Fever in a solid transplant recipient

Management of specific infections

Carolina Garcia Vidal

Infectious Diseases Department

Hospital Clínic de Barcelona

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

15th ESCMID Summer School

2 – 9 July 2016, Seville, Spain

CLINICAL CASE

Previous history

- **77-year-old man**
- **Current smoker, no alcohol intake**
- **Chronic renal failure (obstructive)**
- **Renal transplantation January 2016. Surgery ok.**
- **CMV Serostatus +/+**
- **Induction with rATG**
- **Creatinine level 4 mg/dl**
- **Urine culture: *E. faecalis***
- **Discharged on amoxicillin**

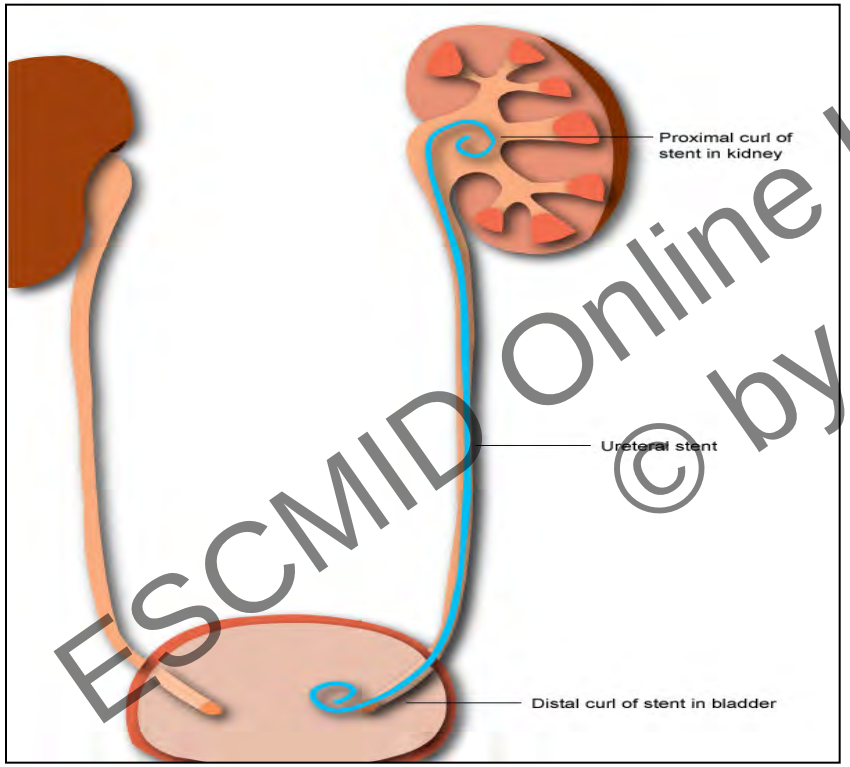
CLINICAL CASE

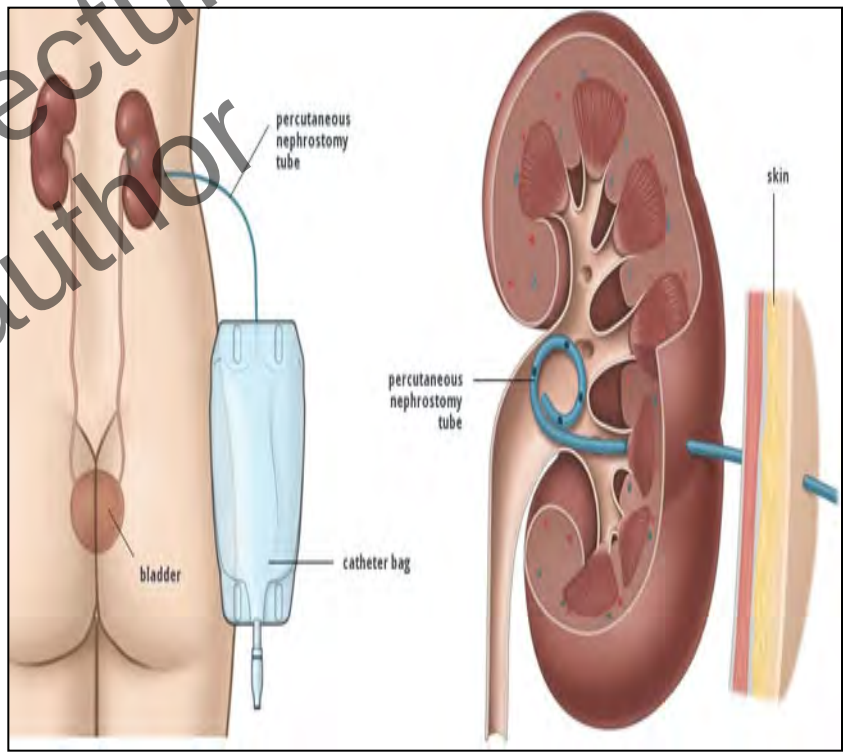
2 months
after transplantation

- worsening of renal function
- urine culture: ESBL Klebsiella -> ertapenem

Replacement double J cathether for nephrostomy

What does having a double J cathether?
What does having a nephrostomy?





