Approches thérapeutiques sur les infections à Candida sp. En 2012

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Conflits d'intérêts

- Budget de recherche: Astellas, Pfizer, Gilead, Merck
- Board étude clinique: Merck
- Participation symposium: Astellas, Gilead, Merck, Pfizer

« Ca n'est pas parce que l'on a un pot de confiture sur la table que l'on doit mettre les mains dedans »

Alain Gérard Slama

Agenda

- **La candidose invasive en réanimation est une maladie grave souvent traitée de manière inadéquate – le traitement précoce d'unecandidose prouvée ne se discute pas**
- Diagnostic difficile, colonisation et scores aboutissent à un sur-traitement
- Le sur-traitement a des conséquences
- Le traitement des malades colonisés ou des malades septiques avec des facteurs de risque n'a pas prouvé son efficacité
- L' arrêt précoce (desescalade) est-il possible?

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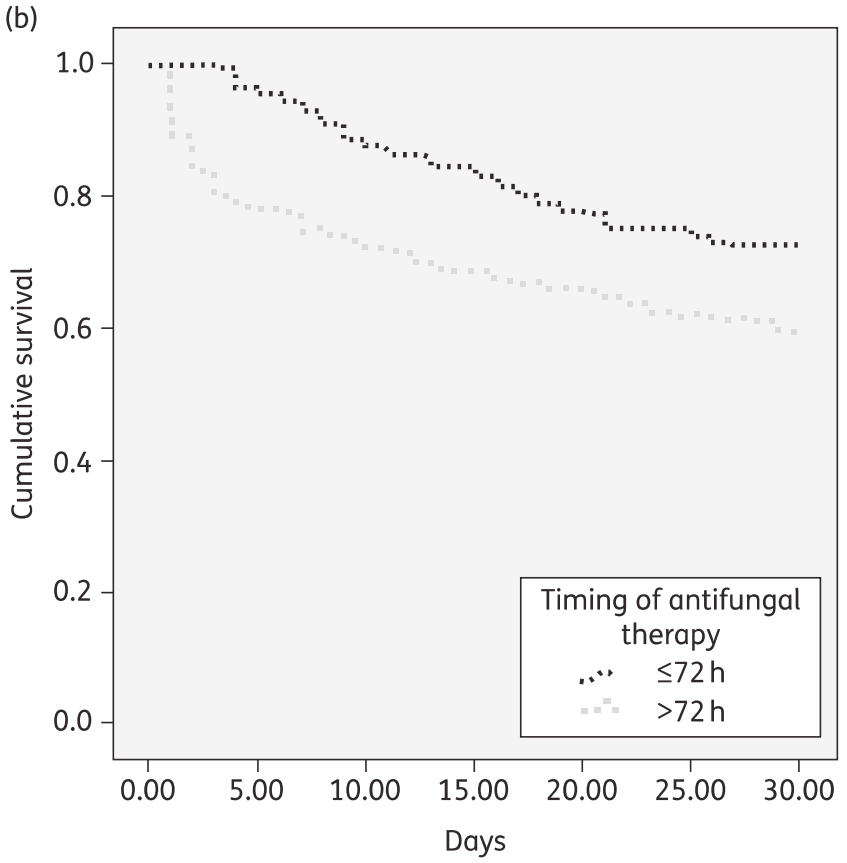
Journal of Antimicrobial Chemotherapy

Timing of susceptibility-based antifungal drug administration in patients with *Candida* bloodstream infection: correlation with outcomes

Shellee A. Grim[1,2]*, Karen Berger[1]†, Christine Teng[3], Sandeep Gupta[4], Jennifer E. Layden[2], William M. Janda[5] and Nina M. Clark[2]

Appropriate therapy	*n*=349
fluconazole	177
400 mg/day[a]	
800 mg/day[b]	
echinocandin (for all *Candida* species)	125
caspofungin 70 mg ×1 then 50 mg daily	
micafungin 100 mg daily	
amphotericin B (for all *Candida* species except for *C. lusitaniae*)	41
≥0.5 mg/kg/day amphotericin B deoxycholate	
≥3 mg/kg/day lipid formulation of amphotericin B	
voriconazole (for all *Candida* species except for *C. glabrata*)	6
6 mg/kg every 12 h ×2 doses then ≥3 mg/kg twice daily	
posaconazole (for all *Candida* species except for *C. glabrata*)	0
Inappropriate therapy	*n*=97
no antifungal therapy	55
insufficient fluconazole	42
<400 mg/day for fluconazole-susceptible isolates	21
<800 mg/day for fluconazole-SDD isolates	11
<800 mg/day for *C. glabrata* without susceptibilities	3
fluconazole-resistant isolate	5
infection caused by *C. krusei*	2
amphotericin B for *C. lusitaniae*	0
Unable to assess appropriateness	*n*=1
voriconazole for *C. glabrata* without antifungal susceptibilities	1
posaconazole for *C. glabrata* without antifungal susceptibilities	0



Early antifungal treatment: a mouse model

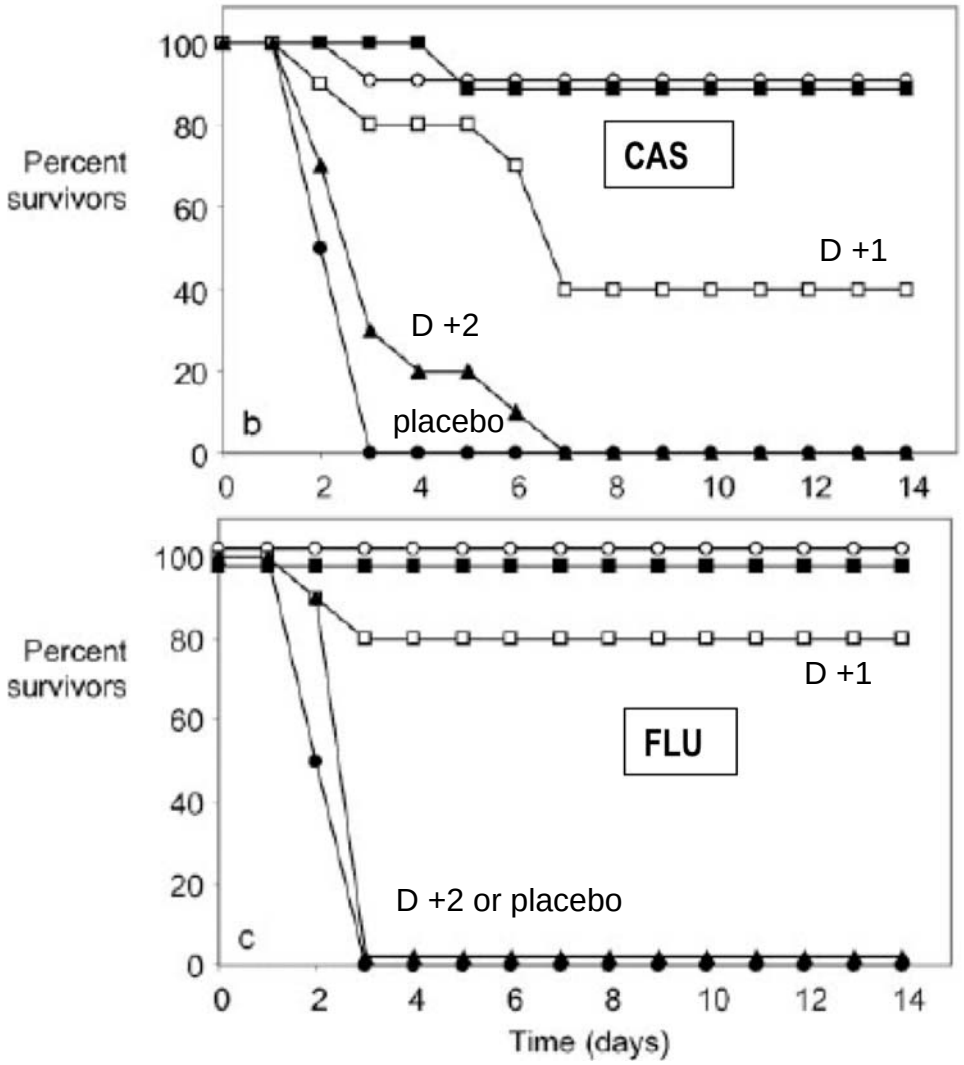
- Challenge with 2 X 10^4 and 10^5 *C albicans* intravenously
- Treatment at D-1, Day0, Day1, 2 and 3
- AmB, Flu, CAS
- 12 mice per experiments

