Infections fongiques invasives Actualités épidémiologiques et nouveaux antifongiques

Pr Fanny Lanternier (National Reference Center for Invasive Mycoses, Institut Pasteur, Paris - Infectious Disease Department, Necker Hopsital)

Actualités en Réanimation, Novembre 2024, Lyon

COI

- Speaker bureau F2G, Gilead, Airnspace, Pfizer 2021-2022
- Advisory board F2G 2022

Mortalité
Liste des pathogènes prioritaires

1,6 millions décès/ an*

research, development and public health action

Table 3. WHO fungal priority pathogens list

Critical group	High group	Medium group
Cryptococcus neoformans	*Nakaseomyces glabrata (Candida glabrata)*	*Scedosporium* spp.
Candida auris	*Histoplasma* spp.	*Lomentospora prolificans*
Aspergillus fumigatus	Eumycetoma causative agents	*Coccidioides* spp.
Candida albicans	Mucorales	*Pichia kudriavzeveii (Candida krusei)*
	Fusarium spp.	*Cryptococcus gattii*
	Candida tropicalis	*Talaromyces marneffei*
	Candida parapsilosis	*Pneumocystis jirovecii*
		Paracoccidioides spp.

Organisation mondiale de la Santé

* GAFFI

Clinical challenges in fungal infections

Epidemiology

- travel
- global warming

At risk risk population

- Fragile
- New treatments
- Viral disease
- Age
- Modification of zone of endemy
- Absence of known risk factors: PID, immunogenetics

Emergence new species, resistance

Diagnosis: in fragile population, Rapid diagnosis tools/ availbility

Antifungal availability

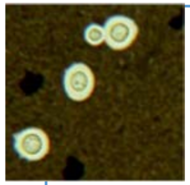
Role of immune restoration/control

Virulence

Treatment: new drugs

Resistance surveillance

- Natural resistance



Basidiomycètes

Candida krusei

Mucorales

- Acquired resistance

Environnement
Aspergillus

Preexposition to antifungals

Impact of climate change and natural disasters on fungal infections

Danila Seidel, Sebastian Wurster*, Jeffrey D Jenks*, Hatim Sati, Jean-Pierre Gangneux, Matthias Egger, Ana Alastruey-Izquierdo, Nathan P Ford, Anuradha Chowdhary, Rosanne Sprute, Oliver Cornely, George R Thompson III, Martin Hoenigl†, Dimitrios P Kontoyiannis†*

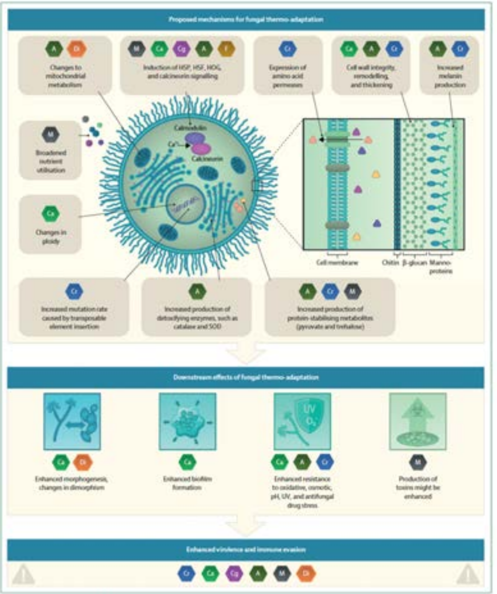


Figure 1: Proposed mechanisms of fungal thermo-adaptation
The proposed mechanism underlying fungal thermo-adaptation and downstream effects that could lead to enhanced virulence and immune evasion. A=Aspergillus. ATPase=adenosine triphosphatase. Ca=Candida albicans. Cg=Candida glabrata. Cr=Cryptococcus. Di=dimorphic fungi. F=Fusarium. HOG=high-osmolarity glycerol. HSF=heat shock factor. HSP=heat shock protein. M=Mucorales. SOD=superoxide dismutase. UV=ultraviolet.

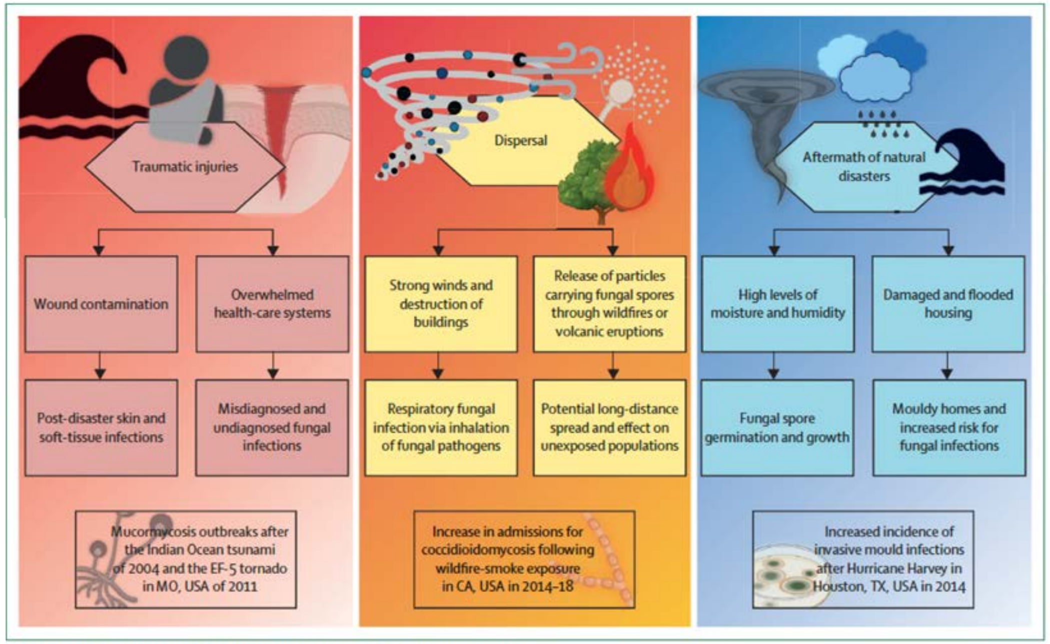


Figure 3: Mechanisms through which natural disasters trigger fungal outbreaks
The mechanisms outlined include traumatic injuries, dispersal of fungal spores, and housing damage in the aftermath of floodings.

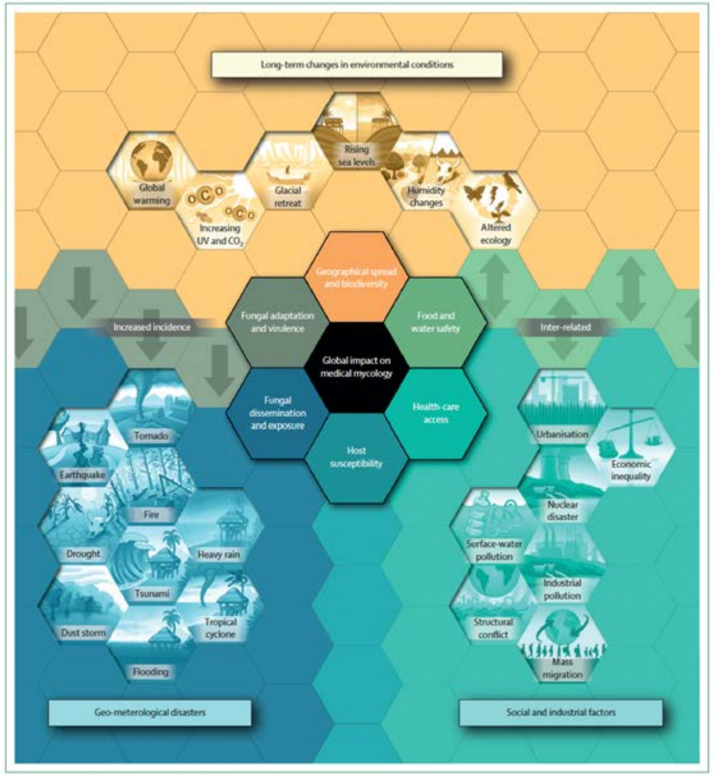


Figure 2: Impact of climate change and natural disasters on fungi
Long-term changes in environmental conditions are interrelated with social and industrial factors and lead to increased incidences of geo-meteorological disasters. All these factors have a global impact on medical mycology. CO_2=carbon dioxide. UV=ultraviolet.

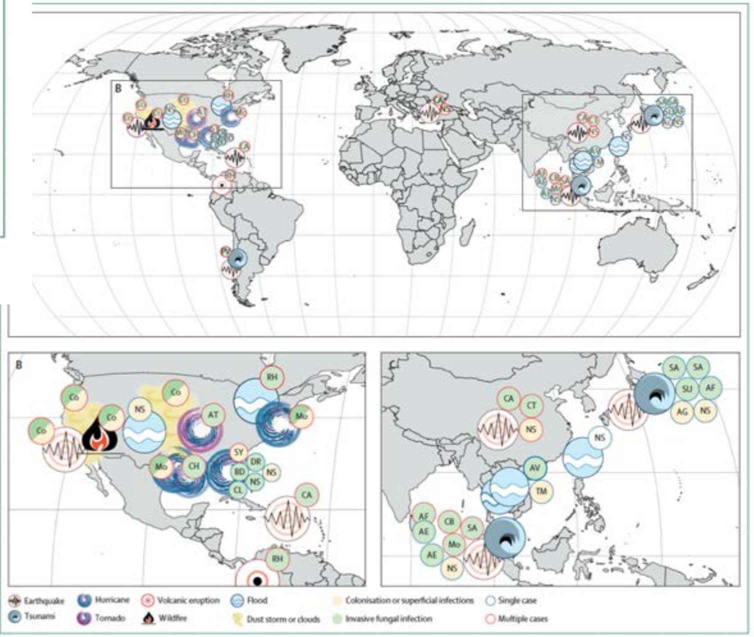


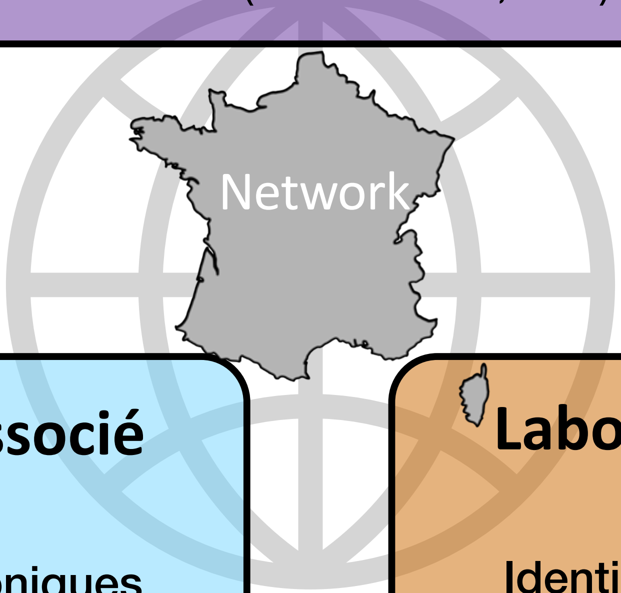
Figure 4: Global distribution of fungal outbreaks related to natural disasters
(A) World map. (B) North and middle America. (C) Southeast Asia. AE=*Apophysomyces elegans*. AF=*Aspergillus fumigatus*. AG=*Aspergillus glaucus*. AT=*Apophysomyces trapeziformis*. AV=*Aspergillus flavus*. BD=*Blastomyces dermatitidis*. CA=*Candida albicans*. CB=*Cladophialophora bantiana*. CH=unknown (chromoblastomycosis). CL=*Cladosporium* spp. CT=*Candida tropicalis*. CO=*Coccidioides immitis*. DR=*Drechslera* spp. Mo=moulds. NS=not specified. RH=*Rhizopus arrhizus*. PV=*Paecilomyces variotii*. SA=*Scedosporium apiospermum*. SU=*Scedosporium aurantiacum*. SY=*Syncephalastrum* spp. TM=*Trichosporon mucoides*.

Epidemiology of invasive fungal infections in France: focus on emerging or R species

CNRMA-IFI
Expertise IFI
Conseil IFI
Surveillance IFI
Alerte IFI
F. Lanternier (Institut Pasteur, Paris)

Support thérapeutique IFI
SMIT
Hôpital Necker

Support diagnostic moléculaire IFI
Laboratoire mycologie
Hôpital Saint-Louis

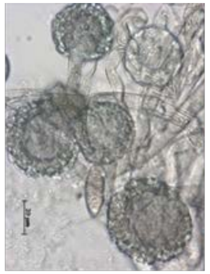


Laboratoire associé
AspC
Aspergilloses chroniques
L. Delhaes (CHU Bordeaux)
JP. Gangneux (CHU Rennes)

Laboratoire associé
INuSuAl
Identification Numérique
Surveillance Alerte
A. Fekkar (CHU Pitié Salpétrière, Paris)

How to deal with surveillance

- Prospective surveillance for all IFI with the collaboration of 60 hospitals on the territory
  - Including epidemiological and mycological data including ATF suseptibility
  - For non commun fungi or fungi with atypical resistance profil
    - Strains centralization
    - Polyphasic approach
      - Phenotypic
      - Genotypic identification
      - EUCAST ATF

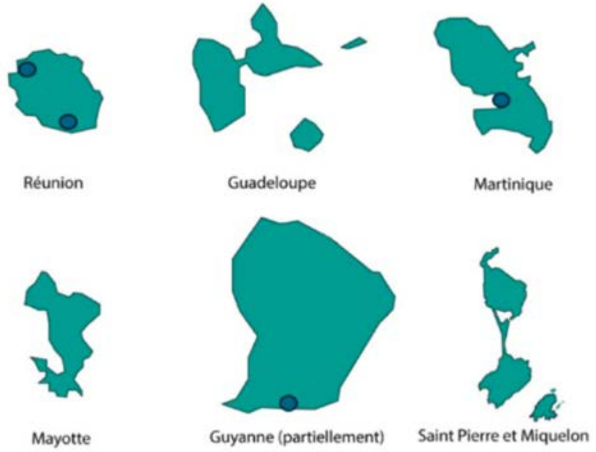



CNRMA
IFI

INSTITUT
PASTEUR

SINFONI: hospital (n=60) network for IFI surveillance

- 49 centres actifs



2023 surveillance data in France

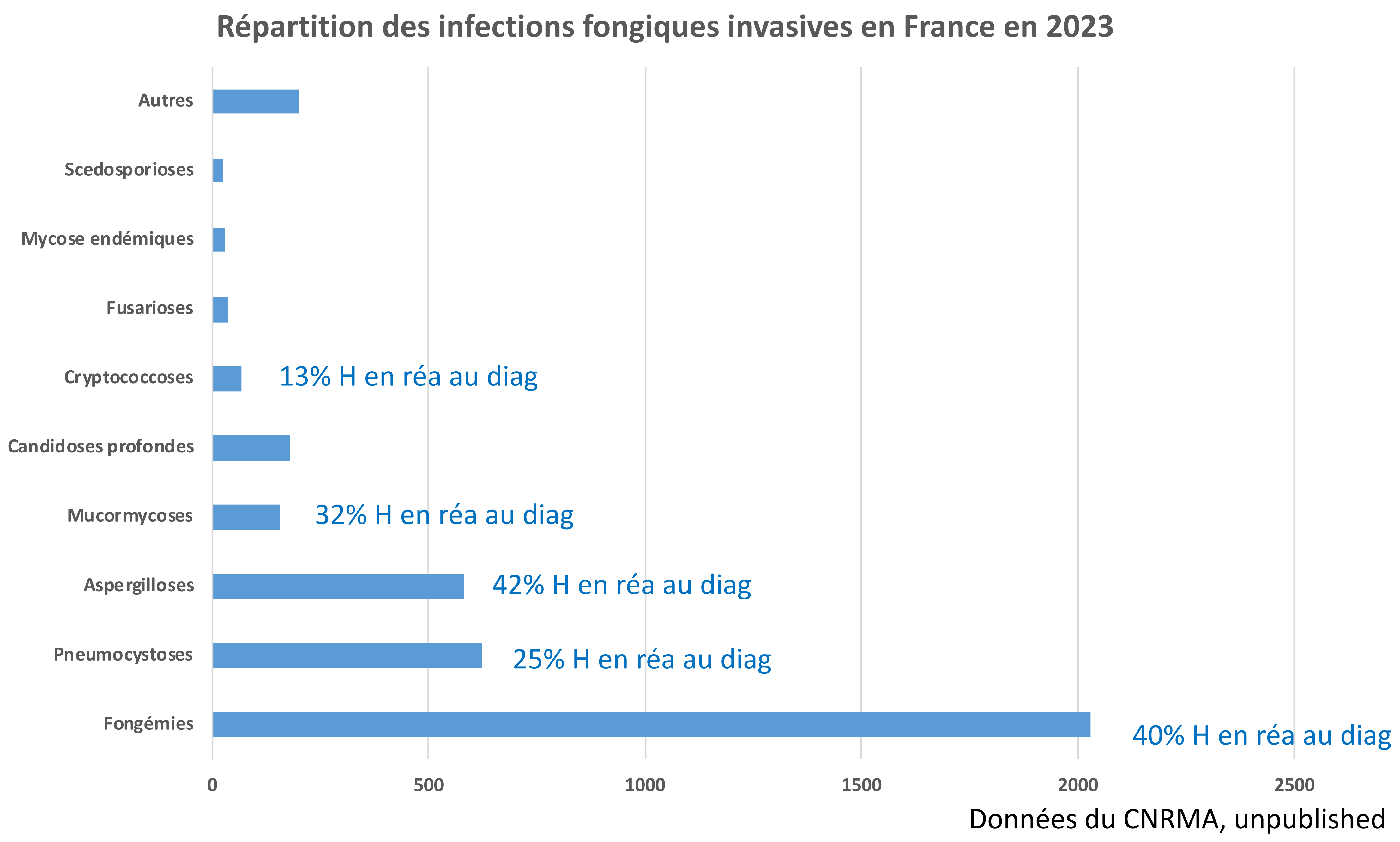
- 3772 IFI declared
  - 2029 fungemia
  - 622 pneumocystosis
  - 581 Invasive aspergillosis
  - 156 mucormycosis
  - 66 cryptococosis
  - others

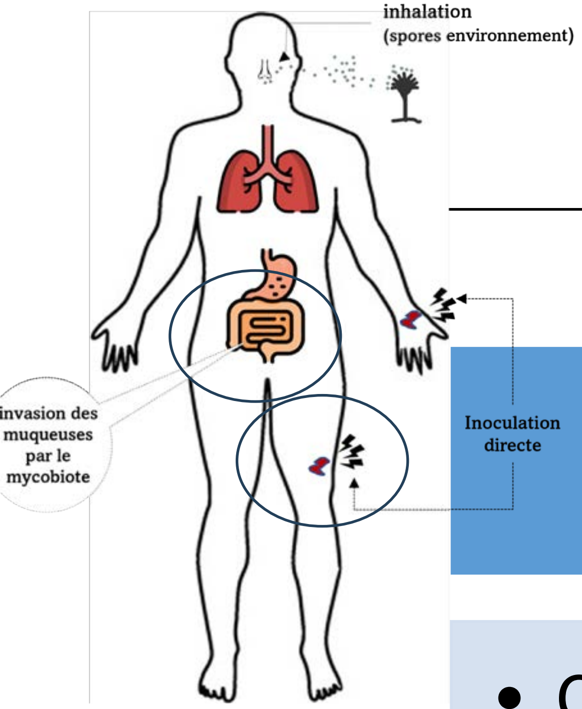
- 36% death at 3 months
- Risk factors:
  - 20% hematological malignancy
  - 19% solid cancer
  - 10% SOT
  - 6% SID
  - 15% diabetes mellitus
  - 5% HIV

CNRMA IFI

SINFONI

Données du CNRMA, unpublished


Répartition des infections fongiques invasives en France en 2023
Autres
Scedosporioses
Mycose endémiques
Fusarioses
Cryptococcoses
Candidoses profondes
Mucormycoses
Aspergilloses
Pneumocystoses
Fongémies
13% H en réa au diag
32% H en réa au diag
42% H en réa au diag
25% H en réa au diag
40% H en réa au diag
0
500
1000
1500
2000
2500
Données du CNRMA, unpublished



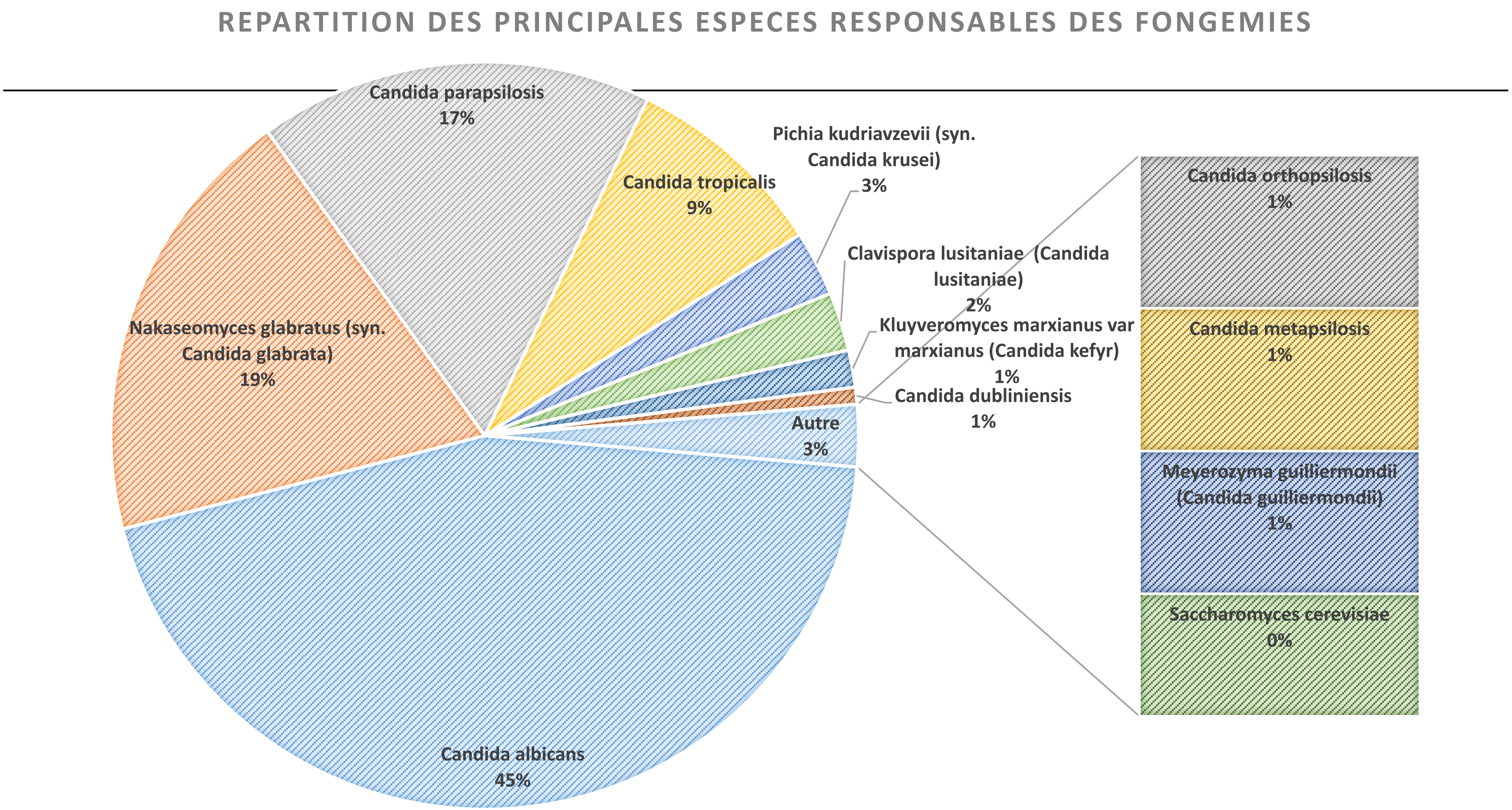
Candidemia

2029 cases in 2023

Patients	Outcome
• Cancer 25% • Hematology 11% • Surgery 30% • 40% H en USI	• 41% 3 months mortality

Importance of early adapted AF treatment
Candida species with natural or acquired antifungal resistance

Données du CNRMA, unpublished



Données du CNRMA, unpublished

Challenges in *Candida* resistance

- *Evolution of* Candida parapsilosis *causing outbreaks in Spain: Azole resistance distribution and related molecular mechanisms of resistance*
- Laura Alcazar-Fuoli (Instituto de Salud Carlos III, Spain)

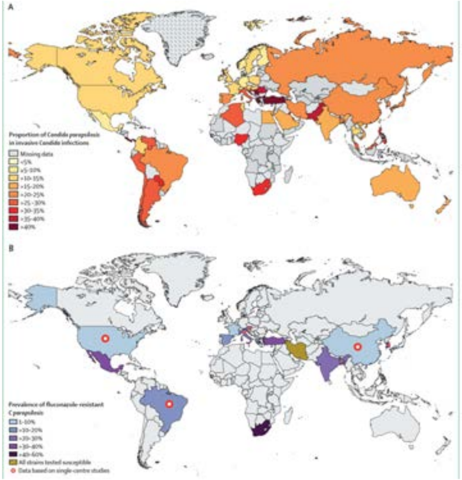
- Still lot of challenges:
  - Transmission
  - Outbreak prevention measure
  - Optimal treatment

- *Challenges of diagnosing superficial* Candida *infections*
- Riina Richardson (University of Manchester, UK)
  - Diagnosis challenge
  - New therapeutic options

Open Forum Infectious Diseases
MAJOR ARTICLE
IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

