La Situación actual

Epidemiology of Candidaemia in Europe: Results of 28-Month European Confederation of Medical Mycology (ECMM) Hospital-Based Surveillance Study

Underlying conditions[a,b]	No. (%) of patients
Surgery	933 (44.7)
Intensive care	839 (40.2)
Solid tumour	471 (22.5)
Haematological malignancy	257 (12.3)
Premature birth	125 (6.0)
Solid organ transplantation	74 (3.5)
HIV infection	63 (3.0)
Burns	29 (1.4)

2.089 episodios (43% *Candida* no-*albicans*)

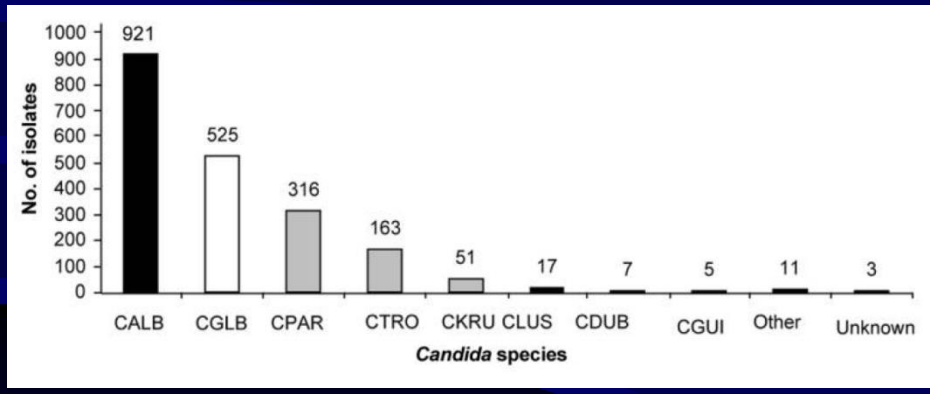
Parameter	No. of episodes	Percent mortality	*P* value[a]
Aetiologic agent			
C. albicans	1,090	38.5	0.65
C. glabrata	269	45.0	0.02
C. parapsilosis	263	25.9	<0.001
C. tropicalis	140	41.4	0.42
Underlying condition			
Surgery	892	35.3	0.26
Intensive care	791	42.4	0.02
Solid tumor	442	49.2	<0.001
Haematological malignancy	247	44.9	0.03
HIV infection	61	23.4	0.03
Premature birth	123	26.8	0.02
Age group			
<1 y	142	26.0	0.006
1–19 y	148	22.3	<0.001
20–69 y	1,096	36.6	0.46
≥70 y	556	47.7	<0.001
Total	1,942	37.9	

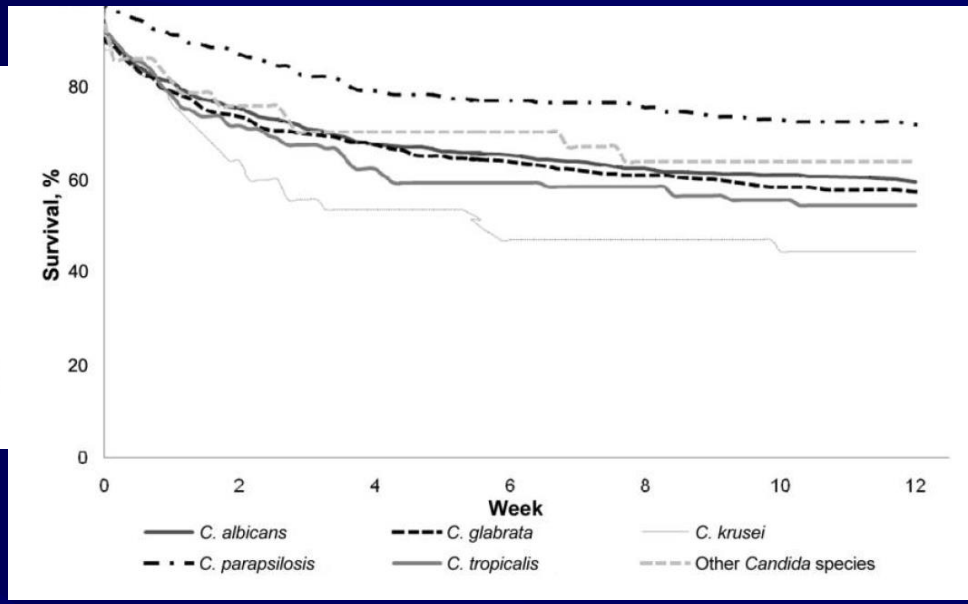
[a]Calculated against overall crude mortality

Tortorano AM, Pemán J et al, Eur J Clin Infect Dis 2004; 23:317

Epidemiology and Outcomes of Candidemia in 2019 Patients: Data from the Prospective Antifungal Therapy Alliance Registry

David L. Horn,[1] Dionissios Neofytos,[1,2] Elias J. Anaissie,[3] Jay A. Fishman,[4] William J. Steinbach,[5] Ali J. Olyaei,[6] Kieren A. Marr,[2] Michael A. Pfaller,[7] Chi-Hsing Chang,[8] and Karen M. Webster[9]





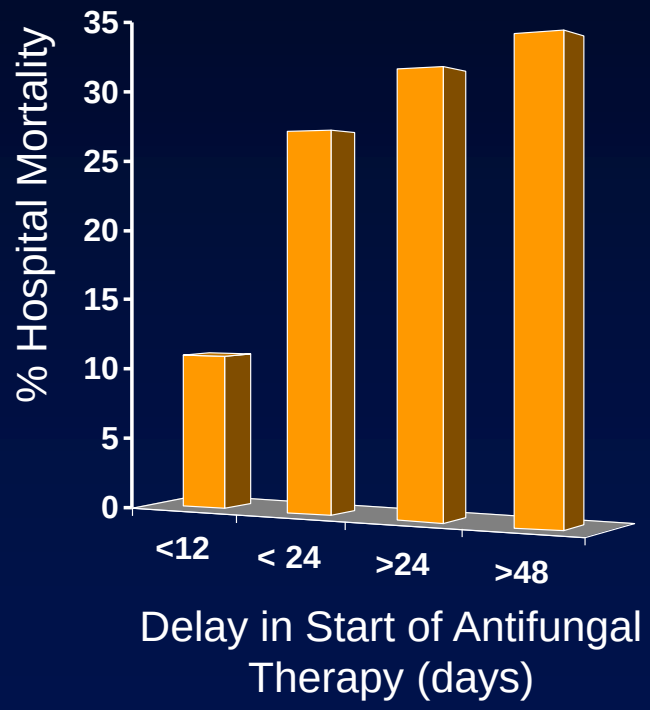
- **2019 pacientes (pediátricos y adultos)**
- **2004-2008**
- **23 hospitales Norte América**

Clinical Infectious Diseases 2009; 48:1695–703

Dados estos cambios ...
¿cómo aconsejas realizar el tratamiento anticipado,cómo y con qué?

Delaying the Empiric Treatment of Candidemia

An Independent Risk Factor for Hospital Mortality



Multivariate analysis of independent risk factors for hospital mortality

Variable	OR	95% CI	*P*
APACHE II	1.24	(1.18-1.31)	<0.001
Prior antibiotics	4.05	(2.14-7.65)	0.028
Delay in antifungal therapy	2.09	(1.53-2.84)	0.018

Morrell et al. *Antimicrob Agent Chemother* 2005;49:3640.

Time to Initiation of Fluconazole Therapy Impacts Mortality in Patients with Candidemia: A Multi-Institutional Study

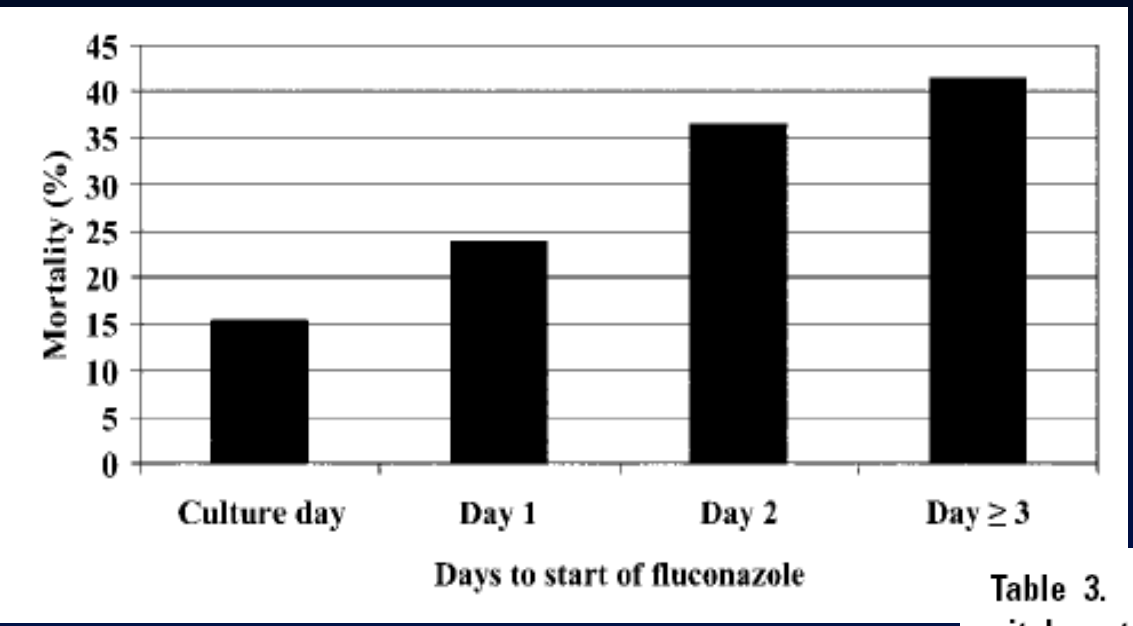


Table 3. Multivariate model of independent risk factors for hospital mortality.

Variable	Adjusted OR (95% CI)	*P*
Time from culture date to start of fluconazole therapy, days	1.50 (1.09–2.09)	.0138
APACHE II score, 1-point increments	1.13 (1.08–1.18)	<.001

Garey KW, Clin Infect Dis 2006; 43:25-31

Intensive Care Med
DOI 10.1007/s00134-008-1338-7

REVIEW

Benoît P. Guery
Maiken C. Arendrup
Georg Auzinger
Élie Azoulay
Márcio Borges Sá
Elizabeth M. Johnson
Eckhard Müller
Christian Putensen
Coleman Rotstein
Gabriele Sganga
Mario Venditti
Rafael Zaragoza Crespo
Bart Jan Kullberg

Management of invasive candidiasis and candidemia in adult non-neutropenic intensive care unit patients: Part I. Epidemiology and diagnosis

Intensive Care Med
DOI 10.1007/s00134-008-1339-6

REVIEW

Benoît P. Guery
Maiken C. Arendrup
Georg Auzinger
Élie Azoulay
Márcio Borges Sá
Elizabeth M. Johnson
Eckhard Müller
Christian Putensen
Coleman Rotstein
Gabriele Sganga
Mario Venditti
Rafael Zaragoza Crespo
Bart Jan Kullberg

Management of invasive candidiasis and candidemia in adult non-neutropenic intensive care unit patients: Part II. Treatment

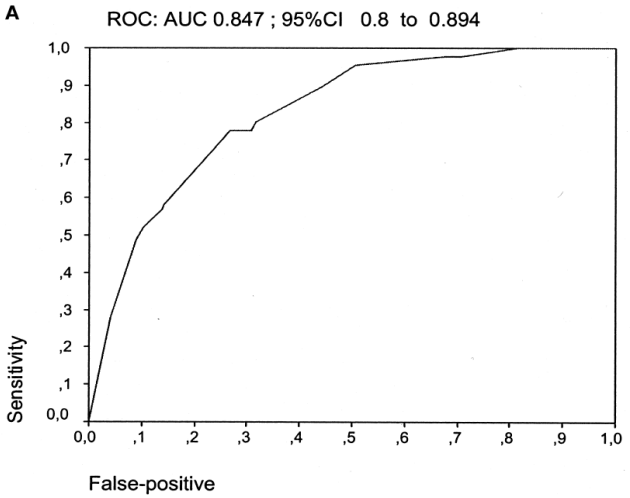
"Multidisciplinary approach to the treatment of invasive fungal infections in adult patients. Prophylaxis, empirical, preemptive or targeted therapy, which is the best in the different hosts?"

Rafael Zaragoza, Javier Pemán, Miguel Salavert, Ángel Viudes, Amparo Solé, Isidro Jarque, Emilio Monte, Eva Romá, Emilia Cantón.

	Strategy	Antifungal agent	References
Prophylaxis	No generally recommended. Patients with upper gastrointestinal perforation, heavy *Candida* colonization or with severe acute pancreatitis might be benefit	Fluconazole	(Pelz et al. 2001) (Garbino et al. 2002) (De Waele et al. 2003;Piarroux et al. 2004)
Empirical	Use of "*Candida* score" or the Ostrosky-Zeichner prediction rule	De-escalation therapy (*), the choice of antifungal drug must be based on the individual characteristics of the patient	(Leon et al. 2006;Ostrosky-Zeichner et al. 2007)
Pre-emptive	Based on detection of galactomannan, (1,3)-β-d-glucan or *C. albicans* germ tube antibodies or PCR.	De-escalation therapy (*) the choice of antifungal drug must be based on the individual characteristics of the patient	(Meersseman et al. 2008;Ostrosky-Zeichner et al. 2005;Zaragoza et al. 2006)
Targeted	Based on sterile site culture results	De-escalation therapy(*), the choice of antifungal drug must be based on the individual characteristics of the patient (**)	(Kullberg et al. 2005;Kuse et al. 2007;Mora-Duarte et al. 2002;Pappas et al. 2007;Phillips et al. 1997;Rex et al. 1994;Zaragoza & Peman 2006)

Clin Ther Risk Man 2008 Dec

Candida Score



A score >2.5 will help intensivists select patients who will benefit from early anti-fungal administration.

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

Variable	Coefficient (β)	Standard Error	Wald χ^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.

Leon C et al. Crit Care Med 2006

Resultados

1.107 pacientes: 215 no colonizados/infectados, 834 colonizados, 58 infectados

End point principal

De los 565 pacientes con CS < 3: 13 desarrollaron CI **(2.3%** : 95% CI (1.06 ; 3.54); 13 IC fueron tratados

End point secundarios

Relación de la presencia de cirugía abdominal (CA) y *Candida score*

- Pacientes con **CS > 3**, la presencia de CA influyo de manera determinante en el desarrollo de de CI; 30.3% (95% CI = 19.2%; 41.4%) vs.11.5% (95% CI = 5.1%; 17.8%)
  p = 0.003 (riesgo de CI)

Utilidad del (1→3)ß-D-Glucano (BG) y CS para discriminar entre colonización candidiásica y CI.

- 240 pacientes, 18 desarrollaron CI y el resto 222 colonizados.
- El área bajo la curva ROC fue**: 0.709** (95% CI = 0.591; 0.828).
- El punto de corte **fue = 75 pg/ml** [S: 77.8% (95% CI: 58.6%-97%),E: 52,7%(95% CI: 46.1%-9.3%]

Usefulness of the "*Candida* score" for discriminating between *Candida* colonization and invasive candidiasis in non-neutropenic critically ill pat[illegible]

Cristóbal León, MD; Ser[illegible]alván, MD;
Armando Blanco, MD; C[illegible]ázquez, MD;
Francisco J. González c[illegible]pez, MD;
Pierre Emmanuel Charle[illegible]era, MD; on behalf of
the Cava Study Group

Abdominal Surgery, IC, and CS: Of the 892 patients with *Candida* species colonization or IC, 182 underwent abdominal operations. In patients with CS < 3, the presence of abdominal surgery for predicting IC was irrelevant (1.9% vs. 2.3%, *p* 0.85). Similar findings were obtained in patients with CS = 3 (12.5% vs. 5.9%, *p* 0.14). **However, in patients with CS > 3, abdominal surgery significantly predicted IC (30.3%, 95% CI 19.2–41.4%) compared with onabdominal surgery (11.5%, 95% CI 5.1–17.8%) (*p* 0.003).**

Table 3. Risk for [illegible]

Patient [illegible]ve Risk (95% CI)

Table 7. Discriminating [illegible]

Factor	[illegible]	[illegible]	[illegible]	[illegible] (95% CI)
Sepsis, no. (%)				
Multifocality; n (%)				
Total parenteral nutrition, no. (%)	19 (95.0)	26 (70.3)	0.029	8.0 (1.0–67.7)
Surgery, no. (%)	18 (90.0)	16 (43.2)	0.001	11.8 (2.4–58.5)
Abdominal surgery, no. (%)	18 (90.0)	11 (29.7)	<0.001	21.3 (4.2–107)

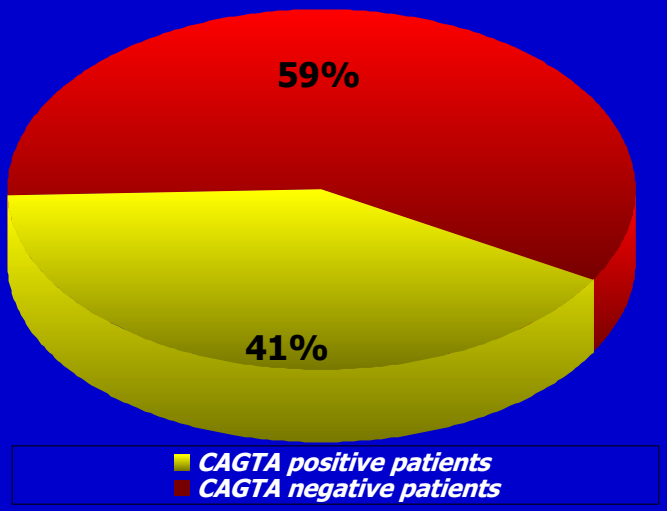
CS, *Candida* score; CI, confidence interval; OR, odds ratio.

