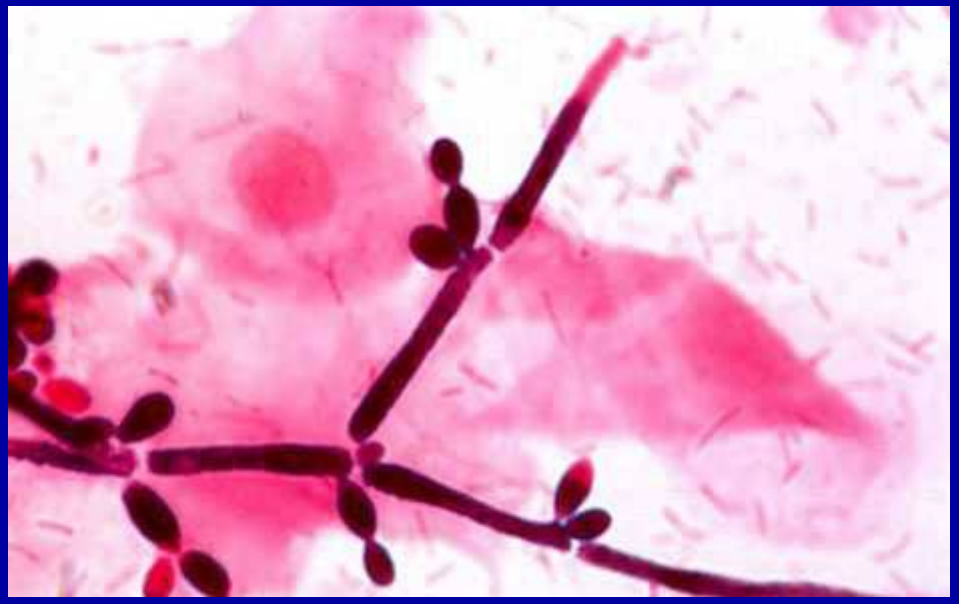
# Candidoses invasives en 2009: quelle place pour les échinocandines?



