

Tratamiento endocarditis por *Candida*



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Introducción

- Incidencia creciente
- Aproximadamente la mitad de los pacientes tienen válvula protésica
- >80% nosocomial o RAS
- Válvulas izquierdas
- Retraso diagnóstico medio: **32 d !!**
- Mortalidad muy elevada
- Dudas y algunas certezas con respecto al tto

Scheme

1. Early detection

2. Surgical management

3. Antifungals

4. New drugs

5. Prognosis

Clinical suspicion

■ Clinical suspicion if:

1. Preexisting valvular disease and fungemia
2. Relapsing or persistent fungemia
3. Embolic complications and negative bacterial cultures



¿Es necesario un ETE en todas las fungemias?

Review

Candidaemia in the non-neutropenic patient: A critique of the guidelines

A. Deshpande^a, S. Gaur^b, A.M. Bal^{c,*}

Comparison of the five guidelines on key areas.

	IDSA [16]	CCP guidelines [17]	GSMS-PES [18]	ESCMID [19]	Brazilian guidelines [20]
Ophthalmic investigation	Advised	Not specified	Advised	Advised	Advised if visual symptoms present. If not, advised after 1 week
TTE/TOE	Not specified	Not specified	Not routinely indicated	TOE advised	Not specified
Follow-up BC	Daily or every other day	Not specified	Not specified	Daily or even more frequently	Serial BC but at least on Days 3 and 5

- Risk-based approach?
- Cost? Risk?

Microbiological alerts in HGUGM

Microbiological Alerts	Nº patients	Echocardio done	TEE	IE	Yield TEE in IE episodes (%)
<i>S. aureus</i>	317	227 (72%)	126 (55%)	23 (7%)	23/126 (18%)
C.N.S.	347	136 (39%)	48 (35%)	7 (2%)	7/48 (14%)
<i>Enterococcus</i> spp.	215	139 (64%)	65 (47%)	14 (6%)	14/65 (21%)
<i>Streptococcus</i> spp.	122	86 (70%)	39 (45%)	10 (8%)	10/39 (25%)
<i>Candida</i> spp.	103	71 (69%)	33 (46%)	7 (7%)	7/33 (21%)
Other	17	8 (47%)	3 (37%)	3 (17%)	3/3 (100%)
TOTAL	1121	667 (59%)	314 (47%)	64 (6%)	64/314 (20%)

