

# Best of Infections fongiques

Fanny Lanternier

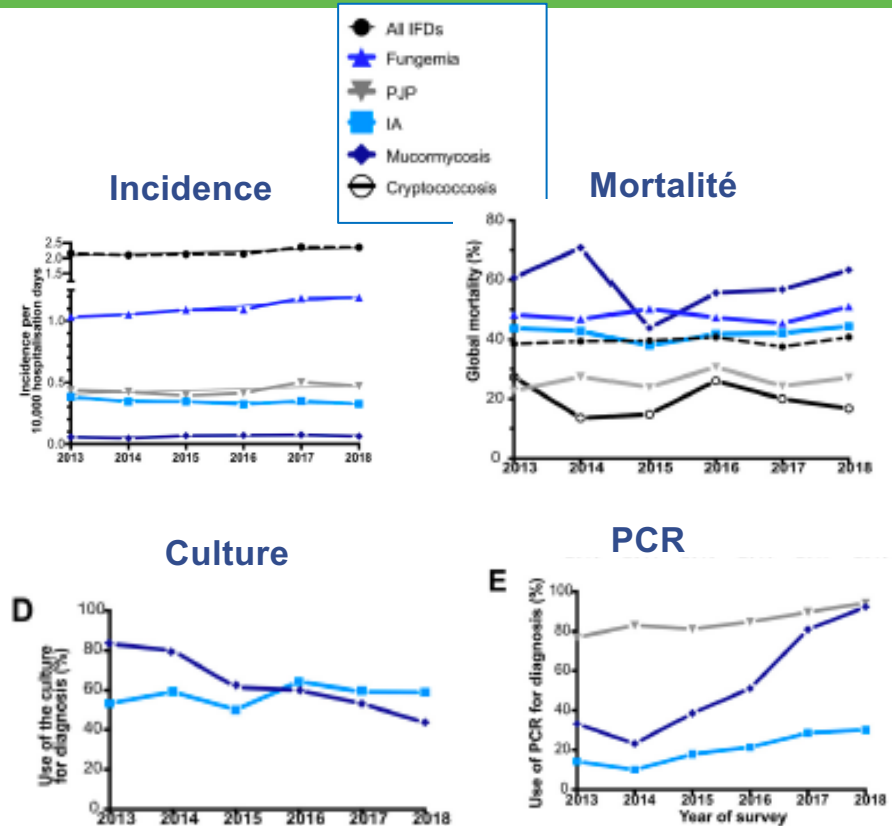
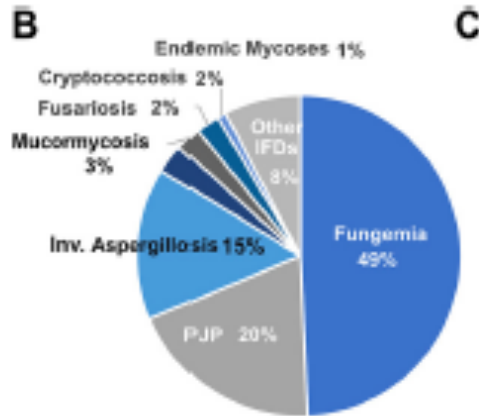
SMIT Necker  
Université Paris Cité  
Institut Pasteur, CNRMA,

## Déclaration d'intérêts de 2014 à 2021

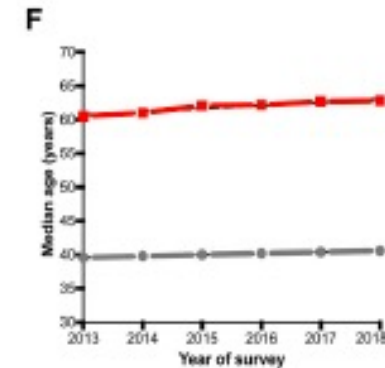
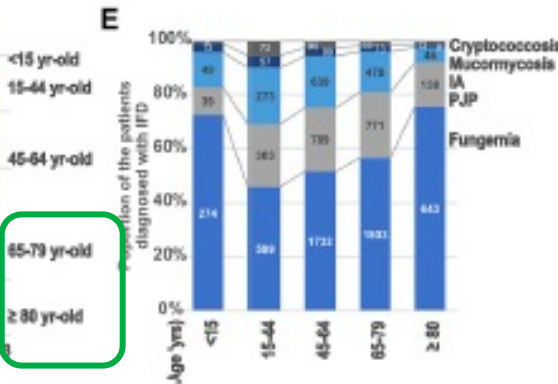
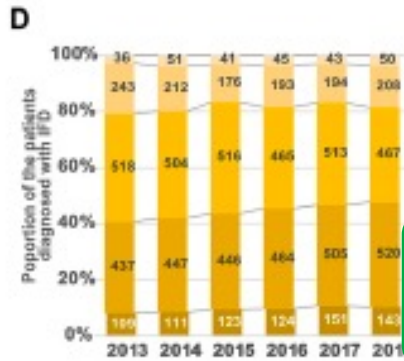
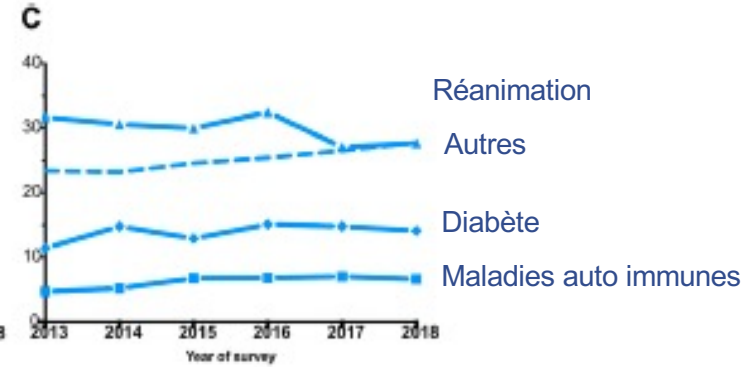
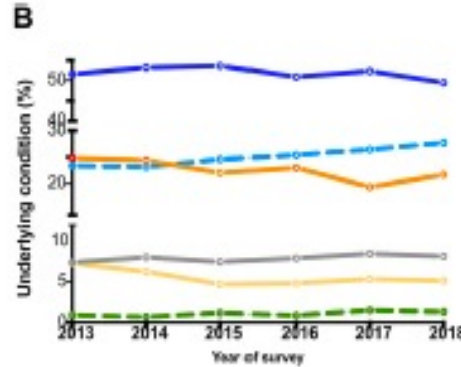
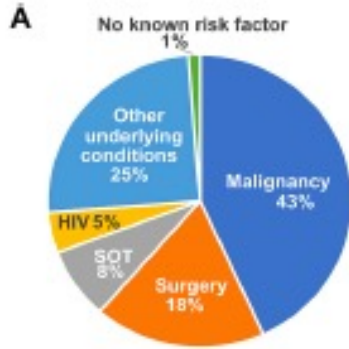
- Interventions ponctuelles : Gilead, Pfizer, F2G, Basilea

# Données nationales sur l'épidémiologie des IFI en France

- RESSIF: 27 centres, coordonné CNRMA
- 10 886 IFD 2012-2018
- Augmentation incidence
- Augmentation plus de 65 ans



# Données nationales sur l'épidémiologie des IFI en France



# Epidémiologie CAPA en France au cours de la première vague de COVID

- 565 patients COVID avec VM ayant eu des prélèvements respiratoires
- 25% IFI
- 15% CAPA prouvées ou probables

## Facteurs de risque de CAPA

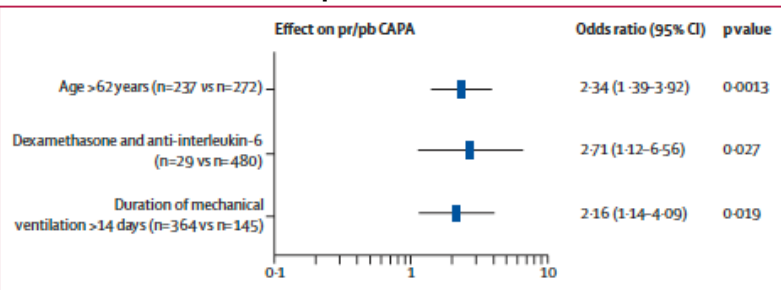


Figure 1: Multivariate analysis of factors associated with pr/pb CAPA. All significant variables in univariate analysis were included in the multivariate model, but only significant variables in the multivariate analysis are shown in the figure. CAPA=COVID-19-associated pulmonary aspergillosis. pr/pb=proven or probable.

