# Infections à levures

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# Active Surveillance Program to Increase Awareness on Invasive Fungal Diseases: the French RESSIF Network (2012 to 2018)

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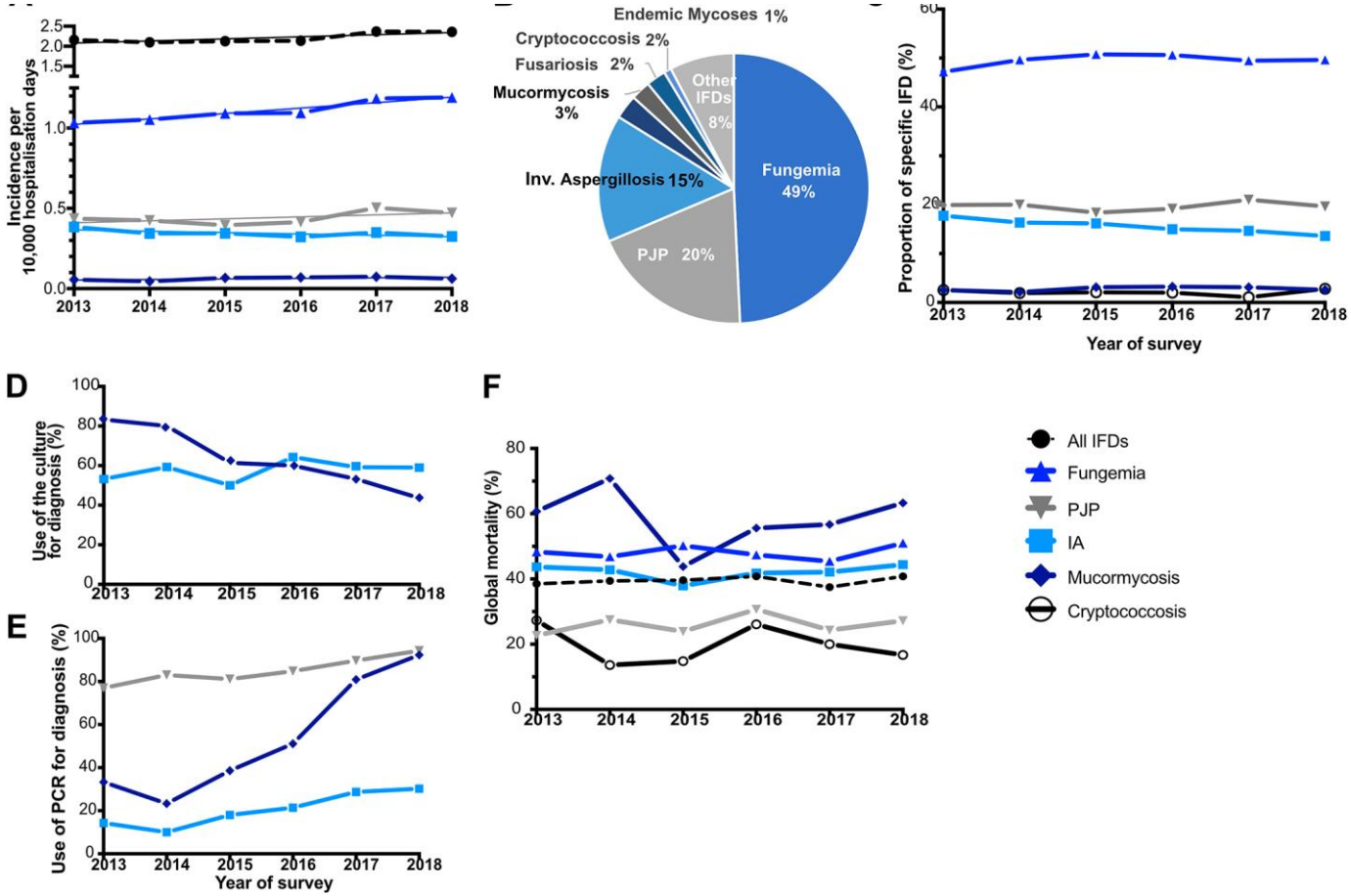
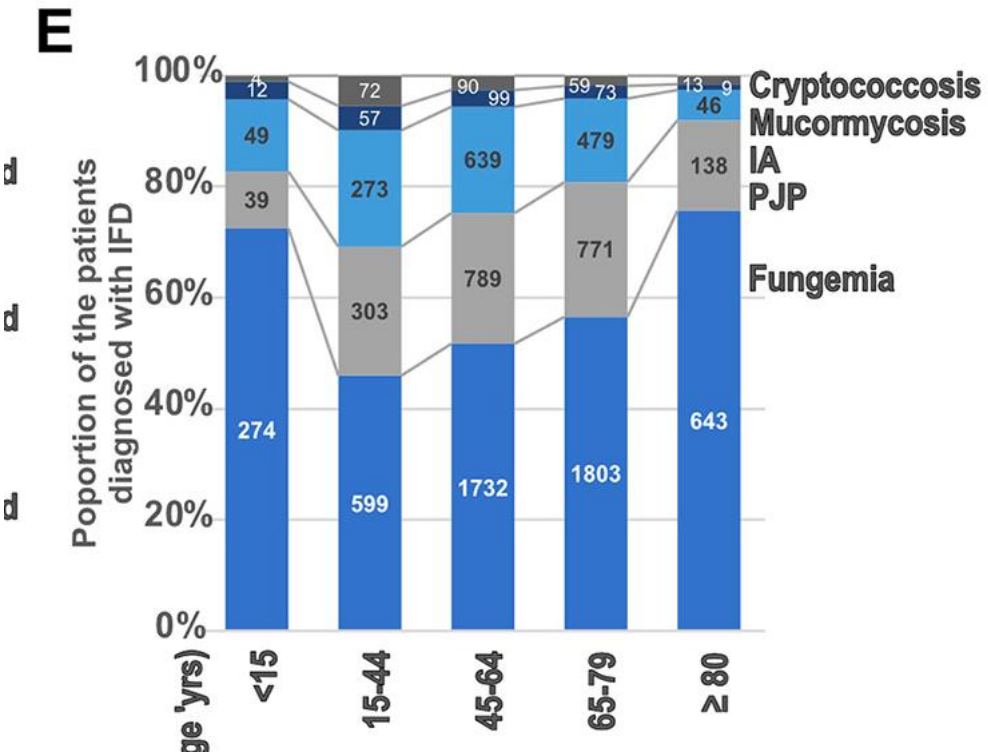



Bretagne et al, mBio 2022

| arameter | Results[b] by IFDs<br>Fungemia[c] ($n$ = 5,363) |
|---|---|
| haracteristics of the patients | |
| Male sex | 3,106/5,056 (61.4) |
| Median age (years [IQR[e]]) | 63.4 (22.8) |
| Main underlying risk factor | |
| Malignancy | 1,908/5,056 (37.7) |
| Malignancy, including hematological malignancy | 782/1,908 (41.0) |
| SOT | 162/5,056 (3.2) |
| Recent surgery | 1,610/5,056 (31.8) |
| HIV infection | 11/5,056 (0.2) |
| Other risk factor | 1,351/5,056 (26.7) |
| No known underlying condition | 14/5,056 (0.3) |
| haracteristics of the isolates | |
| Intensive care unit | 1,924/5,363 (35.9) |
| Type of IFD | |
| Proven | 5,363/5,363 (100.0) |
| Probable | |
| PCR only | |
| Means of diagnosis | |
| Positive culture | 5,363/5,363 (100.0) |
| Fungal elements in fluids/ tissues | 1,715/5,363 (32.0) |
| Positive antigen detection | 253/5,363 (4.7) |
| Positive PCR test | 9/5,363 (0.2) |
| Initial antifungal treatment | |
| Caspofungin | 2,366/4,592 (51.5) |
| Fluconazole | 1,424/4,592 (31.0) |
| Voriconazole | 100/4,592 (2.2) |
| Liposomal amphotericin B | 150/4,592 (3.3) |
| Cotrimoxazole | |
| Other drugs or combinations | 552/4,592 (12.0) |
| obal mortality at 3 mo | 2,003/4,204 (47.6) |

rance, 2012 to 2018




Bretagne et al, mBio 2022

# Candidemia: frequent deadly BSI

- Brazilian Scope (BSI):
  - 16 hospitals, 2007-2010
  - 2563 patients
  - Gram negative = 58.5%
  - Gram positive = 35.4%
  - Fungi = 6.1%
  - *Candida* spp.
    - N° 7 pathogen
    - N° 1 killer

- Japan BSI
  - 22 hospitals 2008-2012
  - 2941 patients
  - *Candida* spp.
    - N°6 pathogen
    - N°1 killer

Marra JCM 2011

Nagao, CMI 2013

# Fongémies à levures

- 2,4% (n=201) étaient des basidiomycètes (115 *Cr. neoformans*, 42 *Rhodotorula mucilaginosa*, 30 *Trichosporon* spp. et 15 *Malassezia* spp.).
- 6878 levures ascomycètes, les principales étaient:
  - *C. albicans* (50,4%)
  - *C. glabrata* (17,3%)
  - *C. parapsilosis* (12,5%)
  - *C. tropicalis* (7.1%)
  - *C. krusei* (3,1%)
  - *C. kefyr* (1,8%)
  - *Cl. lusitaniae* (2.0%)

Rapport CNRMA 2020

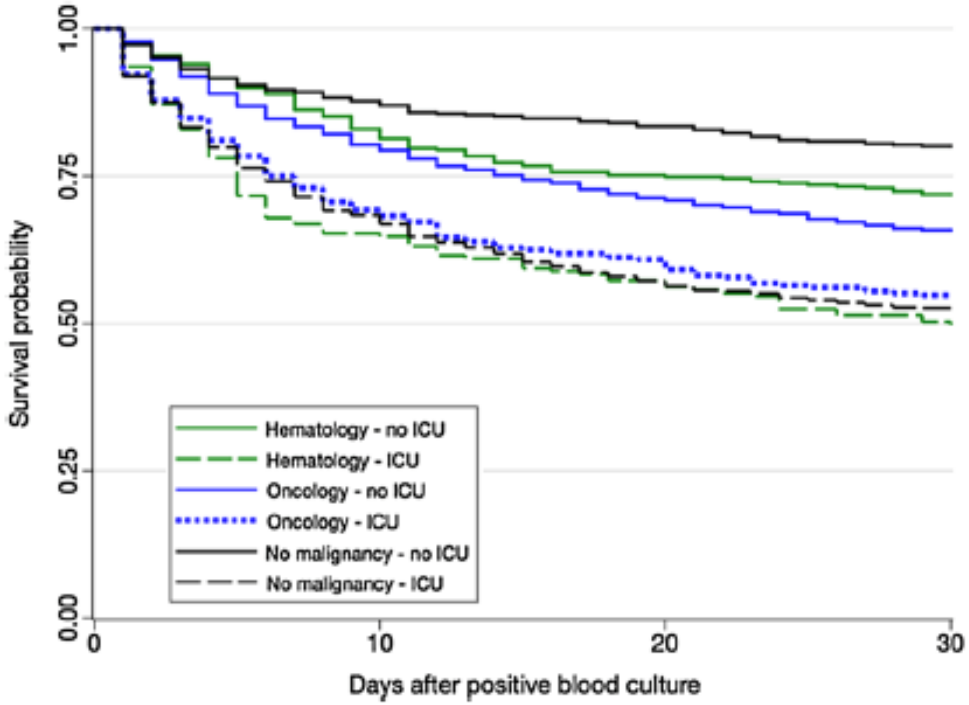
# Fungemia epidemiology in HM

- Fungemia 2003-2014
- 3417 patients with fungemia in France
- 586 with HM
- HM:
  - AL: 33.5%
  - Allo HSCT 11% (GVH, 5%)
  - Less ICU (34%)
  - More surgery in ICU for lymphoma

Lortholary O, ICM 2017

# Fungemia epidemiology in HM

- HM:
  - Younger
  - Preexposed AF
  - More *C. tropicalis, C. krusei, C. kefyr*
  - *29% C. albicans in AL*
  - *C. parapsilosis* less frequent in ICU
  - More first line echinocandin treatment
  - No influence on Candida species on mortality




Lortholary O, ICM 2017

# Physiopathologie

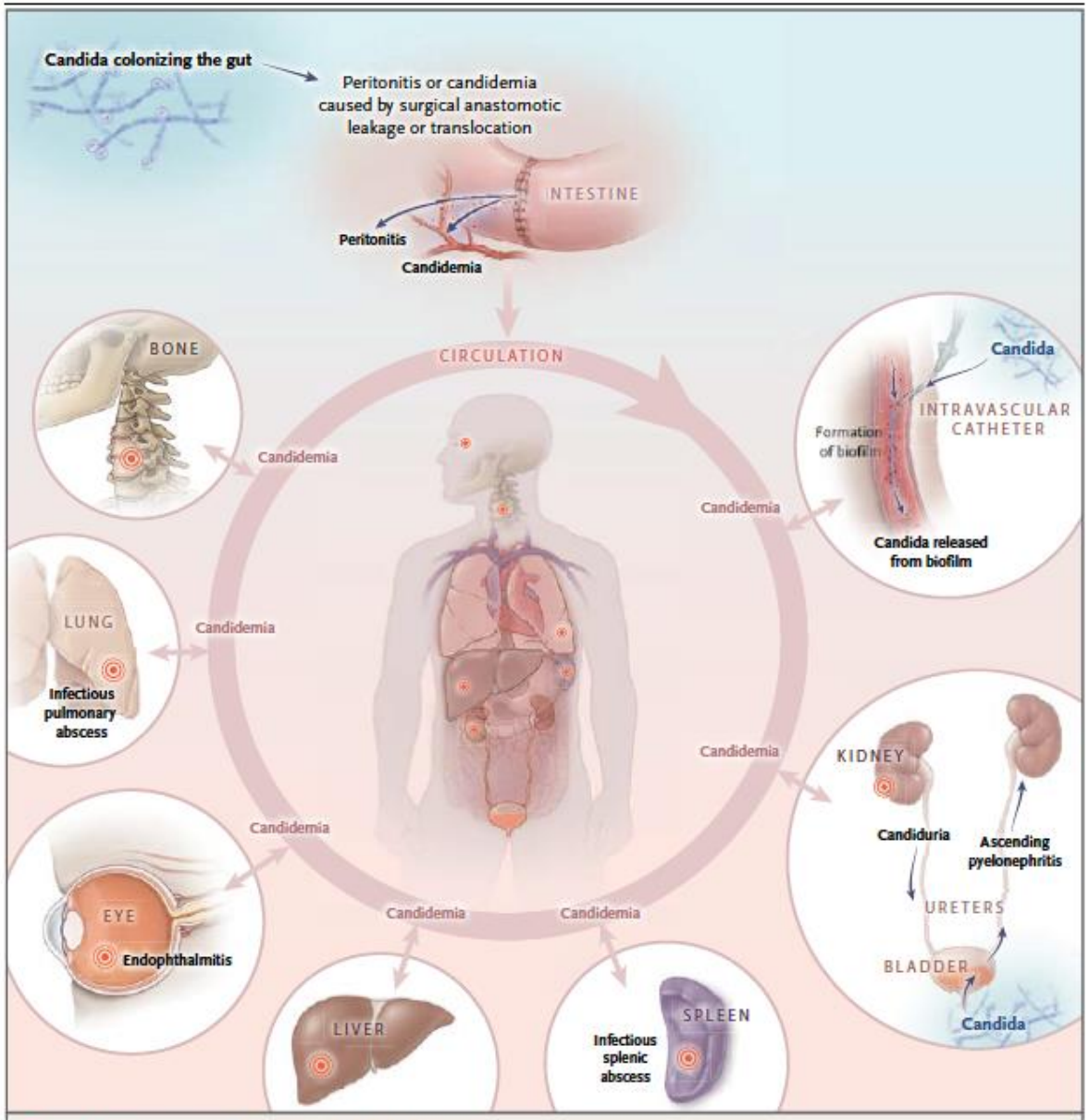
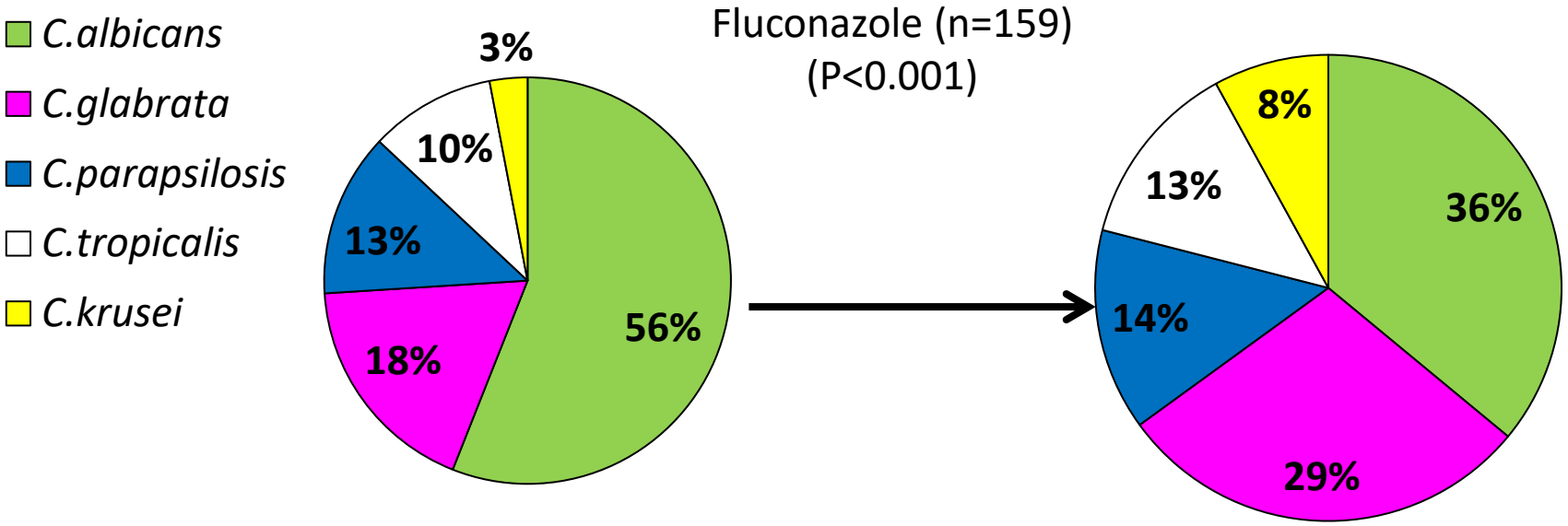



Figure 1. Pathogenesis of Invasive Candidiasis.