Clinical Significance of *Candida albicans* Germ Tube Antibody (CAGTA) Detection in Critically Ill Patients

R. Zaragoza, J. Pemán, G. Quindós , J.Iruretagoyena P. Ramirez, M Cuètara, M. Gómez ,J. Camarena, A. Viudes, J. Pontón on behalf of the study group Candida albicans Germ Tube Antibody Detection in Critically Ill Patients (CAGTAUCI)*

Clin Microbiol Infect. 2009 Jun;15(6):592-5.

This work has been supported by a Pfizer grant



Prevalence of CAGTA positive results among the critically ill patients included..

	No. of patients (%)			
	Total	CAGTA +	CAGTA -	*p* value
Patients	53	22 (41.5)	31 (58.5)	-
Age (years)	71.5 ± 18.4	69.2 ± 22.2	73.1 ± 15.3	0.46
Male:Female (ratio)	1.65	1.2	2.3	0.25
APACHE II (score)	14.9 ± 5.4	12.2 ± 4.4	16.9 ± 5.2	0.001
Septic shock	15 (28.3)	4 (18.2)	11 (35.4)	0.16
Respiratory failure	15 (28.3)	7 (31.8)	8 (25.8)	0.63
Coma	5 (9.4)	2 (9.1)	3 (9.7)	0.92
Renal failure	24 (45.3)	6 (27.3)	18 (58.1)	0.02
Extra-renal depuration	16 (30.2)	4 (18.2)	12 (38.7)	0.10
Hepatic failure	19 (35.8)	9 (40.9)	8 (25.8)	0.24
Neutropenia	4 (7.5)	0	4 (12.9)	0.10
Broad spectrum antibiotics	36 (67.9)	17 (77.3)	19 (61.3)	0.21
Parenteral nutrition	33 (62.3)	14 (63.7)	19 (61.3)	0.86
Hepatic transplant	2 (3.8)	1 (4.5)	1 (3.2)	0.80
Acute pancreatitis	3 (5.7)	2 (9.1)	1 (3.2)	0.36
Diabetes mellitus	12 (22.6)	4 (18.2)	8 (25.8)	0.51
Previous surgery	20 (37.7)	12 (54.5)	8 (25.8)	0.03

Main clinical characteristics of patients according to CAGTA results.

Clinical Significance of *Candida albicans* Germ Tube Antibody (CAGTA) Detection in Critically Ill Patients

R. Zaragoza, J. Pemán, G. Quindós , J.Iruretagoyena P. Ramirez, M Cuètara, M. Gómez ,J. Camarena, A. Viudes, J. Pontón on behalf of the study group Candida albicans Germ Tube Antibody Detection in Critically Ill Patients (CAGTAUCI)*

This work has been supported by a Pfizer grant

Clin Microbiol Infect. 2009 Jun;15(6):592-5.

Variable	Parameter estimates				
	Parameter estimate	Standard error	95% Confidence limits		*p* value
Constant	-0.2196	0.24665	-0.27655	0.71586	0.3777
CAGTA-positive	-0.3143	0.14268	-0.60135	-0.02729	0.0325
APACHE score	0.0223	0.01320	-0.00417	0.04892	0.0966
Antifungal treatment	-0.0967	0.12835	-0.35496	0.16145	0.4547

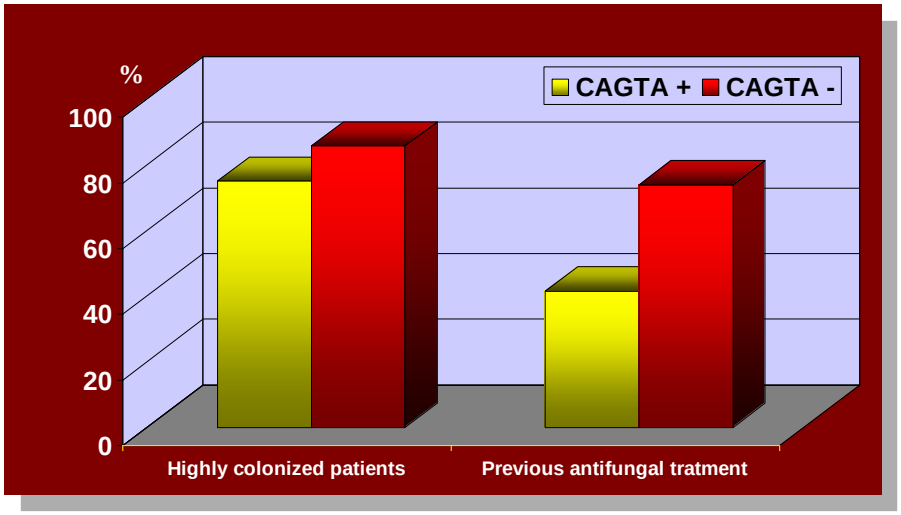
Multivariate analysis of ICU mortality

Anticuerpos antimicelio (CAGTA)

Influencia de la colonización pesada y del tratamiento antifúngico.

Pemán J & Zaragoza R. EJCMID in press

·p >0,05



·Porcentaje de pacientes altamente colonizados y tratados con antifúngicos según los resultados de CAGTA

CLINICAL AND VACCINE IMMUNOLOGY, Oct. 2009, p. 1527–1528 Vol. 16, No. 10
1556-6811/09/$08.00+0 doi:10.1128/CVI.00183-09

Kinetic Patterns of *Candida albicans* Germ T
Ill Patients: Influence on M

Rafael Zaragoza,[1]* Javier Pemán,[3] Guillermo Quindós,[5] Jose
Paula Ramírez,[4] Maria D. Gómez,[3] Juan J. Camarena,[2] A
on behalf of the *Candida albicans* Germ Tube
Critically Ill Patients (CAGTAUCI) S

*Intensive Care Unit[1] and Department of Microbiology,[2] Hospital Universitar
Microbiology[3] and Intensive Care Unit,[4] Hospital Universitario La Fe, Va
Bilbao, Spain[5]; Intensive Care Unit, Hospital Universitario Cruces, B
Microbiology Hospital Severo Ochoa, Lega*

Received 6 May 2009/Accepted 28 July 2009

- **22/53 CAGTA +**
  - **31.8%** Títulos crecientes
  - **36.4%** Títulos decrecientes
  - **22.8%** Títulos invariables

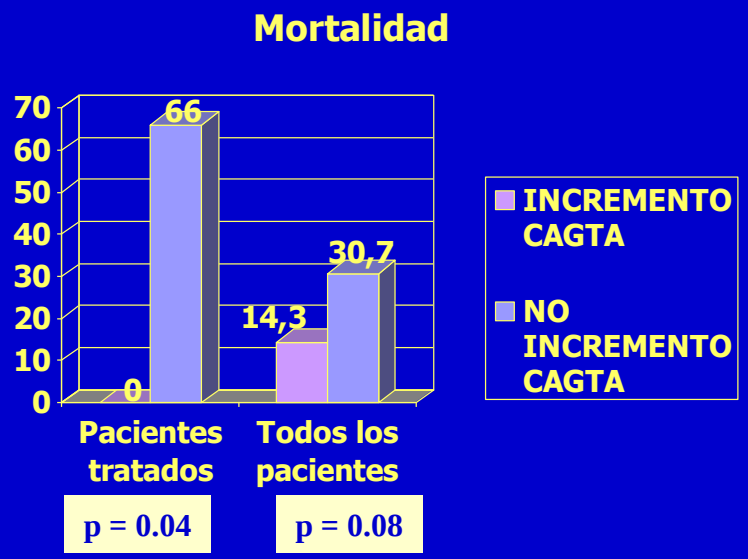


TABLE 1. Mortality of CAGTA-positive patients according to their dynamic patterns and the administration of antifungal treatment

Dynamic pattern	No. (%) of patients with indicated outcome			
	Total	Died	Treated with antifungals	Treated with antifungals and died
CAGTA positive	22 (100)	5 (22.7)	10 (45.4)	4 (40)
Not determinable	2 (9)	0 (0)	0 (0)	
Increasing titers	7 (31.8)	1 (14.2)	4 (57.1)	0 (0)
No change	5 (22.7)	1 (20)	2 (40)	1 (50)
Decreasing titers	8 (36.3)	3 (37.5)	4 (50)	3 (75)

A Prospective Clinical Trial of a Real-Time Polymerase Chain Reaction Assay for the Diagnosis of Candidemia in Nonneutropenic, Critically Ill Adults

R. McMullan,[1] L. Metwally,[1] P. V. Coyle,[1] S. Hedderwick,[2] B. McCloskey,[3] H. J. O'Neill,[1] C. C. Patterson,[4] G. Thompson,[1,3] C. H. Webb,[1] and R. J. Hay[4]

Departments of [1]Medical Microbiology and [2]Infectious Diseases, [3]Regional Intensive Care Unit, The Royal Hospitals, and [4]School of Medicine and Dentistry, The Queen's University of Belfast, Belfast, Northern Ireland

Table 3. Summary of assay performance analyses.

	Overall performance		Excluding participant with *Candida famata* infection	
Performance measure	Proportion (%)	95% CI, %	Proportion (%)	95% CI, %
Sensitivity	20/23 (87)	66.4–97.2	20/22 (90.9)	70.8–98.9
Specificity	491/491 (100)	99.3–100	491/491 (100)	99.3–100
Positive predictive value	20/20 (100)	83.2–100	20/20 (100)	83.2–100
Negative predictive value	491/493 (99.6)	98.5–100	491/492 (99.8)	98.9–100

NOTE. Analysis excludes the specimens from the 6 participants in the probable category.

Table 2. Definitions of invasive *Candida* infection categories.

Definition
Proven disease: any 1 of the following
Histologic evidence of yeast cells or hyphae or pseudohyphae from normally sterile site
Blood culture positive for *Candida* species; positive culture of blood obtained via a central venous catheter were not accepted if specimens contemporaneously taken either via an arterial catheter or from a peripheral vein yielded negative results
Positive culture result for sample from any other normally sterile site (excludes urine, sputum, bronchoalveolar lavage, mucous membrane swabs, and specimens from skin sites)
Probable disease
1 of the following
Fever (temperature, >38°C) persisting despite receipt of broad-spectrum antibacterial therapy for >96 h
Temperature <36°C or >38°C, plus
Receipt of immunosuppressive therapy for ≥7 of the preceding 30 days (excluding corticosteroids)
Symptomatic AIDS
Receipt of corticosteroid therapy for ≥21 days in past 60 days
Plus 1 of the following
Cultures positive for the same *Candida* species from at least 2 noncontiguous (including nonsterile) sites
Bulls-eye lesions in liver and/or spleen on ultrasound or CT imaging accompanied by an elevation in serum alkaline phosphatase level
Unlikely disease: neither of the above categories met

BMC Infectious Diseases

BioMed Central

Research article

Open Access

Comparative evaluation of (1, 3)-β-D-glucan, mannan and anti-mannan antibodies, and *Candida* species-specific snPCR in patients with candidemia

Fasahat F Alam, Abu S Mustafa and Zia U Khan*

BMC Infectious Diseases 2007, **7**:103

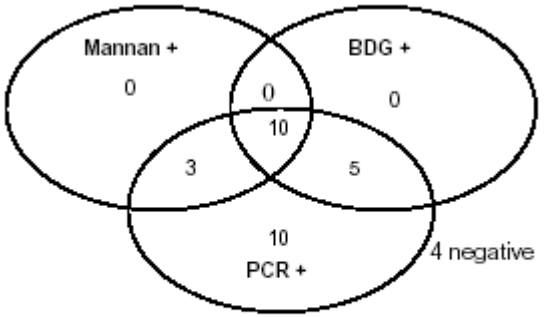


Figure 1
Venn diagram showing number of sera with positive results in each combination of mannan, BDG and snPCR (n = 32).

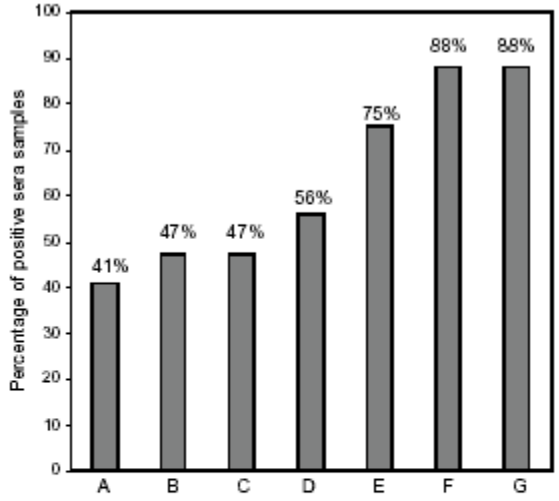


Figure 3
Bar diagram showing the increasing sensitivity of the diagnostic tests to detect *Candida* infection in candidemia patients. A: Mannan Ag, B: BDG, C: Anti-mannan Abs, D: Mannan + BDG, E: Mannan + Anti-mannan Abs, F: *Candida* DNA, G: Mannan + BDG + *Candida* DNA

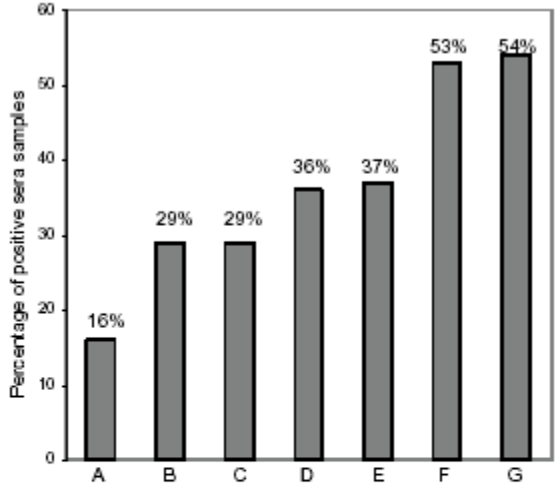
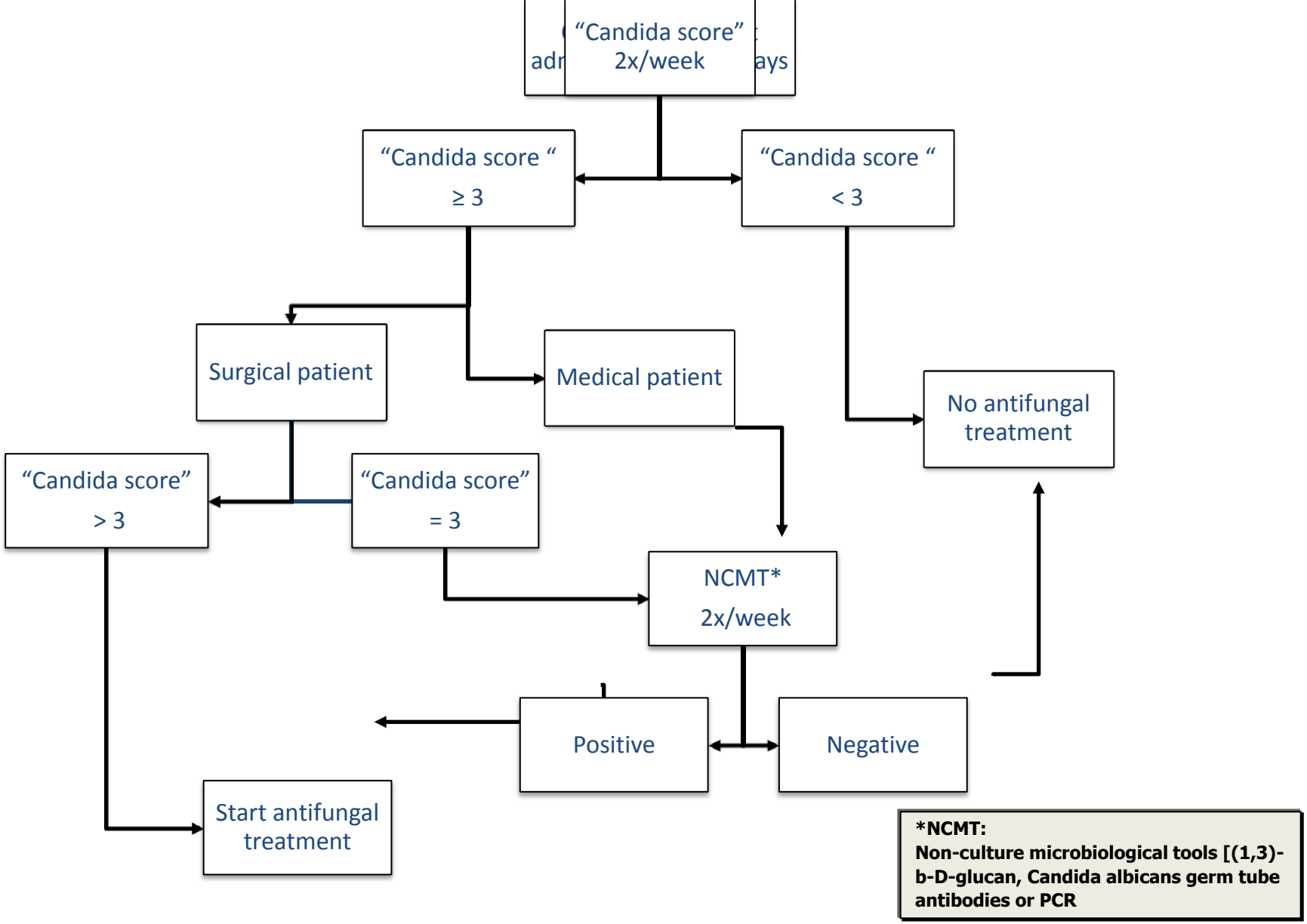