Placebo ●

Start d-1 ❍ Start d0 ■

Start D+1 □ Start D+2 ▲

Example of the 10^5 challenge

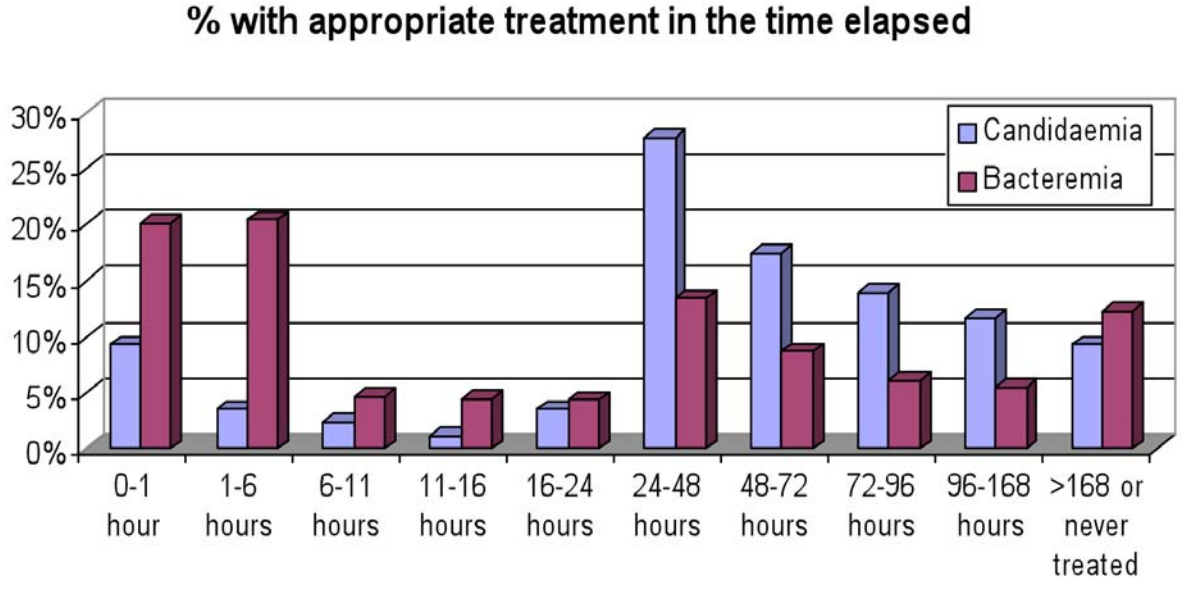


Mac-Callum AAC; 2004: 4911-4914

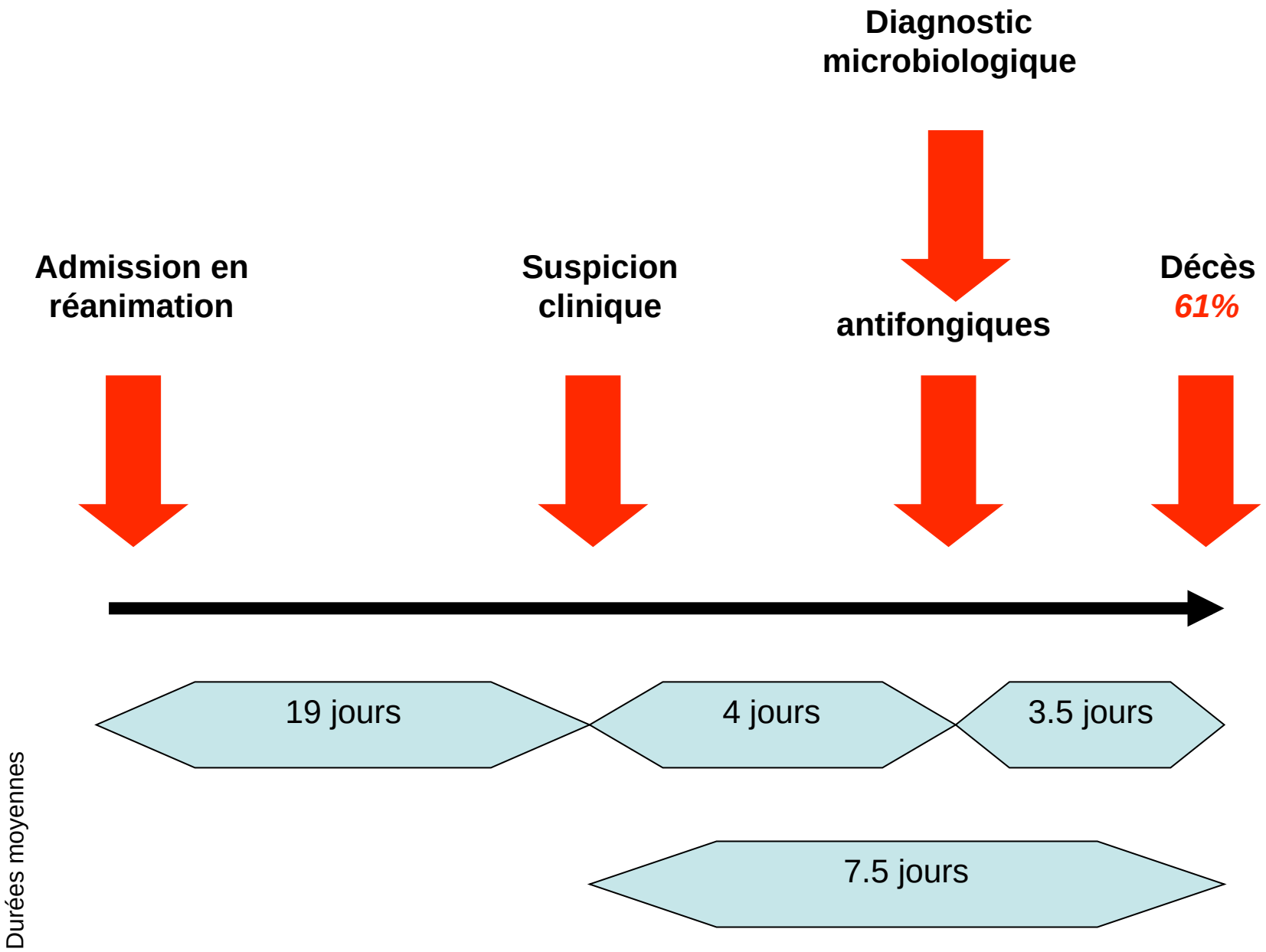
Dans les septicémies de réanimation, les candidémies sont traitées avec retard

Eurobact

p<0.001



Tabah A et al – Intens Care Med 2012 submitted



Bougnoux et al. Intensive Care Med 2007

En cas de candidémies ou de candidoses prouvées, le traitement ne se discute pas…

Pensez:

Cathéters
ETT, ETO
FO

PK/PD

Spectre antifongique

	Polyènes	Fluco	Itra	Vorico	Posaco	Candines
C. albicans	+	+	+	+	+	+
C. krusei	+	-	+/-	+	+	+
C. glabrata	+	+/-	+/-	+	+	+
Cryptocoque	+	+	+	+	+	-
Aspergillus spp	+	-	+	+	+	+
Zygomycetes	+	-	-	-	+	-
Fusarium spp	+	-	-	+/-	+/-	-

and flucytosine…?

In vitro susceptibility testing :
C. albicans 97 % ; *C. glabrata* 99 % ; *C. krusei* 5 %

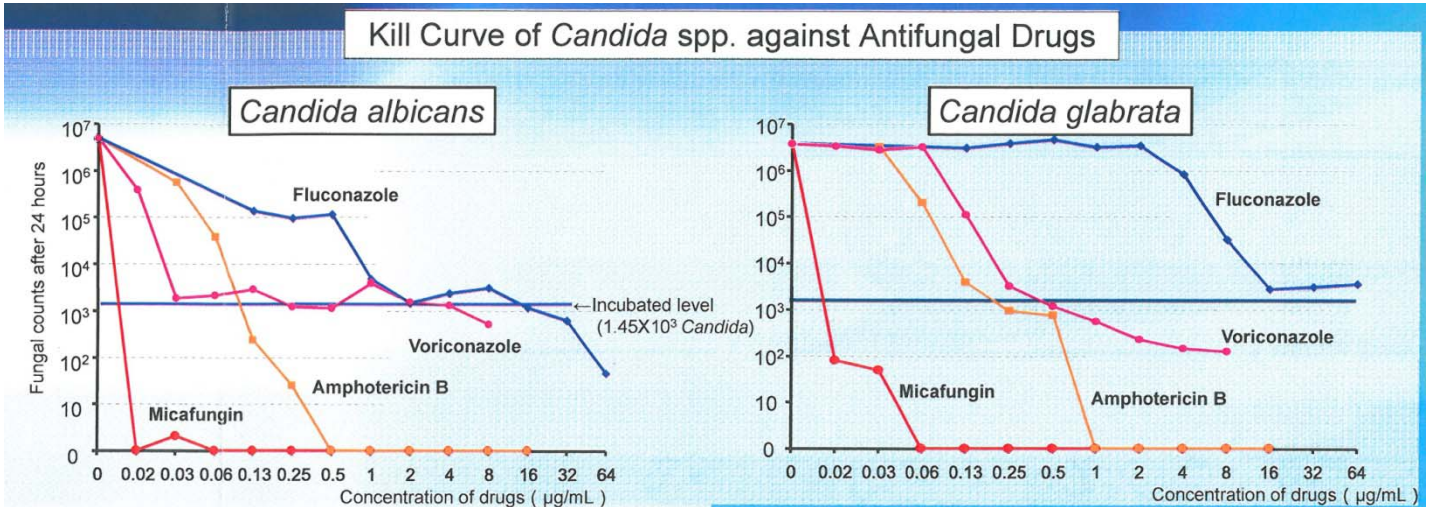
Pfaller MA et al. *AAC* 2002; 46: 3518-21.

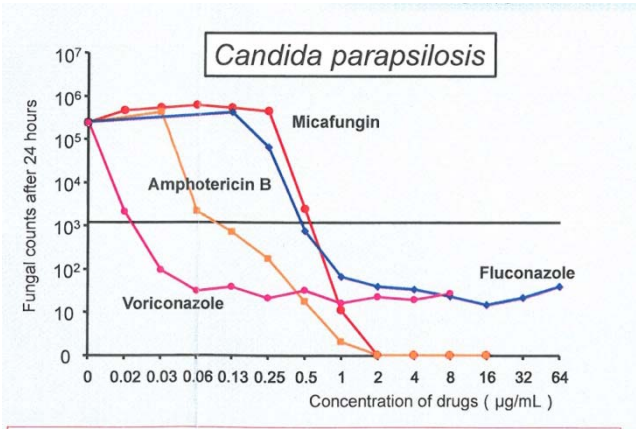
- **When combining flucytosine ? [+ AmB]**
  - **Some clinical sites (meningitis, endocarditis, urosepsis, ± eye ± bone)**
    [IDSA guidelines; Pappas et al. *CID* 2004]

- **Role of caspofungin + 5FC in severe candidiasis ? (peritonitis, endocarditis)**

