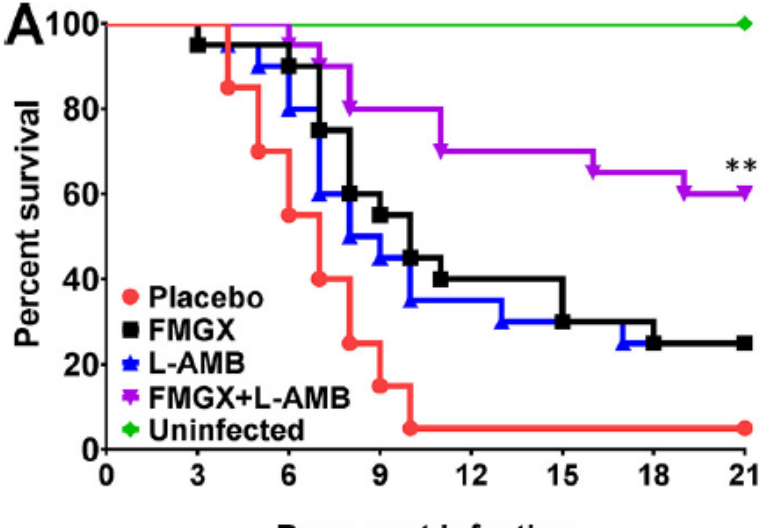
EXPERIMENTAL THERAPEUTICS

The Combination Treatment of Fosmanogepix and Liposomal Amphotericin B Is Superior to Monotherapy in Treating Experimental Invasive Mold Infections

Teclegiorgis Gebremariam,[a] Yiyou Gu,[a] Sondus Alkhazraji,[a] Eman Youssef,[a,b] Karen Joy Shaw,[c] Ashraf S. Ibrahim[a,d]

Survival of immunosuppressed mice infected with A. fumigatus. Kaplan-Meier survival curves (A) and median and percent survival values (B)

A



B

Treatment	Median survival (days)	% Survival	*P* value (*vs.* placebo)
Placebo	7	5	N/A
FMGX	10	25	0.004
L-AMB	8.5	25	0.02
FMGX + L-AMB	>21	60	<0.0001

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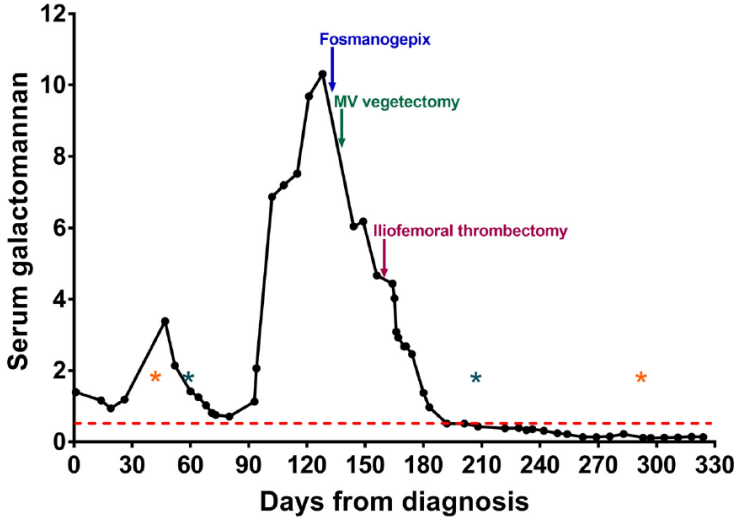
CHALLENGING CLINICAL CASE IN ANTIMICROBIAL RESISTANCE

Successful Treatment of Disseminated Disease Due to Highly Resistant *Aspergillus calidoustus* with a Novel Antifungal Therapy

Jose F. Camargo,[a] Ra'ed Jabr,[a] Anthony D. Anderson,[b] Lazaros Lekakis,[c] Meilin Diaz-Paez,[c] Laurence M. Briski,[d] Mohammed Raja,[a] Michele I. Morris,[a] Krishna V. Komanduri,[c] Denise Pereira[c]