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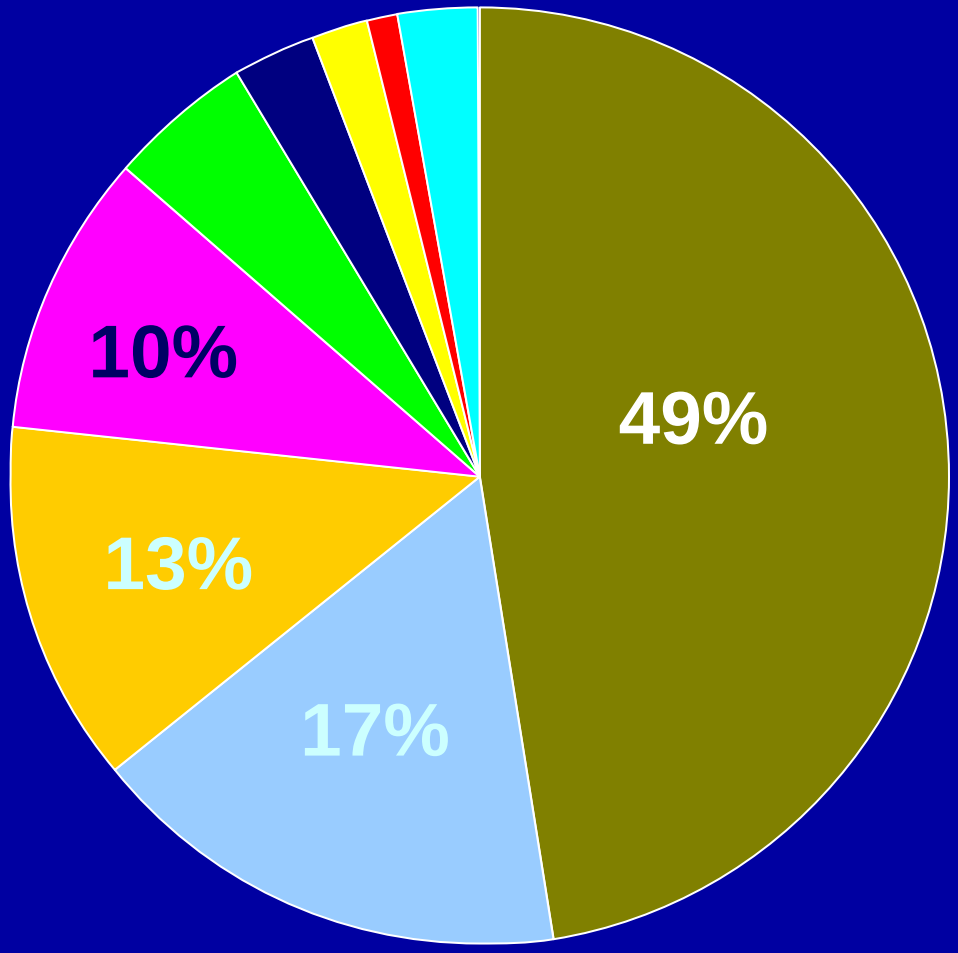
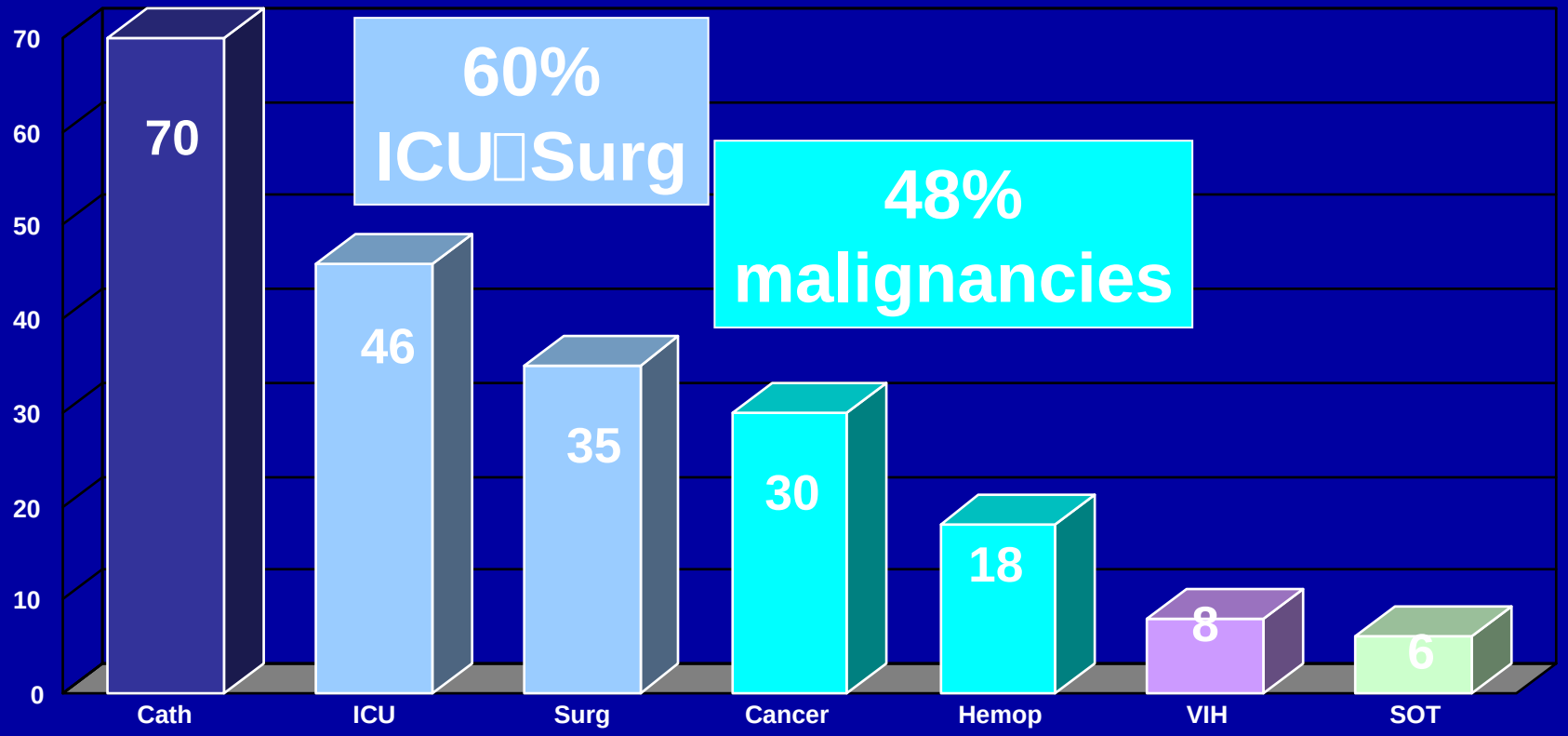
# Prospective analysis of 1,936 yeast isolates in blood cultures in Paris hospitals (2002–2007)




- ***C. albicans***
- ***C. glabrata***
- ***C. parapsilosis***
- ***C. tropicalis***
- ***Cryptococcus neoformans***
- ***C. krusei***
- ***C. kefyr***
- ***C. guilliermondii***
- **Other species**