Prospective study of echocardiogram in candidemia

January 2007 - October 2012

263 episodes of candidemia



No Echo
76 patients



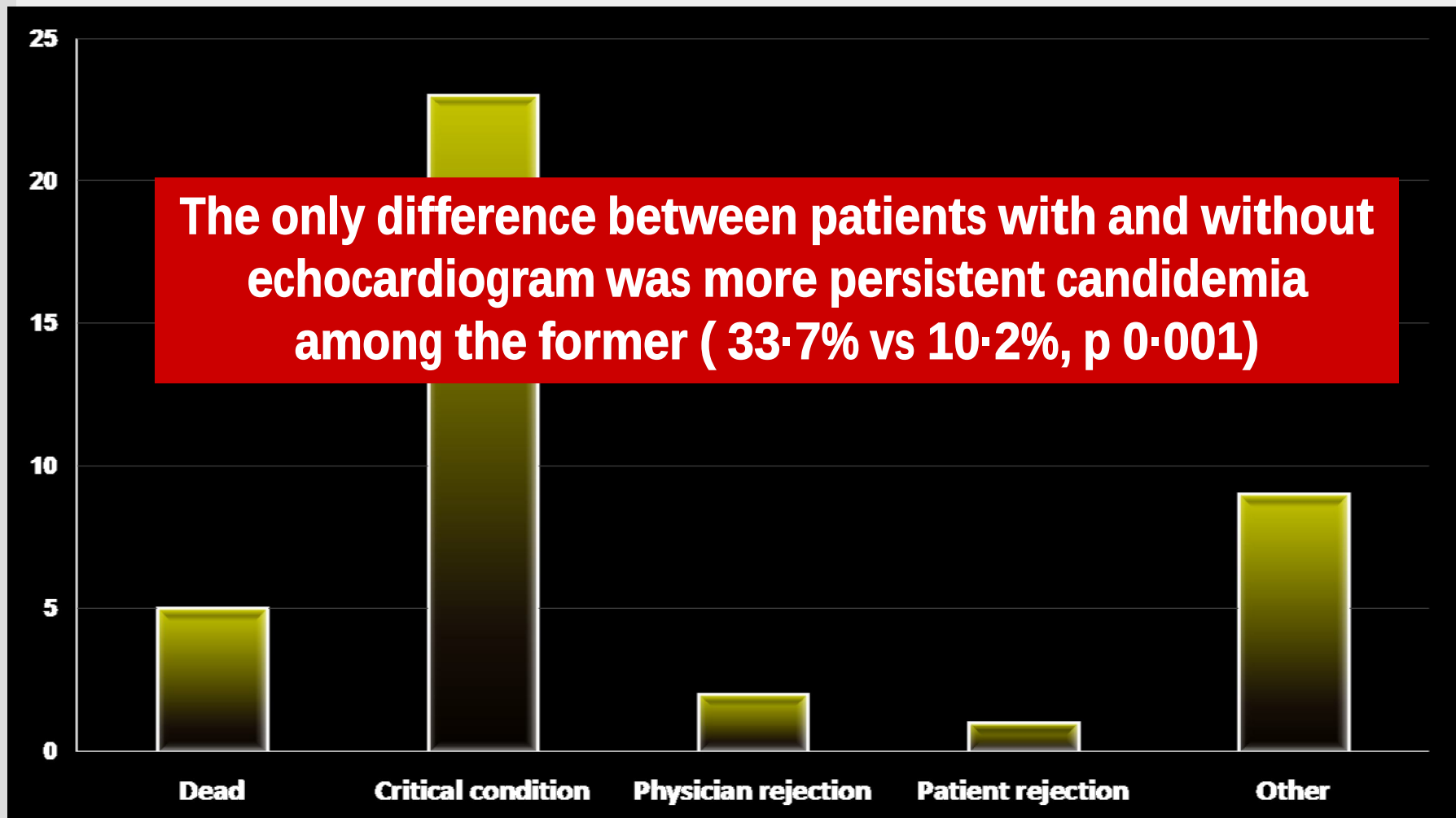
Median of 5 d after BC

Echo
187 patients



11 endocarditis (6%)
11.5% among those with TEE

Patients with no echocardiogram



General characteristics of 187 patients with candidemia and an echocardiogram performed

Characteristic	Number
Male gender	119 (63.6%)
Age, mean ($\pm$ SD), y	65.2 ($\pm$ 14.8)
Charlson's comorbidity index (mean $\pm$ SD)	3.3 ($\pm$ 2.5)
Charlson's with age (mean $\pm$ SD)	5.4 ($\pm$ 2.7)
Underlying disease	
Cancer	77 (41.2%)
Cardiovascular	27 (14.4%)
Neurological	15 (8%)
Diabetes	10 (5.3%)
Liver	9 (4.8%)
Other	43 (23%)
None	6 (3.2%)
Area of admission	
Medical	82 (43.9%)
Surgical	64 (34.2%)
Intensive care	41 (21.9%)
<i>C. albicans</i> (%) vs non- <i>albicans</i>	91 (48.7%) vs 96 (51.3%)
Classical risk factors for Candida endocarditis	
% of positive BC*	77.2% ($\pm$ 25.4)
Persistent candidemia	63 (33.7%)
Valvular prosthesis	12 (6.4%)
Pacemaker	2 (1.1%)
Previous valve disease (prosthesis not included)	26 (13.9%)
No persistent candidemia, prosthesis, pacemaker, or valve disease	98 (52.4%)
In-hospital death	57 (30.5%)