## Facteurs associés à la mortalité de CAPA

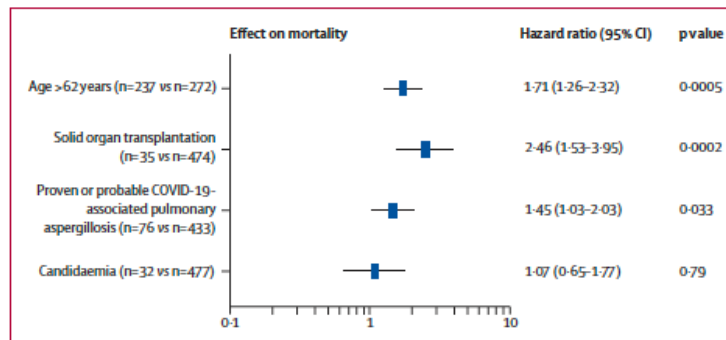


Figure 3: Multivariate analysis of factors associated with death. All significant variables in univariate analysis were included in the multivariate model; only significant variables in the multivariate analysis and variables of interest (candidaemia) are shown in the figure.

Fréquence CAPA selon définition ECMM/ISHAM  
Pas de modification de la mortalité en cas de traitement AF  
Question des définitions CAPA à traiter  
Quid après la première vague?

# Epidémiologie *C. gattii* et *C. neoformans*

**Table 1. Characteristics of Patients With Cryptococcosis**

Characteristic	Total (N = 709)	<i>Cryptococcus neoformans</i> (n = 452)	<i>Cryptococcus gattii</i> (n = 257)	PValue
<b>Location</b>				
Australia	82 (11.9)	15 (3.3)	67 (26.1)	<.0001
British Columbia	111 (16.2)	0 (0.0)	111 (46.2)	
Duke University Medical Center	178 (25.9)	178 (39.4)	0 (0.0)	
Oregon/Washington	112 (16.3)	34 (7.5)	78 (30.4)	
University of Alabama	226 (31.9)	225 (49.8)	1 (0.4)	
Age, y, mean ± SD	50.2 ± 16.2	49.0 ± 15.7	52.5 ± 16.9	.0064
Time to diagnosis from symptom onset, d, mean ± SD	41.7 ± 65.5	36.0 ± 68.7	52.2 ± 57.7	.0032
<b>Sex</b>				
Male	432 (61.4)	295 (66.0)	137 (53.3)	.0009
Female	272 (38.6)	152 (34.0)	120 (46.7)	
<b>Site of infection*</b>				
Central nervous system	419 (59.1)	291 (64.4)	128 (49.8)	.0001
Pulmonary	301 (42.5)	145 (32.1)	156 (60.7)	<.0001
Blood	174 (24.5)	154 (34.1)	20 (7.8)	<.0001
Skin	18 (2.5)	18 (4.0)	0 (0.0)	.0012
Bone or joint	11 (1.6)	9 (2.0)	2 (0.8)	.34
Soft tissue	13 (1.8)	12 (2.7)	1 (0.4)	.039
Prostate	2 (0.3)	2 (0.4)	0 (0.0)	.54
Disseminated <sup>b</sup>	493 (69.5)	353 (78.1)	140 (54.5)	<.0001
Other	21 (3.0)	18 (4.0)	3 (1.2)	.034
<b>Underlying diseases</b>				
None	150 (21.2)	46 (10.2)	104 (40.5)	<.0001
Corticosteroids	242 (34.1)	174 (38.5)	68 (26.5)	.0012
HIV	183 (25.8)	174 (38.5)	9 (3.5)	<.0001
Solid organ transplant	129 (18.2)	113 (25.0)	16 (6.2)	<.0001
<b>Malignancy<sup>c</sup></b>				
Hematologic	49 (6.9)	31 (6.9)	18 (7.0)	.94
Nonhematologic	61 (8.6)	26 (5.8)	35 (13.6)	.000