Lortholary et al. Submitted for publication

# Major underlying factors during yeast fungemia in Paris




Lortholary et al. Submitted for publication

# In vitro susceptibility to fluconazole in ICU

- Prospective multicenter study in France
- 305 identified isolates, 210 tested isolates
- 17% R or S-DD to fluconazole (validated methods)

| Species | Distribution | *in vitro* susceptibility to fluconazole | | |
|---|---|---|---|---|
| | | Nb. tested | S | S-DD or R |
| *Candida albicans* | 174 (57%) | 113 | 96% | 4% |
| *Candida glabrata* | 51 (17%) | 38 | 50% | 50% |
| *Candida parapsilosis* | 23 (7,5%) | 19 | 90% | 10% |
| *Candida krusei* | 16 (5,2%) | 6 | 17% | 83% |
| *Candida tropicalis* | 15 (4,9%) | 14 | 86% | 14% |
| *Candida kefyr* | 11 (3,6%) | 9 | 100% | 0 |
| *Candida guilliermondii* | 5 (1,6%) | 5 | 80% | 20% |
| *Candida lusitaniae* | 2 (0,7%) | 2 | 100% | 0 |
| Autres *Candida* | 8 (2,6%) | 4 | 50% | 50% |
| Total | 305 | 210 | 83% | 17% |

Leroy et al. Crit Care Med 2009

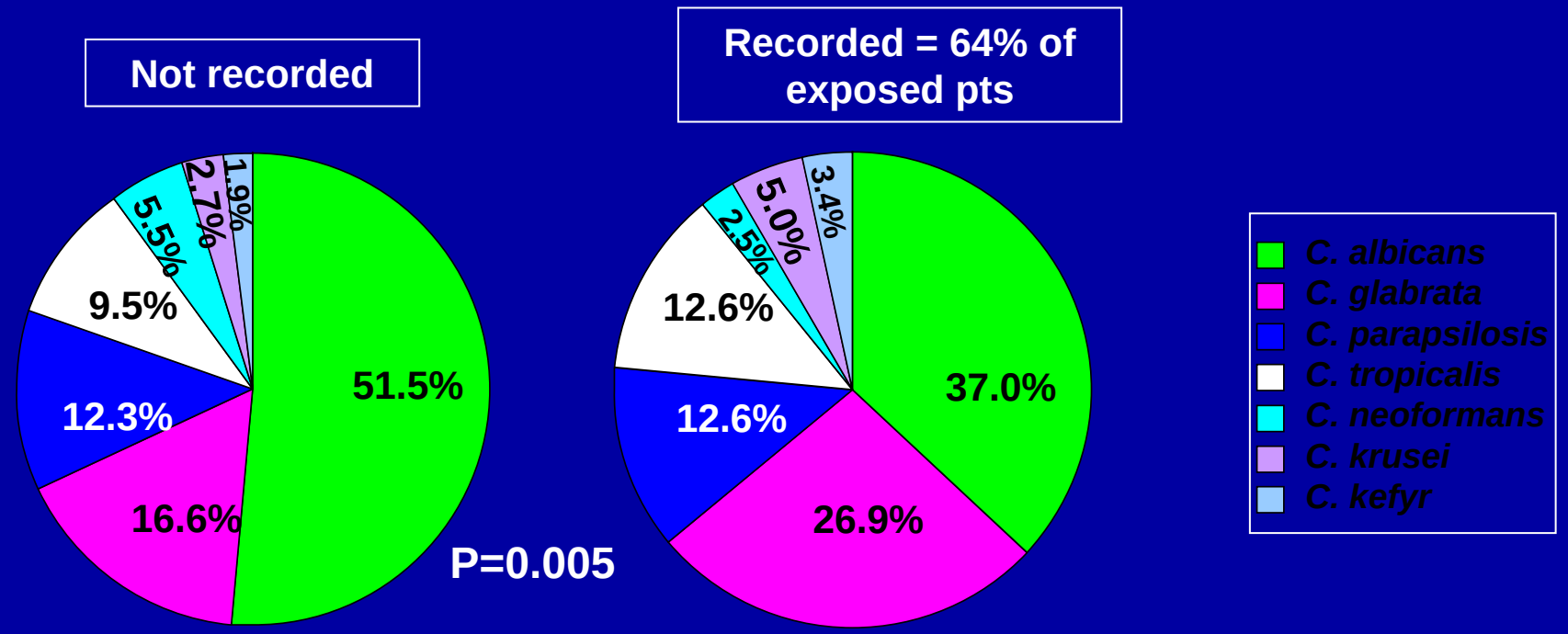
# Cross-"resistance" to azoles in *C. glabrata* blood isolates (n=149)

| FCZ (µg/ml) \ VRZ (µg/ml) | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | ≥ 8 |
|---|---|---|---|---|---|---|---|---|---|
| ≤0.12 | 1 | | | | | | | | |
| 1 | 1 | 1 | | | | | | | |
| 4 | | 1 | 4 | 6 | 1 | | | | |
| 8 | | 2 | 15 | 21 | 16 | 2 | | | |
| 16 | | 1 | 1 | 8 | 20 | 2 | | | |
| 32 | | | 1 | 1 | 8 | 2 | | | 1 |
| ≥64 | | | | **1** | **3** | **2** | **3** | **14** | **10** |