Choukroun, Transplantation 2006, MYCENDO study France

Fongicidide *vs.* fongistatisme

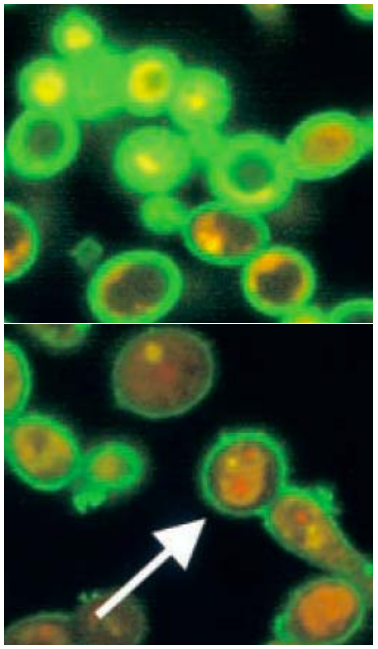




Ohge *et al A1-032.* ICAAC 2010

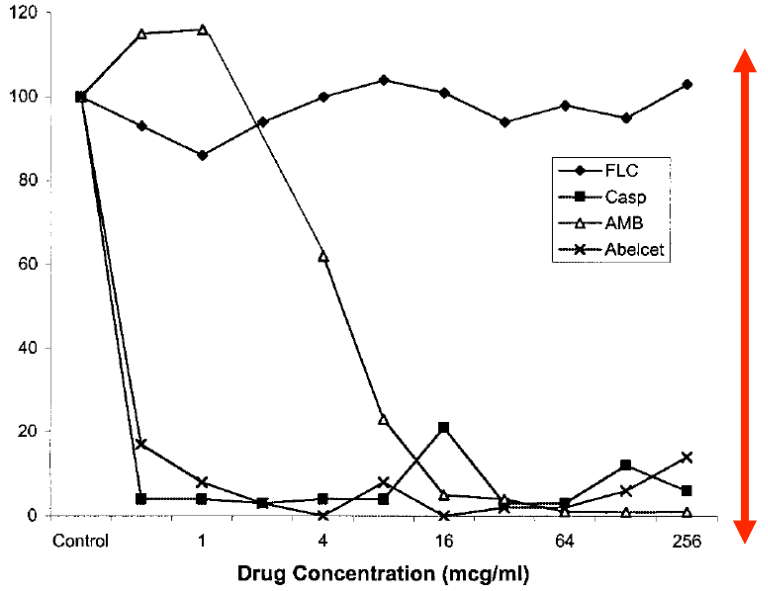
Activité sur le biofilm

Candida species	Patients infected by biofilm-positive isolate		Patients infected by biofilm-negative isolate		OR (95% CI)	*P*[a]
	Total no.	No. (%) who died	Total no.	No. (%) who died		
C. albicans	38	32 (84.2)	130	65 (50)	3.90 (1.72–8.83)	<0.001
C. parapsilosis	14	10 (71.4)	50	14 (28)	4.16 (1.46–11.82)	0.003
C. tropicalis	20	8 (40)	8	4 (50)	0.88 (0.54–1.45)	0.62
C. glabrata	6	4 (66.6)	20	11 (55)	1.46 (0.32–6.62)	0.61
Other[b]	2	2 (100)	6	4 (66.6)		0.34
Total	80	56 (70)	214	98 (45.7)	2.76 (1.55–5.00)	<0.001



Casp

FLC



Tumbarello et al JCM 2007; 45:1843

RCTs : to make a long story short

- FLUCONAZOLE 400 mg/d is not inferior to AmB deo 0.5-0.6 mg/kg/d

  REX et al 1994 (237: 1989-1993)

- CASPOFUNGIN 50mg/d is not inferior to AmB deo 0.6-0.7 mg/kg/d

  C has a better success rate at EOT

  MORA-DUARTE et al 2002 (239: 1997-2001)

- VORICONAZOLE 6 mg/k/d is not inferior to AmB deo 0.7-1 mg/kg/d

  KULLBERG et al 2005 (422: 1998-2003)

- ANIDULAFUNGIN 100 mg/d is not inferior to FLUCONAZOLE 400 mg/d in non *C krusei* invasive candidiasis.

  In a secondary planned analysis C was better than F especially for C *albicans and C tropicalis*

  REBOLI et al – 2007 (245: 2003-2004)

- MICAFUNGIN (100mg/d) is equivalent to L-AmB (3mg/kg/d)

  KUSE et al 2007 (264: 2003-2004)

- MICAFUNGIN (100 mg/d) is equivalent to CASPOFUNGIN (50 mg/d)

  PAPPAS et al – 2007 (595: 2004-2006)

TABLE 6. DRUG-RELATED ADVERSE EVENTS AND OTHER SAFETY END POINTS.

VARIABLE	CASPOFUNGIN (N=114)	AMPHOTERICIN B (N=125)	P VALUE
	no./total no. (%)		
Clinical events	33/114 (28.9)	73/125 (58.4)	0.002
Chills	6/114 (5.3)	33/125 (26.4)	0.003
Fever	8/114 (7.0)	29/125 (23.2)	0.01
Hypertension	2/114 (1.8)	8/125 (6.4)	
Phlebitis or thrombophlebitis	4/114 (3.5)	6/125 (4.8)	
Tachycardia	2/114 (1.8)	13/125 (10.4)	
Nausea	2/114 (1.8)	7/125 (5.6)	
Vomiting	4/114 (3.5)	10/125 (8.0)	
Tachypnea	0/114	13/125 (10.4)	
Rash	1/114 (0.9)	4/125 (3.2)	
Laboratory abnormalities*	27/111 (24.3)	67/124 (54.0)	0.002
Elevated serum alanine aminotransferase	4/109 (3.7)	10/123 (8.1)	
Elevated serum aspartate aminotransferase	2/108 (1.9)	11/122 (9.0)	
Elevated serum alkaline phosphatase	9/109 (8.3)	19/122 (15.6)	
Elevated total serum bilirubin	3/109 (2.8)	11/124 (8.9)	
Elevated blood urea nitrogen	2/108 (1.9)	19/120 (15.8)	0.02
Elevated serum creatinine	4/109 (3.7)	28/124 (22.6)	0.05
Decreased serum potassium	11/111 (9.9)	29/124 (23.4)	0.04
Decreased hemoglobin	1/111 (0.9)	13/124 (10.5)	
Clinical event or laboratory abnormality	48/114 (42.1)	94/125 (75.2)	0.002
Withdrawal because of adverse event	3/114 (2.6)	29/125 (23.2)	0.003
Infusion-related event	23/114 (20.2)	61/125 (48.8)	0.002
Hypokalemia requiring supplementation within 72 hr after onset	13/114 (11.4)	33/125 (26.4)	0.02
Nephrotoxic effect†	8/95 (8.4)	26/105 (24.8)	0.02

Mora-Duarte et al N Eng J Med 2002

	Micafungin n=264	Liposomal amphotericin B n=267	p value
Treatment-related adverse events			
Serious	11 (4·2%)	20 (7·5%)	0·138
Treatment discontinuation	13 (4·9%)	24 (9·0%)	0·087
Overall	114 (43·2%)	136 (50·9%)	0·082
Hypokalaemia	18 (6·8%)	32 (12·0%)	0·053
Pyrexia	21 (8·0%)	34 (12·7%)	0·087
Rigors	2 (0·8%)	17 (6·4%)	0·0006
Increased blood creatinine	5 (1·9%)	17 (6·4%)	0·015
Nausea	12 (4·5%)	9 (3·4%)	0·513
Back pain	1 (0·4%)	12 (4·5%)	0·003
Vomiting	9 (3·4%)	9 (3·4%)	>0·999
Increased alanine or aspartate aminotransferase concentration	8 (3·0%)	3 (1·1%)	0·140
Infusion-related reaction*	45 (17·0%)	77 (28·8%)	0·001

Kuse et al Lancet 2008

Tolérance & toxicité hépatique…

TABLE 3. Pooled risk estimates of safety outcomes from randomized controlled trials of therapy against invasive fungal infection

Drug(s)	No. of trial arms included	Total no. of patients included	% of patients with:					
			Treatment discontinuation due to adverse effects		Elevation of liver enzyme levels requiring stopping of treatment		Elevation of liver enzyme levels not requiring stopping of treatment	
			Pooled estimate	95% CI	Pooled estimate	95% CI	Pooled estimate	95% CI
Amphotericin B formulations[a]	41	4,775	13.4	8.9–17.8	0.4	0.1–0.8	14.1	10.3–18.0
Itraconazole	3	293	18.8	14.3–23.2	1.5	0–4.0	17.4	3.9–31.0
Fluconazole	10	697	2.2	0–4.6	0.7	0–1.4	9.3	4.0–14.5
Voriconazole	3	881	9.5	2.3–16.8	NA[b]	NA	19.7	16.8–22.6
Anidulafungin	4	251	8.4	3.6–13.1	0.8	0–2.3	2.0	0.3–3.7
Caspofungin	5	1,075	3.8	2.7–5.0	0.2[c]	0.1–0.4[c]	7.0	4.1–9.9
Micafungin	3	666	3.6	2.2–5.0	2.7	0.7–4.6	3.0	1.0–5.1

Wang et al. Antimicrob Agent Chemother 2010

Traitement curatif candidémies

Avant identification

Tous patients	**ECIL**	**IDSA**
– Candines	**A1**	**A1 (**si sévère ou expo azolés)**:** **A3**
– Ambisome	**A1**	**si intolérance**
– Autre AmB-L	**A2**	**Non**
– AmB-D	**Non**	**A1** (ressources limitées)
– Fluconazole *	**A1**	**A1** (peu sévère et pas d'expo): **A3**
– Voriconazole **	**A1**	**Non**

*: hors sévère ou proph azolé° **: pas si proph azolé

Après identification

- *C.albicans*: Désescalade fluco **A2**
- *C.glabrata*: candine: **B3**
  - Si tt initial efficace par azolés: continuer: **B3**
- *C.parapsilosis*: fluconazole ou AmB-L: **B3**
- *C.kruzei*: candine ou AmB-L ou vori: **B3**

Pappas CID 2009
Herbrecht ICHS 2009

Recommandations Europe 2011
Candidoses invasives en réanimation (non publié)

- Candidémies avant identification
  - Candines **A1**
  - AmB-L ou Vorico **B1**
  - AmB deo **non**
  - Fluco **C1**
- Désescalade à J10

ECCMID 2011

Impact of treatment strategy on Outcomes

Andes DR et al – Clin Infect Dis 2012; 54:1110

1915 patients/ 7 RCTs (15 years)/54% ICU/84% BSI/9% neutropenia

Table 4. Multivariate Analysis of Host, Disease, and Treatment Factors and Outcome in Patients With Invasive Candidiasis

	Mortality				Success		
Organisms[a]	Factor	*P*	OR	95% CI	Factor	*P*	OR	95% CI
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
	Study	NS			Study	NS		
Candida glabrata (n = 104)	CVC removed	.001	0.13	.04–.45	APACHE II score	.05	0.95	.90–.99
	Study	NS			Echinocandin	.05	2.63	1.10–625
					Study	NS		

Limitations

- Patients enroled in RCTs are not the ones treated in ICU (empiric therapy+++)
- Advances in care between the early 90s (polyenes, azoles) and the 21st century
- NO exprapolation to
  - Meningitis encephalitis (PK)
  - Endophtalmitis (PK)
  - Urosepsis (PK)
  - Endocarditis (limited data)
  - Breakthrough infections (selection pressure)
- Polyenes…

Adapted from Clancy J & Nguyen MH CID 2012; 54:1123

PK-Caution

- Severe patients → increase of VD distribution
- Interaction: azoles and candins
- Unpredictable variability of the concentration certainly (azoles) or probably (candins, polyenes) associated with efficacy and toxicity
  - VRZ, PCZ
  - 5 FC (tox)
  - Candins?