**Table 2. Baseline Clinical Findings in Patients With Any Central Nervous System Cryptococcosis**

Characteristic	Total (N = 419)	<i>Cryptococcus neoformans</i> (n = 291)	<i>Cryptococcus gattii</i> (n = 128)	PValue		
<b>Clinical presentation</b>						
Headache	303 (72.3)	199 (68.4)	104 (81.3)	.0067		
Vomiting	155 (37.0)	108 (37.1)	47 (36.7)	.94		
Altered mental status	153 (36.5)	121 (41.6)	32 (25.0)	.0012		
<b>Lumbar Puncture*</b>						
No.	Total (N = 419)	<i>Cryptococcus neoformans</i> (n = 291)	<i>Cryptococcus gattii</i> (n = 128)	PValue	PValue <sup>b</sup>	
<b>Opening pressure, mm H<sub>2</sub>O</b>						
Mean ± SD	237	312 ± 149	314 ± 152	306 ± 138	.72	.90
Median (IQR)	237	300 (190–420)	290 (190–430)	310 (190–400)	.90	NA
<b>WBCs<sup>d</sup>/μL, mean ± SD</b>						
	369	158 ± 339	115 ± 265	267 ± 460	<.0001	.014
<b>WBCs<sup>d</sup>/μL, median (IQR)</b>						
	369	46 (9–150)	30 (6–104)	119 (44–360)	<.0001	NA
<b>% Polymorphonuclear leukocytes</b>						
	136	21 ± 27	18 ± 26	37 ± 29	.002	.003
<b>% Lymphocytes</b>						
	164	67 ± 27	70 ± 26	59 ± 27	.02	.032
<b>Protein, mg/L, mean ± SD</b>						
	372	112 ± 137	116 ± 133	100 ± 146	.31	.067
<b>Glucose, mg/dL, mean ± SD</b>						
	374	35 ± 30	44 ± 28	14 ± 23	<.0001	<.001
<b>CT findings</b>						
	Total (N = 419)	<i>Cryptococcus neoformans</i> (n = 291)	<i>Cryptococcus gattii</i> (n = 128)	PValue	PValue <sup>b</sup>	
<b>Normal</b>						
	192 (59.1)	152 (69.4)	40 (37.7)	<.0001		
<b>Hydrocephalus</b>						
	36 (11.1)	17 (7.8)	19 (17.9)	.0062	NA	
<b>Mass lesion</b>						
	32 (9.9)	7 (3.2)	25 (23.6)	<.0001		
<b>MRI</b>						
	Total (N = 419)	<i>Cryptococcus neoformans</i> (n = 291)	<i>Cryptococcus gattii</i> (n = 128)	PValue	PValue <sup>b</sup>	
<b>Normal</b>						
	63 (49.6)	56 (57.7)	7 (23.3)	.0010		
<b>Hydrocephalus</b>						
	10 (7.9)	9 (9.3)	1 (3.3)	.45		
<b>Mass lesion</b>						
	23 (18.1)	12 (12.4)	11 (36.7)	.0025		
<b>Outcomes</b>						
	Total (N = 709)	<i>Cryptococcus neoformans</i> (n = 452)	<i>Cryptococcus gattii</i> (n = 257)	Unadjusted OR (95% CI)	Adjusted <sup>d</sup> OR (95% CI)	
<b>Mortality at 3 mo</b>						
	131 (18.8)	89 (19.7)	42 (17.0)	1.20 (0.90–1.60)	0.95 (0.53–1.70)	
<b>Mortality at 12 mo</b>						
	178 (25.5)	128 (28.4)	50 (20.2)	1.56 (1.09–2.26)	1.45 (0.86–2.45)	
<b>IRIS present</b>						
	34 (4.8)	16 (3.6)	18 (7.1)	0.49 (0.24–0.97)	0.28 (0.10–0.82)	
<b>Any CNS infection</b>						
	Total (N = 419)	<i>Cryptococcus neoformans</i> (n = 291)	<i>Cryptococcus gattii</i> (n = 128)	PValue	PValue <sup>b</sup>	
<b>Shunt placement</b>						
	70 (22.4)	38 (13.0)	32 (25.0)	0.78 (0.45–1.33)	1.26 (0.58–2.72)	
<b>Mortality at 3 mo</b>						
	69 (16.6)	54 (18.6)	15 (11.9)	1.69 (0.91–3.12)	1.40 (0.58–3.37)	
<b>Mortality at 12 mo</b>						
	98 (23.5)	78 (26.8)	20 (15.9)	1.94 (1.13–3.34)	1.99 (0.91–4.33)	
<b>Pulmonary infection only</b>						
	Total (N = 204)	<i>Cryptococcus neoformans</i> (n = 104)	<i>Cryptococcus gattii</i> (n = 100)	PValue	PValue <sup>b</sup>	
<b>Mortality at 3 mo</b>						
	38 (18.6)	17 (16.4)	21 (21.0)	0.74 (0.36–1.49)	0.46 (0.17–1.29)	
<b>Mortality at 12 mo</b>						
	50 (24.5)	27 (26.0)	23 (23.0)	1.17 (0.62–2.23)	1.12 (0.46–2.70)	

## *C. gattii*:

- plus de patients sans facteur de risque identifié
- délai diagnostique plus long
- plus de forme pulmonaires
- moins de troubles de la conscience
- plus de cellularité dans le LCS et d'IRIS

# Screening CrAg HIV positifs <100 CD4 Espagne

- 576 patients PPVIH
- 2004-2017
- CD4<100
- CrAg sur plasma banque
- 43/576 positifs : 7.5%
- Pas de différence lieu de naissance
- CrAg + associé mortalité à S8 et 6 mois
- Méningite chez 10 des 43 CrAg +
  - 5 au moment du prélèvement
  - 5 par la suite
- Pas de cas parmi neg
- 114 sujet à screener pour 1 diagnostic de méningite
  - ❖ Modifications des recommandations espagnoles

**Table 2**

Uni- and multivariate analysis of risk factors predicting the positivity of cryptococcal antigen (CrAg)

Variable	CrAg+ (n = 43)	CrAg- (n = 528)	p	Univariate analysis			Multivariate analysis		
				OR	95% CI	p	OR	95% CI	p
Age, years (mean ± SD)	41.95 ± 11.18	40.68 ± 10.83	0.791	1.011 <sup>b</sup>	0.983–1.039	0.459			
Male gender (n (%))	38 (88.4%)	422 (79.2%)	0.148	1.999	0.769–5.198	0.155			
CD4 <sup>+</sup> /μL (mean ± SD)	48.88 ± 28.22	44.43 ± 28.39	0.323	1.005 <sup>b</sup>	0.995–1.016	0.323	1.009 <sup>b</sup>	0.997–1.021	0.152
Viral load copies/ml (mean ± SD)	547,762 ± 614,246	588,344 ± 953,410	0.786						
<b>Educational level</b>									
Primary school or less (n (%))	12 (10.7%)	100 (89.3%)	0.241	1.53	0.600–3.902	0.373			
High school (n (%))	15 (5.8%)	245 (94.2%)	0.781	0.321	–1.898	0.585			
University (n (%))	8 (7.3%)	102 (92.7%)		Reference					
<b>HIV Transmission route</b>									
IDUs (n (%))	7 (17.9%)	32 (82.1%)	<b>0.003</b>	<b>3.625</b>	<b>1.47–8.937</b>	<b>0.005</b>	<b>3.952</b>	<b>1.582–9.871</b>	<b>0.003</b>
Sexual (n (%))	28 (5.7%)	464 (94.3%)							
Other opportunistic diseases <sup>a</sup> (n (%))	14 (32.6%)	243 (45.6%)	0.098	0.576	0.298–1.115	0.102			
AIDS defining condition <sup>a</sup> (n (%))	17 (39.5%)	273 (51.2%)	0.140	0.623	0.330–1.174	0.143			
<b>Birthplace</b>									
Spain (n (%))	27 (7.4%)	338 (92.6%)	0.888	1.038	0.234–4.611	0.960			
Latin America (n (%))	9 (6.8%)	124 (93.2%)		0.944	0.193–4.624	0.943			
Sub Saharan Africa (n (%))	4 (9.8%)	37 (90.2%)		1.405	1.405–8.250	0.706			
Asia (n (%))	1 (16.7%)	5 (83.3%)		2.6	0.196–34.458	0.469			
Other (n (%))	2 (7.1%)	26 (92.9%)		Reference					

CI, confidence interval; IDU, intravenous-drug user; OR, odds ratio; SD, standard deviation. The bold in the tables is used to remark the statistically significant values.

<sup>a</sup> Previous or within the first month after determining CrAg (excluding cryptococcal meningitis).

<sup>b</sup> Per unitary increment.

Essai crypto traité dans la partie VIH

# Cryptococcose: pas de corrélation entre la CMI et la clearance fongique

Clinical Infectious Diseases

## BRIEF REPORT

### Antifungal Susceptibility Does Not Correlate With Fungal Clearance or Survival in AIDS-Associated Cryptococcal Meningitis

Lacy O'Connor,<sup>1</sup> Duong Van Anh,<sup>2</sup> Tran Thi Hong Chau,<sup>2</sup> Nguyen Van Vinh Chau,<sup>3</sup> Lan Nguyen Phu Hoang,<sup>2</sup> Marcel Wolbers,<sup>2</sup> and Jeremy N. Day<sup>2,4</sup>

