

VI REUNIÓN CIENTÍFICA DEL GRUPO DE ESTUDIO DE MICOLOGIA MEDICA DE LA SEIMC

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Conflicto de intereses

- ❑ Ponencias remuneradas para Merck Sharp and Dohme, y Angellini.
- ❑ Becas de investigación actuales:
 - Proyecto “PI15/00439”, financiado por el Instituto de Salud Carlos III, integrado en el Plan Nacional I+D+i 2013-2016 y cofinanciado por la Unión Europea (FEDER/FSE)

Guión

Cuestión planteada: ¿Debemos usar tratamiento empírico con fluconazol en la candidemia?

1. Epidemiología & resistencia a azoles
2. Recomendaciones TE guías IDSA 2016
3. Potenciales “inconvenientes” de utilizar fluconazol como TE
4. Resultados cohorte CANDIPOP
5. Conclusiones

Epidemiología candidemias

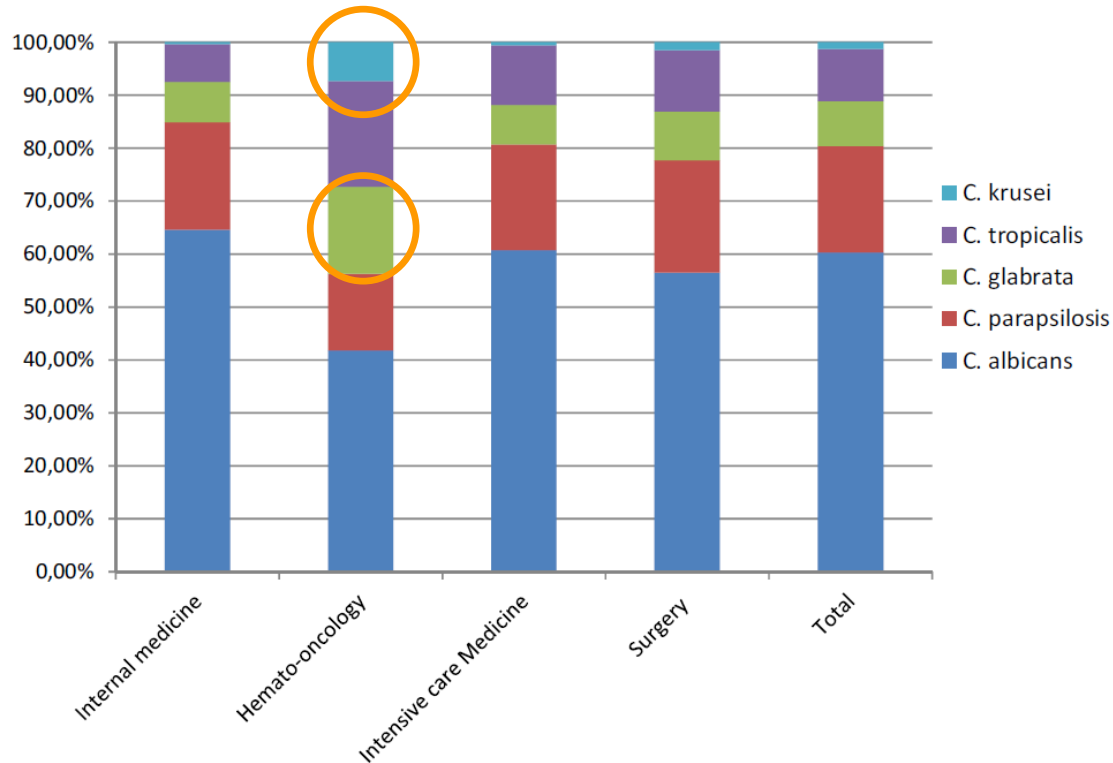
- 2008 -2010: 955 casos → HU Trieste (700 camas), HU Santa Maria Misericordia (1.200 c), Policlínico Gemelli (1.500 c), H Val d'Hebron (1.150 c) y HU Virgen Del Rocio (850 c)
- Mortalidad cruda media en el día 30: **39,9%**

TABLE 2 Incidence of candidemia in the study period

Hospital	Mean incidence (no. of episodes/1,000 admissions) by period:			
	2008	2009	2010	2008–2010
Udine, Italy	0.73	0.79	0.84	0.8
Trieste, Italy	2.11	1.73	1.4	1.74
Rome, Italy	2.35	2.53	2.71	2.53
Barcelona, Spain	1.6	1.57	1.54	1.55
Seville, Spain	0.98	1.08	1.25	1.12
Overall	1.55	1.54	1.71	1.55

Epidemiología candidemias (2)

- 2008 -2010: 955 casos Italia / España
 - **49,6%** de los casos en pacientes ingresados en MI
 - Tipo de servicio ↔ distribución de especies



Algo de bibliografía...

