# Candidoses invasives en réanimation. Nouvelles stratégies diagnostiques et thérapeutiques. Place des échinocandines

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**samedi 21 novembre 2015 à 11 heures - Le Royal Hôtel Hammamet**

# Introduction

- Dans le passé : mycoses opportunistes (candidoses, aspergilloses) = immunodéprimé.
  Actuellement : incidence de + en + élevée chez les non neutropéniques surtout en chirurgie et en réanimation.

- Lourde motalité et morbidité surtout si un ttt AF adéquat et rapide n'est pas instauré.

- Simple atteinte cutanée → C.I et C.Disséminée

- Défis multiples : surtout détection des malades à traiter

# Cas Clinique HDM

- Femme de 69 ans, admitse au Sce de réa pour état de choc fébrile
- ATCD : Obésité (BMI 35), Db (metformine), P.R (methotrexate), lithiase urinaire (plusieurs épisodes d'infection urinaire), IRC depuis une année.

- HDM : 10 j : admise au Sce de néphrologie pour aggravation de l'IR et poussée de sa PR, un KT S/Clav est mis en place → séances d'hémodialyse sont débutées.

- Admission : Etat général moyen, mais consciente et lucide

  TA: 75/40 mmHg, T: 38.5°C, P: 125/min, RR: 30/min

  Hb: 8.0 g/dL, GB: 22.600/mm$^3$, créatinine 30 mg/l, CRP 200mg/l, lactate 4 mmol/l

  Rx thorax : Normale, Echo : lithiase non obstructive calicielle inf. du rein dt

**Diagnostic retenu à l'admission** :

choc septique /pyélonéphrite aigue

**Traitement:** expansion volémique + NAD

+ ATB : Ctx + Amk (doses adaptées)

**Evolution:**

H 48: ECBU –, légère amélioration clinique (sevrage NAD)

H 72: ECBU –, **HC +** Staph MS ➔ arrêt Ctx Amk remplacés par Oxa + Genta

J4 (H 96): agitation, état de choc, T°40 ➔ série d'HC (périphérie et cathéter)

**Quelle aurait été votre conduite ?**

A. **Elargir ATB → IMP +/- ?**

B. **Ajouter un antifongique**

C. **A + B**

D. **C + remove CVC**

E. **Autres options**

**Pourquoi un AF ?**

A. **Grande incidence et mauvais pronostic des IF en réa**

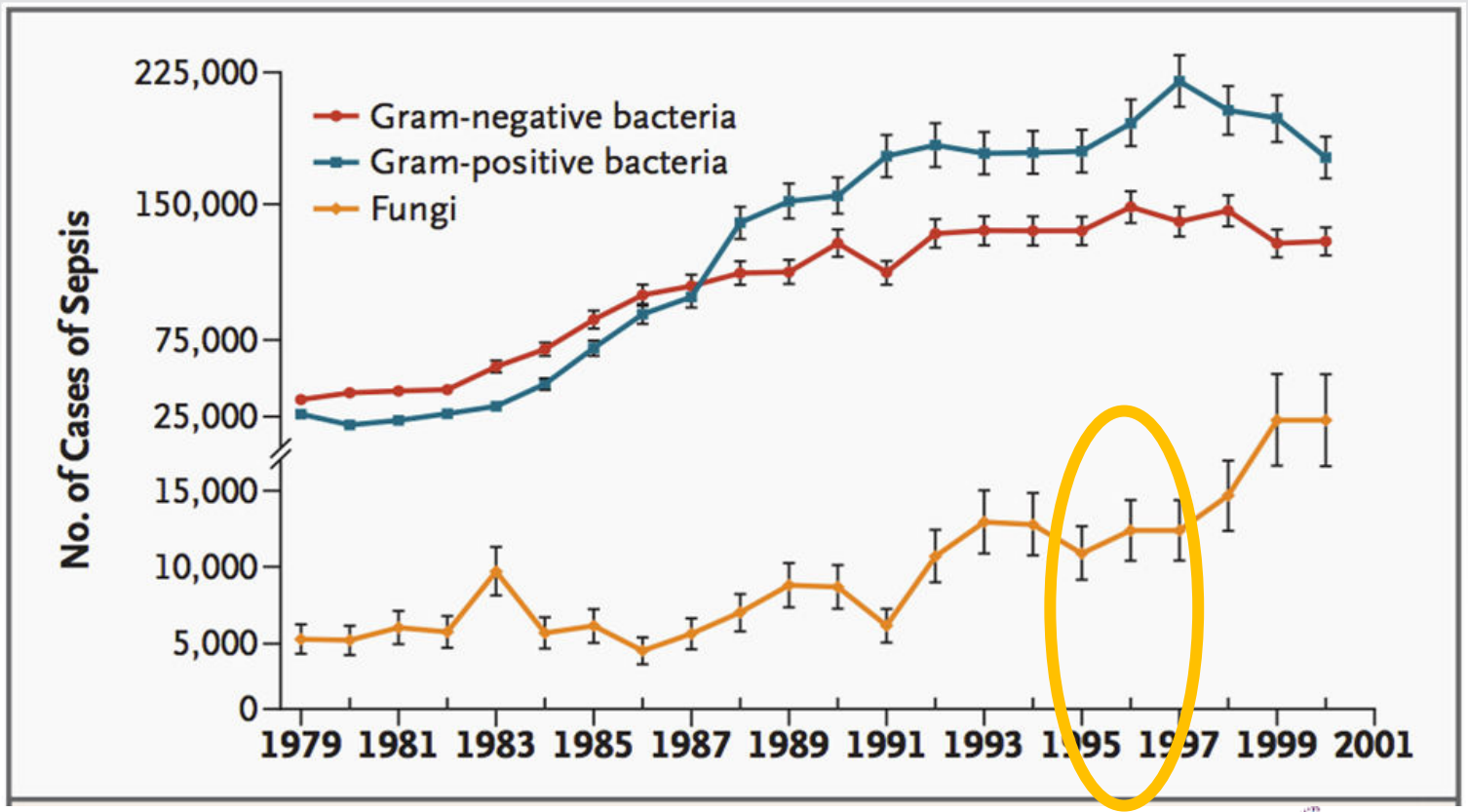
B. **Facteurs de risque de CI**

C. **L'état de choc**

D. **A + B**

E. **A + B + C**

# Increasing Rate of Candidiasis in the US




Pfizer Anti-Infectives

Martin GS, et al,. NEJM 2003;348:1546-54.

## Epidemiology

- IC related infections
- The incidence is increasing
  - Third etiology in septic shock: among 10,941 patients, 1495 had septic shock (GNB 48.7%, GPC 35.9%, fungus 3.2%) [EPISS Study 2013[1]]
- Incidence:
  - 7/1000p [EPIC II Study 2009[2-4]]
  - 16.5/1000p [AURORA Study 2013[5]]
- Higher mortality (+14.5%)[2-4]
- Longer LOS (+10 days)[2-4]


1. Quenot JP, et al. Crit Care 2013;17:R65.
2. Kett DH, et al. Crit Care Med. 2011;4:665-70.
3. Bougnoux ME, et al. Intensive Care Med. 2008;2:292-9.
4. Zaoutis TE, et al. Clin Infect Dis. 2005;9:1232-9.
5. Montagna MT, et al. Infection. 2013;3:645-53.

## Sce réa méd «La Rabta»

- Etude rétrospective
- 2001–2010
- Candidémies
- **26.5 pour 10.000 jp (densité d'incidence )**
  - Kett DH, et al. Crit Care Med 2011[1]: **20 to 69 per 10,000 d**

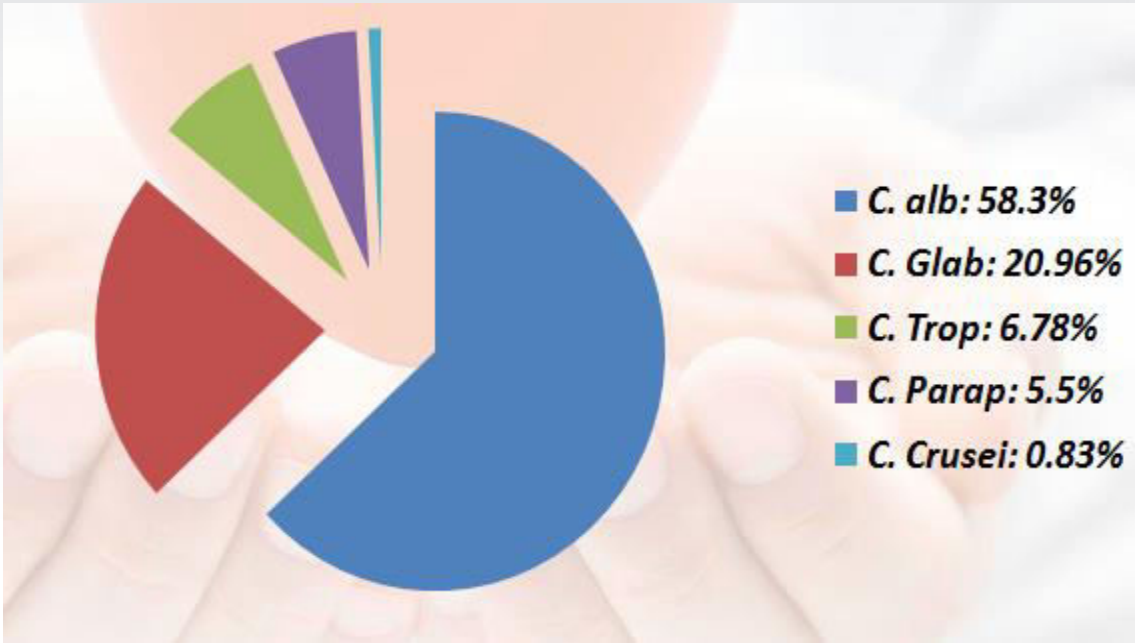
- Souches isolées:
  - *C. albicans*: 53.3%
  - *C. parapsilosis*: 23.3%
  - *C. glabrata*: 13.3%
- *A. baumannii, P. aeruginosa, S. aureus*, Candidas (4ème place)

Pfizer Anti-Infectives

1. Kett DH, et al. Crit Care Med. 2011;39:665-70.

## Etude Multicentrique Tunisienne

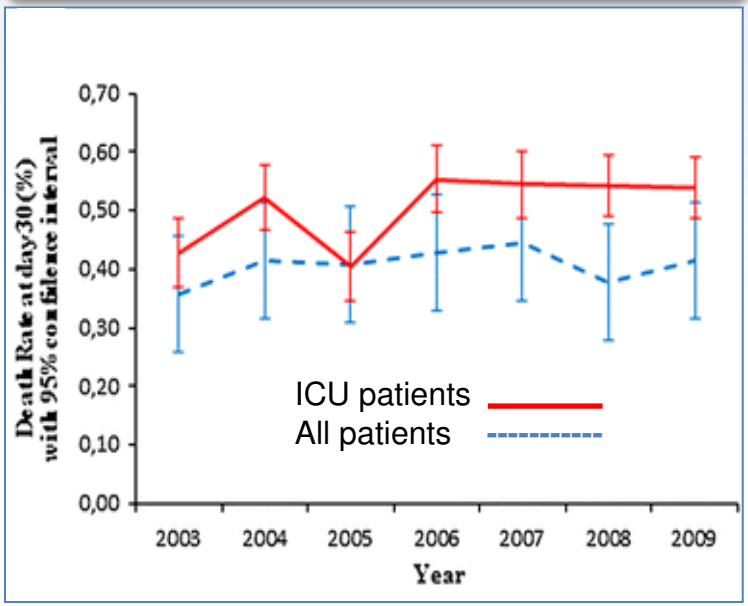
- 2014
- 11 réa M+Ch (142 lits)
- Candidémies
- 38.4 pour 10.000 jp



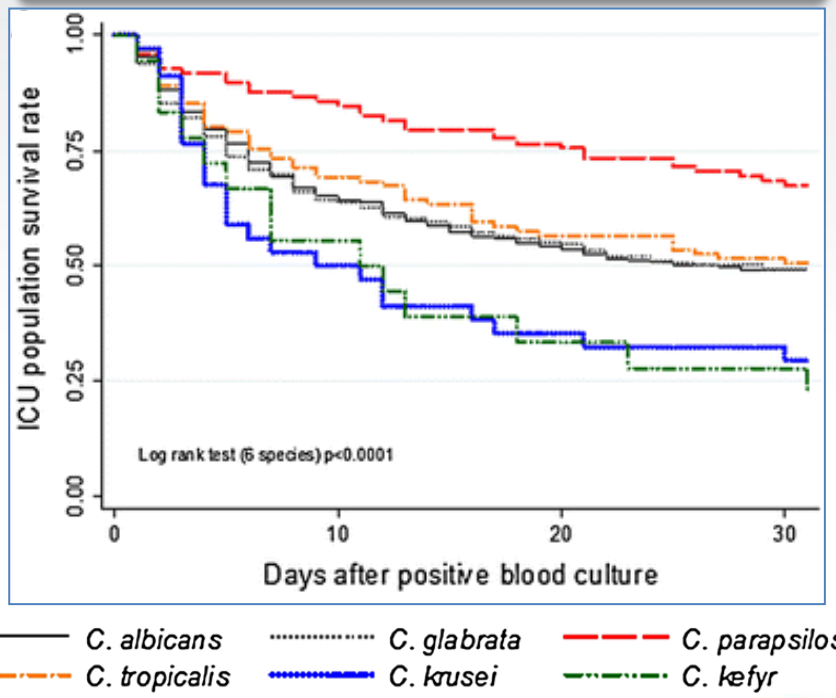
# Prognosis of Candidemia: The French Mycosis Study Group[1]

- 24 tertiary hospitals, 2507 patients, 2571 *Candida* isolates
- Crude mortality, 30-60%

**2507 candidemia in Paris area (2002-2010)**




**1206 candidemia cases in ICU patients (2002-2010)**

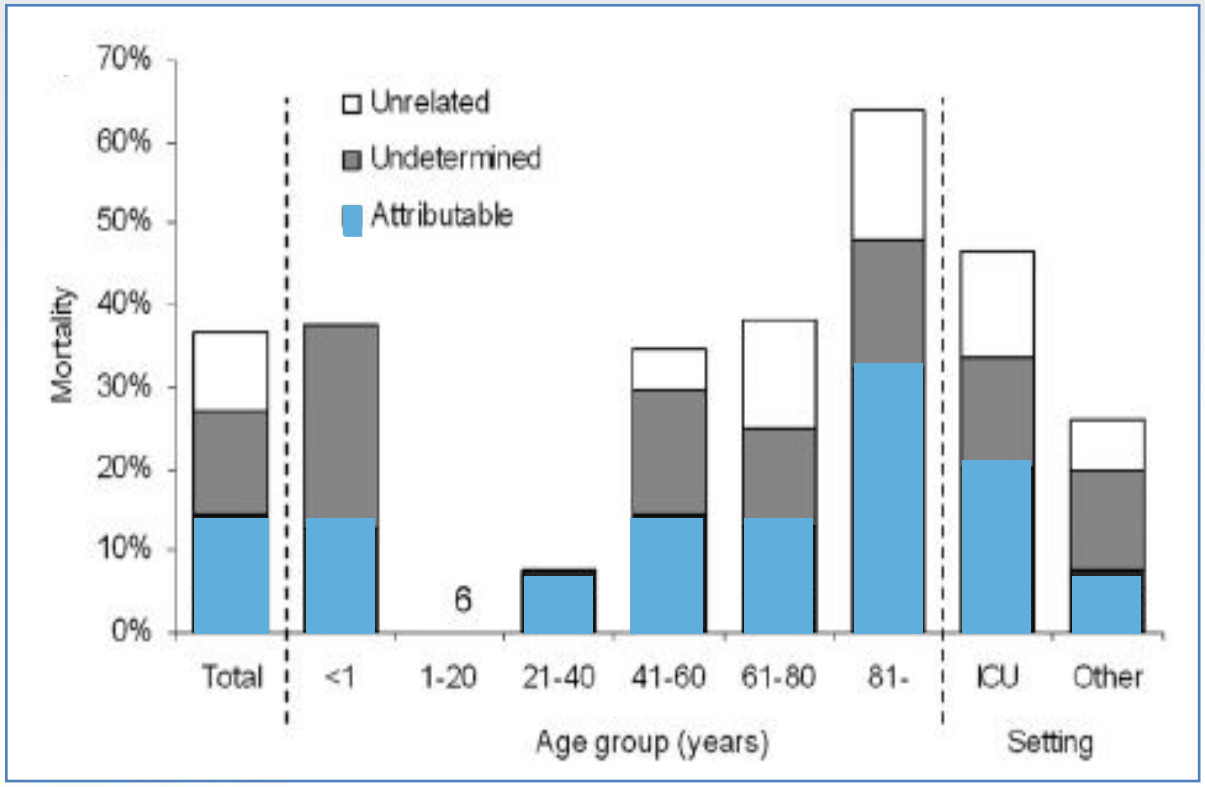



Lortholary O, et al. Intensive Care Med. 2014;40:1303-12.