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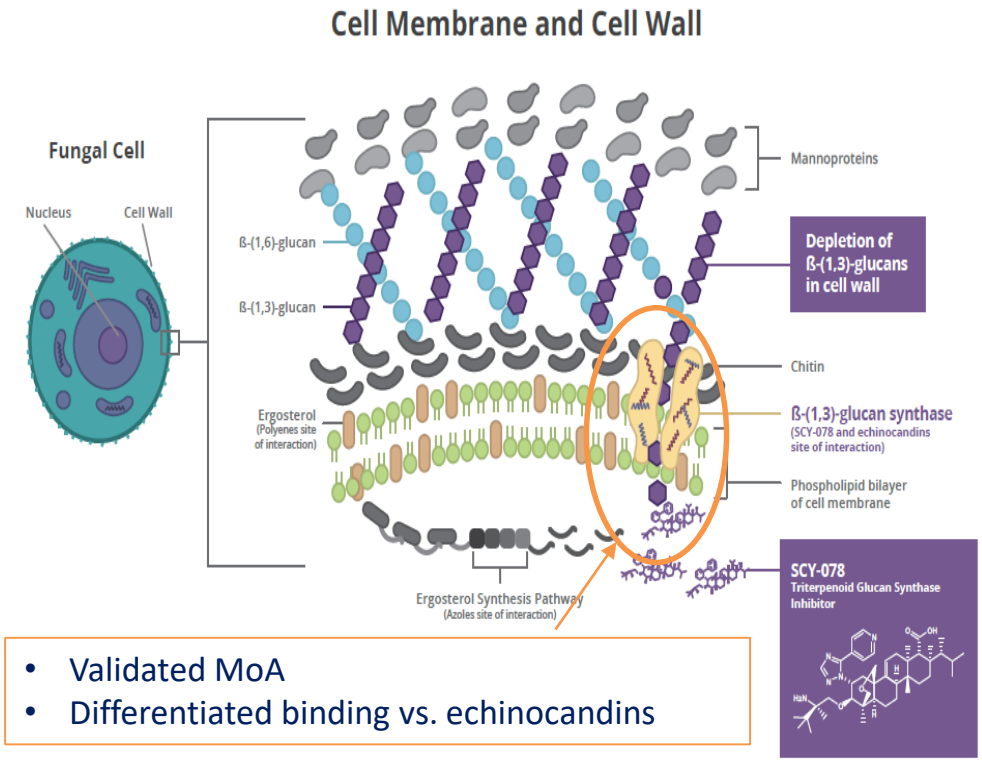
CHALLENGING CLINICAL CASE IN ANTIMICROBIAL RESISTANCE

Case Commentary: Long-Term Fosmanogepix Use in a Transplant Recipient with Disseminated Aspergillosis Caused by Azole-Resistant *Aspergillus calidoustus*

Ahnika Kline,[a] Michail S. Lionakis[a]

The use of fosmanogepix in additional patients and the completion of its phase 2 clinical trial for the treatment of various invasive mold infections will shed more light on the safety, tolerability, extrapulmonary penetration, and efficacy of this novel antifungal

Ibrexafungerp: Glucan Synthase Inhibitor



- Validated MoA
- Differentiated binding vs. echinocandins

Key Attributes

- Activity against:
  - *Candida* spp.
  - *Aspergillus* spp.
  - *Pneumocystis* spp.
- Active against azole-resistant and most echinocandin-resistant strains
- Oral (and IV?) formulations
- Favorable safety profile > 500 exposed
  - **Low risk of drug-drug Interactions (IBX does not induce CYP3A)**
- Extensive tissue distribution
  - (V_{dss} > 8 L/kg)

Larkin E., et al. AAC . May 2017

Ibrexafungerp: *in vitro* Activity against *Candida* spp.