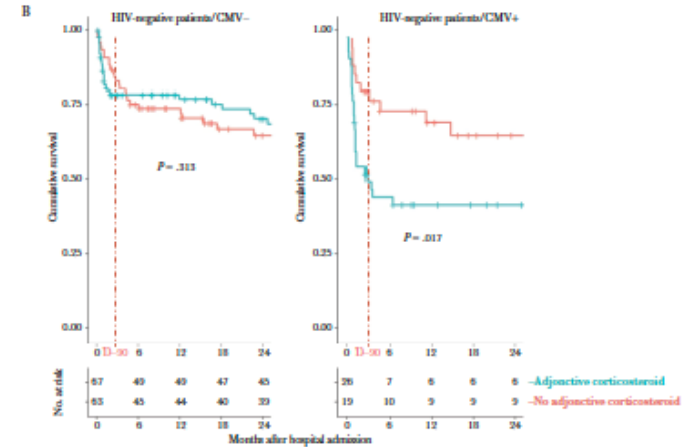
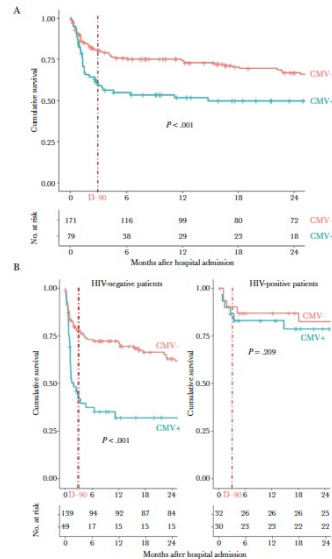
**Table 1.** The estimated effect, defined by hazard ratio (HR) and 95% confidence intervals, of a 2-fold increase in the MICs estimated at 72 hours for amphotericin, fluconazole, and flucytosine on survival outcomes at 14, 70, and 182 days postrandomisation for the primary analysis population and the effect on mycological outcome (the rate of decline of CSF fungal count, log<sub>10</sub> Colony Forming Units/mL CSF/day)

	Group 1 Amphotericin (n = 92)		Group 2 Amphotericin and Flucytosine (n = 96)		Group 3 Amphotericin and Fluconazole (n = 88)	
	HR	P value	HR	P value	HR	P value
<b>Death by day 14</b>						
Effect on the rate of death per 2-fold increase in the MIC (95% CI) of:						
Amphotericin	0.64 (.28, 1.44)	.28	0.86 (.35, 2.13)	.75	0.69 (.27, 1.75)	.43
Flucytosine	-	-	0.70 (.33, 1.47)	.34	-	-
Fluconazole	-	-	-	-	1.23 (.63, 2.43)	.54
<b>Death by day 70</b>						
Effect on the rate of death per 2-fold increase in the MIC (95% CI) of:						
Amphotericin	0.94 (.65, 1.36)	.83	0.58 (.31, 1.09)	.09 <sup>a</sup>	0.97 (.47, -2.01)	.94
Flucytosine	-	-	0.88 (.55, 1.39)	.58	-	-
Fluconazole	-	-	-	-	0.87 (.51, 1.49)	.61
<b>Death by 6 months (day 182)</b>						
Effect on the rate of death per 2-fold increase in the MIC (95% CI) of:						
Amphotericin	1.10 (.65, 1.86)	.72	0.62 (.34, 1.11)	.11 <sup>b</sup>	1.28 (.71, 2.30)	.42
Flucytosine	-	-	0.89 (.58, 1.39)	.62	-	-
Fluconazole	-	-	-	-	0.86 (.54, 1.36)	.51
<b>Change in CSF fungal decline in first 14 days (log<sub>10</sub> CFU/mL of CSF per day) per 2-fold increase in MIC</b>						
Numbers in brackets are 95% Confidence Intervals						
	Effect estimate	P value	Effect estimate	P value	Effect estimate	P value
Amphotericin	-0.01 (-.07, .04)	.59	0.02 (-.03, .07)	.40	0.00 (-.04, .04)	.95
Flucytosine	-	-	1.10 (.80, 1.49)	.63	-	-
Fluconazole	-	-	-	-	0.01 (-.02, .04)	.53



# Pneumocystose et coinfections: épidémiologie et impact

- Bicentrique (Nantes, Bordeaux)
- Rétrospective 2011-2019
- Coinfections pulmonaires PCP
- 328 patients PCP
  - 57 ans
  - 23% HIV +, 60% HIV – recevaient une CoT préalable (dose moyenne de 30mg/j)
- 54% coinfection
  - 38% virale (29% CMV)
  - 23% bactérienne (*S. aureus*, *P.seudomonas spp.*)
  - 11% fongique



Coinfection CMV associée à la mortalité chez les patients HIV -  
Corticothérapie associée mortalité patients HIV - avec coinfection  
CMV

- ❖ Marqueur ID probable
- ❖ Connaître réplication CMV LBA pour discuter CoT

# Pneumocystose en néonatalogie

- 2018-2019
  - NN prématurés < 32 SA ET
  - Détresse respiratoire
  - PCR PCP sur aspirations NN et prélèvement mère
  - 14% positivité aspirations NN
  - 21% mère
- **Positivité des aspirations associée:**
    - ❖ dysplasie broncho pulmonaire
    - ❖ durée oxygénothérapie

# Dermatophytose résistante à la terbinafine

- 7 cas dermatophytoses extensives depuis 2018
- Pas de cas autochtones (sous continent Indien)
- Echec terbinafine
- *T. interdigitale/mentagrophytes* (habituellement onychomycose)
- Séquencage ITS *T. indotinea*



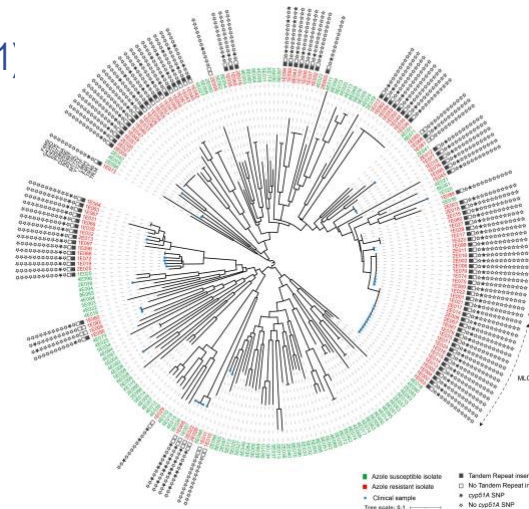
# Dermatophytes résistants

- Etude prospective multicentrique sur la R dermatophytes à la terbinafine.
- 3/580 isolats résistants in vitro: 1 *T. rubrum*, 1 *T. interdigitale*, 1 *T. indotinea*
- Mutation Phe397Leu ( $n = 2$ ) ou Leu393Ser ( $n = 1$ ) SQLE
- Séquencage *T. mentagrophytes/interdigitale* complex ( $n = 125$ ) fréquence 4.8% *T. indotineae*

- **A SUIVRE**

# Approche One health résistance aux antifongiques

- Genotypage *A. fumigatus* (9 microsatellites) pour étude diversité en France
- 225 isolats *A. fumigatus*
  - 112 azole S, 113 azole R
  - Bourgogne-Franche-Comté region
  - Cliniques ( $n = 34$ ) et environnement ( $n = 191$ )
- Azole-resistant ( $n = 29$ ) patients muco et isolats environnementaux ( $n = 84$ )
- TR<sub>34</sub>/L98H 80% isolats R.
- Géotypes très diverses
- Population *A. fumigatus* mixtes.
- Genotypes clonaux similaires à l'Australie , d'autres non décrits