Figure 5
Bar diagram showing the increasing sensitivity of the diagnostic tests to detect *Candida* infection in clinically suspected candidiasis patients. A: Mannan Ag, B: BDG, C: Anti-mannan Abs, D: Mannan + BDG, E: Mannan + Anti-mannan Abs, F: *Candida* DNA, G: Mannan + BDG + *Candida* DNA



Current diagnostic approaches to invasive candidiasis in critical care settings

Mycoses 2009 Jul

Javier Pemán[1] and Rafael Zaragoza[2]

[1]*Servicio de Microbiología, Hospital Universitario La Fe, Valencia, Spain and* [2]*Servicio de Medicina Intensiva, Hospital Universitario Dr. Peset, Valencia, Spain*

Intensive Care Med
DOI 10.1007/s00134-008-1339-6

REVIEW

Benoît P. Guery
Maiken C. Arendrup
Georg Auzinger
Élie Azoulay
Márcio Borges Sá
Elizabeth M. Johnson
Eckhard Müller
Christian Putensen
Coleman Rotstein
Gabriele Sganga
Mario Venditti
Rafael Zaragoza Crespo
Bart Jan Kullberg

Management of invasive candidiasis and candidemia in adult non-neutropenic intensive care unit patients: Part II. Treatment

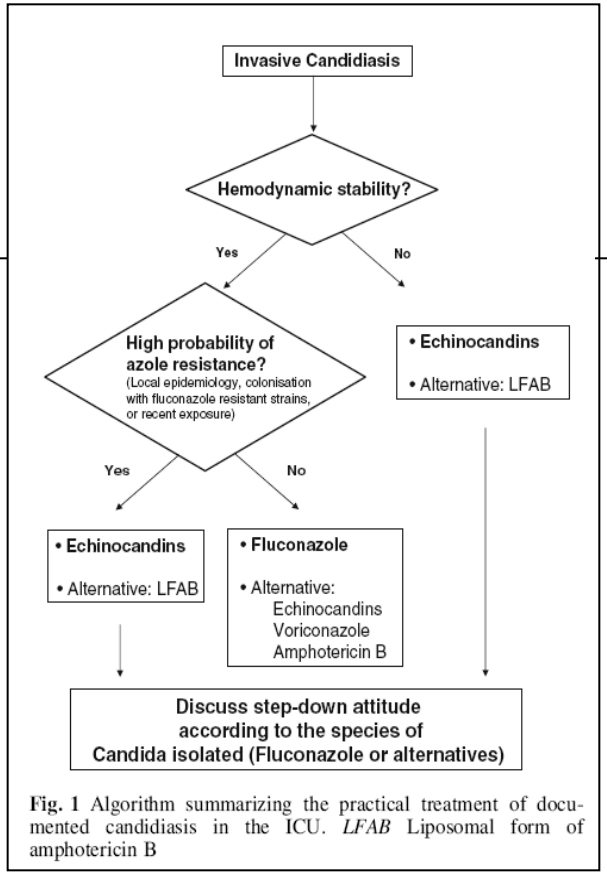


Fig. 1 Algorithm summarizing the practical treatment of documented candidiasis in the ICU. *LFAB* Liposomal form of amphotericin B

TRATAMIENTO CANDIDEMIA
- Guías IDSA 2009 -

- Tto empírico: FLUCONAZOL 800mg/d y pasar a 400mg/d o EQUINOCANDINA (AI)
- EQUINOCANDINA si infección moderada-severa o exposición a azoles (AIII)
- Inf probada o sospechada por *C.glabrata:* EQUINOCANDINA y pasar a FLUCONAZOL con fungigrama (BIII)
- *C.parapsilosis:* FLUCONAZOL(BIII). Si respuesta a equinocandina empírica puede seguir.
- VORICONAZOL no indicado como tratamiento inicial. Podría usarse si se necesita via oral o si *C.krusei* confirmada

¿Fluconazol, por qué no?

Papel de la aparición de resistencias en la mortalidad

Trick WE; CID Sep 2002

- Disminución de la incidencia de *C. albicans* y aumento de *C. glabrata*
- ¿Existen diferencias de mortalidad significativas entre ellas?

  C. glabrata 60% vs *C. albicans* 41%

90% Mortalidad *Candida* non-albicans

Dimopoulos G, Ntziora F, Rachiotis G, Armaganidis A, Falagas ME. Candida albicans versus non-albicans intensive care unit-acquired bloodstream infections: differences in risk factors and outcome.
Anesth Analg. 2008 Feb;106(2):523-9,

Blot S; Journal of Hospital Infection 2001

FR x

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2008, p. 3022–3028 Vol. 52, No. 9
0066-4804/08/$08.00+0 doi:10.1128/AAC.00116-08

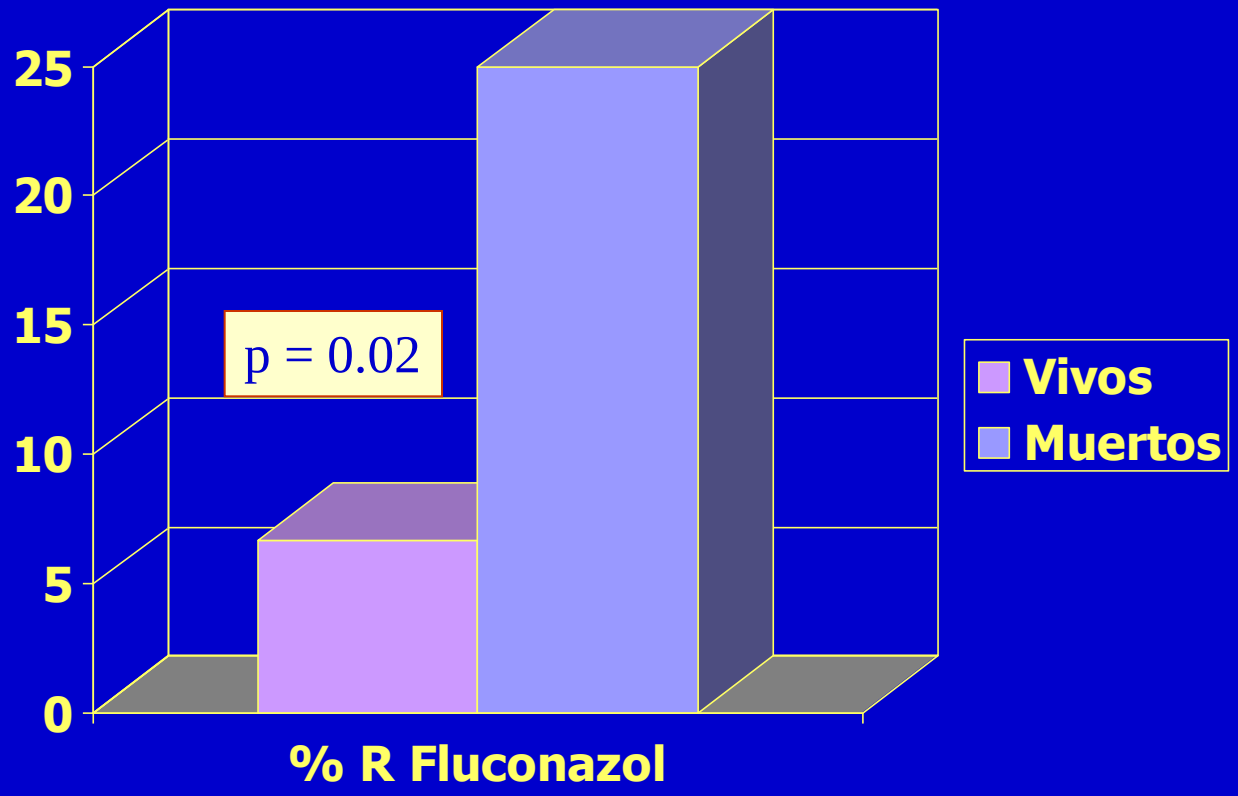
Association of Fluconazole Pharmacodynamics with Mortality in Patients with Candidemia[▽]

John W. Baddley,[1,3]* Mukesh Patel,[1,3] Sujata M. Bhavnani,[4] Stephen A. Moser,[2] and David R. Andes[5]

Department of Medicine, Division of Infectious Diseases,[1] and Department of Pathology,[2] University of Alabama at Birmingham, Birmingham, Alabama; Birmingham Veterans Administration Medical Center, Birmingham, Alabama[3]; Institute for Clinical Pharmacodynamics, Ordway Research Institute, Albany, New York[4]; and Department of Medicine and Medical Microbiology and Immunology, University of Wisconsin, Madison, Wisconsin[5]

Received 25 January 2008/Returned for modification 21 March 2008/Accepted 23 June 2008

- Mortalidad global 28% (n=84)



Empirical treatment of candidemia in intensive care units: Fluconazole or broad-spectrum antifungal agents?

- The fear of candidemia caused by a fluconazole-resistant species of Candida is causing many intensive care units (ICUs) to switch empiric therapy from this drug to broad-spectrum antifungal agents. We studied the epidemiology and antifungal susceptibility of Candida isolates involved in cases of candidemia among adult and pediatric patients in ICUs from 1984 to 2006. We documented 307 episodes of candidemia in 307 patients, of which only eight episodes (2.6%) were caused by a fluconazole-resistant isolate. At least three of the eight patients from whom fluconazole-resistant strains were recovered had recently received fluconazole. Overall, only 1.6% of the episodes of candidemia caused by fluconazole-resistant strains (five patients) occurred in individuals with no evidence of previous fluconazole administration. In conclusion, the use of broad-spectrum antifungal agents is not justified in ICUs with a low proportion of candidemia episodes caused by fluconazole-resistant strains of Candida.

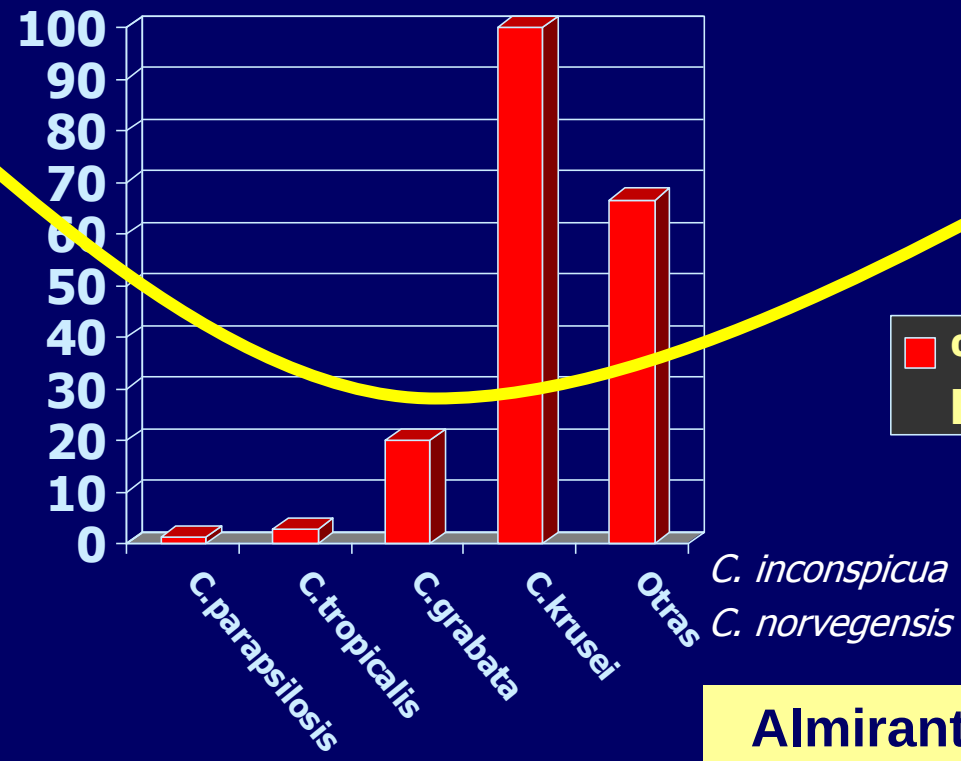
Guinea J, **Pelaez T**, **Rodriguez-Creixems M**, **Torres-Narbona M**, **Munoz P**, **Alcala L**, **Bouza E**. Med Mycol. 2008 Oct 29:1-6.

¿Quiénes y cuántas son resistentes a fluconazol en UCI?

Epidemiology and Predictors of Mortality in Cases of *Candida* Bloodstream Infection: Results from Population-Based Surveillance, Barcelona, Spain, from 2002 to 2003

33% UCI

7% GLOBAL



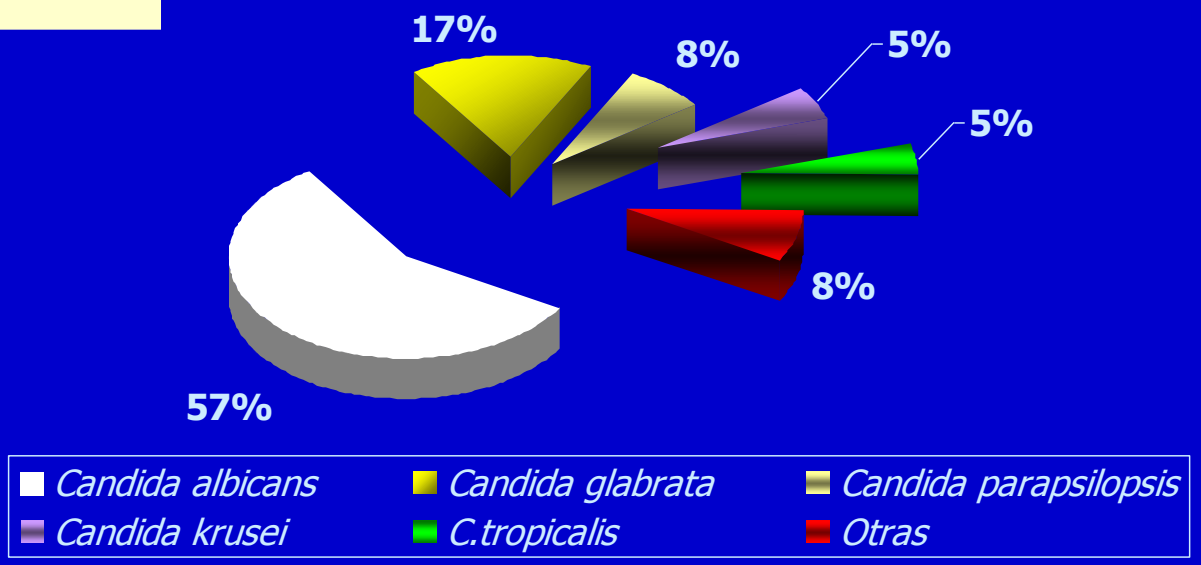
Almirante B, JCM 2005; 43:1829

Epidemiology, management, and risk factors for death of invasive Candida infections in critical care: A multicenter, prospective, observational study in France (2005–2006)

N =271

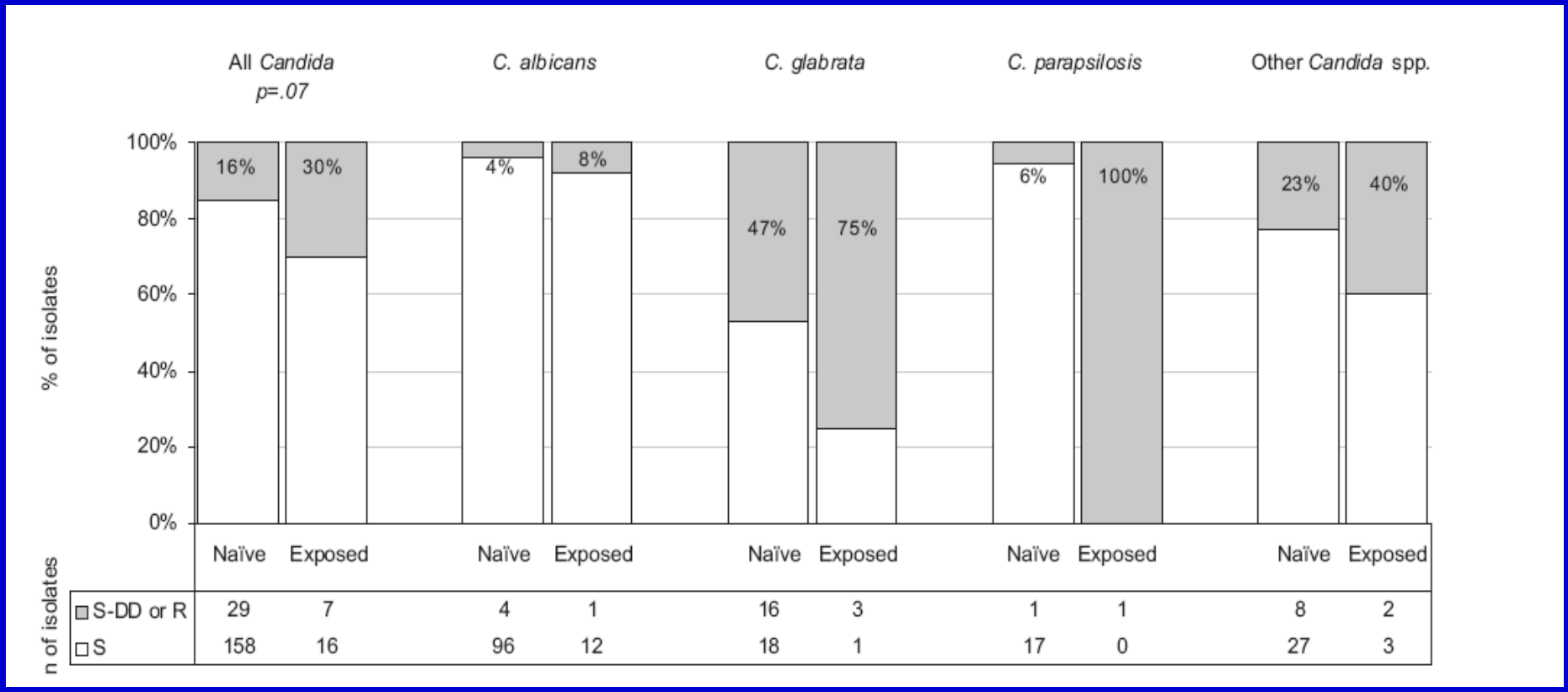
Sensibilidad reducida a fluconazol 17,1%