RF for *Candida* endocarditis

(n=187)	No endocarditis (n=176)	Endocarditis (n=11)	p
Male gender	111 (63.6%)	8 (70.0%)	0.7
Age, mean ($\pm$ SD), y	65.2 ($\pm$ 14.9)	64.9 ($\pm$ 13)	0.9
Charlson's	3.25 $\pm$ 2.4	4.7 $\pm$ 3.5	0.1
Charlson's with age	5.3 $\pm$ 2.6	6.9 $\pm$ 3.3	0.05
Underlying disease			0.3
Cancer	73 (41.5%)	4 (36.4%)	
Cardiovascular	23 (13.1%)	4 (36.4%)	
Neurological	15 (8.5%)	0 (0%)	
Diabetes	10 (5.7%)	0 (0%)	
Liver	9 (5.1%)	0 (0%)	
Other	40 (22.7%)	3 (27.3%)	
None	6 (3.4%)	0 (0%)	
% of positive BC*	76.9 ($\pm$ 25.5)	81.1($\pm$ 24.8)	0.5
Persistent candidemia	57 (32.4%)	6 (54.5%)	0.1
<i>C. albicans</i> (%) vs non- <i>albicans</i>	86 (48.9%)	5 (45.5%)	1.0
Valvular prosthesis	8 (4.5%)	4(36.4%)	0.003
Previous valve disease(prosthesis not included)	25 (15.9%)	1 (14.3%)	1.0
Pacemaker	2 (1.1%)	0 (0%)	1.0
In-hospital death	51 (29.0%)	6 (54.5%)	0.008
Persistent candidemia, prosthesis, pacemaker, or valve disease	81 (46.0%)	8 (72.7%)	0.07

Description of 11 patients with *Candida* IE

Age	Risk factor	Prosthesis	Persistent candidemia	Valve	Heart surgery	Outcome
62	Previous candidemia	Yes	Yes	A	No	Death
81	Antibiotics	Yes	Yes	A	No	Death
72	30% of <i>Candida</i> IE were found in patients with neither persistent candidemia nor previous heart valve disease and that were clinically unsuspected					
73						
72						
48						
71	Abdominal surgery, CVC	No	No	T	No	Death
72	Previous candidemia, antibiotics, abdominal surgery	No	Yes	T	Yes	Death
52	Abdominal surgery, CVC	No	No	Right atrium	No	Alive
35	CVC, parenteral nutrition, previous antibiotics	No	No	T	No	Alive
69	Abdominal surgery, antibiotics	No	No	Right atrium	No	Alive

Scheme

1. Early detection
- 2. Surgical management**
3. Antifungals
4. New drugs
5. Prognosis



La felicidad es la certeza

Review

Fungal endocarditis: current challenges[☆]

Pierre Tattevin^{a,b,c,*}, Matthieu Revest^{a,c}, Agnès Lefort^d,
Christian Michelet^a, Olivier Lortholary^e

European
guidelines on
infective
endocarditis,
2009 [16]^a

- Valve replacement for all patients

US guidelines on
Candida
infections, 2009
[21]^b

- Valve replacement strongly recommended
- Lifelong fluconazole suppressive treatment in patients with prosthetic valve *Candida* endocarditis who were not operated

Fungal endocarditis: current challenges[☆]

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European
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[20]^b

- Surgical valve replacement within a week if native valve
- Surgical valve replacement within days if prosthetic valve

British guidelines
on infective
endocarditis,
2012 [22]^a

- Valve replacement highly desirable if technically feasible for *Candida* endocarditis
- Valve replacement mandatory for survival in *Aspergillus* endocarditis

Reasons to operate

- High mortality without surgery
- Limited activity of drugs within biofilm, vegetations and prosthetic devices
- Persistent fungemia
- Myocardial abscess
- Large vegetations may lead to severe embolic events
- Late relapses

How many patients are operated in the real world??

- 41% (1965-1995) (Ellis, CID 2001)
- 52% (1995-2000) (Pierrotti, Chest 2002-152)
- 31% (80'-90')(Benjamin 2004- 16 cases)
- 45% (00'-05')(Baddley 2009- 33 cases)
- 31% (93-2007) (H Gregorio Marañón-16 cases)
- 33% (2004-2007)(Falcone 2009-15 cases)
- 37% (2005-2007)(MYCENDO -30 cases)
- 27% (2008-2009)(GAMES-11 cases)
- 46% (2000-2010) (ICE- 70 cases)

38%

Indications for cardiac surgery

	Candida	Non fungal
Myocardial abscess	47%	22%
Embolization	40%	20%
Persistent fungemia	33%	10%
Valvular regurgitation	40%	68%
Heart failure	13%	43%
Vegetation	40%	49%

Literature make me mad ...

■ Baddley 2009 ICE data

	Candida	Non fungal	
Mortality with surgery	33%	14%	0.03
Mortality without surgery	28%	20%	0.8

■ Steinbach meta-analysis

- Antifungal monotherapy without surgery associated with the poorest outcome
- But.... **no difference** in mortality between **two antifungals** and **M+S** approach
- Surgery (OR 0.56; 95% CI 0.16-1.99)

Candida IE. Treatable without surgery?