Kullberg B, NEJM 2015

# Influence of recent FCZ exposure on *Candida* spp. distribution during fungemia

Recent ≤ 30 d



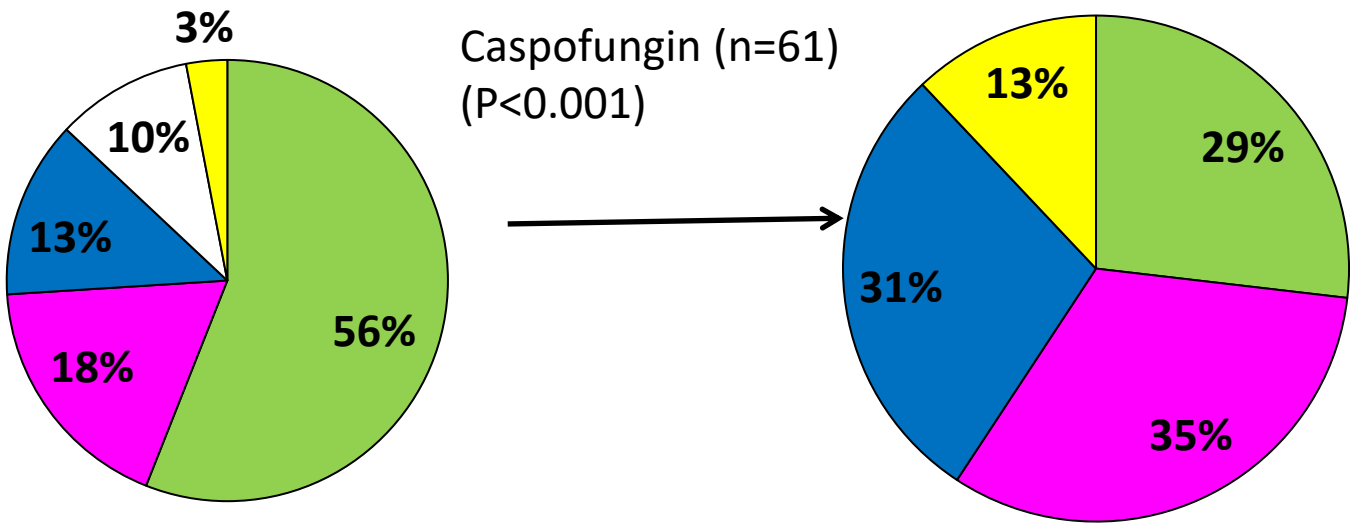

2618 isolats sur 7 ans

Lortholary AAC 2011

# Influence of recent CAS exposure on *Candida* spp. distribution during fungemia

Recent ≤ 30 d

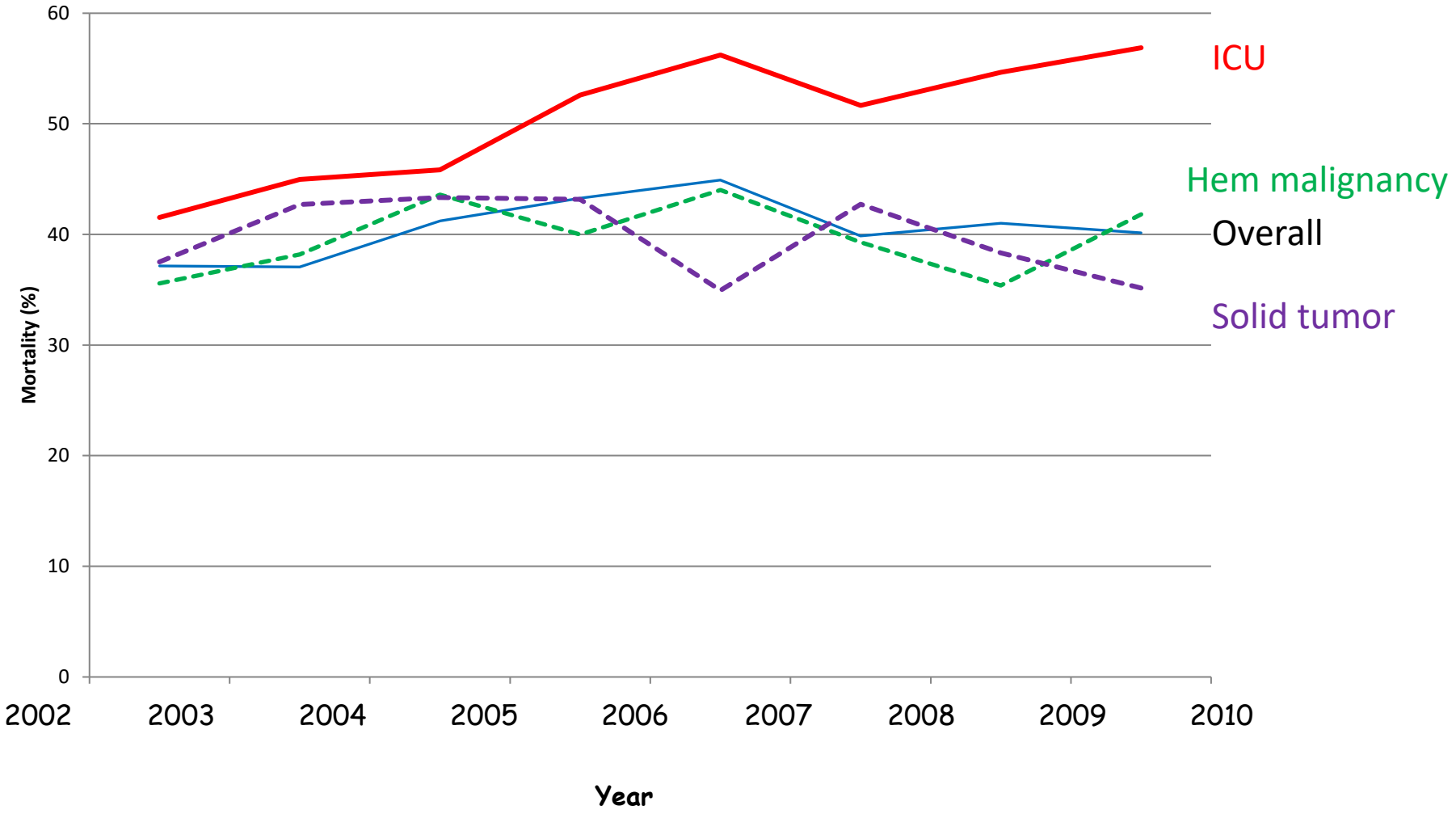
- *C.albicans*
- *C.glabrata*
- *C.parapsilosis*
- *C.tropicalis*
- *C.krusei*




| | No preexposure recorded | | Preexposure recorded | | |
|---|---|---|---|---|---|
| | N | GMIC[a] (mg/L) [95% CI] | N | GMIC[a] (mg/L) [95% CI] | *P*[b] |
| Exposure to caspofungin | | | | | |
| Total | 1920 | 0.07 [0.07-0.08] | 61 | 0.16 [0.12-0.22] | < 0.001 |
| *C. albicans* | 993 | 0.05 [0.05-0.05] | 13 | 0.09 [0.04-0.22] | 0.252 |
| *C. glabrata* | 365 | 0.07 [0.07-0.08] | 21 | 0.12 [0.08-0.19] | 0.418 |
| *C. parapsilosis* | 299 | 0.28 [0.26-0.31] | 19 | 0.32 [0.23-0.45] | 0.893 |
| *C. tropicalis* | 199 | 0.06 [0.05-0.06] | 0 | | |
| *C. krusei* | 64 | 0.15 [0.13-0.17] | 8 | 0.19 [0.11-0.33] | 0.571 |

Lortholary AAC 2011

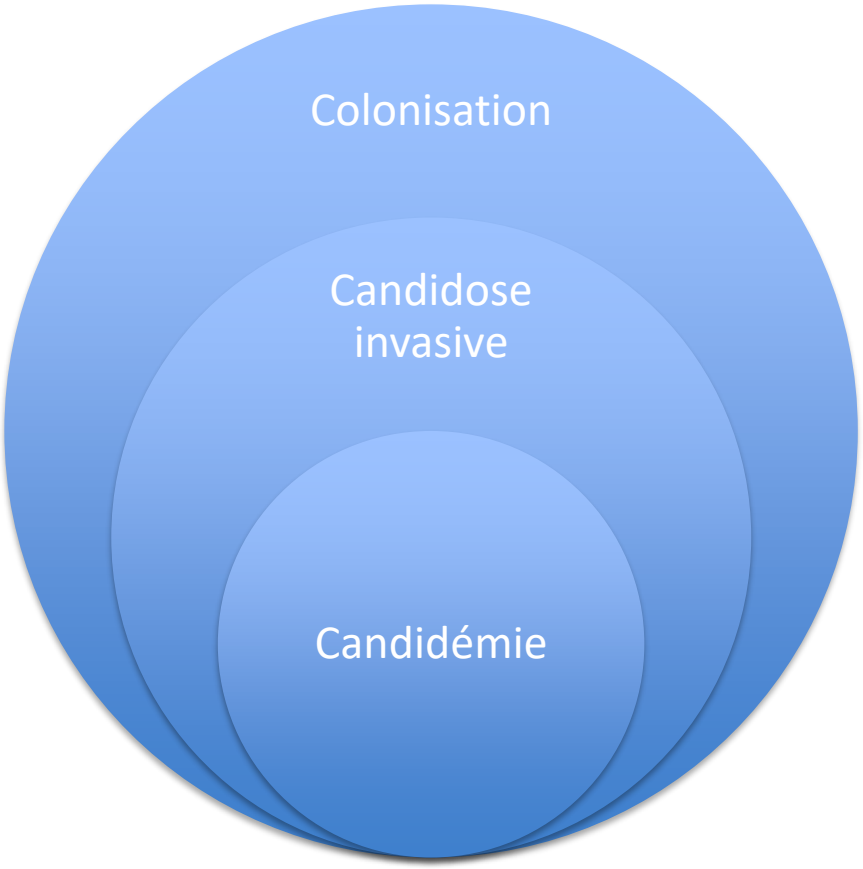
# Mortalité à J30



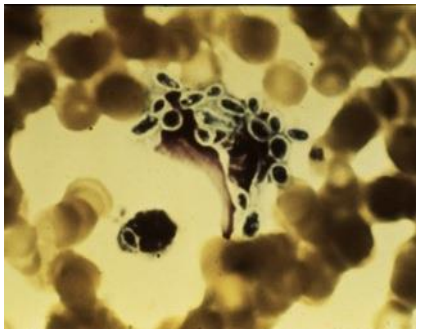

Lortholary et al. ICM sept 2014

# Traitement curatif: Candidoses invasives

# Candidoses invasives



# Prise en charge

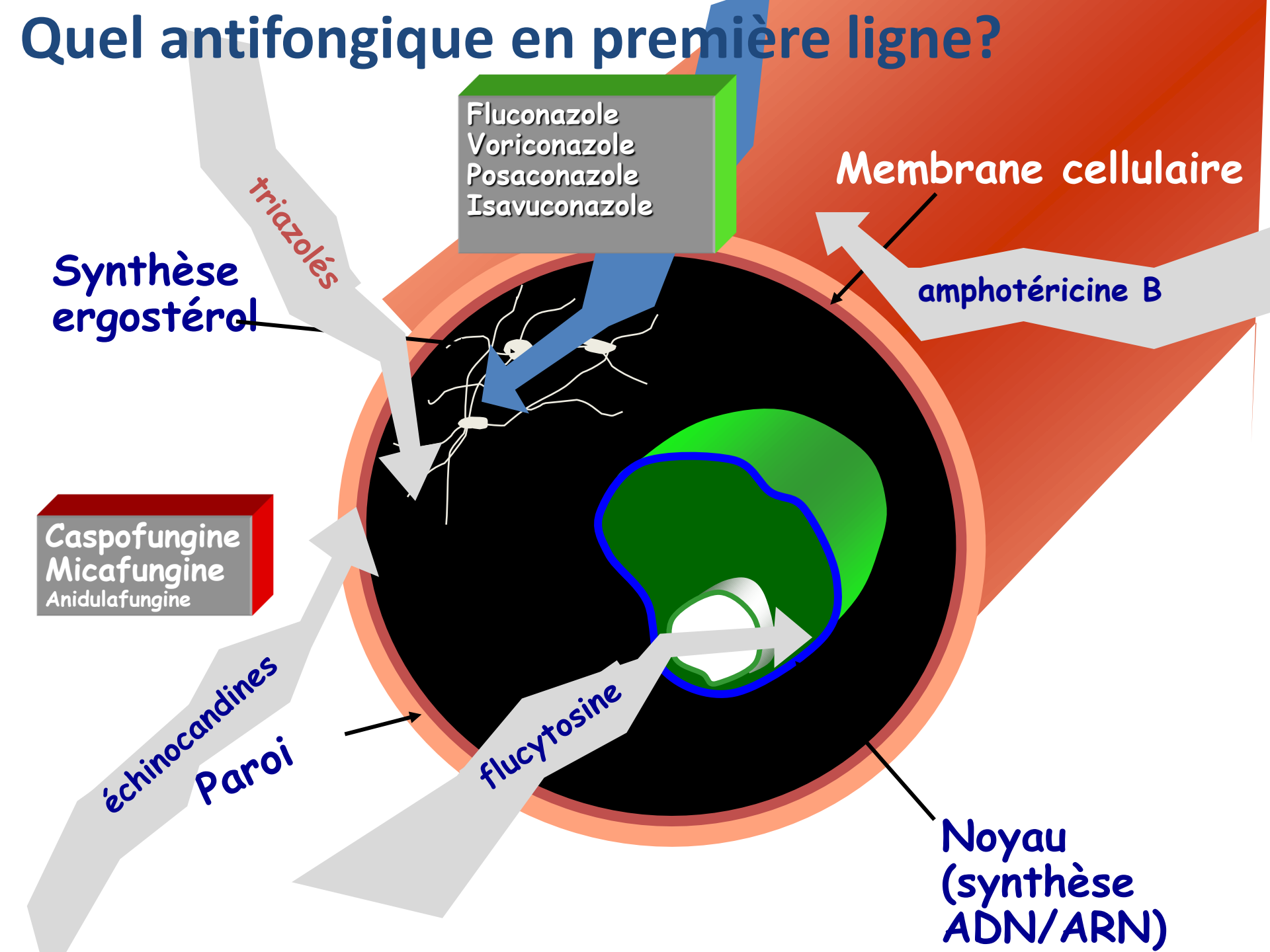


Hémoculture positive

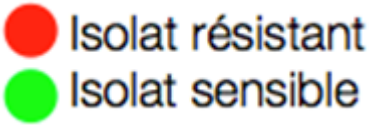
=

Candidémie

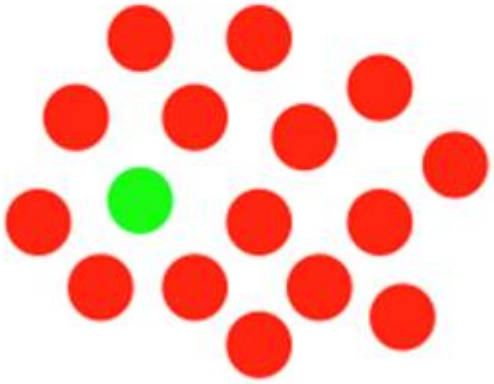
# Quel antifongique en première ligne?



# Antifongiques et résistance




**Résistance naturelle**



Particularités intrinsèques de la cible

*C. krusei* /fluconazole

**Résistance acquise**

Pression de sélection par les antifongiques

C. glabrata / azolés

5FC

# Importance du spectre antifongique

| | Polyènes | Fluconazole | Vori | Posaconazole | Isavuconazole | Candines |
|---|---|---|---|---|---|---|
| **Candida** | | | | | | |
| *C. albicans* | + | + | + | + | + | + |
| *C. glabrata* | + | +/- | +/- | +/- | +/- | + |
| *C. Krusei (R 5 FC)* | + | - | + | + | + | + |
| *C. parapsilosis (+/- S 5 FC)* | + | +/- | + | + | + | +/- |
| **Basidiomycetes** | | | | | | |
| *Cryptococcus neoformans* | + | + | + | + | + | - |
| *Trichosporon* | - | - | + | + | ? | - |
| *Rhodotorula* | + | - | - | - | ? | - |
| *Geotrichum* | + | - | + | + | ? | - |

# Importance du spectre antifongique

**Identification de l'espèce suffit habituellement à prédire la sensibilité aux antifongiques**

Breakpoint de CMI établis par l'EUCAST

| Antifungal agent | MIC breakpoint (mg/L) | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Candida albicans* | | | *Candida dubliniensis* | | *Candida glabrata* | | *Candida krusei* | | *Candida parapsilosis* | | *Candida tropicalis* | | *Candida guilliermondii* | | *Cryptococcus neoformans* | | Non-species related breakpoints for *Candida*[1] | |
| | S ≤ | R > | ATU | S ≤ | R > | S ≤ | R > | S ≤ | R > | S ≤ | R > | S ≤ | R > | S ≤ | R > | S ≤ | R > | S ≤ | R > |
| Amphotericin B | 1 | 1 | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | IE | IE | 1 | 1 | IE | IE |
| Anidulafungin | 0.03 | 0.03 | | | | 0.06 | 0.06 | 0.06 | 0.06 | 4 | 4 | 0.06 | 0.06 | IE[2] | IE[2] | - | - | IE | IE |
| Caspofungin | Note[3] | Note[3] | | | | Note[3] | Note[3] | Note[3] | Note[3] | Note[3] | Note[3] | Note[3] | Note[3] | IE[2] | IE[2] | - | - | IE | IE |
| Fluconazole | 2 | 4 | | 2 | 4 | 0.001[4] | 16 | - | - | 2 | 4 | 2 | 4 | IE[2] | IE[2] | IE | IE | 2 | 4 |
| Isavuconazole | IE | IE | | IE | IE | IE | IE | IE | IE | IE | IE | IE | IE | IE | IE | IE | IE | IE | IE |
| Itraconazole | 0.06 | 0.06 | | 0.06 | 0.06 | IE[3] | IE[3] | IE[3] | IE[3] | 0.125 | 0.125 | 0.125 | 0.125 | IE[2] | IE[2] | IE | IE | IE | IE |
| Micafungin | 0.016 | 0.016 | 0.03 | | | 0.03 | 0.03 | IE[5] | IE[5] | 2 | 2 | IE[5] | IE[5] | IE[5] | IE[5] | - | - | IE | IE |
| Posaconazole | 0.06 | 0.06 | | 0.06 | 0.06 | IE[3] | IE[3] | IE[3] | IE[3] | 0.06 | 0.06 | 0.06 | 0.06 | IE[2] | IE[2] | IE | IE | IE | IE |
| Voriconazole[6] | 0.06[7] | 0.25[7] | | 0.06[7] | 0.25[7] | IE | IE | IE | IE | 0.125[7] | 0.25[7] | 0.125[7] | 0.25[7] | IE[2] | IE[2] | IE | IE | IE | IE |