CLINICAL CASE

One month after

- **Nephostomy was clogged. Renal insufficiency**
- **Replaced by internal-external urinary catheter**
- **More antibiotic therapy during hospitalization**

Current medication

- **Prednisone 5mg 24h**
- **Mycophenolate mofetil 250 mg/12h**
- **Tacrolimus**
- **Trimethoprim-sulfamethoxazole 400 mg/24h (prophylaxis)**
- **Amoxicillin-clavulanate 875mg/ 8h (4 days)**

CLINICAL CASE

Nowadays

- **Fever and chills, 2 days**
- **Worsening of his usual state of health**
- **Diarrhea and vomiting**

CLINICAL CASE

Examination

EXAMINATION

- Milder ill
- T 37,5º BP 100/50 Pulse 90x' RR 20x' Ox Sat 95%
- ABD: soft and tender to palpation
- No neurologic abnormalities
- The remainder of the examination was normal

CLINICAL CASE

Nowadays

TEST AND LAB

- **Blood lab:** Hb 10 g/L, pl 108000, L 19 700 (96% PMN),

Cr 5.1, Urea 25, Na 133, K 5.78, lact 2

- **Chest radiograph:** normal
- **Urine:** 8000 L; full of bacteria
- **Urine culture:** pending
- **Blood culture:** pending

Raise your hand if the sentence is rigth!

1.- This patient may has a septic shock for CMV infection — F

2.- The most likely he has an infection caused by multiresistant gram-negative bacilli — T

3.- Recent reports alert about the increasing prevalence of ESBL-producing Enterobacteriaceae in this population. — T

4.- The only thing that I am sure is that he has no fungal infect — F

Management of Urinary Tract Infections and Lymphocele in Renal Transplant Recipients

Patricia Muñoz
Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario "Gregorio Marañón," Madrid

ETIOLOGY AND SPECIFIC MICROORGANISMS

The most common pathogens causing UTIs in this population include Enterobacteriaceae, enterococci, staphylococci, and *Pseudomonas*. Other, less frequent microorganisms, however, such as *Salmonella*, *Candida*, or *Corynebacterium urealyticum*, pose specific management problems. It is also important to remember the possibility of infection caused by unusual pathogens such as *Mycoplasma hominis*, *Mycobacterium tuberculosis*, or BK and JC viruses [24]. Polyomavirus has recently been described as a cause of interstitial nephritis, mainly in patients receiving mycophenolate mofetil [25].

As many as 15% of renal transplant recipients had positive blood cultures in some series, and the urinary tract is the origin

Muñoz P et al, CID 2001

Epidemiology of urinary tract infection in kidney transplant recipients

The most frequent pathogen identified was *Escherichia coli*, followed by *Klebsiella* species, *Pseudomonas aeruginosa*, and *Enterococcus* species. The antimicrobial susceptibilities of the isolates are shown in Fig. 2. ESBL-producing *Klebsiella* species accounted for 74% of all *Klebsiella* species isolates, ESBL-producing *E. coli* for 25%, and MDR *P. aeruginosa* for 38%.

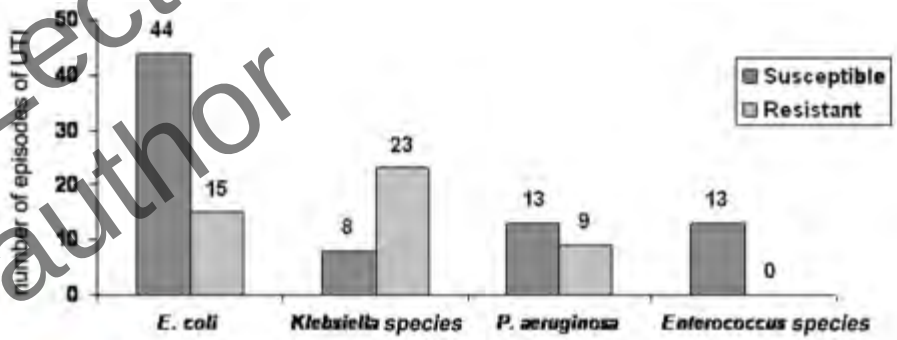


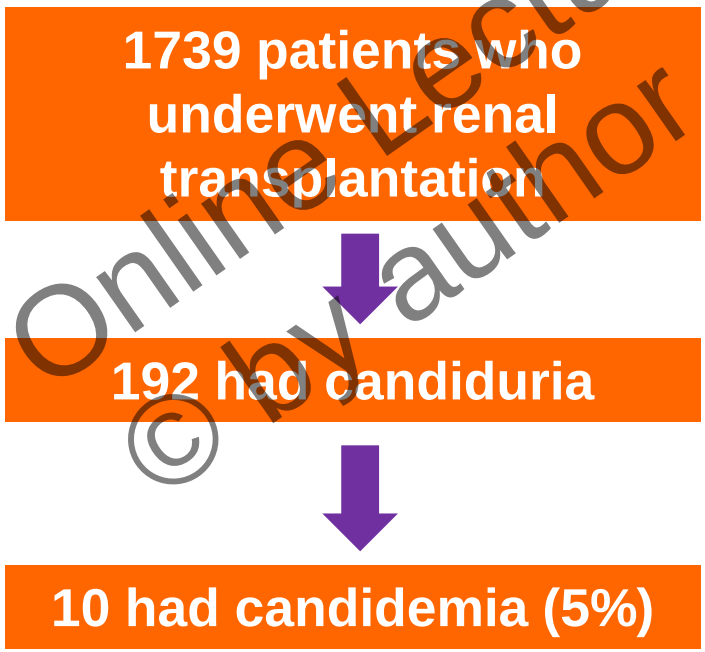
FIG. 2. Microbiology study of urinary tract infection episodes by antimicrobial susceptibility. *Escherichia coli* and *Klebsiella* species strains were classified according to the presence or absence of extended-spectrum β-lactamase-production. *Pseudomonas aeruginosa* strains were classified according to multidrug resistance, and *Enterococcus* species strains were classified according to vancomycin susceptibility.