Lortholary et al. AAC 2007

# Influence of recent (±30 days) exposure to fluconazole on the distribution of species responsible for BSI

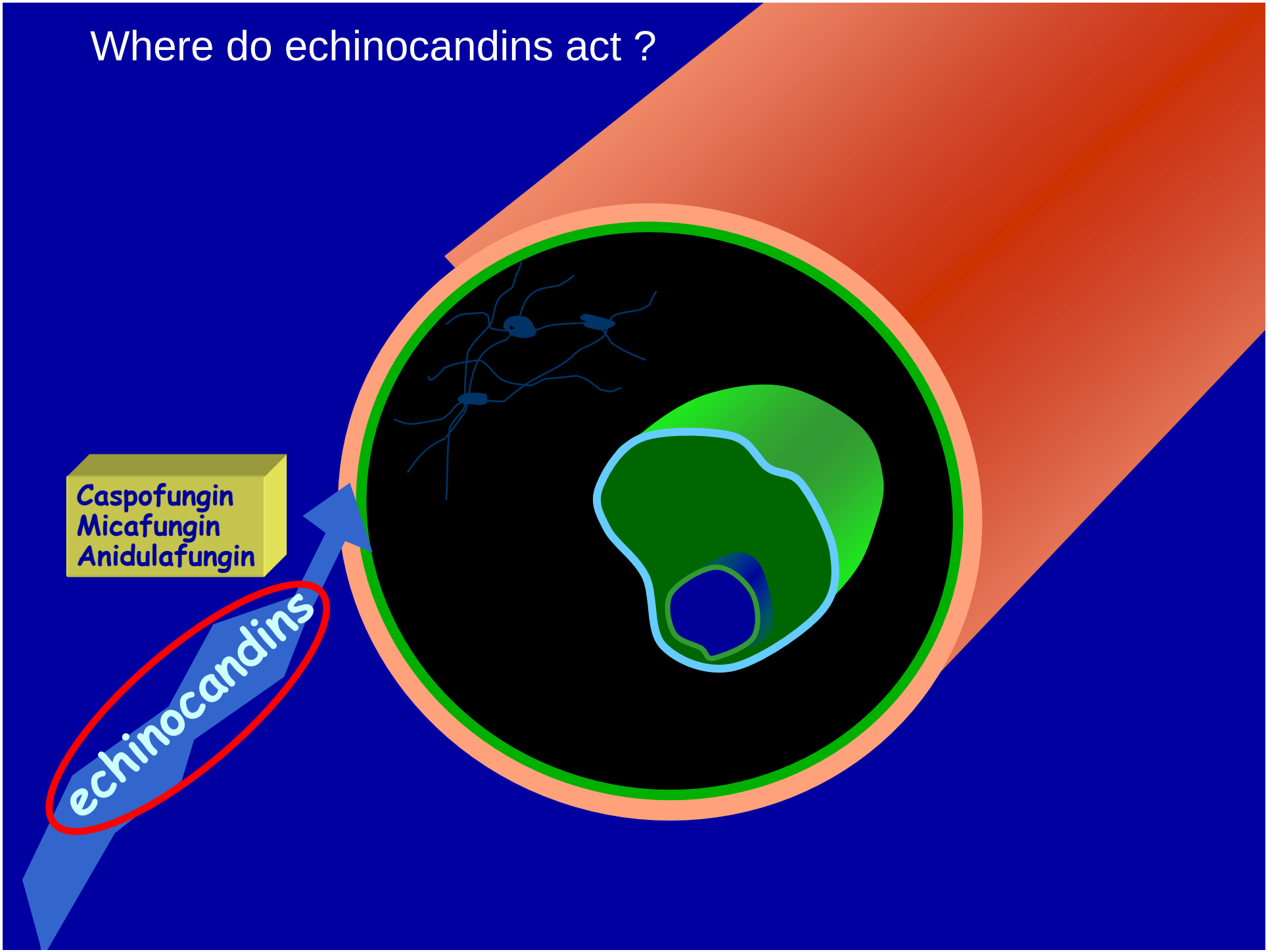
**(French YEASTS group, n = 1685)**




**Risk of Fluco-resistant isolate causing BSI significantly associated with prior exposure to Fluco (OR =1.95** [1.25-3.06], P=0.003**)**

Lortholary et al. Submitted for publication

# Where do echinocandins act ?



# Echinocandins have excellent *in vitro* activity vs. *Candida* spp., including fluconazole-resistant isolates

## Caspofungin *in vitro* Activity

| Organism | All isolates (EUCAST method)[1] | | | Resistant isolates (CLSI method)[2] | | |
|---|---|---|---|---|---|---|
| | No. of isolates | $MIC_{50}$ (µg/ml) | $MIC_{90}$ (µg/ml) | No. of isolates | $MIC_{50}$ (µg/ml) | $MIC_{90}$ (µg/ml) |
| *C. albicans* | 404 | 0.5 | 0.5 | 41 | 0.03 | 0.06 |
| *C. glabrata* | 157 | 0.5 | 1 | 110 | 0.03 | 0.06 |
| *C. tropicalis* | 62 | 0.5 | 1 | – | – | – |
| *C. parapsilosis* | 109 | 2 | 2 | – | – | – |
| *C. krusei* | 21 | 1 | 2 | 146 | 0.12 | 0.25 |