Notes:

# Profils habituels de sensibilité
## Rapport du CNRMA

| Espèces étudiées | | Valeurs des CMI50 / CMI90 mg/L pour les antifongiques* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Nom d'usage en clinique (nbre d'isolats testés) | Nom actuel | AMB | 5-FC | Fluco | Vori | Posa | Caspo** | Mica** |
| *C. albicans* (n=2854) | | 0.06/0.12 | ≤0.12/0.5 | 0.25/0.5 | ≤0.01/≤0.01 | 0.03/0.06 | 0.03/0.06 | 0.03/0.03 |
| *C. dubliniensis* (n=103) | | 0.03/0.06 | ≤0.12/≤0.12 | ≤0.12/0.25 | ≤0.01/≤0.01 | 0.03/0.06 | 0.03/0.03 | 0.03/0.03 |
| *C. glabrata* (n=1103) | | 0.12/0.25 | ≤0.12/≤0.12 | 16/64 | 0.25/1 | 0.5/2 | 0.06/0.12 | 0.03/0.03 |
| *C. parapsilosis* (n=680) | | 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=35) | | 0.03/0.06 | ≤0.12/≤0.12 | 0.5/16 | 0.03/1 | 0.12/0.12 | 0.12/0.25 | 0.12/0.25 |
| *C. metapsilosis* (n=28) | | 0.06/0.12 | ≤0.12/≤0.12 | 1/2 | 0.03/0.06 | 0.06/0.12 | 0.06/0.25 | 0.12/0.25 |
| *C. tropicalis* (n=558) | | 0.06/0.12 | ≤0.12/64 | 0.5/4 | 0.03/0.25 | 0.06/0.25 | 0.03/0.06 | 0.03/0.03 |
| *C. krusei* (n=290) | *Pichia kudriavzevii* | 0.12/0.25 | 2/4 | 32/64 | 0.25/0.5 | 0.25/0.25 | 0.12/0.25 | 0.06/0.12 |
| *C. inconspicua* (n=31) | | 0.12/0.25 | 2/4 | 16/32 | 0.12/0.5 | 0.12/0.25 | 0.03/0.12 | 0.03/0.03 |
| *C. kefyr* (n=154) | *Kluyveromyces marxianus* | 0.06/0.25 | 0.5/8 | 0.25/1 | ≤0.01/≤0.01 | 0.06/0.12 | 0.015/0.03 | 0.03/0.06 |
| *C. guilliermondii* (n=93) | *Meyerozyma guilliermondii* | 0.03/0.06 | ≤0.12/≤0.12 | 8/32 | 0.06/0.5 | 0.25/0.5 | 0.06/0.25 | 0.25/0.25 |
| *C. fermentati* (n=32) | *Meyerozyma caribbica* | 0.12/0.25 | ≤0.12/≤0.12 | 8/64 | 0.12/2 | 0.25/0.5 | 0.12/0.5 | 0.25/2 |
| *C. lusitaniae* (n=160) | *Clavispora lusitaniae* | 0.06/0.25 | ≤0.12/1 | 0.25/0.5 | ≤0.01/≤0.01 | 0.03/0.06 | 0.03/0.06 | 0.06/0.06 |
| *C. haemulonii* (n=38) | | 0.5/4 | ≤0.12/0.25 | 32/≥64 | ≥8/≥8 | 2/≥8 | 0.03/0.06 | 0.06/0.12 |
| *C.haemulonii* type II (n=36) | *Candida duobushaemulonii* | 2/8 | ≤0.12/≥64 | 32/≥64 | ≥8/≥8 | 8/≥8 | 0.03/0.03 | 0.03/- |
| *C.palmioleophila* (n=20) | | 0.12/0.5 | ≤0.12/0.5 | 8/64 | 0.12/0.25 | 0.12/0.25 | 0.06/0.25 | 0.03/0.25 |
| *Pichia jadinii* (n=20) | *Cyberlindnera jadinii* | 0.06/0.12 | ≤0.12/1 | 1/4 | 0.06/0.12 | 0.12/0.25 | 0.015/1 | 0.015/2 |
| *C. pelliculosa* (n=30) | *Wickerhamomyces anomalus* | 0.06/0.12 | ≤0.12/16 | 2/4 | 0.12/0.2 | | | |

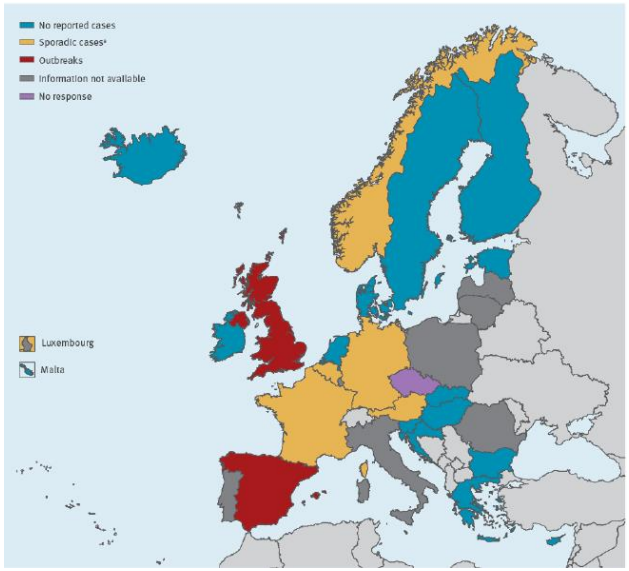
Rapport cNRMA, unpublished data

# Profils habituels de sensibilité
## Rapport du CNRMA

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *Geotrichum candidum* (n=33) | *Galactomyces candidus* | 0.25/0.5 | 0.25/1 | 16/64 | 0.25/1 | 0.25/1 | 1/≥8 | 0.5/≥8 |
| *G. capitatum* (n=51) | *Magnusiomyces capitatus* | 0.25/0.5 | ≤0.12/0.25 | 8/16 | 0.12/0.5 | 0.25/1 | ≥8/≥8 | ≥8/≥8 |
| *G. clavatum* (n=136) | *Saprochaete clavata* | 0.25/0.5 | 0.25/1 | 32/64 | 0.5/2 | 0.5/1 | ≥8/≥8 | ≥8/≥8 |
| *Cr. neoformans* var. *grubii* (n=860) | | 0.25/0.5 | 4/16 | 4/8 | 0.06/0.12 | 0.12/0.25 | ≥8/ ≥8 | 4/≥8 |
| *Cr. neoformans* var. *neoformans* (n=197) | | 0.12/0.25 | 4/16 | 1/4 | ≤0.015/0.06 | 0.03/0.25 | ≥8/ ≥8 | 1/4 |
| *Cr. neoformans* hybrides AD (n=72) | | 0.12/0.25 | 4/8 | 2/8 | 0.03/0.12 | 0.03/0.12 | ≥8/ ≥8 | 4/≥8 |
| *Cr. gattii* (n = 27) | | 0.12/0.25 | 2/8 | 8/16 | 0.12/0.5 | 0.25/0.5 | ≥8/ ≥8 | ≥8/≥8 |
| *Rhodotorula mucilaginosa* (n=36) | | 0.25/0.5 | 0.25/0.5 | ≥64/≥64 | 2/8 | 1/2 | ≥8/ ≥8 | ≥8/≥8 |
| *Trichosporon asahii* (n=45) | | 2/≥8 | 32/≥64 | 4/16 | 0.12/0.25 | 0.25/0.5 | ≥8/≥8 | 4/≥8 |

Rapport CNRMA, unpublished data

# *Candida auris*: fungal superbug




- Premier cas en 2009
- A évoquer devant:
  - *C. auris*
  - *C. haemulonii, C. famata, C. sake*
- Identification CNRMA en urgence
- Résistance: fluconazole, souches multi R (autres azoles, AmB, echinocandines)
- Transmission horizontale avec épidémies
- Infections liées aux soins

**Table 1. Number of *Candida auris* cases detected in the EU/EEA, 2013–2017 (n = 620)[a] [16]**

| Year | *C. auris* bloodstream infection | | Other type of *C. auris* infection | | *C. auris* colonisation | | Cases of unknown infection/colonisation status | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n |
| **2013** | 1 | 33.3 | 0 | 0.0 | 0 | 0.0 | 2 | 66.7 | 3 |
| **2014** | 0 | 0.0 | 1 | 100.0 | 0 | 0.0 | 0 | 0.0 | 1 |
| **2015** | 6 | 26.1 | 11 | 47.8 | 6 | 26.1 | 0 | 0.0 | 23 |
| **2016** | 53 | 18.3 | 13 | 4.5 | 223 | 76.9 | 1 | 0.3 | 290 |
| **2017** | 50 | 16.5 | 15 | 5.0 | 237 | 78.2 | 1 | 0.3 | 303 |
| **2013–2017** | 110 | 17.7 | 40 | 6.5 | 466 | 75.2 | 4 | 0.6 | 620 |

*All percentages are row percentages. [a] One additional case was detected in Austria in January 2018 and is not included in the table.*

ECDC, 2018

# Comment choisir le traitement de première ligne

- Hémoculture positive à levure
- Pensez qu'une levure peut être Résistante aux échinocandines (Cryptococcus, Trichosporon, Geotrichum)
- Quel antifongique choisir?
  - Gravité clinique: choc
  - Gravité liée au terrain: neutropénie
  - Risque de Candida R au fluconazole: pré exposition aux azolés
  - Porte d'entrée:
    - Urines: seuls le fluconazole et l'amphotéricine B deoxycholate diffusent dans les urines
  - Diffusion au site de l'infection

# Facteurs de risque spécifiques aux espèces non *albicans*?

*C. glabrata*
Age > 80 ans
Tumeur digestive
Préexposition : fluco ou candines

*C. krusei*
Tumeurs non digestives
Leucémies aigues/ lymphomes
Préexposition: fluco ou candines

*C. parapsilosis*
Cathéter veineux central
Préexposition: candines

*C. kefyr*
Age entre 65 et 79 ans
Leucémie aiguë

*C. tropicalis*
Hémopathies malignes hors lymphomes

Plusieurs espèces

Toxicomanie IV

Lortholary O *et al.* Intensive Care Med 2017

# Caspofungine dans candidoses invasives

Étude randomisée, double-aveugle, multicentrique Caspofungine *vs*. Amphotéricine B déoxycholate

- Étude de non-infériorité ; évaluation (I) : fin du TT i.v.

| Analyse | Caspofungine 70/50 mg n/m (%) | Amphotéricine B 0,6-1,0 mg/kg n/m (%) | Différence estimée % (95,6 % CI) |
|---|---|---|---|
| **Réponse en fin de traitement (n = 224)** | 80/109 **(73,4)** | 71/115 **(61,7)** | 12,7 % * (–0,7, 26,0) |

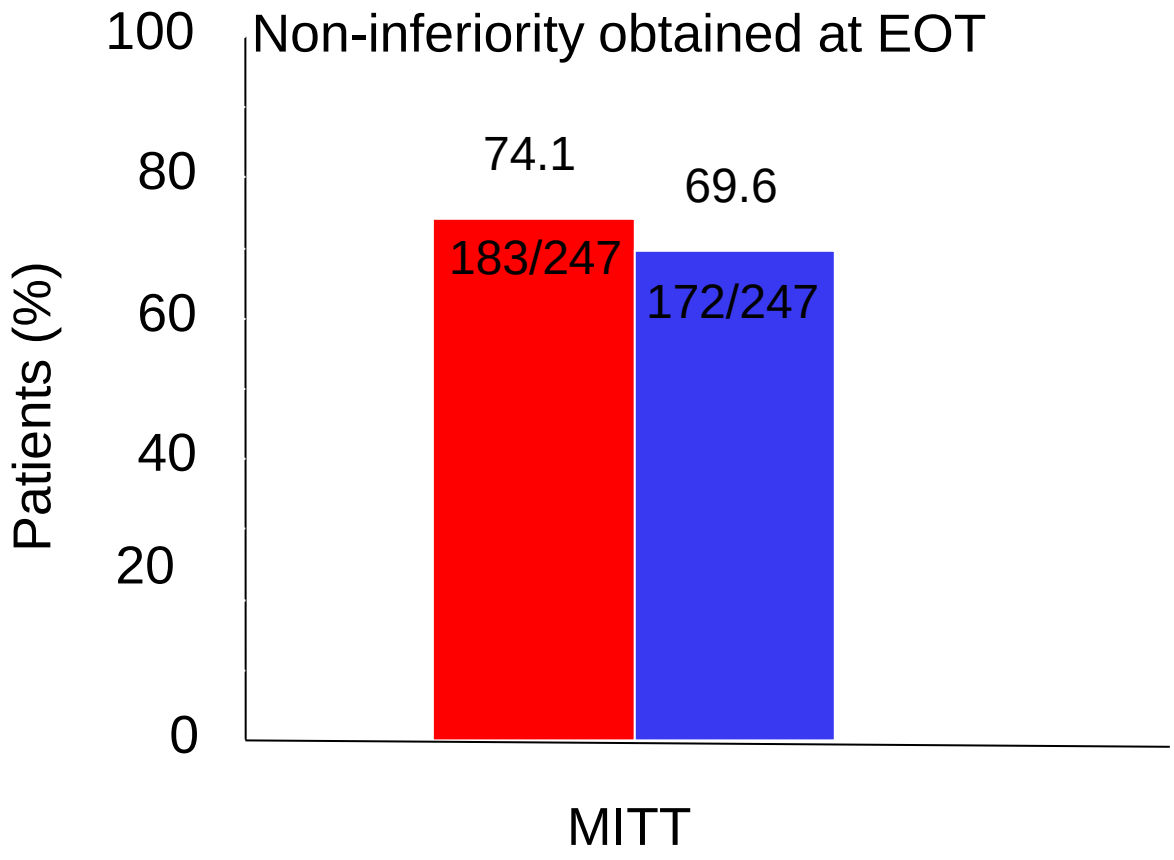
| | Caspofungine 70/50 mg | Amphotéricine B 0.6-1.0 mg/kg |
|---|---|---|
| Neutropéniques (PNN ≤ 500 mL à inclusion) | 7/14 (50) | 4/10 (40) |
| Non-neutropéniques (PNN > 500 mL à inclusion) | 73/95 (77) | 67/105 (64) |

* P = 0,09

Mora-Duarte J et al. *N Engl J Med* 2002.

# Micafungin et candidoses invasives

Randomized, multicentre, double-blind, non-inferiority phase III trial; non-neutropenic and neutropenic patients

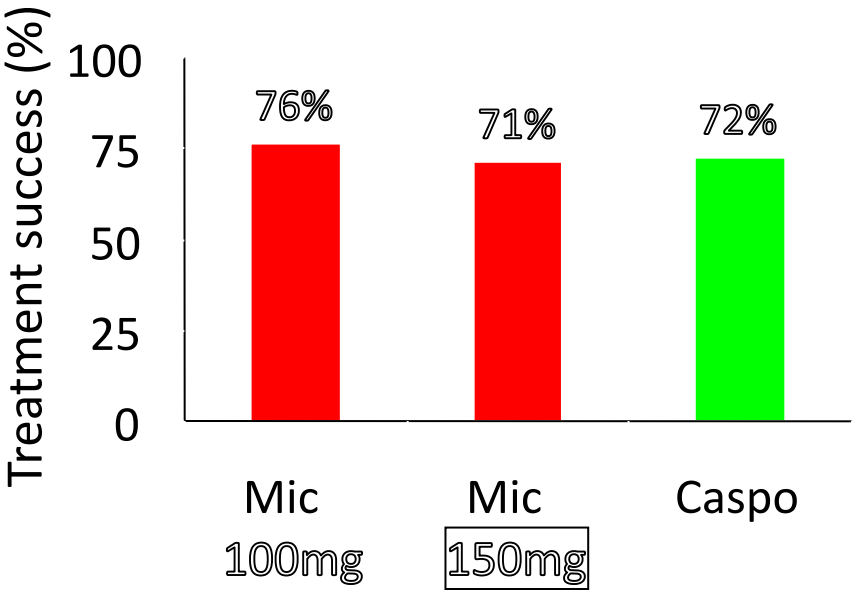



*531 pts*

Kuse et al. *Lancet* 2007.

# Micafungin vs caspofungin et candidémie

- Double-blind, randomized trial in adults with candidemia or invasive candidiasis (IC) comparing:
  - micafungin 100mg/d (N=191)
  - micafungin 150mg/d (N=199)
  - std. dose caspofungin (N=188)
- Approximately 85% of patients had candidemia, 15% had IC.
- No significant differences in treatment success at EoT, mortality, relapsing/emergent infections, or AEs.




Micafungin 100mg/d and 150mg/d equivalent to standard dose caspofungin for candidemia/IC.

Pappas et al. *CID* 2007.