Anidulafungin versus Fluconazole for Invasive Candidiasis

Successful global response: clinical success (resolution of signs and symptoms and no need for additional systemic antifungal therapy) + microbiologic success

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. (%)		
<i>Candida albicans</i>	77/81 (95)	57/70 (81)	0.01	60/74 (81)	38/61 (62)	0.02
<i>C. glabrata</i>	15/20 (75)	18/30 (60)	0.37	9/16 (56)	11/22 (50)	0.75
<i>C. parapsilosis</i>	9/13 (69)	14/16 (88)	0.36	7/11 (64)	10/12 (83)	0.37
<i>C. tropicalis</i>	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

ORIGINAL ARTICLE

Anidulafungin versus Fluconazole for Invasive Candidiasis

RESULTS

Eighty-nine percent of the 245 patients in the primary analysis had candidemia only. *Candida albicans* was isolated in 62% of the 245 patients. In vitro fluconazole resistance was infrequent. Most of the patients (97%) did not have neutropenia. At the end of intravenous therapy, treatment was successful in 75.6% of patients treated with anidulafungin, as compared with 60.2% of those treated with fluconazole (difference, 15.4 percentage points; 95% confidence interval [CI], 3.9 to 27.0). The results were similar for other efficacy end points. The statistical analyses failed to show a “center effect”; when data from the site enrolling the largest number of patients were removed, success rates at the end of intravenous therapy were 73.2% in the anidulafungin group and 61.1% in the fluconazole group (difference, 12.1 percentage points; 95% CI, -1.1 to 25.3). The frequency and types of adverse events were similar in the two groups. The rate of death from all causes was 31% in the fluconazole group and 23% in the anidulafungin group ($P=0.13$).

CONCLUSIONS

Anidulafungin was shown to be noninferior to fluconazole in the treatment of invasive candidiasis. (ClinicalTrials.gov number, NCT00056368).

Revisiones sistemáticas y metaanálisis

Treatment of Invasive Candidal Infections: Systematic Review and Meta-analysis

ANAT GAFTER-GVILI, MD; LIAT VIDAL, MD; ELAD GOLDBERG, MD; LEONARD LEIBOVICI, MD;
AND MICAL PAUL, MD

Mayo Clin Proc 2008; 83(9):1011-21

Meta-analysis 15 studies:

- ❑ All assessed antifungal agents showed **similar efficacy**
- ❑ The rate of **microbiological failure** increased with fluconazole vs anidulafungin

Antifungal treatment for invasive Candida infections: a mixed treatment comparison meta-analysis

Edward J Mills*^{1,2}, Dan Perri³, Curtis Cooper⁴, Jean B Nachega^{5,6}, Ping Wu²,
Imad Tleyjeh^{7,8} and Peter Phillips⁹

Ann Clin Microbiol
Antimicrob. 2009; 8:23.

Meta-analysis 11 studies:

- ❑ Treatment options appear to offer preferential effects **on response rates and mortality**

Treatment for candidemia in nonneutropenic

IDSA 2009

- ❑ **B-III:** alternatives
 - Fluconazole 800 mg → 400 mg/d
 - Caspofungin 70 mg → 50 mg/d
 - Anidulafungin 200 mg → 100 mg/d
 - Micafungin 100 mg/d.
- ❑ **B-III:** An echinocandin preferred for patients
 - Recent azole exposure
 - Moderately severe to severe illness
 - High risk of infection due to *C. glabrata* or *C. krusei*

IDSA 2016

- ❑ **Strong recommendation; moderate-quality evidence:** An echinocandin is the preferred empiric therapy
- ❑ **Strong recommendation; moderate-quality evidence:** Fluconazole is an **acceptable alternative** for patients who have had **no** recent azole exposure and are not colonized with azole-resistant *Candida* species

ESCMIC Guidelines

TABLE 4. Recommendations on fever-driven and diagnosis-driven therapy of candidaemia and invasive candidiasis