Impact of treatment strategy on Outcomes

Andes DR et al – Clin Infect Dis 2012; 54:1110

Catheter removal

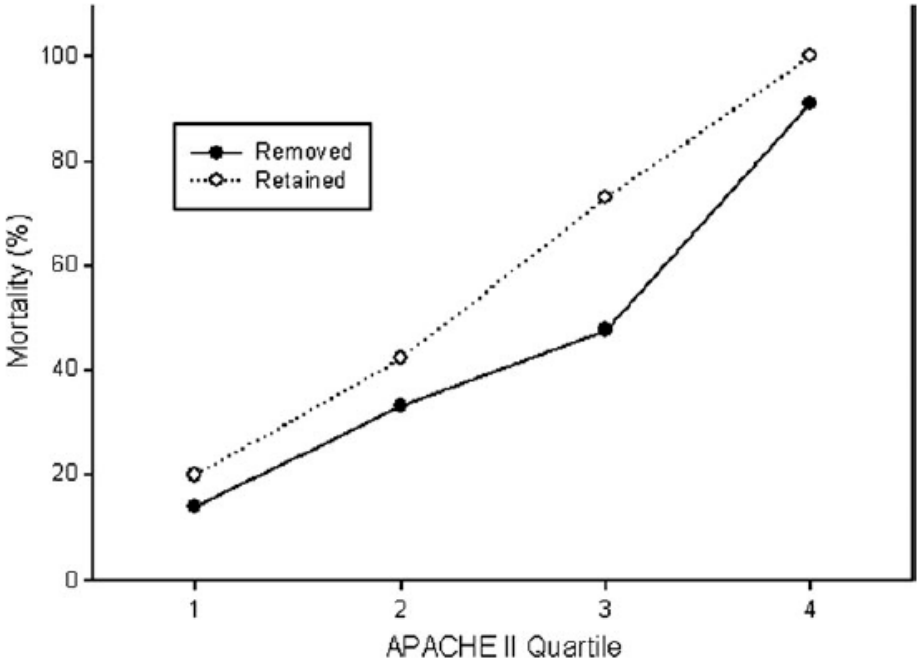


Figure 1. Impact of severity of illness and central venous catheter (CVC) management on patient mortality. Each symbol represents the mortality rate as a percentage for patients in 1 of 4 Acute Physiology and Chronic Health Evaluation (APACHE) II score quartiles: quartile 1, 0–11; 2, 12–23; 3, 24–35; and 4, 36–47. Closed symbols represent patients with CVC removal; open symbols, patients with CVC retention. Differences in mortality were statistically significant for quartiles 1, 2, and 3 (quartile 1, $P = .05$; 2, $P = .01$; 3, $P = .002$; and 4, $P = .41$).

Agenda

- La candidose invasive en réanimation est une maladie grave souvent traitée de manière inadéquate- le traitement précoce d'unecandidose prouvée ne se discute pas
- **Diagnostic difficile, colonisation et scores aboutissent à un sur-traitement**
- Le traitement des malades colonisés ou des malades septiques avec des facteurs de risque n'a pas prouvé son efficacité
- Le sur-traitement a des conséquences
- L' arrêt précoce est-il possible?

La candidose invasive est rare, les traitements antifongiques sont fréquents…

- Un jour donné, 17% des patients dans le monde sont considérés comme infectés à levures

EPIC2-

Vincent et al – JAMA 2009

- Un jour donné, en réanimation, 7.5% des malades reçoivent un traitement anti-fongique

Fongiday – Azoulay et al – Crit Care Med 2012

- Dans les séries espagnoles, seulement 22% des TAF sont des traitements curatifs

Leon C, et al. *Eur J Clin Microbiol Iinfect Dis* 2009;28:233–42; Leon C, et al. *Crit Care Med* 2009;37:1624–33

- Sur 8 mois, 101 centres (>5000 pat) → 271 IFI !!

Armarcand – Leroy O et al – Crit Care Med 2009

- Les candidémies représentent 7% des septicémies (0,3% des patients)

Rea-Raisin 2009

Examens diagnostiques

- Hémocultures
  - tardives ou négatives (C glabrata, coinfection bactérienne, antifongiques préalables)
  - Milieux spécifiques+++
- Mannane/antimanane: valeur du couple…
- BD glucan
  - Non spécifique
  - Peu de données en dh de l'hématologie
  - En réanimation cohorte avec 10-15 cas d'IFI prouvée ou non..
  - Faux positifs + (bactériémie, albumine, pansement de paroi, hémodialyse)
- PCR
  - Variable en f^n de la technique utilisée…

Les déterminants de la décision thérapeutique

Facteurs de risque
Immunodépression
Chirurgie
Procédures
Antibiotiques
Hémodialyse, CS
Durée de séjour

Sepsis

Défaillance viscérale

Histoire fongique
Colonisation
Biomarqueurs (BD glucane, PCR)
Candidémie ou CI prouvée

La colonisation à Candida

- Concerne 75% des patients ventilés depuis 7 jours
- Le nombre de sites et l'intensité de la colonisation augmente le risque d'IFI
- La colonisation trachéale est le reflet de la colonisation oropharyngée est n'est pas associée à la pneumonie à candida chez les patient non-neutropénique

Leon et al - Crit Care Med 2006 and Crit Care Med 2009; Charles et al ICM 2005; Pelz Ann Surg 2001; Pittet Ann Surg 1994; Meersseman et al. ICM 2009

Candida score (≥7 jours)

- **Construction n =1699 pts (Leon CCM 2006)**
  - Parenteral nutrition 1pt OR = 2,48 IC95:1,16 - 5,31
  - Surgical admission 1pt OR = 2,71 IC95:1,45 - 5,06
  - Multiple Colonization 1pt OR = 3,04 IC95:1,45 - 6,39
  - Severe sepsis 2pts OR = 7,68 IC95:4,14 - 14,22
- **External Validation n =1107 pts (Leon CCM 2009)**

	***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 (60.0-83.9)
Specificity	66.2 (63.0-69.4)	47.4 (44.0-50.8)
Positive predictive value	13.8 (10.0-17.5)	8.7 (6.2-11.3)
Negative predictive 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)

PPV (*Candida* score)=Proba (Dis+/CS +) = 13.8%…
PPV (Colonization index)=Proba (Dis/CI+) = 8.7%…

Leon et al - Crit Care Med 2006; 34:730–737 and Crit Care Med 2009; 37:1624 –1633

Systemic antifungal therapy in critically ill patients without invasive fungal infection

Elie Azoulay, MD, PhD; Hervé Dupont; Alexis Tabah; Olivier Lortholary; Jean-Paul Stahl; Adrien Français; Claude Martin; Bertand Guidet; Jean-François Timsit; on behalf of the French Society for Critical Care (SRLF) in Collaboration With the French Society for Infectious Diseases (SPILF) and the French Society for Anesthesia and Intensive Care (SFAR)

Crit Care Med 2012 (40) Epub ahead of print

Table 2. Factors associated with systemic antifungal treatment[a]

Effect	Odds Ratio	95% Confidence Interval Minimum	95% Confidence Interval Maximum	$p > F$
Patient-related variables				
Emergency surgery	2.4014	1.420	4.062	.0011
Hematologic malignancies	7.1390	3.268	15.597	<.0001
From intensive care unit admission to the study day				
Candida colonization	12.3905	7.342	20.911	<.0001
Severe sepsis and septic shock	4.6872	2.554	8.602	<.0001
Intensive care unit-related variables				
Hospital with ≤800 beds	2.9971	1.452	6.187	.0033
Prescription practices such as widespread use of fluoroquinolones	2.3653	1.280	4.370	.0063
Organ transplant activity	2.6411	1.255	5.556	.0109
More than 3 patients with intensive care unit-acquired candidemia in 2007	1.9126	1.037	3.528	.0381
Routine SAT use in case of[b]				
Hospital-acquired sepsis and risk factors for candidemia	1.9714	0.967	4.018	.0615
Hospital-acquired sepsis with microbiological documentation	2.2173	0.983	5.003	.0551
Hospital-acquired sepsis without microbiological documentation	2.0995	1.120	3.934	.0209
		Estimate	SE	
Covariance parameter	N_Center	0.6316	0.2964	

[a]The hierarchical logistic model included the 100 patients receiving systemic antifungal treatment and excluded the 54 patients with documented invasive fungal infections; [b]this information was extracted from the intensive care unit characteristics questionnaire completed by the local investigators before the study day.