# Anidulafungine et candidoses invasives

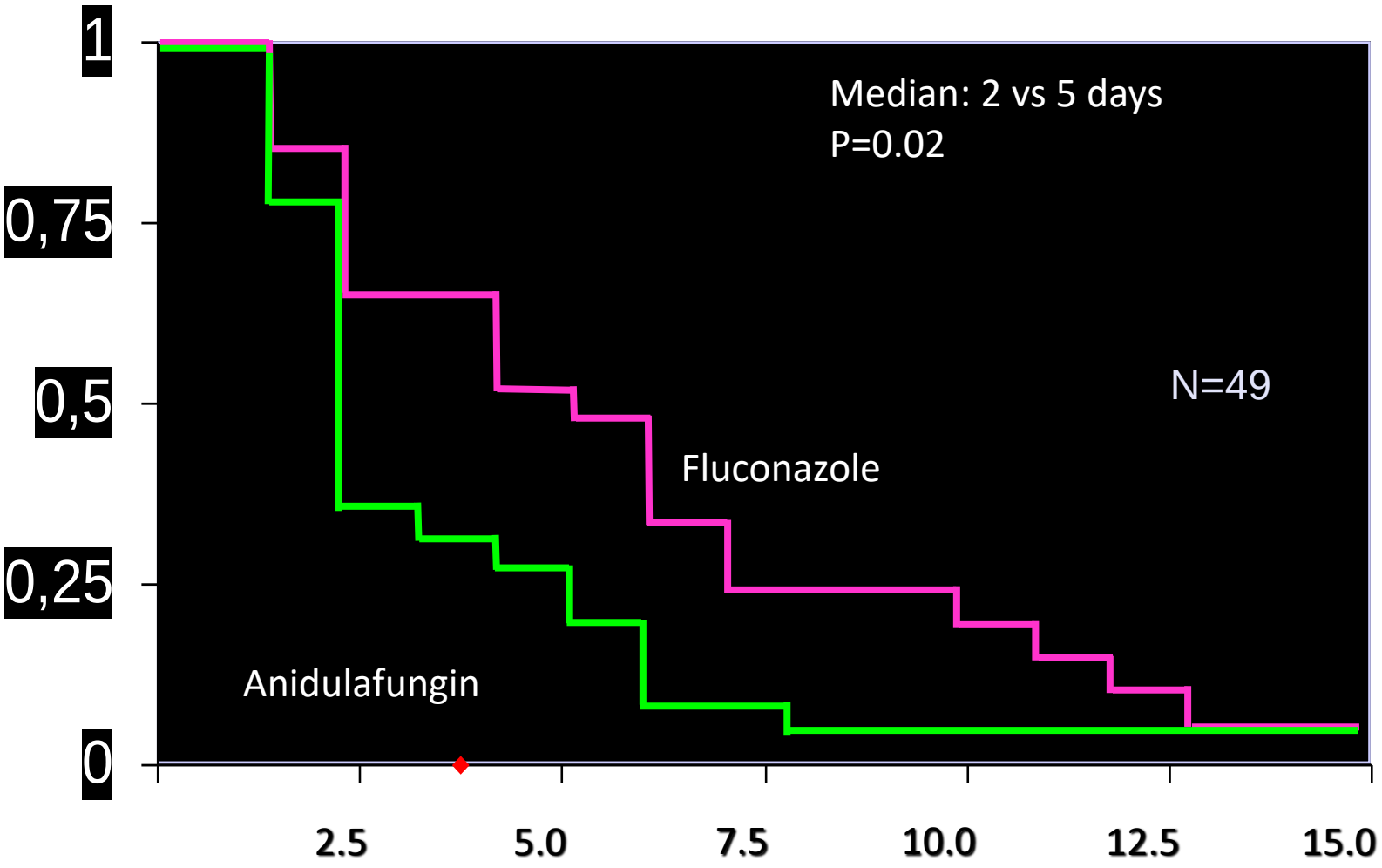
- Essai de phase III, randomized, double-aveugle
- 3% de patients non neutropéniques
- anidulafungine IV 200 mg puis 100 mg /j
- fluconazole IV 800 mg puis; 400 mg /j
  - ± fluconazole 400 mg/j PO après J10 NEJM 2007

Objectif principal: Réponse globale en fin de traitement

| Réponse (MITT) | | | Différence (%) | 95% CI |
|---|---|---|---|---|
| | Anid N =127 | Flu N =118 | | |
| Succès, n (%) | 96 (75.6) | 71 (60.2) | 15.42 | 3.85, 26.99 |

Reboli, NEJM 2007

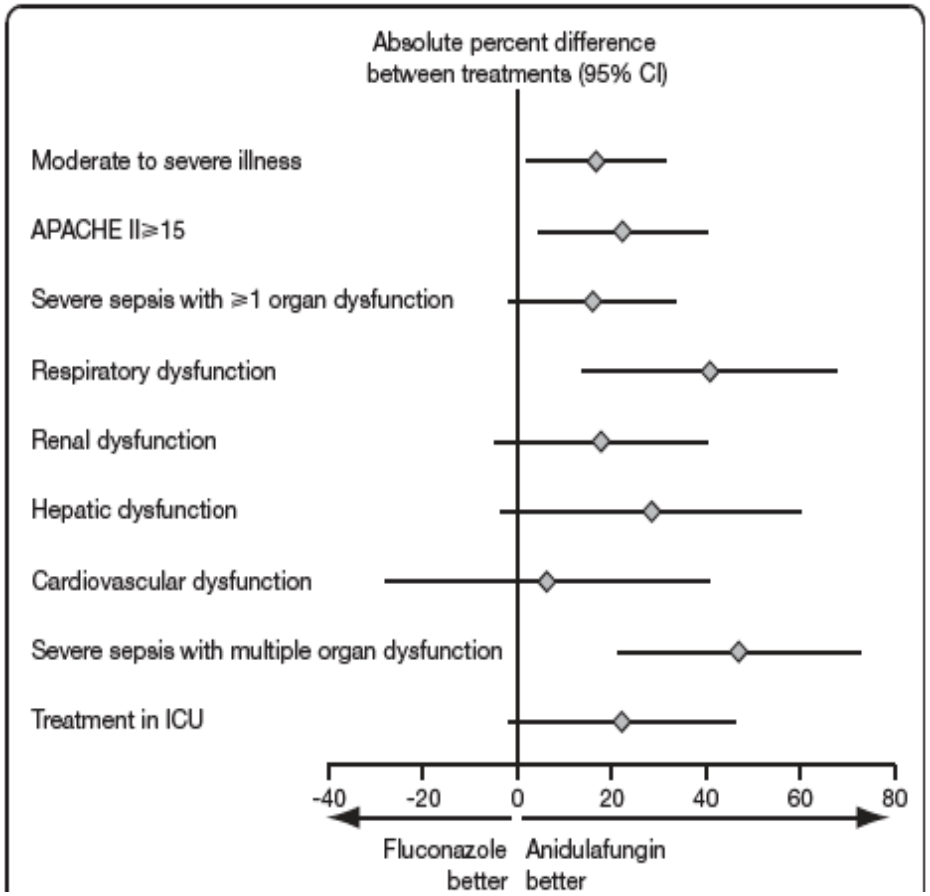
# Anidulafungin vs fluconazole : time to first negative blood culture: *C. albicans*

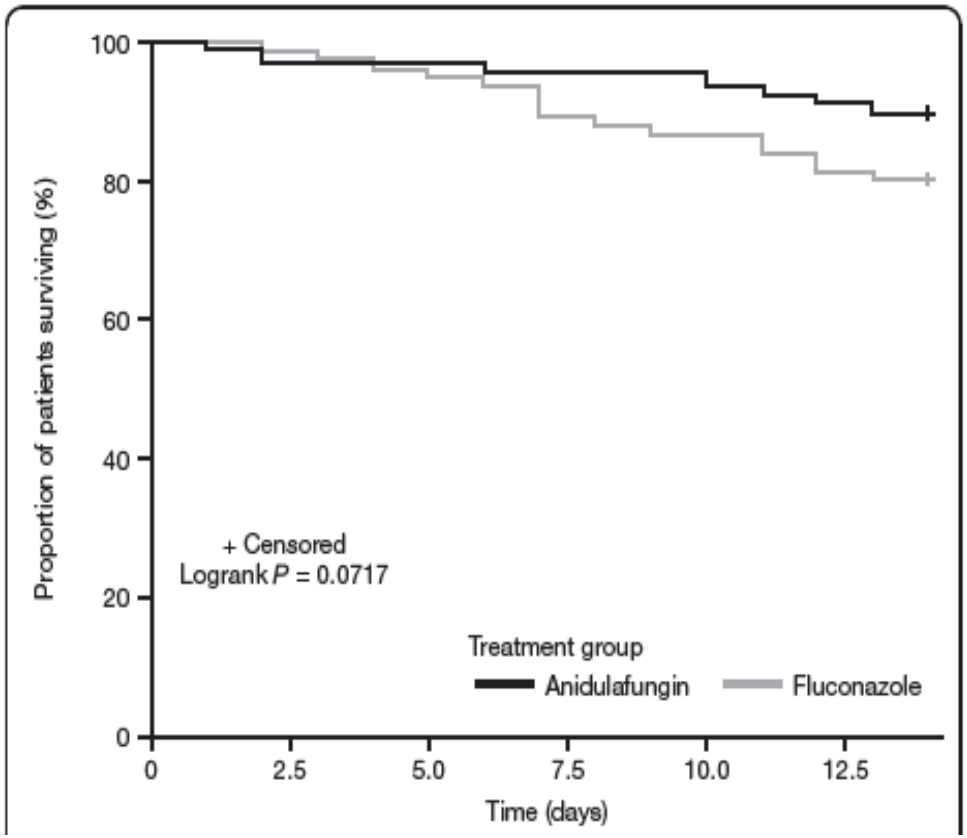



Reboli BMC Infectious Diseases 2011

# Anidulafungin compared with fluconazole in severely ill patients with candidemia and other forms of invasive candidiasis: Support for the 2009 IDSA treatment guidelines for candidiasis

Daniel H Kett[1*], Andrew F Shorr[2], Annette C Reboli[3], Arlene L Reisman[4], Pinaki Biswas[5] and Haran T Schlamm[4]




Crit Care 2011

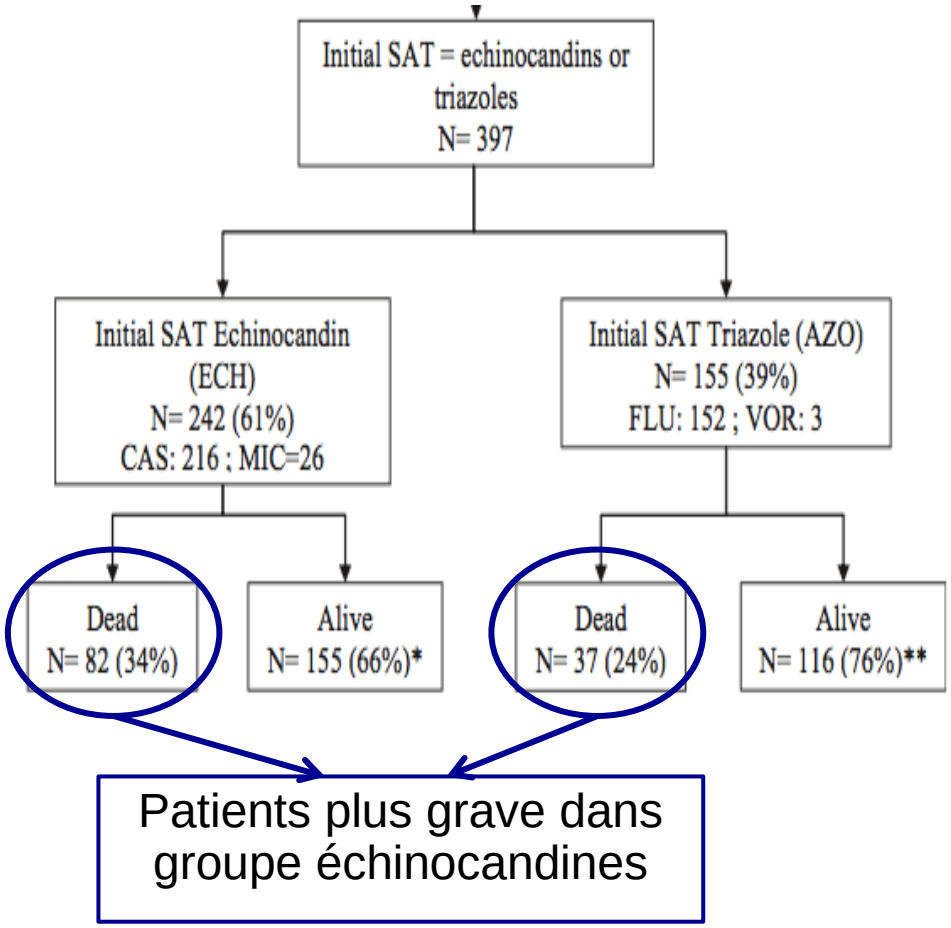
# Multivariate analysis of prognostic factors during invasive candidiasis (7 randomized trials)

Andes CID 2012

| | | Mortality | | | | Success | | |
|---|---|---|---|---|---|---|---|---|
| Organisms[a] | Factor | *P* | OR | 95% CI | Factor | *P* | OR | 95% CI |
| All organisms (n = 978) | Age | .02 | 1.01 | 1.00–1.02 | APACHE II | .0001 | 0.94 | .93–.96 |
| | APACHE II score | .0001 | 1.11 | 1.08–1.14 | Echinocandin | .01 | 2.33 | 1.27–4.35 |
| | Immunosuppressive therapy | .001 | 1.69 | 1.18–2.44 | CVC removed | .001 | 1.69 | 1.23–2.33 |
| | *Candida tropicalis* | .01 | 1.64 | 1.11–2.39 | Study | NS | | |
| | Echinocandin | .02 | 0.65 | .45–.94 | | | | |
| | CVC removed | .0001 | 0.50 | .35–.72 | | | | |
| | Study | NS | | | | | | |
| *Candida albicans* (n = 408) | APACHE II score | .0001 | 1.09 | 1.05–1.13 | APACHE II score | .005 | 0.92 | .92–.99 |
| | Immunosuppressive therapy | .002 | 2.22 | 1.30–3.70 | Echinocandin | .005 | 3.70 | 1.49–9.09 |
| | Surgery | .05 | 0.58 | .34–.98 | Study | NS | | |
| | Malignancy | .03 | 1.89 | 1.05–3.45 | | | | |
| | Echinocandin | .03 | 0.55 | .32–.95 | | | | |
| | CVC removed | .01 | 0.52 | .31–.90 | | | | |
| | Study | NS | | | | | | |
| Non-*albicans* species (n = 570) | APACHE II score | .0001 | 1.14 | 1.1–1.17 | Age | .004 | 1.02 | 1.01–1.03 |
| | Echinocandin | .04 | 0.52 | .36–.78 | APACHE II score | .0001 | 0.93 | .91–.96 |
| | CVC removed | .05 | 0.69 | .48–.98 | CVC removed | .007 | 1.74 | 1.16–2.61 |

# Impact of echinocandin on prognosis of proven invasive candidiasis in ICU: A post-hoc causal inference model using the AmarCAND2 study

403 candidoses invasives prouvées
Choc septique 45 %




Après ajustement
sur facteurs confondants

- Mortalité à J28 : pas de différence significative (*p = 0,82*)
- Mortalité à J7 (proche mortalité attribuable) : pas de différence significative (*p = 0,88*)
- Si choc septique :
  - tendance en faveur, des échinocandines (HR: 0.46 [0.19; 1.07]; *p =0.07*)
  - même après exclusion *C. krusei* et *glabrata* (HR: 0,43 [0,16; 1,13], *p= 0,09*)

*Bailly S J Infect 2017 ; 74 : 408*

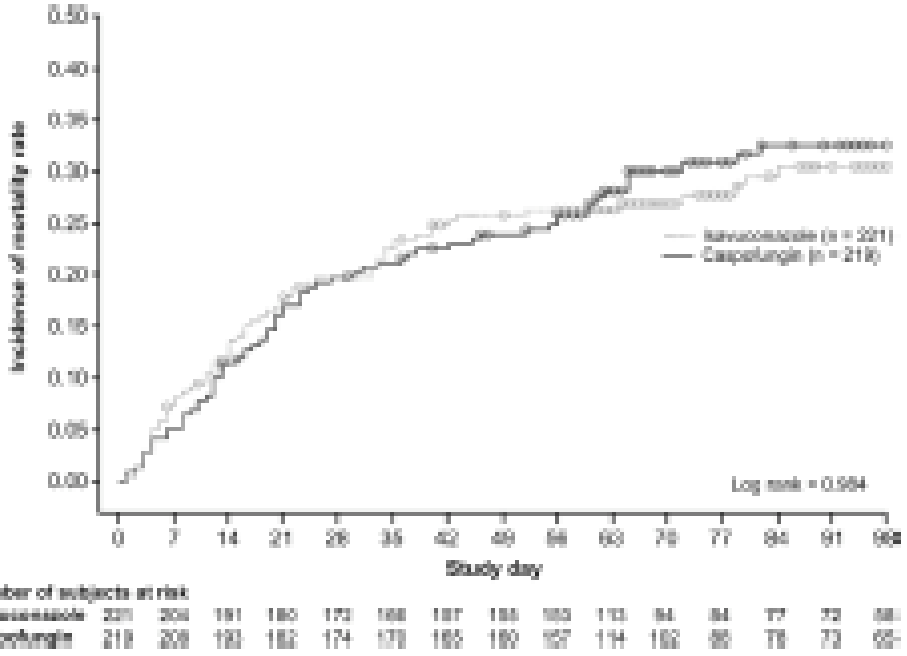
*Clinical Infectious Diseases*

MAJOR ARTICLE

# Isavuconazole Versus Caspofungin in the Treatment of Candidemia and Other Invasive *Candida* Infections: The ACTIVE Trial

Bart Jan Kullberg,[1] Claudio Viscoli,[2,3] Peter G. Pappas,[4] Jose Vazquez,[5] Luis Ostrosky-Zeichner,[6] Coleman Rotstein,[7] Jack D. Sobel,[8] Raoul Herbrecht,[9] Calla Rahav,[10] Sutep Jurutanasirikul,[11] Phoenchan Chaichotisakul,[12] Eric Van Wijngaerden,[13] Jan De Waele,[14] Christopher Lademacher,[15] Marc Engelhardt,[16] Laura Kovanda,[15] Rodney Cross-Dabrera,[15] Christine Fredericks,[15] and George R. Thompson III[17]

- Etude de Phase iii
- Randomisée:
- Isavuconazole
- Caspofungine
- Relais PO à J10
- Succès en fin de traitement IV
- 400 patients m ITT 60% isavu vs 71% caspo
- **Pas de non infériorité**



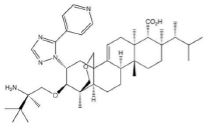
**SCYNEXIS**

# Ibrexafungerp (formerly SCY-078)

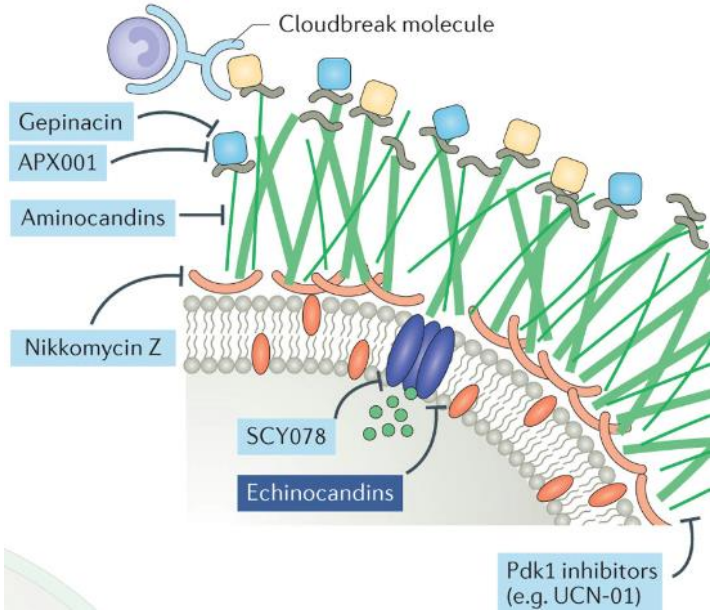
Nouvel inhibiteur de ß-1,3-glucan synthase
Triterpenoides - enfumafungine
Disponible IV et Oral
Fongicide sur *Candida*
1/2 vie longue (20h)
Distribution tissulaire importante

Etudes en cours ou finies:
-candidose vulvo vaginale  récidivante
-candidose invasive relais
-aspergillose invasive

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*)




*Perfect JR*,  (2017) Nat Rev Drug Discov.