Population	Intention	Intervention	SoR	QoE	References
Adult ICU patients with fever despite broad-spectrum antibiotics and APACHE II >16	To resolve fever	Fluconazole 800 mg/day	D	I	[30]
ICU patients persistently febrile, but without microbiological evidence	To reduce overall mortality	Fluconazole or echinocandin	C	II _u	[28] [163] [164] [7] [27]
ICU patients with candida isolated from respiratory secretions	To cure invasive candidiasis or candidaemia early	Any antifungal	D	II _u	[42]
ICU patients with positive (1,3)- β -D-glucan test ^a	To cure invasive candidiasis or candidaemia early	Any antifungal	C	II _u	[39] [31] [37] [35] [32] [36] [34] [33]
Any patient with <i>Candida</i> isolated from a blood culture	To cure invasive candidiasis	Antifungal treatment	A	II	[46] [47] [48] [49]

APACHE, acute physiology and chronic health evaluation.

^aThe (1,3)- β -D-glucan tests have low specificity and sensitivity with false-positive results in the presence of haemodialysis, other fungal or bacterial infection, wound gauze, albumin or immunoglobulin infusion.

**Potenciales “inconvenientes” al utilizar
fluconazol como tratamiento empírico**

Probabilidad de “fallar” con fluconazol

Species (n)	Antifungal agent	No. (%) of isolates resistant, intermediate, or SDD to the antifungal agent in“:					Total no. of nonsusceptible strains (% SDD, intermediate, or resistant)
		U	T	B	R	S	
<i>C. albicans</i> (558)	Amphotericin B	NA	NA	NA	NA	NA	NA
	Caspofungin	0	0	0	0	0	0
	Fluconazole	2 (3.8)	1 (1)	0	5 (1.8)	0	8 (1.4)
	Itraconazole	2 (6)	1 (1)	18 (23.1)	5 (1.8)	0	26 (4.7)
	Voriconazole	2 (3.8)	1 (1)	0	4 (1.5)	0	7 (1.2)
<i>C. parapsilosis</i> complex (186)	Amphotericin B	NA	NA	NA	NA	NA	NA
	Caspofungin	1 (4.5)	0	2 (10)	2 (2.3)	1 (4.3)	5 (2.7)
	Fluconazole	1 (4.5)	1 (3)	0	3 (3.4)	0	5 (2.7)
	Itraconazole	NA	NA	NA	NA	NA	NA
	Voriconazole	2 (9)	0	0	0	0	2 (1)
<i>C. glabrata</i> (79)	Amphotericin B	NA	NA	NA	NA	NA	NA
	Caspofungin	0	0	0	0	0	0
	Fluconazole	1 (10)	7 (50)	16 (48.5)	9 (27.3)	3 (42.8)	36 (45.6)
	Itraconazole	NA	NA	NA	NA	NA	NA
	Voriconazole	NA	NA	NA	NA	NA	NA
<i>C. tropicalis</i> (89)	Amphotericin B	NA	NA	NA	NA	NA	NA
	Caspofungin	0	0	0	0	0	0
	Fluconazole	0	0	1 (6.7)	2 (5.3)	1 (4.8)	4 (4.5)
	Itraconazole	NA	NA	NA	NA	NA	NA
	Voriconazole	0	0	0	1 (2.6)	2 (9.5)	3 (3.4)

Criterios CLSI

- ❑ Resistentes
- ❑ Intermedias
- ❑ SDD

96/955 (10%)
“no susceptibles” a
fluconazol
(incluidas *C. krusei*,
n=43)

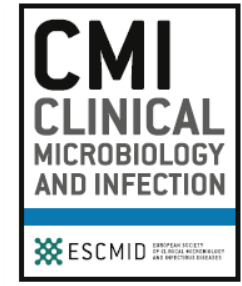
Candidemias de brecha

- ❑ Multicentre study of hospitalized adults with candidaemia at six hospitals in three countries.
- ❑ 409 episodes of candidaemia → 37 (9%) were BrC
 - ❑ 18/242 (7,4%) during fluconazole treatment
 - ❑ **11/73 (15%) during echinocandin therapy**

	BrC (n = 37) (%)	Non-BrC (n = 372) (%)	p
Outcomes			
Intensive care unit admission	10 (27)	113 (30.4)	0.573
Mechanical ventilation	11 (29.7)	101 (27.1)	0.766
Instability (at 48 h)	13 (35.1)	135 (36.3)	0.680
Persistent candidaemia	3 (8.1)	62 (16.7)	0.236
Septic metastases	1 (2.7)	22 (5.9)	0.663
Recurrence	0	13 (3.5)	0.506
Early mortality (5 days)	4 (10.8%)	50 (13.4%)	0.802
Overall mortality (30 days)	15 (40.5)	149 (40.1)	0.954