Bodro M et al, CMI 2016

CLINICAL CASE

Blood cultures: yest!

Predictors of candiduria in renal trasplant recipients



Safdar N et al, CID 2005

Predictors of candiduria in renal trasplant recipients

Table 4. Univariate and multivariate analyses of predictors of candiduria in case and control patients who received a renal transplant at the University of Wisconsin (Madison) during 1994–2001

Variable	No. (%) of patients with candiduria		Univariate analysis		Multivariate analysis	
	Cases (n = 192)	Controls (n = 192)	OR (95% CI)	P	OR (95% CI)	P
Female sex	148 (77)	70 (36)	5.9 (3.8–9.2)	<.001	12.5 (6.7–23)	<.001
Diabetes	91 (47)	62 (32)	1.9 (1.2–2.9)	.003	2.2 (1.3–3.9)	.006
Glomerulonephritis	45 (23)	57 (30)	0.7 (0.4–1.1)	.14	…	
Cardiovascular disease	101 (53)	80 (42)	1.5 (1.0–2.3)	.036	…	
Peripheral vascular disease	73 (38)	46 (24)	1.9 (1.2–2.9)	.005	…	
Malignancy	17 (9)	10 (5)	1.8 (0.8–3.9)	.17	…	
Urologic abnormality	69 (36)	48 (25)	1.9 (1.2–3.0)	.004	…	
Neurogenic bladder	30 (16)	4 (2)	9.1 (3.1–26)	<.001	7.6 (2.1–27)	.002
Nephrolithiasis	11 (6)	4 (2)	2.9 (0.9–9.1)	.077	2.9 (0.7–12)	.15
Malnutrition	95 (49)	47 (25)	3.0 (1.9–4.6)	<.001	2.4 (1.3–4.4)	.006
Dialysis	169 (88)	151 (79)	2.0 (1.1–3.5)	.015	1.9 (0.9–4.0)	.10
Other active infection	139 (72)	117 (61)	1.7 (1.1–2.6)	.018	…	
Detection of cytomegalovirus IgG	34 (18)	20 (10)	1.7 (0.9–3.0)	.077	…	
Hepatobiliary disease	28 (15)	18 (9)	1.6 (0.9–3.1)	.12	…	
Antibiotic use						
1 Month before candiduria diagnosis	166 (86)	143 (74)	2.2 (1.3–3.7)	.004	3.8 (1.7–8.3)	.001
At the time of candiduria diagnosis	159 (83)	134 (70)	2.1 (1.3–3.4)	.003	…	
Presence of an indwelling bladder catheter						
At the time of candiduria diagnosis	67 (35)	19 (10)	4.8 (2.7–8.3)	<.001	4.4 (2.1–9.4)	<.001
1 Month before candiduria diagnosis	111 (58)	88 (46)	1.6 (1.1–2.4)	.019	…	
Ureteral stent	91 (47)	110 (57)	0.7 (0.4–1.0)	.053	0.2 (0.1–0.4)	<.001
Intensive care unit admission	38 (20)	3 (2)	15.5 (4.7–51)	<.001	8.8 (2.3–35)	.002
Total parenteral nutrition use	18 (9)	2 (1)	9.8 (2.2–43)	.002	…	
Recurrent urinary tract infection	77 (40)	28 (15)	4.0 (2.4–6.6)	<.001	…	
Presence of a central venous catheter	134 (70)	105 (55)	1.9 (1.2–2.9)	.003	…	

Safdar N et al, CID 2005

Raise you hand with the correct sentences! Don't be shy!!!

1.- *Candida albicans* is usually the most frequent specie isc in candidemias from any source — T