POPULATION

Clinical samples

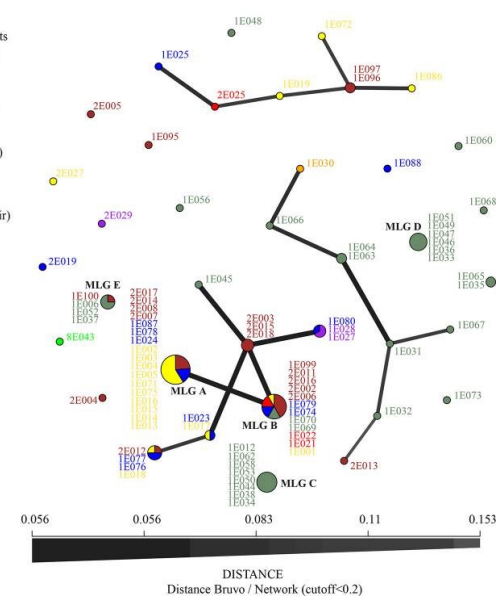
- Cystic fibrosis patients
- Hematology patients
- Other patients

Environmental samples

- Cereals crops (soil)
- Market gardens (soil)
- Sawmills (soil)
- Dwellings (dust)
- Hospital corridors (air)

Samples/Node

- 17
- 8
- 1

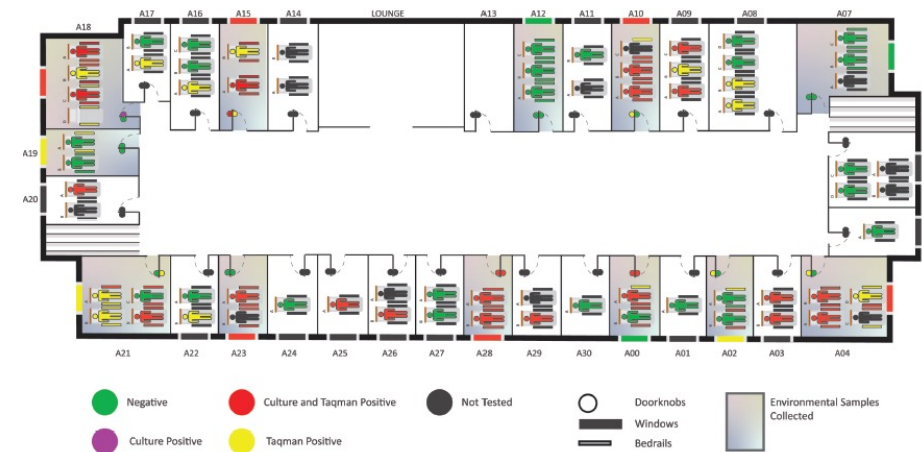


Rocchi S, Front Cell Infect Microbiol 2021

# Epidémies de *C.auris*: contamination de l'environnement hospitalier

## Positive Correlation Between *Candida auris* Skin-Colonization Burden and Environmental Contamination at a Ventilator-Capable Skilled Nursing Facility in Chicago

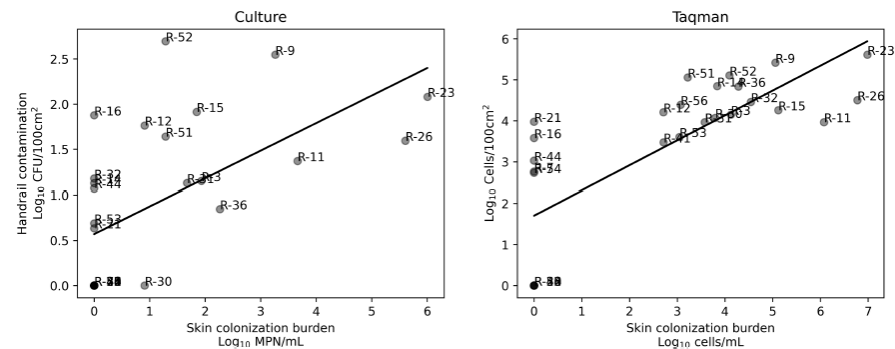
D. Joseph Sexton,<sup>1,6</sup> Meghan L. Bentz,<sup>1</sup> Rory M. Welsh,<sup>1</sup> Gordana Derado,<sup>2</sup> William Furin,<sup>3</sup> Laura J. Rose,<sup>3</sup> Judith Noble-Wang,<sup>2</sup> Massimo Pacilli,<sup>4</sup> Tristan D. McPherson,<sup>4,5</sup> Stephanie Black,<sup>4</sup> Sarah K. Kemble,<sup>4</sup> Owen Herzegh,<sup>6</sup> Ausaf Ahmad,<sup>6</sup> Kaitlin Forsberg,<sup>1</sup> Brendan Jackson,<sup>1</sup> and Anastasia P. Litvintseva<sup>1</sup>



**Figure 1.** Facility map with culture-based and qPCR results for residents and associated environmental surfaces. The specific organization of beds within a room may differ from the image.

**Table 1.** Results From Environmental Sampling Organized by Sample Type

Sample Type	Taqman Results			Culture Results <sup>a</sup>					
	Positive/Total	Interpolated cells/100 cm <sup>2</sup>			Positive/Total		CFU/100 cm <sup>2</sup>		
		Mean	Min	Max	Broth	Plates	Mean	Min	Max
Window	9/12	$8.2 \times 10^2$	660	$3.2 \times 10^4$	6/12	6/12	80	4.7	410
Indoor knob	7/12	$4.6 \times 10^3$	460	$1.5 \times 10^5$	3/12	2/12	2.9	2.4	3.4
Outdoor knob	3/12	$1.2 \times 10^3$	840	$1.8 \times 10^3$	3/12	1/12	350	-	-
Left handrail	26/32	$5.1 \times 10^4$	570	$3.7 \times 10^5$	18/32	17/32	58	2.7	270
Right handrail	25/32	$5.4 \times 10^4$	590	$4.5 \times 10^5$	20/32	18/32	120	3.3	970
Total	70/100	$4.0 \times 10^4$	460	$4.5 \times 10^5$	50/100	44/100	92	2.4	970



**Figure 2** (panel A) for visual

Lien entre la colonisation cutanée et l'environnement hospitalier immédiat (barrières+++)

# Intérêt de la PCR Histoplasma

- 53 patients histoplasmoses
- PCR Histoplasma sang, prélèvement respiratoire, moelle, tissu, LCS, etc

**Table 3** Proportion of RT-qPCR–Positive Specimens in Patients Belonging to the Four Most Frequent Clinical Presentations