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

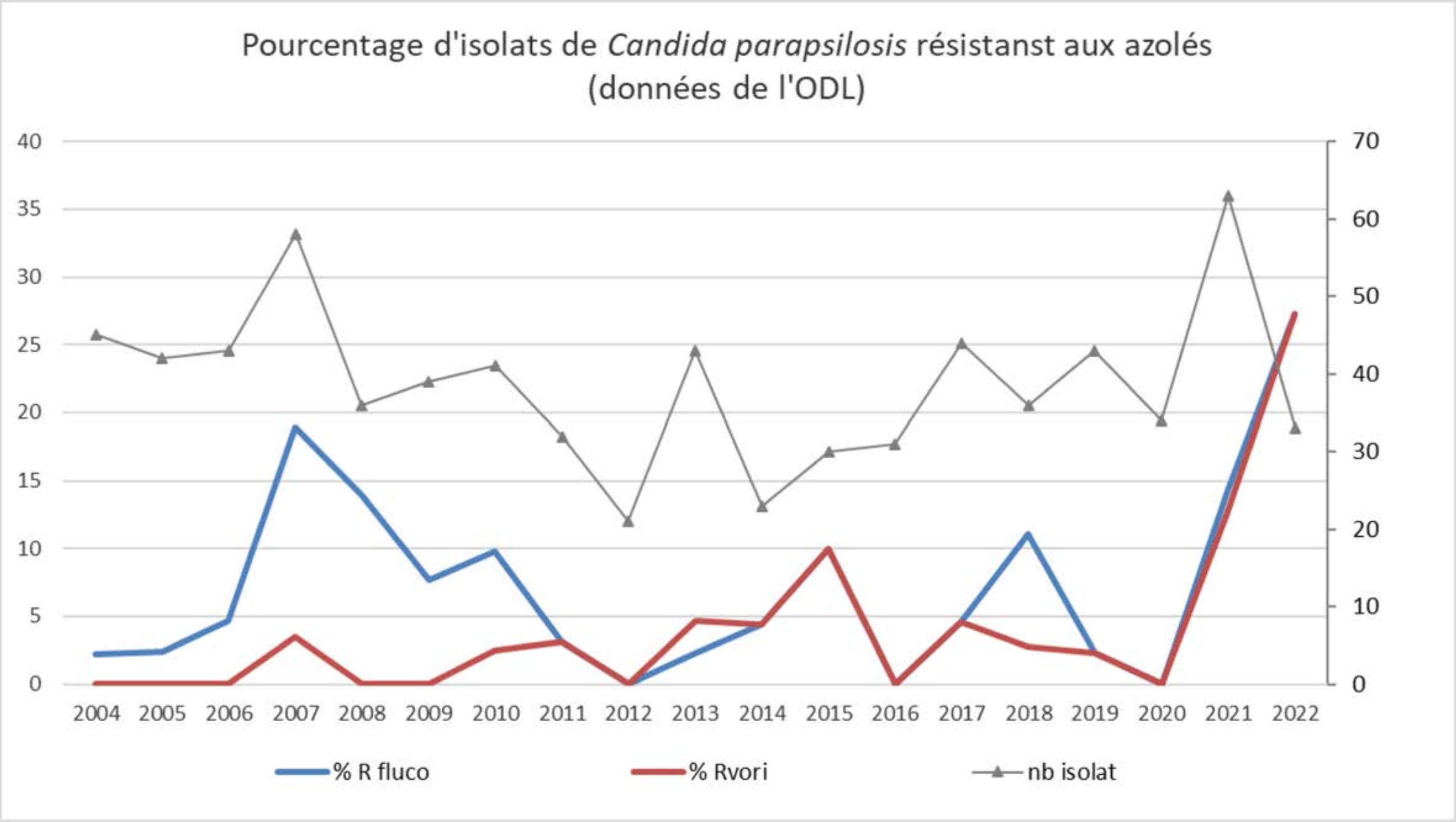
Nuria Trevijano-Contador,[1] Alba Torres-Cano,[1] Cristina Carballo-González,[1] Mireia Puig-Asensio,[2,3] María Teresa Martín-Gómez,[4] Emilio Jiménez-Martínez,[2] Daniel Romero,[4] Francesc Xavier Nuvials,[5] Roberto Olmos-Arenas,[6] María Clara Moretó-Castellsagué,[6] Lucía Fernández-Delgado,[6] Graciela Rodríguez-Sevilla,[6] María-Mercedes Aguilar-Sánchez,[6] Josefina Ayats-Ardite,[6] Carmen Ardanuy-Tisaire,[6,7] Isabel Sanchez-Romero,[8] María Muñoz-Algarra,[8] Paloma Merino-Amador,[9,10,11] Fernando González-Romo,[9,10,11] Gregoria Megías-Lobón,[12] Jose Angel García-Campos,[12] María Ángeles Mantecón-Vallejo,[12] Eva Alcoceba,[13] Pilar Escribano,[14,15] Jesús Guinea,[15,16] María Teresa Durán-Valle,[17] Arturo Manuel Fraile-Torres,[17] María Pía Roiz-Mesones,[18] Isabel Lara-Plaza,[18] Ana Pérez de Ayala,[19] María Simón-Sacristán,[20] Ana Collazos-Blanco,[20] Teresa Nebreda-Mayoral,[21] Gabriel March-Roselló,[21] Laura Alcázar-Fuoli,[1,22] and Oscar Zaragoza[1,22]



Daneshnia F et

Candida parapsilosis

Increasing proportion of *C. parapsilosis* resistant to fluconazole and voriconazole since 2020.

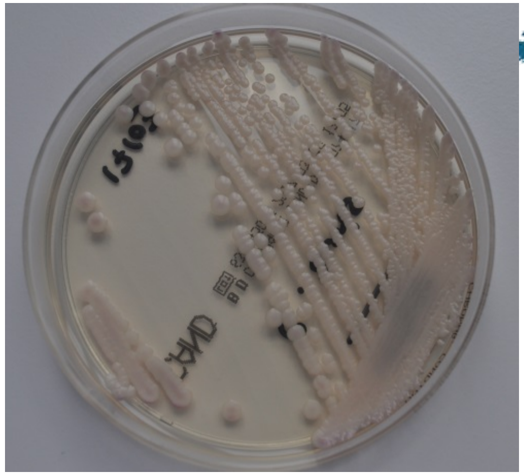


2023: 1.5% *C. parapsilosis* fluco R

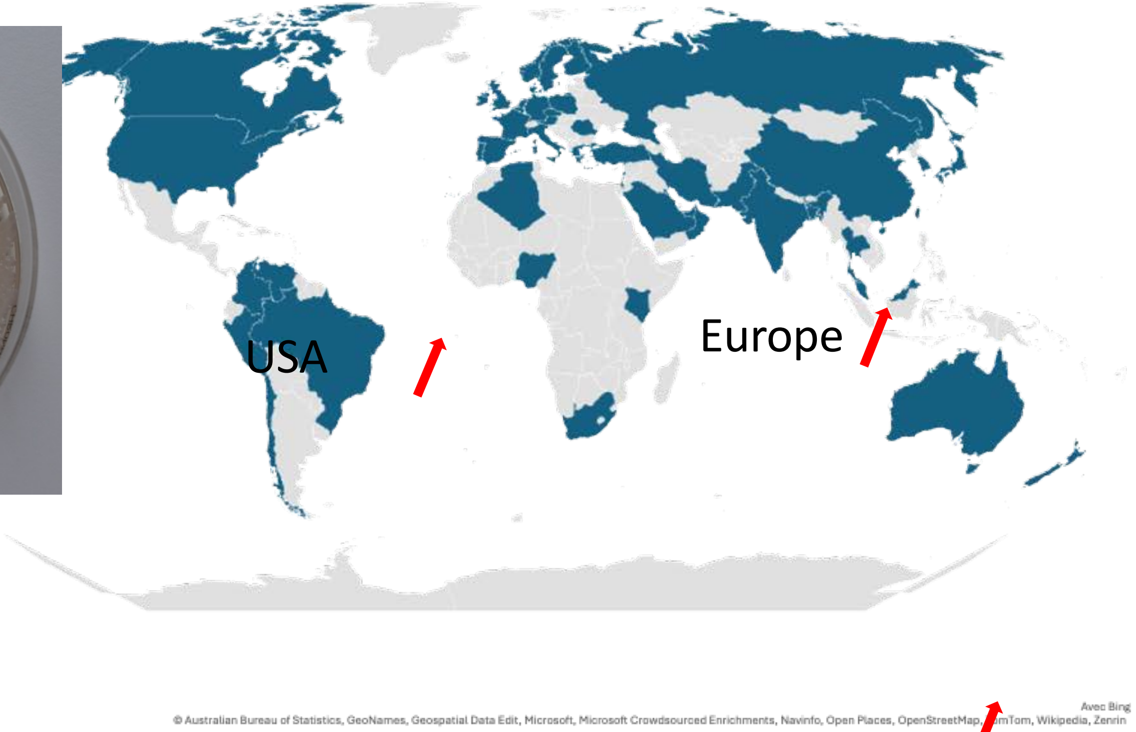
Candida auris

- Description 2009, Japon oreille
- Identification rétrospective premier cas hémoculture 1996 Corée du Sud
- France: premier cas 2007
- 2011-2012 : apparition simultanée d'infection invasives en Afrique, Asie et Amérique du Sud
- Épidémie, infection nosocomiale car transmission inter-patients lié au support sur les surfaces autour du lit des patients
- Virulence identique à *C. albicans*
- Taux de mortalité: 30-60%

Surveillance and alert of epidemic agents



Candida auris



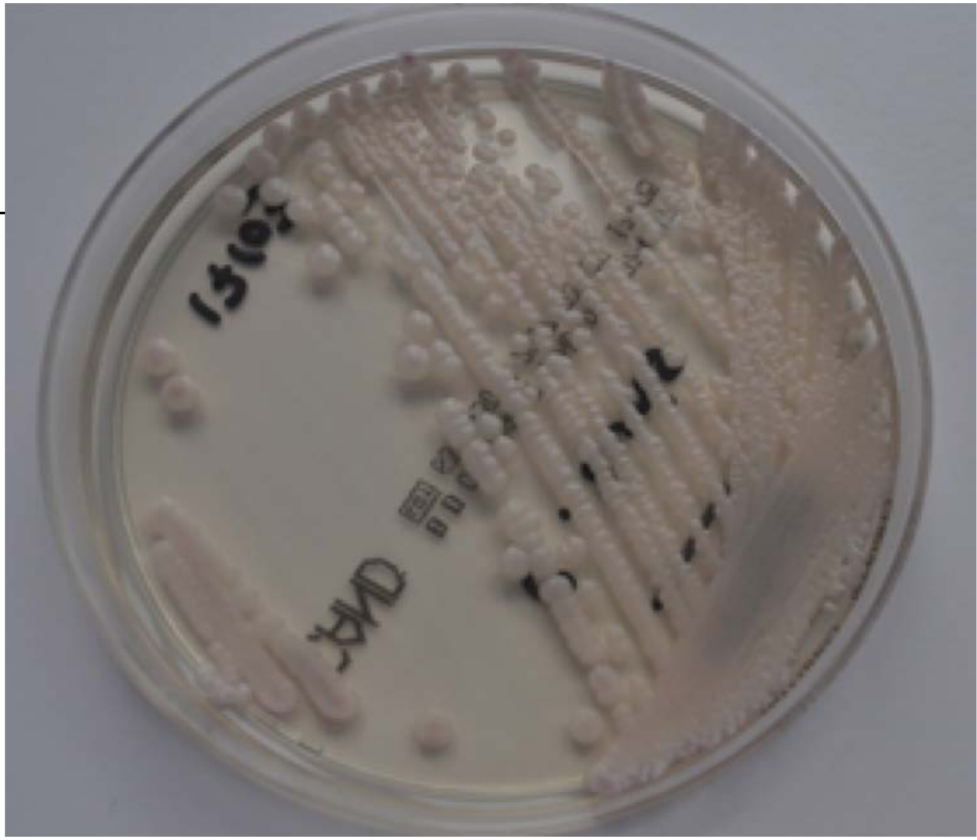
Afrique du Sud

Inscrease from 2020

Environnement

- Croissance à 37 et jusque 42°C
- Réservoir environnemental: sable dans les iles Andaman (Océan Indien), supposition réservoir aquatique
- Émergence hypothèse réchauffement climatique=> augmentation température entraine augmentation des températures de tolérance des champignons et donc émergence de nouvelles souches pouvant pousser et se multiplier à la température des mammifères

Identification

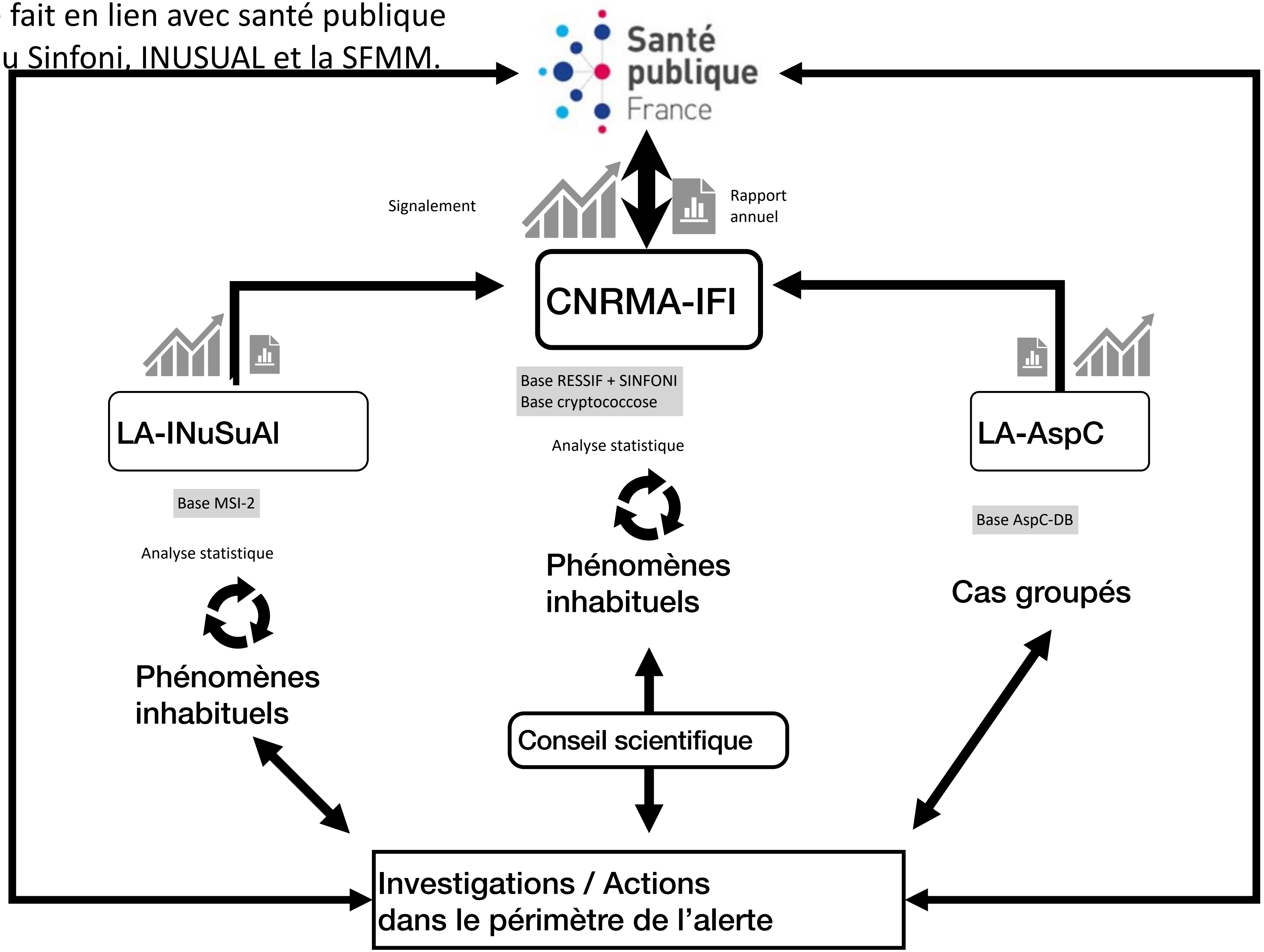


- Beige/rosé sur BBL Chromagar (BD)
- Milieu spécifique CHROMagar TM Candida Plus
- Identification efficace par MALDI-Tof, séquençage 26S/ITS, PCR en temps réel
- Génotypage: microsatellites, séquençage génome entier
    - 6 clades distincts liés à l'origine géographique
        - Clade I, Inde
        - Clade II, Japon
        - Clade III, Afrique du Sud
        - Clade IV, Amérique du Sud (isolats résistants aux échinocandines)
        - Clade V, Iran
        - Clade VI

        - Étude phylogénétiques=> seuil 5 SNPs associés aux données cliniques pour déterminer la clonalité

Alerte

La surveillance et l'alerte sur les phénomènes épidémiques se fait en lien avec santé publique France, le réseau Sinfoni, INUSUAL et la SFMM.



Note Centre National de Référence des Mycoses invasives & Antifongiques (CNRMA)/de la Société Française de Mycologie Médicale (SFMM)/Société Francaise d’Hygiène Hospitalière (SF2H)

En cas de colonisation ou d’infection à *Candida auris* dans un centre

- Déclaration par le mycologue de l’hôpital au CNRMA
- Envoi de la souche au CNRMA
- Déclaration simultanée par l’hygiéniste de l’hôpital par e-SIN à SPF

Indications de dépistage de *Candida auris* par culture d’écouvillons inguinal, axillaire et nasal sont préconisés pour tout patient:

- Hospitalisé dans les 12 mois précédents, notamment pour les patients rapatriés d’une réanimation d’un pays étranger.
- Dépistage à réitérer si réadmission dans les 12 mois suivant le retour.
- Antérieurement colonisé ou infecté par *C. auris*
- Contact d’un cas

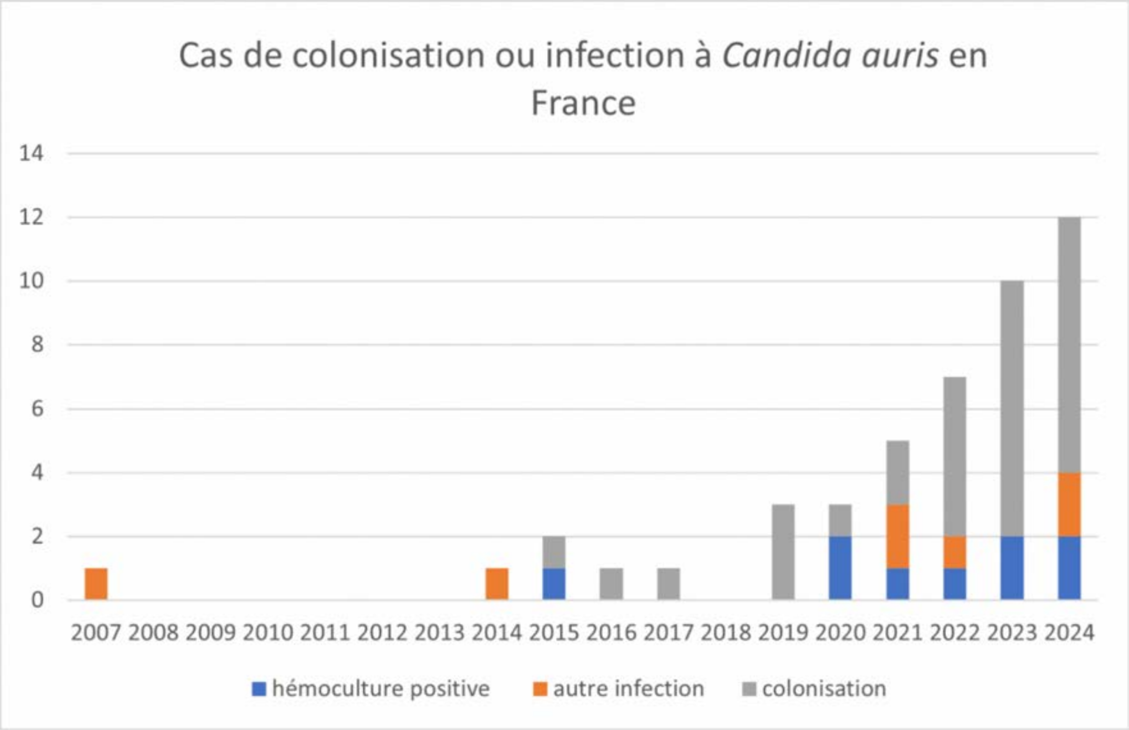
Modalité de dépistage des infections ou colonisation à *C. auris*

- Identification MALDI-TOF de toutes les colonies:
  - rosées/blanches sur milieu BBL™ CHROMmagar Candida ™
  - ou colonies avec halo bleu sur Chromagar Candida Plus ™.
- Incubation:
  - au moins 10 jours
  - idéalement à 40°C ou 35°C (favorise la croissance de *C. auris*)
- Nettoyage approfondi du PSM
  - solution d'hypochlorite de sodium 0.5% ou sporicide (type Incidin™)

Nouveautés internationales 2023

- Description Clade VI, Singapour (https://doi.org/10.1101/2023.08.01.23293435)
- Découverte d'une adhésine spécifique de *C.auris* (Surface Colonization Factor, Scf1) associée avec une adhesine conservée Iff4109 => Adhésion sur les supports biotiques et abiotique (Santana *et al* Science 2023)
- Épidémie en néonatologie en Afrique du Sud (Kekada *et al.* EID 2023)
- Tentative Breakpoint technique CLSI (valable pour Etest) (https://www.cdc.gov/candida-auris/hcp/laboratories/antifungal-susceptibility-testing.html):
  - Fluconazole ≥32mg/L
  - Amphotéricin B ≥2mg/L
  - Caspofungin ≥2mg/L
  - Micafungin ≥4mg/L

Candida auris en France



46 épisodes
Patients transférés d'hôpitaux à l'étranger
Transmission: 4 épisodes (1 patient, 2 patients, 1 patient, 3 patients)

Sensibilité *in vitro* des souches de *C. auris* reçues au CNRMA (EUCAST)

- 3 isolats environnementaux Clade I
- 50 isolats cliniques de 34 patients Clade I et Clade III
- Tous résistants au fluconazole (CMI ≥64 mg/L)
- Aucun isolat CMI élevée aux échinocandines ni à l'amphotéricinB

Valeurs des CMI_{50} / CMI_{90} (mg/L) pour les antifongiques de 53 isolats de *Candida auris*								
	AMB	5-FC	Fluco	Vori	Posa	Isavu	Caspo	Mica
Clade I (n=43)	1/1	≤0.12/≥64	64/≥64	1/2	0,03/0,125	0,06/0,25	0.03/0.03	0,25/0,5
Clade III (n=10)	0,5/-	0,124/0,25	≥64/≥64	1/2	0,06/-	0,06/0,125	0,015/0,03	0,25/-

Classification cas *C. auris*

- Culture + : cas certain
- PCR+/culture - : cas possible à renouveler et élargir les sites de prélèvements
- 1 seule PCR+ suivie d'au moins 4 PCR et cultures négatives à une semaine d'intervalle : pas de portage
- Au moins 2 PCR+ : cas possible.

Saprochaete clavata Outbreak Infecting Cancer Center through Dishwasher

Estelle Menu, Alexis Criscuolo, Marie Desnos-Ollivier, Carole Cassagne, Evelyne D'Incan, Sabine Furst, Stéphane Ranque, Pierre Berger, Françoise Dromer

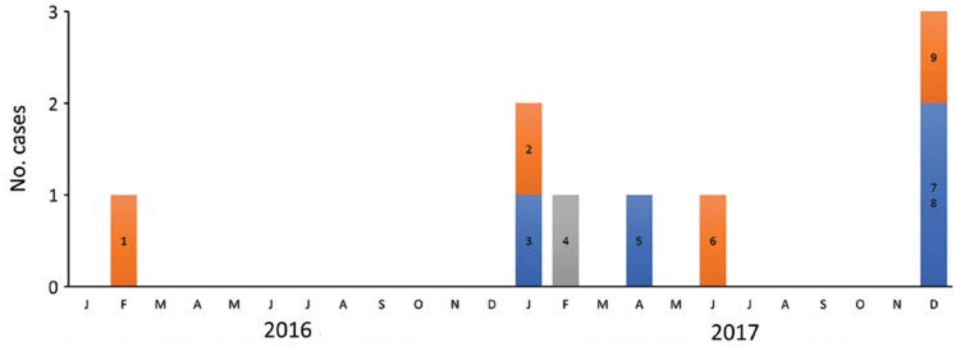


Figure 1. Timeline of outbreak for 9 cases of infection with *Saprochaete clavata* identified in a single center at the Institut Paoli-Calmettes, Marseille, France, February 2016–December 2017. The patients were hospitalized in 3 wards: the hematology unit (orange bar sections), the stem cell transplant unit (blue bar sections), and the intensive care unit (gray bar sections). Numbers 1–9 correspond to patient numbers in the Table.

Table. Characteristics of patients with a culture positive for *Saprochaete clavata* in Marseille, France, February 2016–December 2017*

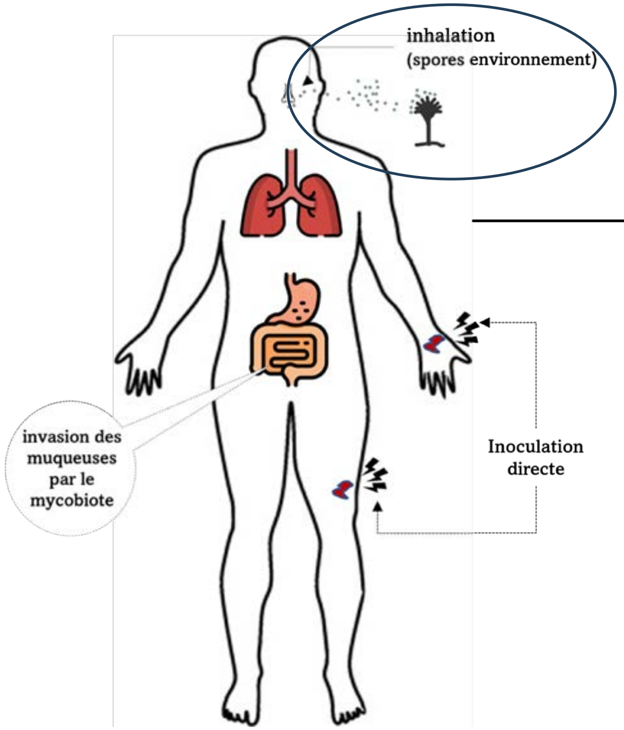
	Patient no.								
Characteristic	1	2	3	4	5	6	7	8	9
Age, y	58	38	45	66	57	68	65	56	68
Sex	M	F	M	F	M	M	F	M	M
Hospitalization ward	H	H	T	ICU	T	H	T	T	H
Immune status									
Underlying disease	Lymphoma	AML	MDS	Lymphoma	CLL	AML	ALL	AML	AML
Lymphocyte count, G/L	<0.1	0.1	5.6	0.2	0.1	0.1	0.8	0.1	0.1
Severe neutropenia, <500 /mm^3	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Duration of neutropenia at time of positive culture, d	6	51	0	4	36	27	0	21	21
BMT	Yes	No BMT	Yes	No BMT	Yes	No BMT	Yes	Yes	Yes
Days from BMT to first positive culture	9		90		75		61	3	>90
Clinical signs at the time of positive culture									
Fever, temperature >38°C	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Digestive symptoms	Yes	Yes	NA	NA	NA	NA	Yes	Yes	Yes
Diarrhea	Yes		NA	NA	NA	NA	Yes	Yes	
Constipation	NA	Yes	NA	NA	NA	NA		NA	Yes
Pulmonary symptoms	NA	Yes	Yes	NA	NA	NA	Yes	NA	Yes
Skin lesions	NA	NA	NA	Yes	Yes	NA	Yes	NA	NA
Positive culture results									
Date of first positive culture	2016 Feb 3	2017 Jan 16	2017 Jan 18	2017 Feb 26	2017 Apr 17	2017 Jun 29	2017 Dec 5	2017 Dec 10	2017 Dec 29
Days after admission	16	51	6	14	80	27	68	20	21
No. positive samples	1	1	2	7	5	9	1	10	5
Blood	1	1	None	5	4	9	1	9	5
Respiratory tract	None	None	2	2	1	None	None	None	None
Stool, rectal swab	None	None	None	None	None	None	None	1	None
Outcome									
Death within 90 d	No	Yes	Yes	Yes	No	Yes	Yes	No	No
Days after first positive culture	DNA	12	57	7	DNA	4	6	DNA	DNA
Treatment									
Venous access	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Echinocandins	Micafungin	NP	NP	NP	NP	NP	Caspo	NP	NP
Azoles	NP	PCZ	NP	NP	VCZ	PCZ	VCZ	VCZ	VCZ, PCZ
Cytarabine	Yes	Yes	NP	NP		Yes	Yes	Yes	Yes
Ibrutinib	NP		NP	NP	Yes				
Apheresis platelet concentrates	NP	Yes	NP	NP	Yes	Yes	Yes	Yes	Yes

*ALL, acute lymphoblastic leukemia; ANL, acute myeloid leukemia; BMT, bone marrow transplant; Caspo, caspofungin; CLL, chronic lymphocytic leukemia; DNA, does not apply; H, hematology; ICU, intensive care unit; MDS, myelodysplastic syndromes; NA, not available; NP, not prescribed; PCZ, posaconazole; T, stem-cell transplant; VCZ, voriconazole.