Empirical and targeted therapy of candidemia with fluconazole versus echinocandins: a propensity score–derived analysis of a population-based, multicentre prospective cohort

L.E. López-Cortés¹, B. Almirante², M. Cuenca-Estrella³, J. Garnacho-Montero⁴, B. Padilla⁵, M. Puig-Asensio², I. Ruiz-Camps², J. Rodríguez-Baño^{1,6,*} for the members of the CANDIPOP Project from GEIH-GEMICOMED (SEIMC) and REIPI*



- ❑ The CANDIPOP project: prospective, population-based cohort study on candidemia
 - ❑ May 2010 → April 2011 in 29 Spanish hospitals
- ❑ Main objective: to compare the clinical efficacy of fluconazole and echinocandins in the treatment of candidemia in real practice.
 - ❑ Primary outcome: all-cause mortality until day 30
 - ❑ Secondary outcomes:
 - ❑ **Persistent candidemia**: *Candida* spp. in BC for ≥ 3 days despite active antifungal therapy
 - ❑ **Clinical failure**: mortality until day 30 $\pm$ persistent candidemia $\pm$ therapy change due to persistent symptoms or toxicity.

Azoles vs. candins in candidemia

❑ Inclusion criteria for Empirical therapy cohort (ETC):

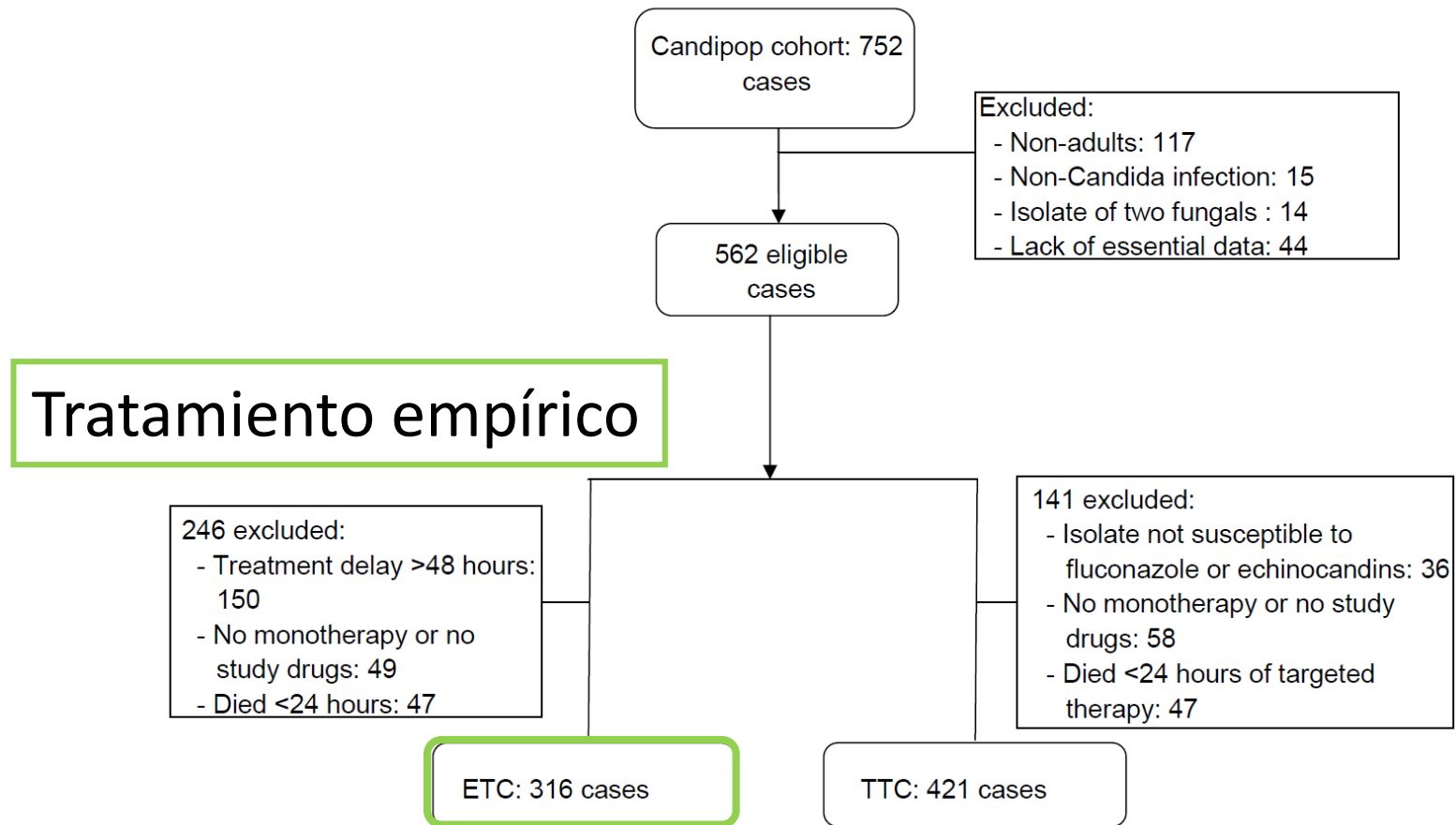
- ❖ Empirical antifungal **monotherapy** with an echinocandin or fluconazole (adequate doses)
- ❖ First dose administered **within 48 hours of the blood culture**
- ❖ Drug administered **for at least 48 hours**, except for cases who died before (were included if they had received at least 24 hours of therapy)
- ❖ Resistant isolates to the drugs of interest **were not excluded**.