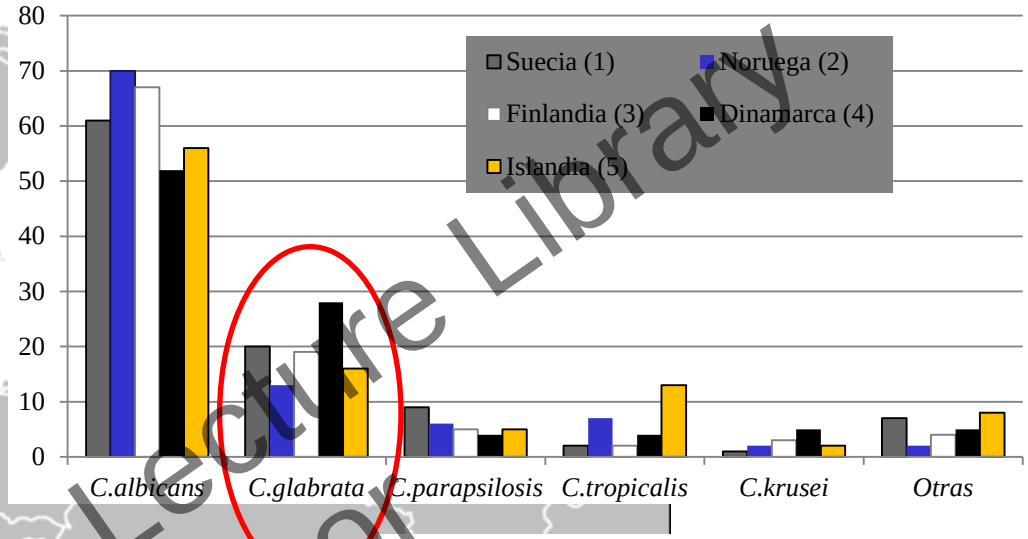
2.- It is impossible to predict candidemia caused by stra resistant to azoles — F T

3.- *Candida parapsilosis* is poor frequent (less than 5%) in european countries. — F

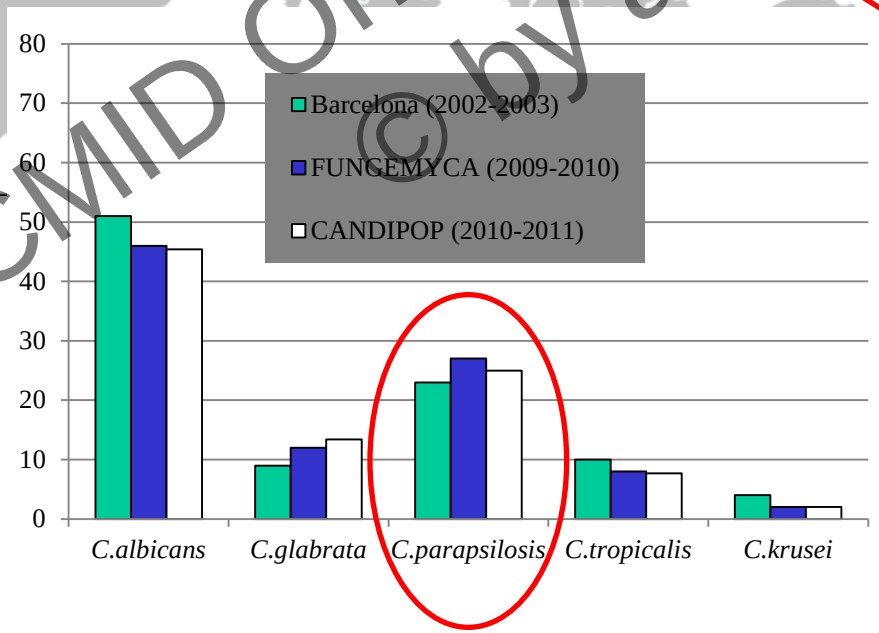
4.- Most *Candida krusei* are susceptible to azoles — F

5.- *Candida glabrata* is more frequent from catheter source infections than from other sources — F