1. Dannaoui E, *et al*. *Antimicrob Agents Chemother* 2008; **52:**778–81;
2. Messer SA, *et al*. *J Clin Microbiol* 2006; **44:**324–6

# Caspofungin in candidemia

Randomized, multicentre, double-blind trial
Non-neutropenic and neutropenic patients

## Global response at end of intravenous therapy

| Analysis | Caspofungin 70/50 mg n/m (%) | Amphotericin B 0,6-1.0 mg/kg n/m (%) | Estimated difference % (95.6% CI) |
|---|---|---|---|
| MITT (n=224) | 80/109 (73.4) | 71/115 (61.7) | 12.7% * (–0,7, 26,0) |
| Evaluable patients (n=185) | 71/88 (80.7) | 63/97 (64.9) | 15.4% ** (1.1, 29.7) |

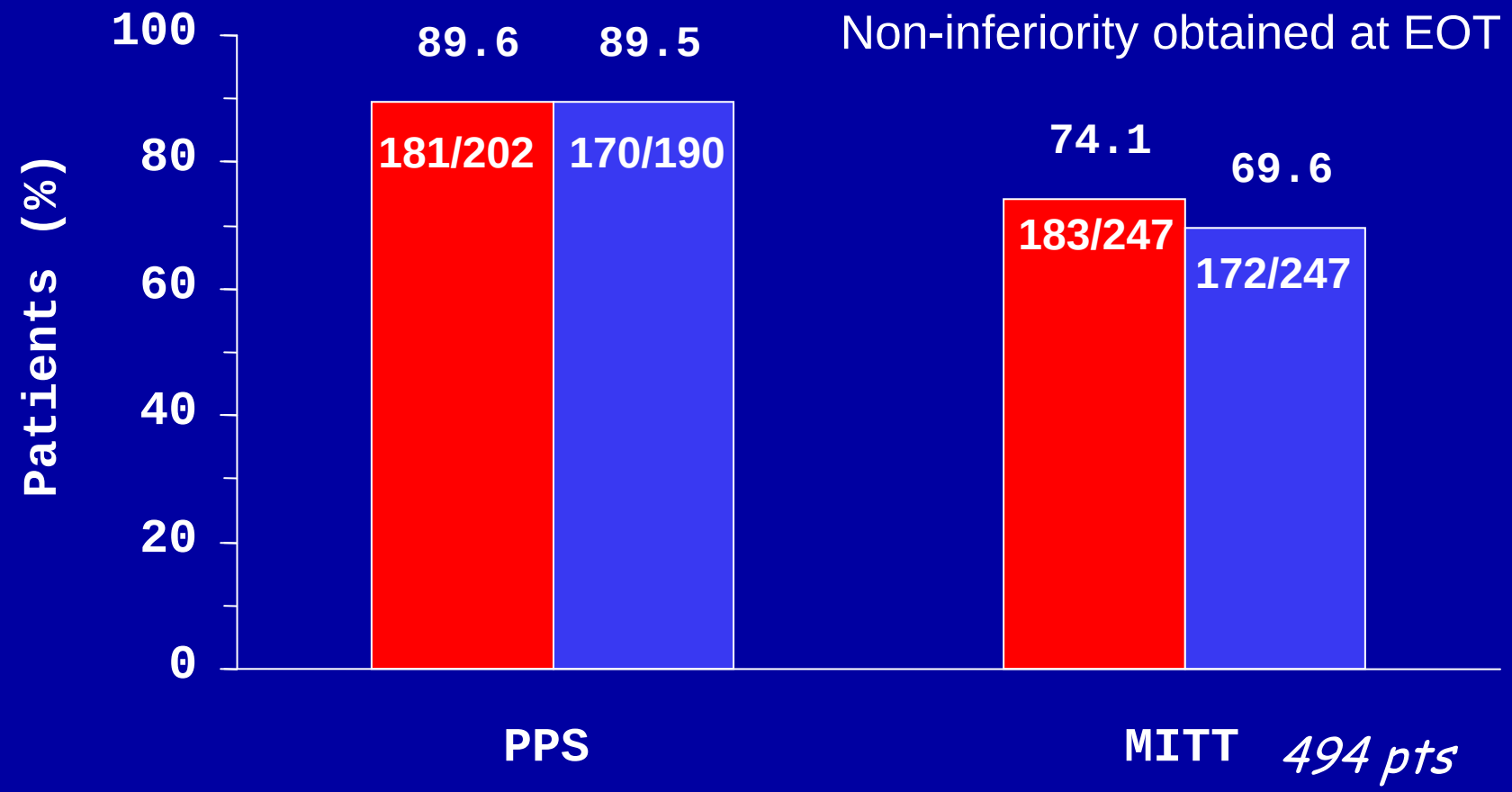
No difference according to species

* P = 0.09
** P = 0.03

Mora-Duarte et al. *NEJM* 2002.