❑ Statistical analysis:

- ❖ Cox multivariate regression model
- ❖ Logistic regression models to calculate PS → covariate and matching
- ❖ Sensitivity analysis: severe sepsis or septic shock

Results

□ CANDIPOP cohort: 752 cases of candidemia in 729 patients



Características basales

Characteristic	ETC, all cases (n = 316)	Empirical fluconazole (n = 198)	Empirical echinocandin* (n = 118)	p
Age, years, median (IQR)	66 (54–75)	66 (56–76)	62 (48–73)	0.001
Male gender	182 (57.6)	112 (56.6)	70 (59.3)	0.63
Comorbidities				
Diabetes mellitus	89 (28.2)	59 (29.8)	30 (25.4)	0.40
Chronic pulmonary disease	36 (11.4)	24 (12.1)	12 (10.2)	0.60
Cirrhosis	12 (3.8)	6 (3)	6 (5.1)	0.38
Malignancy	137 (43.4)	92 (46.5)	45 (38.1)	0.15
Neutropenia ($\leq 500/\text{mm}^3$)	19 (6)	5 (2.5)	14 (11.9)	0.001
Hemodialysis	19 (6)	10 (5.1)	9 (7.6)	0.35
Age-weighted Charlson index, median (IQR)	4 (3–6)	5 (3–6)	4 (2–6)	0.01
Pitt score, median (IQR)	1 (1–4)	1 (1–3)	2 (1–5)	<0.001
Severe sepsis or septic shock	96 (30.4)	47 (23.7)	49 (41.5)	0.001
Previous therapy with azoles	66 (20.9)	27 (13.6)	39 (33.1)	<0.001

* Caspofungin (59.3%); anidulafungin (33.1%); micafungin (7.6%)

Características basales (2)

Characteristic	ETC, all cases (n = 316)	Empirical fluconazole (n = 198)	Empirical echinocandin (n = 118)	p
Source of infection				
Unknown	151 (47.8)	93 (47)	58 (49.2)	0.71
Catheter related	130 (41.1)	84 (42.4)	46 (39)	0.59
Urinary tract	20 (6.3)	12 (6.1)	8 (6.8)	0.80
Intra-abdominal	15 (4.7)	9 (4.5)	6 (5.1)	0.83
Inadequate empirical treatment	24 (7.6)	18 (9.1)	6 (5.1)	0.19
<i>Candida</i> species				
<i>Candida albicans</i>	163 (51.6)	111 (56.1)	52 (44.1)	0.04
<i>Candida glabrata</i>	37 (11.7)	21 (10.6)	16 (13.6)	0.43
<i>Candida parapsilosis</i>	66 (20.9)	35 (17.7)	31 (26.3)	0.07
<i>Candida tropicalis</i>	28 (8.9)	21 (10.6)	7 (5.9)	0.16
Other species	22 (7)	10 (5.1)	12 (10.2)	0.08
Polymicrobial BSI	51 (16.1)	31 (15.7)	20 (16.9)	0.76

Multivariate Cox regression model (PS was included in the analysis)