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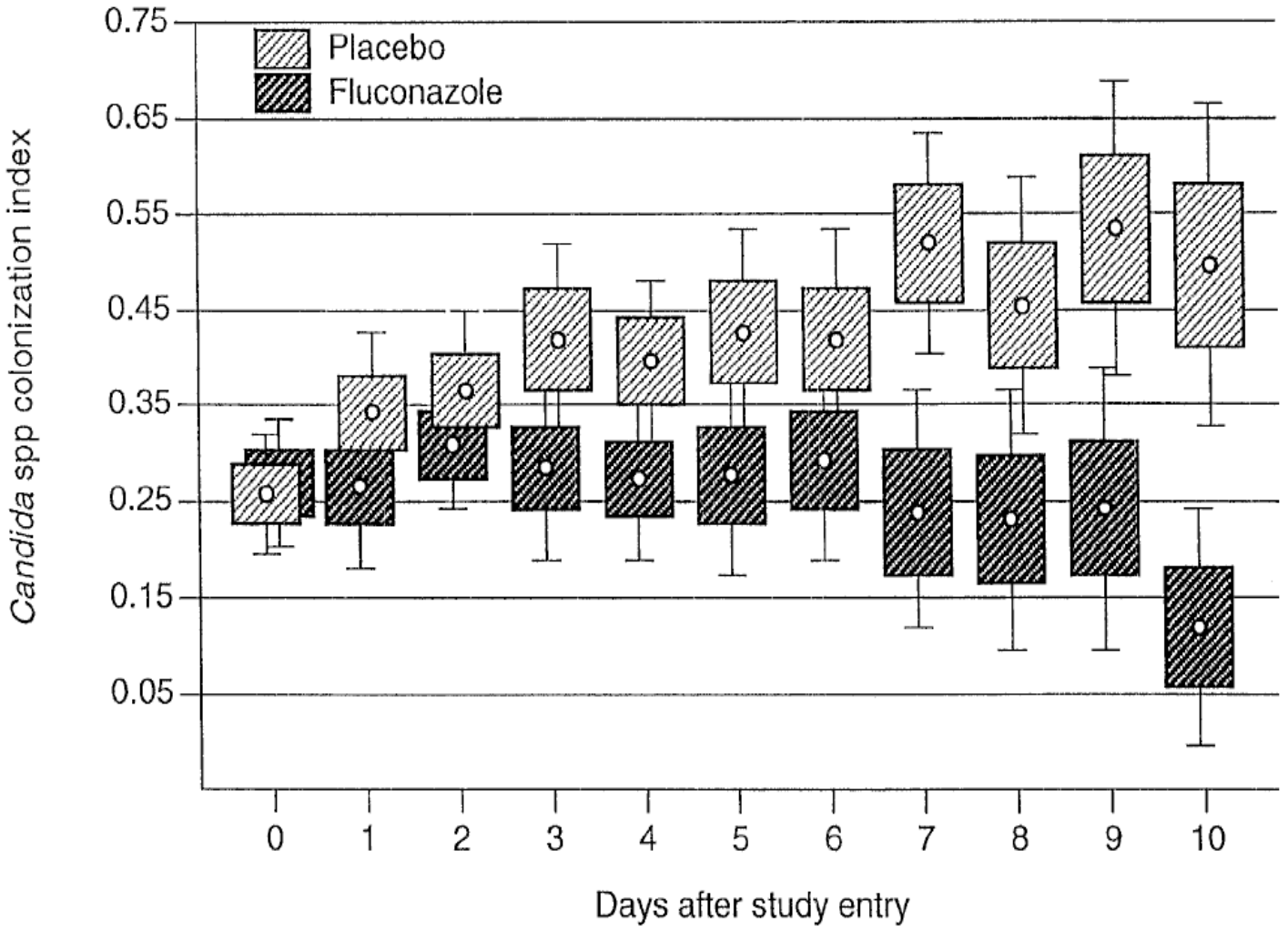
Treatment of colonized patients in ICU?

- **No RCTs**

SAT decreased colonization index



Garbino, Intensive Care Med 2002

Assessment of preemptive treatment to prevent severe candidiasis in critically ill patients

- Before/after study SICU>4 days
  - 8/98-7/00: no treatment, colonization sampled not known
  - 12/00-11/02: screening and known results
    - 5 samples (trachea, gastric, urine, oropharyngeal, rectal)
    - Admission then 1/week
    - + if « highly » positives: (>100 ou 10^5 CFU according to samples)
    - Corrected colonization index:

$$\frac{\text{\# highly positive samples}}{\text{\# samples}}$$

  - Patients colonised with CCI ≥ 0,4
    - 20% of the cohort:
    - fluconazole: 800 mg D1 and then 400 mg/j IV x 14days

R. Piarroux et Al - Crit Care Med 2004; 32:2443–2449

Assessment of preemptive treatment to prevent severe candidiasis in critically ill patients

Table 1. Characteristics of patients included during the two periods of the study

Characteristics of Patients	Retrospective Cohort n = 455	Prospective Cohort n = 478	*p*
Overall SICU mortality, n (%)	76 (16.7)	73 (15.3)	.55
Nonseptic conditions	47 (10.3)	49 (10.3)	.96
Septic conditions[a]	29 (6.4)	24 (5.0)	.37
Bacterial infections	8 (1.8)	6 (1.3)	.53
Candidiasis	7 (1.5)	2[b] (0.4)	.10
Aspergillosis	—	2 (0.4)	.49
Undocumented sepsis[c]	14 (3.1)	14 (2.9)	.89
Occurrence of proven candidiasis, n (%)	32 (7)	18 (3.8)	.03
Diagnosed at admittance (imported cases)	22 (4.8)	18 (3.8)	.42
SICU-acquired[d]	10 (2.2)	0	<.001

R. Piarroux et Al - Crit Care Med 2004; 32:2443–2449

Empirical fluconazole vs placebo

- RCT double blind Fluconazole 200 mg (n=18) vs placebo (n=19)
- Septic shock with nosocomial pneumonia or intra-abdominal sepsis

30-days death: Fluco 22% vs Placebo 54% p = 0,015

Pneumonia			Intra-abdominal		
Fluco		Placebo	Fluco		Placebo
28%	(ns)	42%	14%	P=0,013	65%

But only one candidemia! And parameters imbalanced

	Fluco		Placebo
Immunocompromised	4		8
Organ dysfunctions	1,7	P=0,01	2,8

Jacobs S et al. CCM 2003

Empirical Fluconazole vs Placebo for ICU Patients

- Double blind randomized placebo-controlled trial: 270 adults, 6 years
- Fluconazole: 800 mg vs placebo 2 weeks if:
  - > 18 years old
  - ICU duration > 96h
  - Apache 2 > 16
  - Temperature > 38,3°within 72 hours
  - Received large spectrum antibiotics for at least the 4 to 6 previous days
  - Central venous catheter
  - 50% medical ICU
- Assessment criteria = composite score
  - Initial fever resolution
  - No emerging IFI
  - No toxicity-related trial stopping
  - No use of another systemic AF

Schuster et Al, Ann Intern Med . 2008 Jul 15;149(2):83-90

Empirical Fluconazole vs Placebo for ICU Patients

Patient Characteristics at Baseline		
characteristics	**Fluconazole recipients (n=122)**	**Placebo recipients (n=127)**
Mean age (SD), y	53 (19)	51 (19)
Women, n (%)	29 (24)	28 (22)
Median previous ICU stay (range), d	9.5 (4-171)	9 (4-57)
Median previous hospital stay (range), d	11 (5-173)	11 (4-58)
Median baseline APACHE II score (range)	22 (9-28)	20 (11-42)
Corticosteroids, n (%)	19 (16)	15 (12)
Total parenteral nutrition, n (%)	70 (57)	65 (51)
Renal insufficiency, n (%) †	70 (57)	65 (51)
Colonized with yeast in ≥1 site, n (%)	28 (23)	24 (19)
Diabetes mellitus, n (%)	23 (19)	26 (20)
Cancer, n (%)	12 (10)	8 (6)
Surgery within 7 d before study entry, n (%)	65 (53)	65 (51)

Schuster et Al, Ann Intern Med. 2008 Jul 15;149(2):83-90

Empirical Fluconazole vs Placebo for ICU Patients

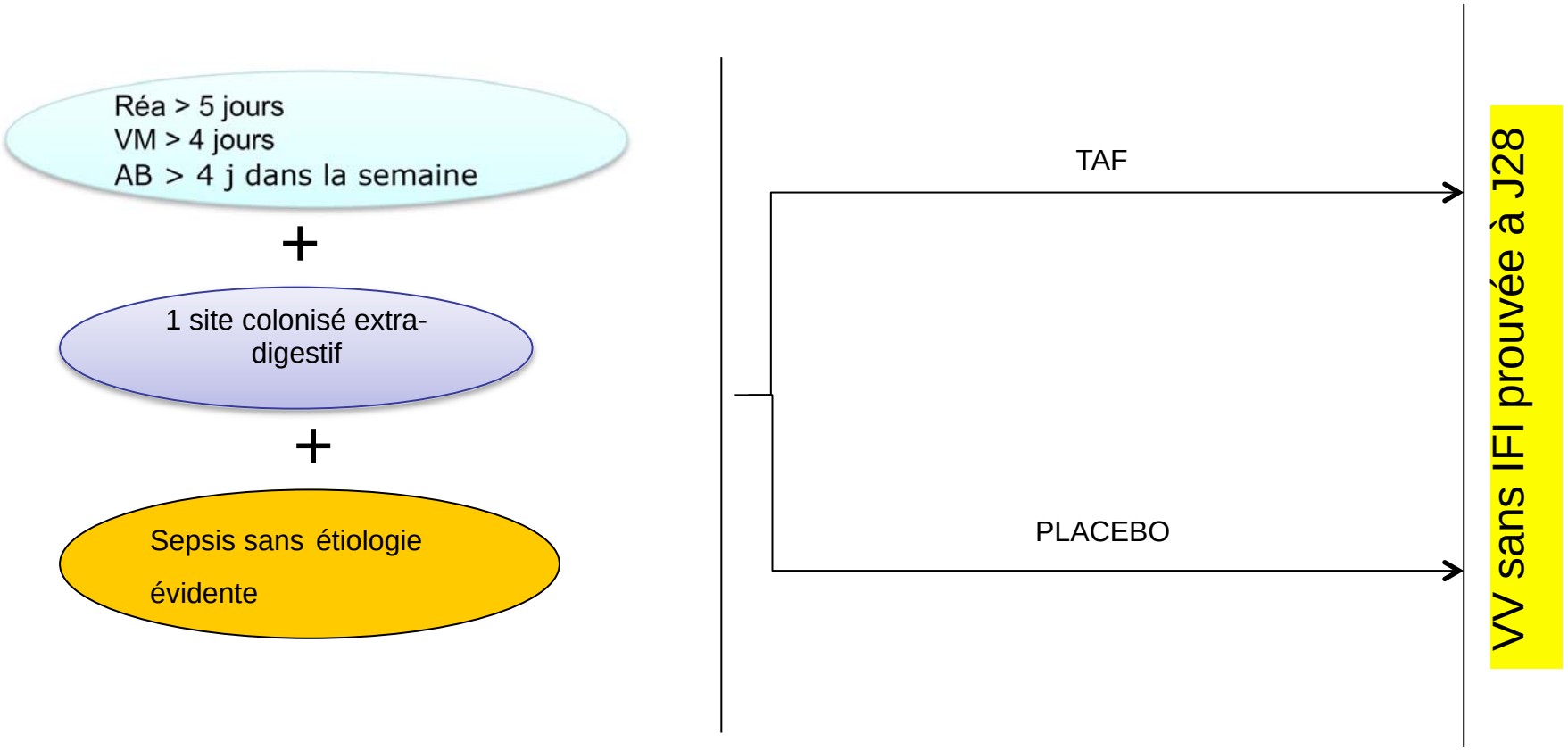
- Overall success:
  - fluconazole: 36% vs PCB 38% (RR 0,95 IC95:,69-1,32)

	F	vs	Placebo
• Per item			
– Initial fever resolution	49	vs	46%
– Candidaemia	0	vs	2
– Emerging IFI	5	vs	9%
– Other systemic AF	10	vs	16%
– Death	24	vs	17%

- N.B.: all IFIs occur in colonized patients

Schuster et Al, Ann Intern Med . 2008 Jul 15;149(2):83-90

Faut –il traiter les malades colonisés avec un sepsis qui ne fait pas sa preuve??