†Bronchoalveolar lavage, tracheal aspirate.

Source

- Multidosciplinary work
- Genetic link between environmental and clinical strains
- Local outbreak due to dishwasher



Invasive aspergillosis

581 invasive aspergillosis in 2023

Quels patients

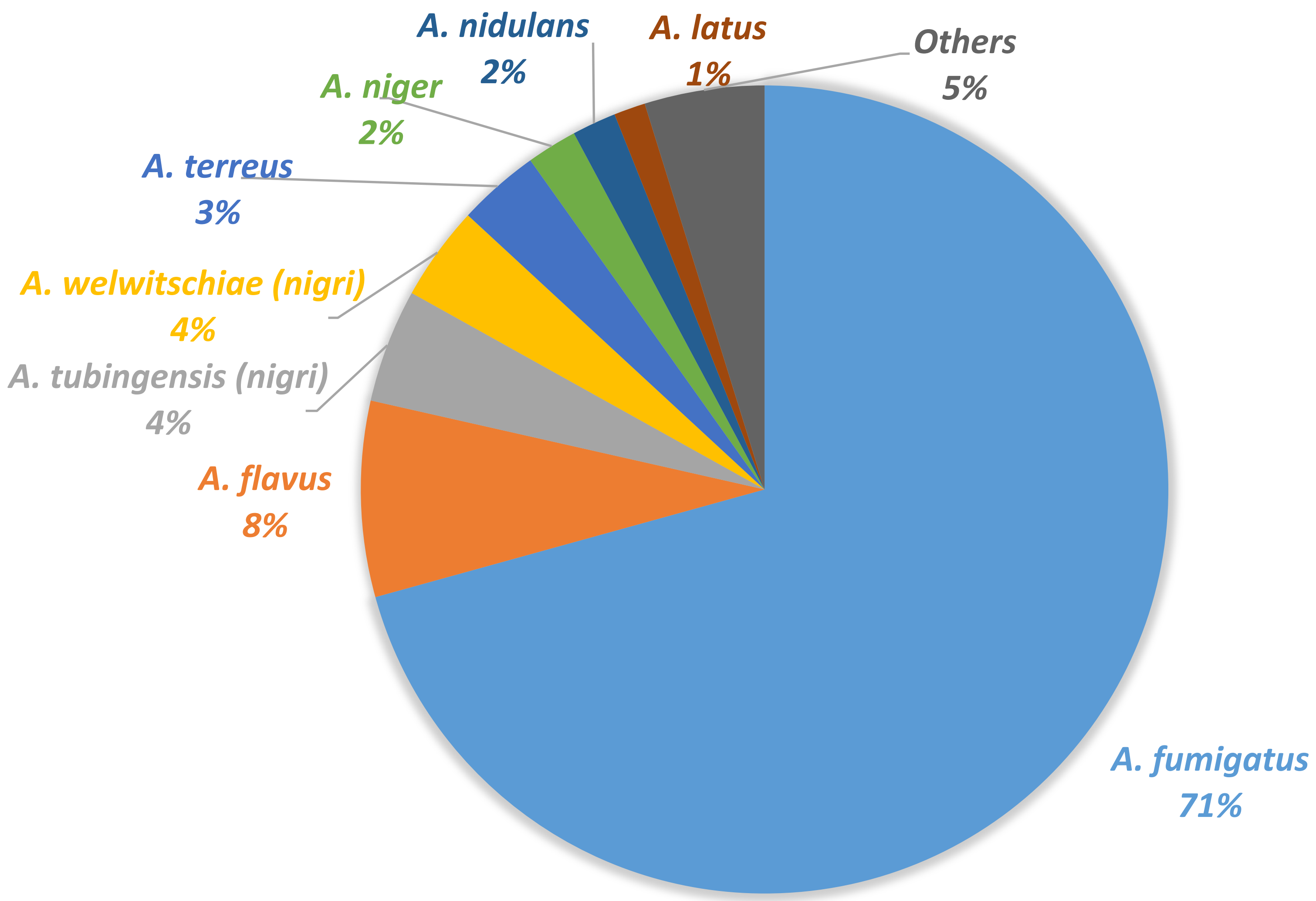
- Cancer 7%
- Hémopathie 44%
- Transplantation d’organe 19%
- Grippe 4%
- COVID 8%

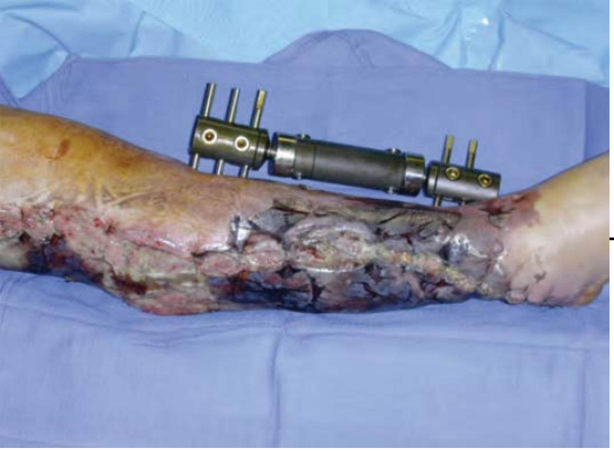
Devenir?

- Mortalité: 44% 3M
- Retard traitement hémopathie

Aspergillus acquired resistance (prexposure or environment)
Long term treatment with toxicity and interactions

Répartition des espèces d'Aspergillus responsables d'aspergilloses invasives



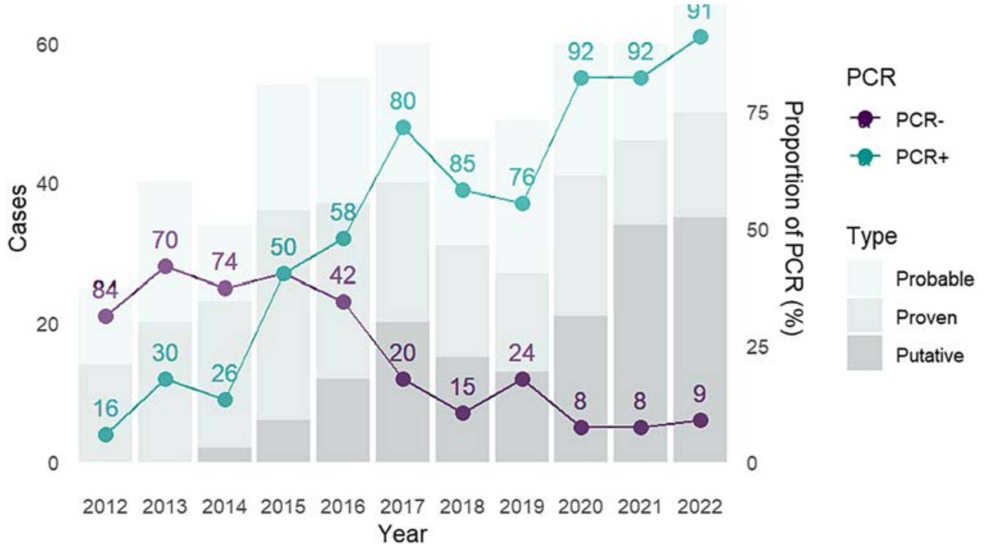


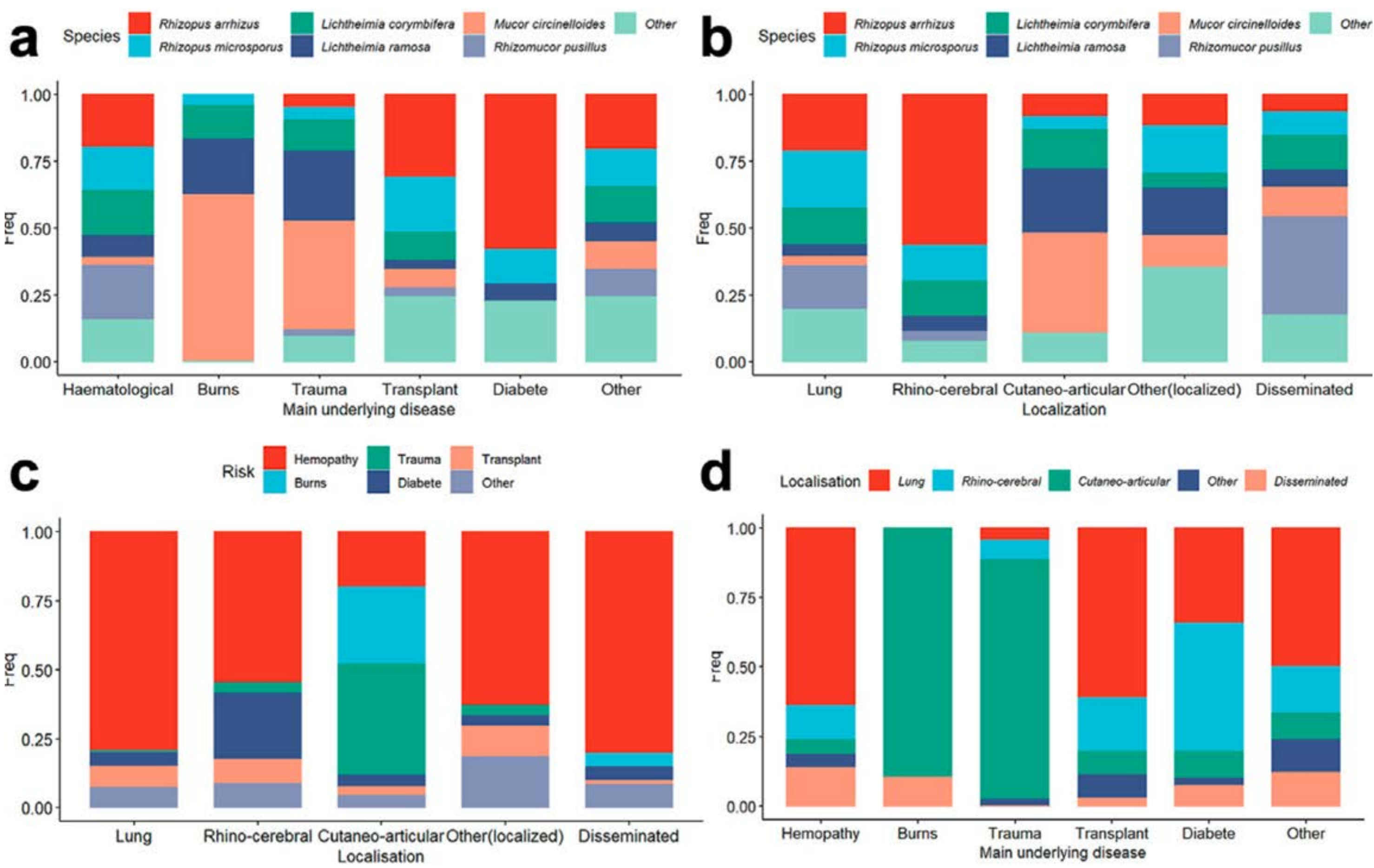
Mucormycosis

156 cases in 2023

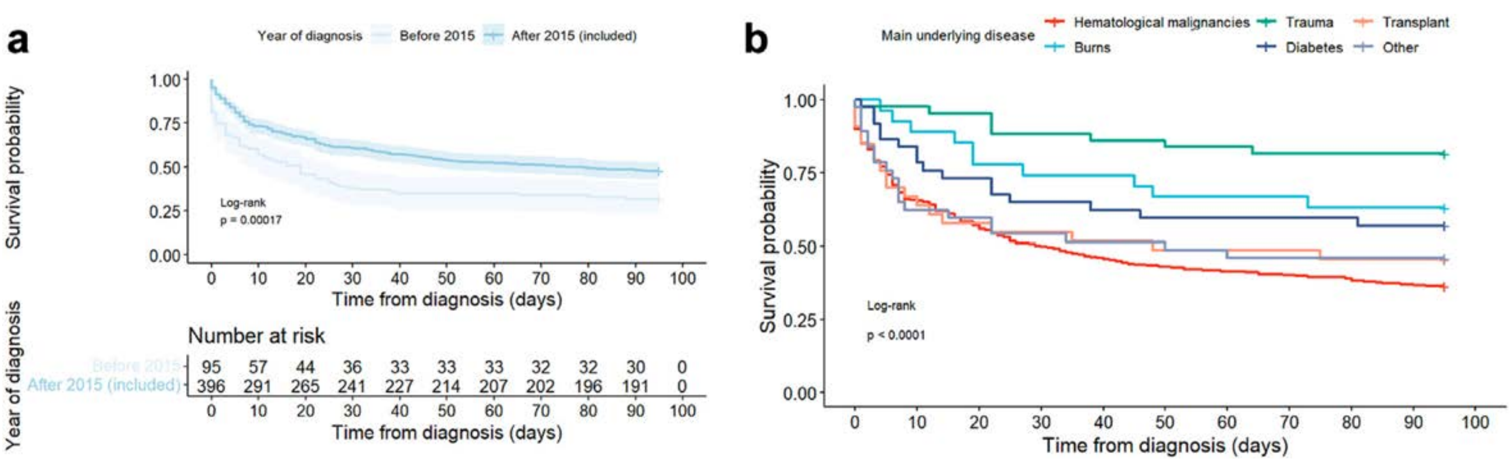
patients	Disease	Outcome
• Cancer • Hémopathie • Diabetes • Trauma • COVID	• Lung • Sinus • Disseminated	• 47% 3 months mortality

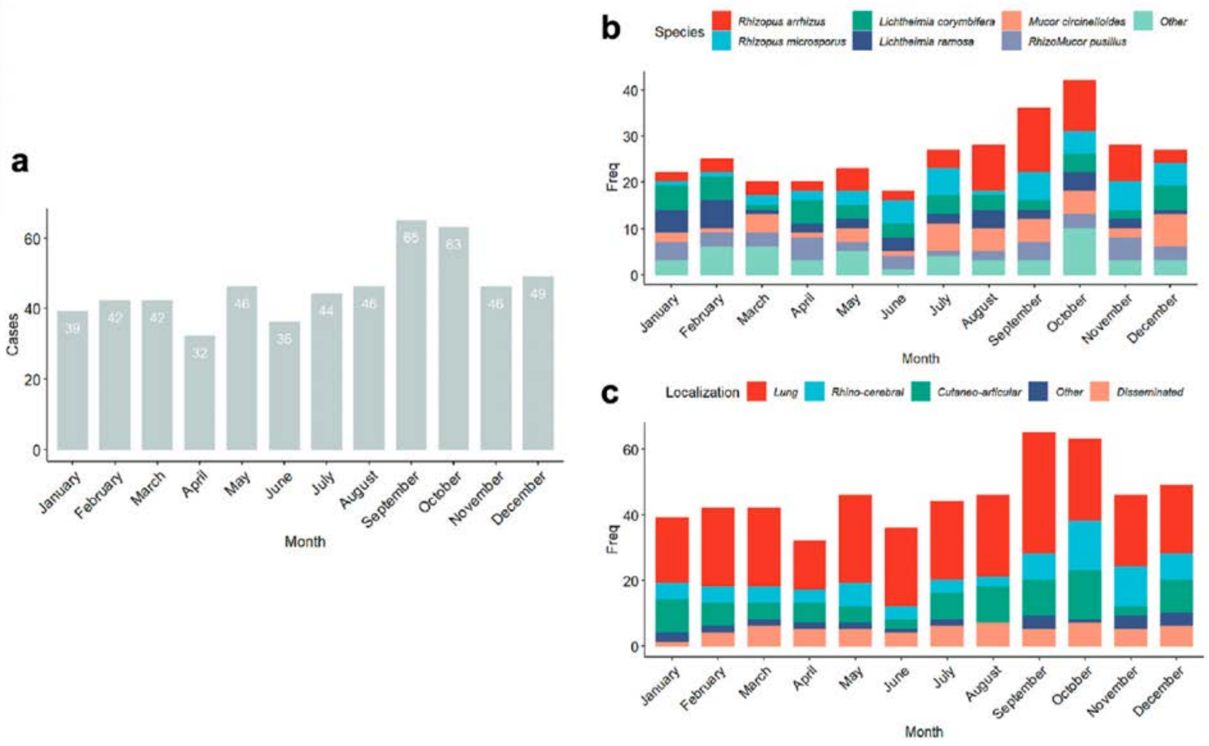
Mucormycosis epidemiology: RESSIF surveillance





Gouzien et al, Lancet Regional Health Europe, 2024





Gouzien et al, Lancet Regional Health Europe, 2024

	Univariable		Multivariable	
	OR (95% CI)	p	OR (95% CI)	p
Male	0.95 (0.65–1.38)	0.78		
Age	1.02 (1.01–1.03)	**<0.0001**	**1.02 (1.01–1.03)**	**0.0009**
Intensive Care Unit at diagnosis	3.25 (2.17–4.92)	**<0.0001**	**8.88 (4.96–16.8)**	**<0.0001**
Haematological malignancy	2.51 (1.73–3.66)	**<0.0001**		
Solid organ transplant	1.26 (0.66–2.47)	0.48		
Diabetes	1.07 (0.67–1.70)	0.76		
Burns	0.45 (0.19–0.98)	0.048		
Trauma	0.17 (0.07–0.34)	**<0.0001**		
Haematopoietic stem cell transplantation	1.66 (1.07–2.63)	**0.027**		
Neutropenia	2.11 (1.47–3.03)	**<0.0001**		
Corticosteroids	1.52 (0.99–2.34)	0.058		
Main underlying disease		<0.0001		
Hemopathy	1			**1**
Burn	0.33 (0.14–0.74)	0.007	**0.09 (0.02–0.30)**	**0.0001**
Solid organ transplant	0.71 (0.35–1.48)	0.35	**0.34 (0.14–0.80)**	**0.01**
Trauma	0.13 (0.05–0.27)	<0.0001	**0.10 (0.03–0.29)**	**<0.0001**
Diabete	0.43 (0.21–0.85)	0.02	**0.17 (0.07–0.42)**	**0.0001**
Other	0.66 (0.33–1.34)	0.24	**0.30 (0.12–0.71)**	**0.007**
Localisation		**0.004**		
Disseminated	1			1
Lung (localized)	0.70 (0.36–1.31)	0.27	0.65 (0.31–1.33)	0.25
Rhino-cerebral (localized)	0.52 (0.24–1.08)	0.08	0.75 (0.31–1.74)	0.50
Cutaneo-articular (localized)	0.17 (0.08–0.34)	**<0.0001**	**0.34 (0.13–0.9)**	**0.03**
Other (localized)	0.61 (0.23–1.62)	0.32	0.66 (0.22–1.97)	0.44
Species[b]		<0.0001		
Rhizopus arrhizus	1			
Rhizopus microsporus	2.91 (1.26–7.14)	0.02		
Lichtheimia corymbifera	2.06 (0.91–4.86)	0.09		
Mucor circinelloides	0.42 (0.18–0.97)	0.04		
Rhizomucor pusillus	3.66 (1.46–10.17)	0.01		
Lichtheimia ramosa	0.53 (0.22–1.25)	0.15		
Others	1.45 (0.67–3.19)	0.35		
Diagnosis after 2015	0.51 (0.32–0.82)	**0.006**	**0.42 (0.23–0.72)**	**<0.0001**
Diagnosis after 2020	0.72 (0.49–1.06)	0.10		
PCR positive	1.13 (0.77–1.65)	0.52		
Putative cases	1.05 (0.70–1.57)	0.82		
Fungal coinfection	1.22 (0.80–1.87)	0.35		

Results highlighted with [bold] were statistically significant. [a]Data for survival at day 90 were available in 495 cases only. [b]Analysis was performed only on complete cases. Missing data for species were 108.

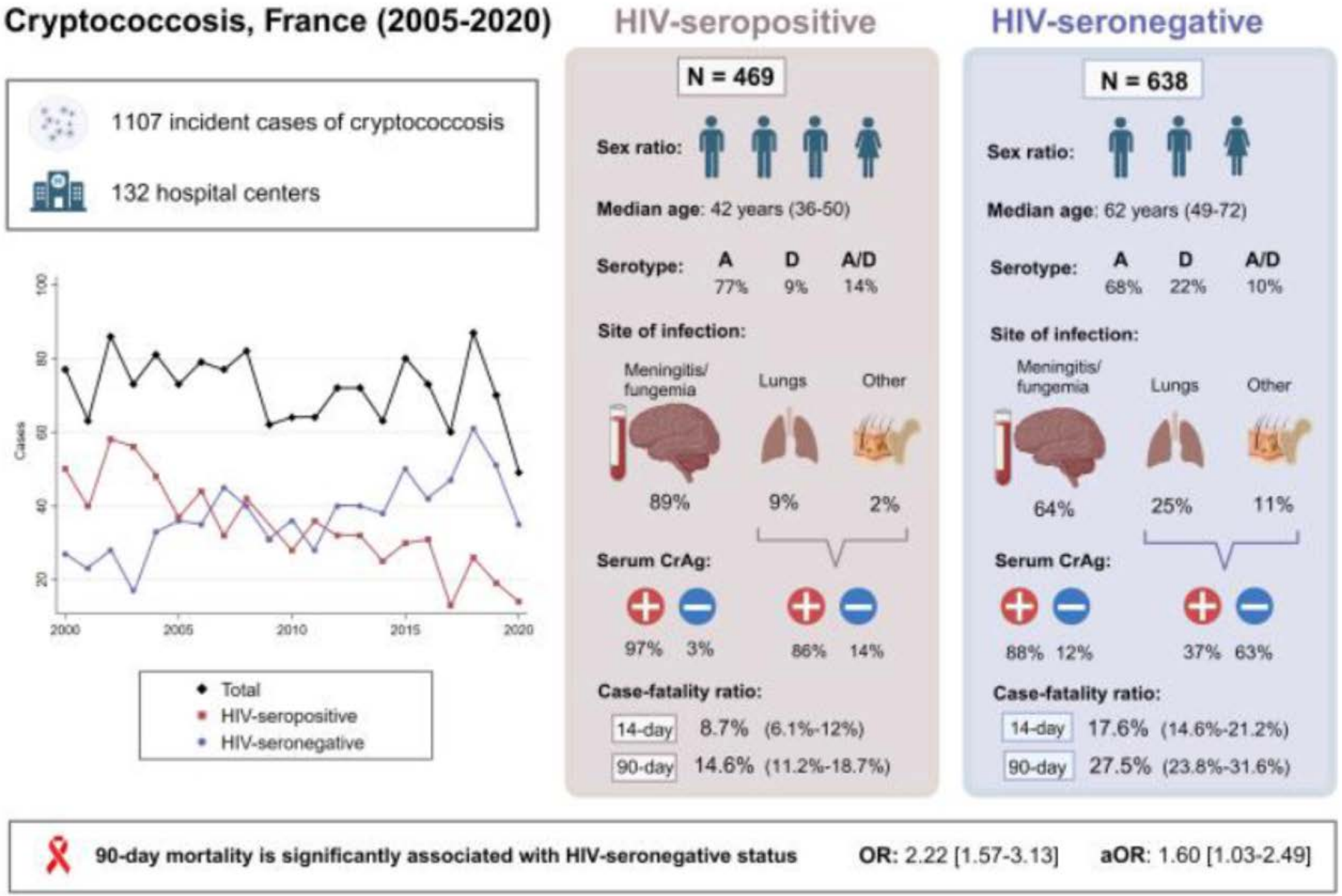
Table 4: **Factors related to outcome on univariable and multivariable analysis (N = 495).**[a]

Open Forum Infectious Diseases

BRIEF REPORT

Cryptococcus neoformans Infections Differ Among Human Immunodeficiency Virus (HIV)–Seropositive and HIV-Seronegative Individuals: Results From a Nationwide Surveillance Program in France

Olivier Paccoud,[1] Marie Desnos-Ollivier,[2] Sophie Cassaing,[3] Karine Boukris-Sitbon,[2] Alexandre Alanio,[2,4] Anne-Pauline Bellanger,[5] Christine Bonnal,[6] Julie Bonhomme,[7] Françoise Botterel,[8] Marie-Elisabeth Bougnoux,[9,10] Sophie Brun,[11] Taieb Chouaki,[12,13] Muriel Cornet,[14] Eric Dannaoui,[2,9] Magalie Demar,[15] Nicole Desbois-Nogard,[16] Marie-Fleur Durieux,[17] Loïc Favennec,[18,19] Arnaud Fekkar,[20,21] Frederic Gabriel,[22] Jean-Pierre Gangneux,[23,24] Juliette Guitard,[25] Lilia Hasseine,[26] Antoine Huguenin,[27] Solène Le Gal,[28] Valérie Letscher-Bru,[29] Caroline Mahinc,[30] Florent Morio,[31] Muriel Nicolas,[32] Célia Rouges,[33] Estelle Cateau,[34] Florence Persat,[35,36] Philippe Poirier,[37] Stéphane Ranque,[38] Gabrielle Roosen,[39] Anne-Laure Roux,[40,41] Milène Sasso,[42] Olivier Lortholary,[1,2] and Fanny Lanternier[1,2]; for the French Mycoses Study Group[a]