# Pronostic des Candidémies

***Mortalité Attribuable***

**25% to 40%**




- **Increased of length of stay: 8 to 25 days**
- **Increased costs: 5.000 to 40.000 $**

Pfizer Anti-Infectives

Wey SB, et al. Arch Intern Med. 1988;148:2462-5; Voss A, et al. Infection. 1997;25:8-11; Blot et al. Am J Med. 2002;113:480-5; Wisplinghoff H, et al. Clin Infect Dis. 2004; 39:309-17; Guldlaugsson O, et al. Clin Infect Dis. 2003; 37:1172-7; Zaoutis TE, et al. Clin Infect Dis. 2005; 41:1232-9; Arendrup MC et al, J Clin Microbiol. 2011;49:3300-8

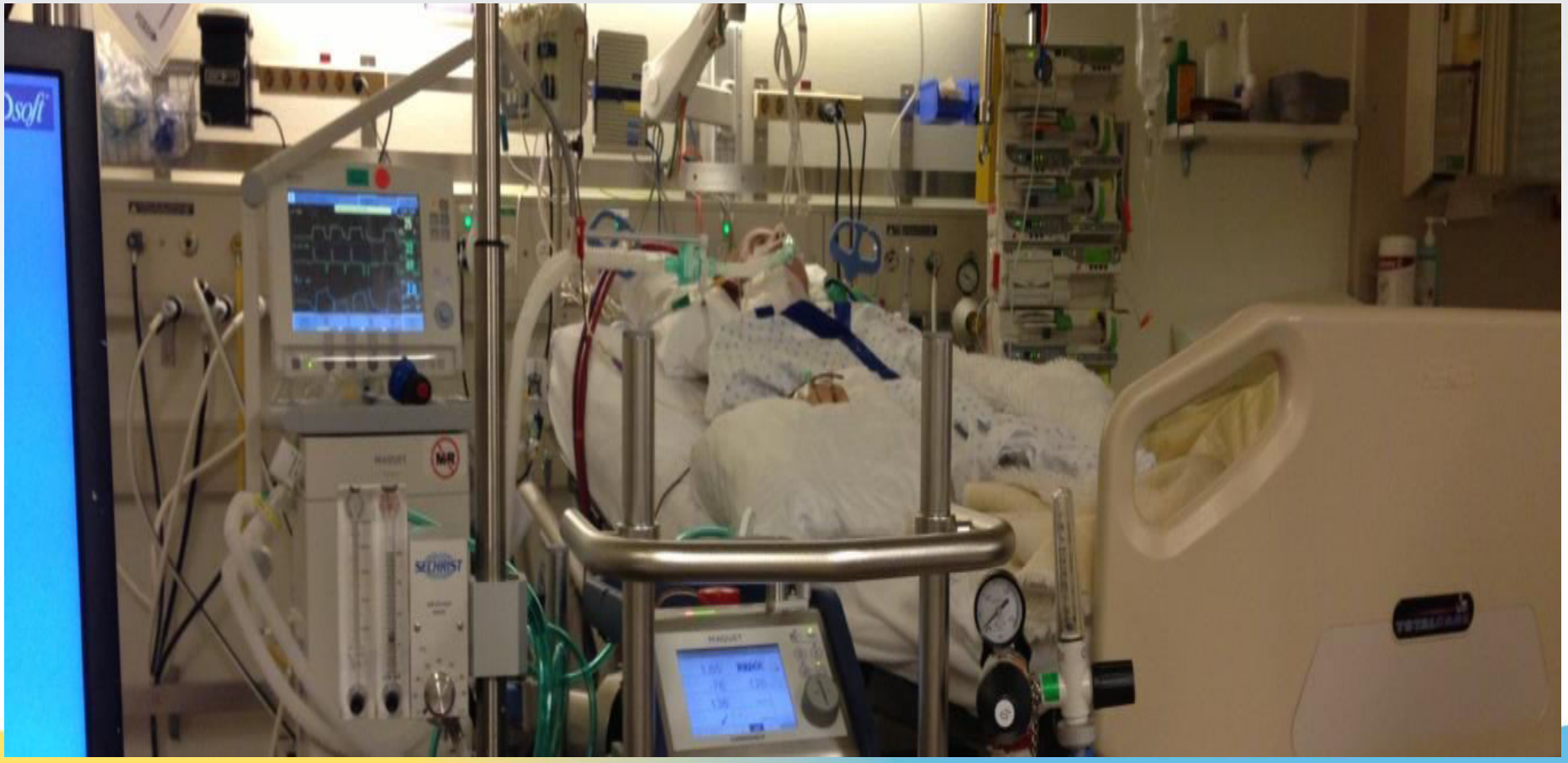
# Risk Factors for Invasive Candidiasis

- Malignant tumors (hematol. or solid)
- Neutropenia
- Prolonged corticosteroid therapy
- Chemotherapy
- Acute renal failure
- Severe acute pancreatitis
- Organ transplantation
- Prolonged stay in ICU
- APACHE II > 20

- Hemodialysis
- Antifungal use
- Large-spectrum ATB
- Central venous access
- Mechanical Ventilation
- TPN
- Immunosuppressive therapy
- *Candida* spp. colonization
- Recent abdominal surgery
- Extensive burns (>50%)

Length of stay in ICU

# Facteurs de risque = durée de séjour en réa → F.R



## Comment qualifieriez-vous notre stratégie adoptée?

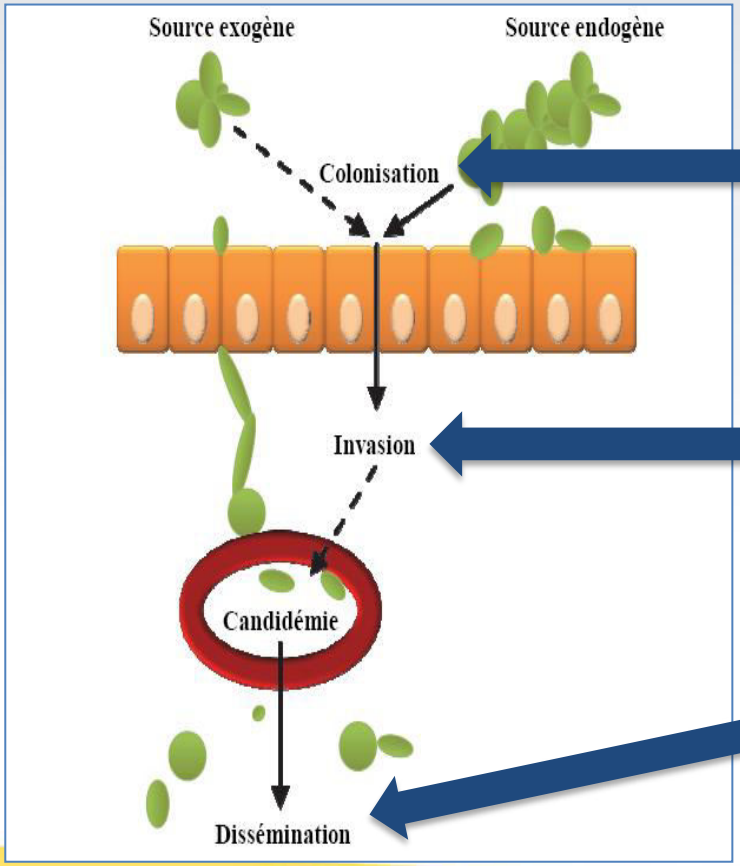
A. Prophylactique

B. Preemptive

C. Empirique

D. Ciblée

# Pathophysiology of Invasive Candidiasis




**Colonization:** presence of *Candida* spp. in at least 2 sites (concomitantly), without clinical impact

**Invasive candidiasis:** presence of *Candida* spp. in a normally sterile site. Candidemia (at least 1, BS culture), visceral candidiasis in which the first point is usually an haematogenous diffusion

**Disseminated candidiasis:** is the presence of *Candida* in at least two non-adjacent organs or sites

Eggimann P, et al. Lancet Infect Dis. 2003;11:685-702.

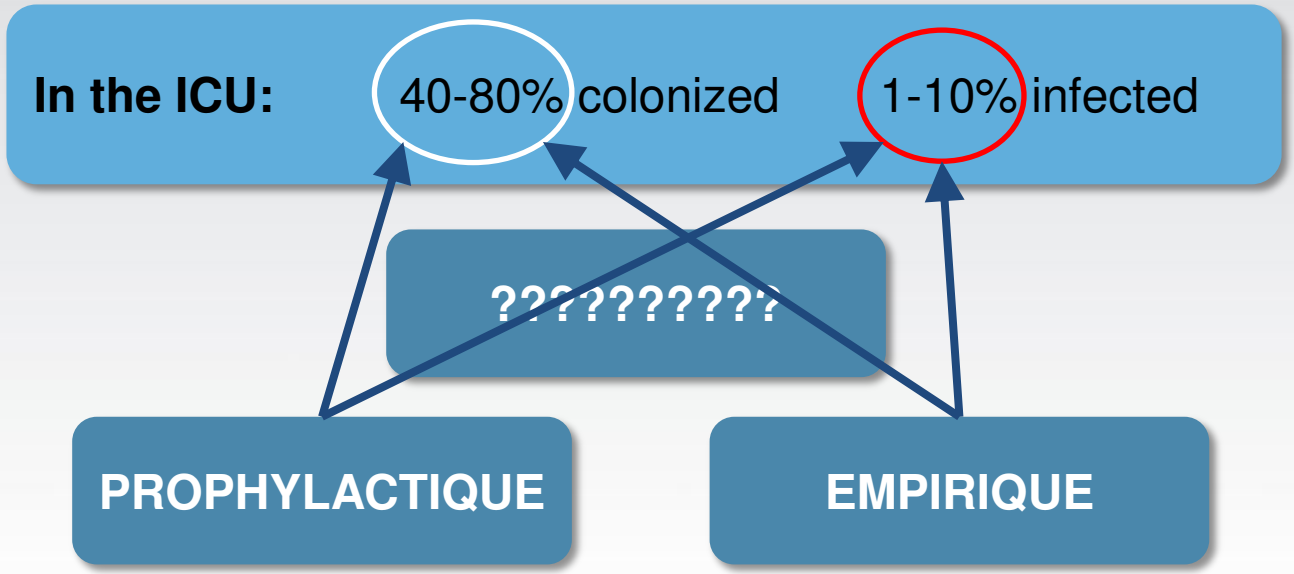
## Physiopathology

- **The colonizing strain is the infecting strain[1]**
- **Characteristics involved in virulence:**
  - **morphological variability,**
  - **adhesion capacity (parietal adhesins),**
  - **production of hydrolytic enzymes**
- ***Candida* spp. form a biofilm → easier colonization and more resistance to antifungals[2,3]**

Pfizer Anti-Infectives

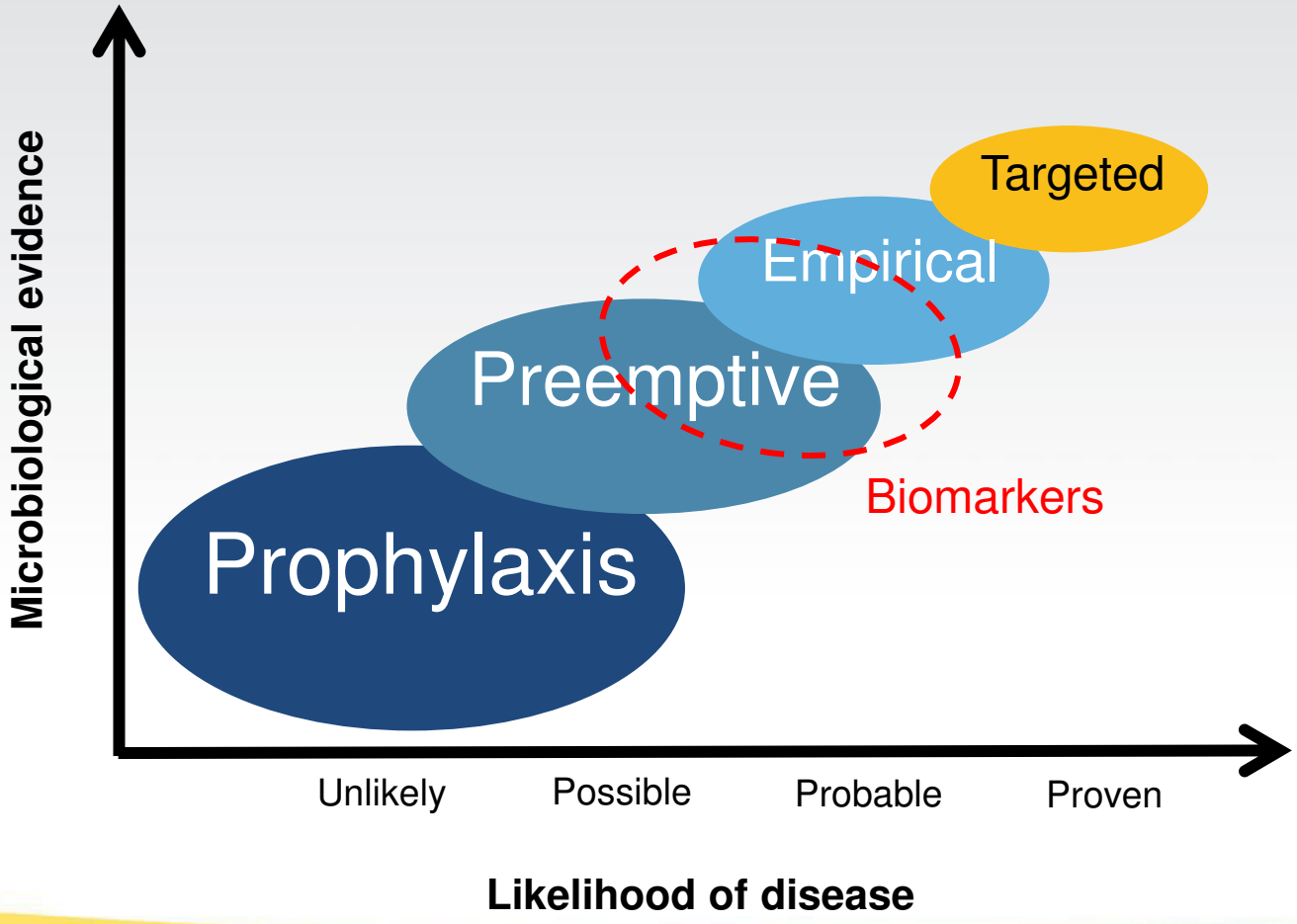
1. Stephan F, et al. Clin Infect Dis. 2002;12:1477-83.
2. Douglas LJ, et al. Trends Microbiol 2003;1:30-6.
3. Ramage G, et al. Eukariot Cell. 2005;4:633-8.

# Traitement Prophylactique vs. Empirique




- F. risque, scores, biomarqueurs…
- Le défi est:
  - Quand SE ↑↑➔ grand % patients traités avec AF abusivement
    VPN >> VPP
  - Quand SP↑↑ ➔ grand % patients “loupés” (grande VPP)

# Biomarkers of Candidiasis in Critically Ill Patients




Eggimann P, et al. Ann Intensive Care. 2011;1:37.