Critères secondaires: PK , survie J28, survie sans TAF à J28, colonisation, tests diagnostiques

Agenda

- La candidose invasive en réanimation est une maladie grave souvent traitée de manière inadéquate- le traitement précoce d'unecandidose prouvée ne se discute pas
- Diagnostic difficile, colonisation et scores aboutissent à un sur-traitement
- Le traitement des malades colonisés ou des malades septiques avec des facteurs de risque n'a pas prouvé son efficacité
- **Le sur-traitement a des conséquences**
- L' arrêt précoce est-il possible?

Impact de la prescription sur les ecosystèmes et les CMIs

- Impact de l'exposition préalable aux candines et au fluconazole sur les espèces et les CMI aux azoles et au fluconazole isolé des candidémies

  Lortholary O et al – AAC 2011

  Forrest GN et al – J infect 2008; 56:126

- Diminution du fluconazole prophylactique → diminution des candidémies à *non albicans*, pas d'augmentation des *C albicans*

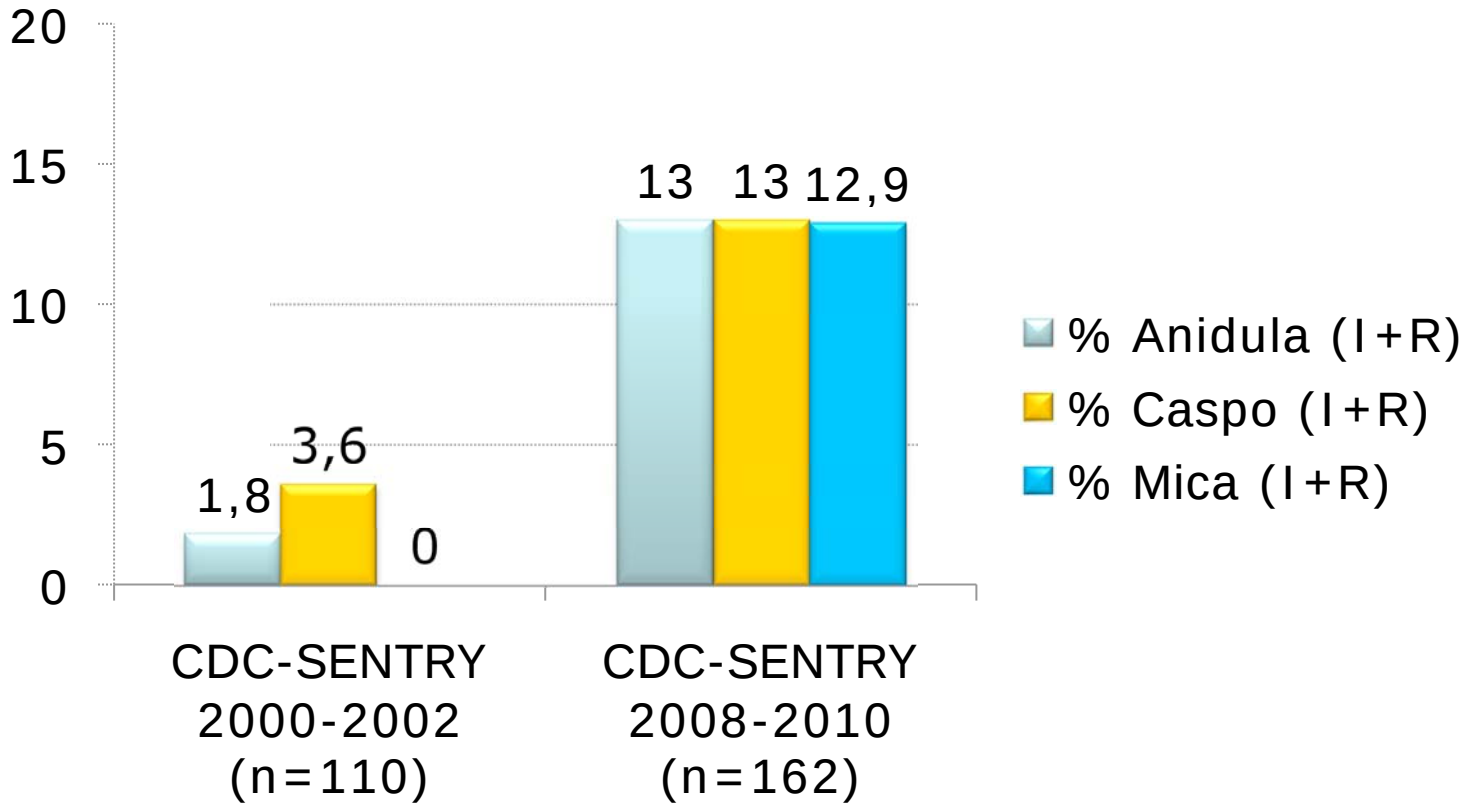
  Bassetti et al – JAC 2009; 64:625-629

- Impact immédiat sur les CMI au sein de chaque espèce colonisantes ou infectantes en réanimation

  Fournier P et al – JAC 2011

Decreased Susceptibility and Resistance to Echinocandins Among Fluconazole-Resistant Bloodstream Isolates of *Candida glabrata*

Pfaller et al – JCM E pub 25 janv 2012



a. CLSI document M27-A3 (8). Fluconazole resistance defined as an MIC ≥64 µg/ml.
b. Number of isolates for which the echinocandin MICs were intermediate (I; anidulafungin and caspofungin MIC 0.25 µg/ml, micafungin MIC 0.12 µg/ml) or resistant (R; anidulafungin and caspofungin MIC ≥0.5 µg/ml, micafungin MIC ≥0.25 µg/ml.)

Candida spp. with Acquired Echinocandin Resistance, France, 2004–2010[1]

Eric Dannaoui,[2] Marie Desnos-Ollivier,[2]
Dea Garcia-Hermoso, Frédéric Grenouillet,
Sophie Cassaing, Marie-Thérèse Baixench,
Stéphane Bretagne, Françoise Dromer,
Olivier Lortholary,
and the French Mycoses Study Group[3]

- 20 résistances acquises *(C albicans 10, C glabrata 8, C krusei 2)*
- 12/20 souches mutées (non *parapsilosis/guillermondi*)
- 19/20 après pré-exposition aux candines
- Rare: 0.4% surveillance+++

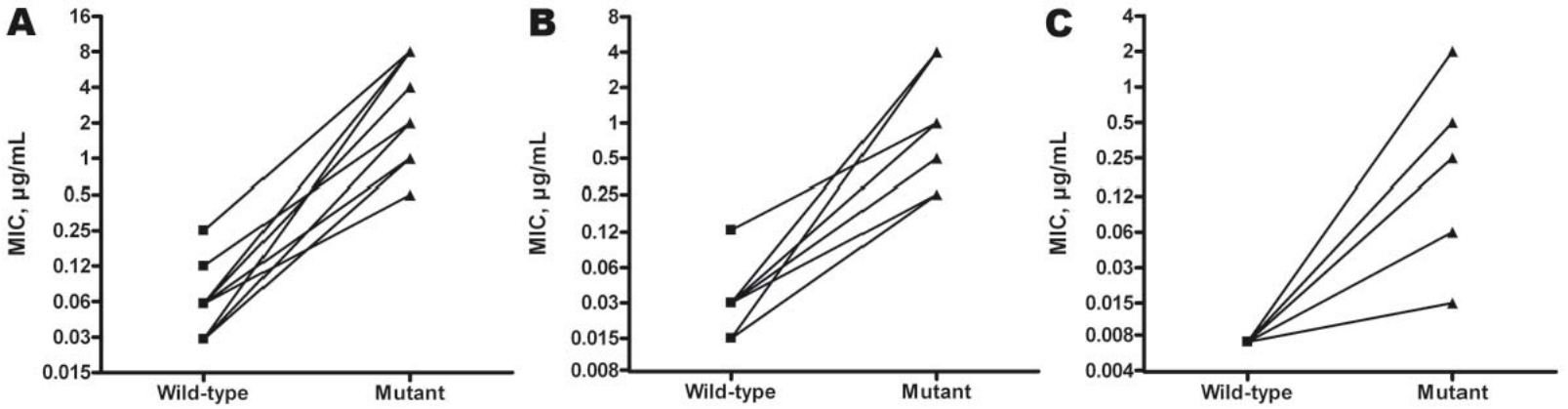


Figure. Corresponding caspofungin (A), micafungin (B), and anidulafungin (C) MICs in 12 Fksp mutant *Candida* spp. isolates and their wild-type parent isolates, France, 2004–2010. Susceptibility testing was performed by using the European Committee for Antimicrobial Susceptibility Testing method (*6*) and AM3 medium (*7*).

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 18, No. 1, January 2012

Les antifongiques doivent être épargnés

- Pensez antifongiques avec les mêmes règles que pour les antibiotiques
  - Efficacité (attention PK en réa++)
  - Sécurité (pour le patient, pour l'écosystème)
  - Coûts

Agenda

- La candidose invasive en réanimation est une maladie grave souvent traitée de manière inadéquate- le traitement précoce d'unecandidose prouvée ne se discute pas
- Diagnostic difficile, colonisation et scores aboutissent à un sur-traitement
- Le sur-traitement a des conséquences
- Le traitement des malades colonisés ou des malades septiques avec des facteurs de risque n'a pas prouvé son efficacité
- **L' arrêt précoce est-il possible?**

Arrêt précoce et désescalade?