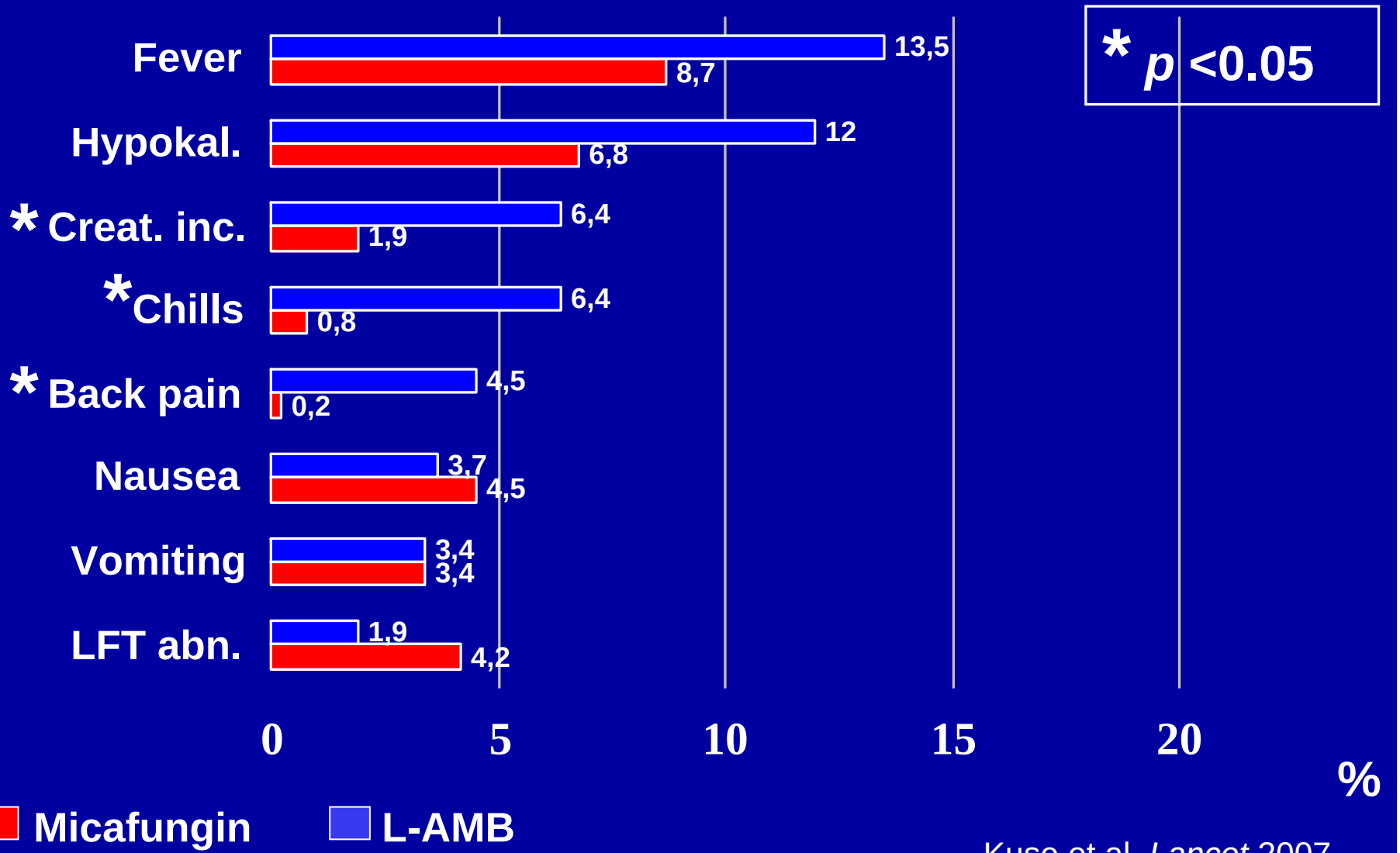
# Micafungin and candidemia / IC

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




Kuse et al. *Lancet* 2007.