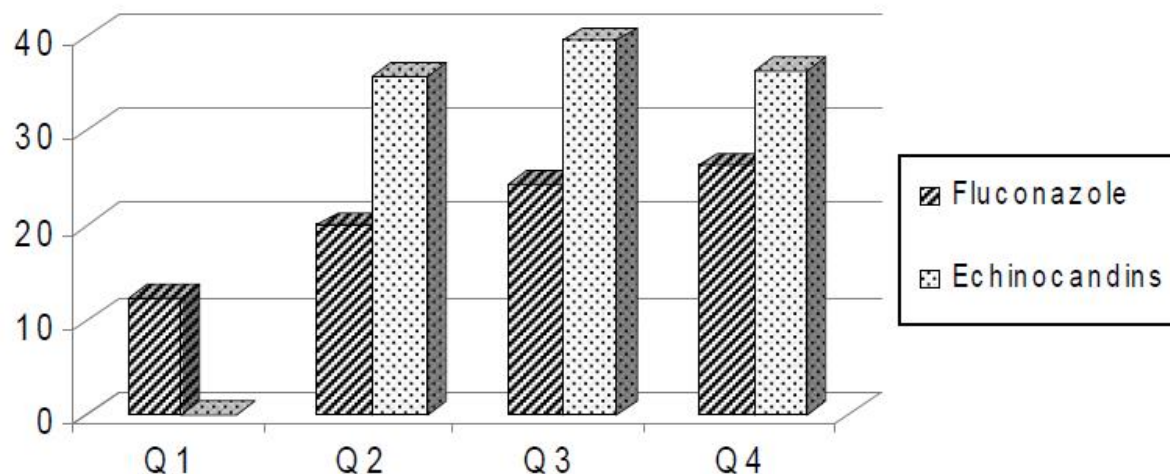
□ 30-day mortality rates:

- ETC: 77/316 (24.4%) → 18.7% fluconazole and 33.9% echinocandins, p=0.02
- TTC: 97/421 (23%) → 19.8% fluconazole and 27.7% echinocandins, p=0.06

Multivariate Cox regression models for impact of empirical and targeted therapy on 30-day mortality

Characteristic	Adjusted hazard ratio (95% confidence interval)	p
Empirical therapy cohort		
Empirical treatment with fluconazole	0.38 (0.17–0.81)	0.01
Age-weighted Charlson comorbidity index	1.21 (1.10–1.33)	<0.001
Hemodialysis treatment	1.73 (0.81–3.70)	0.16
Severe sepsis or septic shock	1.73 (1.02–2.96)	0.04
Present ICU admission	2.16 (1.78–3.95)	0.01
<i>In vitro</i> inadequate empirical treatment	2.29 (0.70–7.46)	0.17
Unknown source	1.46 (0.90–2.37)	0.13
<i>Candida albicans</i>	1.32 (0.81–2.19)	0.27
Targeted treatment with fluconazole	0.59 (0.28–1.23)	0.16

30-day mortality stratified according to PS



	Q1	Q2	Q3	Q4
Fluconazole	9/73 (12.3)	13/65 (20)	10/41 (24.4)	5/19 (26.3)
Echinocandins	-	5/14 (35.7)	15/38 (39.5)	20/60 (33.3)

All comparisons within quartiles $p > 0.1$

AUC PS = 0,85

Propensity score: Hospital, gender, age, therapy with azoles in the previous month, dialysis therapy, diabetes mellitus, immunosuppression, chronic obstructive pulmonary diseases, liver cirrhosis, malignancy, type of admission ward, Pitt score, number of days until receiving an empirical antifungal agent and source of candidemia