- La pression de sélection reste avant tout liée aux traitements empiriques qui représente 80% des traitements
- Traitement empirique/probabiliste a rediscuter à J5
- Candines? Desescalade à 10 j dans les ECTs (plus tôt? *C parapsilosis*...)

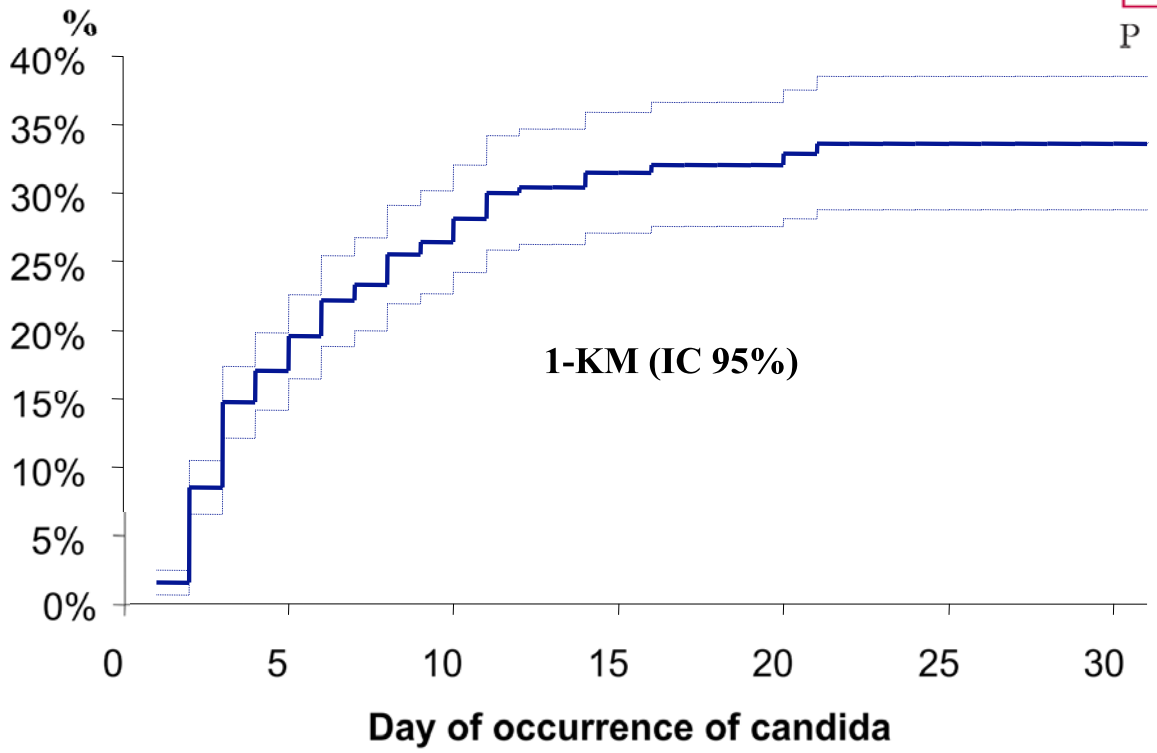
Conclusion: Nous devons apprendre à mieux utiliser les antifongiques…

1. Nous disposons de traitements efficaces des candidémies qui doivent être administrés précocement
2. Les patients de réanimation ont de plus en plus de facteurs de risque
3. La candidémie est un événement rare difficile à diagnostiquer
4. La décision thérapeutique est basée sur le rapport efficacité/toxicité/coût: *se méfier des recettes toutes faites*
5. Les traitements antifongiques entrepris ont des influences sur les écosystèmes fongiques.

Candida Colonization of the Respiratory Tract and Subsequent Pseudomonas Ventilator-Associated Pneumonia*

Elie Azoulay, MD, PhD; Jean-François Timsit, MD, PhD; Muriel Tafflet; Arnaud de Lassence, MD; Michael Darmon, MD; Jean-Ralph Zahar, MD; Christophe Adrie, MD, PhD; Maité Garrouste-Orgeas, MD; Yves Cohen, MD; Bruno Mourvillier, MD; and Benoît Schlemmer, MD; for the Outcomerea Study Group†

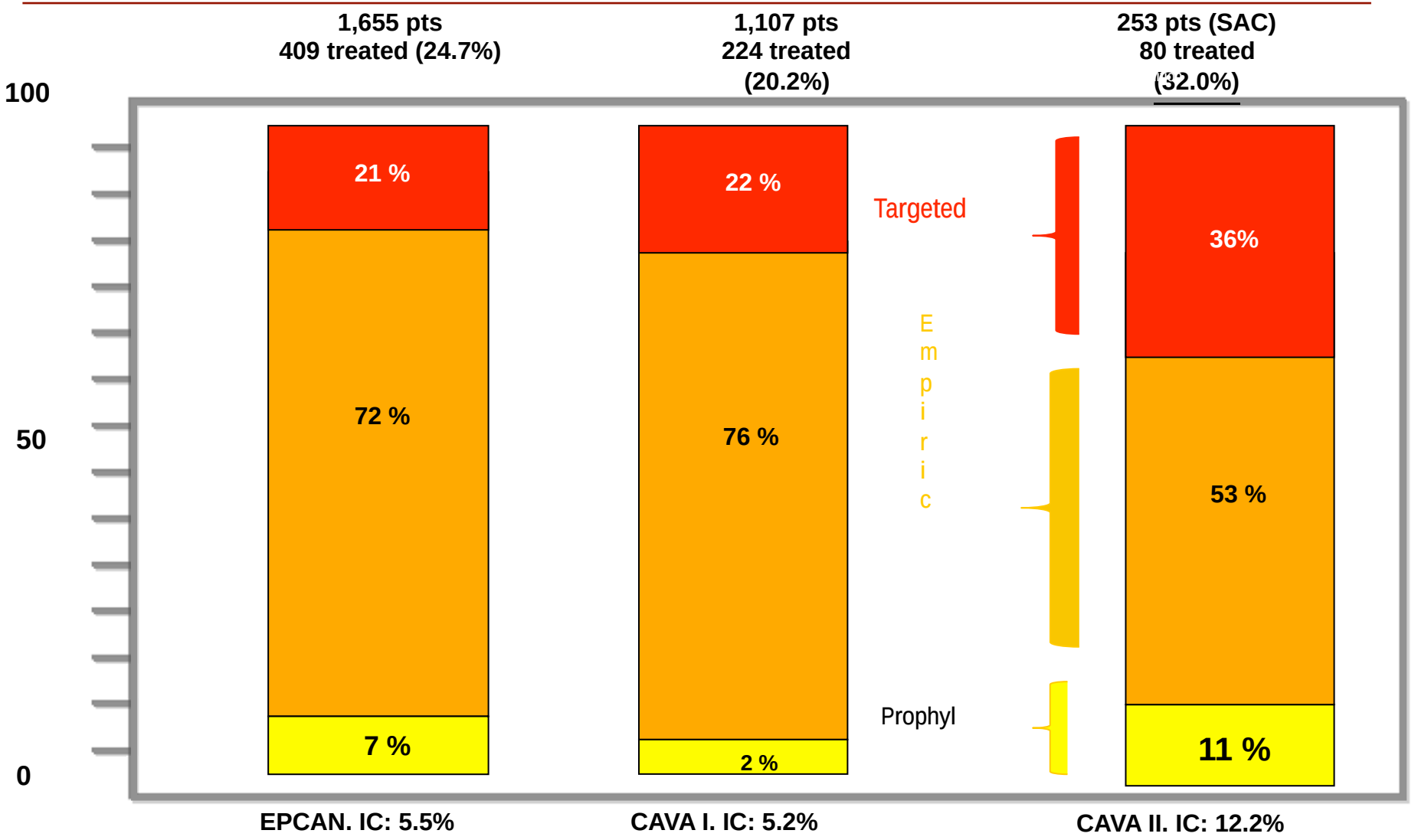
AMERICAN COLLEGE OF CHEST PHYSICIANS



<u>Kaplan-Meier en % :</u>

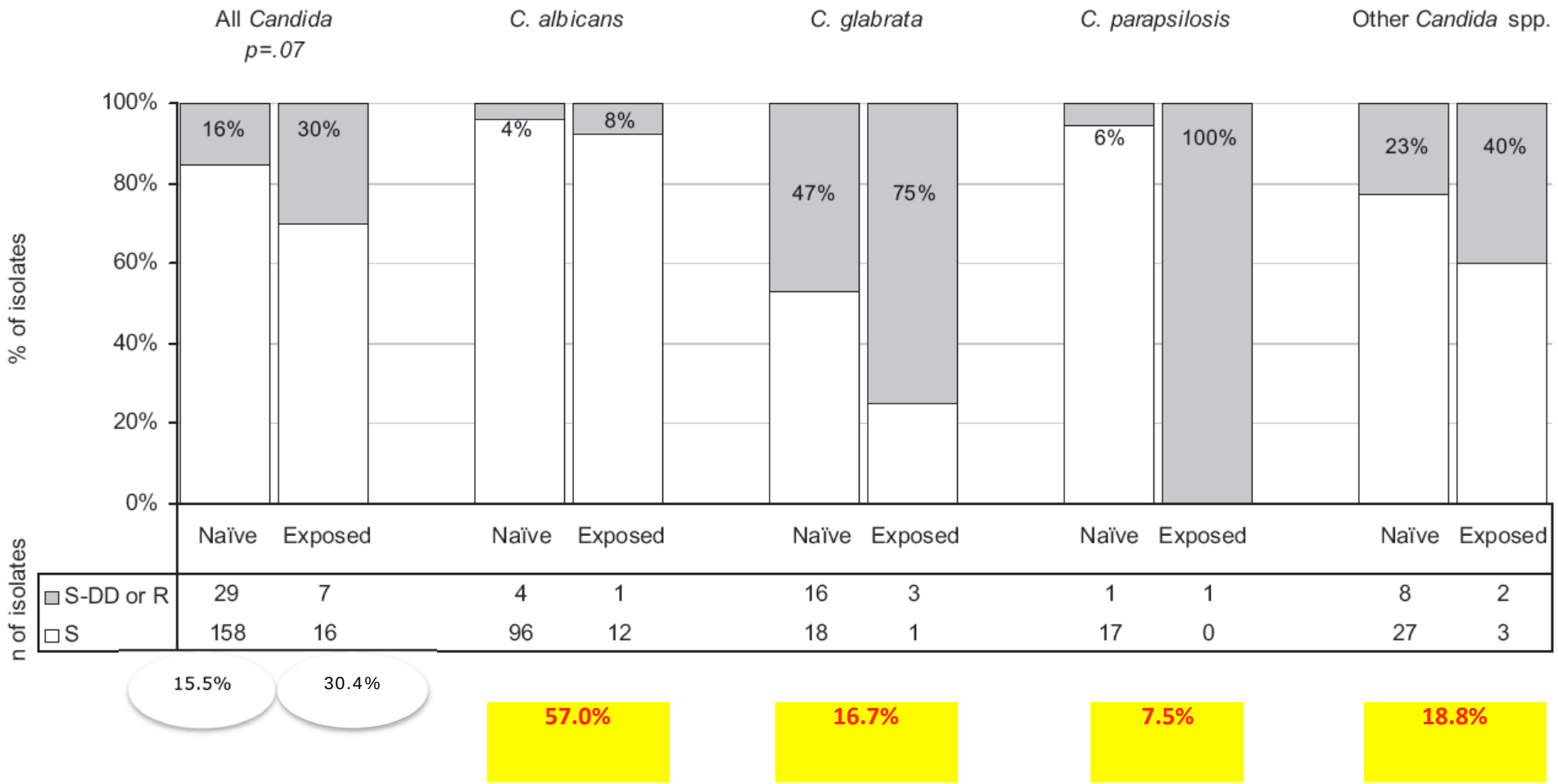
D5 : 19.54 [16.48 ; 22.60]
D10 : 28.14 [24.21 ; 32.07]
D15 : 31.49 [27.10 ; 35.88]
D20 : 32.86 [28.16 ; 37.56]
D30 : 33.66 [28.76 ; 38.56]