Desescalada 37,1%



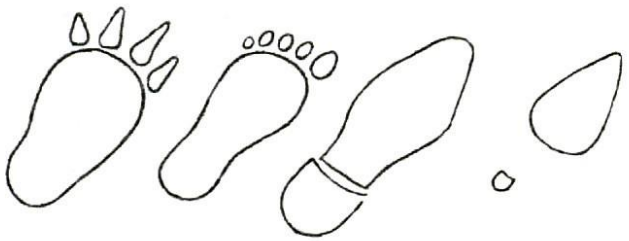
Leroy O et al . Crit Care Med 2009

Epidemiology, management, and risk factors for death of invasive Candida infections in critical care: A multicenter, prospective, observational study in France (2005–2006)



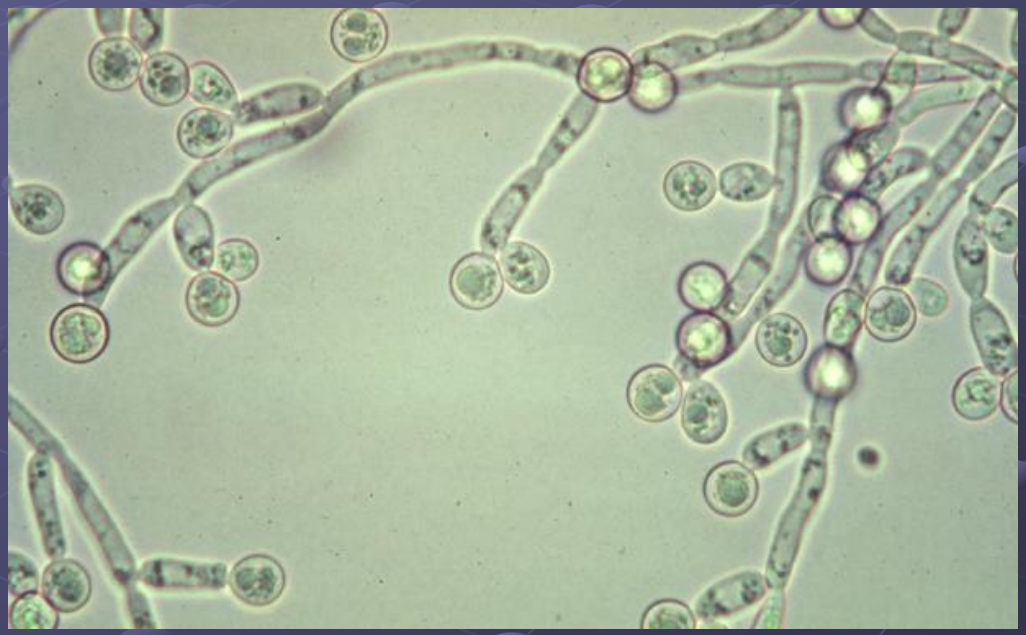
Leroy O et al . Crit Care Med 2009

Entre ellas... ¿cuál es la más bella?



The evolution of authority

Actividad *in vitro* sobre levaduras



Actividad “IN VITRO”

Actividad *in vitro* de anidulafungina sobre *Candida* spp.

Species	No. of isolates	MIC range, μg/mL	MIC_{50}, μg/mL	MIC_{90}, μg/mL
Candida albicans	413	≤0.03–0.25	0.125	0.25
Candida glabrata	275	≤0.03–1	0.25	0.5
Candida parapsilosis	28	0.12 to >2.0	2	4
Candida tropicalis	58	0.06–2	0.25	0.5
Candida krusei	36	0.12–1.0	0.25	0.5
Candida lusitaniae	10	0.125–2	0.5	2
Candida guillermondii	9	1–4	4	…

Johnson EM, 14th ECCMID, 2004; Zhanel GG, AAC 1997

Actividad *in vitro* de las equinocandinas sobre *Candida* spp.

Species (number of isolates tested)	Anidulafungin $MIC_{50/90}$ (µg/ml)	Micafungin $MIC_{50/90}$ (µg/ml)	Caspofungin $MIC_{50/90}$ (µg/ml)
Candida albicans (733)	0.03/0.03	0.03/0.03	0.5/0.5
Candida glabrata (458)	0.03/0.13	0.03/0.06	0.05/1
Candida parapsilosis (391)	2/2	1/2	2/2
Candida tropicalis (307)	0.03/0.13	0.03/0.06	0.5/1
Candida krusei (50)	0.06/0.13	0.13/0.25	1/2
Candida lusitaniae (20)	0.06/0.25	0.06/2	1/2
Candida dubliniensis (18)	0.03/0.06	0.03/0.03	0.5/0.5
Candida guilliermondii (9)	1 (0.06–2)*	0.5 (0.06–0.5)*	1 (0.05–2)*

Total: 1.986

Ostrosky-Zeichner, AAC 2003; 47:3149

Actividad in vitro de los nuevos AF sobre *Candida* spp resistentes a fluconazol

Pathogens	No of isolates tested	Antifungal agent	MIC_{90} (ug/ml)
Candida albicans	41	Anidulafungin	0.03 – 0.06
	41	Caspofungin	0.06
	41	Micafungin	0.03
	92	Voriconazole	0.03 – 16
Candida glabrata	110	Anidulafungin	0.06 – 0.12
	110	Caspofungin	0.06
	110	Micafungin	0.015
	14	Posaconazole	> 16 (0.5 – > 16)
	64	Voriconazole	0.06 – 16
Candida guilliermondii	8	Posaconazole	0.25
	17	Voriconazole	0.03 – 2
Candida krusei	146	Anidulafungin	0.06 – 0.12
	146	Caspofungin	0.06
	146	Micafungin	0.06
	15	Posaconazole	0.5
	135	Voriconazole	0.03 – 4

Aperis y cols. Expert Opin Investig Drugs, 2006

Actividad *in vitro de* anidulafungina sobre cepas de *C. glabrata* con CMI elevadas de caspofungina

Isolate	Anidulafungina			Caspofungina		
	MIC_2/MIC_0/ MFC	IC_{50}/IC_{90}	R^2	MIC_2/MIC_0/ MFC	IC_{50}/IC_{90}	R^2
1	0.25/0.5/0.5	0.063/0.075	0.97	1/2/4	0.81/0.83	0.91
2	0.125/0.25/0.25	0.11/0.18	0.93	1/1/2	0.52/0.60	0.96
3	0.125/0.25/0.25	0.039/0.11	0.86	1/2/4	0.55/0.61	0.95
4	0.125/0.25/0.25	0.086/0.18	0.91	1/2/2	0.91/1.1	0.89
5	0.125/0.25/0.25	0.15/0.65	0.83	1/2/2	0.64/0.85	0.89
6	1/2/4	0.65/2.4	0.96	2/2/128	1.8/23	0.73
7	0.125/0.25/0.5	0.092/0.15	0.96	1/1/2	0.57/0.67	0.95
8	0.25/0.25/0.5	0.049/0.16	0.94	1/1/2	0.90/1.0	0.82
9	0.25/0.5/0.5	0.13/0.15	0.88	1/1/2	0.94/1.0	0.91
10	0.125/0.25/1	0.11/0.19	0.81	1/1/2	0.86/1.2	0.91
11	0.125/0.25/4	0.071/0.12	0.98	1/1/1	0.91/0.98	0.86
12	0.125/0.25/0.5	0.11/0.12	0.93	1/1/4	0.84/0.94	0.95
13	0.25/0.25/1	0.053/0.38	0.89	1/1/2	0.74/1.0	0.89
14	0.125/0.125/1	0.062/0.21	0.92	1/1/2	0.90/0.99	0.90
15	0.125/0.125/1	0.11/0.13	0.83	1/1/4	0.83/0.93	0.94
16	1/2/4	0.17/7.8	0.78	4/8/64	ND[a]	ND
17	2/4/8	0.83/5.3	0.93	64/64/>128	ND	ND
18	0.5/4/8	2.4/3.6	0.90	2/64/64	ND	ND

Cota J et al. AAC, 2006

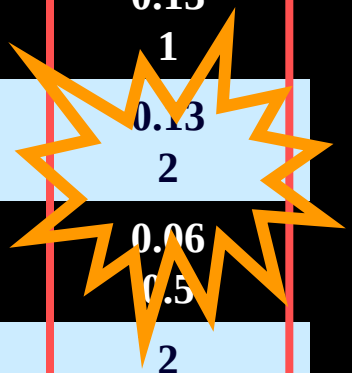
Actividad in vitro de anidulafungina sobre levaduras procedentes de hemocultivo

Especie (nº)	Intervalo	CMI 50	CMI 90
C. albicans (43)	0,016 -2	0,016	0,5
C. parapsilosis (24)	0,25 - 2	1	2
C. guilliermondii (26)	0,016 - 2	1	2
C. glabrata (20)	0,016 - 2	0,016	0,12
C. krusei (18)	0,016 - 0,5	0,06	0,12
C. tropicalis (21)	0,016 - 0,06	0,016	0,03
C. lusitaniae (7)	0,016 - 0,5	0,06	
C. famata (6)	0,016 - 2	0,06	
Otras levaduras (8)	0,016 - 1	0,016	
Total (171)	0,016 - 2	0,06	2

Cantón E, Pemán J et al. Rev Iberoam Micol 2006

Equinocandinas: actividad *in vitro Candida*

Organismo (n)	Antifúngico	MIC 50	MIC 90
C. albicans (733)	Anidulafungina Caspofungina	0.03 0.5	0.03 0.5
C. glabrata (458)	Anidulafungina Caspofungina	0.03 0.5	0.13 1
C. tropicalis (307)	Anidulafungina Caspofungina	0.03 0.5	0.13 1
C. krsei (50)	Anidulafungina Caspofungina	0.06 1	0.13 2
C. dubliniensis (18)	Anidulafungina Caspofungina	0.03 0.5	0.06 0.5
C. parapsilosis (391)	Anidulafungina Caspofungina	2 2	2 2
C. lusitaniae (20)	Anidulafungina Caspofungina	0.06 1	0.25 2



Ostrosky-Zeichner et al. AAC 2003

Actividad *in vitro de* anidulafungina sobre cepas de *C. glabrata* con CMI elevadas de caspofungina

Isolate	Anidulafungina			Caspofungina		
	MIC_2/MIC_0/MFC	IC_{50}/IC_{90}	R^2	MIC_2/MIC_0/MFC	IC_{50}/IC_{90}	R^2
1	0.25/0.5/0.5	0.063/0.075	0.97	1/2/4	0.81/0.83	0.91
2	0.125/0.25/0.25	0.11/0.18	0.93	1/1/2	0.52/0.60	0.96
3	0.125/0.25/0.25	0.039/0.11	0.86	1/2/4	0.55/0.61	0.95
4	0.125/0.25/0.25	0.086/0.18	0.91	1/2/2	0.91/1.1	0.89
5	0.125/0.25/0.25	0.15/0.65	0.83	1/2/2	0.64/0.85	0.89
6	1/2/4	0.65/2.4	0.96	2/2/128	1.8/23	0.73
7	0.125/0.25/0.5	0.092/0.15	0.96	1/1/2	0.57/0.67	0.95
8	0.25/0.25/0.5	0.049/0.16	0.94	1/1/2	0.90/1.0	0.82
9	0.25/0.5/0.5	0.13/0.15	0.88	1/1/2	0.94/1.0	0.91
10	0.125/0.25/1	0.11/0.19	0.81	1/1/2	0.86/1.2	0.91
11	0.125/0.25/4	0.071/0.12	0.98	1/1/1	0.91/0.98	0.86
12	0.125/0.25/0.5	0.11/0.12	0.93	1/1/4	0.84/0.94	0.95
13	0.25/0.25/1	0.053/0.38	0.89	1/1/2	0.74/1.0	0.89
14	0.125/0.125/1	0.062/0.21	0.92	1/1/2	0.90/0.99	0.90
15	0.125/0.125/1	0.11/0.13	0.83	1/1/4	0.83/0.93	0.94
16	1/2/4	0.17/7.8	0.78	4/8/64	ND[a]	ND
17	2/4/8	0.83/5.3	0.93	64/64/>128	ND	ND
18	0.5/4/8	2.4/3.6	0.90	2/64/64	ND	ND

Cota J et al. AAC, 2006

¿Qué ventajas le encuentras *in vivo*?

PK / PD de equinocandinas: tabla comparativa

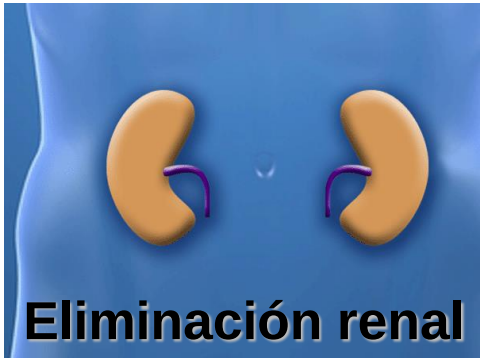
	Caspo	Mica	Anidula
Metabolismo y excreción	Hepático	Hepático	No hepático (degradación química)
Unión a proteínas	97%	> 99%	99%
Vol distribución	8-10 L	27 L	30-50 L
Vida ½ (h)	9-11	14-17	26
Aclaramiento pediatría	Rápido	Rápido	No ajuste de dosis

Anidulafungina presenta un perfil único de eliminación

Anidulafungina

Micafungina

Caspofungina



Eraxis [package insert]. New York, NY: Pfizer Inc; 2007.
Cancidas for Injection [package insert]. Whitehouse Station, NJ: Merck & Co, Inc; 2005.
Mycamine for Injection [package insert]. Deerfield, Ill: Fujisawa Healthcare Inc; 2006.

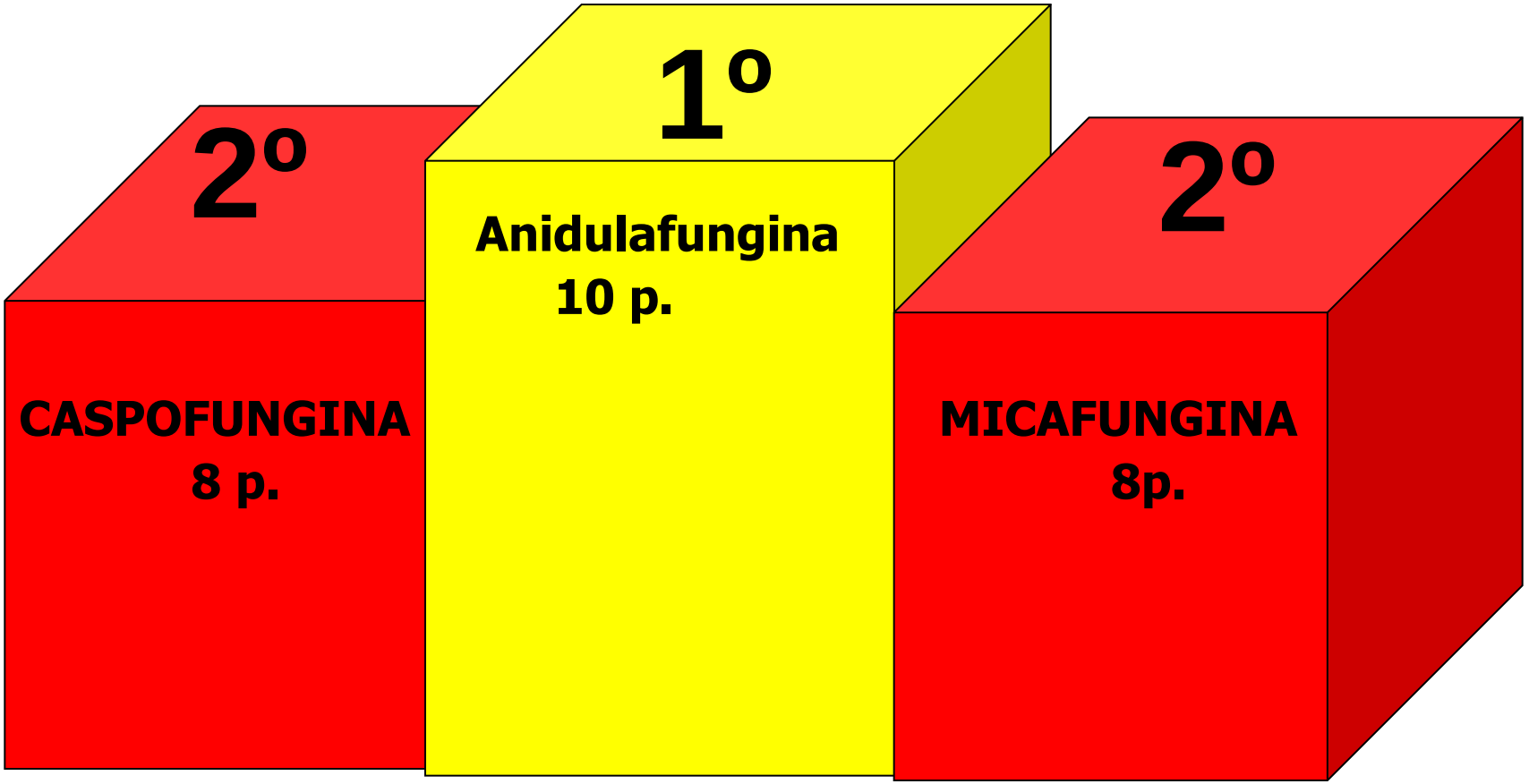
ANIDULAFUNGINA VENTAJAS. Resumen

- **Mejor metabolismo**. **No tóxico hepático** (En el ensayo es significativo). Seguro en Transplante y con uso concomitante con Ciclosporina.
- **Superioridad** en **eficacia clínica y microbiológica** y casi en Mortalidad. Se mueren más tarde los del grupo de Anidulafungina.
- Tendencia a **menor persistencia** casi estadísticamente significativa (6,3% vs 14,4%,p=0,06).
- En los pacientes en los que no se quita el catéter la respuesta a Anídulafungina es mejor (75% vs 27,3%). **Actividad biofilm**?
- **Mejor coste eficacia**