Epidemiology of candidemia in Europe

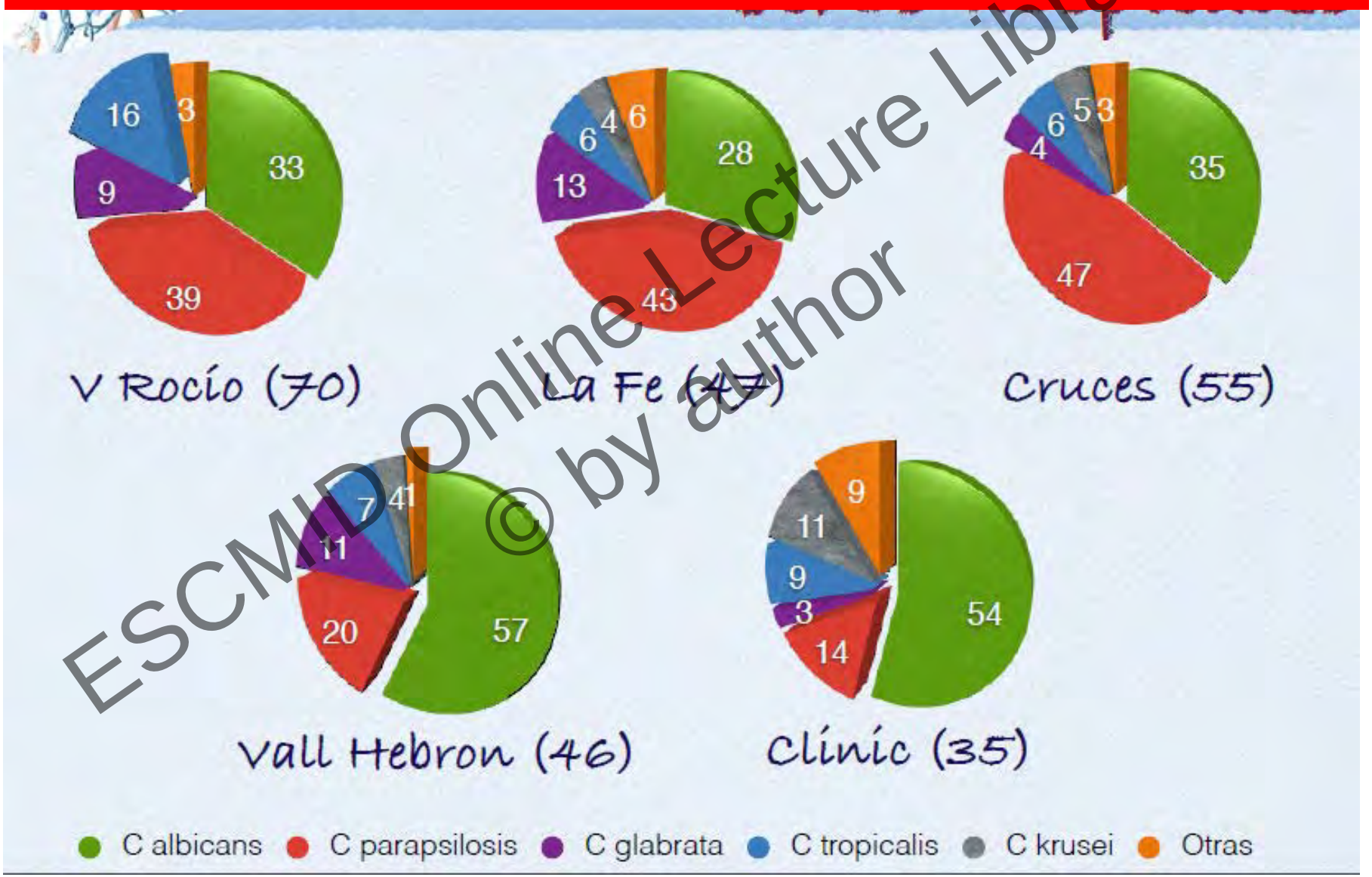


(1) Asmundsdothr LR, J Clin Microbiol 2013; 51:841-848
(2) Poikonen E, BMC Infec Dis 2010, 10:312
(3) Sandven P. J Clin Microbiol 2006, 44: 1977-1981
(4) Arendrup MC. Clin Microbiol Infect 2013;19(8):E343-53
(5) Ericsson J. Clin Microbiol Infect 2013; 19: E218-E221