Clinical Microbiology and Infection xxx (xxxx) xxx

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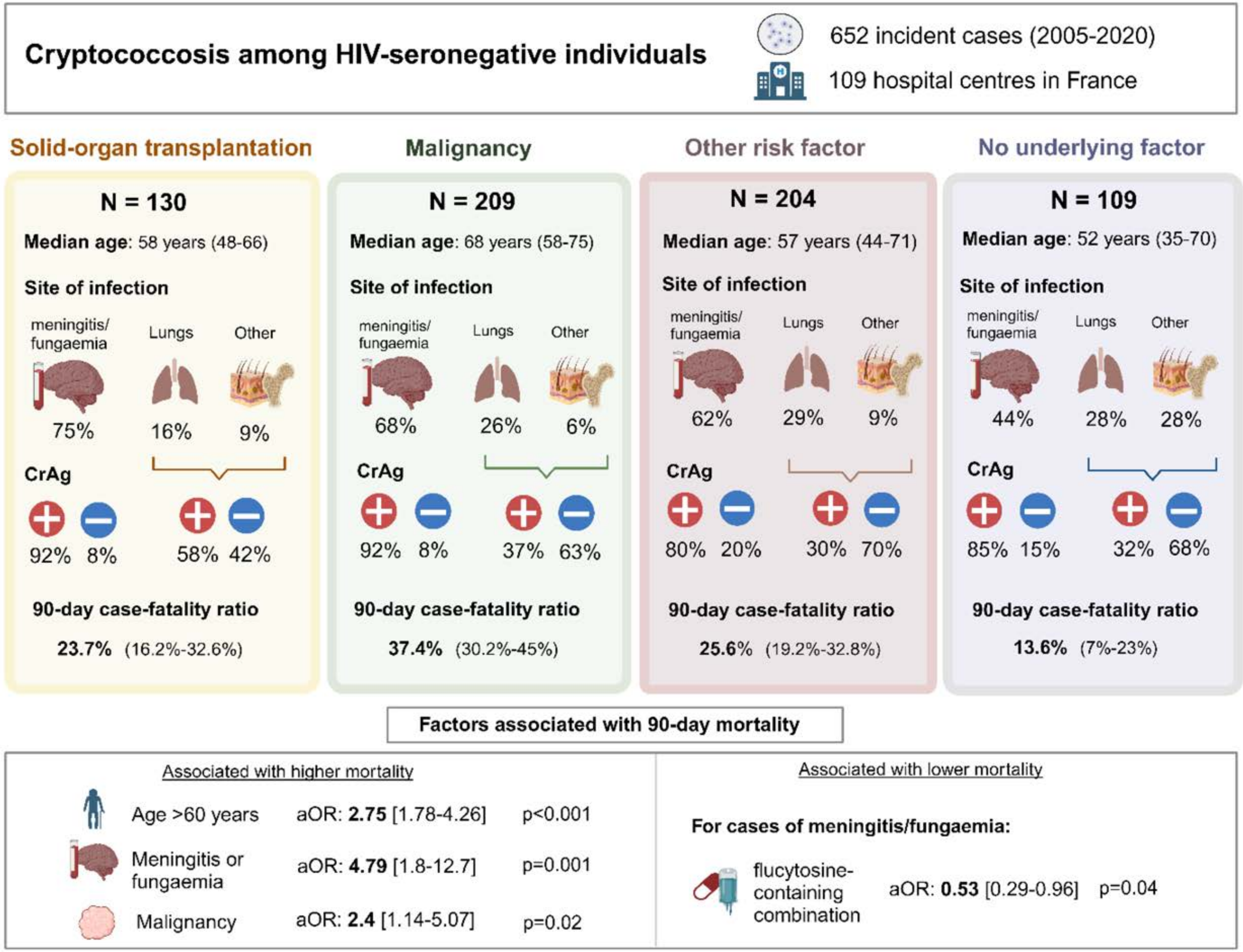
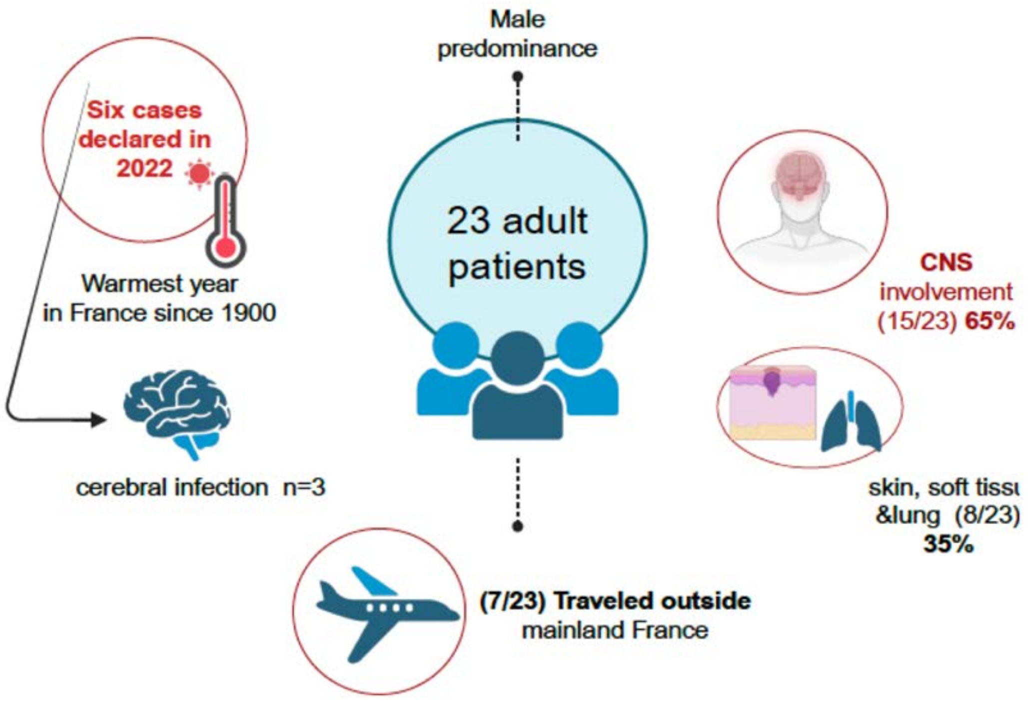
Original article

Features of cryptococcosis among 652 HIV-seronegative individuals in France: a cross-sectional observational study (2005-2020)

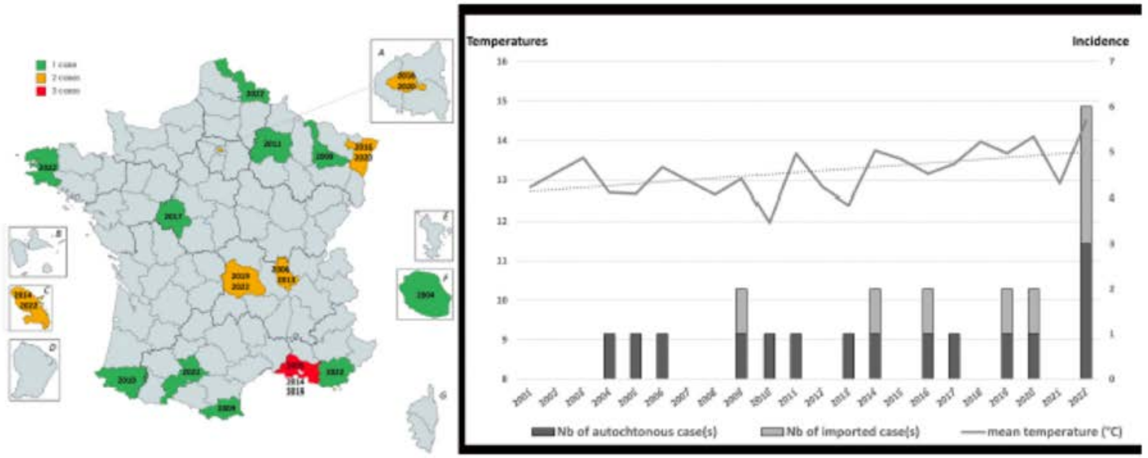
Olivier Paccoud [1,*], Marie Desnos-Ollivier [2], Florence Persat [3,4], Magalie Demar [5], Karine Boukris-Sitbon [2], Anne-Pauline Bellanger [6], Julie Bonhomme [7], Christine Bonnal [8], Françoise Botterel [9], Marie-Elisabeth Bougnoux [10,11], Sophie Brun [12], Sophie Cassaing [13], Estelle Cateau [14], Taieb Chouaki [15,16], Muriel Cornet [17], Eric Dannaoui [2,10], Nicole Desbois-Nogard [18], Marie-Fleur Durieux [19], Loïc Favennec [20,21], Arnaud Fekkar [22,23], Frederic Gabriel [24], Jean-Pierre Gangneux [25], Juliette Guitard [26], Lilia Hasseine [27], Antoine Huguenin [28], Solène Le Gal [29], Valérie Letscher-Bru [30], Caroline Mahinc [31], Florent Morio [32], Muriel Nicolas [33], Philippe Poirier [34], Stéphane Ranque [35], Gabrielle Roosen [36], Célia Rouges [37], Anne-Laure Roux [38,39], Milène Sasso [40], Alexandre Alanio [2,41], Olivier Lortholary [1,2], Fanny Lanternier [1,2], for the French Mycoses Study Group



Cladophialophora bantiana in France



- **CNS infections**: all patients with underlying diseases
- Seven cases of **skin, soft tissue, and bone infection**
- Iidentified **trauma** in four cases



Geographical and temporal representations of 23 cases of C. bantiana infections in France

Garcia-Hermoso, Lortholary et al, Lancet Microbe, in press

- French epidemiological data underlying there use
- Pre clinical data
- Clinical experience

Why do we need new antifungals

- Emergence resistant species: *Mucorales, Lomentospora, Rasamsonia, Candida auris*
- Emergence acquired resistance: azole *Aspergillus* R
- Toxicity actually avilable molecule
- Multiple azole intercation
- No oral formulation for echinocandins and polyene
- Limited diffusion in CNS, eye, urines
- Still high mortality with actual antifungals

New molecules are crucial BUT

- Preserve already avilable antifungals.
  - Exemple 5 FC IV production

- Dissemination of antifungal avilability of antifungals in endemy areas

The current state of laboratory mycology and access to antifungal treatment in Europe: a European Confederation of Medical Mycology survey

Jon Salmanton-García, Martin Hoenigl, Jean-Pierre Gangneux, Esther Segal, Ana Alastruey-Izquierdo, Sevtap Arikan Akdagli, Katrien Lagrou, Volkan Özenci, Antonio Vena, Oliver A Cornely

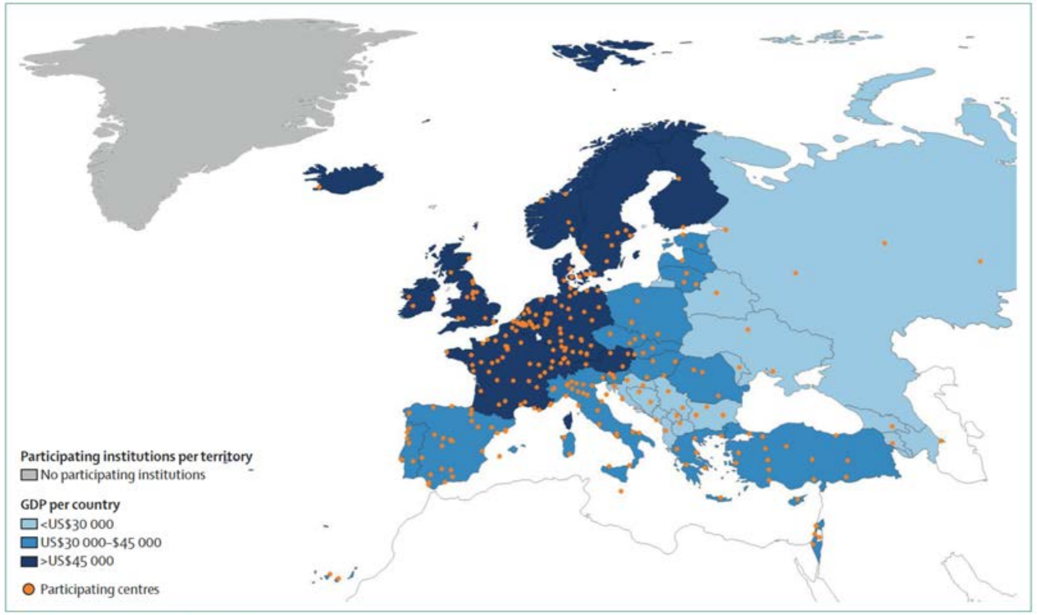


Figure 1: **Map of participating institutions per country**
Number of institutions per country with a GDP greater than US$45 000: Austria (n=4), Belgium (n=15), Denmark (n=7), Finland (n=2), France (n=44), Germany (n=40), Iceland (n=1), Ireland (n=8), Malta (n=1), Netherlands (n=7), Norway (n=4), Sweden (n=9), Switzerland (n=6), and UK (n=19). Number of institutions per country with a GDP US$30 000–$45 000: Cyprus (n=1), Czech Republic (n=6), Estonia (n=5), Greece (n=10), Hungary (n=4), Israel (n=6), Italy (n=38), Latvia (n=2), Lithuania (n=3), Poland (n=4), Portugal (n=12), Romania (n=5), Slovakia (n=5), Slovenia (n=3), Spain (n=38), and Türkiye (n=25). Number of institutions per country with a GDP less than US$30 000: Albania (n=1), Armenia (n=2), Azerbaijan (n=2), Belarus (n=2), Bosnia and Herzegovina (n=2), Bulgaria (n=4), Croatia (n=10), Georgia (n=2), Kosovo (n=1), Moldova (n=1), Montenegro (n=1), North Macedonia (n=1), Russia (n=13), Serbia (n=9), and Ukraine (n=3). In case there is more than one participating institution from the same city, a single point is pictured. GDP=gross domestic product.

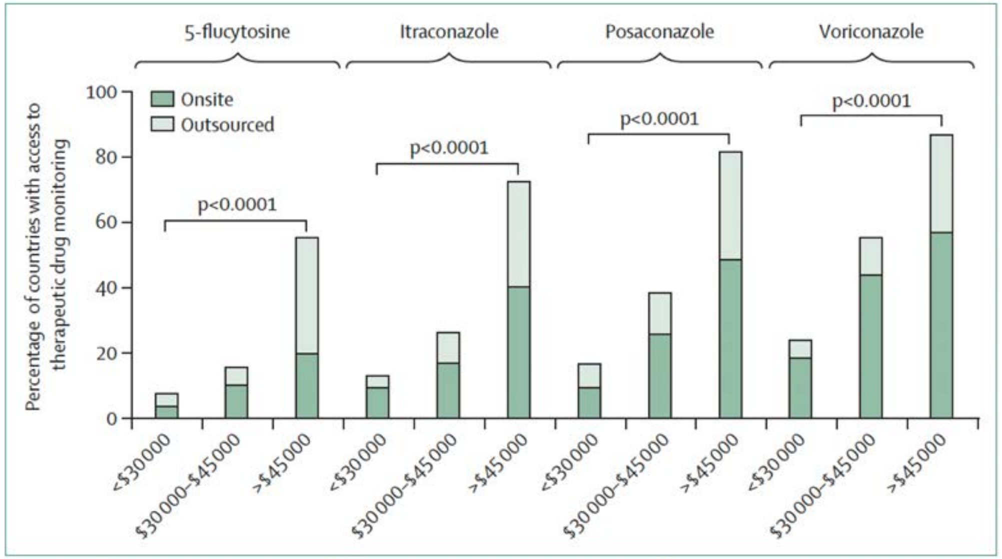


Figure 2: **Histogram of the access to therapeutic drug monitoring in analysed European institutions**
Currency is US$. χ^2 test used to obtain p value.

	All countries (total n=388)	Country division by GDP per capita			p value
		<US$30 000 (n=54)	US$30 000–$45 000 (n=167)	>US$45 000 (n=167)	
(Continued from previous page)					
Molecular tests	329 (85%)	33 (61%)	138 (83%)	158 (95%)	<0·0001†
Aspergillus PCR	256 (66%)	25 (46%)	99 (59%)	132 (79%)	<0·0001†
Onsite	150 (39%)	14 (26%)	62 (37%)	74 (44%)	..
Outsourced	106 (27%)	11 (20%)	37 (22%)	58 (35%)	..
Candida PCR	210 (54%)	24 (44%)	83 (50%)	103 (62%)	0·027†
Onsite	100 (26%)	14 (26%)	51 (31%)	35 (21%)	..
Outsourced	110 (28%)	10 (19%)	32 (19%)	68 (41%)	..
Pneumocystis PCR	288 (74%)	24 (44%)	113 (68%)	151 (90%)	<0·0001†
Onsite	217 (56%)	16 (30%)	86 (51%)	115 (69%)	..
Outsourced	71 (18%)	8 (15%)	27 (16%)	36 (22%)	..
Mucorales PCR	182 (47%)	13 (24%)	59 (35%)	110 (66%)	<0·0001†
Onsite	76 (20%)	4 (7%)	24 (14%)	48 (29%)	..
Outsourced	106 (27%)	9 (17%)	35 (21%)	62 (37%)	..
Other molecular tests	185 (48%)	15 (28%)	64 (38%)	106 (63%)	..
Onsite	101 (26%)	8 (15%)	36 (22%)	57 (34%)	..
Outsourced	84 (22%)	7 (13%)	28 (17%)	49 (29%)	..

CLSI=Clinical and Laboratory Standards Institute. ELISA=enzyme-linked immunosorbent assay. EUCAST=European Committee on Antimicrobial Susceptibility Testing. GDP=gross domestic product. LAT=latex agglutination test. LFA=lateral flow assay. LFD=lateral flow device. MALDI-TOF MS=matrix-assisted laser desorption/ionisation-time-of-flight mass spectrometry. *Compared with Fisher's Exact test. †Compared with χ^2 test. ‡*Aspergillus*-specific LFD is a tool used in clinical microbiology to detect extracellular mannoprotein antigen secretion, which is only active when there is *Aspergillus* growing, by using the JF5 monoclonal antibody.[23] §*Aspergillus*-specific LFA is a tool capable of detecting galactomannan and has a shorter turnaround time as compared with ELISA.[23]

Table 2: **Comparison of available diagnostic techniques for mycological diagnosis in Europe**

Diagnostic et disponibilité des AF en Europe

Yeasts EUCAST MIC from surveillance data

Espèces étudiées	Valeurs des CMI50 / CMI90 mg/L pour les antifongiques*						
Nom d'usage en clinique (nbre d'isolats testés)	AMB	5-FC	Fluco	Vori	Posa	Caspo**	Mica**
***Candida albicans* (n=3621)**	0.06/0.12	≤0.12/0.5	0.25/0.5	≤0.01/≤0.01	≤0.01/0.06	0.03/0.06	0.03/0.03
***C. dubliniensis* (n=162)**	≤0.014/0.03	≤0.12/≤0.12	≤0.12/0.25	≤0.01/≤0.01	0.03/0.06	0.015/0.03	0.015/0.03
***C. glabrata* (n=1420)**	0.12/0.25	≤0.12/≤0.12	16/64	0.25/1	0.5/2	0.06/0.12	0.015/0.03
***C. nivariensis* (n=17)**	0.12/0.25	0.5/1	4/8	0.06/0.12	0.12/0.25	0.03/0.12	0.015/0.03
***C. parapsilosis* (n=943)**	0.06/0.12	≤0.12/0.25	0.5/2	≤0.01/0.06	0.06/0.12	0.25/1	0.25/0.5
***C. orthopsilosis* (n=70)**	0.03/0.06	≤0.12/≤0.12	0.5/8	0.03/1	0.06/0.12	0.06/0.25	0.12/0.25
***C. metapsilosis* (n=57)**	0.06/0.12	≤0.12/≤0.25	1/2	0.03/0.06	0.03/0.12	0.06/0.12	0.12/0.25
***C. tropicalis* (n=707)**	0.06/0.12	≤0.12/32	0.5/4	0.03/0.25	0.06/0.25	0.03/0.06	0.03/0.03
***Pichia kudriavzevii* (n=376)**	0.12/0.25	2/4	32/64	0.25/0.5	0.12/0.25	0.12/0.25	0.06/0.12
***P. cactophila* (n=51)**	0.12/0.25	2/4	16/32	0.12/0.25	0.12/0.12	0.03/0.06	0.015/0.03
***Kluyveromyces marxianus* (n=185)**	0.06/0.12	0.5/8	0.25/1	≤0.01/≤0.01	0.06/0.12	0.015/0.03	0.03/0.06
***Meyerozyma guilliermondii* (n=125)**	0.03/0.06	≤0.12/0.25	8/64	0.06/0.5	0.25/0.5	0.06/0.25	0.12/0.25
***M. caribbica* (n=39)**	0.12/0.25	≤0.12/≤0.12	4/64	0.12/0.5	0.25/0.5	0.12/0.5	0.12/2
***Clavispora lusitaniae* (n=265)**	0.06/0.12	≤0.12/0.5	0.25/0.5	≤0.01/≤0.01	≤0.01/0.06	0.03/0.06	0.03/0.06
***C. haemulonii* (n=50)**	0.5/2	≤0.12/0.5	32/≥64	≥8/≥8	2/≥8	0.03/0.06	0.06/0.06
***C. duobushaemulonii* (n=47)**	2/8	≤0.12/≥64	32/≥64	≥8/≥8	2/≥8	0.015/0.03	0.03/0.06
***C. auris* (n=17)**	0.25/0.5	≤0.12/≥64	32/≥64	0.5/1	≤0.01/0.25	0.03/0.06	0.015/0.03

Fluconazole high MIC

Fluconazole and echino high MIC

***Geotrichum candidum* (n=40)**	0.25/0.5	0.25/1	16/64	0.25/1	0.25/1	1/≥8	0.5/≥8
***Magnusiomyces capitatus* (n=60)**	0.25/0.5	≤0.12/0.25	8/16	0.06/0.5	0.12/1	≥8/≥8	≥8/≥8
***Saprochaete clavata* (n=207)**	0.25/0.5	0.5/1	16/64	0.25/1	0.5/1	≥8/≥8	≥8/≥8
***Cr. neoformans* (n=1040)**	0.12/0.5	4/16	4/8	0.03/0.12	0.06/0.25	≥8/ ≥8	4/≥8
***Cr. deneoformans* (n=228)**	0.06/0.25	4/16	1/4	≤0.01/0.06	0.03/0.12	≥8/ ≥8	1/≥8
***Cr. neoformans* hybrides AD (n=186)**	0.12/0.25	4/16	4/8	0.03/0.12	0.06/0.25	≥8/ ≥8	4/≥8
***Cr. gattii* (n = 34)**	0.12/0.25	2/8	8/16	0.12/0.5	0.25/0.5	≥8/ ≥8	≥8/≥8
***Rhodotorula mucilaginosa* (n=67)**	0.25/0.5	0.25/0.5	≥64/≥64	2/4	0.5/2	≥8/ ≥8	≥8/≥8
***Trichosporon asahii* (n=68)**	2/≥8	32/≥64	4/16	0.06/0.25	0.25/0.5	≥8/≥8	≥8/≥8
***Trichosporon inkin* (n=16)**	0.25/2	64/≥64	1/4	≤0.01/0.06	0.06/0.25	4/≥8	1/≥8

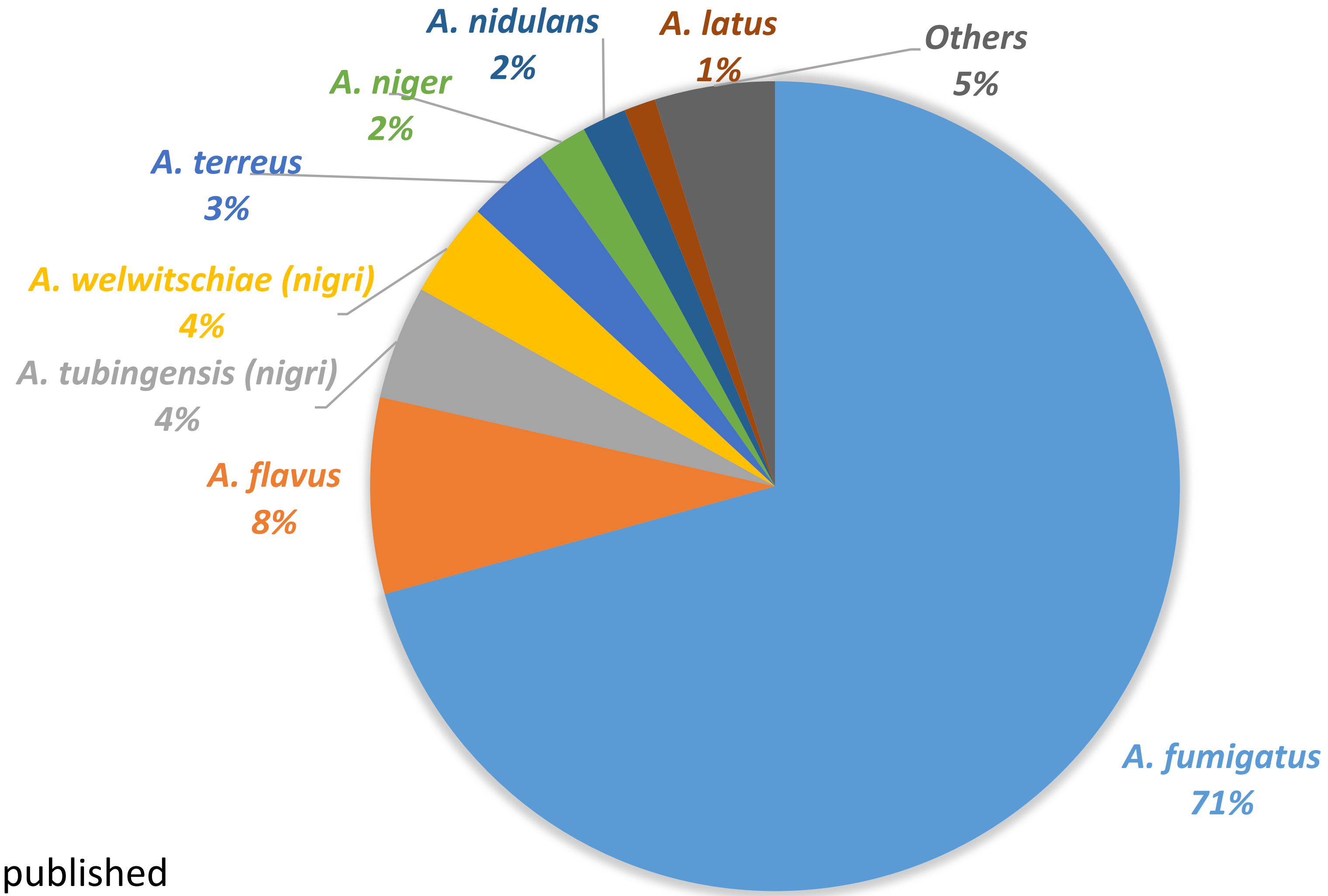
https://www.pasteur.fr/sites/default/files/cmi_lev.pdf