# Apport du Laboratoire

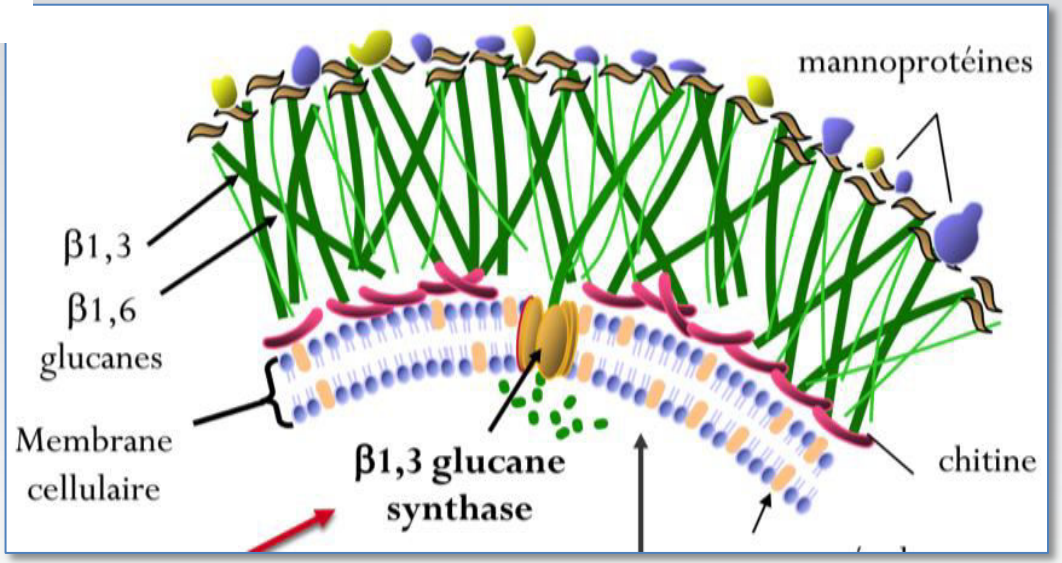
- **Diagnostic Indirect :**
  - **Antigène Mannane**
    - **Sp=98% mais Se=47%[1]**
  - **Association Mannane/Antimannane**
    - **Sp=86% et Se=83%[2] (European Conference recommandation 2010)**
- **Dans les C.I çà *C. albicans:***
  - **Sp 86%, Se 83% quand Ag Mannane >0.25 à 0.5 ng/ml et Ac Anti-mannane >5-10 AU/ml**
- **Cependant, c'est different pour *C. parapsilosis, C. krusei* and *C. kefyr* qui secrètent moins de mannane**

Pfizer Anti-Infectives

1. Yeo SF, et al. Clin Microbiol Rev. 2002;3:465-84.
2. *Mikulska M, et al. Crit Care 2010;6:222.

# (1,3)-β-D-glucane

- **Dosage du (1,3)-β-D-glucane: polysaccharide de la paroi**




  - **Quand >80pg/ml, Se=77%, Sp=85%**
  - **VPN +++ (ESCMID guidelines 2012)**
  - **Bcp de faux positifs**
    - **Infection: autre infection fongique, infection à GNB et à *Streptococcus***
    - **Traitement: Alb, β-lactamines, Immunoglob, hémodialyse**

Pfizer Anti-Infectives

Cuenca-Estrella M, et al. Cin Microbiol Infect. 2012;7:9-18; Ostrosky-Zeichner L, et al. Clin Infect Dis. 2005;41:654-9; Segal BH, et al. Clin Infect Dis. 2008;47: 674-83; Yoshida M, et al. 2010; Marchetti O, et al. Bone Marrow Transplant. 2012;47:846-54.

# β-Glucan Antigenemia Anticipates Diagnosis of Blood Culture-Negative Intraabdominal Candidiasis

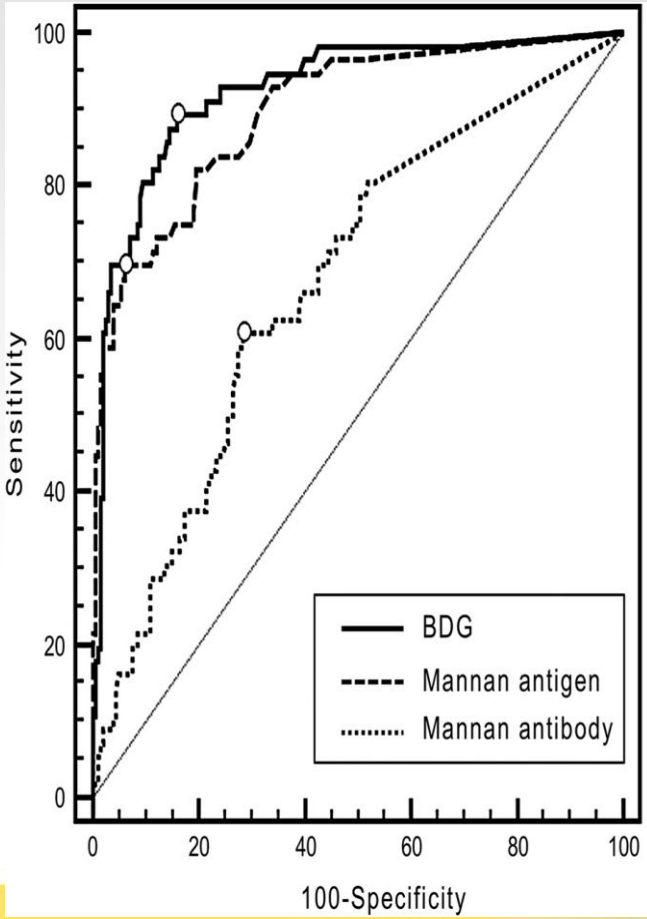
- 89 patients; 921 sera

TABLE 3. ACCURACY OF 1,3-β-D-GLUCAN, *Candida* SCORE, *Candida* COLONIZATION INDEX, AND CORRECTED *Candida* COLONIZATION INDEX FOR THE DIAGNOSIS OF INTRAABDOMINAL CANDIDIASIS (N = 29)

| | Sensitivity | Specificity | PPV | NPV | Efficiency, % |
|---|---|---|---|---|---|
| BG ⩾ 80 pg/ml 1× | | | | | |
| At inclusion | 0.76 (0.56–0.90) | 0.59 (0.43–0.74) | 0.56 (0.40–0.72) | 0.78 (0.60–0.90) | 66 |
| At infection* | 0.83 (0.64–0.94) | 0.40 (0.26–0.57) | 0.49 (0.34–0.64) | 0.77 (0.55–0.92) | 58 |
| BG ⩾ 80 pg/ml 2×† | | | | | |
| At inclusion | 0.66 (0.45–0.82) | 0.83 (0.69–0.93) | 0.73 (0.52–0.88) | 0.78 (0.63–0.89) | 76 |
| At infection* | 0.65 (0.46–0.82) | 0.78 (0.63–0.90) | 0.68 (0.48–0.84) | 0.77 (0.61–0.88) | 73 |
| CS ⩾ 3 | | | | | |
| At inclusion | 0.86 (0.68–0.96) | 0.50 (0.34–0.66) | 0.54 (0.39–0.69) | 0.84 (0.64–0.95) | 65 |
| At infection* | 0.86 (0.68–0.96) | 0.38 (0.23–0.54) | 0.49 (0.35–0.63) | 0.80 (0.56–0.94) | 58 |
| CI ⩾ 0.5 | | | | | |
| At inclusion | 0.26 (0.10–0.48) | 0.76 (0.61–0.87) | 0.35 (0.14–0.62) | 0.67 (0.53–0.80) | 59 |
| At infection* | 0.88 (0.69–0.97) | 0.34 (0.19–0.52) | 0.49 (0.34–0.64) | 0.80 (0.52–0.96) | 57 |
| CCI ⩾ 0.4 | | | | | |
| At inclusion | 0.14 (0.03–0.36) | 0.77 (0.61–0.88) | 0.23 (0.05–0.54) | 0.65 (0.50–0.77) | 56 |
| At infection* | 0.50 (0.29–0.71) | 0.43 (0.28–0.60) | 0.35 (0.20–0.53) | 0.59 (0.39–0.76) | 46 |

Tissot F, et al. Am J Respir Crit Care Med. 2013;188:1100-9.

# Comparison of (1➔3)-β-D-Glucan, Mannan/Anti-Mannan Antibodies, and Cand-Tec *Candida* Antigen as Serum Biomarkers for Candidemia




| | AUC (95%-CI) |
|---|---|
| BDG | 0.925 (0.885-0.954) |
| Mannan-Ag | 0.898 (0.854-0.932) |
| Mannan-Ab | 0.673 (0.612-0.730) |
| | Optimized cut-off |
| BDG | ≥ 70 pg/ml |
| Mannan-Ag | > 50 pg/ml |
| Mannan-Ab | ≥ 15 AU/ml |

| | AUC | Se (%) | Sp (%) |
|---|---|---|---|
| 1,3-β-D-G | 0.92 | **87.5** | 85.5 |
| Ag Mannane | 0.89 | 58.9 | 97.5 |
| Ag/Ac | | 89.3 | 63 |
| 1,3-β-D-G + AgMannan | | 89.3 | 85 |

Held J, et al. J Clin Microbiol. 2013;51:1158-64.

## PCR

- PCR c'est la référence avec:
  - Sensitbilité=95% et Spécificité=92%[1]
  - → Sensitbilité=91% and Spécificité=100%[2]
  - Résultat <2 heures
- Problème:
  - Accessibilité
  - Performance des kits rapides [3]

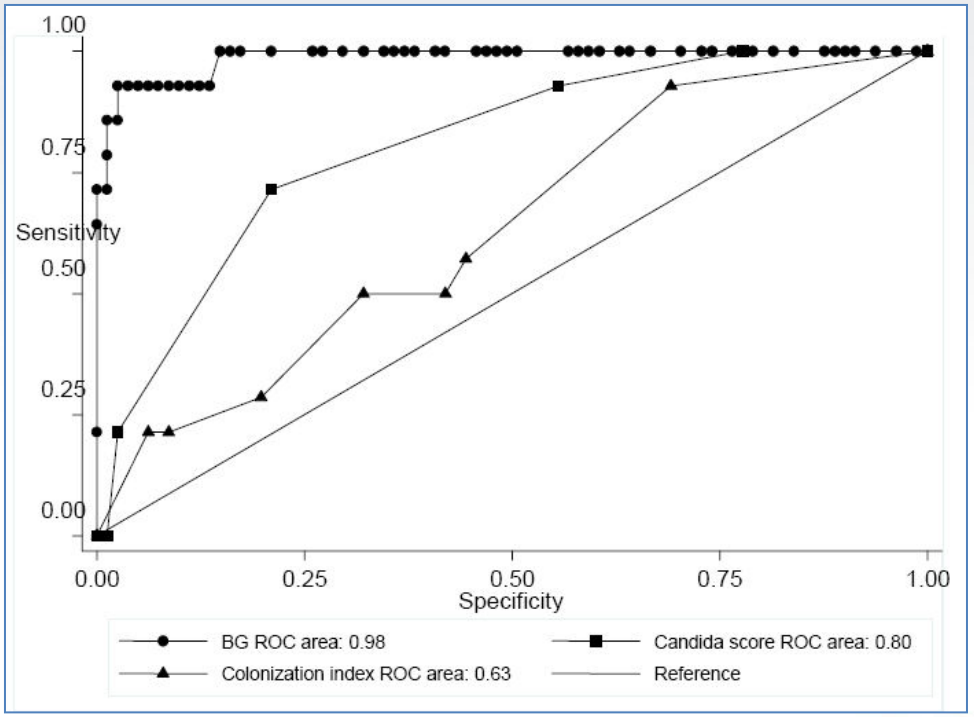


1. Avni T, et al. J Clin Microbiol. 2011;49:665-70.
2. McMullan R, et al. Clin Infect Dis. 2008;6:890-6.
3. Lucignano B, et al. J Clin Microbiol. 2011;6:2252-8.

# Early Diagnosis of Candidemia in Intensive Care Unit Patients with Sepsis: A Prospective Comparison of (1➔3)-β-D-Glucan Assay, *Candida* Score, and Colonization Index

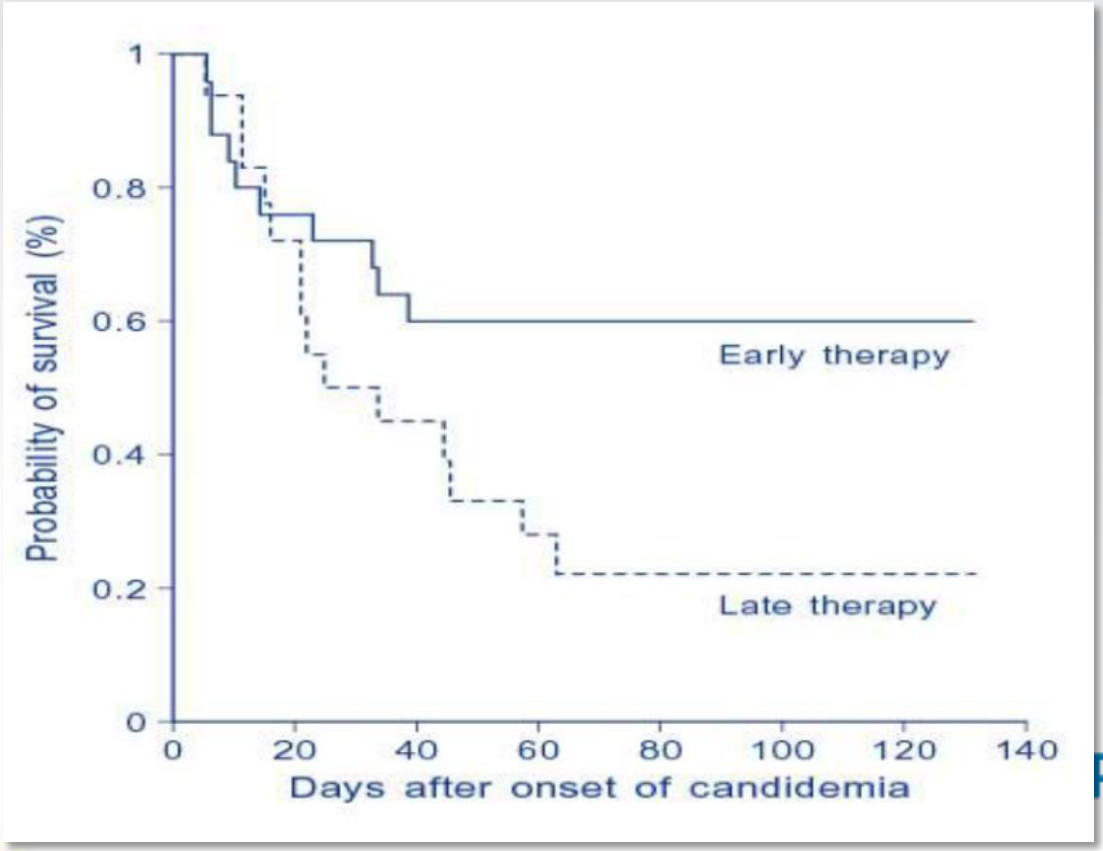
- 377 ICU patients with sepsis
  - 95 patients >5 days
  - 16 IC
- Measurement at onset of clinical sepsis

**ROC AUC curves of BG, CS and colonization index for proven IC Cases***




Posteraro B, et al. Crit Care. 2011;15:R249.

# Prospective Study: 28 ICU in Spain, 15 Months, 46 Candidemia




<48 hours

>48 hours

Pfizer Anti-Infectives

Nolla-Salas J, et al. Intensive Care Med. 1997;12:22-30

# Candidemia

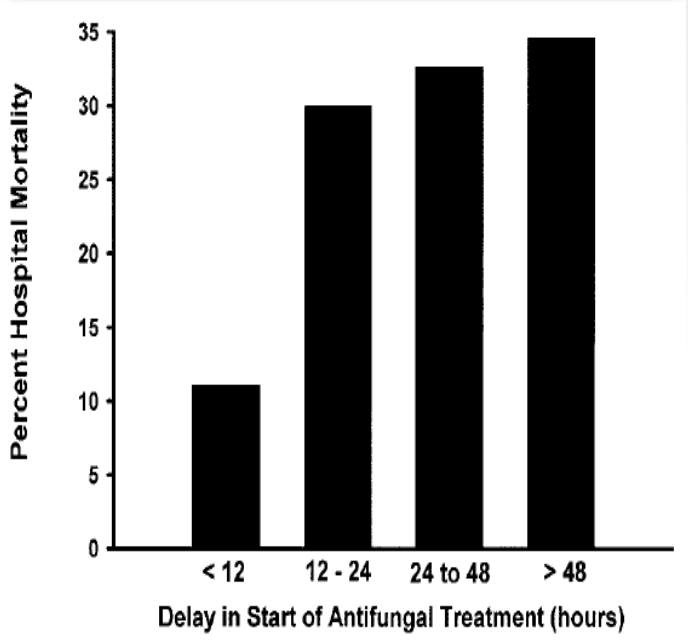
- Candidemia still raises numerous therapeutic issues for Intensive Care physicians
- **The relationship between prognosis and early initiation of adequate antifungal therapy is well established**
- Ideally, adequate therapy must be started some time before candidemia is ascertained, therefore some time before the causative *Candida* species is identified and its susceptibility to antifungals is known

Pfizer Anti-Infectives

Morrell M, et al. Antimicrob Agents Chemother. 2005;49:3640-5.
Parkins MD, et al. J Antimicrob Chemother. 2007;60:613-8.