■**Reboli A et al. ICAAC 2005 M-718**

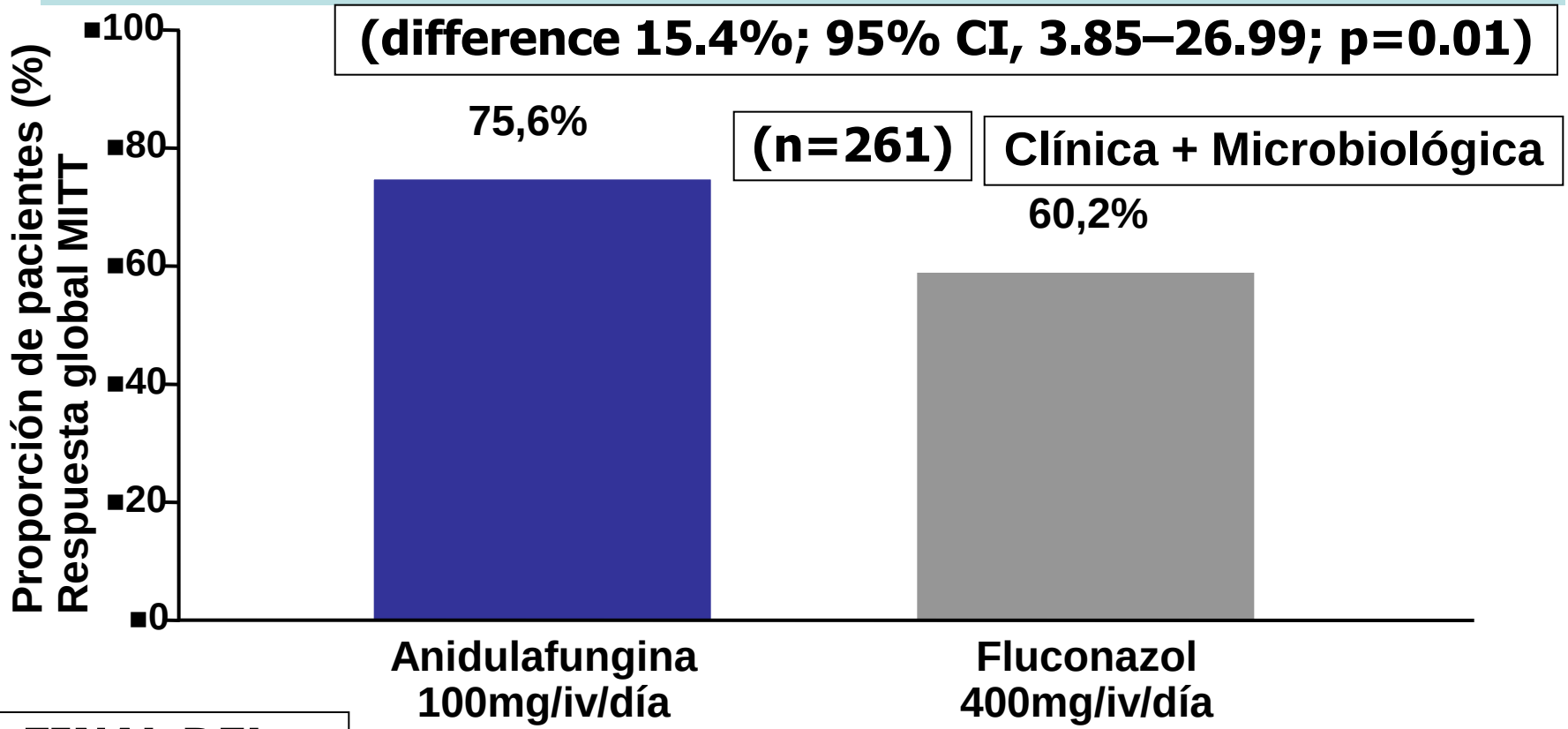
■ **Reboli A et al. N Engl J Med. 2007**

Eficacia global



ANIDULAFUNGINA
Superioridad en Candidemias y CI.

Ensayo clínico fase III doble ciego y randomizado
La diferencia se mantuvo a las 2 semanas.
No toxicidad. No interfiere con Ciclosporina, se degrada y no se biotransforma.



FINAL DEL TRATAMIENTO

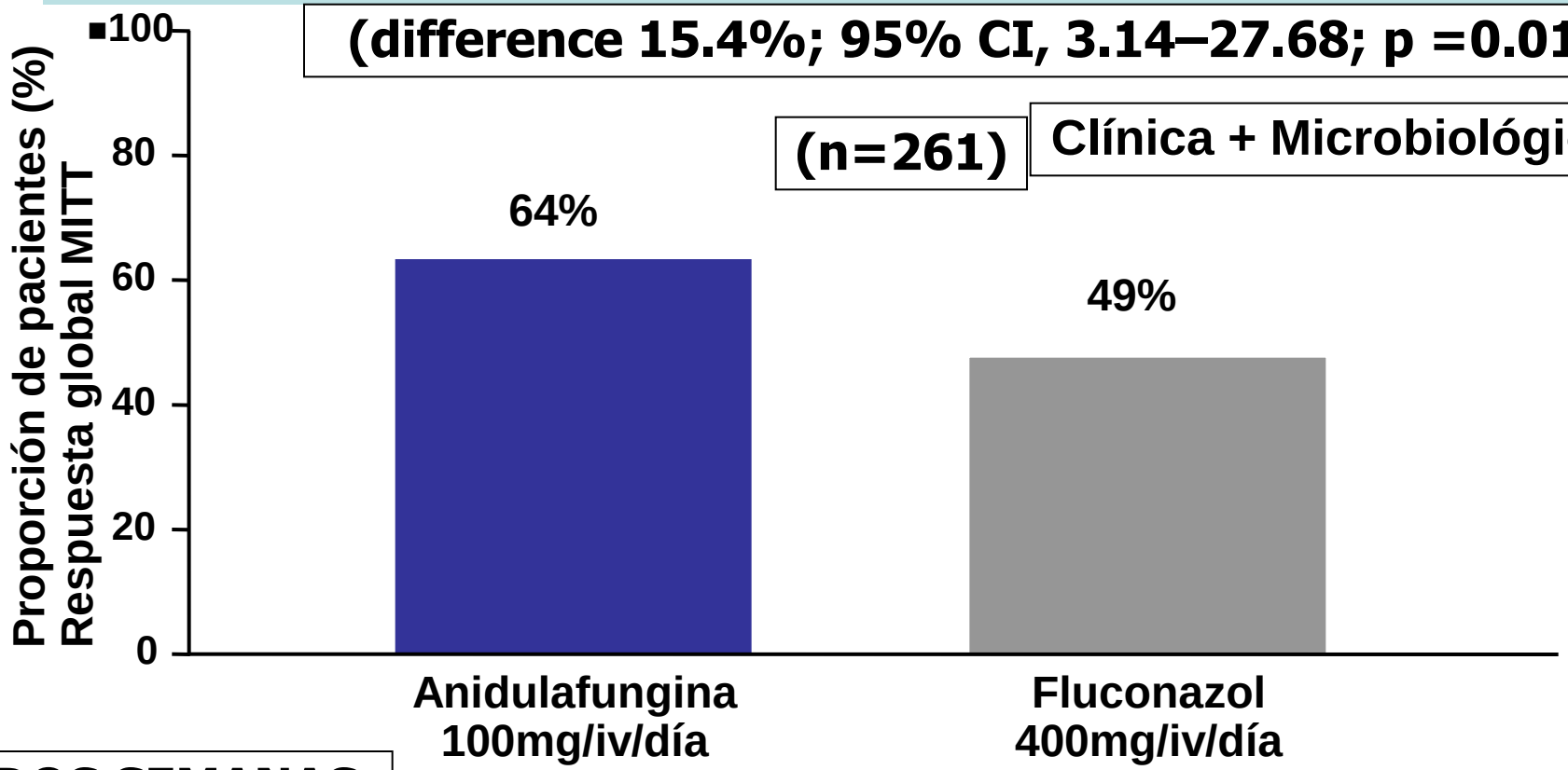
Reboli A et al. ICAAC 2005 M-718
Reboli A et al. N Engl J Med. 2007

ANIDULAFUNGINA
Superioridad en Candidemias y CI.

Ensayo clínico fase III doble ciego y randomizado
No toxicidad. No interfiere con Ciclosporina, se degrada y no se biotransforma.

(difference 15.4%; 95% CI, 3.14–27.68; p =0.01)

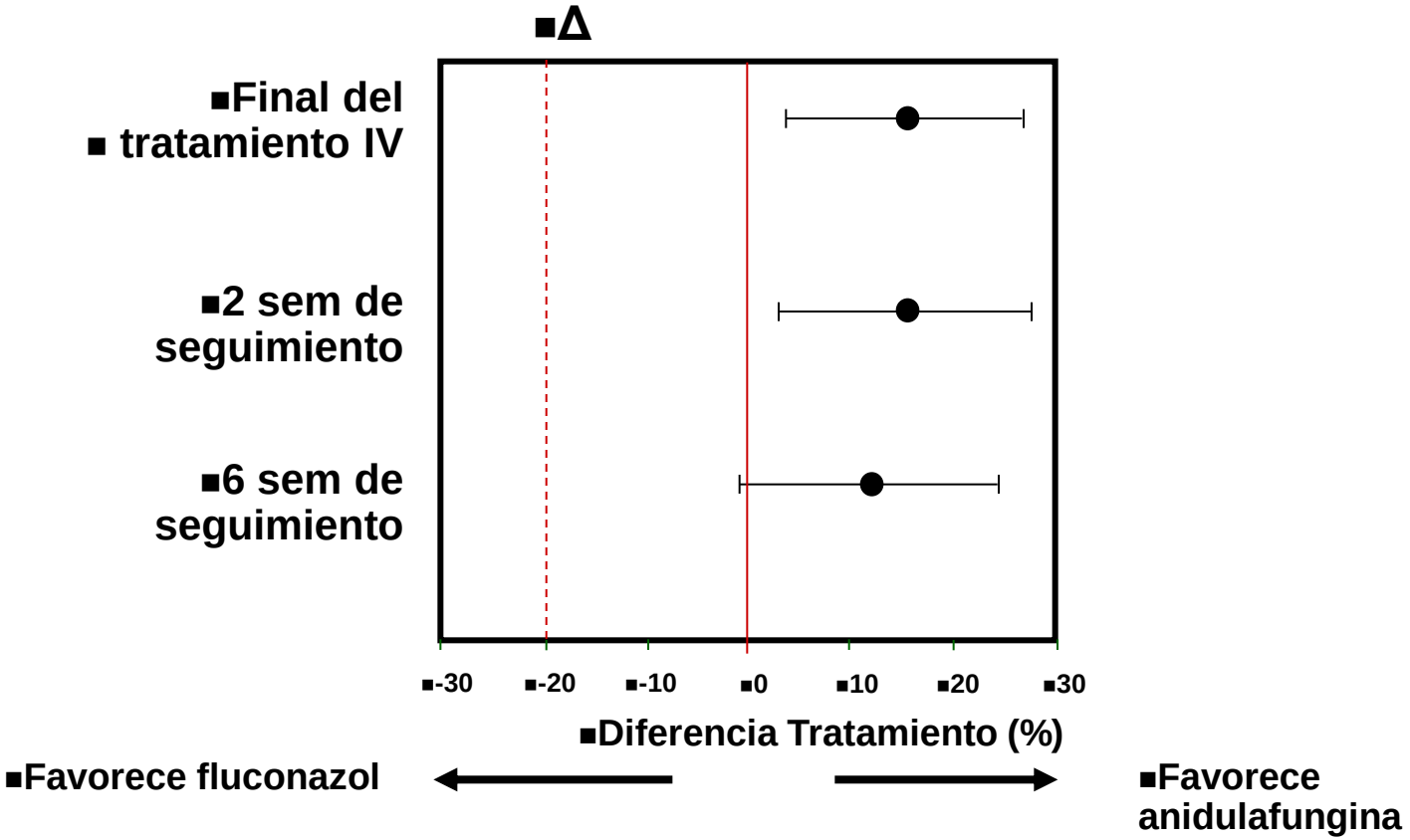
(n=261) **Clínica + Microbiológica**



DOS SEMANAS DESPUES

Reboli A et al. ICAAC 2005 M-718
Reboli A et al. N Engl J Med. 2007

Respuesta Global en todos los tiempos del seguimiento (IC 95%)



■Reboli A et al. N Engl J Med. 2007;356:2472-82

ANIDULAFUNGINA
Comparador Fluconazol.

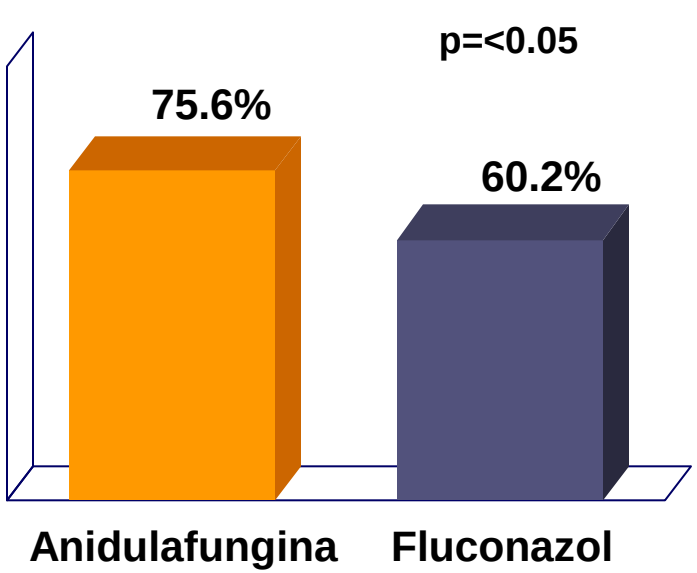
Table 3. Microbiologic and Global Responses at the End of Intravenous Therapy in the Modified Intention-to-Treat Population.*

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

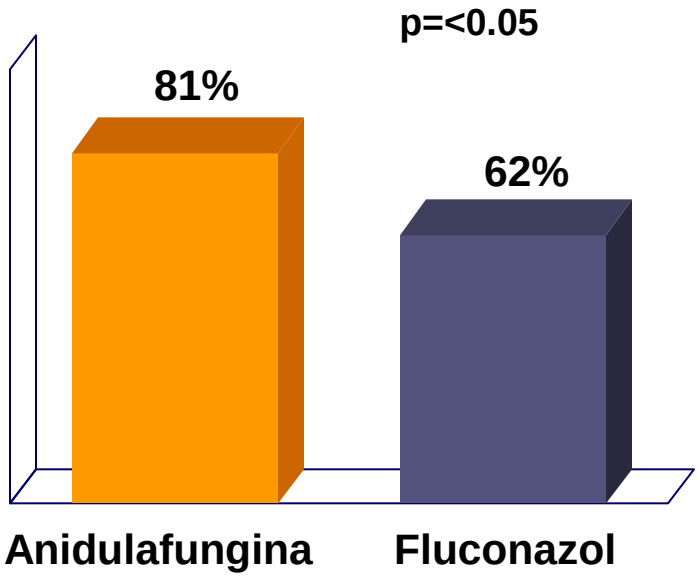
- A favor:
  - Fluconazol es de primera línea para el tratamiento de las candidiasis.
  - Mejores CIM90 para Anidulafungina.
  - Mejores resultados para *C.albicans* y *C.tropicalis*