CNRMA IFI

NRCMA data, unpublished

Repartition of aspergillosis in 2023

581 invasive aspergillosis in 2023
Mortality 44%



NRCMA data, unpublished

Molds EUCAST MIC from surveillance data

Espèce (nombre d'isolats testés)	AMB	Itra	Vori	Posa	Caspo	Mica	Terbi
Aspergillus nidulans (n=37)	2/8	0.12/0.5	0.12/0.2	0.06/0.2	0.5/4	0.015/0.06	0.12/0.5
Aspergillus quadrilineatus (n=17)	0.5/1	0.12/0.25	0.12/0.2	0.12/0.2	2/2	≤0.007/0.03	0.12/0.12
Aspergillus section Nigri (n=24)	0.25/0.5		0.5/1	0.25/0.5	0.25/0.5	0.01/0.25	0.12/0.25
Aspergillus tubingensis (n=29)	0.25/0.5	1/8	1/2	0.25/0.5	0.25/0.5	≤0.007/0.01	0.25/0.25
Aspergillus welwitschiae (n=22)	0.5/1	1/2	0.5/1	0.25/0.5	0.25/0.5	0.007/0.015	0.12/0.25
Aspergillus section Usti (n=28)	0.5/1	2/≥8	4/8	≥8/≥8	2/≥8	0.25/4	0.25/0.5
Aspergillus calidoustus (n=27)	1/2	≥8/≥8	4/8	≥8/≥8	0.5/4	0.015/0.06	0.25/0.5
Aspergillus terreus (n=58)	4/8	0.06/0.25	0.5/1	0.06/0.1	0.5/1	≤0.007/0.03	0.06/0.12
Aspergillus sydowii (n=7)	2/-	0.5/-	0.5/-	0.25/-	0.12/-	≤0.007/-	0.06/-
Aspergillus versicolor (n=9)	1/-	0.25/-	0.25/-	0.12/-	0.5/-	0.03/-	0.25/-

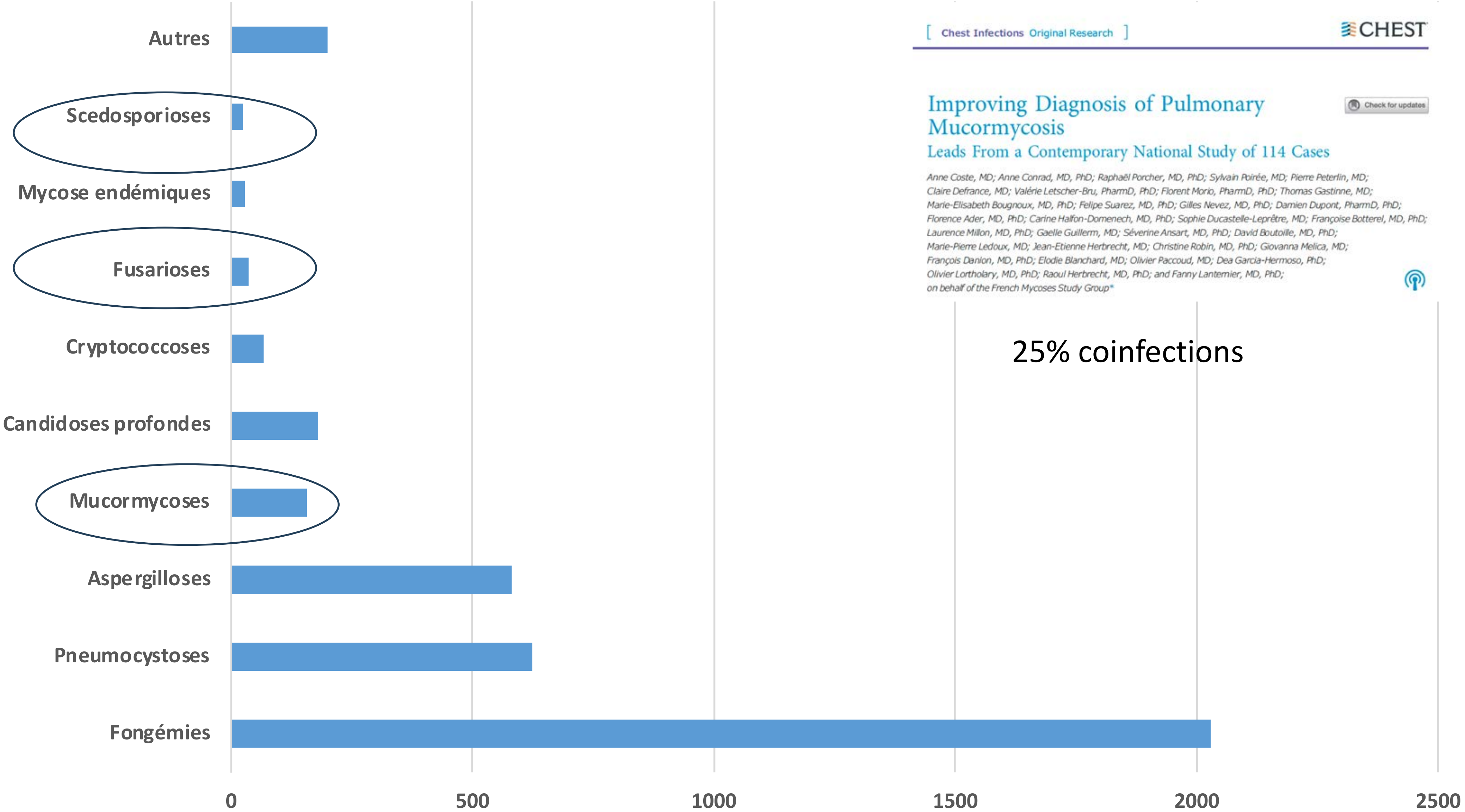
Also A. fumigatus azole R

https://www.pasteur.fr/sites/default/files/cmi_fil.pdf

CNRMA IFI

NRCMA data, unpublished

IFD in France 2023, Other Non Aspergillus mold



[Chest Infections Original Research]

CHEST

Improving Diagnosis of Pulmonary Mucormycosis

Leads From a Contemporary National Study of 114 Cases

Check for updates

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25% coinfections

NRCMA data, unpublished

Molds EUCAST MIC from surveillance data

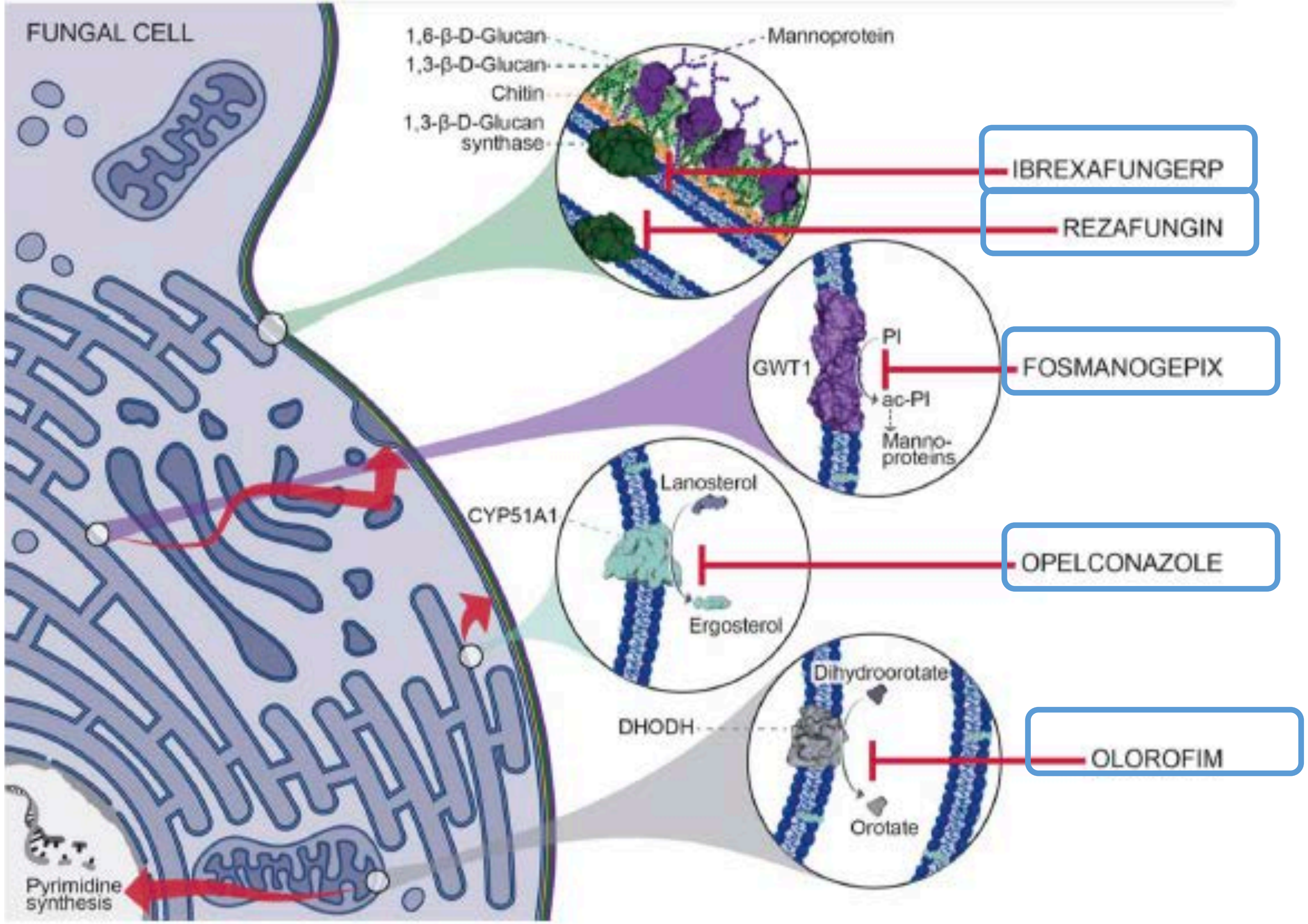
Penicillium spp. (n=27)	0.5/4	1/≥8	8/≥8	1/≥8	2/≥8	0.12/2	0.25/1
Penicillium chrysogenum (n=8)	0.5/-	0.25/-	1/-	0.25/-	0.5/-	0.03/-	0.25/-
Espèce (nombre d'isolats testés)	**AMB**	**Itra**	**Vori**	**Posa**	**Caspo**	**Mica**	**Terbi**
Paecilomyces variotii (n=15)	0.06/0.5	0.12/0.5	8/≥8	0.12/0.5	2/4	0.03/0.25	1/8
Fusarium solani complex (n=249)	4/8	≥8/≥8	8/≥8	≥8/≥8	≥8/≥8	≥8/≥8	≥8/≥8
Fusarium falciforme (n=15)	2/8	8/≥8	8/≥8	≥8/≥8	8/8	8/8	≥8/≥8
Fusarium oxysporum complex (n=185)	2/4	≥8/≥8	2/8	2/≥8	≥8/≥8	≥8/≥8	2/4
Fusarium proliferatum (n=138)	4/8	≥8/≥8	4/8	8/≥8	8/≥8	8/≥8	1/2
Fusarium verticillioides (n=29)	8/8	≥8/≥8	2/4	0.5/1	8/≥8	8/≥8	0.5/1
Bisifusarium dimerum (n= 35)	0.25/0.5	≥8/≥8	2/4	≥8/≥8	≥8/≥8	≥8/≥8	0.5/1
Fusarium incarnatum-equiseti complex (n=6)	1/-	≥8/-	2/-	1/-	≥8/-	≥8/-	4/-
Sarocladium kiliense (n=11)	8/≥8	≥8/≥8	0.5/1	1/≥8	4/≥8	4/≥8	0.5/0.5
Purpureocillium lilacinum (n=55)	8/≥8	2/≥8	0.25/0.5	0.25/0.5	≥8/≥8	2/≥8	0.25/0.5
Trichoderma spp. (n=8)	1/-	≥8/-	1/-	8/-	0.5/-	0.06/-	2/-
Trichoderma longibrachiatum (n=25)	1/2	≥8/≥8	0.5/1	1/2	0.5/1	0.06/0.25	1/2
Phaeoacremonium parasiticum (n=25)	0.5/2	≥8/≥8	0.25/0.2	0.25/0.5	≥8/≥8	≥8/≥8	0.12/0.5
Pleurostomophora richardsiae (n=7)	0.25/-	0.25/-	0.5/-	0.25/-	4/-	1/-	1/-
Coniochaeta hoffmannii (n=7)	0.25/-	0.25/-	1/-	0.12/-	2/-	2/-	0.25/-
Thermothelomyces thermophilus (n=9)	1/-	0.12/-	0.12/-	0.06/-	4/-	0.5/-	2/-
Sporothrix schenckii (n=20)	1/2	0.5/1	8/≥8	0.5/1	≥8/≥8	≥8/≥8	0.06/0.12
Sporothrix globosa (n=5)	8/-	1/-	≥8/≥8	1/2	≥8/-	1/-	0.25
Scedosporium apiospermum (n=118)	8/≥8	1/8	0.5/1	0.5/1	1/2	0.25/1	≥8/≥8
Scedosporium boydii (n=48)	8/≥8	0.5/8	0.25/0.5	0.25/1	1/2	0.25/1	≥8/≥8
Scedosporium ellipsoideum (n=9)	≥8/-	1/-	0.5/-	1/-	0.5/-	0.25/-	≥8/-
Scedosporium aurantiacum (n=9)	8/-	8/-	0.5/-	1/-	8/-	8/-	≥8/-
Scedosporium dehoogii (n=10)	8/≥8	0.5/1	0.25/0.5	0.5/1	2/2	0.25/0.5	≥8/≥8
Scedosporium minutisporum (n=5)	8/-	0.5/-	0.25/-	0.5/-	2/-	0.25/-	≥8/-
Lomentospora prolificans (n=40)	8/≥8	≥8/≥8	8/≥8	≥8/≥8	4/≥8	4/≥8	≥8/≥8
Microascus cirrosus (n=9)	8/-	≥8/-	≥8/-	≥8/-	4/-	≥8/-	2/-
Scopulariopsis brevicaulis (n=21)	8/≥8	≥8/≥8	8/≥8	≥8/≥8	1/4	0.25/1	2/8

https://www.pasteur.fr/sites/default/files/cmi_fil.pdf

CNRMA
IFI

NRCMA data, unpublished

New molecules



- Triterpenoid
- Inhibit 1-3 beta D glucane synthase
- Anidulafungin analog

- Inhibit GWT1
- Inhibit mannoprotein synthesis

- Inhaled triazol

- Orotomid
- Inhibit DHOH
  (Dihydroorotate dehydrogenase), synthèse pyrimidine

Hoenigl M, Drugs 2021

Fosmanogepix

- New class
- Small molecule inhibits GPI-anchored wall transfer protein 1 (Gwt1)
- prodrogue converted in active molecule active (i.e. manogepix) by phosphatase
- Effects:
  - Alters wall integrity
  - Increases exposed beta D glucan immunogenicity
  - Inhibits biofilm formation and hyphae

Antimicrobial Agents and Chemotherapy

Antimicrobial Chemotherapy | Full-Length Text

In vitro activity of manogepix and comparators against infrequently encountered yeast and mold isolates from the SENTRY Surveillance Program (2017–2022)

Michael Pfaller,[1,2] Michael Huband,[1] Paul A. Bien,[3] Cecilia G. Carvalhaes,[1] Abby Klauer,[1] Mariana Castanheira[1]

Fosmanogepix MIC and yeasts

Organism (no. tested)	MIC range	MIC_{50}	MIC_{90}
Trichosporon mycotoxinivorans (5) (*Apiotrichum mycotoxinivorans*)	0.5–> 2	>2	–
Blastobotrys adeninivorans (1)	0.004	–	–
Candida spp. (776)	≤0.002–2	0.008	0.12
C. auris (77)	≤0.002–0.06	0.016	0.03
C. bracarensis (4) (*Nakaseomyces bracarensis*)	0.004–0.03	0.008	–
C. dubliniensis (221)	≤0.002–0.03	0.004	0.008
C. duobushaemulonii (4)	≤0.002–0.004	≤0.002	
C. fabianii (10) (*Cyberlindnera fabianii*)	≤0.002–0.004	0.004	0.004
C. fermentati (33) (*Meyerozyma caribbica*)	≤0.002–0.06	0.008	0.06
C. guilliermondii (27) (*Meyerozyma guilliermondii*)	0.004–0.016	0.008	0.016
C. haemulonii (6)	≤0.002–0.004	≤0.002	–
C. inconspicua (6) (*Pichia cactophila*)	0.5–2	2	–
C. intermedia (2)	0.004–0.03	0.004	–
C. kefyr (78)	0.03–1	0.12	0.5
C. krusei (202)	0.25–>2	>2	>2
C. lipolytica (7) (*Yarrowia lipolytica*)	0.006–0.06	0.03	–
C. lusitaniae (150) (*Clavispora lusitaniae*)	0.004–0.5	0.03	0.06
C. metapsilosis (34)	0.004–0.03	0.008	0.008
C. nivariensis (6) (*Nakaseomyces nivariensis*)	≤0.002–0.008	0.004	–
C. norvegensis (7) (*Pichia norvegensis*)	0.12–1	0.5	–
C. orthopsilosis (66)	0.004–0.03	0.008	0.016
C. pararugosa (3) (*Diutina pararugosa*)	≤0.002	≤0.002	–
C. pelliculosa (13) (*Wickerhamomyces anomalus*)	≤0.002	≤0.002	≤0.002

Organism (no. tested)	MIC range	MIC_{50}	MIC_{90}
C. pseudohaemulonii (2)	0.004	0.004	–
C. quercitrusa (1)	0.016	–	–
C. rugosa (5) (*Diutina rugosa*)	0.004–0.03	0.016	–
C. spencermartinsiae (1)	0.008	–	–
C. sphaerica (3)	0.06–0.25	0.06	–
C. theae (2)	0.004	0.004	–
C. utilis (7)	≤0.002–0.008	≤0.002	–
Cryptococcus gattii species complex (6)	0.12–2	0.25	–
C. laurentii (1) (*Papiliotrema laurentii*)	0.25	–	–
C. neoformans (178) (*C. neoformans* var. *grubii*)	0.016–4	0.25	1
C. deneoformans (13) (*C. neoformans* var. *neoformans*)	0.03–1	0.25	0.5
Hyphopichia burtonii (1)	0.001		
Kodamaea ohmeri (4)	0.008–0.016	0.008	–
Lodderomyces elongisporus (1)	0.004	–	–
Saprochaete (*Magnusiomyces*) *capitatus* (4)	0.016–0.06	0.016	–
Saprochaete (*Magnusiomyces*) *clavatus* (14)	0.016–0.06	0.03	0.06
Ogataea siamensis (1)	0.03	–	–
Pichia cactophila (2)	0.5–1	0.5	–
P. kluyveri (1)	0.06	–	–
Rhodotorula minuta (1)	0.016	–	–
R. mucilaginosa (18)	0.016–0.5	0.03	0.12
Saccharomyces cerevisiae (28)	0.008–0.06	0.016	0.03
Trichosporon asahii (26)	0.25–> 2	>2	>2
T. capitatum (1)	0.03	–	–
T. inkin (2)	1–2	1	–
T. loubieri (1) (*Apiotrichum loubieri*)	0.5	–	–
T. mucoides (2) (*Cutaneotrichosporon mucoides*)	>2	>2	–

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Antimicrobial Chemotherapy | Full-Length Text

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Fosmanogepix MIC and molds

Organism (no. tested)	MIC range
Scedosporium apiospermum/S. boydii (58)	0.004–0.5
S. aurantiacum (11)	0.016–0.06
S. dehoogi (3)	0.03–0.06
S. minutisporum (2)	0.008–0.016
Scopulariopsis brevicaulis/S. brumptii (3)	≤0.002–0.00
Trichoderma longibrachiatum (1)	0.06
Verruconis gallopava (2)	0.5–1

Alternaria alternata (1)	1	–	–
Aspergillus alabamensis (1)	0.008	–	–
A. brasiliensis (2)	0.008–0.016	0.008	–
A. clavatus (2)	0.03	0.03	–
A. flavus species complex (173)	0.004–0.12	0.016	0.06
A. fumisynnematus (1)	0.008	–	–
A. hortai (1)	0.008	–	–
A. lentulus (7)	0.008–0.016	0.008	–
A. melleus (1)	0.016	–	–
A. nidulans species complex (42)	0.008–0.03	0.016	0.03
A. niger species complex (185)	≤0.008–0.12	≤0.008	0.016
A. nomius (1)	0.008	–	–
A. ochraceus species complex (1)	0.12	–	–
A. parasiticus (3)	0.008–0.016	0.008	–
A. sclerotiorum (3)	0.016–0.03	0.016	–
A. sydowii (4)	0.002–0.016	0.016	–
A. tamarii (3)	0.03–0.06	0.03	–
A. terreus species complex (71)	0.004–0.03	0.016	0.03
A. thermomutatus (2)	0.06–0.25	0.06	–
A. tubingensis (23)	≤0.008–0.03	≤0.008	0.03
A. udagawae (2)	0.016	0.016	–
A. unguis (3)	0.03	0.03	–
A. ustus species complex (12)	≤0.008–0.016	≤0.008	0.016
A. versicolor (7)	≤0.002–0.03	0.016	–
A. welwitschiae (1)	0.016	–	–
Aureobasidium pullulans (2)	0.008	–	–
Coprinopsis cinerea (1)	0.004	–	–
Exophiala attenuata (2)	0.008–0.016	0.008	–
E. dermatitidis (10)	≤0.008	≤0.008	≤0.008
Fusarium annalatum (2)	0.008–0.03	0.008	–

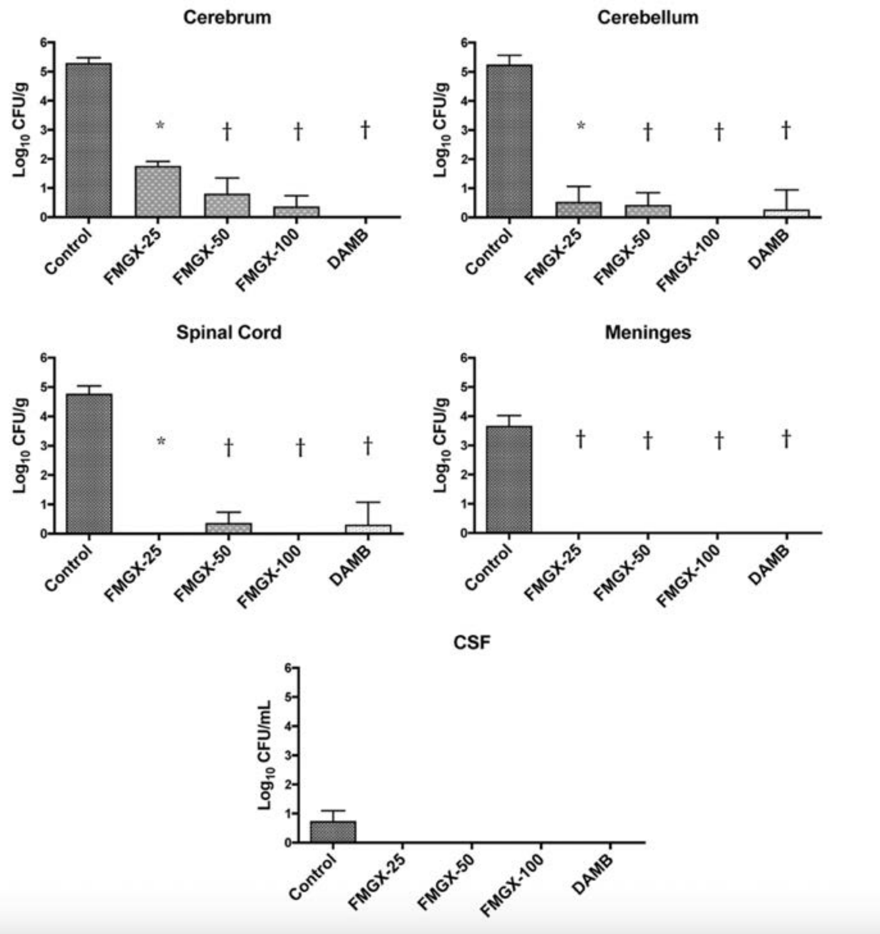
Organism (no. tested)	MIC range	MIC_{50}	MIC_{90}
F. dimerum species complex (1)	0.06	–	–
F. falciforme (1)	0.016	–	–
F. incarnatum-equiseti species complex (4)	≤0.002–8	0.12	–
F. oxysporum species complex (8)	0.008–4	0.03	–
F. petroliphilum (1)	0.016	–	–
F. solani species complex (29)	0.004–0.03	0.016	0.03
F. (Gibberella) fujikuroi species complex (21)	≤0.008–0.12	0.016	0.03
Lichtheimia corymbifera (8)	4–>4	>4	–
L. ramosa (1)	>4	–	–
Lomentospora prolificans (19)	0.004–0.06	0.03	0.06
Medicopsis romeroi (2)	0.03–0.12	0.03	–
Microascus cirrosus (1)	0.008	–	–
Monascus ruber (1)	0.03	–	–
Mucor circinelloides (8)	0.25–>4	2	–
M. circinelloides/M. ramosissimus (2)	1–2	1	–
M. indicus (1)	1	–	–
Paecilomyces variotii (10)	≤0.008	≤0.008	≤0.008
Penicillium citrinum (1)	0.008	–	–
P. onobense (1)	0.008	–	–
Pleurostomophora parasiticum (1)	0.06	–	–
P. richardsiae (1)	0.06	–	–
Pseudopithomyces sacchari (1)	0.25	–	–
Purpureocillium lilacinum (Paecilomyces lilacinus) (15)	≤0.008–0.016	≤0.008	0.016
Rasamsonia argillacea species complex (12)	≤0.008–0.016	≤0.008	0.016
Rhizomucor pusillus (6)	1–>4	4	–
Rhizopus microsporus group (24)	2–> 4	4	>4
Rhizopus oryzae species complex (19)	0.5–>4	>4	>4
Sarocladium kiliense (4)	0.016–0.12	0.03	–

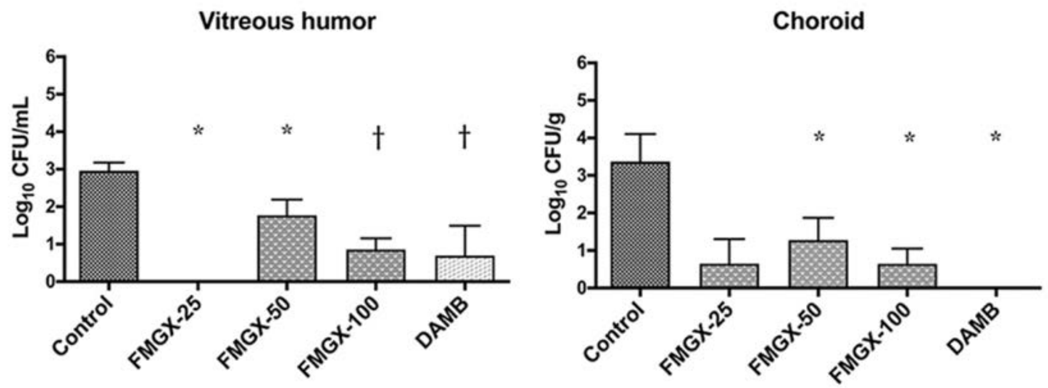
AMERICAN SOCIETY FOR MICROBIOLOGY Antimicrobial Agents and Chemotherapy®