# DONNEES *IN VITRO*

| Species and antifungal drug | MIC (μg/ml) Range[a] |
|---|---|
| *C. albicans* (*n* = 33) | |
| SCY-078 | 0.06–0.25 |
| FLC | ≤0.125 to 128 |
| ANF | ≤0.015 to 1 |
| MCF | ≤0.015 to 1 |
| CAS | ≤0.015 to 0.5 |
| VRC | ≤0.015 to >16 |
| *C. albicans/dubliniensis* not further identified (*n* = 5) | |
| SCY-078 | 0.12 |
| FLC | ≤0.125 to 0.25 |
| ANF | ≤0.125 to 0.03 |
| MCF | ≤0.015 to 0.03 |
| CAS | ≤0.015 to 0.03 |
| VRC | ≤0.015 |
| *C. glabrata* (*n* = 23) | |
| SCY-078 | 0.25–1 |
| FLC | 2 to >128 |
| ANF | 0.03–1 |
| MCF | ≤0.015 to 0.5 |
| CAS | ≤0.015 to 0.5 |
| VRC | 0.03–8 |

| Species and antifungal drug | MIC (μg/ml) Range[a] |
|---|---|
| *C. krusei* (*n* = 6) | |
| SCY-078 | 0.5–4 |
| FLC | 64–128 |
| ANF | 0.03–0.25 |
| MCF | 0.03–0.25 |
| CAS | 0.06–0.5 |
| VRC | 0.5–1 |
| *C. parapsilosis* (*n* = 18) | |
| SCY-078 | 0.25–0.5 |
| FLC | 0.25–4 |
| ANF | 0.06–2 |
| MCF | 0.5–2 |
| CAS | 0.06–0.5 |
| VRC | ≤0.015 to 0.12 |
| *C. tropicalis* (*n* = 12) | |
| SCY-078 | 0.03–0.5 |
| FLC | 0.25–1 |
| ANF | ≤0.015 |
| MCF | ≤0.015 to 0.06 |
| CAS | ≤0.015 to 0.06 |
| VRC | ≤0.015 |

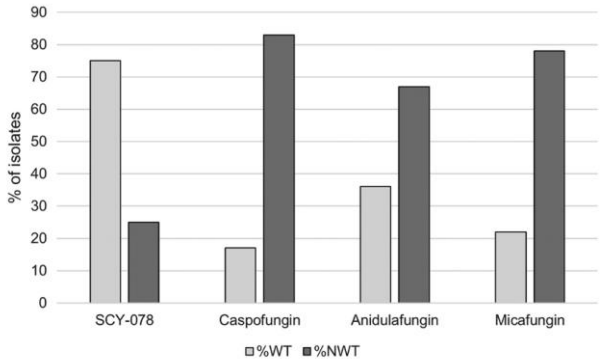



**FIG 1** Activity of SCY-078, anidulafungin, caspofungin, and micafungin against strains displaying *FKS* mutations. %WT, percent wild type; %NWT, percent non-wild type (for SCY-078, %NWT is the percent exceeding the wild-type upper-limit value [WT-UL; two 2-fold dilutions higher than the modal MIC value of each WT population]).


*Pfaller, M., Messer, S., Rhomberg, P., Borroto-Esoda, K., Castanheira, M.* (2017). Differential Activity of the Oral Glucan Synthase Inhibitor SCY-078 against Wild-Type and Echinocandin-Resistant Strains of Candida Species Antimicrobial Agents and Chemotherapy 61(8), e00161-17. https://dx.doi.org/10.1128/aac.00161-17

*Schell, W., Jones, A., Borroto-Esoda, K., Alexander, B.* (2017). Antifungal Activity of SCY-078 and Standard Antifungal Agents against 178 Clinical Isolates of Resistant and Susceptible Candida Species. Antimicrobial Agents and Chemotherapy 61(11), e01102-17. https://dx.doi.org/10.1128/aac.01102-17

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

EXPERIMENTAL THERAPEUTICS

# *In Vitro* Activity of Ibrexafungerp (SCY-078) against *Candida auris* Isolates as Determined by EUCAST Methodology and Comparison with Activity against *C. albicans* and *C. glabrata* and with the Activities of Six Comparator Agents

Maiken Cavling Arendrup,[a,b,c] Karin Meinike Jørgensen,[a] Rasmus Krøger Hare,[a] Anuradha Chowdhary[d]

**TABLE 2** *In vitro* activity of ibrexafungerp (IBX) and comparators against *C. auris* and selected *C. albicans* and *C. glabrata* isolates, as determined by EUCAST E.Def 7.3.1[a]

| Strain and agent | MIC (mg/liter) ≤0.004 | 0.008 | 0.016 | 0.03 | 0.06 | 0.125 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | ≥64 | MIC range (mg/liter) | Modal MIC (mg/liter) | $MIC_{50}$ (mg/liter) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *C. auris* (*n* = 122) | | | | | | | | | | | | | | | | | | |
| IBX | | | | | 1 | 3 | 33 | 63 | 20 | 2 | | | | | | 0.06–2 | 0.5 | 0.5 |
| ANF | | | 1 | 11 | 55 | 30 | 12 | 12 | 11 | 2 | 1 | | | 7 | | 0.016–>32 | 0.06 | 0.125 |
| MCF* | | | | 5 | 30 | 70 | 9 | | | | | | | 8 | | 0.03–>32 | 0.125 | 0.125 |
| AMB* | | | | | | | | 14 | 108 | | | | | | | 0.5–1 | 1 | 1 |
| FLU* | | | | | | | | 1 | | | | | 2 | 10 | 109 | 0.5–≥64 | ≥64 | ≥64 |
| VOR* | 1 | | | 1 | 1 | 16 | 13 | 34 | 38 | 13 | 5 | | | | | ≤0.004–4 | Bimodal | 0.5 |
| ISA* | 20 | 1 | 1 | 19 | 9 | 19 | 21 | 21 | 6 | 5 | | | | | | ≤0.004–2 | Trimodal | 0.125 |
| *C. albicans* (*n* = 16) | | | | | | | | | | | | | | | | | | |
| IBX | | | | 5 | 10 | 1 | | | | | | | | | | 0.03–0.125 | 0.06 | 0.06 |
| ANF | 10 | 6 | | | | | | | | | | | | | | ≤0.004–0.008 | ≤0.004 | ≤0.004 |
| MCF | | 4 | 10 | 2 | | | | | | | | | | | | 0.008–0.03 | 0.016 | 0.016 |
| AMB | | | | | 1 | 6 | 9 | | | | | | | | | 0.06–0.25 | 0.25 | 0.25 |
| FLU | | | | | | 10 | 6 | | | | | | | | | 0.125–0.25 | 0.125 | 0.125 |
| VOR | 12 | 4 | | | | | | | | | | | | | | ≤0.004–0.008 | ≤0.004 | ≤0.004 |
| ISA | 14 | 2 | | | | | | | | | | | | | | ≤0.004–0.008 | ≤0.004 | ≤0.004 |
| *C. glabrata* (*n* = 16) | | | | | | | | | | | | | | | | | | |
| IBX | | | | | | | 10 | 6 | | | | | | | | 0.25–0.5 | 0.25 | 0.25 |
| ANF | | | 4 | 12 | | | | | | | | | | | | 0.016–0.03 | 0.03 | 0.03 |
| MCF | | | 8 | 8 | | | | | | | | | | | | 0.016-0.03 | 0.016/0.03 | 0.016 |
| AMB | | | | 1 | | 1 | 11 | 3 | | | | | | | | 0.03–0.5 | 0.25 | 0.25 |
| FLU | | | | | | | | | | 6 | 10 | | | | | 2–4 | 4 | 4 |
| VOR | | | | 1 | 13 | 2 | | | | | | | | | | 0.03–0.125 | 0.06 | 0.06 |
| ISA | | | 1 | 3 | 6 | 6 | | | | | | | | | | 0.016–0.125 | 0.06/0.125 | 0.06 |

[a]Gray-shaded areas indicate concentrations not tested for that particular compound. An underlined value indicates a modal MIC for unimodal distributions but the lowest MIC peak for multimodal distributions, thus illustrating the modal MIC of the presumed wild-type distribution. The MIC distributions for comparator antifungals against *C. auris* indicated by an asterisk (*) are compiled from reference 1 except that isolates above the tested MIC range in that publication were retested using extended concentration ranges.

122 isolats *C. auris*

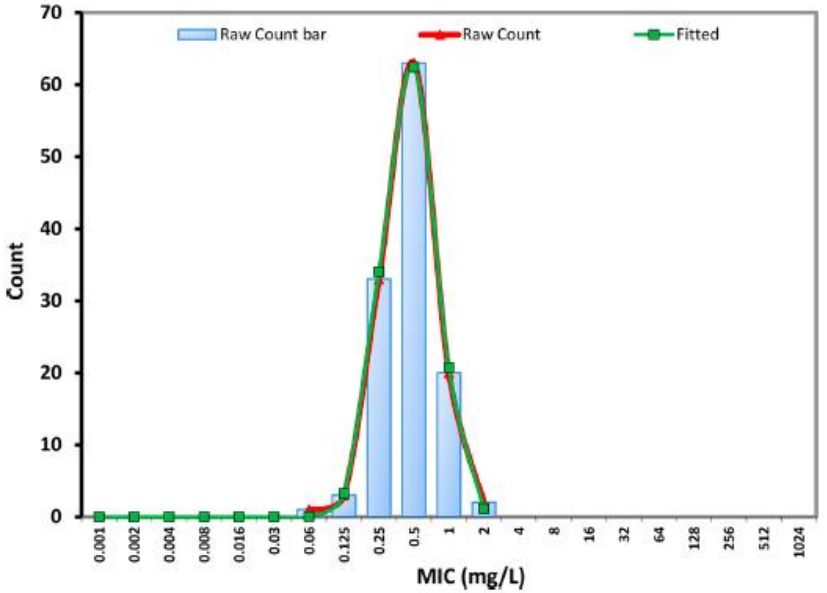
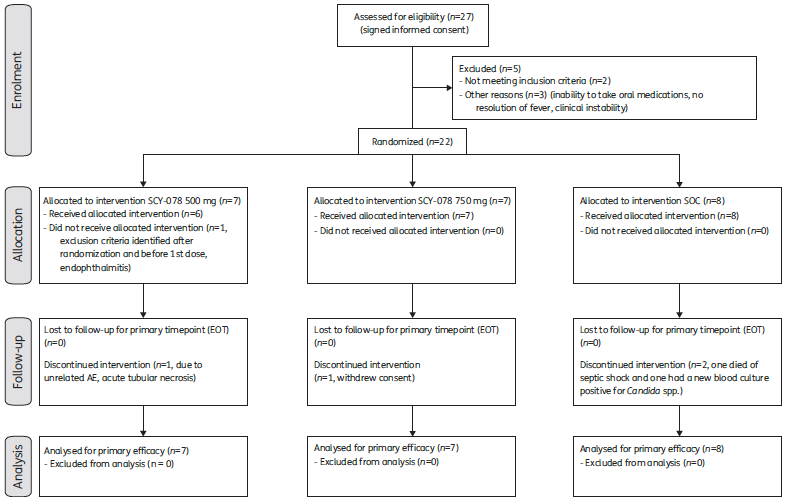



**FIG 1** EUCAST MIC distribution for ibrexafungerp against 122 clinical *C. auris* isolates. Raw counts are presented as bars and a red curve, whereas the fitted curve was determined by the ECOFF finder program (v2.0) that iteratively fits each subset of the data from left to right.

March 2020

# Phase 2 oral ibrexafungerp following initial echinocandin therapy in non neutropenic patients with invasive candidiasis

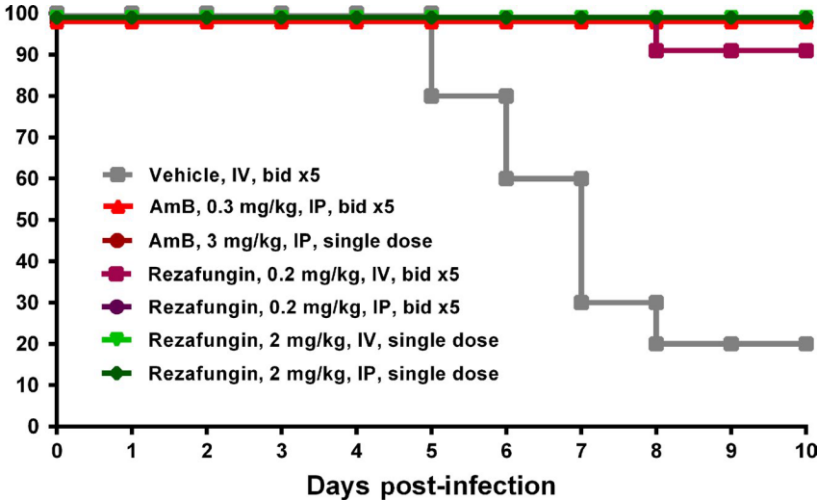
- Meilleure exposition: 1500mg J1 puis 7750mg/j
- Troubles digestifs
- Réponse 6/8 *C. glabrata et C. krusei*




Spec A, JAC 2019

**Table 2.** Global response in the ITT population of 22 patients with invasive candidiasis

| | Ibrexafungerp 500 mg (*N*=7), *n* (%) | Ibrexafungerp 750 mg (*N*=7), *n* (%) | SOC | |
|---|---|---|---|---|
| | | | fluconazole (*N*=7), *n* (%) | micafungin (*N*=1), *n* (%) |
| EOT | | | | |
| global response | 5 (71) | 6 (86) | 5 (71) | 1 (100) |
| clinical response | 5 (71) | 6 (86) | 5 (71) | 1 (100) |
| microbiological response | 6 (86) | 6 (86) | 6 (86) | 1 (100) |
| missing | 1 (14) | 1 (14) | 0 (0) | 0 (0) |
| Week 2 post-treatment | | | | |
| global response | 4 (57) | 4 (57) | 5 (71) | 0 (0) |
| clinical response | 4 (57) | 4 (57) | 5 (71) | 0 (0) |
| microbiological response | 4 (57) | 4 (57) | 5 (71) | 0 (0) |
| missing | 2 (29) | 3 (43) | 2 (29) | 1 (100) |
| Week 6 post-treatment | | | | |
| global response | 3 (43) | 2 (29) | 4 (57) | 0 (0) |
| clinical response | 3 (43) | 2 (29) | 4 (57) | 0 (0) |
| microbiological response | 3 (43) | 2 (29) | 4 (57) | 0 (0) |
| missing | 3 (43) | 5 (71) | 3 (43) | 1 (100) |




ORIGINAL ARTICLE

# Rezafungin treatment in mouse models of invasive candidiasis and aspergillosis: Insights on the PK/PD pharmacometrics of rezafungin efficacy

Lynn Miesel[1] | Kun-Yuan Lin[1] | Voon Ong[2]

# and W715L upstream and downstream substitutions, correlate with high ibrexafungerp MICs against *Candida glabrata*

Aina Mesquida

- We studied a set of *C. glabrata* (*n* = 34) isolates showing resistance to micafungin and anidulafungin (*n* = 28) or only to anidulafungin (*n* = 6) and harbouring 10 different *FKS2* gene substitutions. Antifungal susceptibility to ibrexafungerp was tested according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) E.Def 7.3.2 procedure and isolates were considered ibrexafungerp non-wild type according to the statistical wtUL (minimum inhibitory concentration [MIC] ≥2) or visual wtUL (MIC ≥4).
- **Results**
- Ibrexafungerp MICs against the isolates ranged from 0.06 to 4 mg/L. Four *FKS2* gene substitutions (ΔF659, F659S, E655A, and W715L) were exclusively found in isolates showing an ibrexafungerp MIC above the statistical wtUL (≥2 mg/L) whereas isolates harbouring other substitutions were found to be ibrexafungerp wild type. The use of the visual wtUL (MIC ≥4 mg/L) bisected the population of isolates harbouring such substitutions

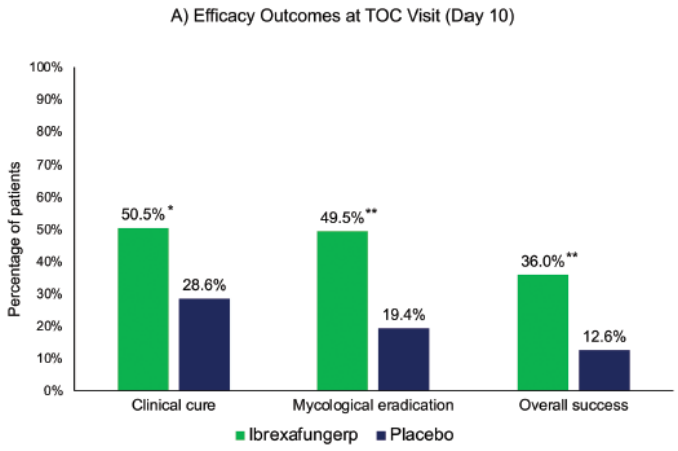
*Clinical Infectious Diseases*

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. J
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




| | 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 |

# CMI Rezafungin

**TABLE 3** (Continued)

| Antimicrobial agent | MIC (μg/ml) 50% | MIC (μg/ml) 90% | CLSI[b] % S | CLSI[b] % R | ECV[b] % WT | ECV[b] % NWT |
|---|---|---|---|---|---|---|
| *Cryptococcus neoformans* var. *grubii* (*n* = 73) | | | | | | |
| Rezafungin | >4 | >4 | | | | |
| Anidulafungin | >4 | >4 | | | | |
| Caspofungin | >4 | >4 | | | | |
| Micafungin | >4 | >4 | | | | |
| Fluconazole | 2 | 4 | | | 100.0 | 0.0 |
| Itraconazole | 0.25 | 0.25 | | | 93.5 | 6.5 |
| Posaconazole | 0.12 | 0.25 | | | 97.3 | 2.7 |
| Voriconazole | 0.03 | 0.12 | | | 100.0 | 0.0 |
| Amphotericin B | 0.5 | 1 | | | 52.1 | 47.9 |
| *Aspergillus fumigatus* (*n* = 183) | | | | | | |
| Rezafungin | 0.015 | 0.03 | | | 100.0 | 0.0 |
| Anidulafungin | 0.015 | 0.03 | | | | |
| Caspofungin | 0.015 | 0.03 | | | 100.0 | 0.0 |
| Micafungin | ≤0.008 | 0.015 | | | | |
| Itraconazole | 0.5 | 1 | | | 98.4 | 1.6 |
| Posaconazole | 0.25 | 0.5 | | | | |
| Voriconazole | 0.25 | 0.5 | | | 98.9 | 1.1 |
| Amphotericin B | 1 | 2 | | | 100.0 | 0.0 |
| *Aspergillus* section *Flavi* (*n* = 45) | | | | | | |
| Rezafungin | ≤0.008 | 0.015 | | | | |
| Anidulafungin | ≤0.008 | 0.015 | | | | |
| Caspofungin | 0.015 | 0.03 | | | 100.0 | 0.0 |
| Micafungin | 0.015 | 0.03 | | | | |
| Itraconazole | 0.5 | 1 | | | 100.0 | 0.0 |
| Posaconazole | 0.25 | 0.5 | | | 100.0 | 0.0 |
| Voriconazole | 0.5 | 1 | | | 100.0 | 0.0 |
| Amphotericin B | 2 | 2 | | | 100.0 | 0.0 |

[a]Abbreviations: S, susceptible; R, resistant; WT, wild type; NWT, non-wild type.
[b]Criteria were published in the CLSI M60 document (40). Epidemiological cutoff value (ECV) criteria were published in the CLSI M59 document (41). The ECVs for rezafungin and each species were determined from data in the present study.
[c]Nonresistant is interpreted as susceptible-dose dependent.