Eficacia de Anidulafungina vs. Fluconazol al final del Tratamiento IV

Eficacia Global



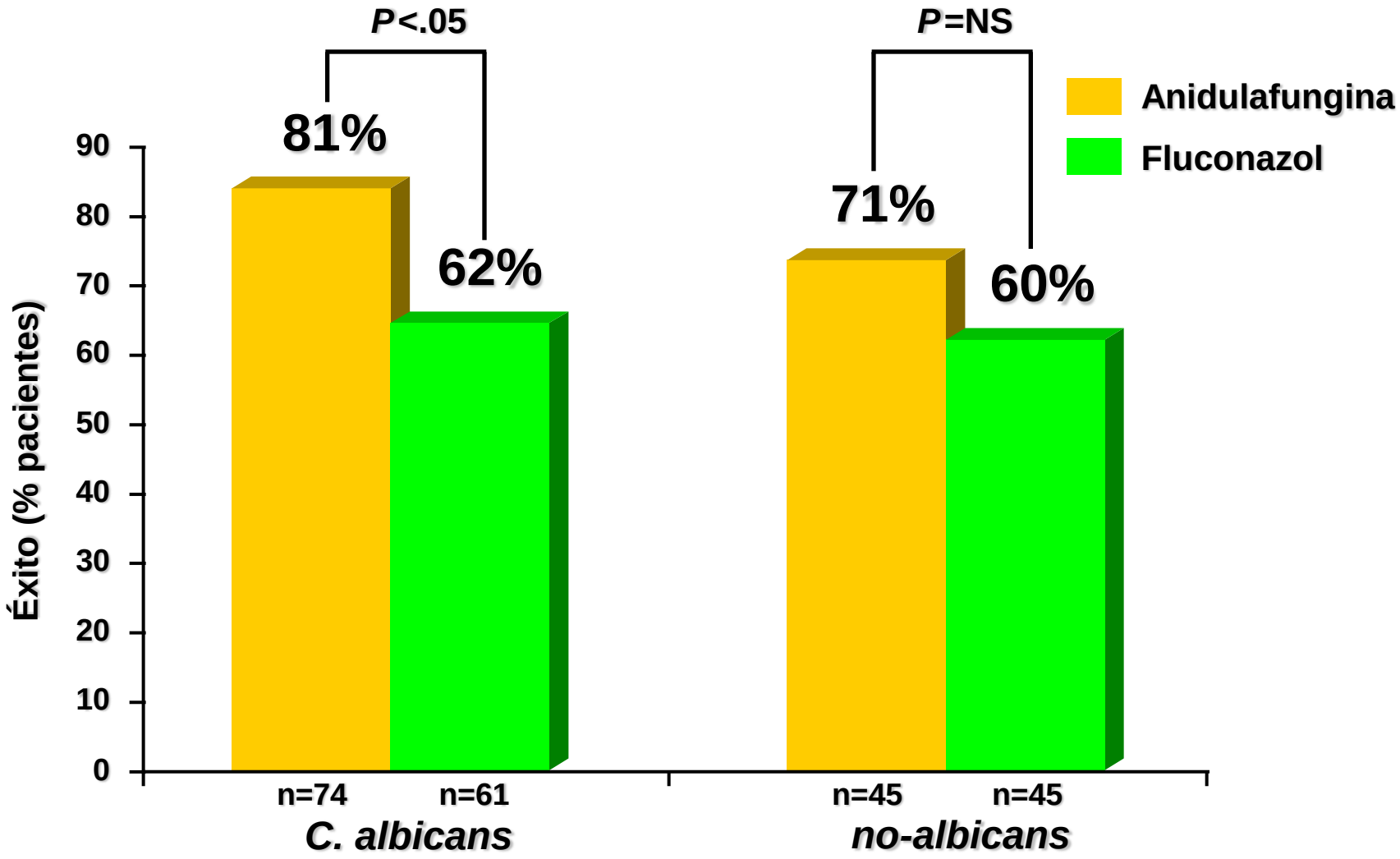
vs. *C. albicans*



(IC95%, 3.9 a 27.0)

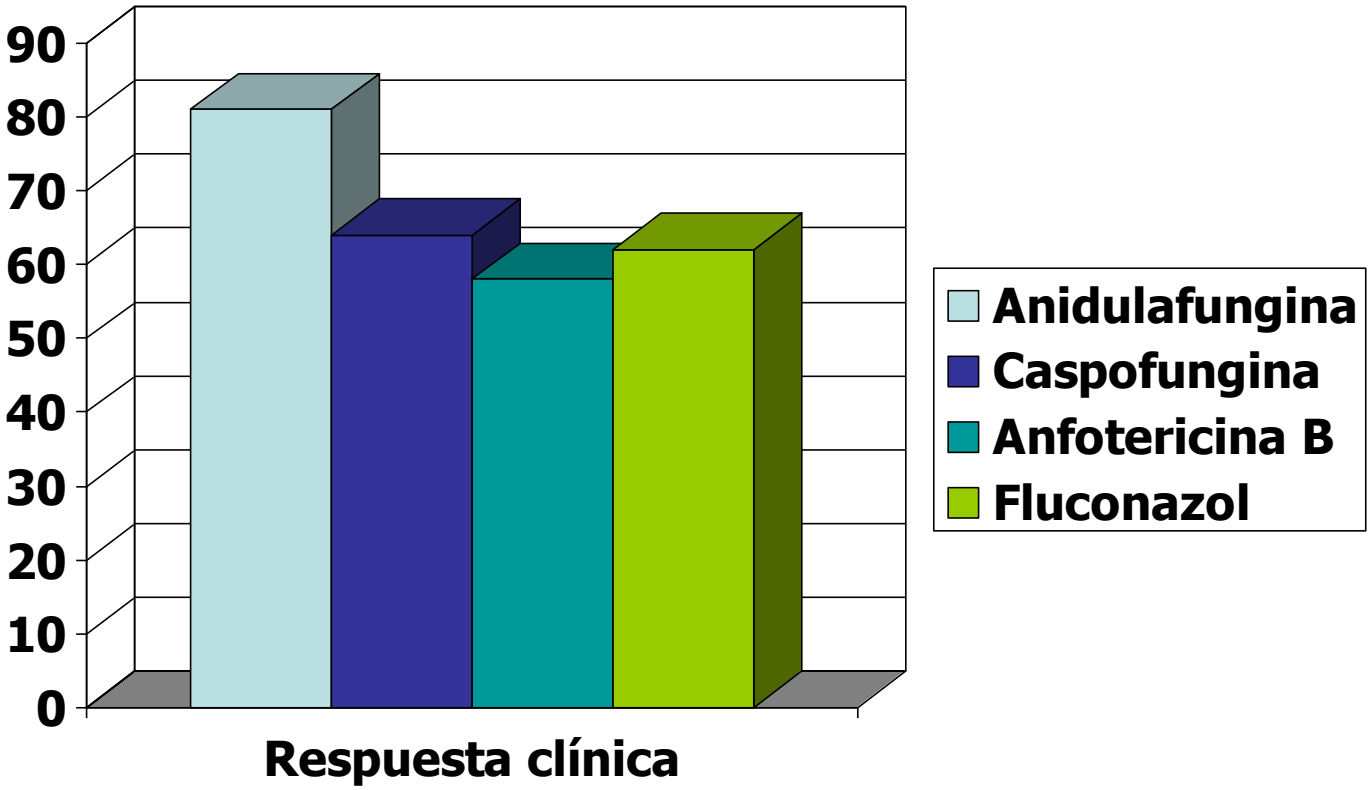
Reboli A et al. N Engl J Med. 2007;356:2472-82

Anidulafungina *vs* fluconazol en candidiasis invasora
Eficacia en *Candida* spp.



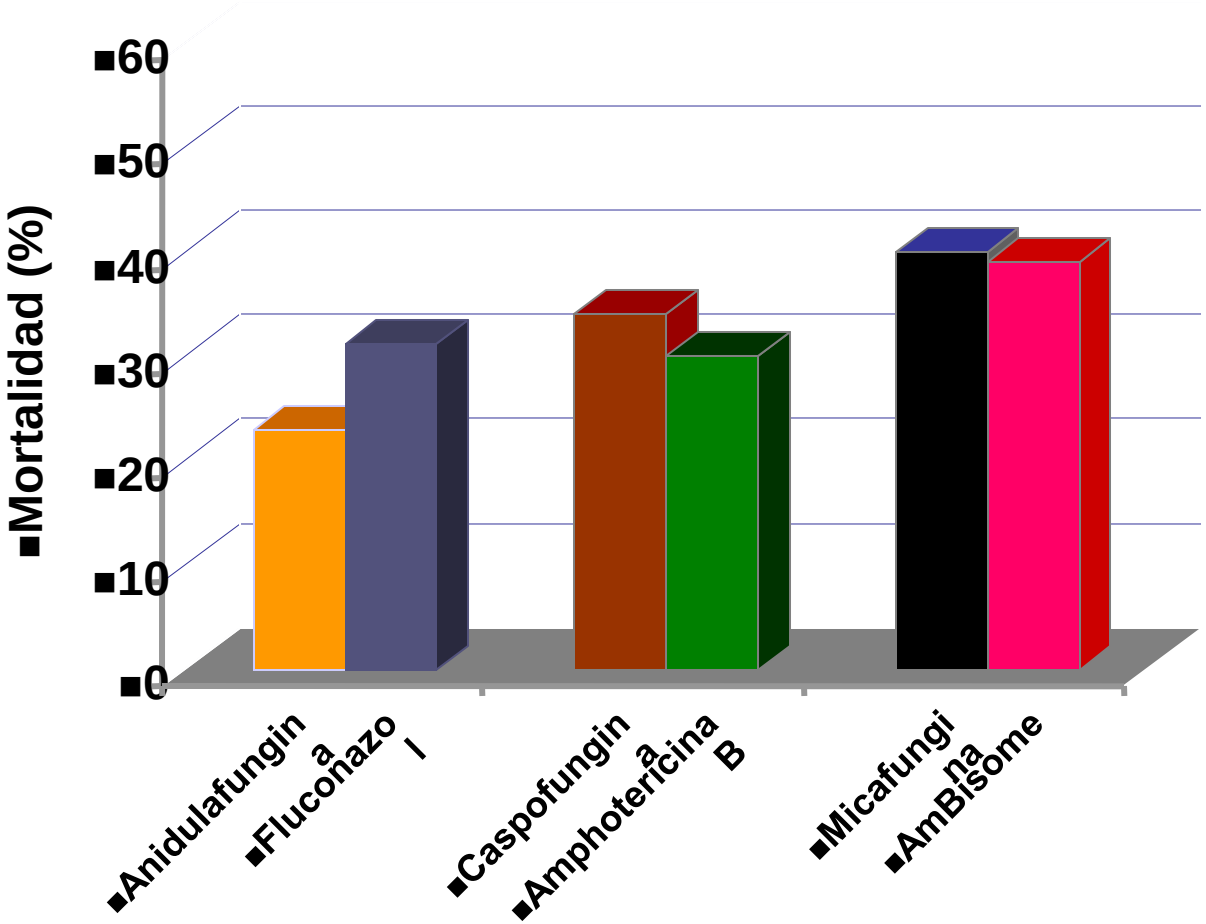
Reboli AM et al. N Engl J Med 2007

Eficacia diferencial antifúngicos frente a *C.albicans*



¿Habría que utilizar siempre Anidulafungina para tratar candidemias causadas por *C.albicans*?

Mortalidad de Pacientes con Candidemia: últimos estudios



- Mora-Duarte et al. *N Engl J Med*. 2002;347:2020-9.
- Ruhnke et al. ICAAC 2005. Kuse E-R Lancet 2007;369:1519-27

ANIDULAFUNGINA
Inconvenientes: Cosas a aclarar.

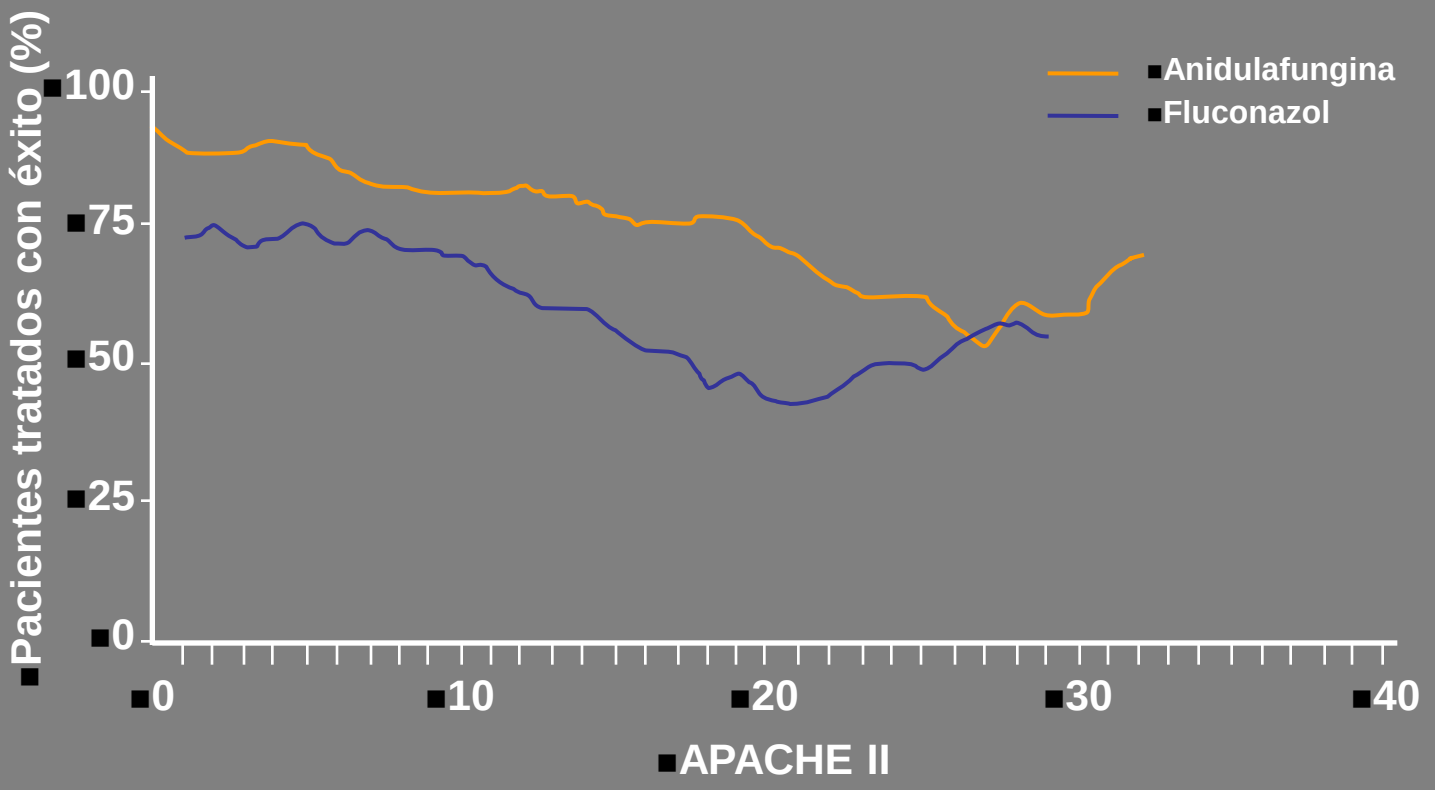
- En cuanto a la familia de antifungicos:
  - Efecto de clase o de anidulafungina?.
  - *C parapsilosis*
- En cuanto al diseño y resultados:
  - Superioridad en eficacia clínica en un ensayo de no inferioridad.
  - **Pobre información** con respecto a la población de estudio:
    - No sabemos cuantos pacientes en UCI
    - No sabemos cuantos en FMO o Shock Séptico.
    - APACHES bajos. No resultados estratificados por gravedad.
    - No cuántos con vasopresores ni en ventilación mecánica-
  - Sabemos poco del catéter y su manejo

■Reboli A et al. ICAAC 2005 M-718

■ Reboli A et al. N Engl J Med. 2007

Respuesta según la gravedad de la Enfermedad

Exito global según APACHE II (población Micro-ITT)



Reboli A et al. N Engl J Med. 2007;356:2472-82

Outcomes in Patients With Invasive Candidiasis Treated With Anidulafungin or Fluconazole: Comparison of Response to Treatment in ICU Patients and/or Patients With End-Organ Dysfunction

Andrew F. Shorr[1], Daniel H. Kett[2], Sonia Sanchez[3], Sabina Gasper[3], Haran T. Schlamm[3]

[1]Washington Hospital Center, Washington, DC, USA; [2]University of Miami and Jackson Memorial Hospital, Miami, FL, USA; [3]Pfizer Inc, New York, NY, USA

- 63 pacientes UCI de 245 (25,7%)
- Disfunción renal 52 (21,2%); Disfunción hepática (34,5%); Disfunción respiratoria (25,3%); Disfunción cardiovascular (13,4%)