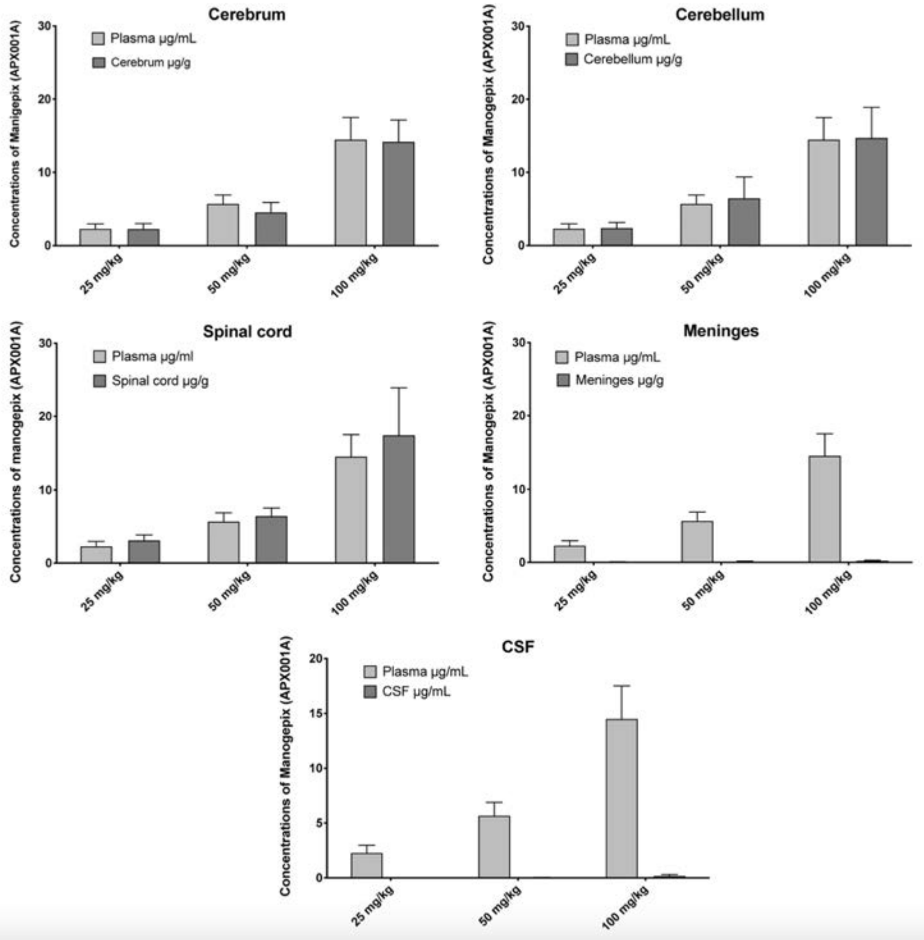
EXPERIMENTAL THERAPEUTICS

Efficacy and Pharmacokinetics of Fosmanogepix (APX001) in the Treatment of *Candida* Endophthalmitis and Hematogenous Meningoencephalitis in Nonneutropenic Rabbits

Ruta Petraitiene,[a] Vidmantas Petraitis,[a] Bo Bo Win Maung,[a] Robert S. Mansbach,[b] Michael R. Hodges,[c] Malcolm A. Finkelman,[d] Karen Joy Shaw,[e] Thomas J. Walsh[a,f,g]







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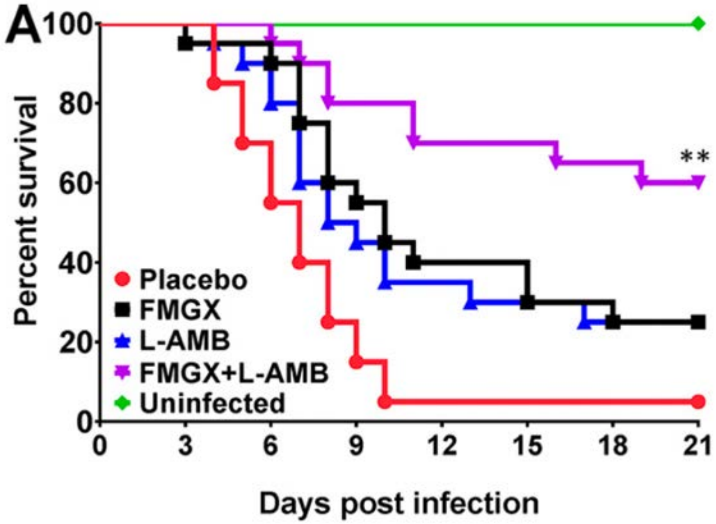
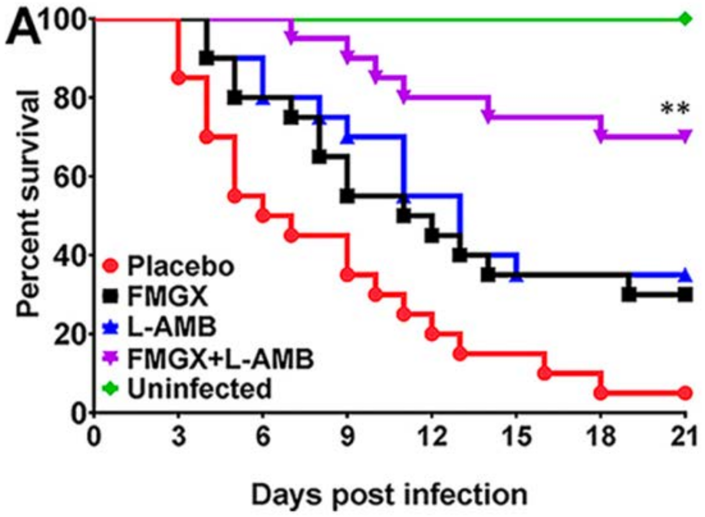
EXPERIMENTAL THERAPEUTICS

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]

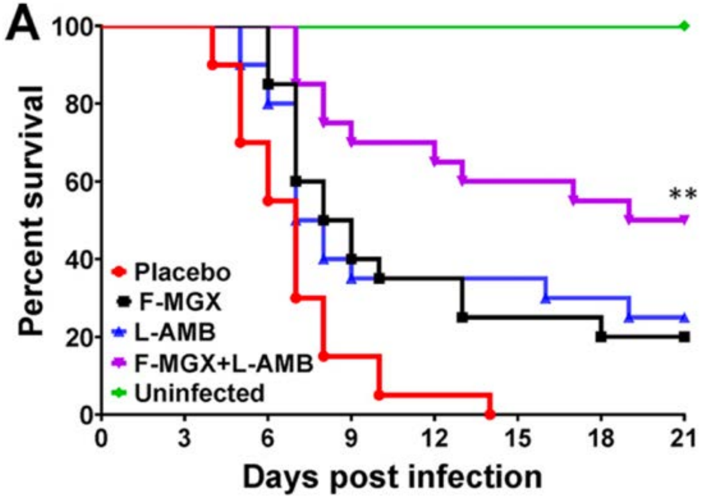


A. fumigatus



R. arrhizus

Mice model
Infection via inhalation

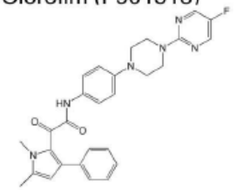


F. solani

Olorofim

- Orotomid
- Selective inhibitor of fungal DHODH (Dihydroorotate dehydrogenase)
  - Pyrimidine synthesis
- Oral
- Interfer with synthesis ADN, ARN, wall
- Lysis

Olorofim (F901318)



Orotomide - Reversible inhibition of dihydroorotate dehydrogenase, part of pyrimidine biosynthesis (*DHODH*)

- Diffusion: kidney, liver, lung, CNS (lower level)
- Oral: 45% biodisponibility
- Metabolised several CYP450 enzymes including CYP3A4
  - CI rifampicine
  - Modification dose anticalcineurine
  - Reduction dose olorofim with azoles

Oliver, J., Sibley, G., Beckmann, N., Dobb, K., Slater, M., McEntee, L., Pré, S., Livermore, J., Bromley, M., Wiederhold, N., Hope, W., Kennedy, A., Law, D., Birch, M. (2016). ***F901318 represents a novel class of antifungal drug that inhibits dihydroorotate dehydrogenase*** *Proceedings of the National Academy of Sciences 113(45), 12809-12814.*
https://dx.doi.org/10.1073/pnas.1608304113

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Short Communication

In vitro activity of olorofim (F901318) against fungi of the genus, *Scedosporium* and *Rasamsonia* as well as against *Lomentospora prolificans, Exophiala dermatitidis* and azole-resistant *Aspergillus fumigatus*

Lisa Kirchhoff[a], Silke Dittmer[a], Jan Buer[a], Peter-Michael Rath[a], Joerg Steinmann[a,b,*]

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[b] Institute for Clinical Hygiene, Medical Microbiology and Infectiology, Klinikum Nuernberg, Paracelsus Medical University, Prof.-Ernst-Nathan-Str. 1, 90419 Nuremberg, Germany

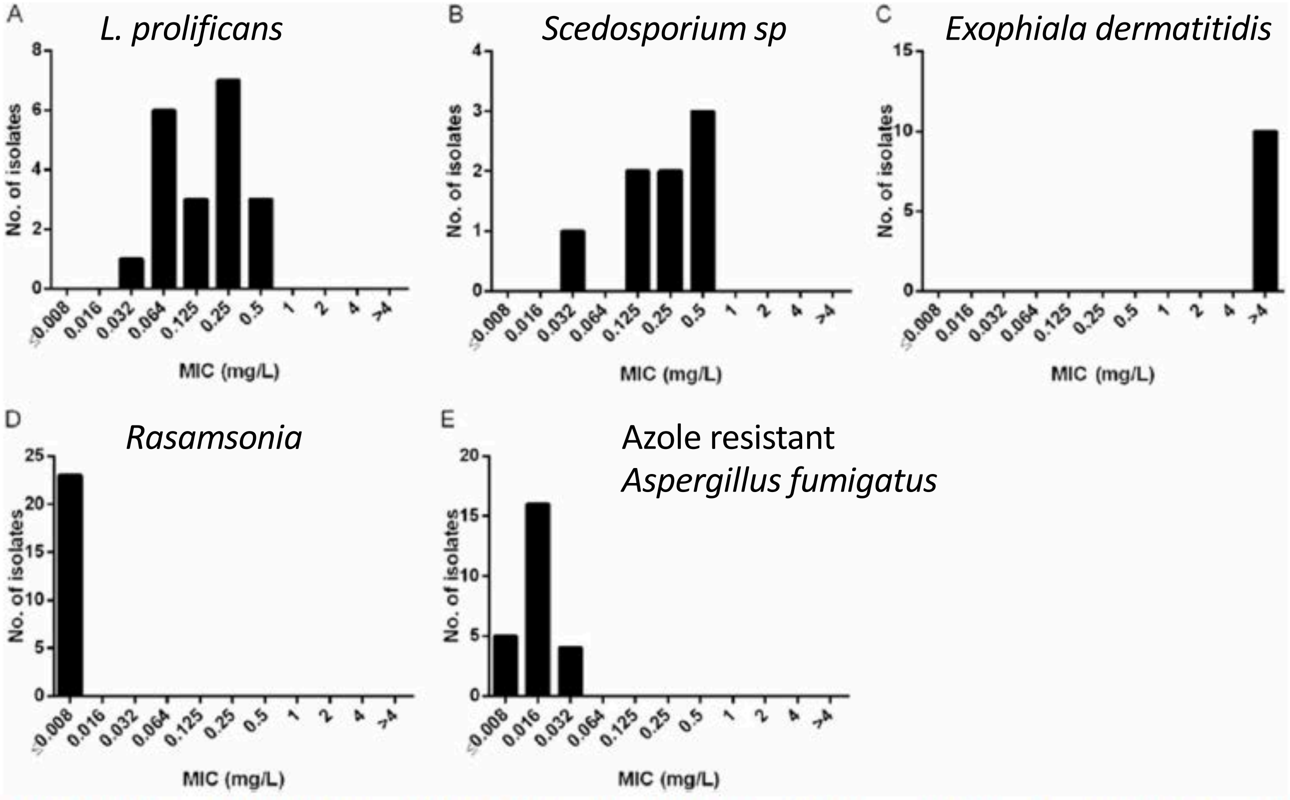


Fig. 1. Minimum inhibitory concentrations (MIC) for olorofim against (A) *Lomentospora prolificans* ($n = 20$), (B) *Scedosporium* spp. ($n = 8$), (C) *Exophiala dermatitidis* ($n = 10$), (D) *Rasamsonia argillacea* species complex ($n = 23$) and (E) azole-resistant *Aspergillus fumigatus* ($n = 25$).

INSTITUT PASTEUR

In vitro activity of olorofim against clinically relevant filamentous fungi collected at the French Reference Center for Invasive Mycosis & Antifungals (NCRMA)

Dea Garcia-Hermoso [1], Emilie Fruquiere [1], Fanny Lanternier [1]

Centre National de Référence Mycoses Invasives et Antifongiques, Institut Pasteur, Paris, France

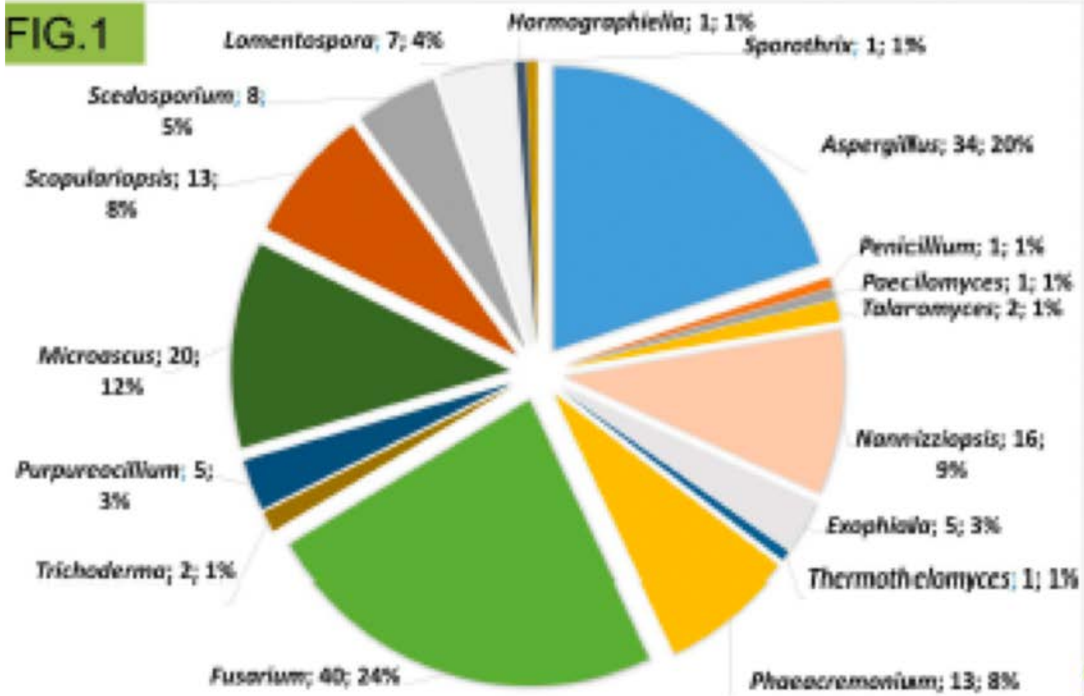
More than 160 clinical isolates morphologically and molecularly identified were tested.

Isolates were distributed among 9 Orders and 17 different genera with a variable number of species per genus (1 to 40) (Fig.1)

In vitro susceptibility testing was performed according to the EUCAST procedure for molds. The MIC testing range (mg/L) was 0.008 to 4. Minimal inhibitory concentrations (MICs) were defined as using an spectrophotometer where 90% growth inhibition defined the endpoint.

Considering that there are no olorofim breakpoints available, an isolate was considered susceptible if the olorofim MIC was lower than or equivalent ≤0.5 mg/L.

FIG.1



Results

Olorofim values (mg/L)	Section or species complex	no. isolates	Species
Low MICs (range 0.007-0.25)	*Aspergillus* sect. *Terrei*	4	*A. terreus (1), A. alabamensis (2)* *A. flocossus (1)*
	Aspergillus sect. *Nidulantes*	6	*A. latus (1); A. nidulans sp. complex (3)* *A. sydowii (2)*
	Aspergillus sect. *Circumdati*	2	*A.persii (1)* *A. sclerotiorum (1)*
MIC50/90 [0.03/0.03]	*Aspergillus fumigatus*	6	Activity was not impaired for the azole-resistant *Aspergillus fumigatus*
Low MICs (range from 0.015 to 0.06)	*Fusarium fujikuroi* sp. complex	7	*F. annulatum (n=4), F. verticillioides (n=3)* (multi-drug resistant)
Low MICs (range from 0.125 to 0.25)	*Fusarium oxysporum* sp. complex	9	*F. contaminatum (n=1), F. veterinarium (n=4), F. odoratissimum (n=1), F. curvatum (n=1), F. oxysporum (n=2)* (multi-drug resistant)
Low MICs (range from 0.06 to 0.25)	*Scedosporium spp.*	8	*Scedosporium aurantiacum* (n=2), *S. apiospermum* (n=2); *S. dehoogii* (n=2), *S. boydii* (n=2)
High MIC ≥4	*F. dimerum* sp. complex	2	*Bisifusarium delphinioides (n=1), B. dimerum (n=1)* (multi-drug resistant)
High MIC ≥4	*F. solani* sp. complex	16	*F. keratoplasticum (n=3), F. petroliphilum (n=1), F. neocosmosporiellum (n=1), F. pseudensiforme (n=1), F. suttonianum (n=1), F. falciforme* (n=1), *F. solani (n=8)* (multi-drug resistant)
MIC50/90 [0.007/0.007]	-----	12	*Phaeoacremonium parasiticum*
MIC50/90 [0.06/0.06]	-----	15	*Nannizziopsis obscura* a rare keratinophilic fungi involved in invasive infections and apparently endemic to West Africa
MIC50/90 [0.25/0.5]	-----	11/12	*Microascus cirrosus* a multi-drug resistant species
High MIC ≥4	-----	1/12	One *Microascus cirrosus* isolate had a high MIC
Low MICs (range from 0.03 to 0.25)	-----	4	*Microascus gracilis* (multi-drug resistant species)
MIC50/90 [0.25/0.25]	-----	9/10	*Scopulariopsis brevicaulis* (multi-drug resistant species) . One strain had a MIC ≥4 mg/L
Low MICs (range from 0.03 to 0.25)	-----	3	*Scopulariopsis alboflavescens* (multi-drug resistant species
High MICs ≥4	-----	5	*Purpureocillium lilacinum*

Conclusions

- ✓ Olorofim appears as a promising drug for the treatment of difficult-to-manage species
- ✓ Reproductible low MICs were obtained for various panfungal resistant isolates such as *Fusarium fujikuroi* et *F. oxysporum* species complex, *Microascus* & *Scopulariopsis* species, etc..
- ✓ Further testing is ongoing especially for rare molds involved in IFDs to generate an olorofim MIC database which will constitute a major asset for clinicians

Spectrum olorofim

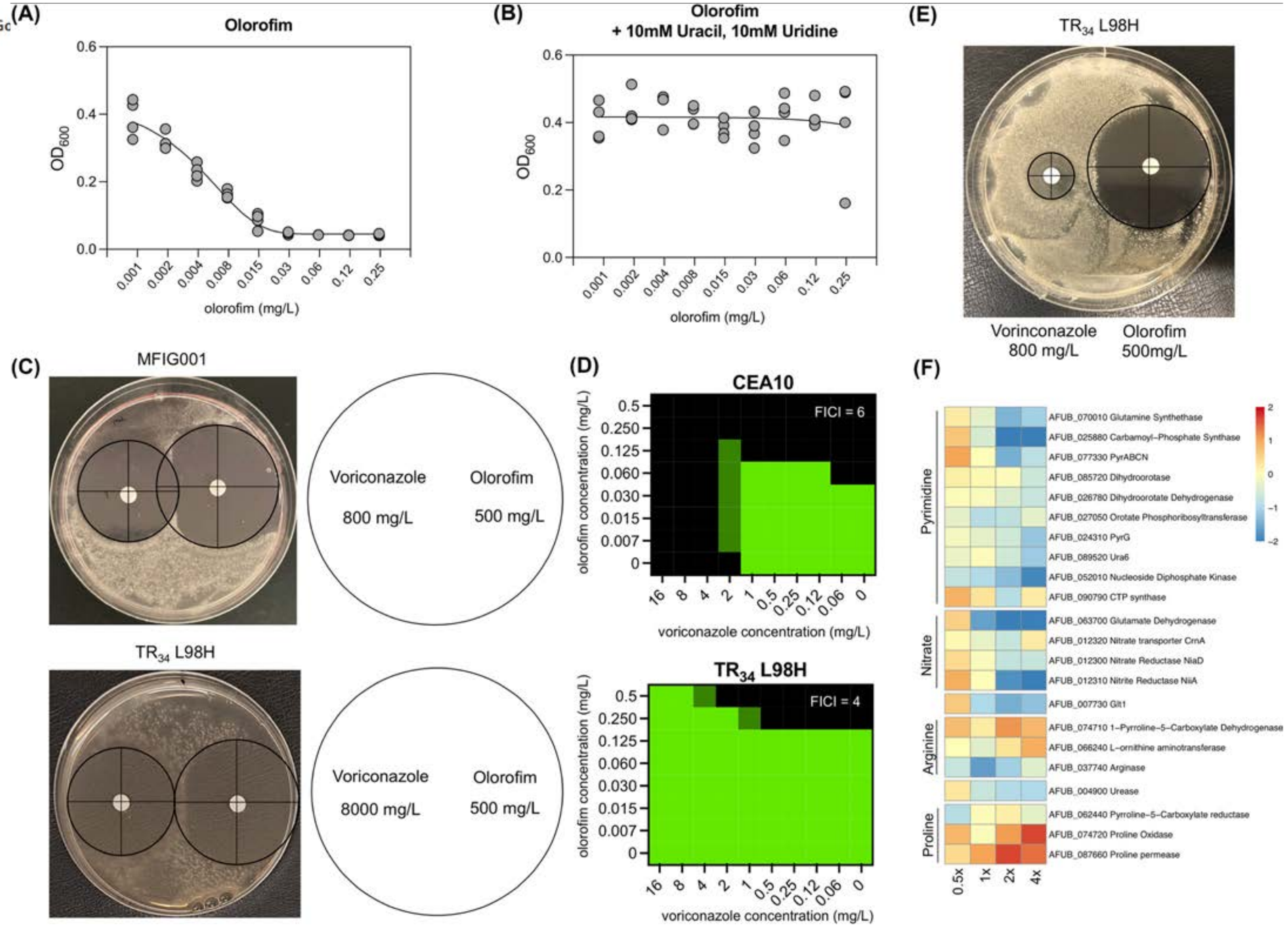
- Molds except Mucorales and Alternaria
- Including Aspergillus azoles R, Scedosporium, Lomentospora, Scopulariopsis, Rasamsonia
- Fusarium: depend on species
- Dimorphic fungi

RESEARCH ARTICLE

Antagonism of the Azoles to Olorofim and Cross-Resistance Are Governed by Linked Transcriptional Networks in *Aspergillus fumigatus*

Norman van Rhijn,[a,b] Sam Hemmings,[a] Isabelle S. R. Storer,[a] Clara Valero,[a,c] Hajer Bin Shuraym,[a] Gustavo H. Go
Fabio Gsaller,[a,d] Jorge Amich,[a,e] Michael J. Bromley[a,b]

azole-induced upregulation of the pyrimidine biosynthesis pathway



AMERICAN SOCIETY FOR MICROBIOLOGY Antimicrobial Agents and Chemotherapy®

PHARMACOLOGY

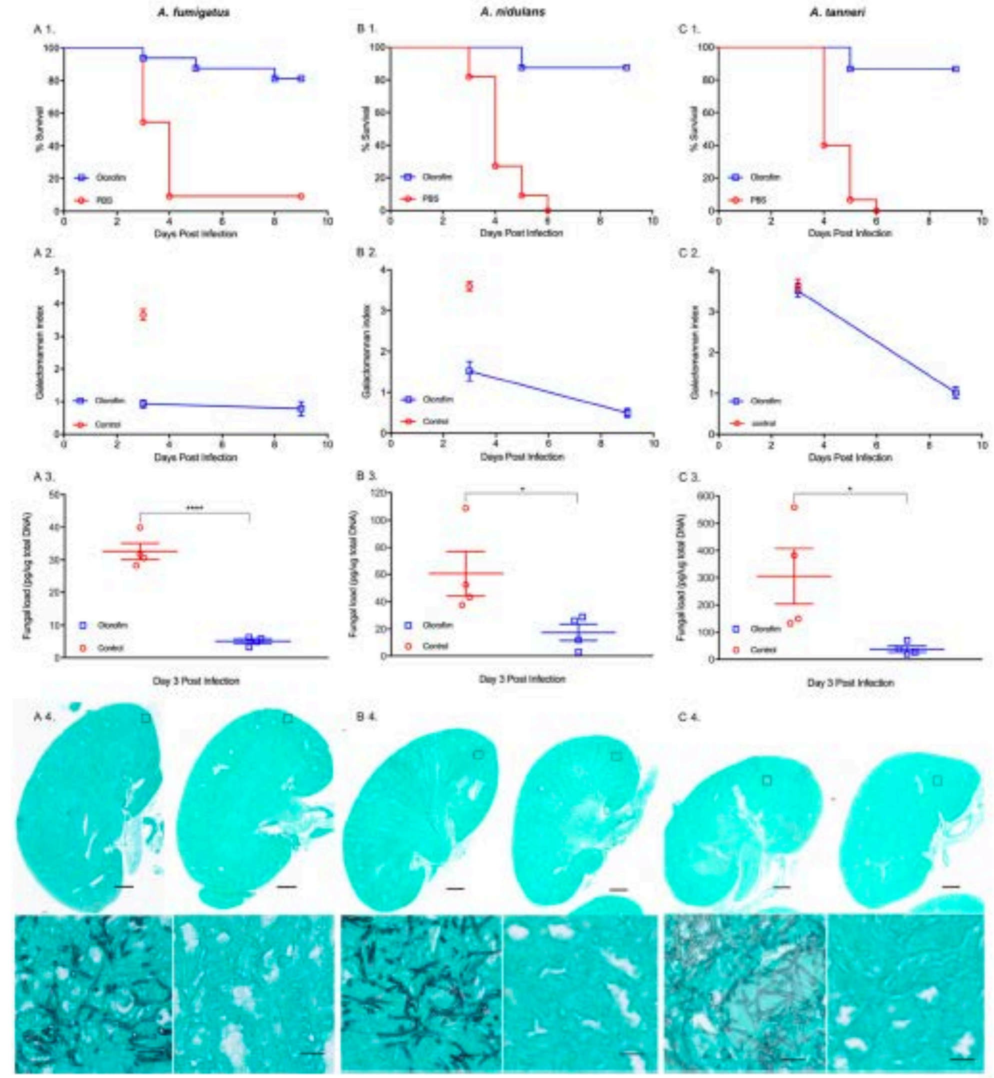
Efficacy of Olorofim (F901318) against *Aspergillus fumigatus*, *A. nidulans*, and *A. tanneri* in Murine Models of Profound Neutropenia and Chronic Granulomatous Disease