— The Role of Fluconazole in the Treatment of *Candida* Endocarditis —

A Meta-Analysis

Meta-analysis.

64 cases treated with FLU and no surgery

49 (77 %) cured or improved

4 relapsed, 11 failed (17 % mortality)

- Only FLU: 11 / 19 (58 %) cured
- FLU + st else: 38 / 45 (84 %) cured

Longterm suppression

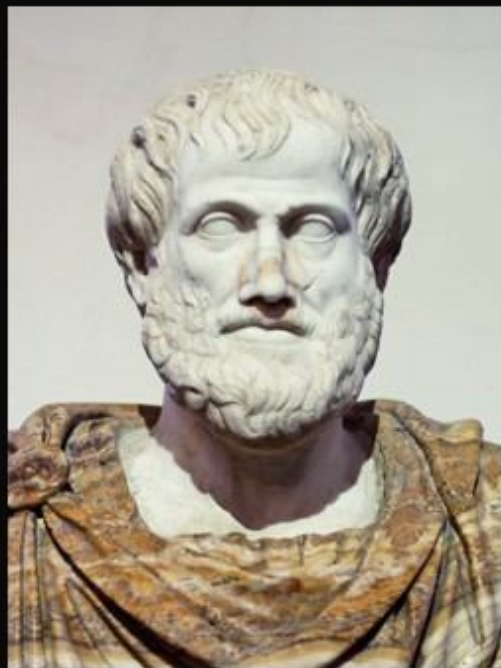
Operated (46%) vs non-operated CIE

Parameter	Adjunctive surgery (N=32)	Medical Therapy Alone (N=38)	P
Age			
Mean ± SD	47.9 ± 17.0	59.7 ± 15.3	<0.01
Organism			
<i>C. albicans</i>	14 (44%)	17 (45%)	0.85
<i>C. parapsilosis</i>	12 (38%)	7 (19%)	0.08
Risk factors			
Prosthetic valve	15 (47%)	17 (45%)	0.86
Endocavitary device	7 (22%)	7 (18%)	0.72
Previous IE	9 (28%)	9 (24%)	0.72
CHF	6 (19%)	11 (29%)	0.32
Renal disease	5 (16%)	13 (34%)	0.08
Echocardiography			
Regurgitation	20 (65%)	17 (46%)	0.13
Paravalvular complication	6 (19%)	7 (19%)	0.99
Prosthetic valve complication	7 (47%)	4 (24%)	0.27
Clinical complications			
Stroke	4 (13%)	4 (11%)	1.00
Embolization	13 (41%)	11 (29%)	0.31
CHF	9 (28%)	13 (34%)	0.58
Intracardiac abscess	12 (38%)	5 (13%)	0.02
Mycotic aneurysm	1 (3%)	1 (3%)	1.00
Persistently positive cultures	7 (22%)	5 (14%)	0.53
Mortality			
In-hospital	12 (38%)	13 (34%)	0.77
1-year	19 (66%)	21 (62%)	0.76

Surgery not related to mortality

Parameter	Death	Alive	P
In-hospital deceased (N=25)			
Organisms			
<i>C. albicans</i>	14 (45%)	10 (26%)	0.10
<i>C. parapsilosis</i>	5 (26%)	19 (38%)	0.36
Age			
≥50 years	20 (45%)	5 (19%)	0.03
≥60 years	15 (50%)	10 (25%)	0.03
≥70 years	8 (44%)	17 (33%)	0.37
Risk factors			
Prosthetic valve	11 (34%)	14 (37%)	0.83
Diabetes Mellitus	6 (40%)	19 (35%)	0.70
CHF at baseline	11 (65%)	14 (26%)	<0.01
Previous IE	6 (33%)	19 (37%)	0.77
Clinical complications			
Stroke	1 (13%)	24 (39%)	0.24
Embolization	8 (33%)	17 (37%)	0.76
CHF as complication	11 (50%)	14 (29%)	0.09
Intracardiac abscess	8 (47%)	17 (32%)	0.26
Persistently positive cultures	9 (75%)	14 (25%)	<0.01
Echocardiographic complications			
Paravalvular complication	4 (31%)	20 (36%)	1.00
Prosthetic valve complication	5 (45%)	6 (29%)	0.34
Hospital acquired/health care associated acquisition	21 (45%)	3 (16%)	0.05

Por tanto ¿hay que operar a todos los pacientes con *Candida*?