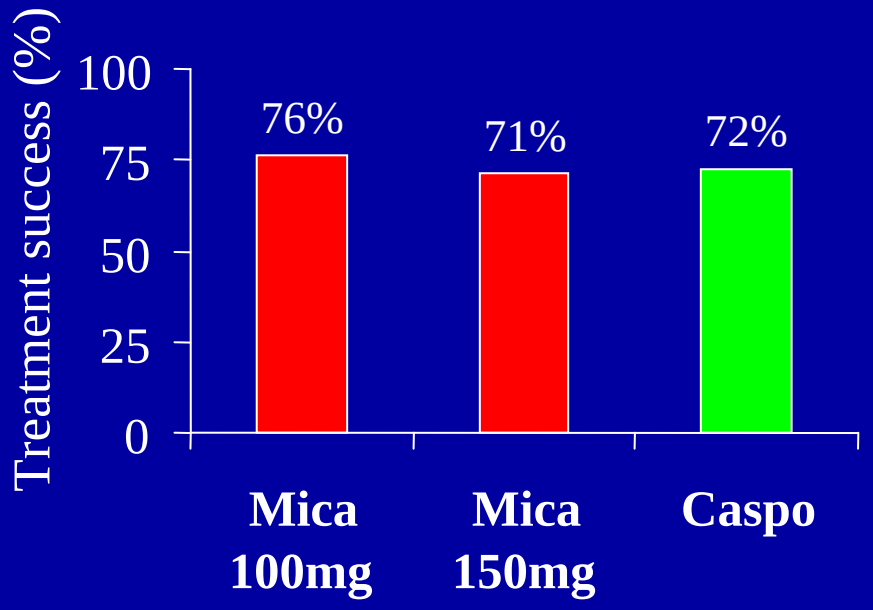
# Adverse events




Kuse et al. *Lancet* 2007.

# Micafungin vs caspofungin in candidemia/IC

- 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.

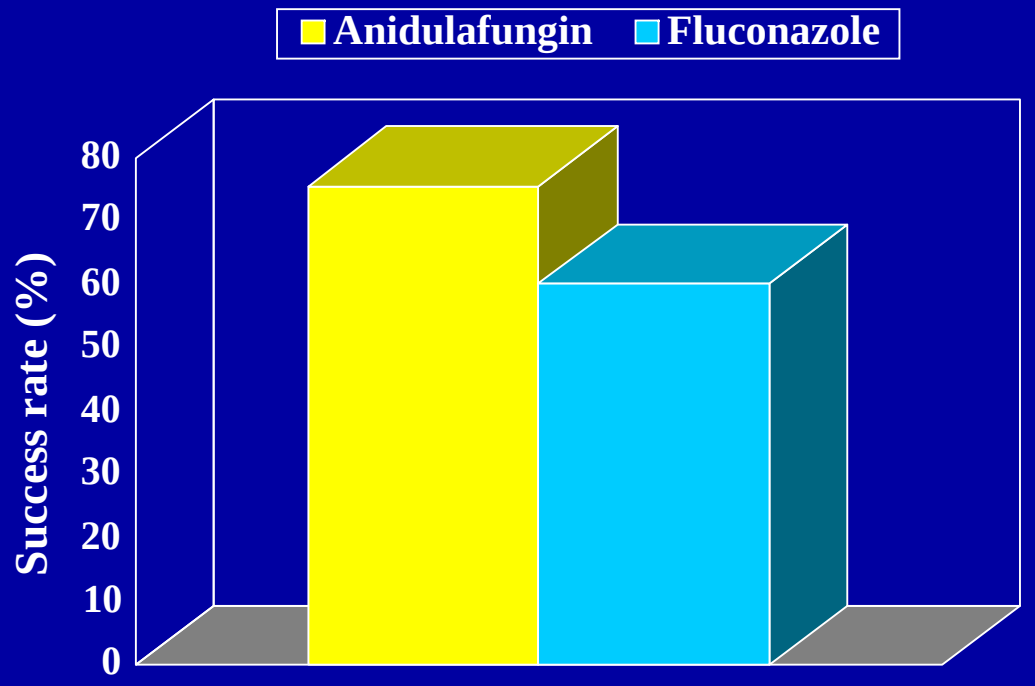



**Micafungin 100mg/d and 150mg/d equivalent to standard dose caspofungin for candidemia/IC.**

Pappas et al. *CID* 2007.

# Anidulafungin in candidemia / IC

- Randomized, double-blind, multicenter, 2-step non-inferiority/superiority, phase III trial
- anidulafungin IV 200 mg load; 100 mg /d
- fluconazole IV 800 mg load; 400 mg /d




**<u>Primary endpoint</u> (global response at end of IV therapy):**

| Response (MITT) | Treatment Group | | Treatment Difference (%) | 95% CI |
|---|---|---|---|---|
| | Anid N =127 | Flu N =118 | | |
| Success, n (%) | 96 (75.6) | 71 (60.2) | 15.42 | 3.85, 26.99 |
| Failure, n (%) | 31 (24.4) | 47 (39.8) | | |

Reboli et al. *NEJM* 2007.