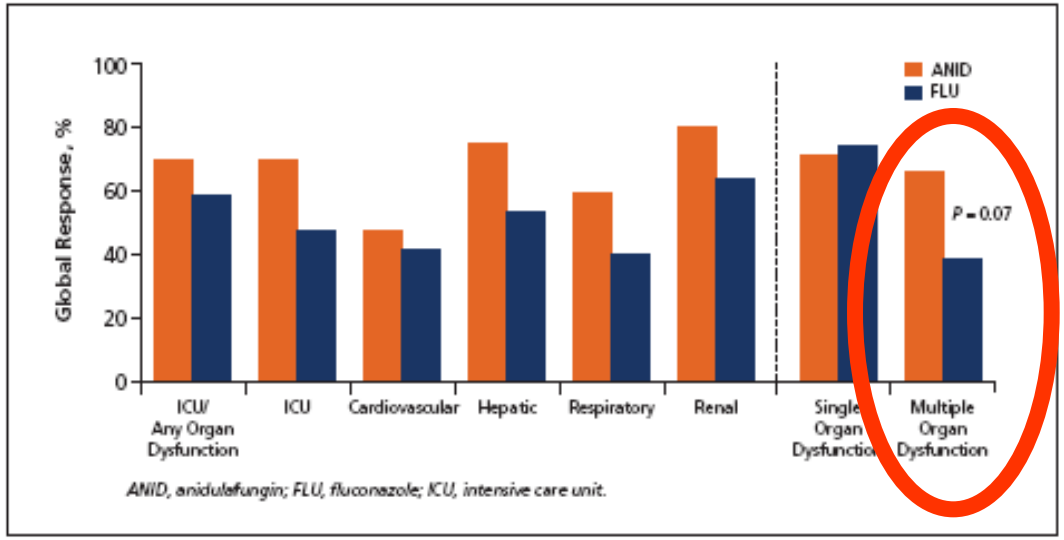
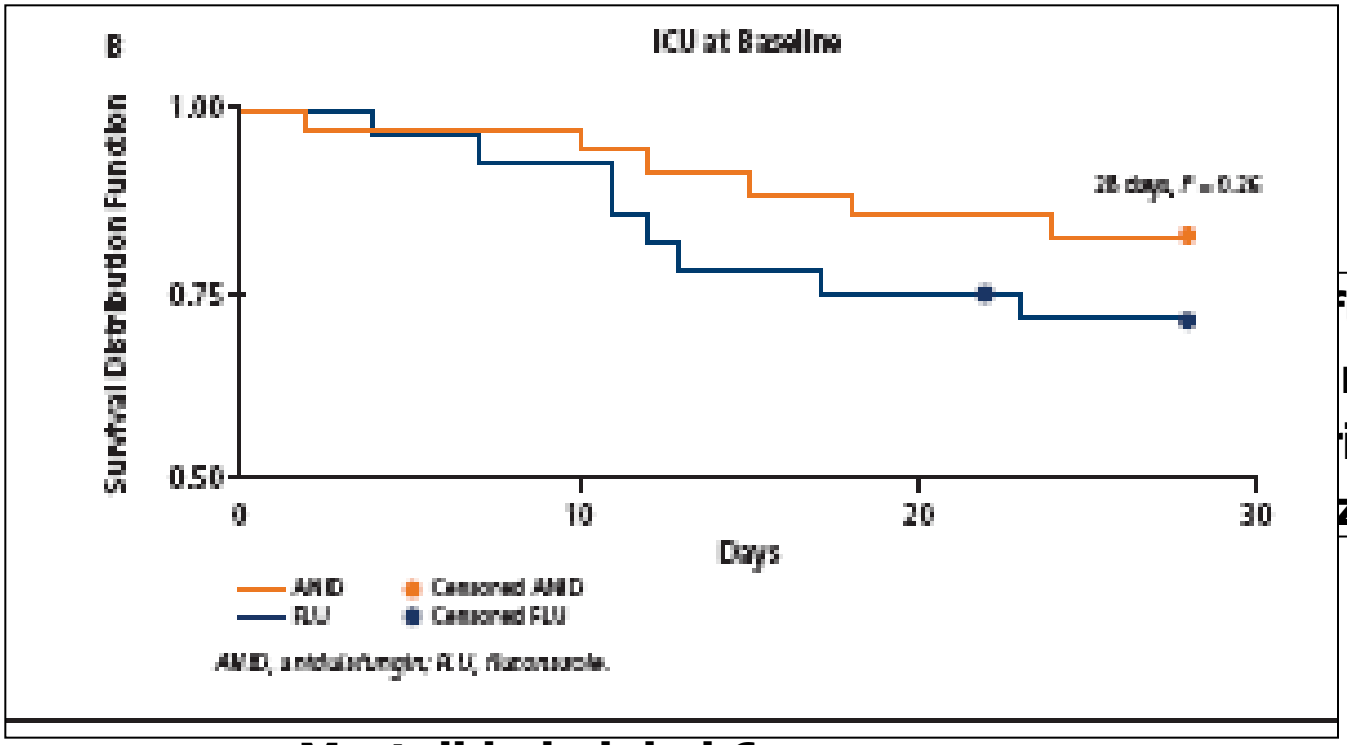


Figure 1. Global response rates at end of intravenous study drug treatment by patient subgroup.

RESPUESTA CLÍNICA

SCCM 2008

Mortalidad global en enfermos críticos con equinocandinas



fungina*
ngina**
icina B
zol*

Mortalidad global 6 semanas

*Shorr A.F, Kett DH, Sanchez S, Gasper S. Outcomes in patients with invasive candidiasis treated with anidulafungin or fluconazole: comparison of response to treatment in ICU patients and/or patients with end-organ dysfunction. Crit Care Med 2007; 35. Abstract 889

** DiNubile MJ, Lupinacci RJ, Strohmaier KM, Sable CA, Kartsonis NA. Invasive candidiasis treated in the intensive care unit: observations from a randomized clinical trial.J Crit Care. 2007 Sep;22(3):237-44.

Anidulafungina *vs* fluconazol en candidiasis invasora

- Candidiasis invasora
- Anidulafungina vs. Fluconazol
- En 187 de 202 pacientes con catéter intravascular → retirada del catéter

Pacientes con catéter (n)	Curación	
Fluconazol (11)	3	27’3%
Anidulafungina (4)	3	75%

■*Reboli AM et al. N Engl J Med 2007*

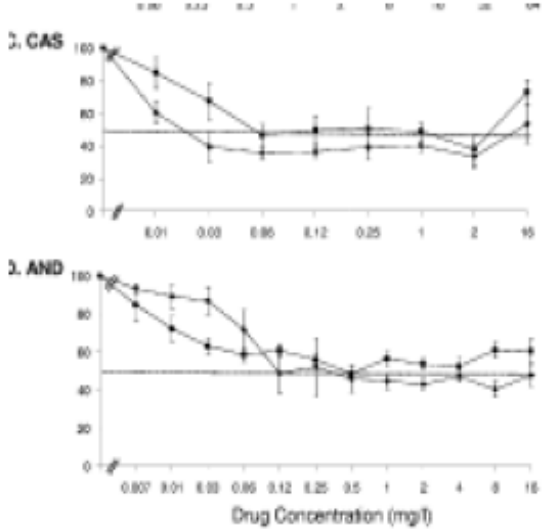
1. Excluyendo los pacientes a los que no se retiró el Catéter IV

	CONTROL	EXPERIMENTAL
Pacientes incluidos	107	123
Pacientes perdidos	0	0
Pacientes con evento	68	93
Pacientes evaluados	107	123
Tasa de pérdidas	0,0%	0,0%

	EVALUADO	IC 95%
RA control	63,6%	54,4% a 72,7%
RA experimental	75,6%	68,0% a 83,2%
RR	1,19	1,00 a 1,42
RRR	19,0%	-0,1% a 41,7%
RAR	12,1%	0,2% a 23,9%
NNT	8	4 a 500
OR	1,78	1,01 a 3,14

Tendríamos que tratar a 8 pacientes con ANI (4-500) en vez de FLU para obtener 1 respuesta más

Biofilm
y Anidulafungina



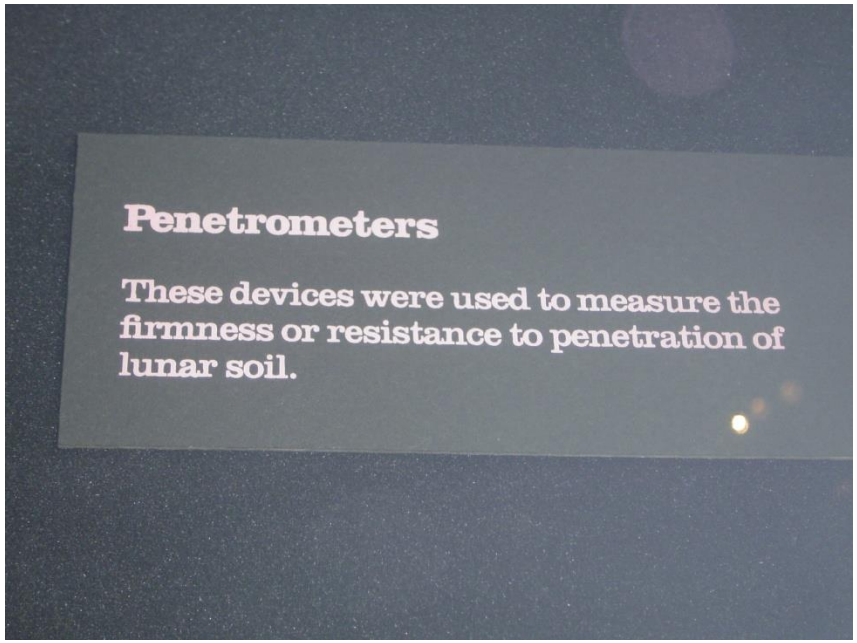
Actividad en biofilm similar a caspofungina (Differential activities of newer antifungal agents against candida albicans and candida parapsilosis biofilms. Antimicrobial agensts and chemotherapy. 2008.p.357-360)

- Mayor actividad en biofilm que FLU, pero similar a CASPO.

Actividad in vitro de la anfotericina B y la anidulafungina sobre biopelículas de *Candida albicans* y *Candida tropicalis*

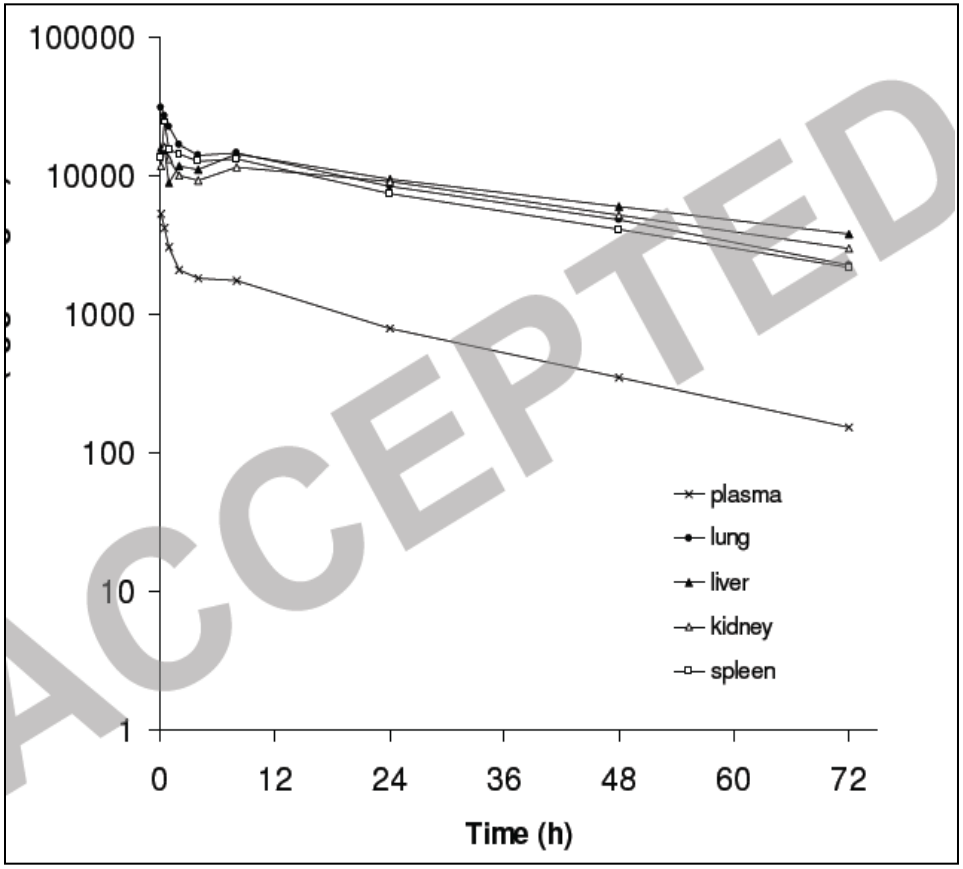
Amparo Valentín[1], Emilia Cantón[1], Javier Pemán[2] y Guillermo Quindós[3]

Penetración



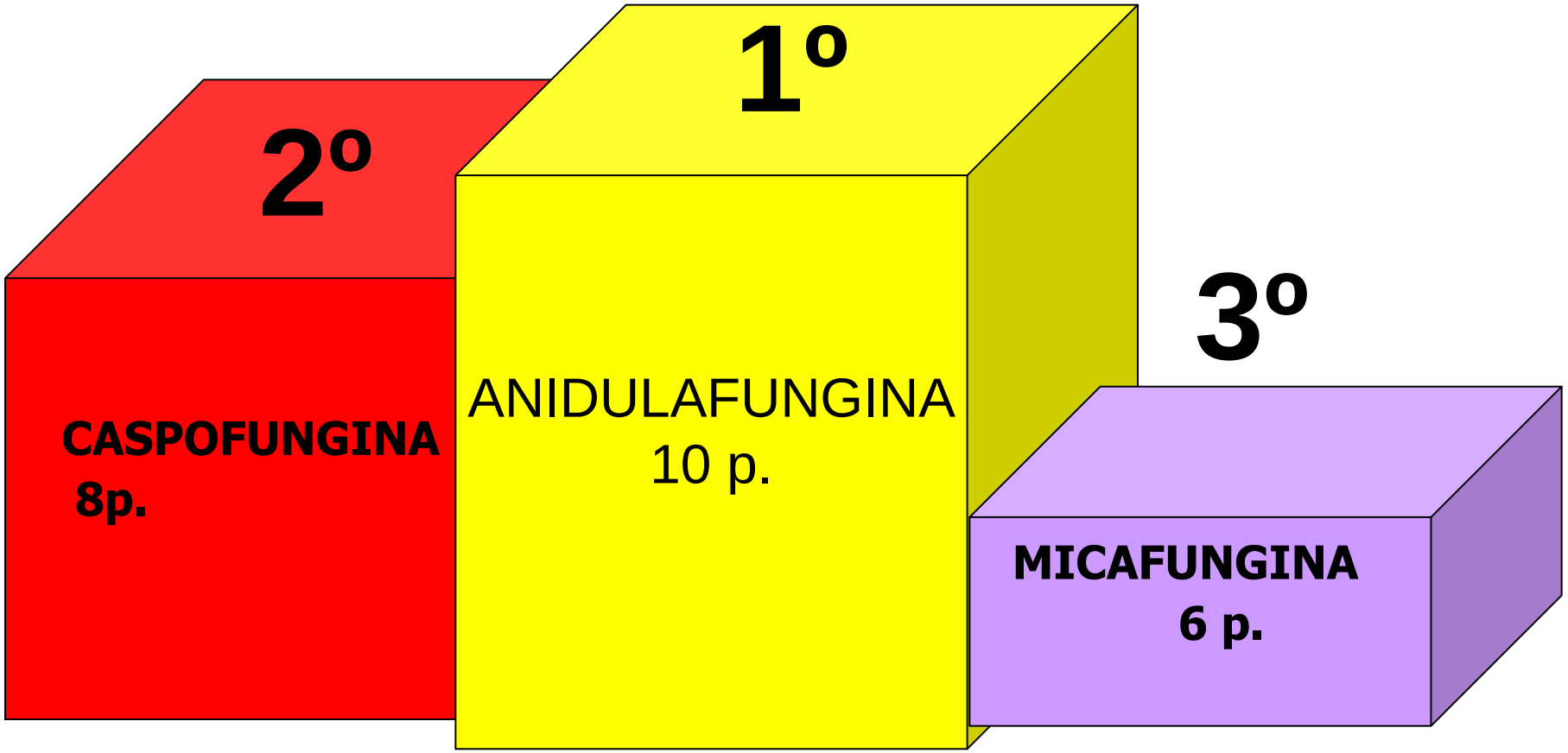
Pharmacokinetics and Tissue Distribution of Anidulafungin 1 in Rats

Bharat Damle, Martin Stogniew, and James Dowell.
Antimicrob. Agents Chemother 2008

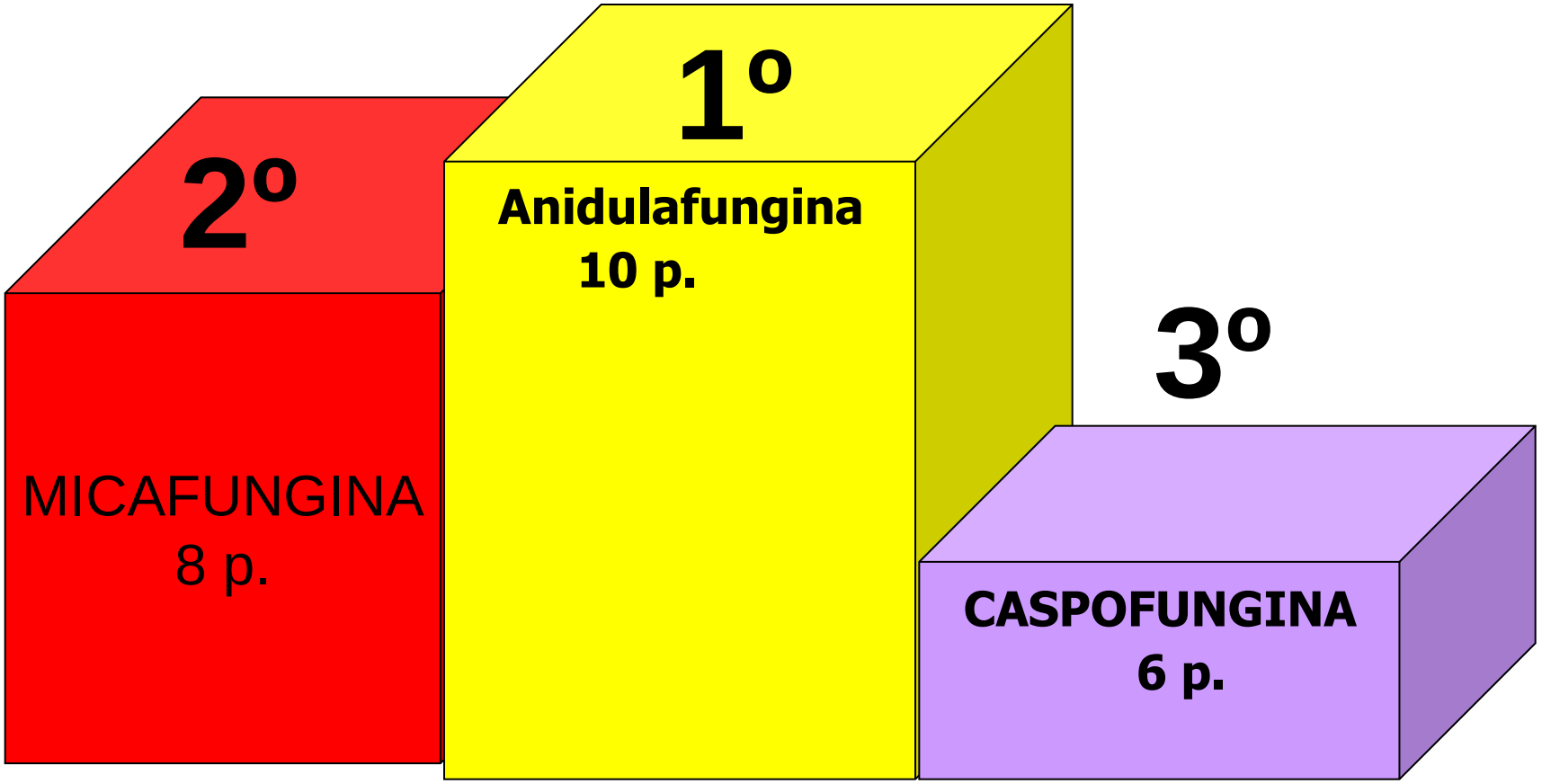


La concentración en tejidos fue de 6 a 9 veces mayor que en plasma

Seguridad


1º
2º
3º
CASPOFUNGINA
8p.
ANIDULAFUNGINA
10 p.
MICAFUNGINA
6 p.