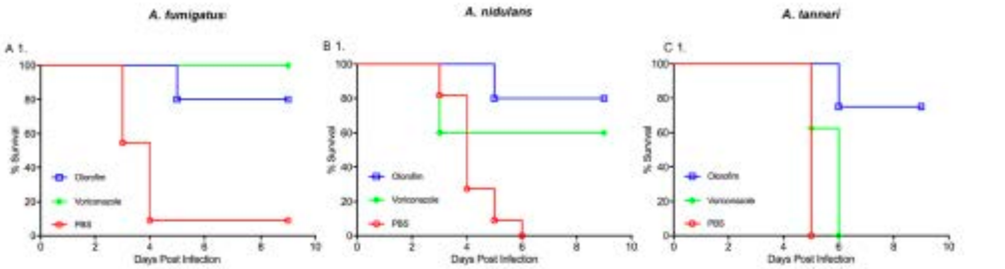
S. Seyedmousavi,[a] Y. C. Chang,[a] D. Law,[b] M. Birch,[b] J. H. Rex,[b] K. J. Kwon-Chung[a]

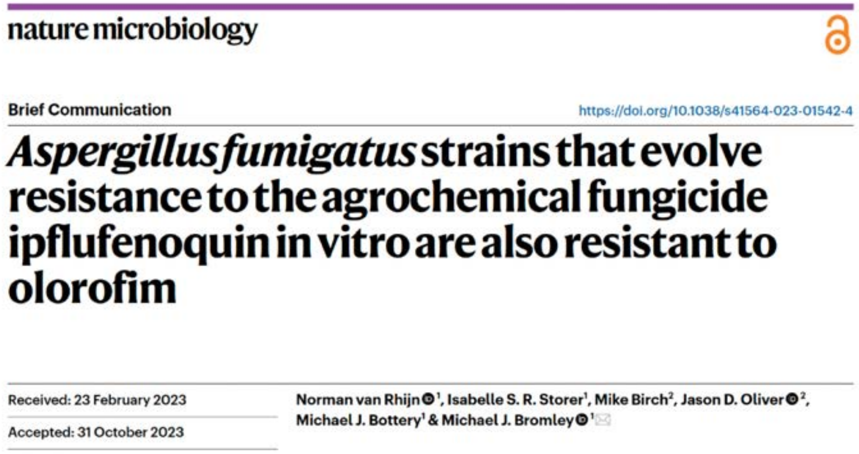
TABLE 1 MICs of six antifungals for *Aspergillus* species

Species (strain)[a]	MIC (μg/ml)[b]					
	AMB	ITC	VRC	POS	TRB	Olorofim
A. fumigatus (B5233)[c]	0.5	0.5	0.5	0.125	4	0.008
A. fumisynnematus (CFN1891)	2	2	2	0.5	1	0.008
A. nidulans (M24)[c]	2	0.5	0.25	0.25	1	0.008
A. pseudoviridinutans (NIHAV1)	2	2	2	0.5	0.5	0.008
A. subramanianii (DI 16-475)	2	0.5	0.25	0.5	0.25	0.016
A. tanneri (NIH1004)[c]	>16	4	4	0.5	0.25	0.062
A. udagawae (F41)	4	1	2	0. 5	1	0.008

[a]All strains are clinical isolates.
[b]The geometric mean MIC from three independent replicates of each strain is reported. AMB, amphotericin B; ITC, itraconazole; VRC, voriconazole; POS, posaconazole; TRB, terbinafine; olorofim, F901318.
[c]Species used for determination of olorofim efficacy in experimental animals.






nature microbiology

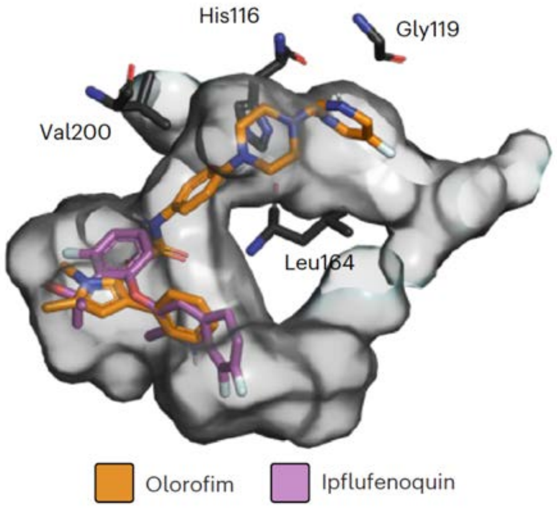
Brief Communication https://doi.org/10.1038/s41564-023-01542-4

Aspergillus fumigatus strains that evolve resistance to the agrochemical fungicide ipflufenoquin in vitro are also resistant to olorofim

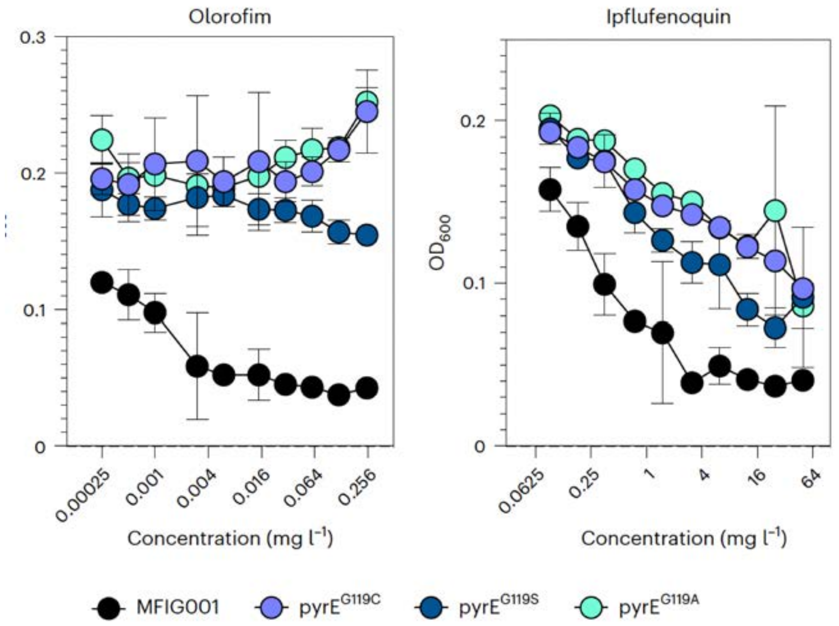
Received: 23 February 2023

Accepted: 31 October 2023

Norman van Rhijn[1], Isabelle S. R. Storer[1], Mike Birch[2], Jason D. Oliver[2], Michael J. Bottery[1] & Michael J. Bromley[1]



- Ipflufenoquin
  - Fungicide
  - Potent inhibitor of DHOH activity in *Neurospora crassa*
  - Approved by the US Environmental Protection Agency for
  - Use in agriculture could drive resistance to the orotomides in *A. fumigatus*?
- Ipflufenoquin active against *A. fumigatus* at levels below concentration of its use in crop protection



Refractory *Microascus* Bronchopulmonary Infection Treated with Olorofim, France

Emmanuel Faure, Olivier Brugière, Sylvie Colin de Verdiere, Fanny Vuotto, Lucie Limousin, Emilie Cardot, Camille Cordier, Pauline Coulon, Dea Garcia-Hermoso, Olivier Lortholary, Fanny Lanternier

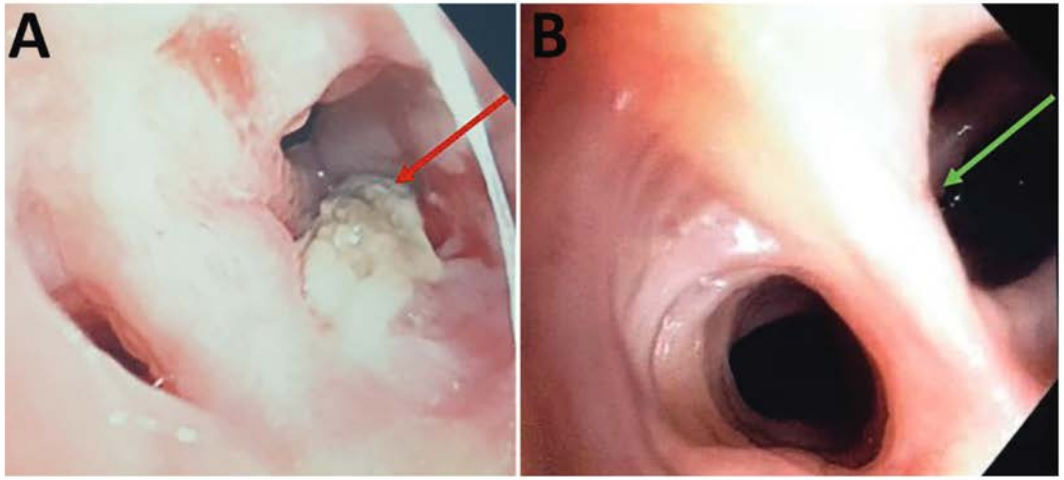


Figure. Macroscopic observation of endobronchial *Microascus cirrosus* lesion in patient in France with refractory microascus bronchopulmonary infection before (A) and after (B) olorofim treatment. Arrows indicate the lesion.

Table. Medical history and keypoints of 3 case-patients with refractory microascus bronchopulmonary infection, France*

Characteristic	Case 1	Case 2	Case 3
Age, y	17	61	65
Immunocompromised status	No	Lung transplant	Lung transplant
Years since transplantation	NA	4	6
Chronic lung allograft dysfunction	NA	Y (for 2 y)	Y (for 5 y)
Intensification of immunosuppressive drug regimen in medical history	NA	Antithymocyte globulin, steroids, rituximab, alemtuzumab, extracorporeal photophoresis	Steroids, rituximab, bortezomib
Maintenance therapy on the onset of *Microascus* infection	NA	Tacrolimus(C_0 4-6 ng/mL), everolimus (C_0 4-6 ng/mL), prednisone (5 mg/d)	Tacrolimus (C_0 4-6 ng/mL), Everolimus (C_0 4-6 ng/mL), prednisone(5 mg/d)
Recent antifungal exposition <3 mo	None	Isavuconazole	Isavuconazole
Tolerance			
Clinical	No SSE	NA	No SSE
Biologic	No ELE	Drug interaction with tacrolimus and everolimus	No ELE

*ELE, elevated liver enzyme; NA, not applicable; SSE, significant side effect.

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https://doi.org/10.1007/s10875-023-01513-8

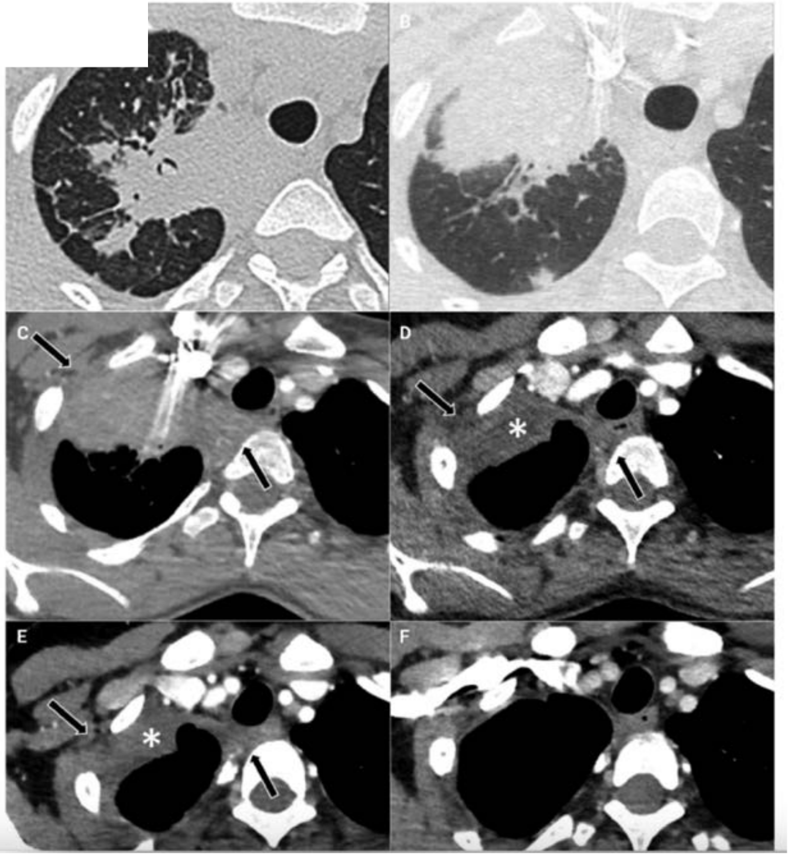
LETTER TO EDITOR

Prolonged Remission of Azole-Resistant Lung Aspergillosis with Olorofim, in an Adolescent with X-Linked Chronic Granulomatous Disease

Victor Michel[1] · Nizar Mahlaoui[1,2] · Marie Elisabeth Bougnoux[3] · Dea Garcia-Hermoso[4] · Fanny Lanternier[4,5] · Romain Lévy[1,6,7]

- 14 years old
- Azole resistant *A. fumigatus*
- Long term olorofim treatment

diagnosis (**A**) showed a segmental area of spiculated consolidation in the right upper lobe with extension towards the pleural space and the upper mediastinum, centered by an air crescent sign; at 14 months of evolution and before lobectomy (**B**), showed progression under treatment with extension to the upper mediastinum and the chest wall. Chest CT scan in axial sections in mediastinal window performed before the lobectomy (**C**): infiltration of the right upper lobe as well as the upper mediastinum up to the trachea and the intercostal space (black arrows). The 3-month follow-up of the lobectomy (**D**): persistence of apical pleural thickening (white asterisk) and mediastinal and parietal infiltration, gradually decreasing on the 6-month follow-up (**E**) with complete resolution on the 14-month follow-up (**F**)



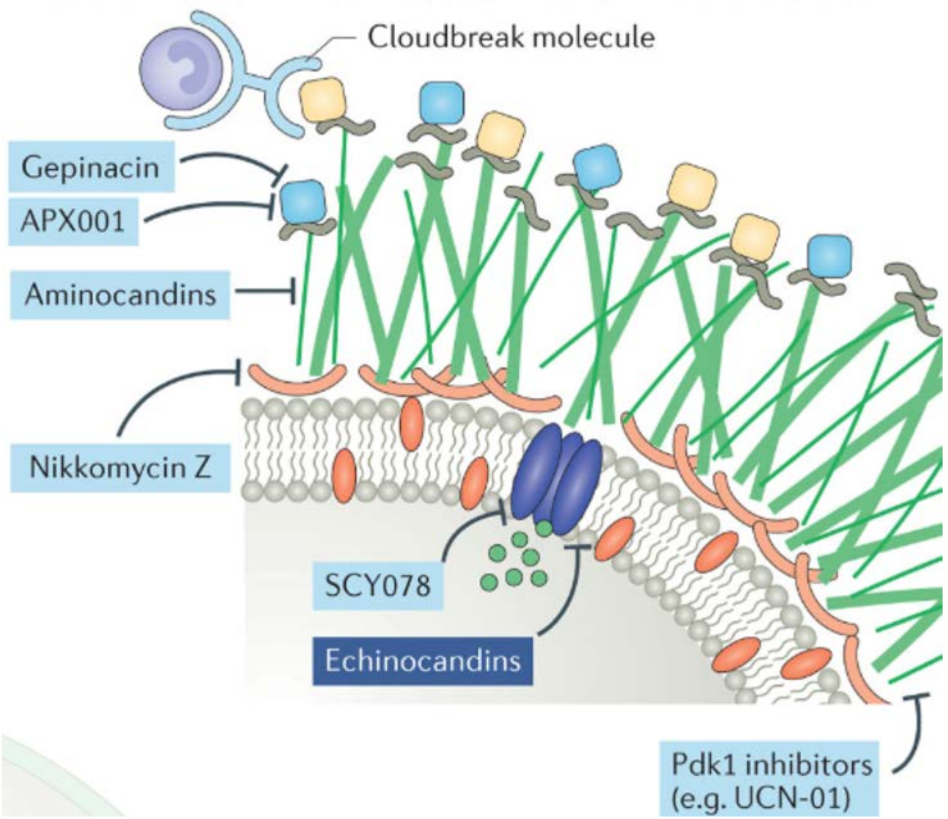
Real-world observational study of olorofim: data from compassionate use in France in 15 patients

Esnault V[1], Godet C[2], Garcia-Hermoso D[3], Charmillon A[4], Parize P[1],C. Rouzaud[1], Bellanger AP[10], Gangneux J-P[11], Sendid B[12], Cardot E[13], Melenotte C[1], Rouzaud C
Eschapasse E[17], Berceanu A[18], Tattevin P[19], Levy R[20], Faure E[21] and Lanternier F[1]

Patient	Age in years, sex	Main underlying diseases	Pathogen	Standard AF drugs MIC (mg/L)	Site of infection	Time on prior AF therapy, in months	Indication of olorofim	Concomitant AF therapy	Outcome at analysis
1	66, M	Lung adenocarcinoma	*Aspergillus fumigatus*	AMB 0,25 ITZ >32 PCZ 1 VCZ 4 ISZ 6	Lung	11,2	Refractory infection	CAS + inhaled AMBL	Died <15 days of olorofim§
2	23, M	HSCT for ALL, complete remission; chronic digestive GVHD	*Aspergillus nidulans* *A. fumigatus*	*A. nidulans*: AMB 0,19 VCZ 0,064 PCZ 0,064 ISZ 0,064 *A. fumigatus:* AMB 0,25 VCZ 0,25 PCZ 0,125 ISZ 0,19	Lung	5,1	Refractory infection	0	Died <15 days of olorofim§
3	17, M	None	*Microascus melanosporus*	AMB ≥4 ITZ ≥8 VCZ 8 PCZ ≥8 ISZ 4 CAS ≥4 MFG ≥4 TBF 0,25	Lung	0,8	Refractory infection	TBF	Success (6 weeks therapy)
4	57, F	Liver transplantation	*A. fumigatus*	AMB 0,5 ITZ ≥8 VCZ ≥8 PCZ 1 ISZ ≥4 CAS 0,5 MFG <0,008	Disseminated	11,2	Stable infection, intolerance to AF	CAS	Success (13 months therapy)
5	64, M	Lung transplantation, CLAD	*Microascus cirrosus**	AMB >32 ITZ >32 VCZ >32 ISZ 1,5 CAS >32	Lung	4,1	Refractory infection	TBF + ISZ	Success (death from unrelated cause)
6	22, M	Craniopharyngioma resection	*A. fumigatus*	NA	CNS	9,1	Stable infection, intolerance to AF	ISZ + intrathecal AMBL > PCZ > stop, ↑ olorofim dose	Partial response, ongoing
7	57, M	Combined liver and lung transplantation	*Scedosporium apiospermum** *Aspergillus calidoustus* *Aspergillus tubingensis*	NA	Lung	26,3	Refractory infection	TBF + VCZ + inhaled CAS > PCZ + inhaled CAS, ↑ olorofim dose	Partial response, ongoing
8	37, M	Sharp syndrome, chronic respiratory disease	*A. fumigatus*	AMB 0,5 ITZ 0,5 PCZ 0,094 VCZ 0,19 CAS 0,023 MFG 0,004	Lung	29,5	Refractory infection	PCZ	Partial response, ongoing
9	60, M	Lung transplantation, CLAD	*Microascus cirrosus** *A. flavus**	*A. flavus*: AMB 0,125 ITZ 0,012 VCZ 0,016 PCZ 0,25 ISZ 0,012 CAS 0,012	Lung	26,4	Refractory infection	0	Partial response, ongoing
10	39, M	CARD9 deficiency	*A. fumigatus*	ITZ 0,38 VCZ 0,19 ISZ 0,5 CAS 0,064	Disseminated	17,2	Refractory infection	ISZ > ISZ + CAS > CAS, ↑ olorofim dose	Partial response, ongoing
11	14, M	CGD	*A. fumigatus**	TR34/L98H +	Lung	15,2	Stable infection, intolerance to AF	CAS	Partial response, ongoing
12	15, M	CGD	*Rasamsonia aegroticola*	AMB 16 ITZ 8 PCZ 1 VCZ 32 ISZ >32 CAS 0,008 MFG 0,003 5FC 0,023	Lung	11,1	Refractory infection	MFG + 5FC	Partial response, ongoing
13	36, M	CGD, liver transplantation	*Aspergillus udagawae** *Aspergillus latus*	*A. latus*: AMB 1 ITZ 1 VCZ 0,5 PCZ 0,5 ISZ 0,5 CAS 0,25 MFG <0,008 *A. udagawae*: AMB >4 ITZ 0,5 VCZ 2 PCZ 0,2 ISZ 2 CAS 0,25 MFG <0,008	Disseminated	6,0	Refractory infection	VCZ > CAS, ↑ olorofim dose	Mycological failure
14	60, M	Cystic fibrosis, lung transplantation, CLAD	*Lomentospora prolificans**	NA	Disseminated	0,2	No effective AF	TBF + VCZ	Mycological failure
15	50, F	Lung transplantation	*Scopulariopsis sp.*	AMB >32 VCZ >32 PCZ >32 ISZ >32 MFG 0,032	Lung	0,5	No effective AF	MFG + VCZ	Mycological failure

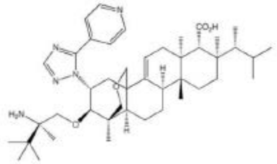
Ibrexafungerp

- ß-1,3-glucan synthase inhibitor
- Triterpenoides - enfumafungine
- Oral
- T1/2 (20h)
- Fongicidal Candida
- Good diffusion in peritoneum



Perfect JR, (2017) Nat Rev Drug Discov.

Ibrexafungerp (SCY-078)



Triterpenoid - Non-competitive inhibition of 1,3-β-D-glucan synthase, depleting 1,3-β-D-glucan in cell wall
(*FKS1* and *FKS2*)

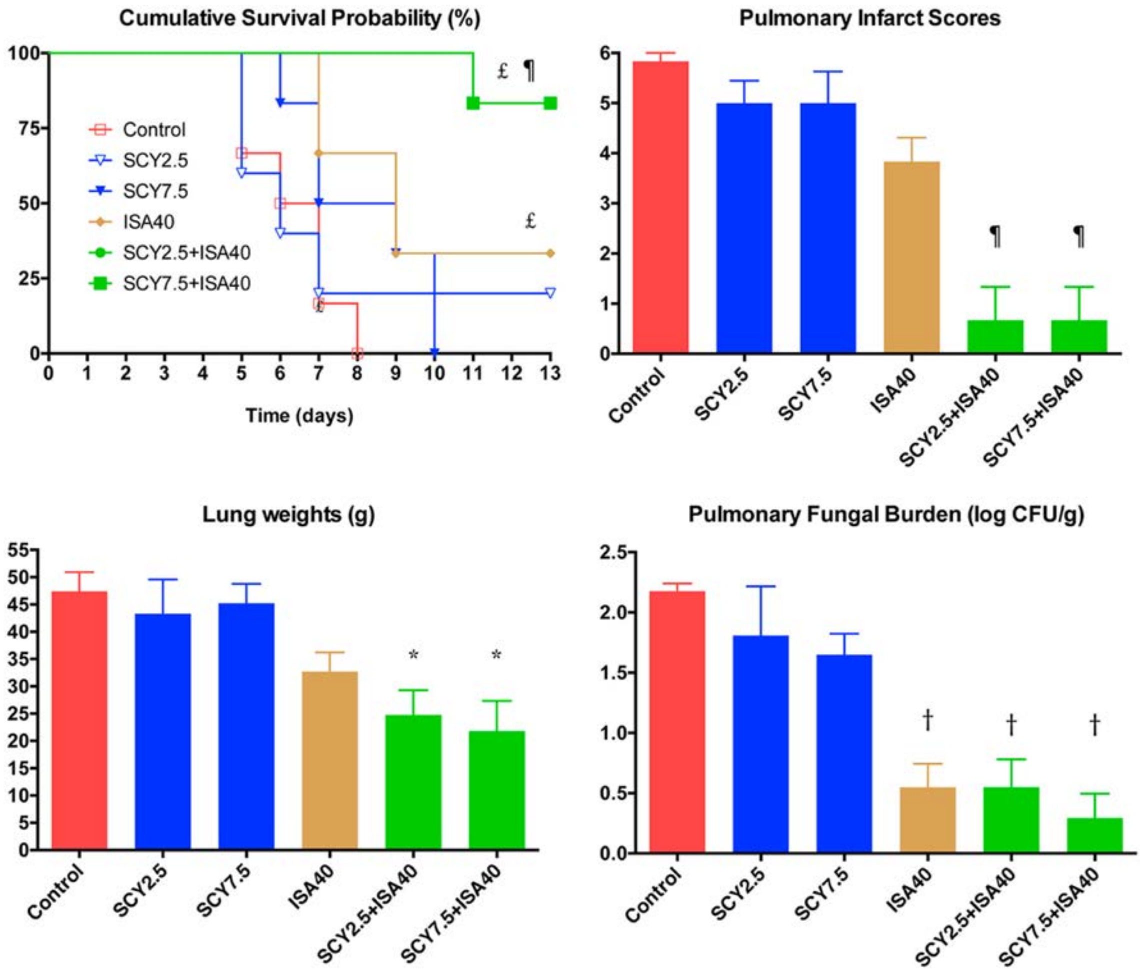
Spectrum ibrexafungerp

- Non basidio yeasts : no activity on *Cryptococcus*, *Trichosporon*
- Molds except *Mucorales, Fusarium* and *Alternaria, Scedosporium, Lomentospora*
- Dimorphic
- PCP

From Hoenigl M

Rabbit model IPA

- Ibrexafungerp and isavuconazole
- combination demonstrated prolonged survival, decreased pulmonary injury, reduced
- residual fungal burden, and lower GMI and (1¡3)- -D-glucan levels in
- comparison to those of single therapy for treatment of IPA.