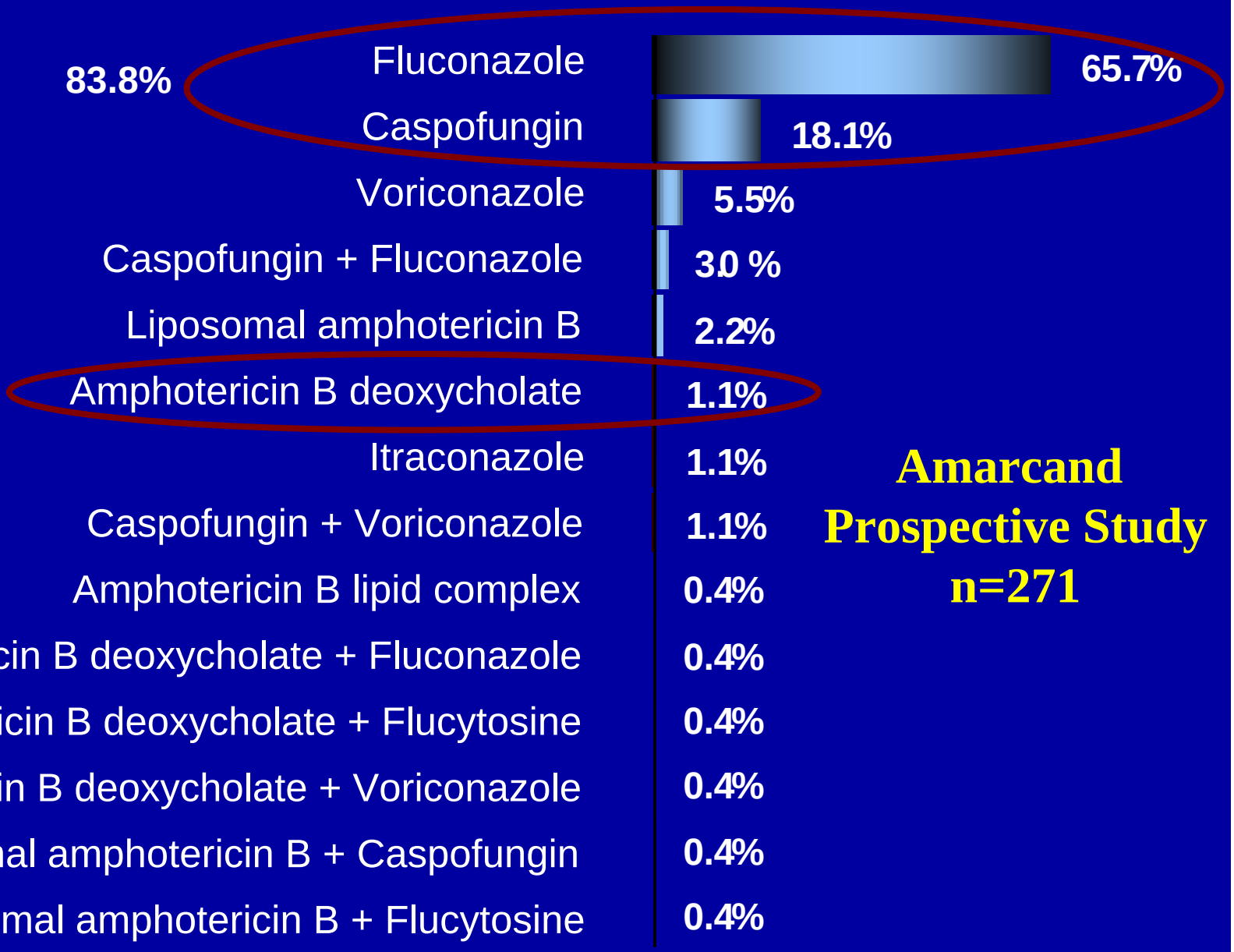
# IDSA 2009 guidelines for invasive candidiasis

| Condition or treatment group | Therapy | | | |
|---|---|---|---|---|
| | Primary | | Alternative | |
| | Recommendation | Rank | Recommendation | Rank |
| Non-neutropenic patients | | | | |
| **Candidaemia (targeted therapy)** | **Fluconazole or an echinocandin** | **A-I** | **Lipid formulation of AmB (LFAmB) or amphotericin B deoxycholate (AmB-d) or voriconazole** | **A-I** |
| **Suspected candidiasis (empirical therapy)** | **As for candidaemia; echinocandin or fluconazole preferred** | **B-III** | **LFAmB or AmB-d** | **B-III** |
| Neutropenic patients | | | | |
| **Candidaemia (targeted therapy)** | **Echinocandin or LFAmB** | **A-II** | **Fluconazole or voriconazole** | **B-III** |
| **Suspected candidiasis (empirical therapy)** | **LFAmB or caspofungin or voriconazole** | **A-I (B-I for VRCZ)** | **Fluconazole or itraconazole** | **B-I** |

- Echinocandins favoured for moderately severe to severe illness and in patients with recent azole exposure, and as initial therapy in patients with or suspected to have *C. glabrata* infection

Pappas et al. CID 2009

# Initial empiric anti-Candida treatment in ICU




**Amarcand Prospective Study n=271**

**Leroy et al. Crit Care Med 2009**

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ONTOGENESE ET ONCOGENESE MOLECULAIRES

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# Fongiday®

7.5 % des patients reçoivent un ttt antifongique en réanimation un jour donné en France

67.9% fluconazole
22.6% caspofungine