# Delaying the Empiric Treatment of *Candida* Bloodstream Infection Until Positive Blood Culture Results are Obtained: A Potential Risk Factor for Hospital Mortality

**Relationship between hospital mortality and the timing of antifungal treatment***

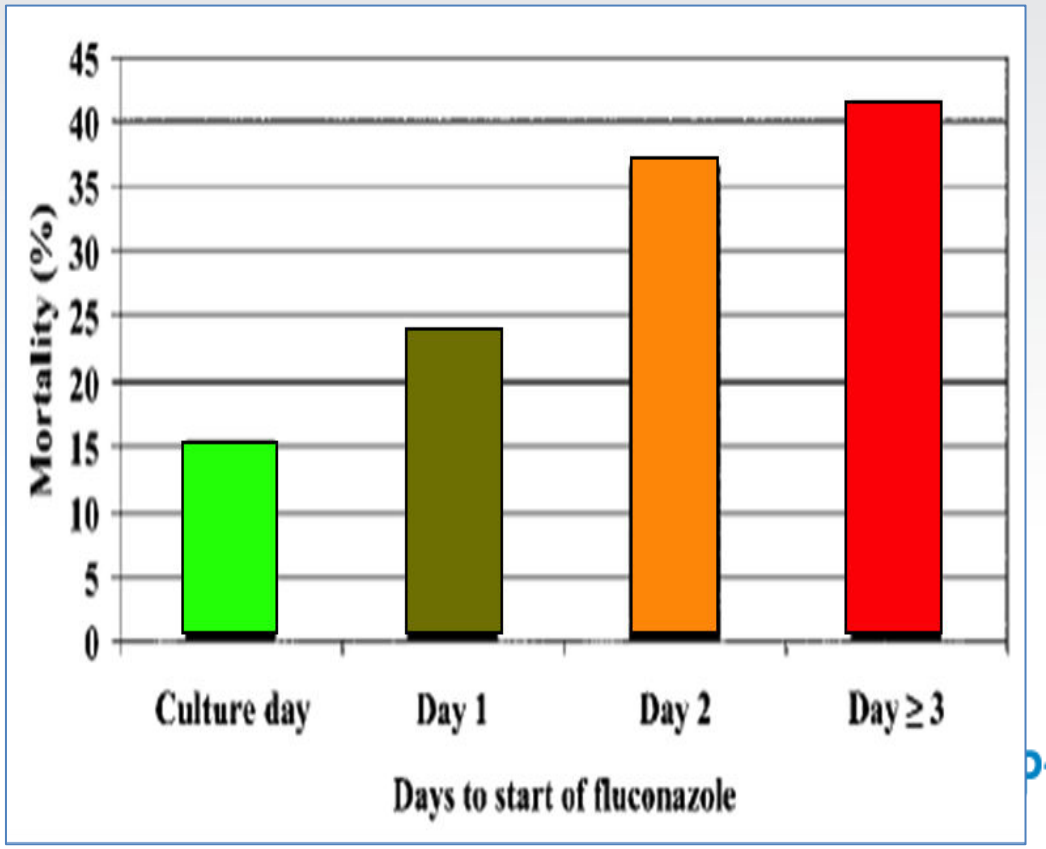



- N=157 Candidemia
- 134 Empiric TTT
- 31.8% mortality
- Multiple logistic regression: ➔ 3 determinants

| | AOR | CI | P |
|---|---|---|---|
| APACHE II | 1.24 | 95% | <0.001 |
| Prior AB TTT | 4.05 | 95% | 0.028 |
| AFT >12h | 2.09 | 95% | 0.018 |

*The timing of antifungal therapy was determined to be from the time when the first blood sample for culture positive for fungi was drawn to the time when antifungal treatment was first administered to the patient.
Morrell M, et al. Antimicrob Agents Chemother. 2005;49:3640-5.

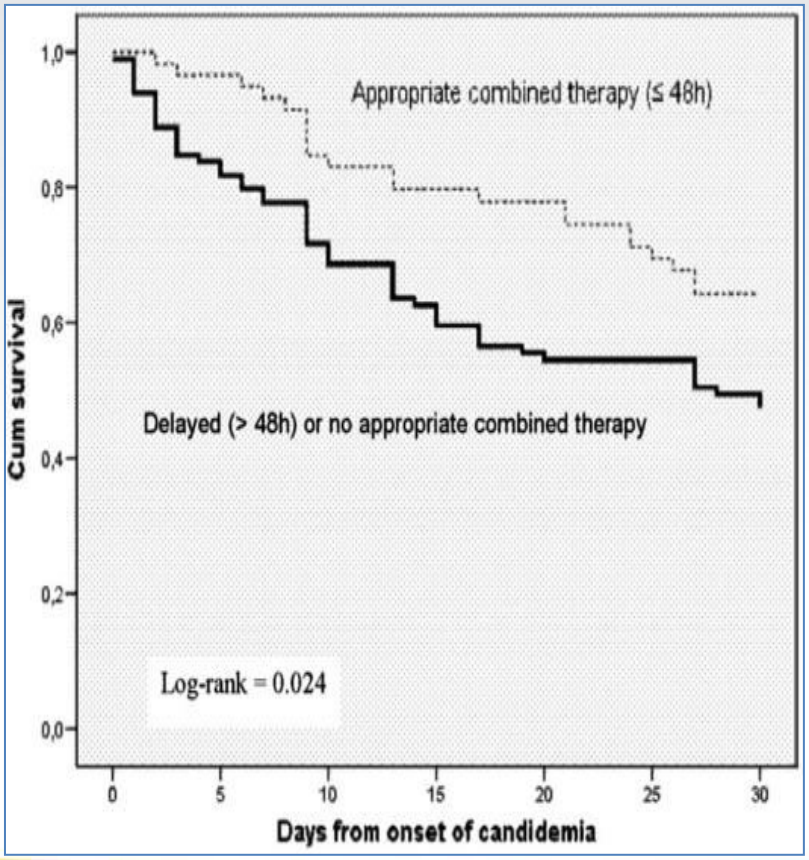
# Delay in Antifungal Treatment




Pfizer Anti-Infectives

Garey K, et al. Clin Infect Dis. 2006;43:25-31.

# Impact of Therapeutic Strategies on the Prognosis of Candidemia in the ICU

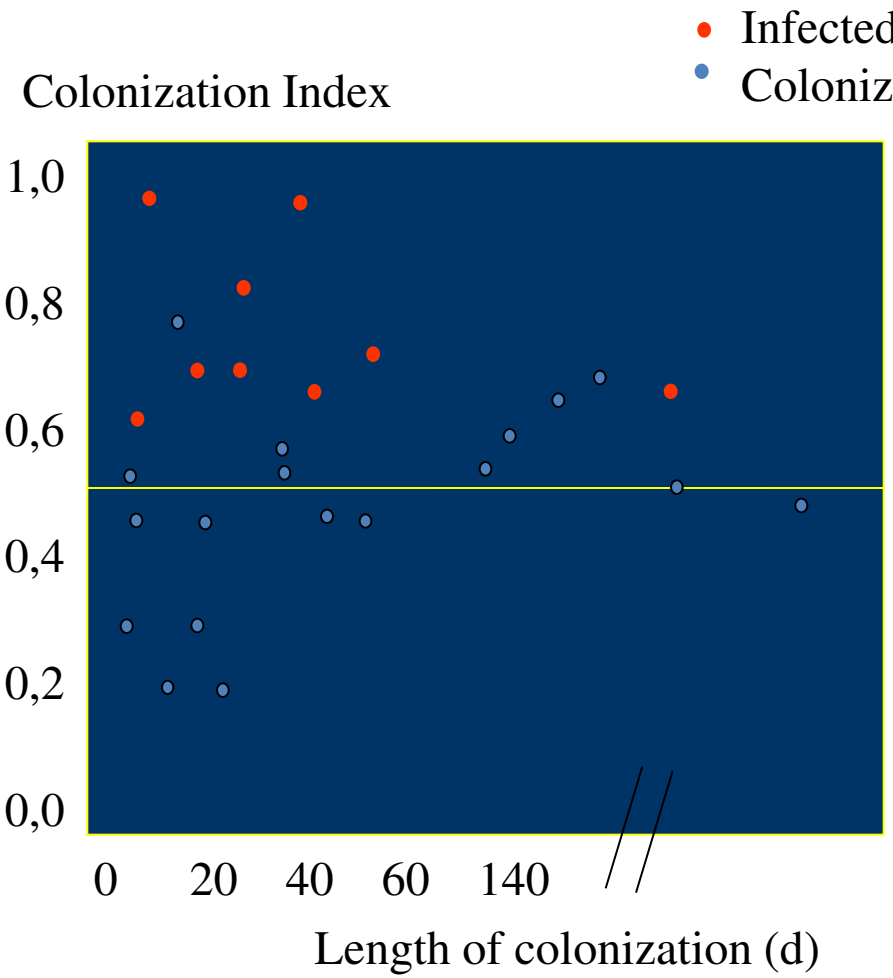



- Central venous catheter removal[b]
- Adequate antifungal treatment[c]

Pfizer Anti-Infectives

Puig-Asensio M, et al. Crit Care Med. 2014;42:1423-32.

# Colonization/Infection




- Prospective cohort study in the ICU
- 5,3 distinct sites /patient

- Colonization Index :
  Prospectively defined
  Measured 3 times/week

$$\frac{\text{nb distinct colonized sites}}{\text{nb distinct sampled sites}}$$

*Pittet. Ann Surg* 1994 Dec;220(6):751-8

(Pittet et al, Ann Surg 94 ; 220 : 751-8)

| | Se | Sp | PPV | NPV |
|---|---|---|---|---|
| >2 colonized sites | 100 | 22 | 44 | 100 |
| Index >0,5 | 100 | 69 | 66 | 100 |

But no consensus in number of sampling neither to initiate any preventive treatment in case of index > 0.5 *

*Massou et Al, Pathol Biol 2013;3:108-12

# Corrected C.I

$$CCI = CI \times \frac{\text{nb sites heavily colonized}}{\text{nb separate sites colonized}}$$

(Heavily : $\geq 10^5$ CFU/ml)

| | Se (%) | Sp (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| Colonized sites $\geq$ 2 | 100 | 22 | 44 | 100 |
| Colonized sites $\geq$ 3 | 73 | 56 | 50 | 77 |
| Colonized sites > 3 | 45 | 72 | 50 | 68 |
| CI $\geq$ 0.5 | 100 | 69 | 66 | 100 |
| **CCI $\geq$ 0.4** | **100** | **100** | **100** | **100** |

D'après Mimoz O, DAR Bicêtre, MAPAR 2000

Petri MG et Al, Intensive Care Med 1997;23:317-25

A bedside scoring system (Candida score) for early antifungal treatment in non neutropenic critically ill patients with Candida colonization.
Leon and al. Crit Care Med 2006

- A prospective, cohort, observational, multicenter study of 1,669 adult ICU Spanish ICUs
- N : 73 medical-surgical
- Candida score =
  - total parenteral nutrition : 0 -1
  - Surgery : 0 -1
  - multifocal Candida species colonization (≥ 2 sites): 0 -1
  - severe sepsis : 0 -**2**

Table 4. Calculation of the Candida score: Variables selected in the logistic regression model

| Variable | Coefficient (β) | Standard Error | Wald $\chi^2$ | *p* Value |
|---|---|---|---|---|
| Multifocal *Candida* species colonization | 1.112 | .379 | 8.625 | .003 |
| Surgery on ICU admission | .997 | .319 | 9.761 | .002 |
| Severe sepsis | 2.038 | .314 | 42.014 | .000 |
| Total parenteral nutrition | .908 | .389 | 5.451 | .020 |
| Constant | −4.916 | .485 | 102.732 | .000 |

ICU, intensive care unit.

Candida score = .908 × (total parenteral nutrition) + .997 × (surgery) + 1.112 (multifocal *Candida* species colonization) + 2.038 (severe sepsis). Candida score (rounded) = 1 × (total parenteral nutrition) + 1 × (surgery) + 1 (multifocal *Candida* species colonization) + 2 × (severe sepsis). All variables coded as follows: absent, 0; present, 1.

Crit Care Med 2006 Vol. 34, No. 3

- Se 81%, Sp 74%

| Cutoff value | Sensitivity | False positive |
|---|---|---|
| 1.055 | .983 | .653 |
| 1.509 | .949 | .495 |
| 1.963 | .898 | .426 |
| 2.069 | .831 | .312 |
| 2.074 | .814 | .301 |
| 2.528 | .814 | .259 |
| 2.982 | .780 | .231 |
| 3.026 | .610 | .132 |
| 3.093 | .593 | .130 |
| 3.547 | .525 | .092 |
| 4.001 | .492 | .077 |

Table 4. Rates of invasive candidiasis according to the *Candida* score

(Crit Care Med 2009; 37:1624–1633)

| Cutoff Value | Incidence Rate (%) (95% CI) | Relative Risk (95% CI) |
|---|---|---|
| <3 | 2.3 (1.1–3.5) | 1 |
| 3 | 8.5 (4.2–12.7) | 3.7 (1.8–7.7) |
| 4 | 16.8 (9.7–23.9) | 7.3 (3.7–14.5) |
| 5 | 23.6 (12.4–34.9) | 10.3 (5.0–21.0) |

The CS
- total parenteral nutrition 1
- surgery 1,
- multifocal Candida colonization 1
- severe sepsis 2

Table 5. *Candida* score vs. colonization index discriminatory power

| | *Candida* Score ≥3 (95% CI) | Colonization Index ≥0.5 (95% CI) |
|---|---|---|
| Area under ROC curve | 0.774 (0.715–0.832) | 0.633 (0.557–0.709) |
| Sensitivity | 77.6 (66.9–88.3) | 72.4 (60.9–83.9) |
| Specificity | 66.2 (63.0–69.4) | 47.4 (44.0–50.8) |
| Predictive positive value | 13.8 (10.0–17.5) | 8.7 (6.2–11.3) |
| Predictive negative value | 97.7 (96.4–98.9) | 96.1 (94.2–98.0) |
| Relative risk for invasive candidiasis | 5.98 (3.28–10.92) | 2.24 (1.28–3.93) |

ROC, receiver operating characteristics; CI, confidence interval.

# Evaluation of "*Candida* score" in critically ill patients: a prospective, multicenter, observational, cohort study

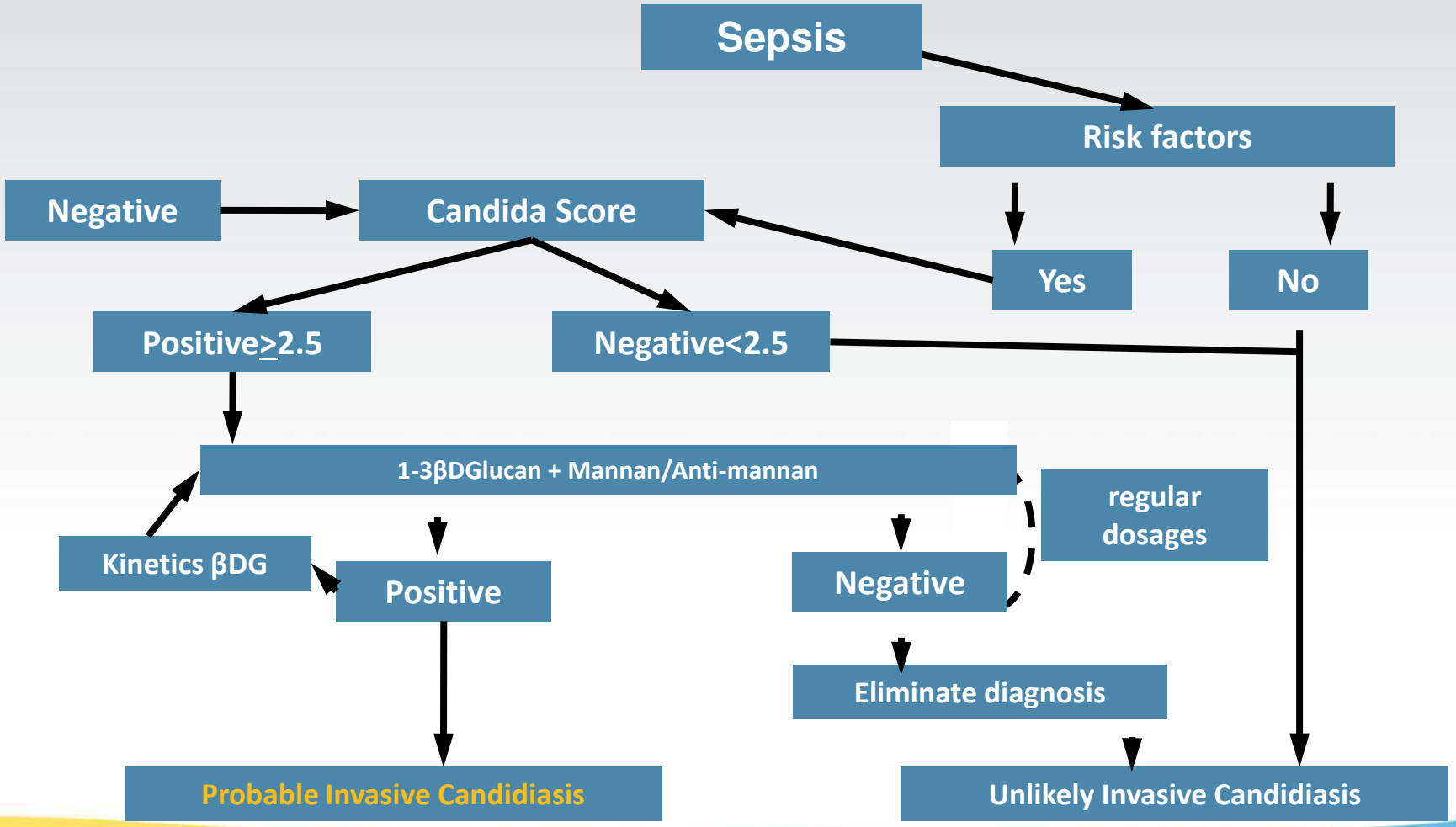
Guillaume Leroy[1], Fabien Lambiotte[2], Didier Thévenin[3], Christian Lemaire[4], Erika Parmentier[5], Patrick Devos[6] and Olivier Leroy[1*]

Annals of Intensive Care 2011, 1:50

- 0% , score = 2
- 0%, score = 3
- 17,6%, score = 4
- 50%, score = 5
- the rate of invasive candidiasis is similar in surgical and medical patients with a "Candida score" >3.