Fungal infections in Spanish ICUs: Antifungal therapy



Leon C, et al. *Eur J Clin Microbiol Iinfect Dis* 2009;28:233–42; Leon C, et al. *Crit Care Med* 2009;37:1624–33.

Resistance au fluconazole (ICUs, France 2005-2006)



Leroy O *et al*, Crit Care Med 2009

COMPARISON OF CASPOFUNGIN AND AMPHOTERICIN B FOR INVASIVE CANDIDIASIS

JORGE MORA-DUARTE, M.D., ROBERT BETTS, M.D., COLEMAN ROTSTEIN, M.D., ARNALDO LOPES COLOMBO, M.D., LUIS THOMPSON-MOYA, M.D., JUANITA SMIETANA, B.S., ROBERT LUPINACCI, M.S., CAROLE SABLE, M.D., NICHOLAS KARTSONIS, M.D., AND JOHN PERFECT, M.D., FOR THE CASPOFUNGIN INVASIVE CANDIDIASIS STUDY GROUP*

TABLE 4. FAVORABLE RESPONSES TO TREATMENT.

TIME POINT	MODIFIED INTENTION-TO-TREAT ANALYSIS		PATIENTS WHO MET CRITERIA FOR EVALUATION	
	CASPOFUNGIN (N=109)	AMPHOTERICIN B (N=115)	CASPOFUNGIN (N=88)	AMPHOTERICIN B (N=97)
	no. with a favorable response/total no. (%)			
End of intravenous therapy	80/109 (73.4)	71/115 (61.7)	71/88 (80.7)	63/97 (64.9)*
Absolute neutrophil count at enrollment				
$<500/mm^3$	7/14 (50.0)	4/10 (40.0)	6/8 (75.0)	3/8 (37.5)
$\geq 500/mm^3$	73/95 (76.8)	67/105 (63.8)	65/80 (81.2)	60/89 (67.4)
APACHE II score				
≤20	68/88 (77.3)	61/92 (66.3)	61/76 (80.3)	53/78 (67.9)
>20	12/21 (57.1)	10/23 (43.5)	10/12 (83.3)	10/19 (52.6)
Day 10 of intravenous therapy†	66/75 (88.0)	64/75 (85.3)	59/67 (88.1)	55/64 (85.9)
At end of all antifungal therapy	79/109 (72.5)	71/115 (61.7)	70/88 (79.5)	63/97 (64.9)‡
2 Weeks after treatment§	56/88 (63.6)	56/104 (53.8)	52/72 (72.2)	49/86 (57.0)
6–8 Weeks after treatment§	47/83 (56.6)	47/99 (47.5)	44/67 (65.7)	41/82 (50.0)

Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial

	Micafungin		Liposomal amphotericin B		Difference in proportion (95% CI)
	Number of patients	Number treated successfully (%)	Number of patients	Number treated successfully (%)	
Overall	247	183 (74·1%)	247	172 (69·6%)	4·5% (–3·5 to 12·4)
Complete response*		159 (64·4%)		150 (60·7%)	
Partial response*		24 (9·7%)		22 (8·9%)	
Neutropenic status at baseline					4·9% (–3·0 to 12·8)†
<500 cells per µL	32	19 (59·4%)	25	14 (56·0%)	
≥500 cells per µL	215	164 (76·3%)	222	158 (71·2%)	

*Both mycological eradication and a complete clinical response were necessary to be deemed a complete response. For a partial response, an improvement in clinical symptoms and any radiographic abnormalities had to be demonstrated in addition to a mycological response. †Stratified by neutropenic status.

Table 3: **Treatment success in the modified intention-to-treat population**

Anidulafungine *versus* fluconazole dans la candidose invasive

Table 3. Microbiologic and Global Responses at the End of Intravenous Therapy in the Modified Intention-to-Treat Population.*

Candida Pathogen	Successful Microbiologic Response			Successful Global Response†		
	Anidulafungin Group	Fluconazole Group	P Value	Anidulafungin Group	Fluconazole Group	P Value
	no. of isolates/total no. (%)			*no. of patients/total no. (%)*		
Candida albicans	77/81 (95)	57/70 (81)	0.01	60/74 (81)	38/61 (62)	0.02
C. glabrata	15/20 (75)	18/30 (60)	0.37	9/16 (56)	11/22 (50)	0.75
C. parapsilosis	9/13 (69)	14/16 (88)	0.36	7/11 (64)	10/12 (83)	0.37
C. tropicalis	13/15 (87)	7/11 (64)	0.35	13/14 (93)	4/8 (50)	0.04
Other candida species	5/6 (83)	3/3 (100)	1.00	3/4 (75)	2/3 (67)	1.00
All candida species	119/135 (88)	99/130 (76)	0.02	92/119 (77)	65/106 (61)	0.01

* Patients may have had more than one pathogen at baseline, but the majority had a single pathogen (94% in the anidulafungin group and 90% in the fluconazole group). Of 227 patients with candidemia, 138 had multiple positive blood cultures at baseline. However, because the protocol did not require blood to be drawn for culture on the first day of administration of the study drug, the number of patients with multiple positive blood cultures is likely to be underestimated.

† Patients included in this analysis had a single pathogen at baseline.

Reboli AC et al. *NEJM* 2007; 356: 2472-82.

Fongiday – a SAT is associated with a lower day 28 mortality…

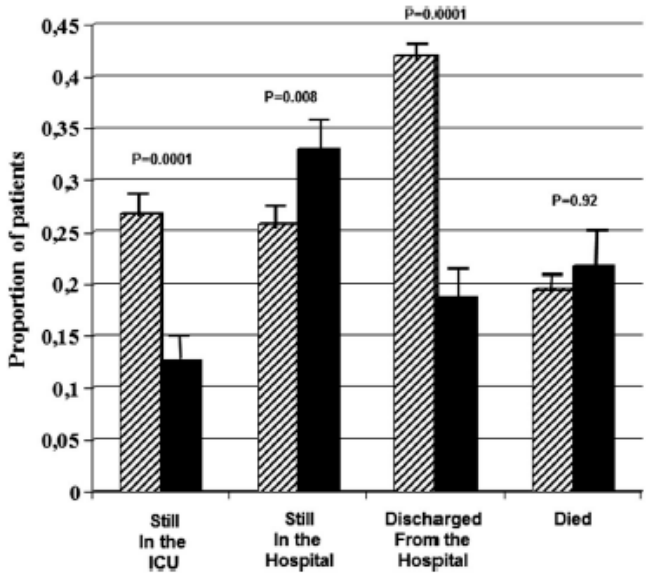
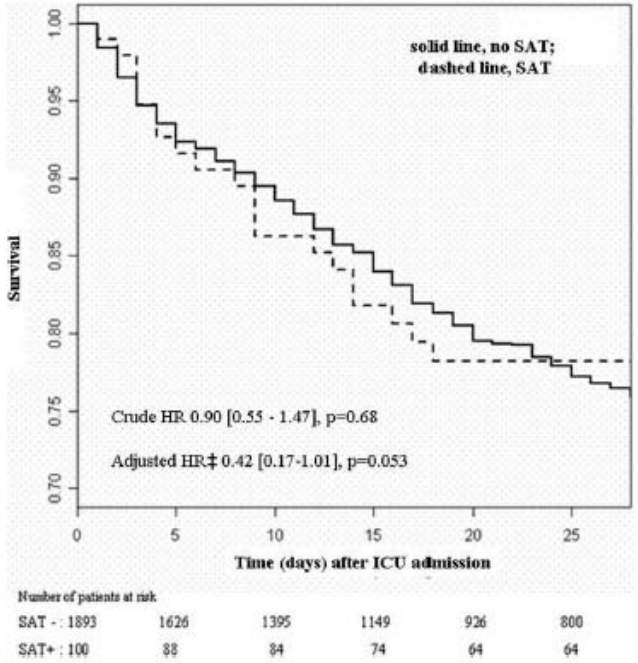


Figure 2. Patient location and status on day 28. The 54 patients treated for documented invasive fungal infections are not included in this graph. *Black bars* are patients receiving systemic antifungal treatment and *hashed bars* patients not receiving systemic antifungal treatment. *SAT*, Systemic antifungal treatment; *ICU*, intensive care unit.

- Cox model with left troncature



igure 3. Day 28 survival by systemic antifungal treatment use. ‡Adjusted hazards ratio obtained with djustment on the propensity score for day 28 mortality and with stratification on the *Candida* score alue. *SAT*, Systemic antifungal treatment; *HR*, hazard ratio; *ICU, intensive care unit.*

Azoulay et al – Crit Care Med 2012 (40) Epub ahead of print