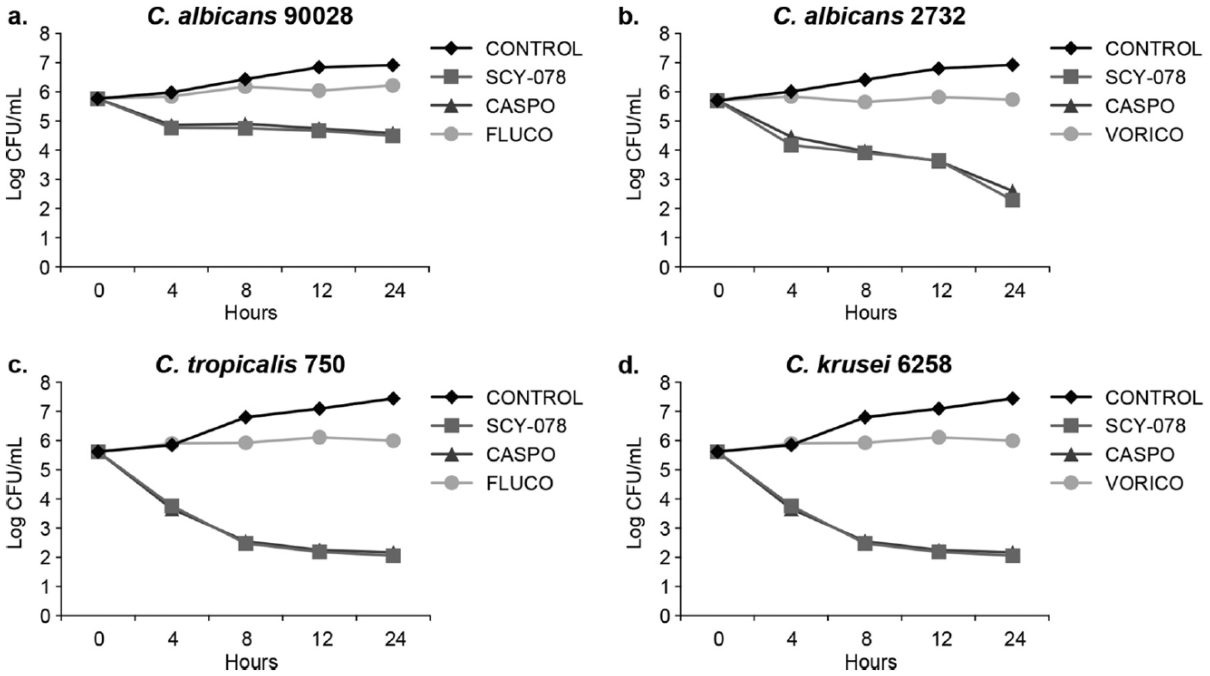


FIG 2 Time-kill curves for SCY-078, caspofungin (CASPO), fluconazole (FLUCO), and voriconazole (VORICO) at 4 times the MIC_{80} against the indicated *Candida* species and a control. 2732, MYA-2732.

Ibrexafungerp has fungicidal activity against *Candida* spp

Scorneaux B, et al. AAC, March 2017

Ibrexafungerp *In vitro* Activity against *Aspergillus* spp.

	Ibrexafungerp		
	MEC		
	Range	MEC_{50}	MEC_{90}
A. fumigatus (n=134)	<0.06 – 4	<0.06	0.125
A. flavus (n=54)	<0.06 – 0.25	<0.06	<0.06
A. niger (n=27)	<0.06 – 0.5	<0.06	<0.06
A. terreus (n=72)	<0.06 – 0.125	<0.06	0.125
Other spp. (n=24)	<0.06 – 0.25	<0.06	<0.06
All isolates (n=311)	<0.06 – 4	<0.06	0.125

Ghannoum M., et al. AAC June 2018

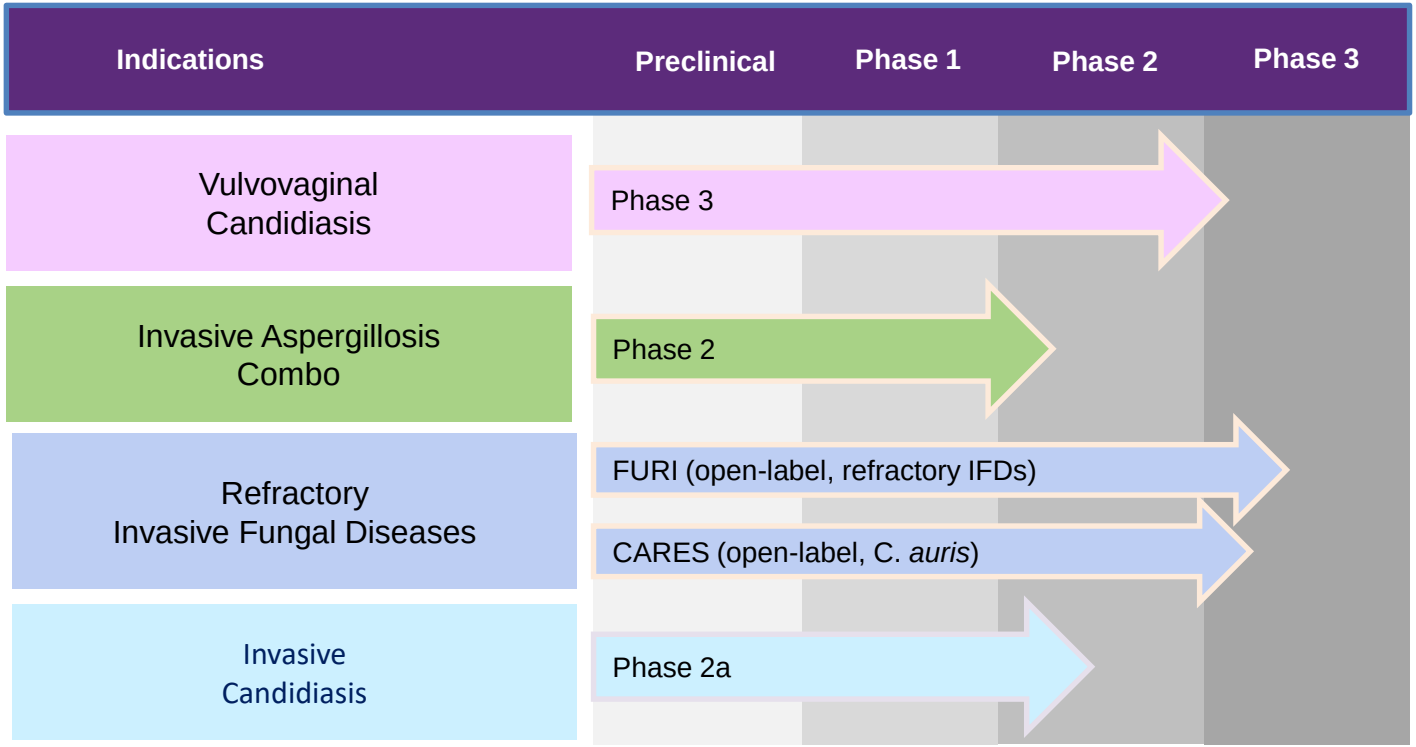
Ibrexafungerp *In vitro* Activity against *Aspergillus fumigatus* in Combination with other Antifungals