Specimen	No. (%) of positive specimens/total specimens	No. (%) of patients with positive specimens/total No. of sampled patients
<b>Progressive disseminated histoplasmosis/<i>Histoplasma capsulatum</i> var. <i>capsulatum</i> (n = 23)</b>		
All pulmonary specimens (BAL, biopsy)	17/19 (88.9)	13/14 (92.8)
Skin/mucosa	8/9 (88.9)	7/7 (100)
Blood	25/48 (52.1)	13/17 (76.5)
Bone marrow aspirate	9/10 (90.0)	8/8 (100)
Digestive tract biopsy	3/3 (100.0)	3/4 (75.0)
Adrenal gland biopsy	1/1 (100)	1/1 (100)
Osteoarticular	1/1 (100)	1/1 (100)
CSF	0/3 (0)	0/3 (0)
<b>Progressive disseminated histoplasmosis and immunocompromised/<i>H. capsulatum</i> var. <i>capsulatum</i> (n = 18)</b>		
All pulmonary specimens (BAL, biopsy)	10/12 (83.3)	8/9 (88.9)
Blood	24/44 (54.5)	12/13 (92.3)
<b>Progressive disseminated histoplasmosis and HIV/<i>H. capsulatum</i> var. <i>capsulatum</i> (n = 12)</b>		
All pulmonary specimens (BAL, biopsy)	8/9 (88.9)	5/5 (100)
Blood	20/38 (52.6)	10/11 (90.9)
<b>Acute pulmonary histoplasmosis with or without mediastinal lymphadenitis/<i>H. capsulatum</i> var. <i>capsulatum</i> (n = 12)</b>		
BAL	2/3 (66.7)	2/3 (66.7)
Lung biopsy	5/6 (83.3)	5/6 (83.3)
Mediastinal lymph node	5/5 (100)	5/5 (100)
All pulmonary specimens	12/14 (85.7)	12/12 (100)
Blood	0/12 (0)	0/9 (0)
<b>CNS histoplasmosis/<i>H. capsulatum</i> var. <i>capsulatum</i> (n = 2)</b>		
CSF	4/7 (57.1)	2/2 (100)
Blood	0/5 (0)	
<b>Disseminated <i>duboisii</i> histoplasmosis/<i>Histoplasma capsulatum</i> var. <i>duboisii</i> (n = 4)</b>		
Bone biopsy	2/2 (100)	2/2 (100)
Skin	6/6 (100)	2/2 (100)
Brain biopsy	4/4 (100)	1/1 (100)
Urinary tract	1/4 (25)	1/3 (33)
Digestive biopsy	1/1 (100)	1/1 (100)
Sputum	0/1 (0)	0/1 (0)
Blood	0/8 (0)	0/3 (0)
Bone marrow	0/1 (0)	0/1 (0)

BAL, bronchoalveolar lavage fluid; CSF, cerebrospinal fluid; CNS, central nervous system; RT-qPCR, reverse transcriptase quantitative real-time PCR.

# Evaluation PCR Mucorales serum: PHRC Modimucor

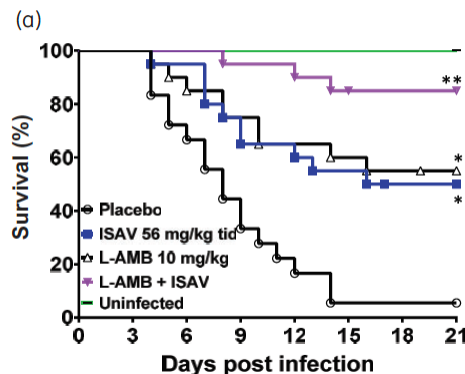
- **232 patients suspicion d'infection à filamenteux**
- **13 patients avec mucormycose probable ou prouvée**
- **Mucorales qPCR x2/sem**
- **Se 85%, Sp 90%**
- **PCR positive 4 jours avant prélèvement conduisant au diagnostic et 1 jour avant l'imagerie**
- **Négativité de la qPCR à J7 associée à une diminution de mortalité de 85%**



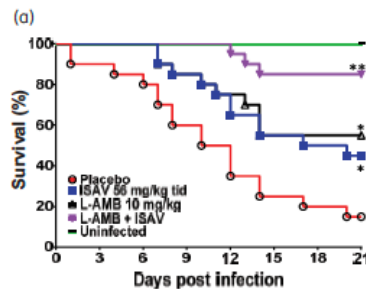
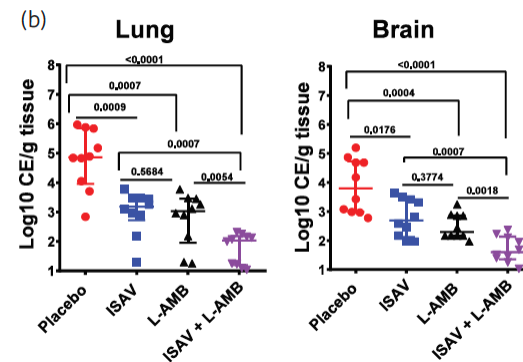
# Association d'antifongique dans les mucormycoses: modèle animal

- Souris neutropéniques
- Infection intratrachéale
  - *Rhizopus delamar*
  - *Mucor circinelloides*
- Association L AmB et isavuconazole

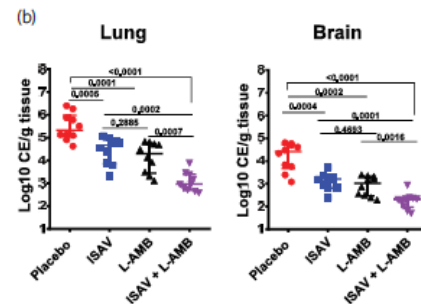
SYNERGIE



*Rhizopus delamar*



*Mucor circinelloides*



Gebremariam, JAC 2021

# PK/PD caspofungine plasma et liquide péritonéal transplantés hépatiques

- **20 patients**
- **Plasma: PTA>90% pour CMI entre 0.008 et 0.12**
- **Liquide péritoneal: CMI 0.008**
- **16 patients colonisés, CMI sous Cmax dans le plasma mais pas le liquide péritonéal**
- **Risque d'émergence de résistance pour les infections péritonéales**

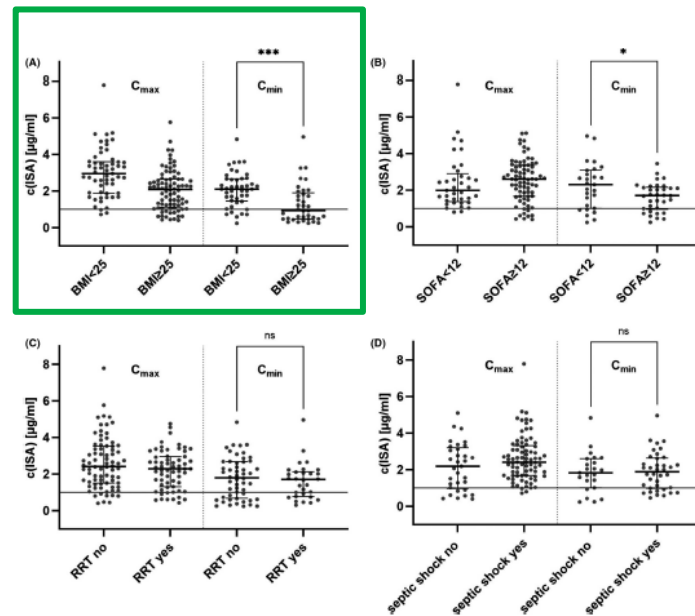
Pressiat C, AAC, 2022

# Isavuconazole en réanimation

- 223 dosages isavuconazole patients ICU
- 32% résiduel <1 microg/mL

TABLE 2 Percentages of isavuconazole through plasma levels <1 µg/ml among characterised sub-cohorts

Sub-cohort	C <sub>min</sub> <1 µg/ml (%)
BMI <25	15.6
BMI ≥25	51.4
SOFA <12	22.2
SOFA ≥12	26.5
RRT no	30.8
RRT yes	33.3
Septic shock no	21.7
Septic shock yes	26.3



Hohl R, Mycoses, 2022

# Isavuconazole dans le traitement de l'aspergillose chronique: quelques données

- **2016-2021**
- **54 patients traités**
- **67% bonne tolérance**
- **62% mauvaise tolérance préalable azoles**
- **9% de patients nécessitant réadaptation taux après dosage**
- **Mauvaise tolérance associée à l'âge et au sexe masculin**

Bonne tolérance isavuconazole en cas de toxicité de l'isavuconazole  
Tolérance associée à l'âge

# POSAFLU

- Essai randomisé international
- Gripes sévères
- 10j de symptômes et 48 heures de réanimation
- Prophylaxie posa IV 7 j vs placebo
- 88 patients avec grippe grave en réanimation
- 24% IAPA , 71% survenues dans les 48h de l'admission
- Incidence IAPA 5.4% vs 5.7%