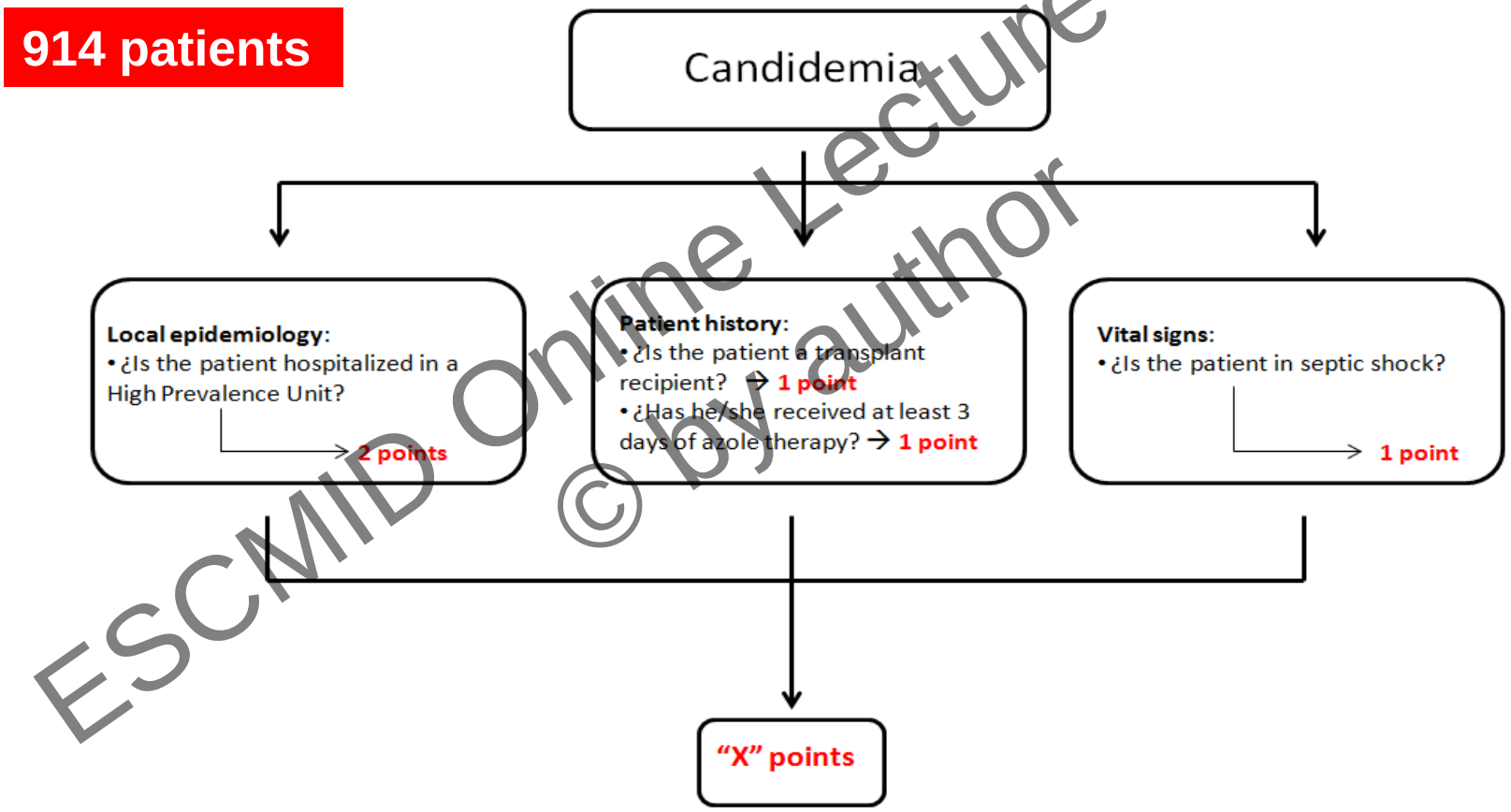


Almirante B. J Clin Microbiol, 2005; 43: 1829-1835
Pemán J. J Antimicrob Chemother, 2012;67:1181-1187
Puig-Asensio M. Clin Microbiol Infec 2014; 20:O245-54

Hospital differences/Same country



How is it “possible” to predict azole resistance?



Cuervo G et al, CMI 2015

How is it “possible” to predict azole resistance?

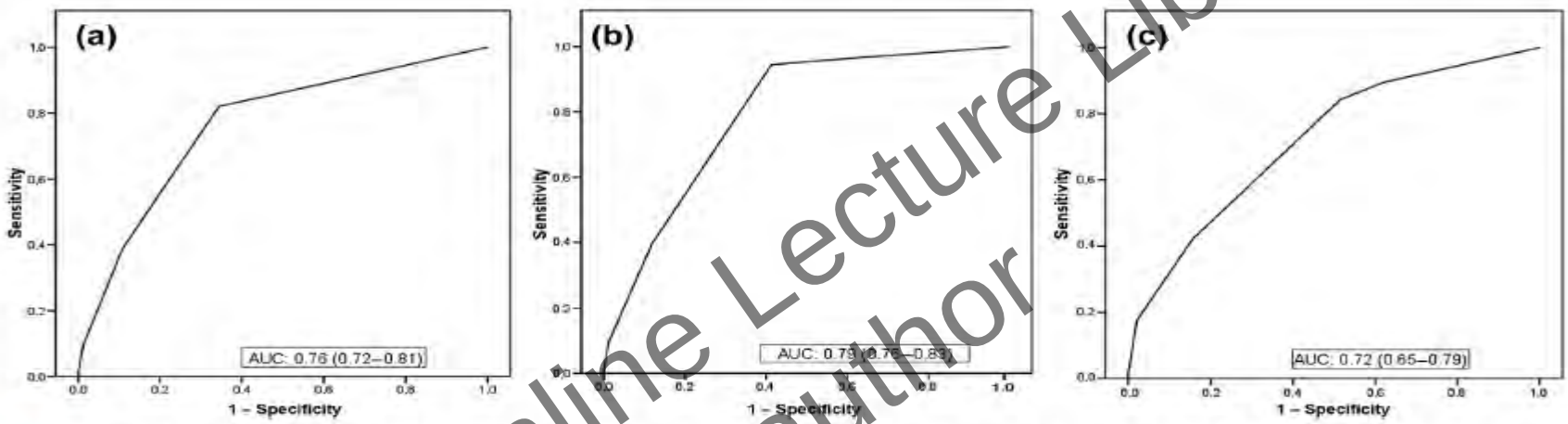


FIG. 1. Receiver operating characteristics (ROC) curve for the Flu-NS score in three cohorts: (a) derivation, (b) EUCAST internal validation and (c) external validation. Abbreviations: EUCAST, European Committee on Antimicrobial Susceptibility Testing; Flu-NS, isolates non-susceptible to fluconazole (i.e. those with an MIC ≥4 mg/L plus *Candida krusei*, *Candida glabrata* and *Candida guilliermondii*, regardless of their MIC value).

TABLE 4. Receiver operating characteristic curve cut-off values for the derivation and validation cohorts

	Derivation cohort				EUCAST internal validation				External validation cohort			
Cut-off point	Sn	Sp	NPV	PPV	Sn	Sp	NPV	PPV	Sn	Sp	NPV	PPV
≥1	85.8	51.8	[illegible]	33	95.8	45.6	[illegible]	35	87.7	39.6	[illegible]	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	[illegible]	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

Abbreviations: EUCAST, European Committee on Antimicrobial Susceptibility Testing; NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity.

Cuervo G et al, CMI 2015

MNEMONIC RULE!!