Matched cases according to PS

	All cases (n = 128)	Empiric fluconazole (n = 64)	Empiric echinocandin (n = 64)	p
Comorbidity				
Malignancy	51 (39.8)	21 (32.8)	30 (46.9)	0.62
Neutropenia	8 (6.3)	1 (1.6)	7 (10.9)	0.66
Hemodialysis treatment	10 (7.8)	8 (12.5)	2 (3.1)	0.27
Age-weighted Charlson comorbidity index ≥ 6	40 (31.3)	23 (35.9)	17 (26.6)	0.26
Pitt score ≥ 4	35 (27.3)	19 (29.7)	16 (25)	0.32
Immunosuppression ^a	82 (64.1)	38 (59.4)	44 (68.8)	0.64
Present ICU admission	44 (34.4)	25 (39.1)	19 (29.7)	0.21
Endotracheal intubation	28 (21.9)	17 (26.6)	11 (17.2)	0.12
Severe sepsis or septic shock	43 (33.6)	23 (35.9)	20 (31.3)	0.59
Source of infection				
Unknown bacteraemia	63 (49.2)	31 (48.4)	32 (50)	0.62
Catheter related	50 (39.1)	24 (37.5)	26 (40.6)	0.99
Other source	15 (11.7)	9 (14.1)	6 (9.4)	0.34
<i>In vitro</i> inactive empirical treatment	9 (7)	7 (0.11)	2 (0.03)	0.34
<i>Candida</i> species				
<i>Candida albicans</i>	63 (49.2)	36 (56.3)	27 (42.2)	0.62
<i>Candida glabrata</i>	16 (12.5)	8 (12.5)	8 (12.5)	0.07
<i>Candida parapsilosis</i>	32 (25)	15 (23.4)	17 (26.6)	0.53
<i>Candida tropicalis</i>	9 (7)	3 (4.7)	6 (9.4)	0.34
Polymicrobial BSI	21 (16.4)	9 (14.3)	12 (18.5)	0.52
30-day mortality	34 (26.6)	15 (23.4)	19 (29.7)	0.49

Sensitivity analysis for severe sepsis or septic shock

	HR (IC95%)	p
Fluconazole	0,42 (0.14-1.25)	0,12
Age-weighted Charlson comorbidity index	1,25 (1,08-1,44)	0,03
Unknown source	1,54 (0,75-3,16)	0,24
<i>C. albicans</i>	0,99 (0,46-2,03)	0,98
Inadequate empirical treatment	1,65 (0,37-7,29)	0,51

Including the PS calculated for this subgroup

❖ Targeted therapy: HR 1.87; 95% CI, 0.84-4.19, p 0.13

Secondary outcomes

- ❑ Persistent candidemia: No crude association was found with the use of empiric fluconazole (RR 1.19; 95% CI, 0.77-1.84, p 0.42)
- ❑ Catheter non-related candidemia (**Empirical therapy cohort**):
 - ❑ 30-day mortality: 22/114 (**19,3%**) fluconazole vs. 28/72 (**38.9%**) candins

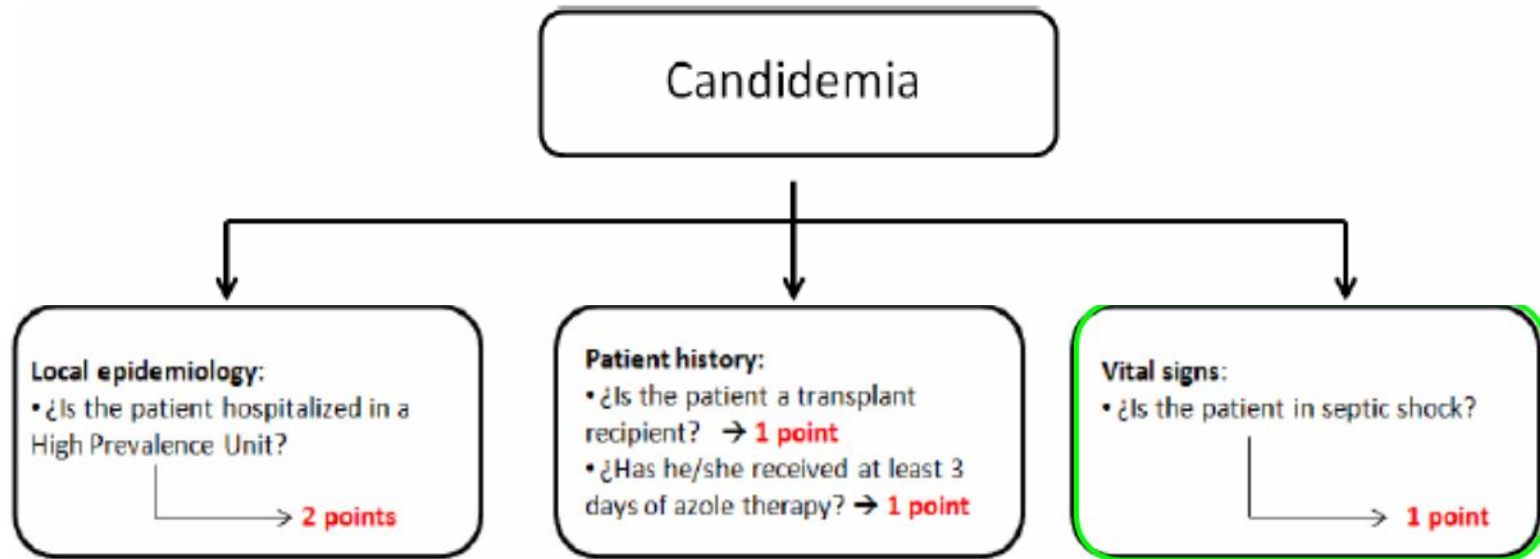
	HR (IC95%)	p
Fluconazole	0,33 (0.12-0.94)	0,04
Age-weighted Charlson comorbidity index	1,11 (0,98-1,26)	0,08
Severe sepsis or septic shock	1,85 (0,98-3,50)	0,06
Present ICU admission	1,84 (0,87-3,88)	0,11
In vitro inadequate empirical treatment	1,85 (0,44-7,86)	0,41
<i>Candida albicans</i>	0,96 (0,53-1,75)	0,89
Hemodialysis	2,52 (1,03-6,21)	0,04
Targeted treatment with fluconazole	1,27 (0,47-3,44)	0,70