Es de importancia para quien desee alcanzar una certeza en su investigación, el saber dudar a tiempo.

(Aristóteles)

akifrases.com

Scheme

1. Early detection
2. Surgical management
- 3. Antifungals**
4. New drugs
5. Prognosis

Fungal endocarditis: current challenges[☆]

Pierre Tattevin^{a,b,c,*}, Matthieu Revest^{a,c}, Agnès Lefort^d,
Christian Michelet^a, Olivier Lortholary^e

European
guidelines on
infective
endocarditis,
2009 [16]^a

- Amphotericin B or derivatives with or without azoles
- or caspofungin
- Prolonged or lifelong fluconazole suppressive treatment

- Valve replacement for all patients

US guidelines on
Candida
infections, 2009
[21]^b

- Liposomal amphotericin B or other lipid formulations with or without flucytosine
- or an echinocandin at high doses (caspofungin 50–150 mg/day, micafungin 100–150 mg/day or anidulafungin 100–200 mg/day)
- Prolonged fluconazole suppressive treatment (400–800 mg/day)

- Valve replacement strongly recommended
- Lifelong fluconazole suppressive treatment in patients with prosthetic valve *Candida* endocarditis who were not operated

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European
guidelines on
Candida
infections, 2012
[20]^b

- **Liposomal amphotericin B** with or without flucytosine
- **or caspofungin 70 mg/day or 50 mg/day** with or without flucytosine
- Prolonged, fluconazole suppressive treatment (400–800 mg/day)

British guidelines
on infective
endocarditis,
2012 [22]^a

- First-line: an **echinocandin at high doses** (caspofungin 70 mg loading dose, then 50–100 mg/day, micafungin 200 mg/day or anidulafungin, licensed doses)
- Second-line: liposomal amphotericin B or other lipid formulations with or without flucytosine
- Prolonged, fluconazole suppressive treatment (400–800 mg/day)

- Surgical valve replacement within a week if native valve
- Surgical valve replacement within days if prosthetic valve

- Valve replacement highly desirable if technically feasible for *Candida* endocarditis
- Valve replacement mandatory for survival in *Aspergillus* endocarditis

A meta-analysis of medical versus surgical therapy for *Candida* endocarditis[☆]

William J. Steinbach^{a,b,*}, John R. Perfect^{b,c}, Christopher H. Cabell^{d,e},
Vance G. Fowler^{c,e}, G. Ralph Corey^{c,e}, Jennifer S. Li^{e,f}, Aimee K. Zaas^{b,c},
Daniel K. Benjamin Jr^{a,e,*}

Table 1 Details of 92 reported cases of *Candida* infective endocarditis (1980-2002)

Variable	No. cases	Reported successful outcome
Specific treatment details		
Medical antifungal monotherapy	15	53.3% (8/15)
Amphotericin B	8	75.0% (6/8)
Fluconazole	6	16.7% (1/6)
Flucytosine	1	100% (1/1)
Medical antifungal combination	19	63.2% (12/19)
Amphotericin B + flucytosine	14	64.3% (9/14)
Amphotericin B + fluconazole	3	66.7% (2/3)
Amphotericin B + rifampin + flucytosine	1	100% (1/1)
Amphotericin B + fluconazole + flucytosine	1	0% (0/1)
Medical antifungal with surgery	58	63% (67/107)
Amphotericin B	28	67.9% (19/28)
Amphotericin B + flucytosine	21	76.2% (16/21)
Miconazole	3	66.7% (2/3)
Fluconazole	3	100% (3/3)
Amphotericin B + fluconazole	1	100% (1/1)
Fluconazole + flucytosine	1	100% (1/1)
Amphotericin B + fluconazole + flucytosine	1	100% (1/1)

Scheme

1. Early detection
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- 4. New drugs**
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In vitro studies

■ AMB - Fluconazole

- Reduced activity against *Candida* biofilm (decreased ergosterol)
- AMB poor penetration into vegetations

■ Echinocandins

- Potent in vitro activity against *Candida* biofilm
- Micafungin superior than AMB-L and 5FC in vitro (Pai MP. AAC 2009)
- Although glucan-associated changes may also occur in biofilm