***K*RUSEI**

***G*LABRATA**

It is “strong/heavy/contundent” to have an azole-resistant candida…

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

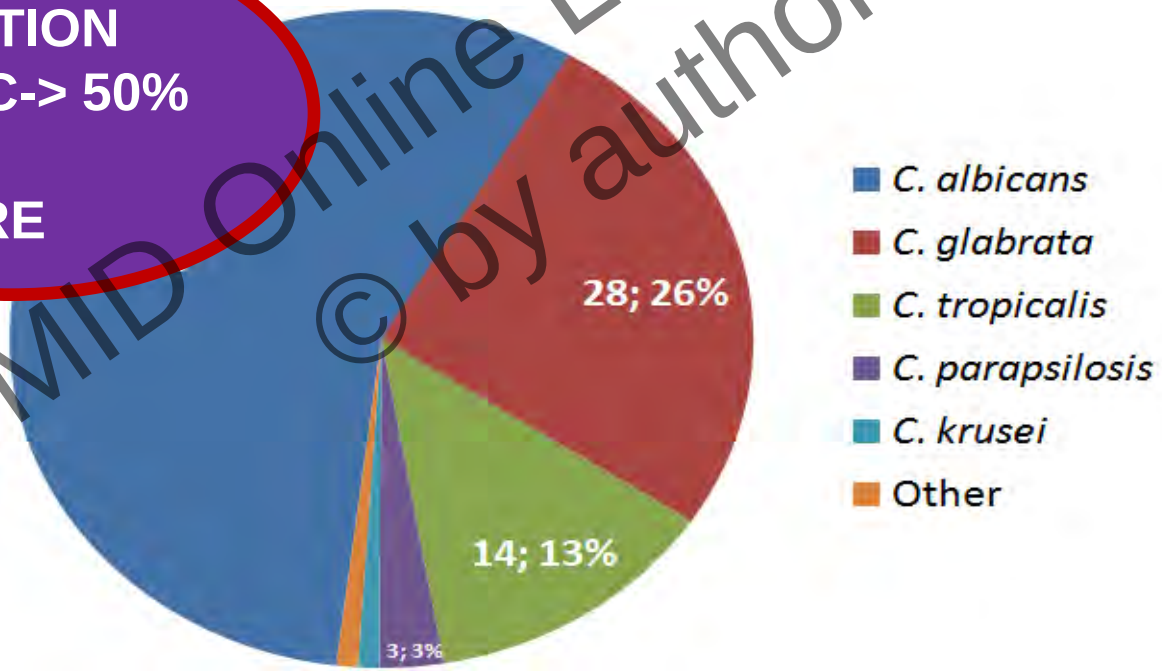
Candida species	Fluconazole	Itraconazole	Voriconazole[d]	Flucytosine	Amphotericin B	Candins[a]
C. albicans	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S
C. parapsilosis	S	S	S	S	S	S (to I?)
C. glabrata	S-DD to R[b]	S-DD to R[c]	S to I[d]	S	S to I[e]	S
C. krusei	R	S-DD to R[c]	S to I[d]	I to R	S to I[e]	S
C. lusitaniae	S	S	S	S	S to R[f]	S

Pappas G et al, CID 2004

Epidemiology of candidemia from urinary source

2044 candidemia episodes → **107 (5.23%) were USC**

DEFINITION OF USC-> 50% RENAL FAILURE



Fluconazole non-susceptible isolates → 31 (28.7%)

Cuervo G et al, submitted

Next question: how I may treat my patient!? Raise your hand with true!

1.- Equinocandins are the best treatment in this setting because they have not interactions with IS drugs F

2.- Azoles remains the first option and usually SOT recipients have not drugs interacting with them F

3.- Amphotericin is perfect due to the wide spectrum F

4.- Those patients' treatment is extremly complicated by several factors: PK/PD of antifungals, interactions, adverse events. T

Antifungal treatment in patients with renal failure

Ampho B

- Reversible decline in GFR develops in up to 80% of patients
- Distal tubule damage that leads to decreased urinary concentration, distal renal tubular acidosis, potassium, magnesium wasting, and occasional renal vasoconstriction
- More frequent in patients with advanced age, history of diuretic use, preexisting renal dysfunction, and hypokalemia
- Prior infusion of normal saline may diminish the risk
- Liposomal<Lipidic complex< deoxycholate

IV Vori

- iv Voriconazole excipient (sulfobutyl cylodextrin) may accomulate

Antifungals and immunosuppressors interactions

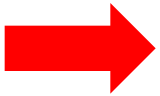
Drugs	Main interactions
Amphotericin B	High number of interactions (Amiodarone, cidofovir, efavirenz, tenofovir, sirolimus, tacrolimus…)
Azoles	High number of interactions (IS: steroids, tacrolimus, sirolimus, ciclosporin; chemotherapeutics, gastrointestinal and cardiovascular drugs, benzodiazepines, rifamycins…)
Equinocandins	Very few drug interaction (ciclosporin, few with tacrolimus…)

Concerns about antifungals and candida urinary infections

Several basic principles are important in the approach to treatment of *Candida* UTI. The ability of the antifungal agent to achieve adequate concentrations in the urine is as important as the antifungal susceptibilities of the infecting species [94].

AmB deoxycholate is active against most *Candida* species (although some *C. krusei* isolates are resistant) and achieves concentrations in the urine that exceed the MICs for most isolates, and even low doses have been shown to be effective in treating *Candida* UTI [497]. The major drawbacks are the need for intravenous administration and toxicity. The lipid formulations of AmB appear to not achieve urine concentrations that are adequate to treat UTI and should not be used [498].