**TABLE 3** Antimicrobial activity of rezafungin and comparator agents tested against fungal isolates from the worldwide 2016 to 2018 rezafungin surveillance program[a]

| Antimicrobial agent | MIC (μg/ml) 50% | MIC (μg/ml) 90% | CLSI[b] % S | CLSI[b] % R | ECV[b] % WT | ECV[b] % NWT |
|---|---|---|---|---|---|---|
| *Candida albicans* (*n* = 835) | | | | | | |
| Rezafungin | 0.03 | 0.06 | | | 99.8 | 0.2 |
| Anidulafungin | 0.015 | 0.03 | 100.0 | 0.0 | 100.0 | 0.0 |
| Caspofungin | 0.015 | 0.03 | 99.9 | 0.1 | | |
| Micafungin | 0.015 | 0.03 | 99.9 | 0.1 | 99.6 | 0.4 |
| Fluconazole | ≤0.12 | 0.25 | 99.5 | 0.4 | 98.1 | 1.9 |
| Itraconazole | ≤0.06 | 0.12 | | | | |
| Posaconazole | 0.03 | 0.06 | | | 96.5 | 3.5 |
| Voriconazole | ≤0.008 | 0.015 | 99.9 | 0.0 | 99.0 | 1.0 |
| Amphotericin B | 0.5 | 1 | | | 100.0 | 0.0 |
| *Candida glabrata* (*n* = 374) | | | | | | |
| Rezafungin | 0.06 | 0.12 | | | 95.7 | 4.3 |
| Anidulafungin | 0.06 | 0.12 | 94.4 | 3.2 | 96.8 | 3.2 |
| Caspofungin | 0.03 | 0.06 | 97.1 | 2.1 | | |
| Micafungin | 0.015 | 0.03 | 96.0 | 2.4 | 93.3 | 6.7 |
| Fluconazole | 2 | 32 | 91.4[c] | 8.6 | 85.6 | 14.4 |
| Itraconazole | 0.5 | 2 | | | 98.7 | 1.3 |
| Posaconazole | 0.25 | 1 | | | 93.0 | 7.0 |
| Voriconazole | 0.06 | 1 | | | 87.2 | 12.8 |
| Amphotericin B | 1 | 1 | | | 100.0 | 0.0 |
| *Candida parapsilosis* (*n* = 329) | | | | | | |
| Rezafungin | 1 | 2 | | | 100.0 | 0.0 |
| Anidulafungin | 2 | 2 | 93.9 | 0.0 | 100.0 | 0.0 |
| Caspofungin | 0.25 | 0.5 | 100.0 | 0.0 | | |
| Micafungin | 1 | 1 | 100.0 | 0.0 | 100.0 | 0.0 |
| Fluconazole | 0.5 | 32 | 86.0 | 12.5 | 83.6 | 16.4 |
| Itraconazole | 0.12 | 0.25 | | | | |
| Posaconazole | 0.06 | 0.12 | | | 100.0 | 0.0 |
| Voriconazole | ≤0.008 | 0.25 | 88.4 | 0.9 | 84.5 | 15.5 |
| Amphotericin B | 0.5 | 1 | | | 100.0 | 0.0 |
| *Candida tropicalis* (*n* = 196) | | | | | | |
| Rezafungin | 0.03 | 0.06 | | | 100.0 | 0.0 |
| Anidulafungin | 0.03 | 0.06 | 99.0 | 1.0 | 98.0 | 2.0 |
| Caspofungin | 0.015 | 0.06 | 99.0 | 1.0 | | |
| Micafungin | 0.03 | 0.06 | 99.0 | 1.0 | 96.4 | 3.6 |
| Fluconazole | 0.25 | 1 | 96.9 | 2.6 | 94.9 | 5.1 |
| Itraconazole | 0.12 | 0.5 | | | 100.0 | 0.0 |
| Posaconazole | 0.06 | 0.12 | | | 92.9 | 7.1 |
| Voriconazole | 0.015 | 0.06 | 96.9 | 0.0 | 96.9 | 3.1 |
| Amphotericin B | 0.5 | 1 | | | 100.0 | 0.0 |
| *Candida krusei* (*n* = 77) | | | | | | |
| Rezafungin | 0.03 | 0.06 | | | 100.0 | 0.0 |
| Anidulafungin | 0.06 | 0.12 | 100.0 | 0.0 | 100.0 | 0.0 |
| Caspofungin | 0.12 | 0.25 | 98.7 | 0.0 | | |
| Micafungin | 0.06 | 0.12 | 100.0 | 0.0 | 100.0 | 0.0 |
| Fluconazole | 32 | 64 | | | | |
| Itraconazole | 0.5 | 1 | | | 100.0 | 0.0 |
| Posaconazole | 0.5 | 0.5 | | | 100.0 | 0.0 |
| Voriconazole | 0.25 | 0.5 | 96.1 | 1.3 | 96.1 | 3.9 |
| Amphotericin B | 1 | 2 | | | 100.0 | 0.0 |
| *Candida dubliniensis* (*n* = 93) | | | | | | |
| Rezafungin | 0.06 | 0.12 | | | 100.0 | 0.0 |
| Anidulafungin | 0.03 | 0.12 | | | 100.0 | 0.0 |
| Caspofungin | 0.03 | 0.03 | | | | |
| Micafungin | 0.03 | 0.03 | | | 100.0 | 0.0 |
| Fluconazole | ≤0.12 | 0.25 | | | 96.8 | 3.2 |
| Itraconazole | ≤0.06 | 0.25 | | | | |
| Posaconazole | 0.03 | 0.06 | | | | |
| Voriconazole | ≤0.008 | 0.015 | | | | |
| Amphotericin B | 0.5 | 0.5 | | | | |

(Continued on next page)

Pfaller, AAC, 2020

*Rezafungin In Vitro Activity against Contemporary Nordic Clinical Candida Isolates and Candida auris Determined by the EUCAST Reference Method*
*Marie Helleberg,a,b Karin Meinike*

| Organism | Mutation[a] | | MIC[b] (mg/liter) | | | | |
|---|---|---|---|---|---|---|---|
| | Fks1 | Fks2 | RZF | ANF | MCF | AMB | FLU |
| *C. albicans* | S645P | NT | **1** | **0.25** | **2** | 0.25 | 0.25 |
| | D648Y | NT | **0.5** | **0.06** | **0.125** | 0.25 | 0.125 |
| | P1354S | NT | **0.5** | **0.06** | **0.125** | 0.5 | **>64** |
| | P1354S | NT | **0.25** | 0.016 | **0.06** | 0.5 | **>32** |
| | P1354S | NT | **0.25** | 0.016 | **0.06** | 0.5 | **64** |
| | P1354S | NT | **0.25** | 0.016 | **0.06** | 0.5 | **64** |
| | P1354P/S | NT | **0.25** | 0.03 | **0.06** | 0.5 | **>64** |
| | P1354P/S | NT | **0.25** | **0.06** | **0.06** | 0.5 | **>64** |
| | R1361R/S | NT | **0.25** | **0.06** | **0.125** | 0.125 | 0.125 |
| | R1361G | NT | **0.25** | **0.06** | **0.125** | 0.125 | 0.25 |
| | R1361G | NT | **0.25** | 0.016 | **0.06** | 0.5 | **64** |
| *C. glabrata* | L630Q | S663F | **2** | **1** | **0.5** | 0.5 | 1 |
| | L630Q | S663F | **2** | **1** | **0.5** | 0.5 | 32 |
| | WT | S663F | **2** | **1** | **0.5** | 0.5 | 2 |
| | WT | S663F | **1** | **0.25** | **0.125** | 0.125 | 2 |
| | WT | S663F | **0.5** | **0.25** | **0.125** | 0.5 | 2 |
| | WT | S663F | **0.5** | 0.06 | **0.06** | 0.5 | 2 |
| | WT | S663P | **2** | **1** | **0.5** | 0.125 | 2 |
| | WT | S663P | **0.5** | **0.125** | **0.125** | 0.25 | 4 |
| | Y1429X | Y658N/L664Q | **0.5** | **0.125** | **0.06** | 0.125 | **>32** |
| | WT | F659del | **0.5** | 0.06 | **0.06** | 0.25 | **>64** |
| *C. tropicalis* | F650S | NT | **1** | **0.25** | **1** | 0.25 | 0.5 |
| | S654P | NT | **2** | **2** | **2** | 0.5 | 0.5 |
| *C. dubliniensis* | S645P | NT | **2** | **0.25** | **2** | 0.03 | 0.125 |
| | S645P | NT | **1** | **0.25** | **2** | 0.03 | 0.125 |
| *C. krusei* | S659F | NT | **1** | **0.25** | **4** | 0.5 | 32 |
| *C. auris* | S639F | NT | **16** | **4** | **>32** | 1 | **>256** |
| | S639F | NT | **16** | **>32** | **>32** | 1 | **>256** |
| | S639F | NT | **8** | **>32** | **>32** | 1 | **>256** |
| | S639F | NT | **8** | **>32** | **>32** | 1 | **>256** |
| | S639F | NT | **8** | **>32** | **>32** | 1 | **>256** |
| | S639F | NT | **8** | **>32** | **>32** | 1 | **>256** |
| | S639F | NT | **8** | **>32** | **>32** | 1 | **>256** |
| | S639F | NT | **8** | **>32** | **>32** | 1 | **>256** |
| | WT | NT | **2** | **2** | 0.25 | 1 | **>256** |
| | WT | NT | **2** | **1** | 0.25 | 1 | **256** |
| | WT | NT | **2** | 0.03 | 0.03 | 0.5 | **256** |

- CMI *C. auris fks1 CMI moins élevées Reza vs autres echino*

AAC 2020

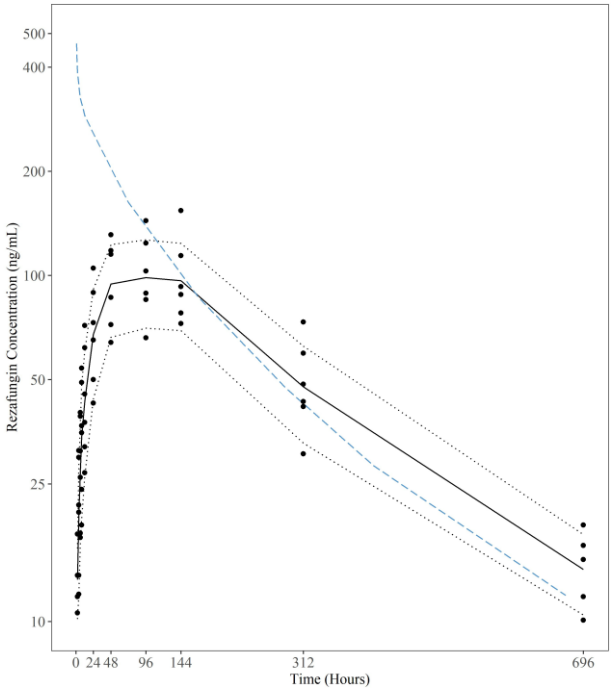
# Rezafungine sous cutanée phase I

TABLE 1 Number and percentage of subjects experiencing solicited reactogenicity symptoms by symptom and dose group

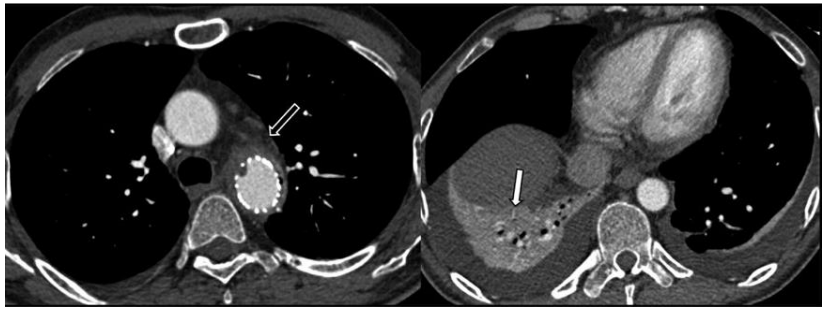
| | Any dose ($N = 9$) | | | 1 mg ($N = 3$) | | | 10 mg ($N = 6$) | | | Placebo ($N = 3$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Symptom** | ***n*** | **%** | **95% CI** | ***n*** | **%** | **95% CI** | ***n*** | **%** | **95% CI** | ***n*** | **%** | **95% CI** |
| Any symptom | 7 | 78 | 45, 94 | 1 | 33 | 6, 79 | 6 | 100 | 61, 100 | – | – | – |
| Pain | 3 | 33 | 12, 65 | 1 | 33 | 6, 79 | 2 | 33 | 10, 70 | – | – | – |
| Tenderness | 4 | 44 | 19, 73 | – | – | – | 4 | 67 | 30, 90 | – | – | – |
| Pruritus (itching) | 1 | 11 | 2, 43 | – | – | – | 1 | 17 | 3, 56 | – | – | – |
| Ecchymosis (bruising), functional grade | 2 | 22 | 6, 55 | – | – | – | 2 | 33 | 10, 70 | – | – | – |
| Ecchymosis (bruising), measurement grade | 1 | 11 | 2, 43 | – | – | – | 1 | 17 | 3, 56 | – | – | – |
| Induration (hardness)/swelling, functional grade | 1 | 11 | 2, 43 | – | – | – | 1 | 17 | 3, 56 | – | – | – |
| Induration (hardness)/swelling, measurement grade | 1 | 11 | 2, 43 | – | – | – | 1 | 17 | 3, 56 | – | – | – |
| Erythema (redness), functional grade | 6 | 67 | 35, 88 | – | – | – | 6 | 100 | 61, 100 | – | – | – |
| Erythema (redness), measurement grade | 6 | 67 | 35, 88 | – | – | – | 6 | 100 | 61, 100 | – | – | – |
| Nodule, functional grade | 5 | 56 | 27, 81 | – | – | – | 5 | 83 | 44, 97 | – | – | – |
| Nodule, measurement grade | 4 | 44 | 19, 73 | – | – | – | 4 | 67 | 30, 90 | – | – | – |
| Ulceration, functional grade | – | – | – | – | – | – | – | – | – | – | – | – |
| Ulceration, measurement grade | – | – | – | – | – | – | – | – | – | – | – | – |

*Note*: $N$ = Number of subjects in safety population.

Abbreviation: CI, confidence interval.

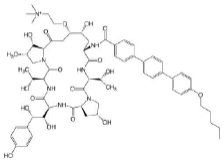


- *We report on the successful ongoing*
- *compassionate use of rezafungin obtained through expanded*
- *access for over 1 year in a patient with a multidrug-resistant*
- *Candida glabrata mediastinal infection from a vascular graft infection*
- *and retained foreign material*



# Rezafungin / Cidara

Rezafungin (CD101)



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

- Echinocandine action prolongée
- 1 injection IV par semaine

Detailed Description:

A Phase 3, multicenter, prospective, randomized, double-blind, efficacy and safety study of Rezafungin for Injection versus an active comparator regimen of caspofungin followed by optional oral fluconazole step-down therapy in subjects with candidemia and/or invasive candidiasis.