Datos coincidentes

- ❑ Prospective, 1100-bed university hospital in Rome, Italy
- ❑ All cases of *Candida* BSIs observed in adult patients (Nov 2012 to April 2014)
- ❑ 130 patients: 58% *C. albicans*, 23% *C. parapsilosis*, 7% *C. glabrata*, 5.4% *C. tropicalis*, 1.5% *C. krusei*
- ❑ First antifungal: fluconazole (40%) and echinocandin (57%).

	Unadjusted HR 95 % CI	p-Value	Adjusted HR 95 % CI	p-Value
APACHE II score above 15	1.07 (0.80–1.72)	0.35	2.25 (0.85–5.93)	0.10
At least two comorbidities	1.56 (1.01–2.39)	0.05	1.22 (0.46–3.24)	0.69
Clinical presentation of <i>Candida</i> bloodstream infection				
SIRS	Ref	–	Ref	–
Severe sepsis	1.20 (0.70–1.90)	0.17	3.57 (1.11–11.44)	0.03
Septic shock	6.03 (0.07–512.9)	0.09	14.88 (4.62–47.94)	0.001
Initial antifungal strategy				
Fluconazole	Ref	–	Ref	–
Echinocandin	0.70 (0.28–1.76)	0.45	0.69 (0.14–3.44)	0.65
AmfB	0.90 (0.36–2.23)	0.83	0.19 (0.3–1.33)	0.09

Fluconazole non-susceptible score



❖ Score derivado de cohorte CANDIPOP y validado con cohorte internacional

Cut-off point	Derivation cohort				EUCAST internal validation				External validation cohort			
	Sn	Sp	NPV	PPV	Sn	Sp	NPV	PPV	Sn	Sp	NPV	PPV
≥1	85.8	51.8	92.9	33	95.8	45.6	97.3	35	87.7	39.6	93.1	25.6
≥2	82.1	65.6	93	39.9	94.4	58.7	97.1	41	84.2	49.6	92.9	28.4
≥3	38.8	89.2	84	50	39.6	88.1	82.7	50.4	42.1	84.4	85.8	39.3
≥4	9.7	98.8	79.7	68.4	9.7	98.7	78.2	70	17.5	97.9	83.2	66.7
5	1.5	100	78.5	100	1.4	100	76.9	100	1.8	100	80.9	100

Mensajes finales

- ❑ En mi opinión, las nuevas guías de la IDSA 2016 **sobredimensionan las indicaciones de equinocandinas** como tratamiento empírico sin que existan estudios NUEVOS que lo respalden

- ❑ Cohorte CANDIPOP:
 - ❑ Los pacientes tratados con candinas presentaron mayor gravedad pero no fuimos capaces de **encontrar diferencias respecto a la mortalidad en el día 30**
 - ❑ El bajo número de cepas no susceptibles a fluconazol impide recomendar su uso en pacientes con factores de riesgo para presentar una cepa resistente

- ❑ Las equinocandinas deberían reservarse para:
 - a) Tratamiento empírico del paciente grave
 - b) Pacientes que han recibido azoles en el año previo
 - c) Pacientes colonizados o con episodios previos por candida resistentes a azoles
 - d) Unidades con > 15% candidas resistentes a azoles

Agradecimientos

- ❑ Participantes estudio CANDIPOP
- ❑ Equipo de bacteriemias HU Virgen Macarena
- ❑ Unidad de Enfs. Infecciosas HU Virgen Macarena y REIPI