Interacciones



Micafungina: Interacciones con otros fármacos

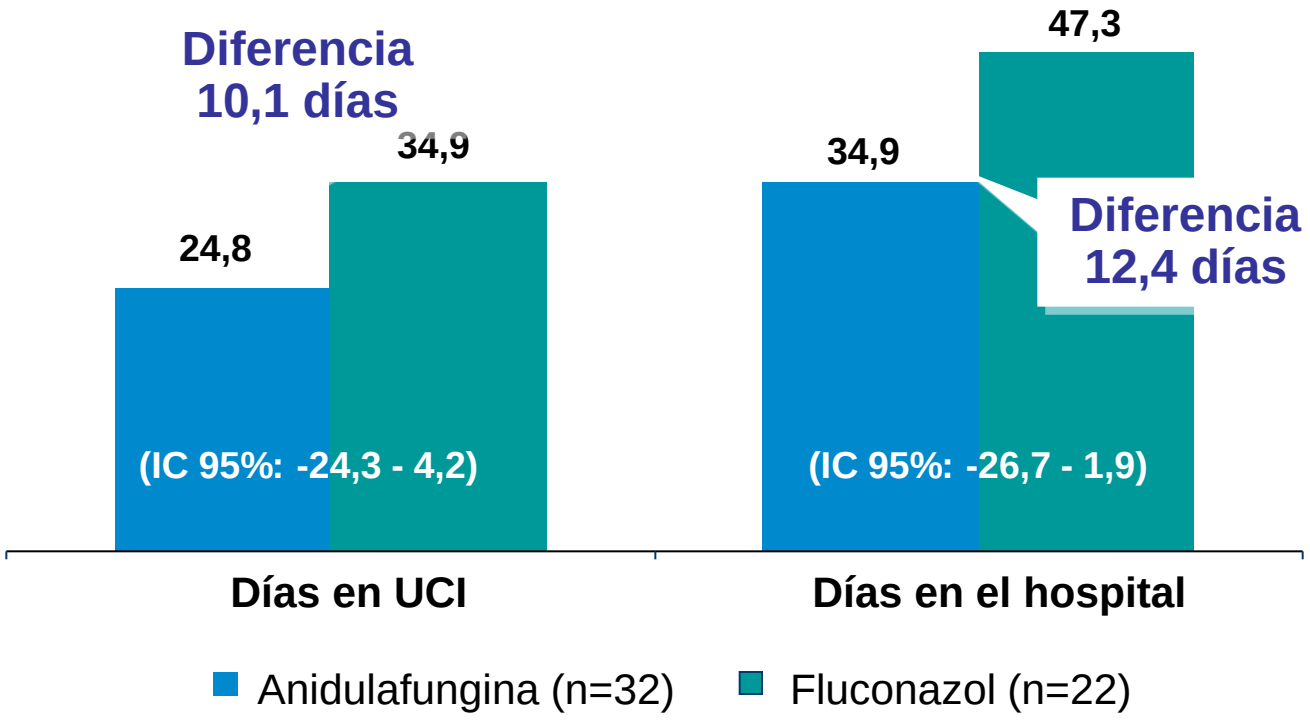
Clase	Fármaco	Efecto de micafungina sobre el metabolismo de los fármacos coadministrados	Efecto del fármaco coadministrado sobre el metabolismo de micafungina
Inmunosupresor	Micofenolato mofetilo Ciclosporina Tacrolimus	Ninguno	**Caspofungina SÍ** **Anidula NO**
Corticoesteroides	Prednisolona	(Micafungina no afecta al metabolismo de los fármacos mencionados)	Ninguno (El metabolismo de micafungina no se ve afectado por ninguno de los fármacos mencionados)
Antiviral	Ritonavir		
Antibacteriano	Rifampicina		
Antifúngico	Anfotericina B Voriconazol Fluconazol		
Bloqueante de los canales de calcio	Nifedipino	Cuando se administra simultáneamente con micafungina: • controlar la toxicidad • reducir la dosis (si fuese necesario)	
Inmunosupresor	Sirolimus		
Antifúngico	Itraconazol		

8 August 2003

Ficha Técnica. Abril de 2008. http://www.emea.europa.eu/htms/human/epar/eparintro.htm

Farmacoeconomía y UCI

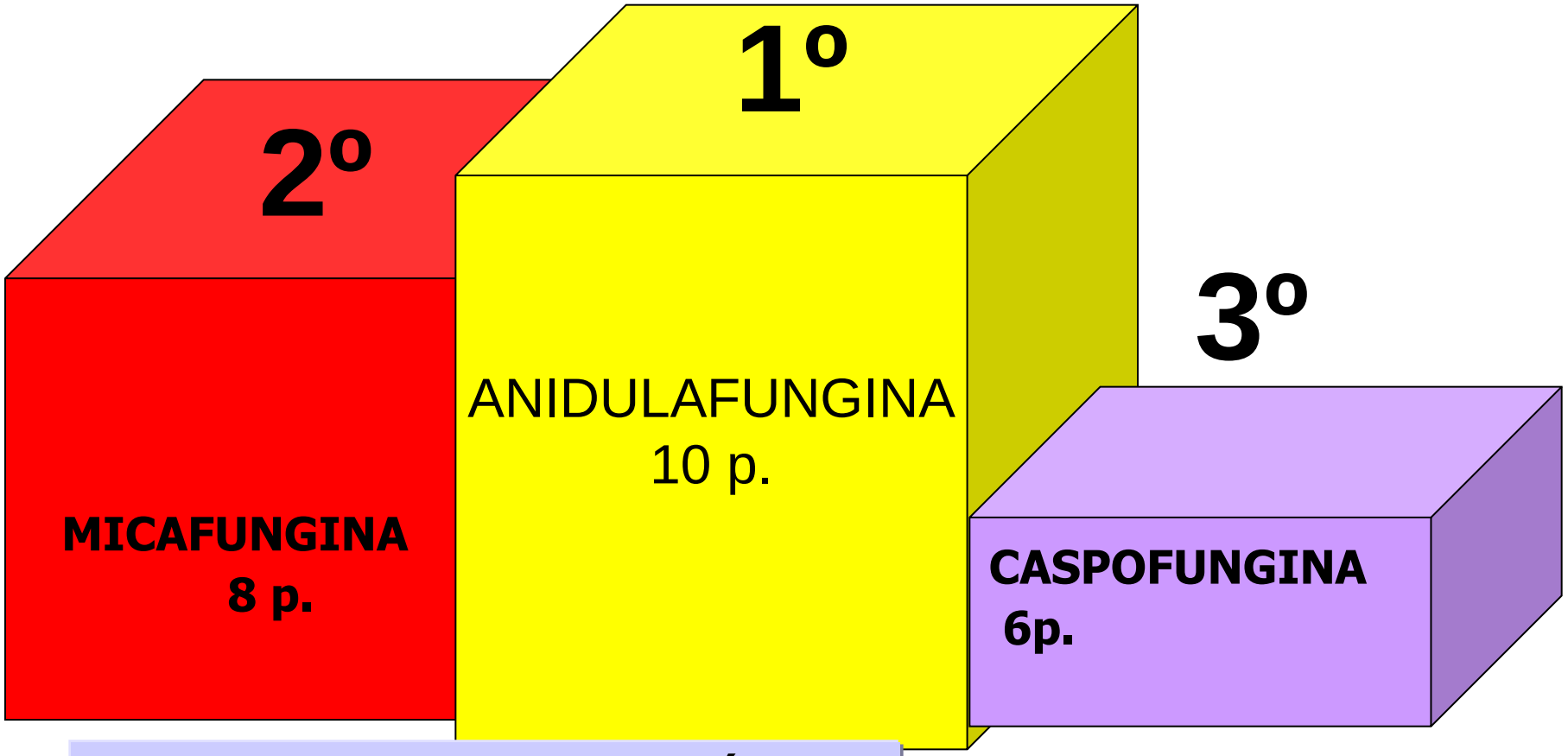
Duración de la estancia en pacientes que sobreviven a las 2 semanas



Mediana UCI: 15,3 (1,5-81,5) ANID y 31,5 (0,5-91,0) FLU

Kett et al., An evaluation of hospital length of stay in intensive care patients with invasive candidiasis treated with anidulafungin versus fluconazole (ECCMID 2008 P 1026)

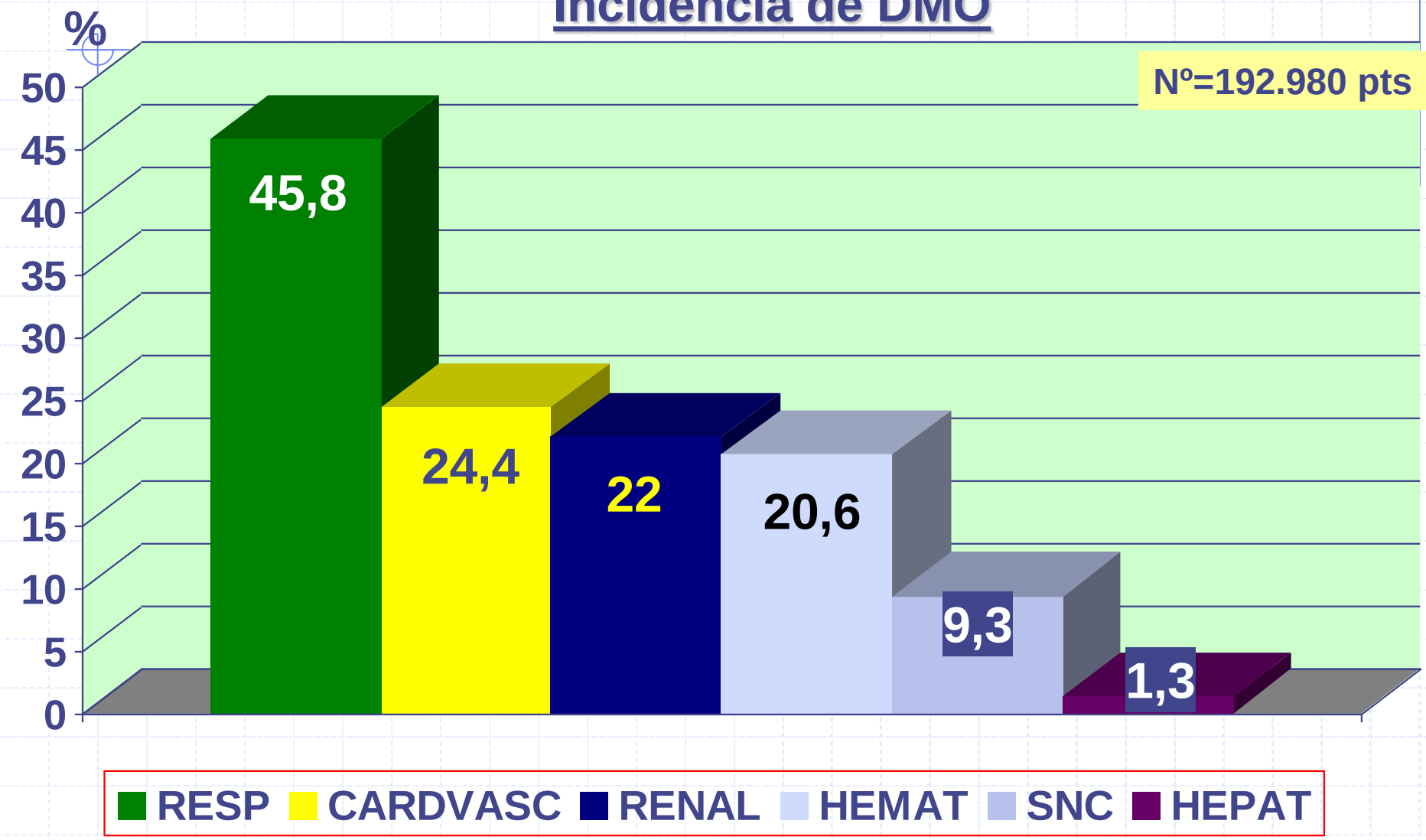
Uso en Insuficiencia hepática grave



La respuesta en las fichas técnicas

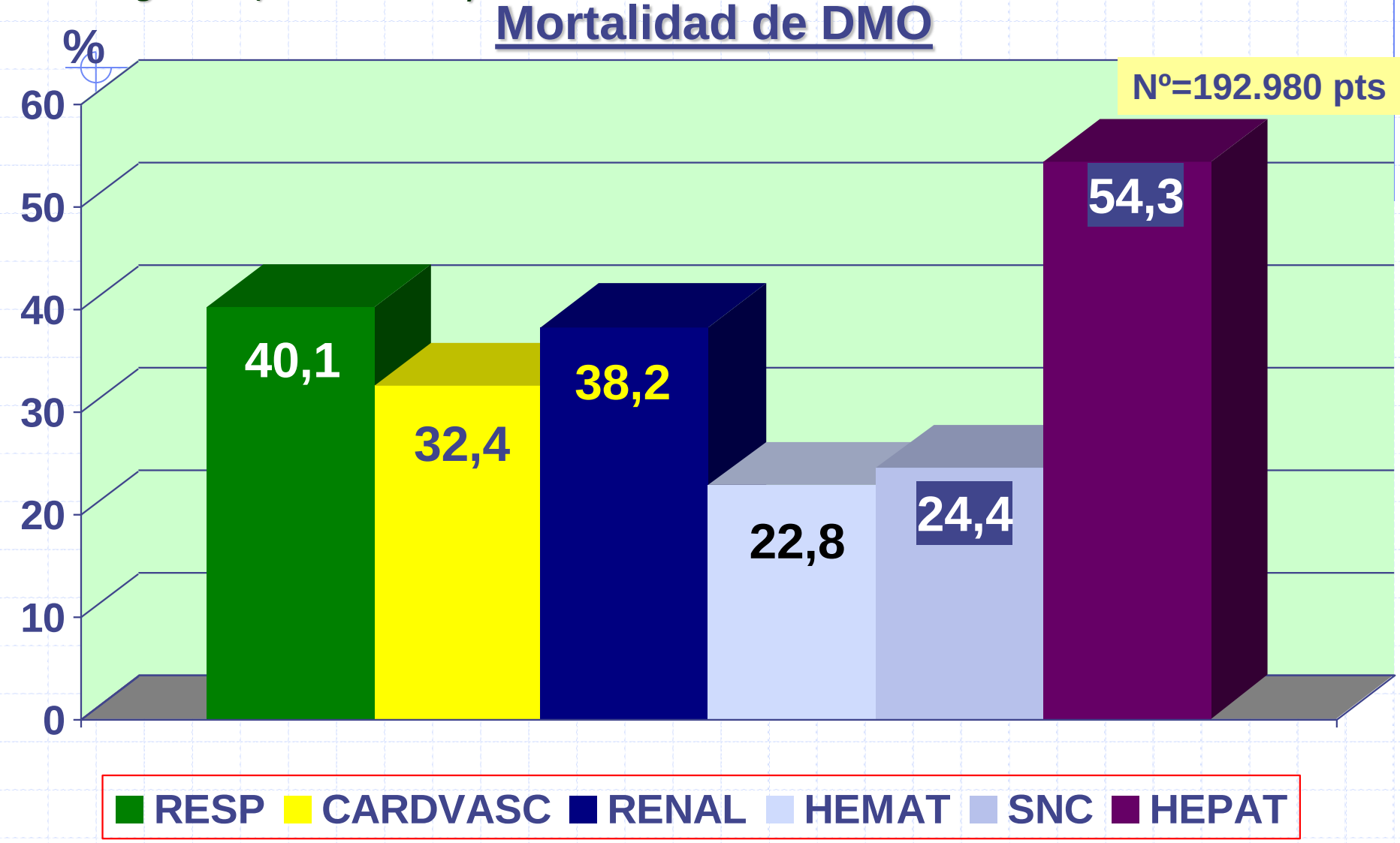
EPIDEMIOLOGÍA SEPSIS EN USA

Angus et al; Crit Care Med; 2001



EPIDEMIOLOGÍA SEPSIS EN USA

Angus et al; Crit Care Med; 2001



Lo que pasa en el Peset….

- De 264 bacteriemias que se presentaron como Sepsis severa o Shock séptico el 25,1 % tuvieron a su diagnóstico un SOFA HEPÁTICO > 1 Y LOS PACIENTES EN SHOCK SÉPTICO EL 27,7%.
- El SOFA HEPÁTICO AL CUARTO DÍA > 1 SE DOCUMENTO EN EL 22.1 % DE LAS SEPSIS SEVERAS SUPERVIVIENTES Y EN EL 22% DE LOS SHOCK SÉPTICOS QUE SEGUÍAN VIVOS.
- El 22,2% de las candidemias tuvieron un un SOFA HEPÁTICO > 1 a su diagnóstico y el 23% al cuarto día…….

Una sorpresa….

Int J Antimicrob Agents. 2009 Sep;34(3):282-3. Epub 2009 Apr 14.
Extended daily dialysis does not affect the pharmacokinetics of anidulafungin.


Muchas gracias...
5th Trends in Medical Mycology (TIMM)
Valencia, 2011