**tudy Design** Go to

| | |
|---|---|
| Study Type : | Interventional (Clinical Trial) |
| Estimated Enrollment : | 218 participants |
| Allocation: | Randomized |
| Intervention Model: | Parallel Assignment |
| Masking: | Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |
| Primary Purpose: | Treatment |
| Official Title: | A Phase 3, Multicenter, Randomized, Double-blind Study of the Efficacy and Safety of **Rezafungin** for Injection vs. Intravenous Caspofungin Followed by Oral Fluconazole Step Down in the Treatment of Subjects With Candidemia and/or Invasive Candidiasis |
| Actual Study Start Date : | October 12, 2018 |
| Estimated Primary Completion Date : | September 2020 |
| Estimated Study Completion Date : | September 2020 |

*Clinical Infectious Diseases*

MAJOR ARTICLE

# 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,[1] Alex Soriano,[2] Athanasios Skoutelis,[3] Jose A. Vazquez,[4] Patrick M. Honore,[5] Juan P. Horcajada,[6] Herbert Spapen,[7] Matteo Bassetti,[8] Luis Ostrosky-Zeichner,[9] Anita F. Das,[10] Rolando M. Viani,[11] Taylor Sandison,[11] and Peter G. Pappas[12]; The STRIVE Trial Investigators

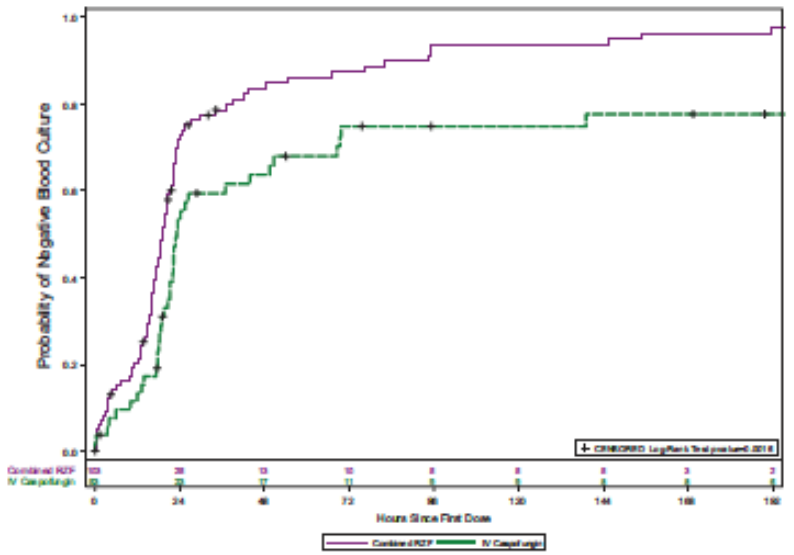
- Rezafungin: demi vie 133h
- Essai de phase 2 randomisé
- Candidémie et candidoses invasives
- RZF 400mg/sem S1 puis 200mg/sem vs 400mg/sem vs Caspo 70mg puis 50mg puis fluco
- Guerison à S2, mortalité à J30
- 207 patients
- Guerison 60%

**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 | Rezafungin Once Weekly 400 mg/200 mg | Caspofungin Once Daily 70 mg/50 mg |
|---|---|---|---|
| | N = 76 | N = 46 | N = 61 |
| Overall cure | 46 (60.5) | 35 (76.1) | 41 (67.2) |
| 95% CI*] | [48.6–71.6] | [61.2–87.4] | [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) |



RESEARCH ARTICLE

# Risk factors and outcomes of patients with ocular involvement of candidemia

**Hyo-Ju Son[1], Min Jae Kim[1]*, Suhwan Lee[2], Sungim Choi[1], Kyung Hwa Jung[1], Jiwon Jung[1], Yong Pil Chong[1], Sung-Han Kim[1], Sang-Ho Choi[1], Yang Soo Kim[1], Jun Hee Woo[1], Joo Yong Lee[3], Sang-Oh Lee[1]**

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Plos one, 2019

- 275 FO candidémie dans les 2 semaines
- 59 (21.5%) anomalies:
  - 51 choriorétinites, 8 endophtalmies
  - 11 symptomatiques
- Candidémie persistante, neutropénie dans les 2 semaines précédentes associées au risue d'atteinte ophtalmologiue
- 24 patients neutropéniques:
  - 41% atteinte ophtalmo

  (positive avant sortie aplasie1/3 des patients)

# Quel traitement de première ligne? ECIL-6

**Table 4. ECIL-6 recommendations for initial first-line treatment of candidemia.**

| | Overall population | Hematologic patients |
|---|---|---|
| Antifungal therapy | | |
| Micafungin[a] | A I | A II |
| Anidulafungin | A I | A II[b] |
| Caspofungin | A I | A II |
| Liposomal amphotericin B | A I | A II |
| Amphotericin B lipid complex | B II | B II |
| Amphotericin B colloidal dispersion | B II | B II |
| Amphotericin B deoxycholate[c] | C I | C II |
| Fluconazole[d,e] | A I | C III |
| Voriconazole[d] | A I | B II |
| Catheter removal[f] | A II | B II |

[a]See warning box in European label; [b]provisional grading; [c]close monitoring for adverse event is required; [d]not in severely ill unstable patients; [e]not in patients with previous azole exposure; [f]if the catheter cannot be removed, use of an echinocandin or a lipid formulation of amphotericin B is recommended.

Tissot F, Haematologica 2016

# Quel traitement en fonction de l'espèce

**Table 5. ECIL-6 recommendations for first-line treatment of candidemia after species identification.**

| Candida species | Overall population | | Hematologic patients | |
|---|---|---|---|---|
| *C. albicans* | Echinocandins[a] | A I | Echinocandins | A II |
| | Fluconazole[b] | A I | Fluconazole | C III |
| | Liposomal amphotericin B | A I | Liposomal amphotericin B | B II |
| | Amphotericin B lipid complex | A II | Amphotericin B lipid complex | B II |
| | Amphotericin B colloidal dispersion | A II | Amphotericin B colloidal dispersion | B II |
| | Amphotericin B deoxycholate | C I | Amphotericin B deoxycholate | C II |
| *C. glabrata* | Echinocandins[a] | A I | Echinocandins | A II |
| | Liposomal amphotericin B | B I | Liposomal amphotericin B | B II |
| | Amphotericin B lipid complex | B II | Amphotericin B lipid complex | B II |
| | Amphotericin B colloidal dispersion | B II | Amphotericin B colloidal dispersion | B II |
| | Amphotericin B deoxycholate | C I | Amphotericin B deoxycholate | C II |
| *C. krusei* | Echinocandins[a] | A II | Echinocandins[a] | A III |
| | Liposomal amphotericin B | B I | Liposomal amphotericin B | B II |
| | Amphotericin B lipid complex | B II | Amphotericin B lipid complex | B II |
| | Amphotericin B colloidal dispersion | B II | Amphotericin B colloidal dispersion | B II |
| | Amphotericin B deoxycholate | C I | Amphotericin B deoxycholate | C II |
| Oral stepdown | Voriconazole | B I | Voriconazole | C III |
| *C. parapsilosis* | Fluconazole | A II | Fluconazole | A III |
| | Echinocandins[c] | B II | Echinocandins | B III |

[a]Same grading for anidulafungin, caspofungin, micafungin; [b]not in severely ill patients; [c]if echinocandin-based regimen introduced before species identification and patient responding clinically and microbiologically (sterile blood cultures at 72 h), continuing use of echinocandin might be considered.

# Candidémie et neutropénie: IDSA 2016

- Candidemia neutropenic
  - Echinocandin (strong recommendation; moderate-quality evidence).
  - Lipid formulation of AmB 3-5 mg/kg/d: alternative (strong recommendation; moderate-quality evidence).
  - Fluconazole 400mg: can be used for step down if patient stable, isolate susceptible and blood culture cleared(weak recommendation; low-quality
- C. krusei
  - Echinocandin, lipid formulation AmB or voriconazole

- Duration: 2 w after clearance if symptoms and neutropenia resolved
- FO: 1 w after neutrophil recovery
- CVC removal

*IDSA guidelines ; Pappas PG et al. Clin Infect Dis 2016.*

# Candidémies: mesures associées

- Ablation du cathéter ou de la chambre implantable
- ETT à J5-J7, ETO non systématique (si ETT douteuse ou candidémie persistante à 72 heures); sinon en sortie d'aplasie
- Doppler veineux non systématique: à réaliser en cas de thrombose ou candidémie persistante à 72 heures
- Fond d'œil pour les non neutropéniques dans les 8 jours (sortie aplasie)
- Contrôle de la négativation des hémoculture
- **Traiter même si une seul hémoculture positive en périph ou sur cathéter ou chambre implantable**

Recommandations COMAI AP-HP, 2018

# Traitement de première ligne candidémie patient non neutropénique

| Ligne de traitement | Traitement | Commentaire |
|---|---|---|
| **Durée du traitement** | *Pendant 14 jours après la dernière hémoculture positive* | |
| 1ère ligne | **Echinocandine :**<br><br>**Caspofungine**<br>Adulte : 70 mg puis 50 mg ou 70 mg si poids > 80kg x 1/j<br>*Dose de charge de 150 mg puis dose de 1 mg/kg/j à discuter chez les patients les + graves (qSOFA>=2)*<br>Enfant : 70mg/m² puis 50mg/m² x1/j<br><br>Ou<br><br>**Micafungine**<br>Adulte : 100 mg x 1/j<br>*Dose 150 mg/j à discuter chez les patients les + graves*<br>Enfant : 2-4 mg/kg/jour | **Tester la sensibilité aux échinocandines :** en cas de traitement antérieur par échinocandine ou d'infection à *Candida glabrata ou parapsilosis*<br><br>***Si C. parapsilosis :*** switch pour le fluconazole (si fluco S) |
| Alternative de choix | **Fluconazole**<br>12 mg/kg à J1 puis 6 mg/kg x 1/j | Si pas de choc ni antécédent de prise d'azolés<br><br>Tester la sensibilité aux azolés de principe |

| Ligne de traitement | Traitement | Commentaire |
|---|---|---|
| **Durée du traitement** | *Pendant 14 jours après la dernière hémoculture positive* | |
| Alternative en cas d'intolérance ou de souche résistante aux autres médicaments | **Amphotéricine B liposomale**<br>3 mg/kg x1/j | |
| Si l'ablation de cathéter ou de chambre implantable impossible | **Amphotéricine B liposomale**<br>Ou<br>**Echinocandine** | |

Si point de départ urinaire:
-Fluconazole ou fluconazole forte posologie (maintien de la dose de charge de 12 mg/kg/j) pour le *Candida glabrata* non R (CMI<32)
-Amho B deoxycholate pour *C. krusei* et *C. glabrata* fluco R

Recommandations COMAI AP-HP, 2018

# Traitement de première ligne candidémie neutropénique

| Ligne de traitement | Traitement | Commentaire |
|---|---|---|
| 1ère ligne | **Echinocandine :**<br><br>**Caspofungine**<br>Adulte : 70 mg puis 50 mg x 1/j Dose de charge de 140 mg puis dose de 1 mg/kg/j à discuter chez les patients les + graves *(qSOFA>=2)*<br>Enfant : 70mg/m² puis 50mg/m²/24h<br><br>Ou<br><br>**Micafungine**<br>Adulte : 100 mg x 1/j<br>Dose 150 mg/j à discuter chez les patients les + graves<br>Enfant : 2-4 mg/kg x1/j<br><br>*Pendant 14 jours après la dernière hémoculture positive* | |
| Alternative de choix | **Amphotéricine B liposomale**<br>3 mg/kg x1/j<br><br>*Pendant 14 jours après la dernière hémoculture positive* | |

| | **Voriconazole** | En cas d'infection à *C. krusei* |
|---|---|---|
| Traitement en cas d'infection à *Candida krusei* | **Amphotéricine B liposomale**<br>Ou<br>**Echinocandine**<br><br>*Pendant 14 jours après la dernière hémoculture positive* | Posologies citées ci-dessus |
| Alternative en cas d'ablation de cathéter ou de chambre implantable impossible | **Echinocandine**<br><br>*Pendant 14 jours après la dernière hémoculture positive* | Posologies citées ci-dessus |

Recommandations COMAI AP-HP, 2018

# Désescalade

| | | |
|---|---|---|
| **Désescalade après 3 à 5 jours si**<br>- stabilité clinique<br>- souche sensible<br>- négativation des hémocultures<br>-ablation du cathéter | **Fluconazole**<br>12 mg/kg à J1 puis<br>6 mg/kg x 1/j | Si espèce sensible :<br>*C. albicans*<br>*C.parapsilosis*<br>*C. tropicalis* |
| | **Voriconazole** | En cas d'infection à<br>*C. krusei* |

**Que le patient soit neutropénique ou non**

Durée: 14 jours après négativation hémocultures

Recommandations COMAI AP-HP, 2018

# Prise en charge des fongémies

- Penser aux basidiomycètes
- Porte d'entrée
- Traitement précoce
- Posologie adaptée
- Molécule en fonction neutropénie, choc, pré exposition, porte d'entrée, retrait cathéter
- Bilan d'extension
- Adapter à l'espèce
- Evaluer la possibilité de désescalade à J5
- Traiter 14 jours après négativation hémocultures

*J Antimicrob Chemother* 2017; **72**: 1784–1793
doi:10.1093/jac/dkx045 Advance Access publication 4 March 2017

Journal of Antimicrobial Chemotherapy

# Predisposing factors and outcome of uncommon yeast species-related fungaemia based on an exhaustive surveillance programme (2002–14)

Stéphane Bretagne[1–3]*, Charlotte Renaudat[1], Marie Desnos-Ollivier[1], Karine Sitbon[1], Olivier Lortholary[1,4] and Françoise Dromer[1] on behalf of the French Mycosis Study Group†

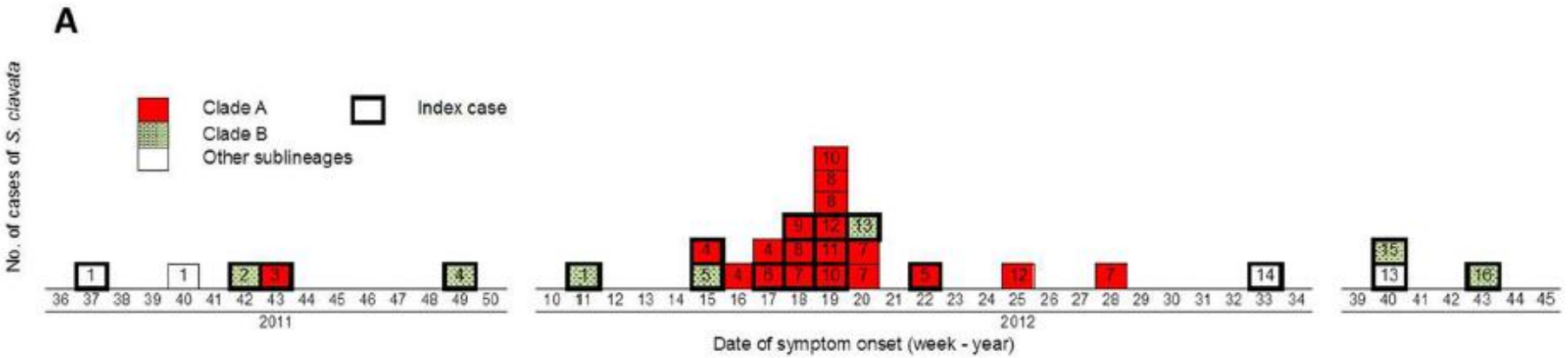
- 338 episodes rare yeasts infections associated with HM and antifungal preexposure
- *Candida kefyr* and *Trichosporon* associated with HM
- *Trichosporon* or *Geotrichum* associated with with preexposure to caspo but not fluco

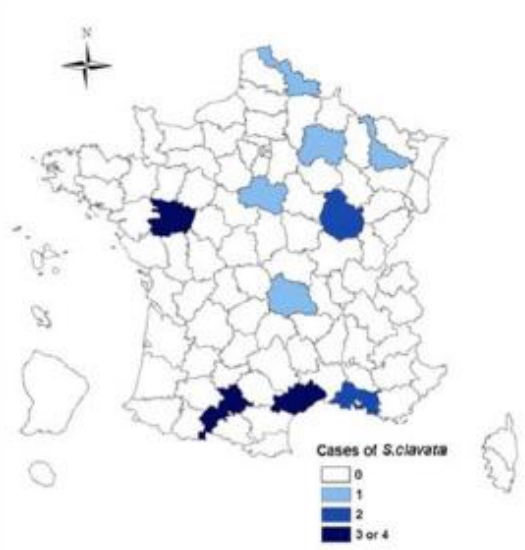
**Table 1.** Information regarding the 35 uncommon yeast species responsible for 338 episodes of fungaemia (YEASTS program 1 October 2002–31 December 2014)[a]

| | | | Antifungal susceptibility profile of all the isolates tested at the NRCMA | | | |
|---|---|---|---|---|---|---|
| | Isolates (n) | | $MIC_{50}$[b] (range) (mg/L) | | | |
| Species (synonym) | present study | total tested | AMB | VCZ | FLC | CAS |
| **Ascomycetes** | 310 | 839 | | | | |
| *Candida dubliniensis* | 37 | 75 | 0.03 (0.03–0.25) | ≤0.015 (≤0.015–0.125) | ≤0.125 (≤0.125–16) | 0.03 (≤0.007–1) |
| *Candida metapsilosis* | 9 | 22 | 0.06 (0.03–0.5) | 0.03 (≤0.015–0.06) | 1 (0.5–8) | 0.125 (0.06–0.5) |
| *Candida orthopsilosis* | 19 | 26 | 0.03 (≤0.015–0.125) | 0.03 (≤0.015–4) | 0.5 (≤0.125–32) | 0.125 (0.03–1) |
| *Meyerozyma guilliermondii* (*Candida guilliermondii*) | 20 | 77 | 0.03 (≤0.015–0.25) | 0.06 (0.03–2) | 8 (1–≥64) | 0.125 (≤0.007–1) |
| *Meyerozyma caribbica* (*Candida fermentati*) | 10 | 29 | 0.125 (0.06–0.5) | 0.125 (0.03–≥8) | 8 (1–≥64) | 0.125 (0.03–≥8) |
| *Candida palmioleophila* | 3 | 18 | 0.125 (0.125–0.5) | 0.125 (0.06–2) | 16 (8–≥64) | 0.125 (≤0.007–0.25) |
| *Magnusiomyces capitatus* (*Geotrichum capitatum*) | 11 | 29 | 0.25 (0.125–2) | 0.125 (0.03–1) | 16 (1–≥64) | ≥8 (≥8–≥8) |
| *Saprochaete clavata* (*Geotrichum clavatum*) | 10 | 80 | 0.25 (0.125–1) | 0.5 (0.03–2) | 32 (4–≥64) | ≥8 (1–≥8) |
| *Clavispora lusitaniae* (*Candida lusitaniae*) | 59 | 116 | 0.125 (≤0.015–1) | ≤0.015 (≤0.015–0.5) | 0.25 (≤0.125–64) | 0.06 (≤0.007–4) |
| *Kodamaea ohmeri* (*Candida ohmeri*) | 3 | 17 | 0.06 (0.03—0.125) | 0.03 (≤0.015–0.25) | 8 (1–64) | 0.06 (0.03–4) |
| *Candida nivariensis* | 1 | 7 | 0.125 (0.06–0.25) | 0.06 (0.06–0.125) | 4 (1–8) | 0.06 (0.03–0.125) |
| *Candida inconspicua* | 10 | 26 | 0.125 (0.06–0.5) | 0.125 (0.06–1) | 16 (8–≥64) | 0.06 (0.03–0.5) |
| *Pichia norvegensis* | 13 | 13 | 0.125 (0.03–0.125) | 0.25 (0.06–0.5) | 32 (8–64) | 0.06 (0.03–0.06) |
| *Pichia manshurica* | 1 | 1 | 0.25 | 0.125 | 64 | 0.06 |
| *Saccharomyces cerevisiae* | 11 | 35 | 0.06 (0.03–0.25) | 0.125 (≤0.015–1) | 8 (0.25–32) | 0.125 (0.03–2) |
| *Kluyveromyces marxianus* (*Candida kefyr*) | 69 | 117 | 0.125 (0.03–0.5) | ≤0.015 (≤0.015–0.25) | 0.5 (≤0.125–16) | 0.03 (≤0.007–0.5) |
| *Kluyveromyces lactis* (*Candida sphaerica*) | 1 | 2 | 0.03 | ≤0.015 | 0.25–2 | 0.03 |
| *Cyberlindnera fabianii* | 1 | 5 | 0.06 (0.03–0.125) | 0.03 (≤0.015–0.03) | 1 (0.5–2) | 0.03 (0.03–0.06) |
| *Cyberlindnera jadinii* (*Candida utilis*) | 10 | 18 | 0.06 (≤0.015–0.125) | 0.06 (0.03–1) | 1 (0.5–16) | ≤0.015 (≤0.007–1) |
| *Wickerhamomyces anomalus* (*Candida pelliculosa*) | 8 | 22 | 0.06 (0.03–0.125) | 0.125 (0.03–0.5) | 2 (0.5–8) | 0.06 (0.03–0.5) |
| *Candida haemulonii* | 2 | 37 | 0.5 (0.125–≥8) | ≥8 (0.125–≥8) | 32 (4–≥64) | 0.03 (≤0.007–0.25) |
| *Candida duobushaemulonii* | 2 | 35 | 2 (0.125–≥8) | ≥8 (0.125–≥8) | 32 (8–≥64) | 0.03 (≤0.007–1) |
| *Candida ruelliae* | 1 | 1 | 2 | 0.03 | 1 | 0.06 |
| *Candida pararugosa* | 1 | 5 | 0.25 (0.125–0.25) | 0.125 (≤0.015–0.25) | 8 (4–8) | 0.125 (0.06–0.5) |
| *Candida rugosa* | 3 | 7 | 0.25 (0.125–0.5) | 0.06 (≤0.015–0.25) | 4 (1–16) | 1 (0.06–≥8) |
| *Candida catenulata* | 1 | 1 | 0.06 | ≤0.015 | 0.5 | 0.125 |
| *Yarrowia lipolytica* | 4 | 18 | 0.25 (0.125–2) | 0.06 (≤0.015–0.25) | 4 (1–16) | 0.25 (0.06–4) |
| **Basidiomycetes** | 28 | 87 | | | | |
| *Trichosporon loubieri* | 1 | 1 | 1 | 0.03 | 2 | 4 |
| *Trichosporon dermatis* | 1 | 4 | 0.03–0.5 | 0.03–0.06 | 4–≥64 | 4–≥8 |
| *Trichosporon mucoides* | 1 | 1 | 0.06 | 0.125 | 2 | ≥8 |
| *Trichosporon asahii* | 9 | 37 | 2 (0.25–≥8) | 0.125 (≤0.015–0.5) | 4 (0.25–32) | 4 (2–≥8) |
| *Trichosporon japonicum* | 1 | 1 | 0.25 | ≤0.015 | 1 | 4 |
| *Trichosporon inkin* | 6 | 9 | 0.5 (0.25–2) | ≤0.015 (≤0.015–0.25) | 4 (0.25–16) | 4 (2–≥8) |
| *Rhodotorula mucilaginosa* | 8 | 27 | 0.25 (0.125–1) | 2 (0.03–≥8) | ≥64 (32–≥64) | ≥8 (≥8–≥8) |
| *Malassezia pachydermatis* | 1 | 7 | NA | NA | NA | NA |