All other antifungal drugs, including the other azole agents and echinocandins, have minimal excretion of active drug into the urine and generally are ineffective in treating *Candida* UTI [94]. However, there are several reports of patients in whom echinocandins were used, primarily because of UTI due to fluconazole-resistant organisms, and both success and failure were reported [499–502]. Infection localized to the kidney, as occurs with hematogenous spread, probably can be treated with echinocandins because tissue concentrations are adequate even though these agents do not achieve adequate urine concentrations [499].



It lacks evidence to recommend the use of echinocandins for candidemia episodes of a likely urinary source

May I treat this patients with echinocandins?

Predictors of clinical failure (7-day mortality and/or persistent candidemia) in patients treated either with echinocandins or fluconazole

Risk Factor	Adjusted odds ratio (95% CI)	*p*-value
Malignancy	74 (0.44-6.84)	.426
Acute Re…		**.007**
Urologic procedure	-0.28)	**.001**
Initial Echinocandin	2.56)	.383
PS Echinocandins	5.91 (… 61)	.284

Solve the obstruction

Initial therapy with echinocandins was not associated with clinical failure

Cuervo G et al, submitted

CLINICAL CASE

Blood cultures: *C. parapsilosis*

Urine culture: *C. parapsilosis*

Concerns about candida parapsilosis and equinocandins

C.parapsilosis

Breakpoints (BPs): S: ≤X; R: >Y Breakpoints currently on global consultation

	CLSI M27-S3	CLSI revised (M27-S4)			EUCAST		
AMB	≤1	≤1			≤1; >1		
ANF	≤2	≤0.25;	>0.5	(alb, krus, trop)	≤0.032;	>0.032	(alb)
		≤0.125;	>0.25	(glab)	≤0.06;	>0.06	(glab, krus, trop)
		≤2;	>4	(para, guillier)	≤0.002;	>4	(para)(guillier IE)
CSF	≤2				-		
MFG	≤2	≤0.25;	>0.5	(alb, krus, trop)	≤0.016;	>0.016	(alb)
		≤0.06;	>0.125	(glab)	≤0.03;	>0.03	(glab)
		≤2;	>4	(para, guillier)	≤0.002;	>2	(para)(trop, krus, guillier IE)
Fluco	≤8; >32	≤2;	>4	(alb, para, trop)	≤2;	>4	(alb, trop, para)
		SDD ≤32;	>32	(glab)	≤0.002;	>32	(glab)
				(krus poor target)			(krus poor target)

✓**EUCAST technical note on anidulafungin: Anidulafungin is not an optimal therapeutic target for *C.parapsilosis***

The NEW ENGLAND JOURNAL of MEDICINE

Anidulafungin versus Fluconazole for Invasive Candidiasis

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

N Engl J Med 2007;356:2472-82.

Initial Use of Echinocandins Does Not Negatively Influence Outcome in *Candida parapsilosis* Bloodstream Infection: A Propensity Score Analysis

Table 4. Univariate and Multivariate Logistic Regression Analyses of Prognostic Factors for Clinical Failure[a]

	Univariate Analysis			Multivariate Analysis		
Variable	OR	95% CI	*P* Value	Adjusted OR	95% CI	*P* Value[b]
Orotracheal intubation at diagnosis	4.67	2.32–9.38	.000	2.81	1.19–6.65	.018
Septic shock	7.17	2.63–19.56	.000	2.91	.88–9.64	.081
Hematogenous dissemination	6.75	1.32–34.56	.016	7.42	.67–82.44	.103
Early CVC removal (≤48 h)	0.41	.20–.86	.016	0.43	.19–.96	.040
Initial antifungal therapy						
Azole-based regimen	1	. . .	. . .	1	. . .	. . .
Echinocandin-based regimen	1.34	.60–2.97	.479	1.73	.66–4.54	.265
Amphotericin B–based regimen	0.99	.40–2.45	.989	0.99	.34–2.89	.996
Combination regimen	0.86	.31–2.36	.769	1.06	.33–3.43	.922

Abbreviations: CI, confidence interval; CVC, central venous catheter; OR, odds ratio.

[a] All-cause mortality within days 3–30 or persistent bloodstream infection (BSI) for ≥72 hours from the initiation of antifungal therapy in 177 evaluable episodes of *Candida parapsilosis* BSI.

[b] Hosmer-Lemeshow $P = .653$.

M. Fernández-Ruiz et al. Clin Infect Dis. 2014

CLINICAL CASE

TO FINISH OUR CASE…

The patient was treated with anidulafungin

We undergo to surgery

He fully recovery

Thank you very much for your attention

cgarciav@clinic.cat

Recommended papers:

1.- Managment of urinary tract infections and limphocele in renal transplant recipients. P. Muñoz, *Clin Infect Dis* 2001.

2.- Predictors and outcomes of candiduria in renal trasplant recipients. Safdar N, et al; *Clin Infect Dis* 2005

3.- Epidemiology and predictive factors for early and late mortality in Candida bloodstream infections: a population-based surveillance in Spain. Puig-asensio M, et al. *Clin Microbiol Infect* 2014

4.- A simple prediction score for estimating the risk of candidaemia caused by fluconazole non-susceptible strains. Cuervo G et al. *Clin Microbiol Infect* 2015

5.- Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of America. Pappas P et al. *Clin Infect Dis* 2016.