## Posaconazole for prevention of invasive pulmonary aspergillosis in critically ill influenza patients (POSA-FLU): a randomised, open-label, proof-of-concept trial

Lore Vanderbeke<sup>1,2</sup>, Nico A. F. Janssen<sup>3,4</sup>, Dennis C. J. J. Bergmans<sup>5</sup>, Marc Bougeots<sup>6</sup>, Jochem B. Bui<sup>4,7</sup>, Yves Diebaveye<sup>8,9</sup>, Pieter Depuydt<sup>10</sup>, Simon Feys<sup>1,2</sup>, Greet Hermans<sup>2,8</sup>, Oscar Hotting<sup>11</sup>, Ben van der Hoven<sup>12</sup>, Cato Jacobs<sup>2</sup>, Katrien Lagrou<sup>1,13</sup>, Virginie Lemaire<sup>14</sup>, Piet Lormans<sup>15</sup>, Johan Maertens<sup>1,16</sup>, Philippe Meersseman<sup>1,2</sup>, Bruno Mégarbane<sup>17</sup>, Saad Nseir<sup>18</sup>, Jos A. H. van Oers<sup>19</sup>, Marijke Reynders<sup>20</sup>, Bart J. A. Rijnders<sup>21</sup>, Jeroen A. Schouten<sup>22</sup>, Isabel Spriet<sup>23,24</sup>, Karin Thevissen<sup>25</sup>, Arnaud W. Thille<sup>26</sup>, Ruth Van Daele<sup>23,24</sup>, Frank L. van de Veerdonk<sup>24</sup>, Paul E. Verweij<sup>17</sup>, Alexander Wilmer<sup>1,2</sup>, Roger J. M. Brüggemann<sup>4,27</sup> and Joost Wauters<sup>1,28</sup> on behalf of the Dutch-Belgian Mycosis Study Group

# Nouvelles molécules: olorofim données in vitro/vivo



EXPERIMENTAL THERAPEUTICS

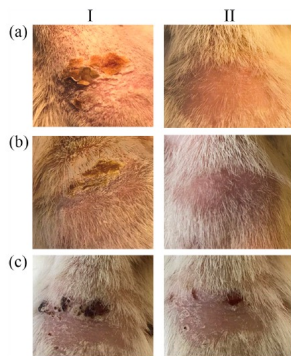


## Olorofim Effectively Eradicates Dermatophytes *In Vitro* and *In Vivo*

Esmat Mirzbadeh Ardakani,<sup>a,b</sup> Atefeh Sharifrad,<sup>a</sup> Nasrin Pashootan,<sup>c</sup> Mahsa Nayebhashemi,<sup>a</sup> Mozhgan Zahmatkesh,<sup>a</sup> Somayeh Enayati,<sup>a</sup> Mehdi Razzaghi-Abyaneh,<sup>c</sup> Vahid Khalaj<sup>a</sup>

TABLE 1 *In vitro* susceptibility of aspergilli and dermatophytes to olorofim, posacon. December 2021 Volume 65 Issue 12 e01386-21

Antifungal compound	MIC (mg/L)							
	<i>Aspergillus</i>		Dermatophytes					
	<i>Aspergillus fumigatus</i> PTCC5009	<i>Aspergillus flavus</i> PTCC5004	<i>Trichophyton mentagrophytes</i> NBRC5809	<i>Trichophyton tonsurans</i> CBS-130814	<i>Trichophyton rubrum</i> B613	<i>Epidermophyton canis</i> floccosum CBS 130793	<i>Microsporium canis</i> PTCC5069	<i>Microsporium gypsum</i> PTCC5070
Olorofim	0.01	0.01	0.01	0.06	0.01	0.03	0.03	0.03
Posaconazole	0.15	0.3	0.04	0.6	0.08	0.12	0.3	0.6
Voriconazole	0.15	0.15	0.15	0.15	0.15	0.12	0.6	0.6
Clotrimazole	2	4	0.25	1	16	2	4	1



*J Antimicrob Chemother* 2022; 77: 1645–1654  
<https://doi.org/10.1093/jac/dkac062> Advance Access publication 15 March 2022

Journal of Antimicrobial Chemotherapy

### Inhibition of azole-resistant *Aspergillus fumigatus* biofilm at various formation stages by antifungal drugs, including olorofim

Lisa Kirchhoff , Silke Dittmer<sup>1</sup>, Don-Tiberiu Furnica<sup>1</sup>, Jan Buer<sup>1</sup>, Elke Steinmann<sup>2</sup>, Peter-Michael Roth<sup>1</sup> and Joerg Steinmann<sup>1,3</sup>

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### Research note

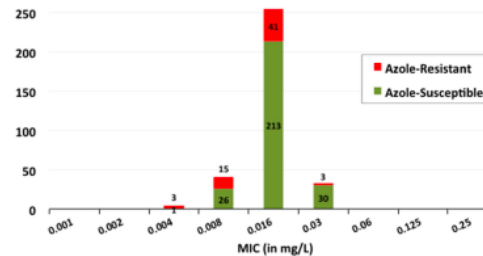
*In vitro* activity of olorofim against *Aspergillus fumigatus* sensu lato clinical isolates: activity is retained against isolates showing resistance to azoles and/or amphotericin B

Pilar Escrbano <sup>1,2,\*</sup>, Ana Gómez <sup>1,2</sup>, Elena Reigadas <sup>1,2</sup>, Patricia Muñoz <sup>1,2,3,4</sup>, Jesús Guinea <sup>1,2,3,\*</sup>, on behalf of the ASPEIN Study Group

MIC distributions of olorofim and comparators against the *A. fumigatus* sensu lato and the cryptic species studied

MIC distributions (number of isolates at each MIC, in mg/L)