	IBX with Isavuconazole (ISA)						IBX with Voriconazole (VRC)						IBX with Amphotericin B (AmB)					
	MIC Alone		MIC Combo		FICI	Interpretation*	MIC Alone		MIC Combo		FICI	Interpretation*	MIC Alone		MIC Combo		FICI	Interpretation*
Strain	IBX	ISA	SCY-078	ISA	IBX + ISA		IBX	VRC	SCY-078	VRC	IBX + VRC		IBX	AmB	SCY-078	AmB	IBX + AmB	
WT	4	1	0.016	0.5	0.50	SY	4	1	0.125	0.25	0.27	SY	4	4	0.016	0.5	0.13	SY
WT	4	1	0.125	0.25	0.28	SY	4	0.25	0.5	0.16	0.19	SY	4	2	0.016	0.5	0.25	SY
WT	4	1	0.063	0.25	0.27	SY	8	0.5	0.5	0.125	0.31	SY	4	4	0.016	1	0.25	SY
WT	4	1	0.25	0.25	0.31	SY	8	2	0.25	0.5	0.28	SY	4	4	0.016	1	0.25	SY
Azole-R	4	>8	0.063	>8	1.02	AD	8	>16	0.031	>16	1.00	AD	4	2	0.125	2	1.03	AD
Azole-R	4	>8	0.125	>8	1.03	AD	4	>16	1	>16	1.25	AD	4	4	0.016	1	0.25	SY

IBX in combination with Voriconazole, Isavuconazole and Amphotericin B demonstrated synergistic activity against the majority of *A. fumigatus* isolates tested

Ghannoum M., et al. AAC June 2018

Ibrexafungerp: Platform of Indications



Additional indications under consideration: Chronic Fungal Infections, Prophylaxis

Drug Design, Development and Therapy

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REVIEW

Ibrexafungerp for the Treatment of Vulvovaginal Candidiasis: Design, Development and Place in Therapy

Phase 2 clinical trial (DOVE): 186 randomized subjects into a single 150 mg Fluconazole versus 5 study doses of oral Ibrexafungerp: 300mg BID of Ibrexafungerp for 1 day was found to have a clinical cure rate of 51.9% versus 58.3% for fluconazole at day 10. Ibrexafungerp 300 mg BID was chosen for the Phase 3 trials

Phase 3 trial (VANISH 303), 376 subjects were randomized to ibrexafungerp (n = 249) or placebo (n = 127). The treatment group had significantly higher rates of clinical cure (50.5% vs 28.6%; P = 0.001), mycological eradication (49.5% vs 19.4%; P < 0.001 compared with placebo at day 11±3)

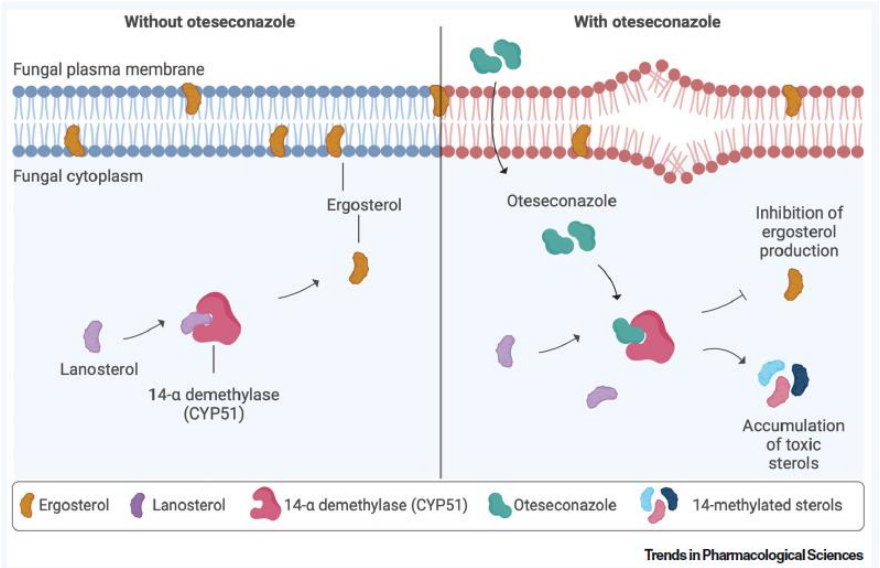
Phase 3 trial (VANISH 306), showed a significantly higher clinical cure rate (63.3% vs 44%) and negative culture result indicating mycological cure (58.5% vs 29.8%) in those receiving Ibrexafungerp (n = 188) versus placebo (n = 88) when evaluated at day 11±3.