- The association between increasing values of the "Candida score" and the rate of invasive candidiasis is statistically significant ($p < 0.0001$).
- In patients with a "Candida score" ≤3, no invasive candidiasis was observed

# Sepsis: Diagnostic Algorithm



## Quelle molécule Antifongique?

A. Amphotéricine B

B. Fluconazole

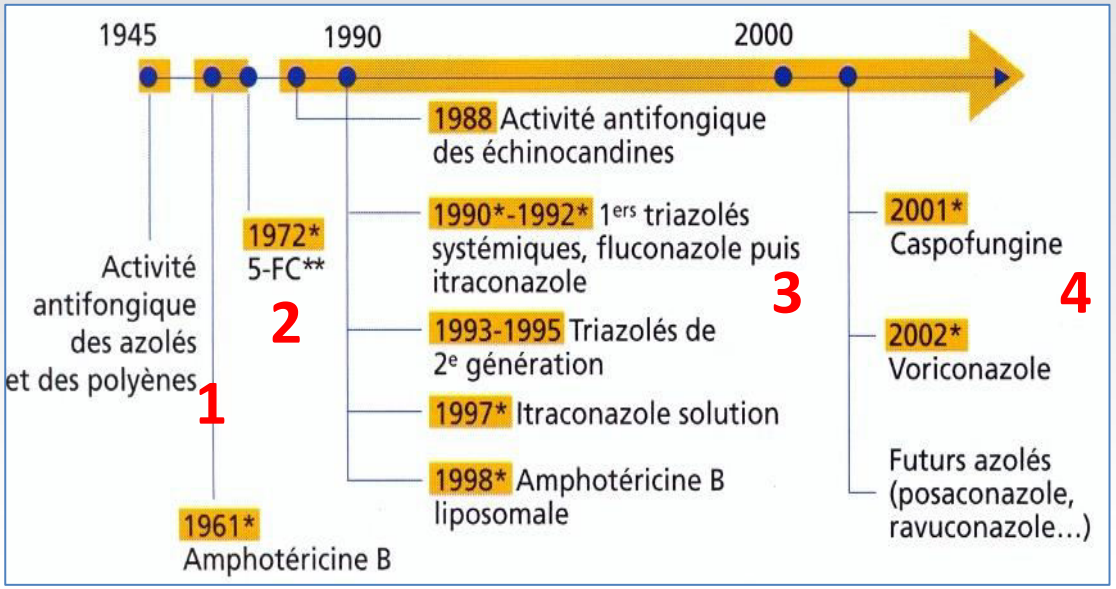
C. Voriconazole

D. Echinocandine

E. Association

# Historique des Antifungiques

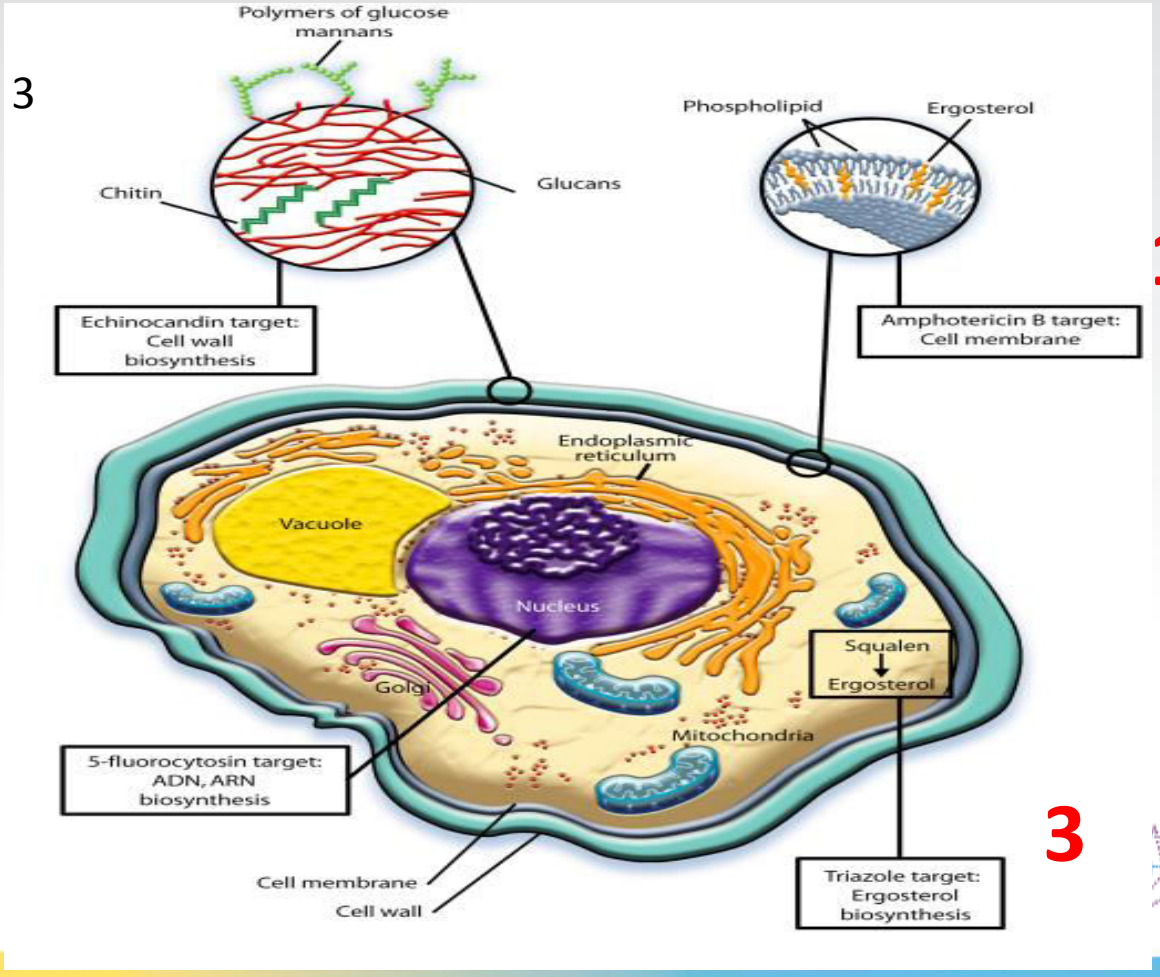
- Polyènes
  - Amphotéricine B desoxycholate (fungizone)
  - Ambisome
- Pyrimidines
  - 5-Fluorocytosine
- Azolés
  - Fluconazole
  - Itraconazole
  - Voriconazole
  - Posaconazole
- Echinocandines
  - Caspofongine
  - Micafongine
  - Anidulafongine



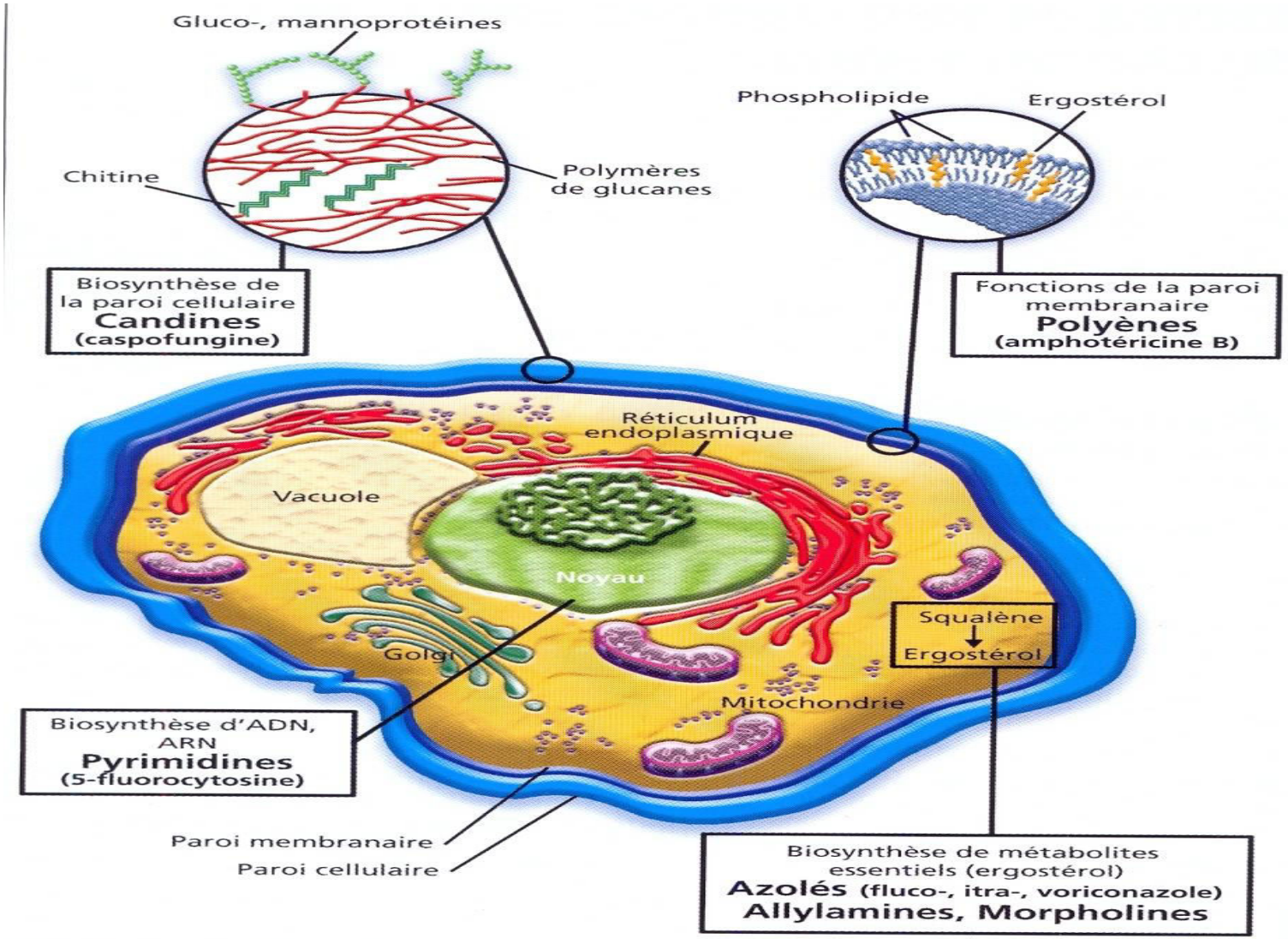

Pfizer Anti-Infectives

# Mécanismes d'action

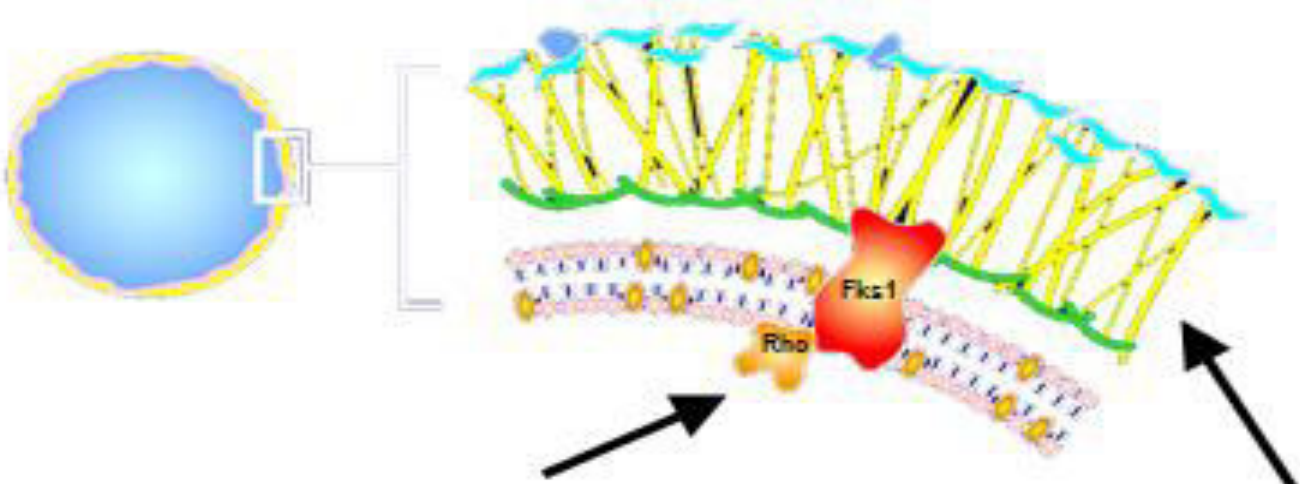
inhibition non compétitive de la 1, 3 β-D-glucane synthétase




Anti-Infectives



# Mechanism of Action




- Anidulafungin is a non-competitive inhibitor of 1,3-β-D-glucan synthase[1]
- Glucan is unique to fungal cells and essential to cell wall integrity[2]
  - Without it, fungal cells are osmotically fragile and easily lysed[3]

•1. Odds FC, et al. Trends Microbiol. 2003;11:272–279
•2. Eraxis for Injection [package insert]. New York, NY: Pfizer Inc; November 2010
•3. Boucher HW et al. Drugs. 2004;64:1997–2020

# Particularités pharmacologiques

| Famille | Paramètre | *Aspergillus* | *Candida* | Effet Post ATB |
|---|---|---|---|---|
| **Azolés** | AUC/CMI | Fongicide | **Fongistatique** | oui |
| **Candines** | $C_{max}$/CMI | Fongistatique | **Fongicide** | oui |
| **Flucytosine** | T/CMI | / | **Fongistatique** | Non |
| **Polyènes** | $C_{max}$/CMI | Fongicide | **Fongicide** | oui |

**Sinnollareddy M, et al. IJAA 2012;39:1-10.**

**Table 3. General patterns of susceptibility of *Candida* species.**

| Species | Fluconazole | Itraconazole | Voriconazole | Posaconazole | Flucytosine | Amphotericin B | Candins |
|---|---|---|---|---|---|---|---|
| *Candida albicans* | S | S | S | S | S | S | S |
| *Candida tropicalis* | S | S | S | S | S | S | S |
| *Candida parapsilosis* | S | S | S | S | S | S | S to R[a] |
| *Candida glabrata* | S-DD to R | S-DD to R | S-DD to R | S-DD to R | S | S to I | S |
| *Candida krusei* | R | S-DD to R | S | S | I to R | S to I | S |
| *Candida lusitaniae* | S | S | S | S | S | S to R | S |

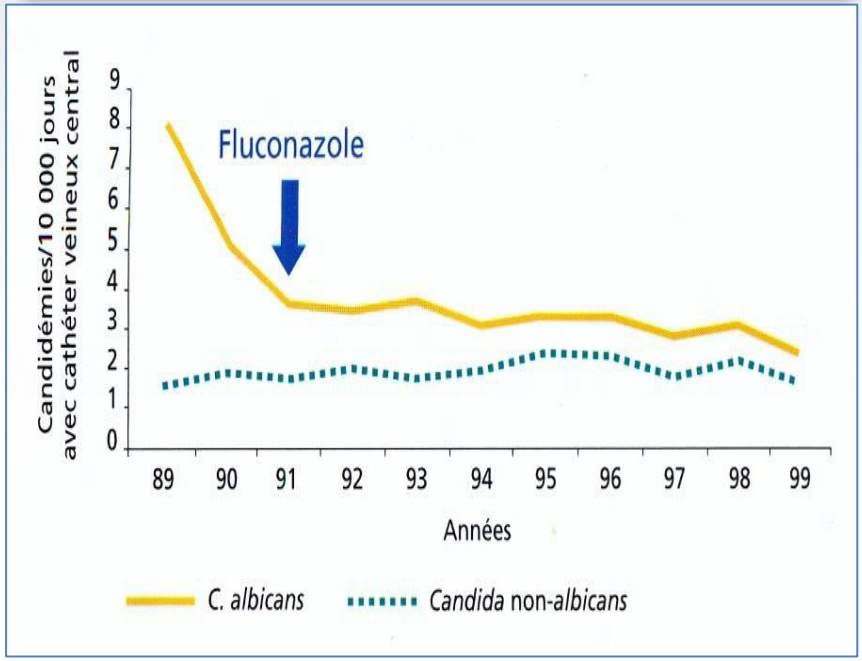
**NOTE.** I, intermediately susceptible; R, resistant; S, susceptible; S-DD: susceptible dose-dependent.