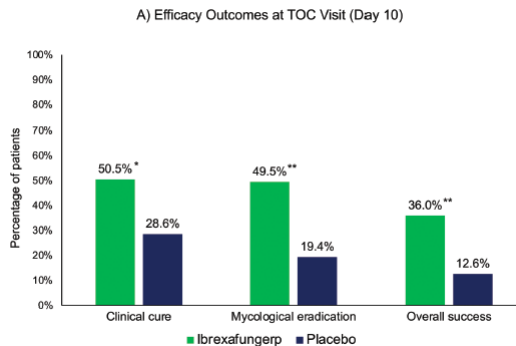
	0.001	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	>16	Resistance (2020 break-points)	No. of isolates	
<b><i>A. fumigatus</i> sensu lato (n = 312)</b>																		
Amphotericin B	—	—	—	0	0	0	14	141	131	26	0 <sup>a,c</sup>	0 <sup>a,c</sup>	0 <sup>a,c</sup>	0	0	0	0	
Isavuconazole	—	—	—	0	0	0	7	114	131	61	2 <sup>a,b,c</sup>	3 <sup>a,b,c</sup>	0 <sup>a,b,c</sup>	3 <sup>a,b,c</sup>	34	103	34	
Voriconazole	—	—	—	0	0	0	1	49	182	32	13 <sup>a,b,c</sup>	19 <sup>a,b,c</sup>	3 <sup>a,b,c</sup>	3 <sup>a,b,c</sup>	38	122	38	
Posaconazole	—	—	—	0	0	0	14	168	94	10 <sup>a,c</sup>	20 <sup>a,c</sup>	3 <sup>a,c</sup>	0 <sup>a,c</sup>	1 <sup>a,c</sup>	6 <sup>a,c</sup>	33	168	
Isavuconazole	—	—	—	0	0	0	0	6	168	98	10 <sup>a,c</sup>	10 <sup>a,c</sup>	1 <sup>a,c</sup>	1 <sup>a,c</sup>	4 <sup>a,c</sup>	35	112	
Olorofim	0	0	0	30	249	33	0	0	0	0	0	0	0	0	0	NA	NA	
<b>Cryptic species (n = 20)</b>																		
Amphotericin B	—	—	—	0	0	0	2	0	1	4	7 <sup>a,c</sup>	5 <sup>a,c</sup>	1 <sup>a,c</sup>	0 <sup>a,c</sup>	0	13	65	
Isavuconazole	—	—	—	0	0	0	0	2	2	4	0 <sup>a,b,c</sup>	1 <sup>a,b,c</sup>	1 <sup>a,b,c</sup>	0 <sup>a,b,c</sup>	0	10	50	
Voriconazole	—	—	—	0	0	0	0	1	1	0 <sup>a,b,c</sup>	0 <sup>a,b,c</sup>	0 <sup>a,b,c</sup>	0 <sup>a,b,c</sup>	0 <sup>a,b,c</sup>	0	18	90	
Posaconazole	—	—	—	0	0	0	2	1	10 <sup>a,c</sup>	7 <sup>a,c</sup>	0 <sup>a,c</sup>	0 <sup>a,c</sup>	0 <sup>a,c</sup>	0 <sup>a,c</sup>	0	12	60	
Isavuconazole	—	—	—	0	0	0	0	1	0	6	0 <sup>a,b,c</sup>	0 <sup>a,b,c</sup>	1 <sup>a,b,c</sup>	0 <sup>a,b,c</sup>	0	13	65	
Olorofim	0	0	4	11	5	0	0	0	0	0	0	0	0	0	0	NA	NA	
<b><i>A. fischeri</i> ATCC 20404</b>																		
Olorofim	0	0	0	0	0	22	2	0	0	0	0	0	0	0	0	NA	NA	
<b><i>A. fumigatus</i> ATCC 204285</b>																		
Olorofim	0	0	0	2	19	3	0	0	0	0	0	0	0	0	0	NA	NA	



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

Jane R. Schwebke,<sup>1</sup> Ryan Sobel,<sup>2</sup> Janet K. Gersten,<sup>3</sup> Steven A. Sussman,<sup>4</sup> Samuel N. Lederman,<sup>5</sup> Mark A. Jacobs,<sup>6</sup> B. Todd Chappell,<sup>7</sup> David L. Weinstein,<sup>8</sup> Alfred H. Moffett Jr.,<sup>9</sup> Nkechi E. Azie,<sup>10</sup> David A. Angulo,<sup>10</sup> Itzel A. Harriott,<sup>10</sup> Katyna Borroto-Esoda,<sup>11</sup> Mahmoud A. Ghannoum,<sup>12</sup> Paul Nyirjesy,<sup>2</sup> and Jack D. Sobel<sup>13</sup>

- Premier agent classe triterpénoïde
- Ibrexafungerp (SCY-078)
- Mécanisme action proche échinocandines: cible glucane synthase
- Action fongicide *Candida*
- CVV aigüe
- 2:1 ibrexafungerp (300mg BID J1) vs placebo
- Bonne tolérance



	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 <sup>2</sup> ), 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)
<i>Candida</i> species		
<i>Candida albicans</i>	173 (92.0)	90 (91.8)
<i>Candida glabrata</i>	11 (5.9)	11 (11.2)
<i>Candida tropicalis</i>	4 (2.1)	1 (1.0)
<i>Candida dubliniensis</i>	2 (1.1)	0
<i>Candida lusitanae</i>	1 (0.5)	1 (1.0)
<i>Candida parapsilosis</i>	1 (0.5)	0
<i>Candida krusei</i>	0	1 (1.0)
<i>Saccharomyces</i> species	1 (0.5)	0

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

George R. Thompson III,<sup>1</sup> Alex Soriano,<sup>2</sup> Athanasios Skoutelis,<sup>3</sup> Jose A. Vazquez,<sup>4</sup> Patrick M. Honore,<sup>5</sup> Juan P. Horcajada,<sup>6</sup> Herbert Sproten,<sup>7</sup> Matteo Bassetti,<sup>8</sup> Luis Ostrosky-Zelchner,<sup>9</sup> Anita F. Das,<sup>10</sup> Rolando M. Viani,<sup>11</sup> Taylor Sandison,<sup>12</sup> and Peter G. Pappas<sup>13</sup>, The STRIVE Trial Investigators

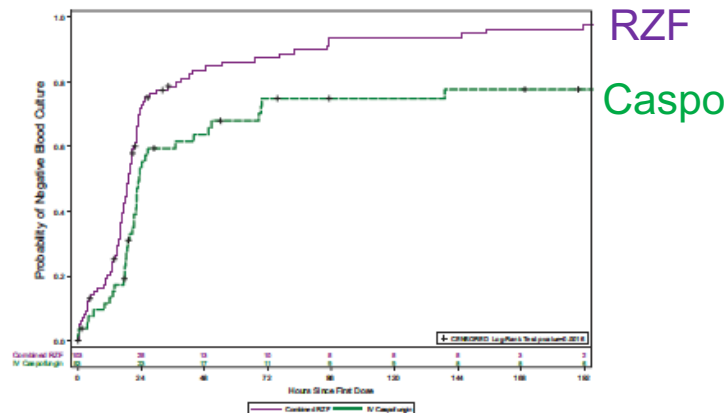
- Rezafungin: demi-vie 133h
- Essai de phase 2 randomisé
- Candidémie et candidoses invasives
- RZF 400mg/sem S1 puis 200mg/sem vs 400mg/sem vs Caspo 70mg puis 50mg puis fluco
- Guérison à S2
- 207 patients

**Table 3. Primary Efficacy Endpoint: Overall Response at Day 14 (Microbiological Intent-to-Treat [mITT] Population)—Part A, Part B, and Combined**

Overall Response, n (%)	Rezafungin Once Weekly 400 mg N = 76	Rezafungin Once Weekly 400 mg/200 mg N = 46	Caspofungin Once Daily 70 mg/50 mg N = 61
Overall cure [95% CI]	46 (60.5) [48.6–71.6]	35 (76.1) [61.2–87.4]	41 (67.2) [54.0–78.7]
Failure/indeterminate	30 (39.5)	11 (23.9)	20 (32.8)
Failure	20 (26.3)	8 (17.4)	17 (27.9)
Indeterminate	10 (13.2)	3 (6.5)	3 (4.9)

**Table 5. Secondary Efficacy Outcomes at Day 5 (Microbiological Intent-to-Treat [mITT] Population)—Parts A and B Combined**

Endpoint at Day 5, n (%)	Rezafungin Once Weekly 400 mg N = 76	Rezafungin Once Weekly 400 mg/200 mg N = 46	Rezafungin Once Weekly Pooled N = 122	Caspofungin Once Daily 70 mg/50 mg N = 61
Overall cure	42 (55.3)	34 (73.9)	76 (62.3)	34 (55.7)
Mycological success	50 (65.8)	35 (76.1)	85 (69.7)	38 (62.3)





# MERCI

- **Pour ces belles JNI**
- **CNRMA**
- **Mycologues**
- **Infectiologues SMIT Necker et G2I**