Ibrexafungerp is the first oral non-azole approved for both VVC and RVVC, with broad spectrum coverage of both *C.albicans* and non-*albicans* species. Monthly dosing of ibrexafungerp offers an FDA approved, evidence-based treatment for RVVC

Trends in Pharmacological Sciences | Drug of the Month

Oteseconazole (VIVOJA) for prevention of recurrent vulvovaginal candidiasis

Giel Vanreppelen,[1] Jana Nysten,[1] Silke Baldewijns,[1] Mart Sillen,[1,2] Gilbert Donders,[3,4,5] and Patrick Van Dijck[1,*]



Oteseconazole: First Approved Orally Bioavailable and Selective CYP51 Inhibitor for the Treatment of Patients with Recurrent Vulvovaginal Candidiasis

Surya K. De[1,2,*]

Clinical Infectious Diseases

INVITED COMMENTARY

New Antifungals for Vulvovaginal Candidiasis: What Is Their Role?

Jack D. Sobel

Ibrexafungerp and oteseconazole appear to have the potential to replace fluconazole for women with RVVC invariably caused by susceptible C. *albicans* strains, with ibrexafungerp as a monthly rather than weekly regimen for 6 months and oteseconazole similarly less frequently as weekly in an abbreviated maintenance regimen of 3 months only. Cost, however, will be the defining factor. Are we talking about RVVC cure as opposed to symptom control? Cure is an unlikely outcome given the role of host genes in the pathogenesis of RVVC [35, 36]. Antifungal drug prophylaxis will not eliminate host susceptibility genes but, indirectly, by preventing vaginal colonization, will provide longer duration of symptom control. Nevertheless, the cur-

OLOROFIM

Is a novel mechanism candidate antifungal drug[1]

- It is an **inhibitor of fungal dihydroorotate dehydrogenase** (pyrimidine biosynthesis pathway)
- It shows broad microbiologic **activity vs. mold fungi**
- Low MICs vs. ***Aspergillus spp., Lomentospora prolificans, Scedosporium spp., Fusarium spp., Coccidioides spp.,*** and others
- Fungicidal effects in vitro (*Aspergillus*) and in vivo (*Coccidioides*) [2,3]
- Dosed by mouth (**30-mg tablet**), it has FDA Breakthrough Therapy Designation based on
    - "preliminary clinical evidence indicating that it may …
    - demonstrate substantial improvement over existing therapies …
    - on one or more clinically significant endpoints."

1. Oliver JD et al. (2016). "F901318 represents a novel class of antifungal drug that inhibits dihydroorotate dehydrogenase." PNAS USA 113: 12809-14.
2. du Pre, S., et al. (2018). "Effect of the Novel Antifungal Drug F901318 (Olorofim) on Growth and Viability of Aspergillus fumigatus." AAC 62(8): e00231-18.
3. Wiederhold, N. P., et al. (2018). "The Orotomide Olorofim Is Efficacious in an Experimental Model of Central Nervous System Coccidioidomycosis." AAC 62(9): e00999-18.

In vitro spectrum of activity of antifungals currently under late-stage clinical development

Antifungal	Manogepix	Olorofim	Ibrexafungerp	Rezafungin	Oteseconazole
			Yeasts		
C. albicans	+	–	+	+	+
C. auris	+	–	+	+	+
C. glabrata	+	–	+	+	+
C. krusei	–	–	+	+	+
C. parapsilosis	+	–	+	+	+
C. tropicalis	+	–	+	+	+
C. gattii	+	–	–	–	+
C. neoformans	+	–	–	–	+
Rhodotorula	+	–	–	–	
Trichosporon	+/–	–	–	–	
			Aspergillus		
A. flavus	+	+	+	+	–
A. fumigatus	+	+	+	+	–
A. niger	+	+	+	+	–
A. terreus	+	+	+	+	–
			Fusarium		
F. oxysporum	+	+/–	–		
F. solani	+	–	–		
			Scedosporium		
Scedosporium	+	+	–		
L. prolificans	+	+	–		
			Mucorales		
Mucor	–	–	–	–	
Rhizopus	+/–	–	–	–	+/–
Other Mucorales	–	–	–	–	
			Endemic Fungi		
Blastomyces		+	+		+
Coccidioides	+	+	+		+
Histoplasma		+	+		+
			Dermatophytes		
Trichophyton		+			+