Bretagne et al, JAC 2017

# Epidémie française de *Saprochaeta clavata*




Hémopathies
Sept 2011-0ct 2012
26 hémocultures positives
22 décès
Clone A épidémique
Traitement: voriconazole

Vaux S, Mbio 2014

frontiers in Microbiology

REVIEW
published: 17 October 2016
doi: 10.3389/fmicb.2016.01629

# Invasive Trichosporon Infection: a Systematic Review on a Re-emerging Fungal Pathogen

*João N. de Almeida Júnior*[1,2*] *and Christophe Hennequin*[3,4,5]

**TABLE 1 | Characteristics of 203 cases of invasive *Trichosporon* infection according to the underlying conditions.**

| | Groups of patients | | | | *p*-value |
|---|---|---|---|---|---|
| | Hemopathies | Other immunodeficiency conditions | Newborns | Miscellaneous | |
| No. of cases (%) | 79 (39) | 41 (21) | 25 (12) | 58 (28) | |
| Age (Mean ± SD) | 39.5 ± 21.58 | 39.3 ± 22.2 | NA[a] | 46.8 ± 23.1 | NS[b] |
| Sex ratio (F/M) | 21/53 0.39 | 14/23 0.6 | 8/9 0.8 | 24/34 0.7 | NS |
| **AT THE TIME OF DIAGNOSIS (%)** | | | | | |
| Neutropenia | 67 (85) | 3 (8) | 0 (0) | 0 (0) | **<0.0001** |
| CVC[c] | 36 (46) | 15(36) | 12 (48) | 19 (34) | NS |
| Breakthrough infection | 59 (74) | 12 (27) | 2 (8) | 9(16) | **<0.0001** |
| Previous antimicrobial therapy | 65 (82) | 24 (58) | 24 (96) | 39 (67) | **0.005** |
| **CLINICAL PRESENTATION** | | | | | |
| Disseminated | 79 (100) | 25 (61) | 25 (100) | 33 (56) | **<0.0001** |
| w/skin lesions | 27 (34) | 7 (28) | 0 (0) | 4 (12) | **0.001** |
| w/pulmonary lesions | 33 (42) | 6 (24) | 1 (5) | 3 (9) | **0.0003** |
| w/liver and/or spleen lesions | 11 (14) | 1 (4) | 0 (0) | 1 (3) | **0.06** |
| Localized deep-seated infections | 0 (0) | 16 (39) | 0 (0) | 25 (44) | **<0.0001** |
| **SPECIES** | | | | | |
| *Trichosporon asahii*[d] | 32(40) | 20 (48) | 16 (64) | 27 (46) | NS |
| *Trichosporon inkin*[e] | 1 (1) | 9 (22) | 0 (0) | 6 (11) | **0.0003** |
| *Trichosporon mucoides/dermatis*[f,g] | 2 (2) | 4 (9) | 3 (12) | 2 (3) | NS |
| Other Species[h] | 4 (5) | 2 (5) | 1 (4) | 5 (10) | NS |

Mortalité 44%

Voriconazole, moins de mortalité, CMI plus basse sur tous les isolats

# Epidemiology and outcome
## of *Rhodotorula* infection in haematological patients

- *Rhodotorula* spp. are emergent opportunistic pathogens, particularly in haematological patients.
- 29 reported fungaemias
- acute leukaemia (65.5%)
- *Rhodotorula mucilaginosa* was the species found more frequently (79.3%).
- presence of central venous catheter (100%) and neutropenia (62.1%).
- (81.5%) received amphotericin B.
- The overall mortality was higher (13.8%) than that described in non-haematological patients (5.8% in solid-organ neoplasms and 9% in AIDS or other chronic diseases).
- Patients with acute leukaemia had a higher mortality rate (15.7%) than patients with non-Hodgkin's lymphoma (0%).

Garcia-Suarez, Mycoses, 2011

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doi:10.1093/mmy/myaa051
Advance Access Publication Date: 23 June 2020
Original Article

Original Article

# Central nervous system candidiasis beyond neonates: Lessons from a nationwide study

**Hélène Chaussade[1,2,*], Xavier Cazals[3], Guillaume Desoubeaux[4], Gregory Jouvion[5,6], Marie-Elisabeth Bougnoux[7], Agnes Lefort[8], Claire Rivoisy[1], Marie Desnos-Ollivier[9], Fabrice Chretien[5], Taieb Chouaki[10], Bérengère Gruson[11], Louis Bernard[2,†], Olivier Lortholary[1,9,†], Fanny Lanternier[1,9] and the French Mycosis study group[1]**

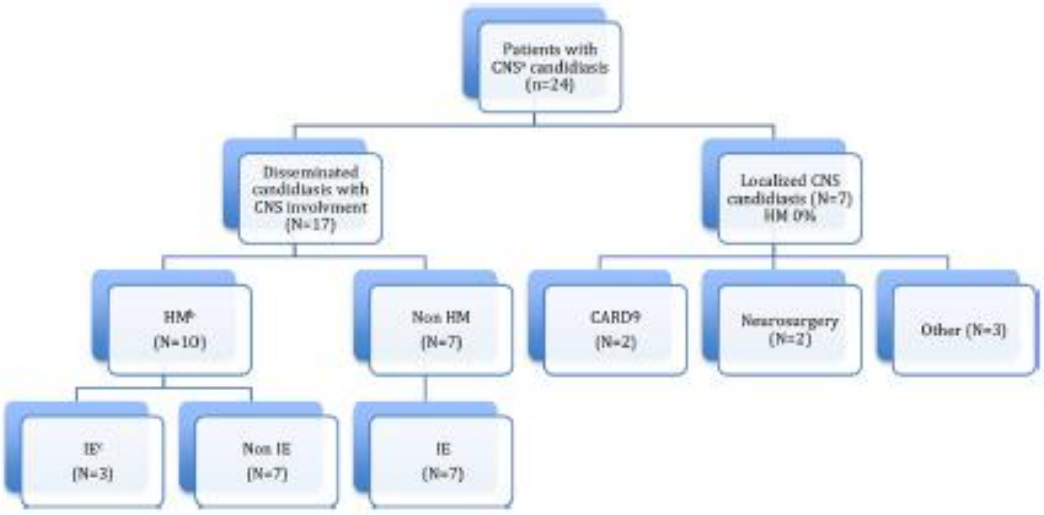

**Table 1.** Underlying conditions and clinical characteristics of 24 patients with central nervous system candidiasis.

| Patients and clinical characteristics | All ($n = 24$) | Disseminated ($n = 17$) | | | Localized (n = 7) |
|---|---|---|---|---|---|
| | | All ($n = 17$) | HM[a] ($n = 10$) | Non HM ($n = 7$) | |
| **Endocarditis** (%) | 10 (42) | 10 (59) | 3 (30) | 7 (100) | 0 |
| **Male sex** (%) | 14 (58) | 11 (65) | 5 (50) | 6 (86) | 3 (43) |
| **Median age years** (range) | 51 [6–82] | 52 [9–82] | 51 [9–75] | 52 [27–82] | 50 [6–72] |
| **Underlying conditions** | | | | | |
| Neutropenia, month before (%) | 9 (38) | 9 (53) | 9 (90) | 0 | 0 |
| Therapeutic LP[b] | 7 | 7 | 7 | 0 | 0 |
| Prosthetic valve (%) | 4 (17) | 4 (24) | 0 | 4 (57) | 0 |
| IVDU[c] (%) | 4 (17) | 3 (18) | 0 | 3 (43) | 1 (14) |
| CARD9 deficiency (%) | 2 (8) | 0 | 0 | 0 | 2 (29) |
| Diabetes mellitus (%) | 2 (8) | 1 (14) | 0 | 1 (14) | 1 (14) |
| Recent neurosurgery (%) | 2 (8) | 0 | 0 | 0 | 2 (29) |
| HIV (AIDS stage) | 1 (4) | 1 (14) | 1 | 0 | 0 |
| Other (%) | 2 (10) | 1 (6) | 0 | 1 (14) | 1 (14) |
| **Symptoms** | | | | | |
| Fever (%) | 20 (83) | 14 (82) | 10 (100) | 4 (57) | 6 (86) |
| Headache (%) | 8 (33) | 3 (18) | 3 (30) | 0 | 5 (71) |
| ICHT[d] signs (%) | 7 (29) | 1 (6) | 1 (10) | 0 | 6 (86) |
| Focal sign (%) | 11 (46) | 8 (47) | 3 (30) | 5 (71) | 3 (43) |
| Impaired consciousness (%) | 5 (21) | 5 (29) | 3 (30) | 2 (28) | 0 |
| Ocular (%) | 3 (13) | 2 (12) | 2 (20) | 0 | 1 uveitis (14) |
| Positive blood cultures (%) | 14 (59) | 14 (82) | 7 (70) | 7 (100) | 0 |
| **Extraneurological locations** | 12 (50) | 12 (71) | 9 (90) | 3 (43) | 0 |
| > 1 location (%) | – | 7 (41) | 5 (50) | 2 (28) | 0 |
| Spleen (%) | – | 8 (47) | 5 (50) | 3 (43) | 0 |
| Liver (%) | – | 4 (24) | 4 (40) | 0 | 0 |
| Kidney (%) | – | 5 (29) | 4 (40) | 1 (14) | 0 |
| Arthritis (%) | – | 2 (12) | 1 (10) | 1 (14) | 0 |
| **Laboratory meningitis** (%) | 8/13 (62) | 2/7 (29) | 2/7 (29) | 0/0 | 6 (100) |
| **MRI performed** | n=19 | n=12 | n=7 | n=5 | n=7 |
| MRI meningitis | 7 (37) | 2 (20) | 1 (14) | 1 (20) | 5 (71) |
| Abscesses | 11 (58) | 7 (58) | 5 (71) | 2 (40) | 4 (57) |
| Micro-abscesses[e] | 9 (47) | 7 (58) | 5 (71) | 2 (40) | 2 (29) |
| Macro-abscesses | 3 (16) | 0 | 0 | 0 | 3 (43) |
| Empyema | 1 (5) | 0 | 0 | 0 | 1 (14) |
| Vascular complications | 9 (47) | 8 (67) | 4 (57) | 4 (80) | 1 (14) |
| Haemorrhage | 7 (37) | 7 (58) | 4 (57) | 3 (60) | 0 |
| Ischemia | 5 (26) | 4 (33) | 1 (14) | 3 (60) | 1 (14) |
| Aneurysm | 0 | 0 | 0 | 0 | 0 |

**Table 2.** Laboratory characteristics of 24 patients with central nervous system candidiasis.

| Laboratory characteristics | All ($n = 24$) | Disseminated ($n = 17$) | | Localized ($n = 7$) |
|---|---|---|---|---|
| | | HM[a] ($n = 10$) | Non HM ($n = 7$) | |
| **CSF[b] analysis** | $n = 13$ | $n = 7$ | $n = 0$ | $n = 6$ |
| Meningitis (%) | 8 (62) | 2 (29) | – | 6 (100) |
| Median leucocyte count (/mm$^3$) | 46 [3–410] | 11 [3–20] | – | 176 [9–410] |
| Median lymphocyte % | 73 [29–96] | 29 | – | 80 [65–96] |
| Median neutrophils % | 27 [2–62] | 62 | – | 20 [2–60] |
| Clinical ICHT[c] | 7 | 1 | – | 6 |
| IC[d] pressure (cmH2O) | – | – | – | 35 |
| Protein (g/L) | 1.09 [0.19–5.69] | 0.44 [0,19–1.09] | – | 1.33 [0.36–5.69] |
| Hypoglycorachia (%) | 5 (38) | 2 (29) | – | 3 (50) |
| Positive microscopic exam (%) | 2 (15) | 0 | – | 2 (33) |
| Positive culture (%) | 4 (31) | 1 (14) | – | 3 (50) |
| Positive BG[e] | 6/7 | 3/4 | – | 3/3 |
| Median positive BG (pg/ml) | 377 [122→500] | 495 [122→500] | – | 259 [151 – >500] |
| Positive *Candida* mannan Ag | 4/5 | 2/2 | – | 2/3 |
| **Blood** | | | | |
| Median C reactive protein (mg/l) | 108 [12–385] | 135 [75–385] | 98 [12–284] | 2.7 [1–155] |
| Positive blood cultures (%) | 14 (58) | 7 (70) | 7 (100) | 0 |
| Positive serum BG (%) | 14/14 (100) | 7/7 (100) | 2/2 (100) | 5/5 (100) |
| Median serum BG (pg/ml) | 453 [95–500] | 500 [95–500] | 357 [214–500] | 188 [145–407] |
| Positive mannan antigen and/or anti-mannan antibody (%) | 10/14 (71) | 4/6 (67) | 2/2 (100) | 4/6 (67) |

**Table 3.** Treatment and outcome of 24 patients with CNS candidiasis.

| Treatment and outcome | All ($n = 24$) | Disseminat |
|---|---|---|
| | | HM[a] ($n = 10$) |
| **Antifungal treatment** | | |
| LAmB[b] (%) | 19 (79) | 9 (90) |
| Median days LAmB | 23 [11–92] | 28 [11–47] |
| 5FC (%) | 19 (79) | 8 (80) |
| Median days 5FC | 19 [4–92] | 24 [6–44] |
| Fluconazole (%) | 17 (71) | 6 (60) |
| Echinocandin (%) | 6 (25) | 3 (30) |
| Combination (%) | 20 (83) | 9 (90) |
| Median days AF duration | 82 [3–393] | 36 [3–158] |
| Secondary AF prophylaxis (%) | 4 (17) | 1 (10) |
| **Surgery** | | |
| EVD[c] (%) | 4 (17) | 0 |
| Neurosurgery (%) | 2 (8) | 0 |
| **Evolution** | | |
| Sequela (%) | 3 (30) | 0 |
| Death at 3 months | 7 (29) | 6 (60) |
| Death with evolutive infection (%) | 10 (42) | 7 (70) |

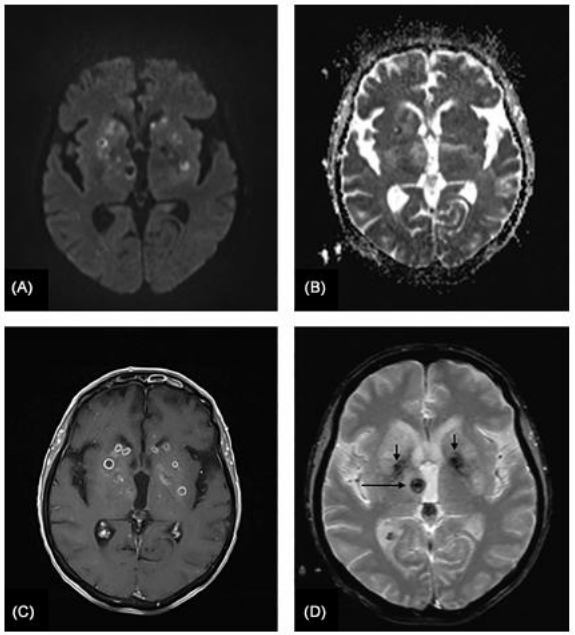


**Figure 3.** MRI of a patient with disseminated infection without IE during neutropenia. (A) Diffusion Weighted Imaging (DWI) (with b-values of 1000 s/mm$^2$) (A and (B) ADC cartography show multiple micro and macro abscesses in the corpus callosum with a variable diffusion signal and cartography ADC value. (C) A micro-abscesses enhance on gadolinium-enhanced 3DT1-weighted image. (D) Axial T2* image shows micro-abscess hemorrhagic phenomena (black arrow) an basal ganglia common calcifications (black arrowhead).