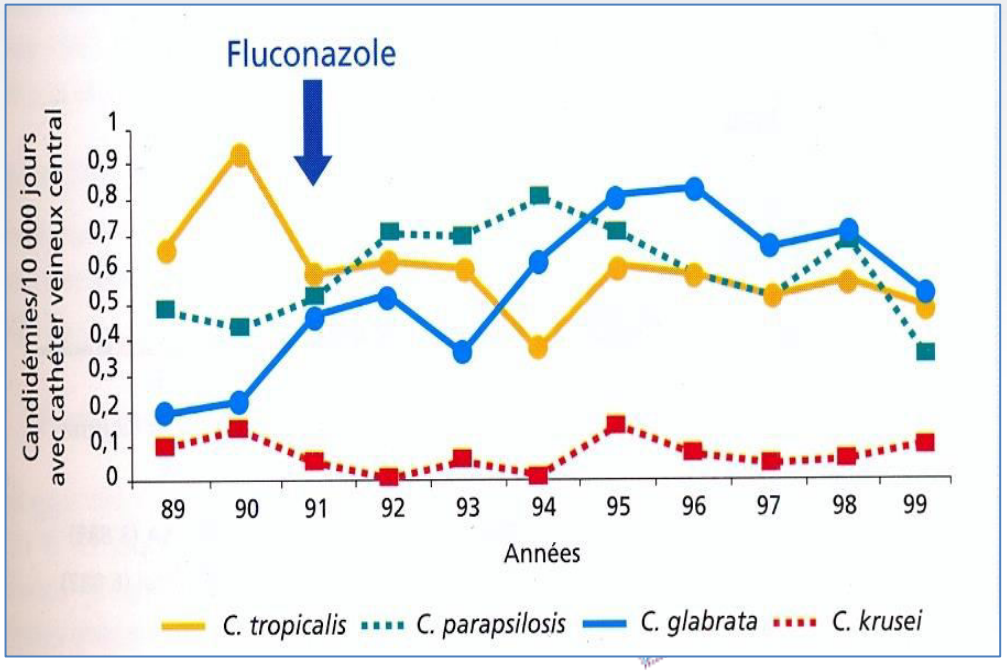
[a] Echinocandin resistance among *C. parapsilosis* isolates is uncommon.

Treatment Guidelines for Candidiasis • CID 2009:48 (1 March)

# Après la 1ère décade d'utilisation des AZOLES

**NNIS 1989-1999 in 790 USA ICUs**

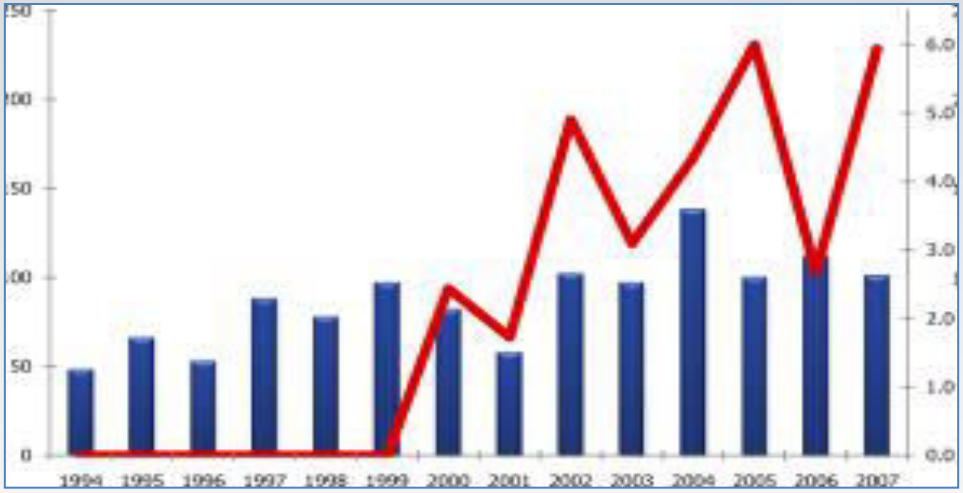


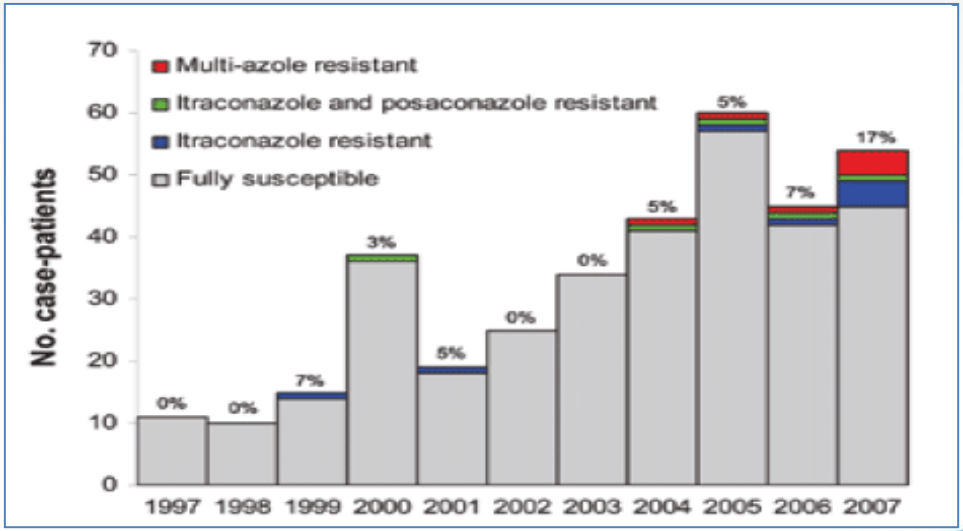




Trick WE, et al. Clin Infect Dis. 2002;35:627-30.

# Resistance to Azoles

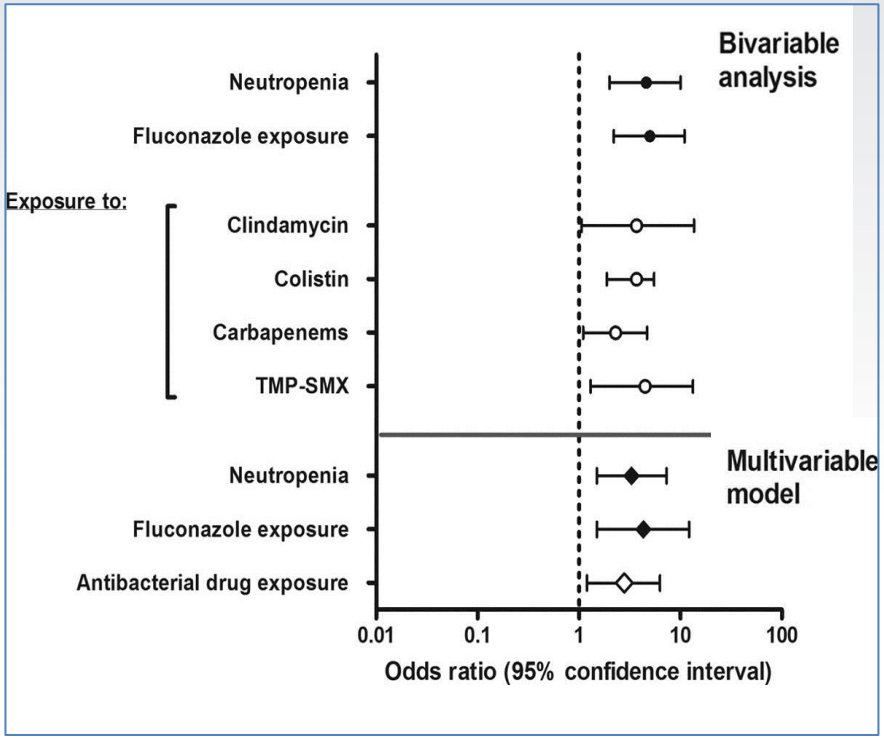
- Snelders et al.[1]
  - Netherlands
  - Itra-R seen in 1999
  - 1.7 to 6% per year
- Howard et al.[2]
  - United Kingdom
  - 519 isolates
  - 34% itra-R, 65% vori-R, 74% posa-R



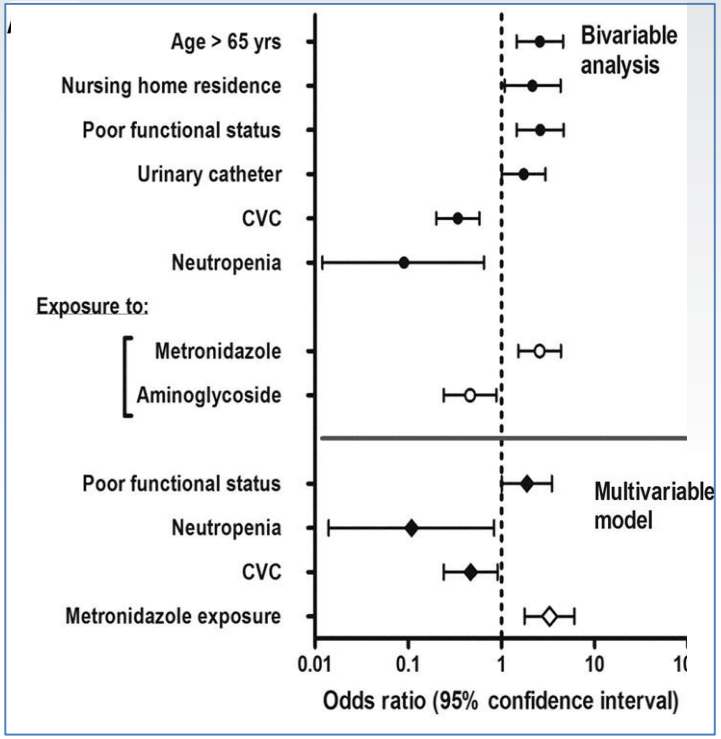




1. Snelders E, et al. PLoS Med. 2008;5:e219.
2. Howard SJ, et al. Emerg Infect Dis. 2009;15:1068-76.

# Antibiotic Exposure as a Risk Factor for Fluconazole-Resistant *Candida* Bloodstream Infection




Fluconazole-R *C. albicans* (n=54)




*C. glabrata* (n=68)

Ben-Ami, R, et al. Antimicrob Agents Chemother. 2012;56:2518-23.

# ESCMID Guidelines

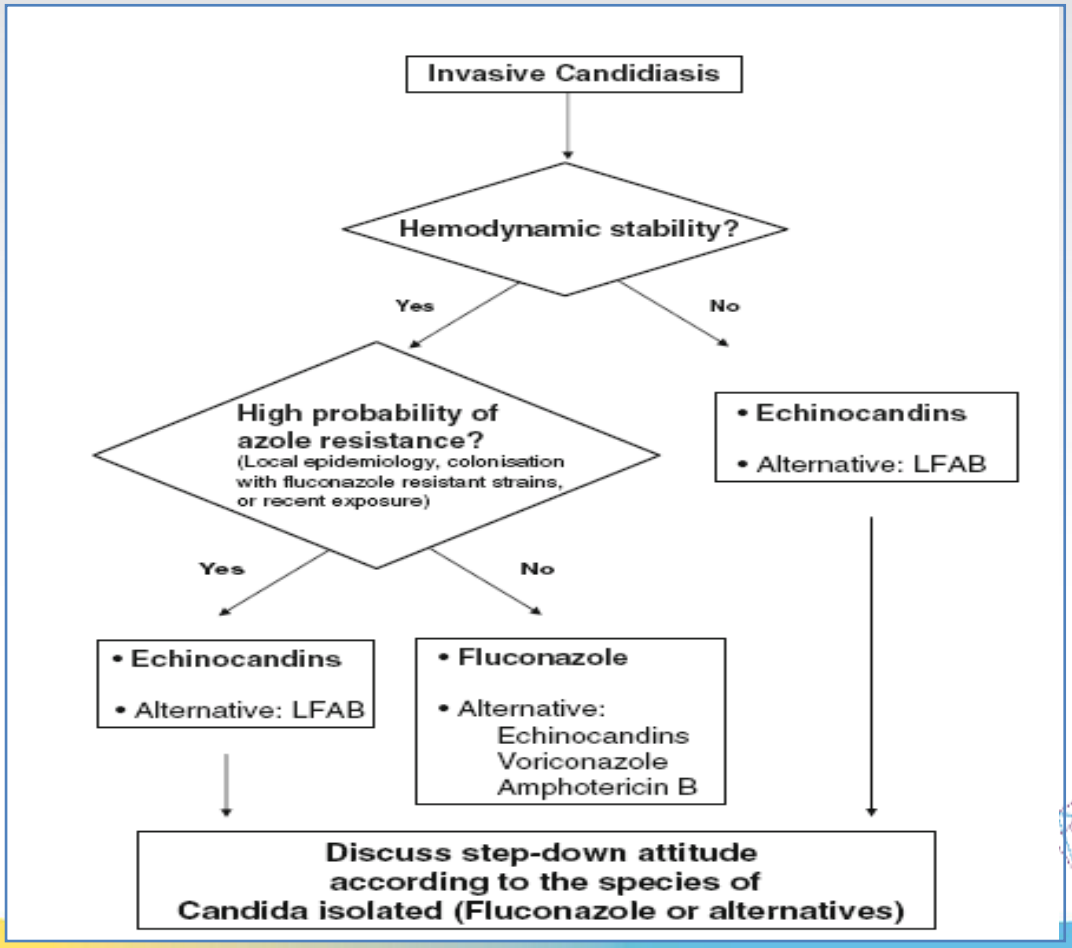
diasis in Adult Patients

| Intervention | SoR | QoE | Reference | Comment |
|---|---|---|---|---|
| Anidulafungin 200/100 mg | A | I | Reboli NEJM 2007 | Consider local epidemiology (*C. parapsilosis*, *C. krusei*), less drug-drug interactions than caspofungin |
| Caspofungin 70/50 mg | A | I | Betts CID 2009<br>Mora-Duarte NEJM<br>Pappas | Consider local epidemiology (*C.* [illegible]) |
| Micafungin 100 mg | | | | local epidemiology (*C.* [illegible]), less drug-drug than caspofungin, MA warning label |
| | | | | acy as micafungin, higher than micafungin |
| | | | | rum compared to drug-drug interactions, formulation in renal nsider therapeutic drug |
| | | | Kofler-Gvili Mayo Clin Proc 2008 | Inferiority to especially in the up with high APACHE scores), may be better than echinocandins against *C. parapsilosis* |
| | C | $II_a$ | Anaissie ICAAC 1995<br>Ito CID 2005 | |
| Amphotericin B deoxycholate 0.7–1.0 mg/kg | D | I | Ullmann CID 2006<br>Bates CID 2001<br>Anaissie CID 1996<br>Rex NEJM 1994<br>Philips EJCMID 1997<br>Mora-Duarte NEJM 2002 | Substantial renal and infusion-related toxicity |
| Amphotericin B deoxycholate plus fluconazole | D | I | Rex CID 2003 | Efficacious, but increased risk of toxicity in ICU patients<br>No survival benefit |
| Amphotericin B deoxycholate plus 5-fluorocytosine | D | II | Abele-Horn Infect 1996 | |
| Efungumab plus lipid-associated amphotericin B | D | II | Pachl CID 2006 | |
| Amphotericin B colloidal dispersion | D | $II_a$ | Noskin CID 1998 | |
| Itraconazole | D | $II_a$ | Tuil CCM 2003 | |
| Posaconazole | D | III | No reference found. | |

- The Panel favors an echinocandin for patients with moderately severe to severe illness, or patients who have had recent azole exposure.
- Fluconazole is recommended for patients who are less critically ill and who have no recent azole exposure.