■ Voriconazole + 5FC

- Best option for *C. parapsilosis* in *in vitro* models

Antifungal Combinations against Simulated *Candida albicans* Endocardial Vegetations[▽]

Manjunath P. Pai*

College of Pharmacy, University of New Mexico, Albuquerque, New Mexico

Received 31 July 2008/Returned for modification 13 November 2008/Accepted 12 March 2009

- 2 *C. albicans* strains that simulated 24-hour-old endocardial vegetations
- **L-AMB + Mica+ 5FC** superior to all other treatments for one strain
- No different from **L-AmB+Mica** for the other strain

Use of new drugs for FIE

Study	AMB	FLU	CAS-VORI
GAMES	51%	33%	23%
Baddley	59%	44%	37%
Falcone	13%	13%	73%
Lefort*	nr	nr	80%
Arnold**	39%	18%	48%

*** Combination 80 % ** Combination 45 %**

Use of new drugs for FIE

Study	AMB	FLU	CAS-VORI	Death
GAMES	60%	20%	30%	42%
Baddley	59%	44%	37%	33%
Falcone	13%	13%	73%	47%
Lefort*	20%	60%	80%	67%
Arnold*	39%	18%	48%	39%

* **Death** 15 / 20 caspofungin, 8 / 20 voriconazole

Hampered by historical paradigms – echinocandins and the treatment of *Candida* endocarditis

B. J. Gardiner,¹ M. A. Slavin,² T. M. Korman^{1,3} and R. L. Stuart^{1,3}

¹Monash Infectious Diseases, Monash Medical Centre, Clayton, Vic., Australia, ²Peter MacCallum Cancer Centre and Faculty of Medicine, University of Melbourne, Melbourne, Vic., Australia and ³Department of Medicine, Monash University, Clayton, Vic., Australia

Table 1 Published articles describing cases of endocarditis treated with echinocandins.

Reference	Total		Total, no surgery		Native valve, no surgery	
	Treated	Cured	Treated	Cured	Treated	Cured
CR	1	1	1	1	1	1
16	9	7	6	5	6	5
17	1	1				
18	23	8	14	4	12	3
19	1	1				
20	6	3	3	1		
21	1	1				
22	10	5	7	2	4	2
23	5	5	3	3	3	3
24	1	0	1	0		
25	3	1				
26	10	6	5	3	3	2
27	1	1	1	1	1	1
28	1	1	1	1		
29	1	1				
30	3	3	2	2	1	1
31	1	1	1	1	1	1
Total	78	46 (59%)	45	24 (53%)	32	19 (59%)

Therapy with AMB vs echinocandin

Parameter	Overall treatment sub-group (N=33)	Amphotericin B group (N=11)	Echinocandin group (N=14)	P*
Therapy				
Majority regimen combination antifungal therapy	13 (39%)	5 (45%)	5 (36%)	0.62
Any combination antifungal therapy	15 (45%)	6 (55%)	6 (43%)	0.56
Suppressive antifungal therapy received	14 (42%)	5 (45%)	6 (43%)	0.90
Adjunctive surgical therapy	13 (39%)	6 (55%)	5 (36%)	0.35
Mortality				
In-hospital	13 (39%)	5 (45%)	4 (29%)	0.43
42-day	14 (42%)	5 (45%)	5 (36%)	0.62
1-year	21 (66%)	7 (64%)	9 (69%)	1.00

Therapy with AMB vs echinocandin

Parameter	Overall treatment sub-group (N=33)	Amphotericin B group (N=11)	Echinocandin group (N=14)	p*
Organism				
<i>C. albicans</i>	13 (39%)	3 (27%)	3 (21%)	1.00
<i>C. parapsilosis</i>	12 (36%)	5 (45%)	7 (50%)	0.82
Age				
Mean (95% CI)	61.0 (55.5-66.4)	52.4 (43.4-61.3)	62.5 (52.6-72.4)	0.12
≥60 years	19 (58%)	3 (27%)	10 (71%)	0.05
≥70 years	14 (42%)	1 (9%)	7 (50%)	0.04
Community acquired	10 (31%)	9 (82%)	6 (42%)	0.05
Risk factors				
Prosthetic valve	13 (39%)	3 (27%)	7 (50%)	0.41
Endocavitary device	8 (24%)	1 (9%)	5 (36%)	0.18
Previous IE	8 (24%)	4 (36%)	2 (14%)	0.35
Underlying disease	5 (15%)	3 (27%)	1 (7%)	0.36