Petraitis, AAC, 2020

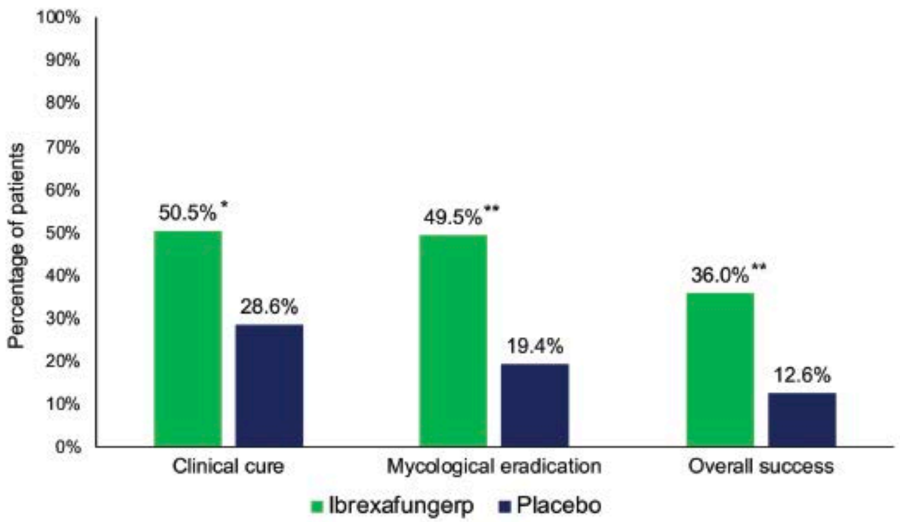
Clinical Infectious Diseases
MAJOR ARTICLE

Ibrexafungerp Versus Placebo for Vulvovaginal Candidiasis Treatment: A Phase 3, Randomized, Controlled Superiority Trial (VANISH 303)

Jane R. Schwebke,[1] Ryan Sobel,[2] Janet K. Gersten,[3] Steven A. Sussman,[4] Samuel N. Lederman,[5] Mark A. Ja
Alfred H. Moffett Jr,[9] Nkechi E. Azie,[10] David A. Angulo,[10] Itzel A. Harriott,[10] Katyna Borroto-Esoda,[11] Mahmo

- CVV aigue
- 2:1 ibrexafungerp (300mg BID J1) vs placebo

A) Efficacy Outcomes at TOC Visit (Day 10)



	Ibrexafungerp (n = 188)	Placebo (n = 98)
Age, y		
Mean ± SD	33.5 ± 10.36	36.0 ± 12.46
Median (min, max)	32.5 (18, 67)	34.0 (17, 66)
Race, n (%)		
White	103 (54.8)	53 (54.1)
Black	73 (38.8)	43 (43.9)
Asian	4 (2.1)	0
American Indian or Alaska Native	2 (1.1)	0
Other	6 (3.2)	2 (2.0)
Ethnicity, n (%)		
Hispanic or Latino	54 (28.7)	18 (18.4)
Non-Hispanic or Latino	134 (71.3)	80 (81.6)
BMI (kg/m^2)[a], n (%)		
≤35	144 (76.6)	76 (77.6)
>35	44 (23.4)	22 (22.4)
Diabetes mellitus		
Yes	18 (9.6)	8 (8.2)
No	170 (90.4)	90 (91.8)
Composite VSS score		
Median (min, max)	9.0 (5, 18)	9.0 (4, 17)
Candida species		
Candida albicans	173 (92.0)	90 (91.8)
Candida glabrata	11 (5.9)	11 (11.2)
Candida tropicalis	4 (2.1)	1 (1.0)
Candida dubliniensis	2 (1.1)	0
Candida lusitaniae	1 (0.5)	1 (1.0)
Candida parapsilosis	1 (0.5)	0
Candida krusei	0	1 (1.0)
Saccharomyces species	1 (0.5)	0

Table 3. Summary of Treatment-Related Treatment-Emergent Adverse Events (TEAEs) Reported in >2% of Patients

	Ibrexafungerp (n = 247)	Placebo (n = 124)
Patients with ≥1 TEAE	98 (39.7)	21 (16.9)
Mild	78 (31.6)	17 (13.7)
Moderate	24 (9.7)	4 (3.2)
Severe	1 (0.4)	0
Diarrhea	55 (22.3)	5 (4.0)
Mild	38 (15.4)	4 (3.2)
Moderate	17 (6.9)	1 (0.8)
Nausea	27 (10.9)	5 (4.0)
Mild	24 (9.7)	5 (4.0)
Moderate	2 (0.8)	0
Severe	1 (0.4)	0
Abdominal pain	13 (5.3)	0
Mild	12 (4.9)	0
Moderate	1 (0.4)	0
Abdominal discomfort	11 (4.5)	2 (1.6)
Mild	6 (2.4)	2 (1.6)
Moderate	5 (2.0)	0
Dizziness	9 (3.6)	2 (1.6)
Mild	7 (2.8)	2 (1.6)
Moderate	2 (0.8)	0
Abdominal pain upper	7 (2.8)	1 (0.8)
Mild	6 (2.4)	1 (0.8)
Moderate	1 (0.4)	0
Flatulence	6 (2.4)	1 (0.8)
Mild	5 (2.0)	1 (0.8)
Moderate	1 (0.4)	0
Headache	6 (2.4)	3 (2.4)
Mild	5 (2.0)	3 (2.4)
Moderate	1 (0.4)	0

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

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	220 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	A Phase 3, Multicenter, Prospective, Randomized, Double-blind Study of Two Treatment Regimens for Candidemia and/or Invasive Candidiasis: Intravenous Echinocandin Followed by Oral Ibrexafungerp Versus Intravenous Echinocandin Followed by Oral Fluconazole (MARIO)
Actual Study Start Date :	August 3, 2022
Estimated Primary Completion Date :	January 2024
Estimated Study Completion Date :	February 2024

Rezafungin

- Rezafungin analog
- Long high life
- Major interest for patients with PID and azole resistant chronic candidiasis
- Data necessary for extreme age of life, vascular and bone infection

Journal of Clinical Immunology (2023) 43:1182–1184
https://doi.org/10.1007/s10875-023-01519-2

LETTER TO EDITOR

Check for updates

Successful Rezafungin Treatment of an Azole-Resistant Chronic Mucocutaneous Candidiasis in a STAT-1 Gain-of-Function Patient

Cléa Melenotte[1] · Robert Ratiney[2] · Olivier Hermine[3] · Marie-Elisabeth Bougnoux[4] · Fanny Lanternier[1,5]

Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE)

- Multicentrique, randomisé double aveugle, phase III
- Adultes (≥18 ans) candidémie et candidose invasive
- Rezafungin 1/sem(400 mg S1, puis 200 mg/S 2 à 4 doses) ou caspo IV (70 mg puis 50mg)
- Guérison à J14
- 2018-2021, 199 patients randomisés
- 7 (13%) des 56 patients groupe rezafongine et 14 (28%) des 51 patients groupe caspofungine ablation cathéter dans les 48 hdu diagnostic.

	Rezafungin group (n=100)	Caspofungin group (n=99)
Age	59·5 (15·8)	62·0 (14·6)
<65 years	60 (60%)	58 (59%)
≥65 years	40 (40%)	41 (41%)
Sex		
Male	67 (67%)	56 (57%)
Female	33 (33%)	43 (43%)
Race		
Asian	27 (27%)	31 (31%)
Black or African American	5 (5%)	4 (4%)
White	61 (61%)	60 (61%)
Other or not reported	7 (7%)	4 (4%)
Diagnosis		
Candidaemia only	70 (70%)	68 (69%)
Invasive candidiasis*	30 (30%)	31 (31%)
Mean modified APACHE II score†	12·5 (8·0)	13·1 (7·1)
≥20	15 (15%)	18 (18%)
<20	84 (84%)	81 (83%)
Body-mass index mean, kg/m²	25·4 (7·0)	24·5 (6·5)
Absolute neutrophil count, <500 cells per µL†	9 (9%)	6 (6%)

Data are n (%) or mean (SD). APACHE=Acute Physiology and Chronic Health Evaluation. *Includes patients who progressed from candidaemia to invasive candidiasis based on radiological or tissue or fluid culture assessment up to day 14. †Reported for patients with data available.

Table 1: **Demographics and baseline characteristics in the intention-to-treat population**

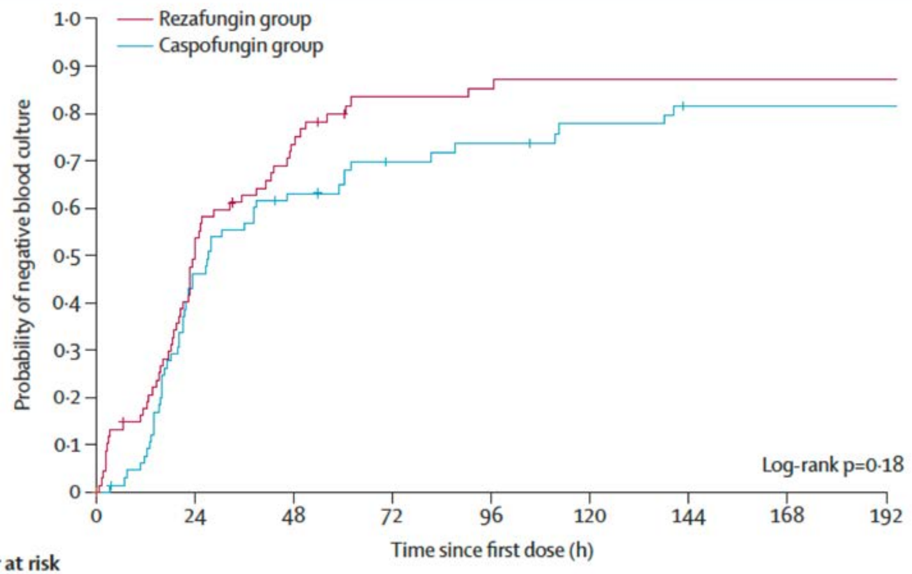
Thompson, Lancet, 2023

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

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

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

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



Number at risk (number censored)									
Rezafungin group	69 (0)	31 (2)	17 (1)	9 (2)	8 (0)	7 (0)	7 (0)	7 (0)	7 (0)
Caspofungin group	69 (0)	35 (4)	23 (1)	16 (3)	14 (0)	11 (1)	8 (1)	8 (0)	8 (0)

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

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

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	462 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Prevention
Official Title:	A Phase 3, Multicenter, Randomized, Double-Blind Study of the Efficacy and Safety of Rezafungin for Injection Versus the Standard Antimicrobial Regimen to Prevent Invasive Fungal Diseases in Adults Undergoing Allogeneic Blood and Marrow Transplantation (The ReSPECT Study)
Actual Study Start Date :	May 11, 2020
Estimated Primary Completion Date :	August 2024
Estimated Study Completion Date :	August 2024

Reza 400/200 vs fluco et TMP/SMX

Opelconazole

- Inhaled triazole
- Local important concentration, prolonged lung retention, low blood concentration

In Vitro and *In Vivo* Antifungal Profile of a Novel and Long-Acting Inhaled Azole, PC945, on *Aspergillus fumigatus* Infection

Thomas Colley,[a] Alexandre Alanio,[b,c,d] Steven L. Kelly,[e] Gurpreet Sehra,[a] Yasuo Kizawa,[f] Andrew G. S. Warrilow,[e] Josie E. Parker,[e] Diane E. Kelly,[e] Genki Kimura,[f] Lauren Anderson-Dring,[a] Takahiro Nakaoki,[f] Mihiro Sunose,[g] Stuart Onions,[g] Damien Crepin,[g] Franz Lagasse,[g] Matthew Crittall,[g] Jonathan Shannon,[g] Michael Cooke,[g] Stéphane Bretagne,[b,c,d] John King-Underwood,[h] John Murray,[a] Kazuhiro Ito,[a] Pete Strong,[a] Garth Rapeport[a]

TABLE 6 Antifungal effects of PC945 and posaconazole on other fungal species

Species (strain[s])	No. of strains tested	Culture method	MIC (μg/ml)[a] PC945	Voriconazole	Posaconazole
Aspergillus carbonarius (ATCC 8740)	1	CLSI	4	0.5	0.063
Aspergillus flavus (ATCC 204304)	1	CLSI	>8	2	0.13
Aspergillus flavus (AFL8, NRRC3357)	2	EUCAST	6	0.63	0.16
Aspergillus niger (ATCC 1015)	1	EUCAST	>8	1	0.20
Aspergillus terreus (AT49, AT7130)	2	EUCAST	0.078	1	0.093
Penicillium chrysogenum (ATCC 9480)	1	CLSI	>8	2	0.13
Penicillium citrinum (ATCC 9849)	1	CLSI	>8	>8	0.5
Trichophyton rubrum (ATCC 10218)	1	CLSI	0.031	0.063	0.031
Aureobasidium pullulans (ATCC 9348)	1	CLSI	>8	>8	1
Cladosporium argillaceum (ATCC 38013)	1	CLSI	>8	0.5	0.25
Candida albicans[b] (20240.047, ATCC 10231)	2	CLSI	0.081	0.14	0.081
AR *Candida albicans*[b,c] (20183.073, 20186.025)	2	CLSI	8.25	10	8.13
Candida glabrata[b] (ATCC 36583, R363)	2	CLSI	0.5	8.13	0.5
Candida krusei (ATCC 6258)	1	CLSI	0.125	0.25	0.125
Chaetomium globosum (ATCC 44699)	1	CLSI	>8	1	0.25
Gibberella zeae (*Fusarium graminearum*) (ATCC 16106)	1	CLSI	>8	>8	>8
Cryptococcus gattii (clinical isolate)	1	EUCAST	0.25	0.125	0.5
Cryptococcus neoformans (ATCC 24067)	1	CLSI	0.008	0.016	0.016
Lichtheimia corymbifera (ATCC 7909)	1	CLSI	>8	>8	>8
Mucor circinelloides (ATCC 8542)	1	CLSI	>8	>8	>8
Rhizomucor pusillus (ATCC 16458)	1	CLSI	>8	>8	>8
Rhizopus oryzae (ATCC 11145)	1	CLSI	2	>8	>8

[a]Due to the limited number of strains tested, the mean isolate MICs are presented.

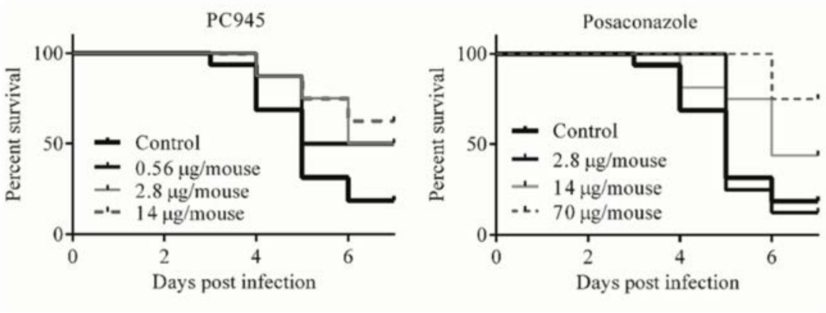


TABLE 3 Antifungal effects of PC945 and known antifungal agents in azole-susceptible and azole-resistant strains of *A. fumigatus*[a]

Strain	Resistance mechanism	IC_{50} (IC_{90}) (μg/ml) of indicated agent: PC945	Voriconazole	Posaconazole	Itraconazole	Amphotericin B	Caspofungin
NCPF2010	None	0.0084 (0.010)	0.16 (0.20)	0.0086 (0.014)	0.057 (0.085)	0.23 (0.48)	0.11 (>1)
AF294	None	0.0020 (0.0043)	0.082 (0.27)	0.0056 (0.011)	0.041 (0.052)	0.21 (0.79)	>1 (>1)
AF293	None	0.0012 (0.0041)	0.25 (0.74)	0.010 (0.028)	0.032 (0.23)	0.24 (0.85)	>1 (>1)
AF72	G54E mutation	0.0061 (0.029)	0.019 (0.062)	0.032 (0.19)	0.43 (>1)	0.18 (0.64)	0.10 (>1)
AF91	M220V mutation	0.0081 (0.059)	0.12 (0.38)	0.024 (0.12)	0.26 (>1)	0.42 (>1)	0.072 (>1)
TR34/L98H	TR34/L98H mutation	0.034 (>1)	>1 (>1)	0.086 (0.13)	0.22 (>1)	0.14 (0.29)	0.082 (>1)

[a]IC_{50} and IC_{90} values were determined from optical density measurements.

AAC, 2017

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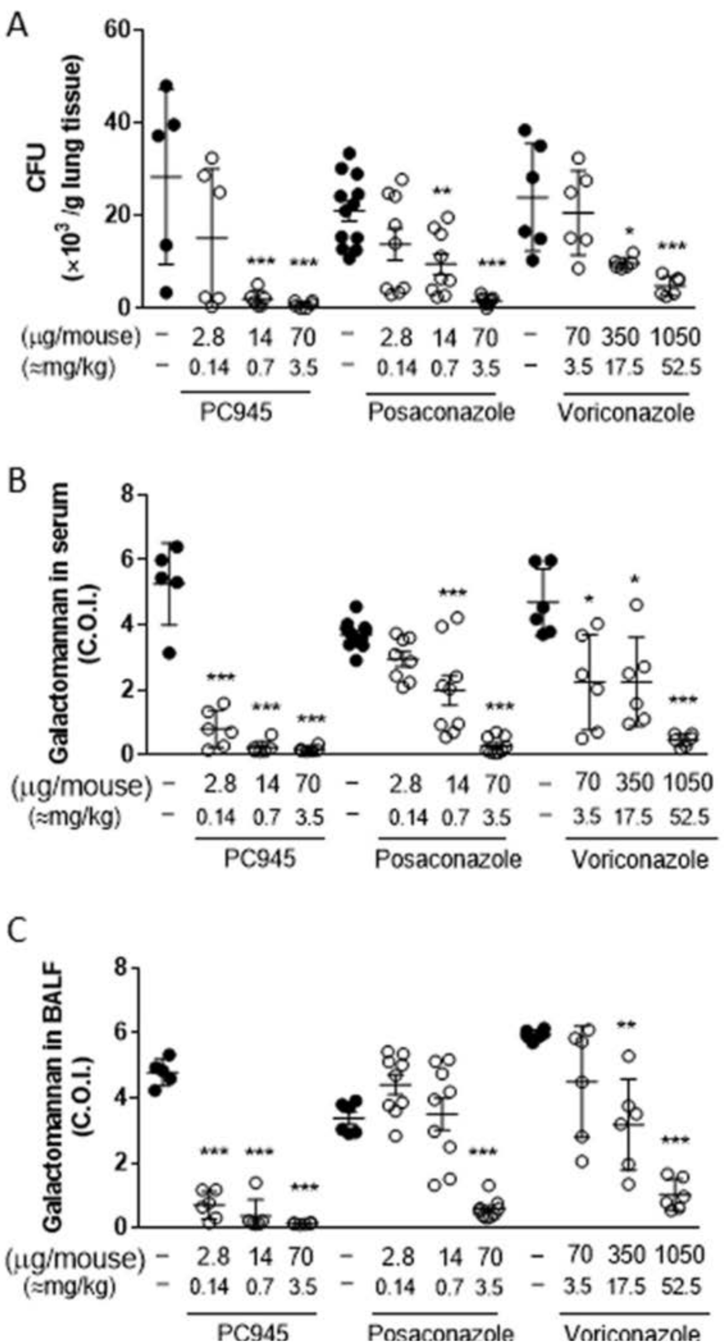
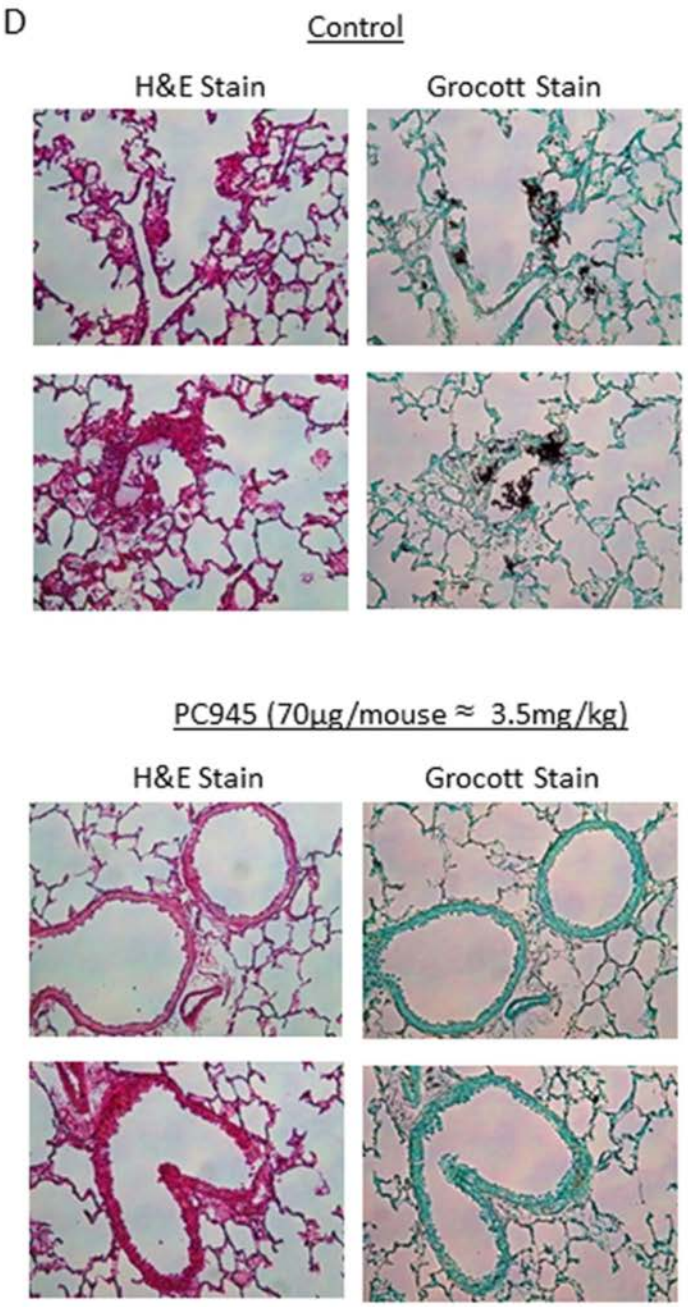
In Vivo Biomarker Analysis of the Effects of Intranasally Dosed PC945, a Novel Antifungal Triazole, on *Aspergillus fumigatus* Infection in Immunocompromised Mice

Genki Kimura,[a] Takahiro Nakaoki,[a] Thomas Colley,[b] Garth Rapeport,[b] Pete Strong,[b] Kazuhiro Ito,[b] Yasuo Kizawa[a]

Laboratory of Physiology and Anatomy, Nihon University School of Pharmacy, Funabashi, Japan[a]; Pulmocide Ltd., London, United Kingdom[b]





The Effect of PC945 on Aspergillus or Candida Lung Infections in Patients With Asthma or Chronic Respiratory Diseases

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	13 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Masking Description:	This is a double-blind study.
Primary Purpose:	Treatment
Official Title:	A Double-blind, Placebo-controlled Study to Assess the Effects of Inhaled PC945 in the Treatment of Culture-positive Aspergillus or Candida Fungal Bronchitis in Subjects With Moderate to Severe Asthma or Other Chronic Respiratory Diseases.
Actual Study Start Date :	November 15, 2018
Actual Primary Completion Date :	June 1, 2020
Actual Study Completion Date :	June 1, 2020

PC945 Prophylaxis or Pre-emptive Therapy Against Pulmonary Aspergillosis in Lung Transplant Recipients

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	100 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	Open-label, randomized, active-controlled, parallel-group multi-center study
Masking:	Single (Outcomes Assessor)
Masking Description:	The study will be an open-label study. For the purposes of the exploratory efficacy assessments, however, the Data Review Committee determining the presence of pulmonary fungal disease will be blinded as to treatment assignment. The Sponsor will limit knowledge of treatment assignment to as few sponsor personnel as possible to reduce bias.
Primary Purpose:	Prevention
Official Title:	A Randomized Controlled Open-label Study to Assess the Safety and Tolerability of Nebulized PC945 for Prophylaxis or Pre-emptive Therapy Against Pulmonary Aspergillosis in Lung Transplant Recipients
Actual Study Start Date :	November 19, 2021
Estimated Primary Completion Date :	November 2023
Estimated Study Completion Date :	November 2023

Safety and Efficacy of PC945 in Combination With Other Antifungal Therapy for the Treatment of Refractory Invasive Pulmonary Aspergillosis

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	123 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Masking Description:	Double Blind
Primary Purpose:	Treatment
Official Title:	A Double-blind, Randomized, Placebo-controlled Study to Assess the Safety and Efficacy of Nebulized PC945 When Added to Systemic Antifungal Therapy for the Treatment of Refractory Invasive Pulmonary Aspergillosis
Actual Study Start Date :	June 14, 2022
Estimated Primary Completion Date :	October 31, 2023
Estimated Study Completion Date :	November 30, 2023

Conclusion

- Olorofim:
  - New class
  - Oral disponibility, efficacy on species without other resources
- Fosmanogepix:
  - New class
  - Yeast and Molds infection incliding Mucorales (?)
- Ibrexafungerp: potentiel major interest in superficial infections
- Rezafungin: PK major interest for long term treatments. Datat in extreme ages and high doses?
- Opelconazole: Prophylaxis? Curative treatment? Different forms of aspergillosis

SINFONI

Clarisse Durand, Taieb Chouaki, Céline Damiani, Marc Pihet, Jean-Philippe Bouchara, Joséphine Dorin, Sophie Brun, Aurore Bousquet, Sébastien Larreche, Laurence Millon, Anne-Pauline Bellanger, Emeline Scherer, Christine Bonnal, Laurence Delhaes, Sébastien Imbert, Frédéric Gabriel, Maxime Lefranc, Isabelle Accocerby, Solène Le Gal, Gilles Nevez, Dorothée Quinio, Julie Bonhomme, Bianca Podac, Maxime Moniot, Philippe Poirier, Céline Nourrisson, Marie-Elisabeth Bougnoux, Eric Dannaoui, André Paugam, Naima Dahane, Célia Rouge
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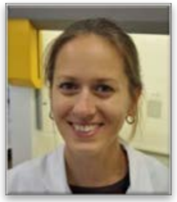




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- Pédiatre: Fanny Alby-Laurent
- Mycologues du CNRMA : Alexandre Alanio, Eric Dannaoui, Laurence Millon, Florent Morio
- Mycologue associée au service support thérapeutique : Marie Elisabeth Bougnoux
- Pharmacologue (en fonction des dossiers) : Vincent Jullien
- Ingénieur du CNRMA (en fonction des dossiers) : Marie Desnos Ollivier, Dea Garcia Hermoso

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- Téléphone: **01 71 39 69 93**
- Avis urgents par téléphone médecin sénior du SMIT validés secondairement en RCP si nécessaires

- **Déroulement de la RCP :**

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- analyse des dossiers par les participants de la RCP
- Avis de la RCP (proposition diagnostique, thérapeutique et de suivi) rendu aux cliniciens et mycologues référents