Cornely OA, et al. Clin Microbiol Infect. 2012;18:19-37.

# Management of Invasive Candidiasis and Candidemia in Adult Non-Neutropenic ICU Patients: Part II. Treatment




Anti-Infectives

Guery BP, et al. Intensive Care Med. 2009;35:206-14.

# Pooled Data From 7 Randomized Adult Studies (1994 to 2007): 1915 Patients

| | | 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 | | | | | | |

Andes DR, et al. Clin Infect Dis. 2012;54:1110-22.

# Prognostic Factors & Historical Trends in the Epidemiology of Candidemia in Critically Ill Patients: An Analysis of 5 Multicenter Studies Sequentially Conducted Over a 9-Year Period

**Table 5** Factors associated with 30-day mortality[a] among 640 ICU patients with candidemia by multivariate analysis

| Variable | Odds ratio | 95 % Confidence interval | *p* value |
|---|---|---|---|
| Receipt of corticosteroids | 4.00 | 1.98–8.13 | <0.001 |
| Period 1 | 2.49 | 1.22–5.08 | 0.01 |
| APACHE II score[b] | 1.05 | 1.01–1.09 | 0.03 |
| Age | 1.03 | 1.01–1.05 | 0.003 |
| Treatment with an echinocandin | 0.20 | 0.07–0.58 | 0.003 |



Colombo AL, et al. Intensive Care Med. 2014;40:1489-98.

## Cas Clinique

- J 7: HC+ (périphérique et à travers le CVC)
  - = *C. glabrata*
  - Aucune croissance bactérienne

- Quelle serait votre attitude?
  - A: continuer
  - B: désescalade

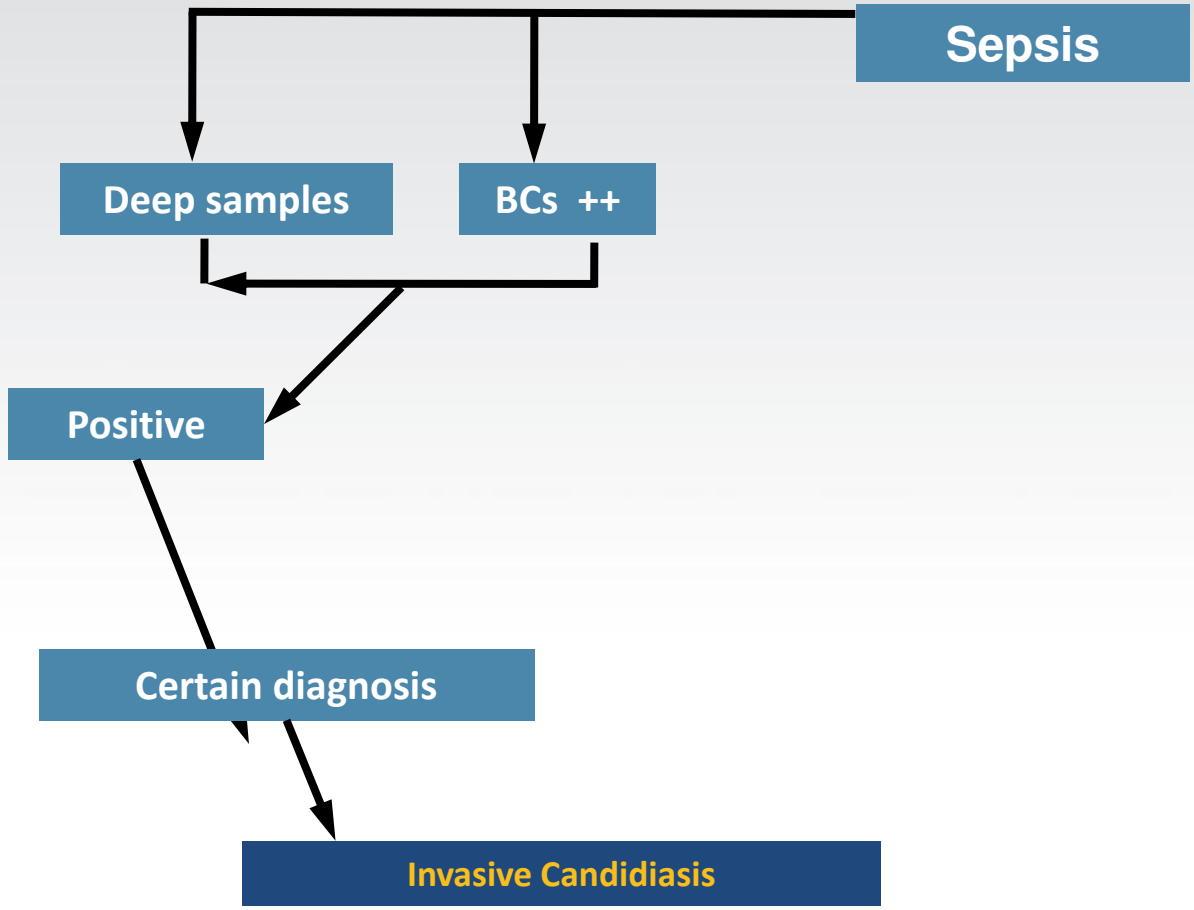
## Apport du Laboratoire

- Diagnostic direct : HC avec identification = gold standard
- *Candida* spp. poussent généralement facilement sur des milieux de culture usuels.
- *C. glabrata*: on peut raccourcir la période de pousse en utilisant des milieux de culture spécifiques
- Mais, de toutes façons le délai moyen est ≥ 2 jours; et la sensibilité peut être <50%



Ericson E-L, et al. Diagn Microbiol Infect Dis. 2012;73(2):153-6.
Avni T, et al. J Clin Microbiol. 2011;49:665-70.

# Sepsis: Diagnostic Algorithm



# Mortalité

| Référence | Antifongique | Taux de mortalité |
|---|---|---|
| Rex J et al. NEJM 1994;331:1325-30 | Amphotéricine B<br>vs.<br>Fluconazole | 40%<br><br>33% |
| Phillips P et al. Eur J Clin Microbiol Infect Dis 1997;16:337-45 | Amphotéricine B<br>vs.<br>Fluconazole | 43%<br><br>46% |
| Rex J et al. CID 2003;36:1221-28 | Amphotéricine B + Fluconazole<br>vs.<br>Fluconazole | 40%<br><br>39% |
| Mora-Duarte J et al. NEJM 2002;347:2020-29 | Amphotéricine B<br>vs.<br>Caspofungine | 30.4%<br><br>34.2% |
| Kullberg BJ et al. Lancet 2005;366:1435-42 | Amphotéricine B<br>vs.<br>Voriconazole | 42%<br><br>36% |
| Reboli A, Rotstein C, Pappas P et al. NEJM 2007;356:2472-82 | Anidulafungine<br>vs.<br>Fluconazole | 22.8%<br><br>31.4% |
| Kuse E-R et al. Lancet 2007;369:1519-27 | Micafungine<br>Vs.<br>Amphotéricine B liposomale | 40%<br><br>40% |
| Pappas P, Rotstein C, Betts RF et al. CID 2007;45:883-93 | Micafungine 100 vs.<br>Micafungine 150 vs.<br>Caspofungine | 29%<br>33.2%<br>26.4% |

Ecalta® (anidulafungin IV)
FOR MORE PATIENTS THAN YOU THINK

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Anidulafungin versus Fluconazole for Invasive Candidiasis

Annette C. Reboli, M.D., Coleman Rotstein, M.D., Peter G. Pappas, M.D., Stanley W. Chapman, M.D., Daniel H. Kett, M.D., Deepali Kumar, M.D., Robert Betts, M.D., Michele Wible, M.S., Beth P. Goldstein, Ph.D., Jennifer Schranz, M.D., David S. Krause, M.D., and Thomas J. Walsh, M.D., for the Anidulafungin Study Group

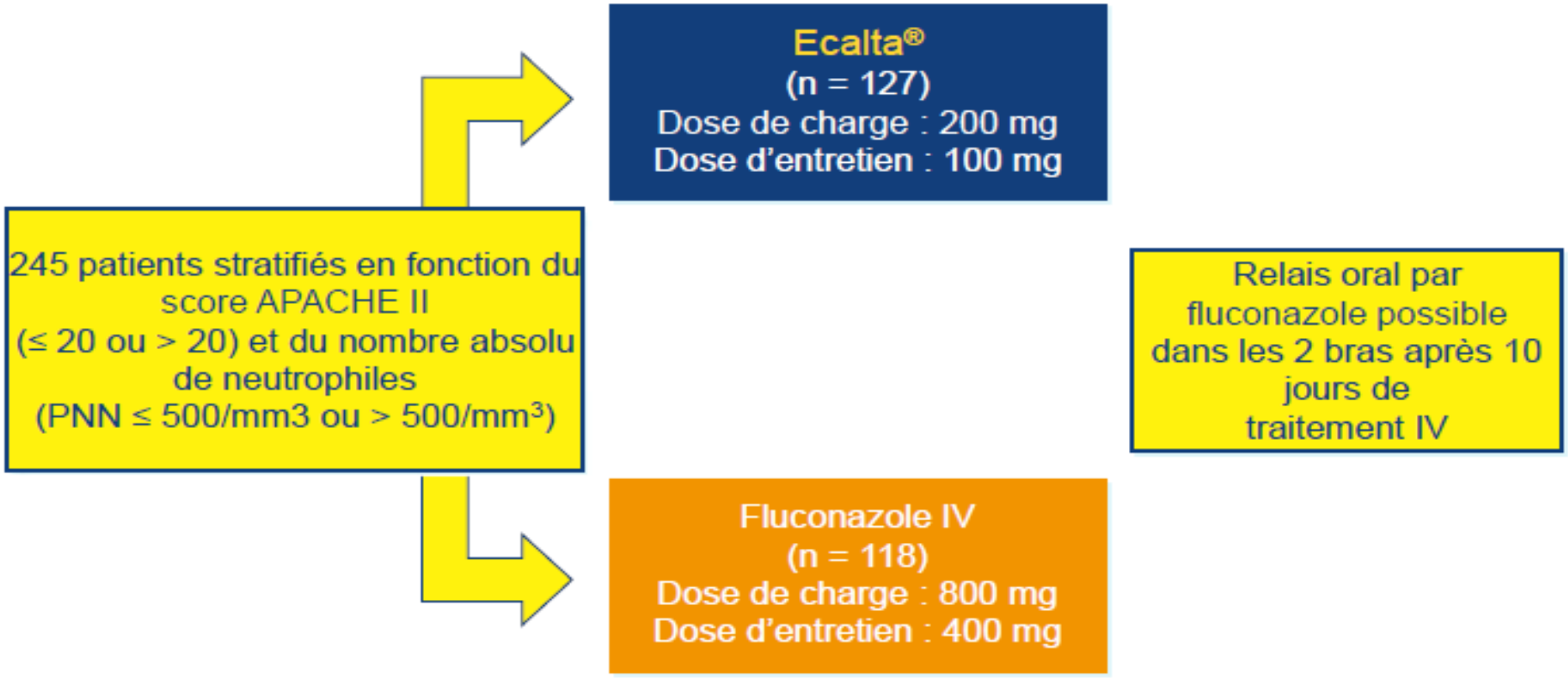
## ETUDE REBOLI. A : ETUDE PIVOT (A.M.M)

N ENGL J MED 356;24 WWW.NEJM.ORG JUNE 14, 2007

The New England Journal of Medicine

Pfizer Anti-Infectives

# Candidémies: anidulafungine




Durée de traitement : au moins 14 jours en ne dépassant pas 42 jours

*Reboli et al.N Engl J Med. 2007;356:2472–82*

# Mortalité

| Référence | Antifongique | Taux de mortalité |
|---|---|---|
| Rex J et al. NEJM 1994;331:1325-30 | Amphotéricine B<br>vs.<br>Fluconazole | 40%<br><br>33% |
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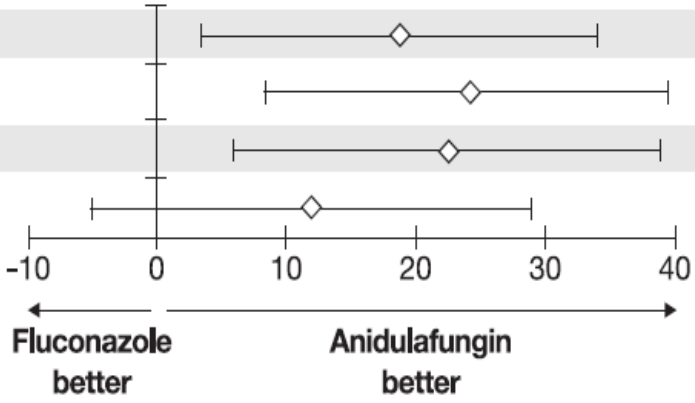
| Mora-Duarte J et al. NEJM 2002;347:2020-29 | Amphotéricine B<br>vs.<br>Caspofungine | 30.4%<br><br>34.2% |
| Kullberg BJ et al. Lancet 2005;366:1435-42 | Amphotéricine B<br>vs.<br>Voriconazole | 42%<br><br>36% |
| Reboli A, Rotstein C, Pappas P et al. NEJM 2007;356:2472-82 | Anidulafungine<br>vs.<br>Fluconazole | 22.8%<br><br>31.4% |
| Kuse E-R et al. Lancet 2007;369:1519-27 | Micafungine<br>Vs.<br>Amphotéricine B liposomale | 40%<br><br>40% |
| Pappas P, Rotstein C, Betts RF et al. CID 2007;45:883-93 | Micafungine 100 vs.<br>Micafungine 150 vs.<br>Caspofungine | 29%<br>33.2%<br>26.4% |