Factores de mal pronóstico más frecuentes en brazo candidas (sesgo en contra)

complication				
Clinical complications				
Stroke	4 (13%)	1 (10%)	3 (21%)	0.61
CHF	13 (39%)	3 (27%)	7 (50%)	0.41
Intracardiac abscess	11 (33%)	5 (45%)	3 (21%)	0.39
Mycotic aneurysm	1 (3%)	1 (10%)	0	0.42

High doses of echinocandins

Accordingly, the recommended first-line treatment of *Candida* endocarditis includes high doses of echinocandins as an alternative to lipid formulations of AmB for primary treatment of *Candida* endocarditis in the USA (caspofungin 50–150 mg/day, anidulafungin 100–200 mg/day or micafungin 100–150 mg/day [21]), caspofungin ± flucytosine as an alternative to lipid formulations of AmB ± flucytosine in Europe [20], and micafungin (200 mg/day), caspofungin (70 mg loading dose, then 50–100 mg/day) or anidulafungin (licensed doses) as primary choices preferably to AmB or derivatives) in the UK [22].

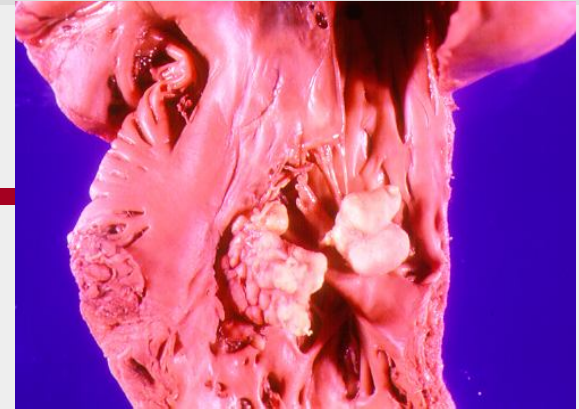
Length of treatment??

- Optimal **dosage** and **duration** undetermined
 - 2-3 g of AMB? High dose of candins??
- **Prolonged suppression**
 - Minimum of two years in operated patients?, mainly in PVE
 - Life-long if not operated?
- Prolonged **follow-up** to dx recurrence (30-40%) even after 9 yrs

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Complications



Stroke	12 vs 16%	0.5
Embolization	30 vs 22%	0.2
	47 vs 41%	0.8
HF	24 vs 31%	0.4
Persistent + BC	39 vs 9 %	<0.001