J. Fungi 2022, 8,

In vitro activity

- Olorofim *Aspergillus* MICs are tightly clustered
  - MIC_{90}s are 0.03-0.06 mg/L (CLSI and EUCAST)
  - MICs are of the same order for all *Aspergillus* spp. tested
    - 5408 isolates from 63 species including:
    - 4880 isolates of *A. fumigatus, flavus, niger, and terreus*
    - >300 isolates of cryptic *Aspergillus* species
- **No induction of resistance** with serial passage
- Spontaneous resistance rarely seen; **no cross resistance**
- *Scedosporium* spp. and *L. prolificans* plus other moulds and endemic fungi have MICs similar to IA
- **No activity against yeasts or mucorales as these have a structurally different DHODH enzyme**

Beckmann et al. ICAAC 2015; Fothergill et al. ICAAC 2015; Buil et al.JAC 2017; Rivero-Menéndez et al ECCMID 2017; Oliver et al PNAS 2016; Jorgensen et al. TIMM 2017

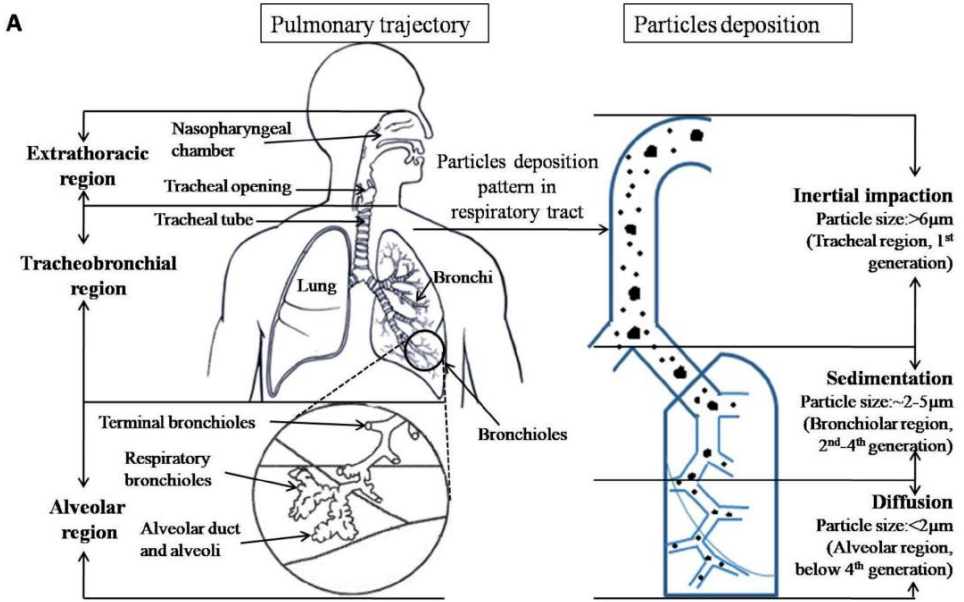
Breakthrough Therapy Designation (BTD) Granted by FDA

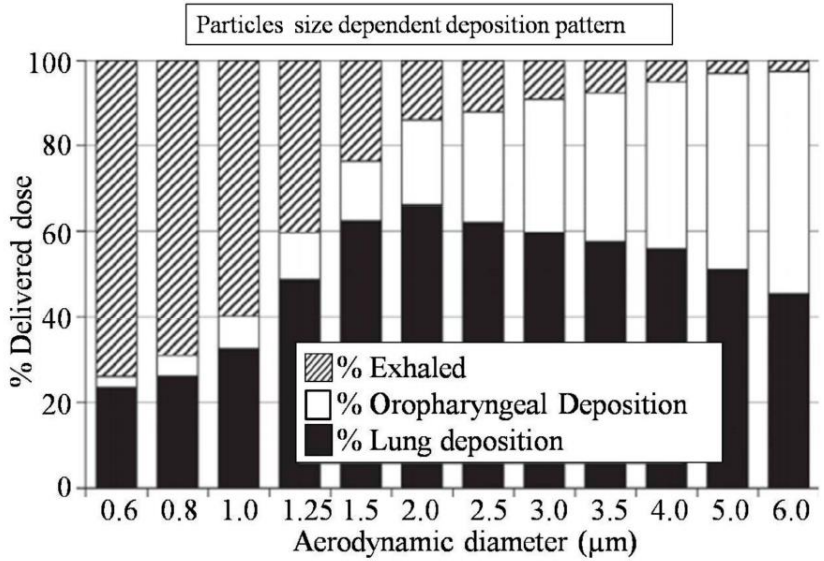
- Olorofim is the first antifungal agent to be granted BTD
- BTD designation is granted by FDA based on "preliminary clinical evidence indicating that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints."
- BTD #1 (Nov 2019): Based on data from the first 28 patients:

  "Treatment of invasive mold infections in patients with limited or no treatment options, including aspergillosis refractory or intolerant to currently available therapy, and infections due to *Lomentospora prolificans*, *Scedosporium*, and *Scopulariopsis* species"
- BTD #2 (Oct 2020): Based on data from the first 7 cocci patients:

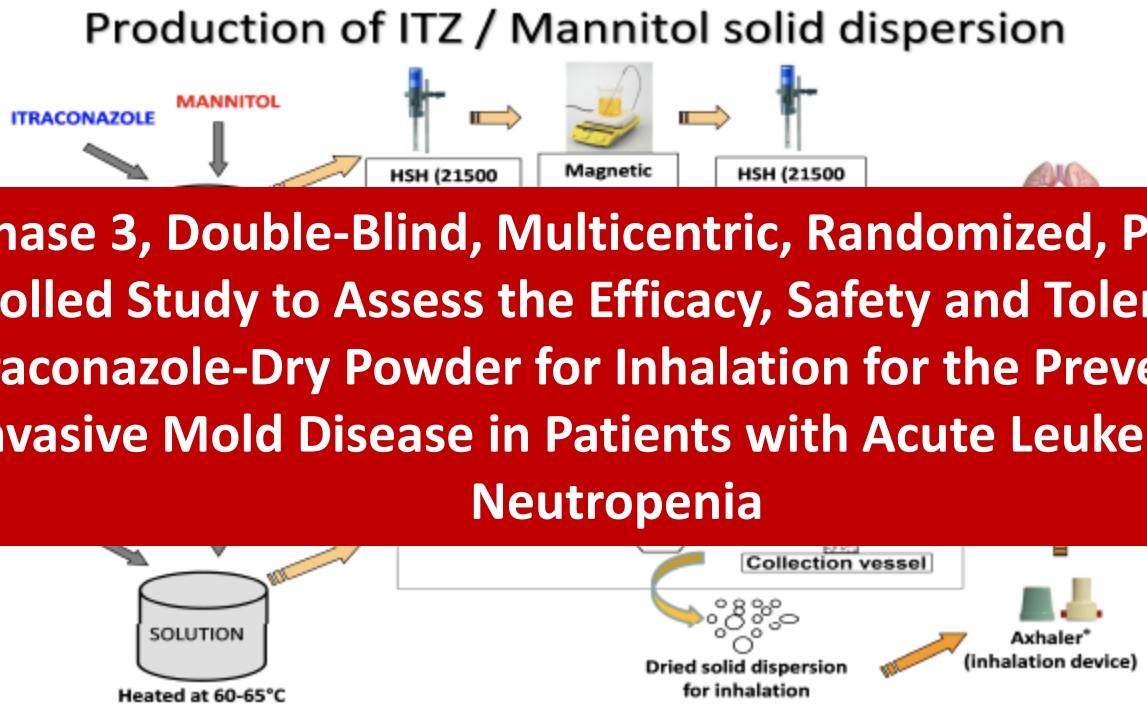
  "Treatment of Central Nervous System (CNS) coccidioidomycosis refractory or otherwise unable to be treated with standard of care therapy"

Dry Powder Inhaler





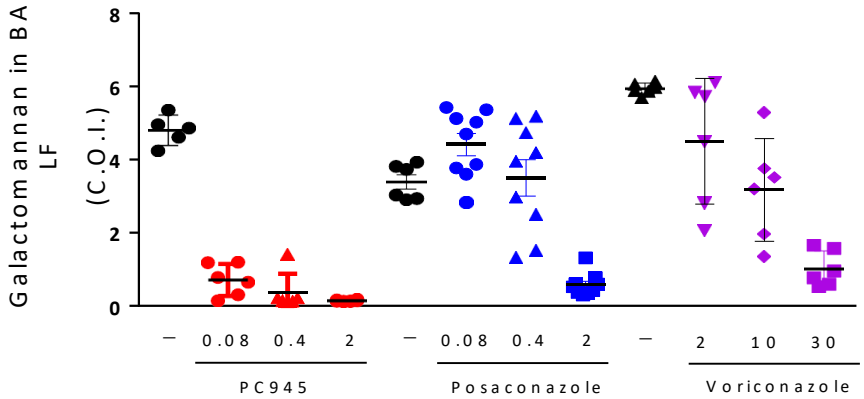
New inhalation-optimized itraconazole nanoparticle-based dry powders for the treatment of invasive pulmonary aspergillosis *Duret et al, Int J Nanomed 2012*