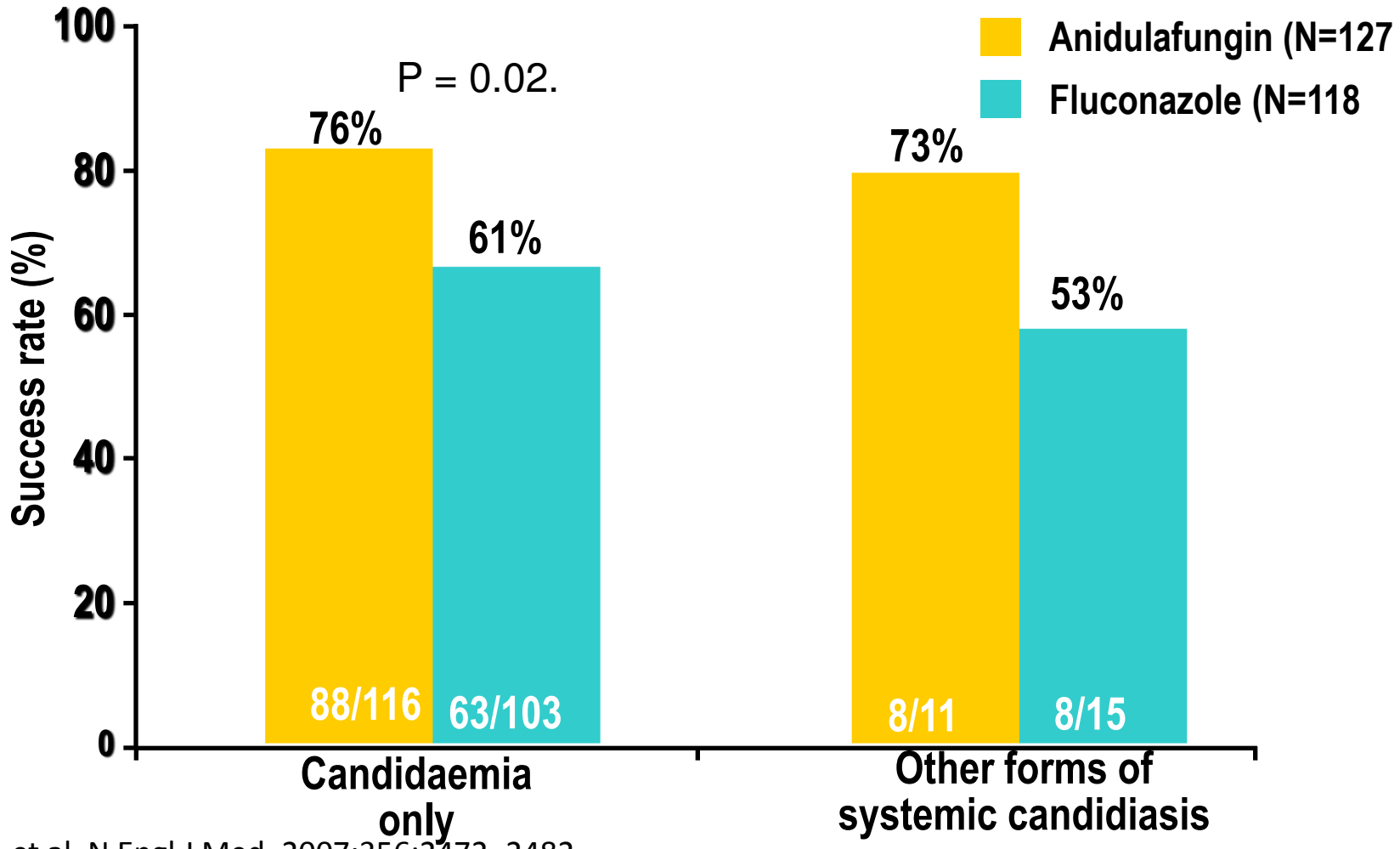
# Treatment of Documented Candidiasis

| End point | Global response n (%) | | Absolute percent difference between treatments (95% CI) |
|---|---|---|---|
| | Fluconazole (n = 61) | Anidulafungin (n = 74) | |
| End of IV therapy | 38 (62.3) | 60 (81.1) | 18.8 (3.7-33.9) |
| End of all therapy | 34 (55.7) | 59 (79.7) | 24.0 (8.5-39.5) |
| 2-Week follow-up | 30 (49.2) | 53 (71.6) | 22.4 (6.2-38.7) |
| 6-Week follow-up | 29 (47.5) | 44 (59.5) | 12.0 (-4.9-28.7) |



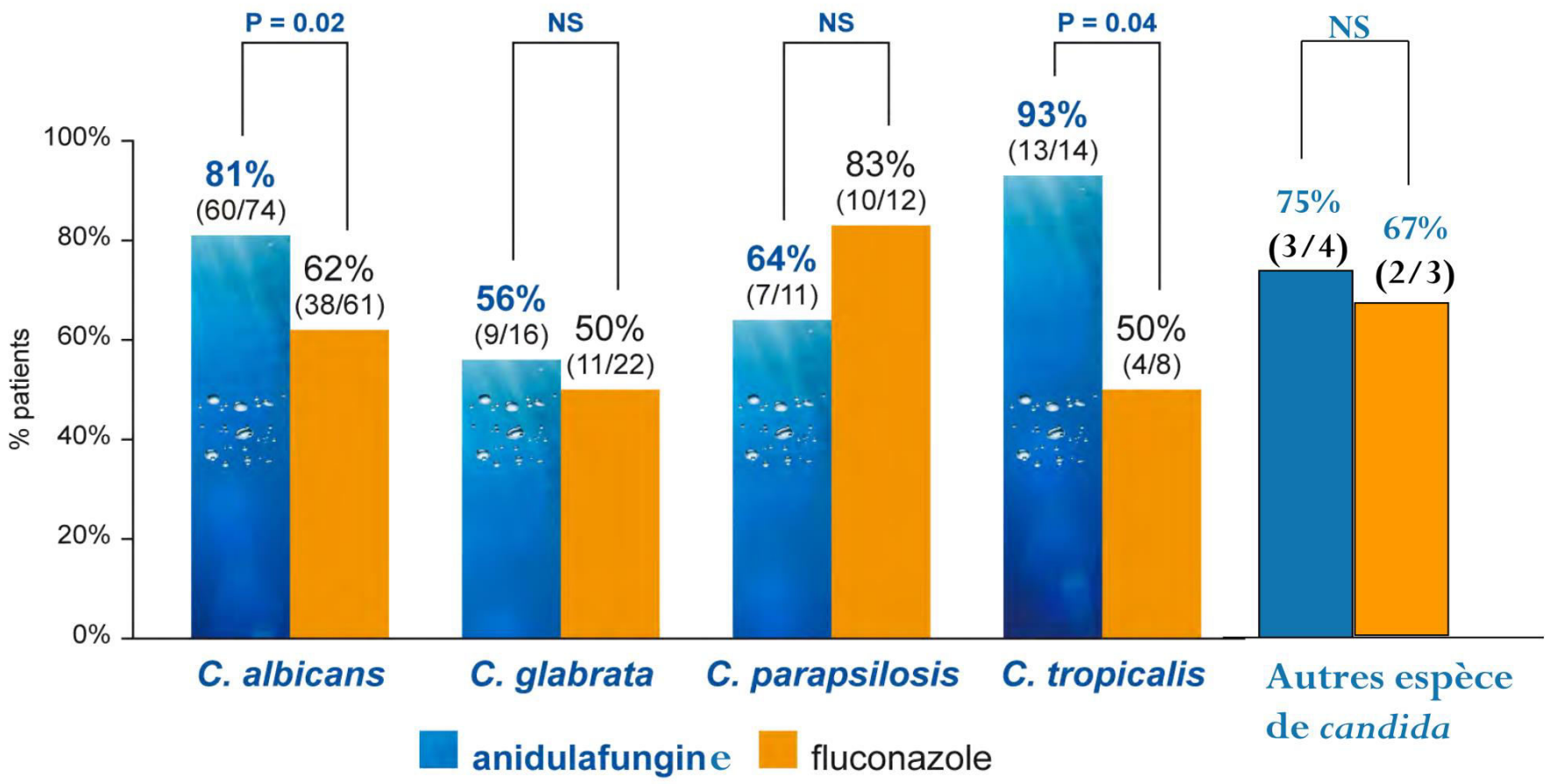

Pfizer Anti-Infectives

Reboli AC, et al. BMC Infect Dis. 2011;11:261.




•Reboli AC, et al. N Engl J Med. 2007;356:2472–2482

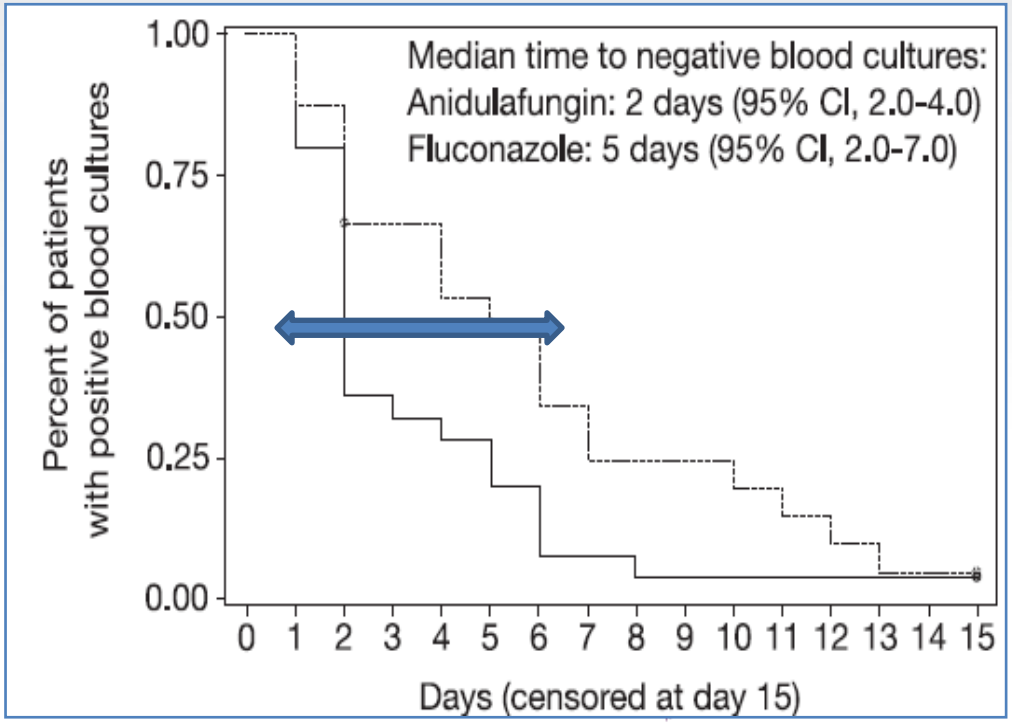
# Succès par pathogène




*Reboli et al. N Engl J Med. 2007;356:2472–82*

# Anidulafungin Compared with Fluconazole for Treatment of Candidemia and Other Forms of Invasive Candidiasis Caused by *Candida albicans*: A Multivariate Analysis of Factors Associated with Improved Outcome

- Time to negative blood culture was significantly shorter for anidulafungin vs. fluconazole (log-rank $P<0.05$)



| | Caspofungin | Micafungin | Anidulafungin |
|---|---|---|---|
| **Metabolism** | Hepatic metabolism by hydrolysis and N-acetylation Spontaneous non hepatic chemical degeneration | Hepatic metabolism by arylsulfatase and catechol-O-methyltransferase | **Non hepatic chemical degradation** |
| **Elimination / excretion** | Urine 41% Feces 34% | Urine + feces 82.5% Feces 71% | Urine <1% Feces ≈30% |
| **Oral Bioavailability** | <5% | <5% | <5% |
| **Dialyzable** | No | No | No |

Adapted from Micafungin US Prescribing Information; Anidulafungin US Prescribing Information; Dodds Ashley ES et al. *Clin Infect Dis.* 2006;43:S28-S39.

# Resource Utilization and Cost of Treatment with Anidulafungin or Fluconazole for Candidaemia and Other Forms of Invasive Candidiasis

## Focus on Critically Ill Patients

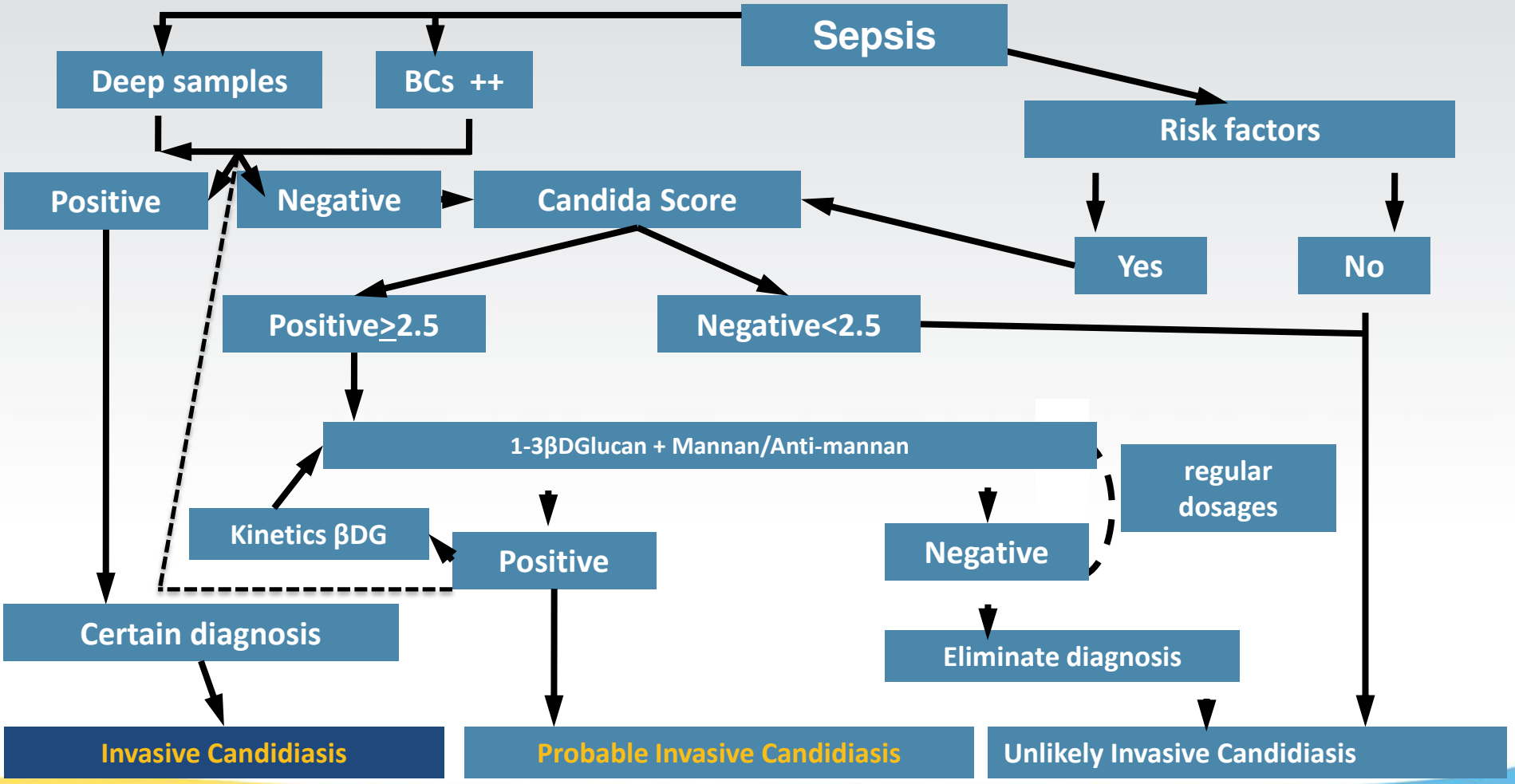
*Annette C. Reboli,[1] Coleman Rotstein,[2] Daniel H. Kett,[3] Michael Maschio,[4] Shannon Cartier,[4] Richard Chambers[5] and Miriam Tarallo[5]*

| | Full chart review population | | | ICU population | | |
|---|---|---|---|---|---|---|
| | anidulafungin (n = 83) | fluconazole (n = 76) | difference[a] | anidulafungin (n = 35) | fluconazole (n = 28) | difference[a] |
| Study intravenous medication[b] | 2 232 | 79 | 2 153[c] | 2 155 | 84 | 2 071[c] |
| Study oral medication[d] | 155 | 184 | –29 | 66 | 17 | 49 |
| Other systemic antifungal medication[e] | 929 | 1 085 | –156 | 1 839 | 1 887 | –48 |
| Hospital stay[b] | 55 193 | 54 656 | 537 | 76 518 | 93 644 | –17 126 |
| Total cost[b] | 58 555 | 55 875 | 2 680 | 80 594 | 95 631 | –15 037 |

[a] Difference in anidulafungin – fluconazole

| | Full chart review survivor population | | | ICU survivor population | | |
|---|---|---|---|---|---|---|
| | anidulafungin (n = 68) | fluconazole (n = 53) | difference[a] | anidulafungin (n = 26) | fluconazole (n = 16) | difference[a] |
| Base case[b] | 60 337 | 60 106 | 231 | 90 833 | 114 179 | –23 346 |
| Difference of ward type cost | | | | | | |
| 25% increase[b] | 58 210 | 57 800 | 410 | 93 080 | 116 564 | –23 484 |
| 25% decrease[b] | 62 433 | 62 355 | 78 | 88 585 | 111 786 | –23 201 |
| Maximum 5 days of intravenous therapy[b] | 59 126 | 60 248 | –1122 | 89 627 | 114 363 | –24 736 |

# Sepsis: Diagnostic Algorithm



## CONCLUSIONS

- Le diagnosis des CI reste difficile en réanimation (sepsis, facteurs de risque, scores)
  - Si HC+ → enlever le KT + AF
  - Si HC− → association BDGlucane + Mannane/Antimannane
- En réa, instabilité hémodynamique : traitement de première ligne = Echinocandine

## Inclusion Criteria

- Age ≥ 16 years
- 1 positive *Candida* blood (or normally sterile site) culture
  - Within 96 h prior to randomization
- Clinical evidence of infection
  - Fever
  - Hypothermia
  - Hypotension
  - Other signs of *Candida* infection

## Exclusion Criteria

- More than 48 hours of prior antifungal therapy
- Failure of previous treatment
- Recent azole prophylaxis
- Elevated hepatic enzyme levels
- Infection with *C krusei*
- Suspected *Candida* endocarditis, osteomyelitis, or meningitis

Reboli AC et al. NEJM, 2007