A Phase 3, Double-Blind, Multicentric, Randomized, Placebo-Controlled Study to Assess the Efficacy, Safety and Tolerability of Itraconazole-Dry Powder for Inhalation for the Prevention of Invasive Mold Disease in Patients with Acute Leukemia and Neutropenia

Opelconazole

First in class, novel inhaled drug for Aspergillus infections



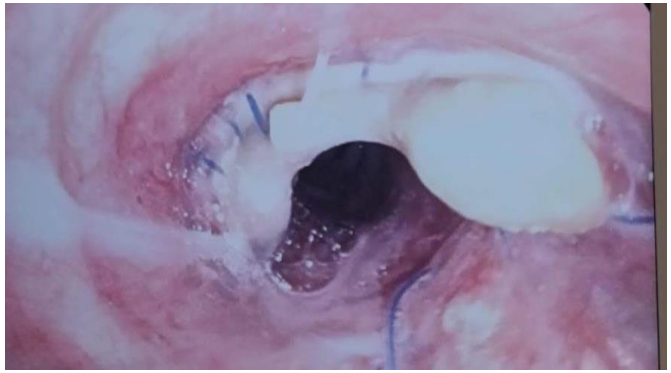
Compounds were treated intranasally on Day 0, 1, 2 and 3 post A.fumigatus conidia inoculation, and GM were measured on Day3.

ID_{50}: µg/kg, in	PC945	Voriconazole	Posaconazole
GM (serum)	<67	3235	393
GM(BALF)	<67	9627	1026
CFU (Lung)	71	5887	205

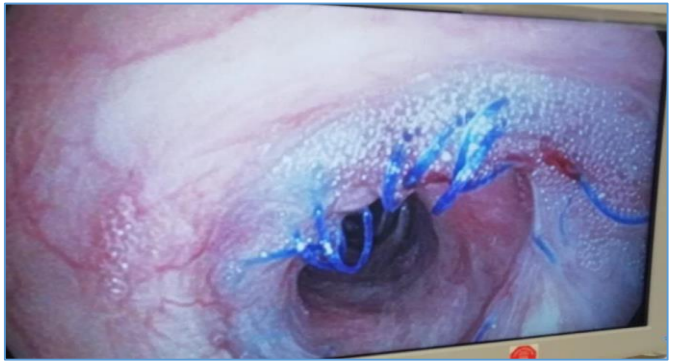
- Novel compound (granted US patent).
- Broad antifungal activity (*Candida, Rhizopus* spp. and pan-azole resistant *Aspergillus*; L98H; Colley et al., 2017).
- Bespoke profile: nanomolar potency; low dose, prolonged lung half-life.
  - Negligible oral absorption.
- **Excellent activity in immuno-suppressed mice in vivo** (Kimura et al., 2017)

Case report

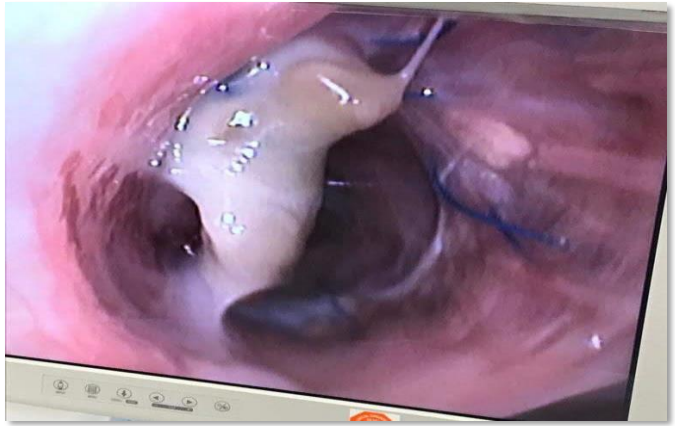
29 y.o. female Lung transplant. Aspergillus tracheobronchitis



December 18th:
Initiate 5mg daily



February 12th review:
Dramatic response evident



Jan 2nd review:
Patient tolerating drug well

Review

PC945, a Novel Inhaled Antifungal Agent, for the Treatment of Respiratory Fungal Infections

Alison Murray [1], Lindsey Cass [1], Kazuhiro Ito [1], Nicole Pagani [2], Darius Armstrong-James [3], Paras Dalal [2], Anna Reed [2] and Pete Strong [1,*]