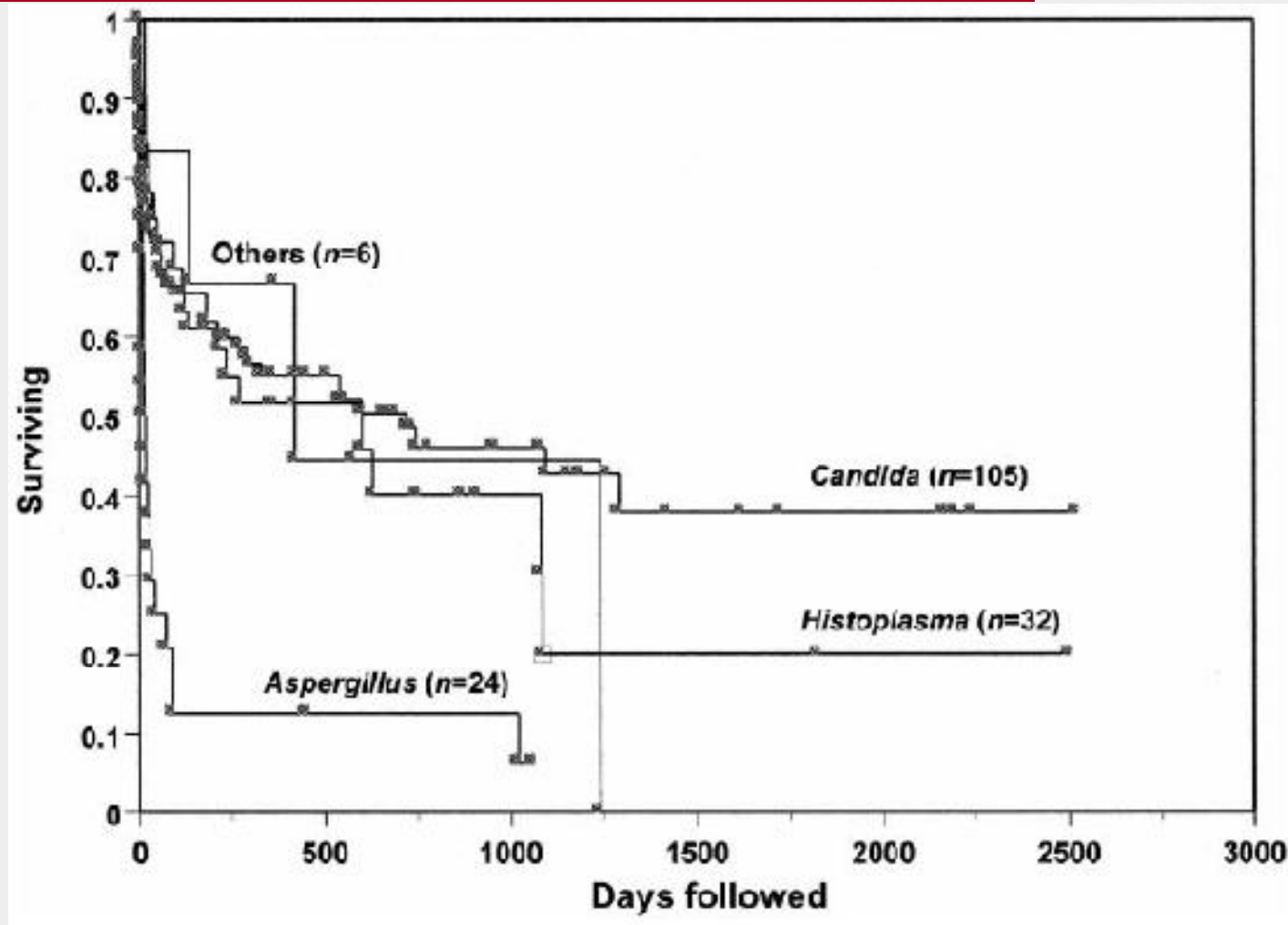
Mortality, improving a little?

- 60's-70's: **86%**
- 80-90's: **69%**
- 2000-2007: **37-67%**
- 2008-2009: **54%**
- 2000-2010: **37%**



Median time to endocarditis R-death: **66 days** (1d-4yr) MYCENDO

Aspergillus IE has higher mortality



Poor prognostic factors

- Age >50 yrs
- CHF at baseline
- Refractory candidemia
- Hospital or HC associated CIE

Parameter	Death	Alive	P
In-hospital deceased (N=25)			
Organisms			
<i>C. albicans</i>	14 (45%)	10 (26%)	0.10
<i>C. parapsilosis</i>	5 (26%)	19 (38%)	0.36
Age			
≥50 years	20 (45%)	5 (19%)	0.03
≥60 years	15 (50%)	10 (25%)	0.03
≥70 years	8 (44%)	17 (33%)	0.37
Risk factors			
Prosthetic valve	11 (34%)	14 (37%)	0.83
Diabetes Mellitus	6 (40%)	19 (35%)	0.70
CHF at baseline	11 (65%)	14 (26%)	<0.01
Previous IE	6 (33%)	19 (37%)	0.77
Clinical complications			
Stroke	1 (13%)	24 (39%)	0.24
Embolization	8 (33%)	17 (37%)	0.76
CHF as complication	11 (50%)	14 (29%)	0.09
Intracardiac abscess	8 (47%)	17 (32%)	0.26
Persistently positive cultures	9 (75%)	14 (25%)	<0.01
Echocardiographic complications			
Paravalvular complication	4 (31%)	20 (36%)	1.00
Prosthetic valve complication	5 (45%)	6 (29%)	0.34
Hospital acquired/health care associated acquisition	21 (45%)	3 (16%)	0.05

Más dudas que certezas

- Es preciso excluir EI en pacientes con candidemia
- Es recomendable operar a las EIC si es posible, pero ya no es dogma indiscutible
- L-AMB no ha demostrado clara superioridad sobre las candinas. Si usamos candinas los expertos recomiendan elevar las dosis.
- Es dudoso si hemos de administrar tratamiento inicial combinado
- Mantener luego fluconazol (mínimo 2 a o para siempre si no se ha operado)
- El seguimiento ha de ser muy prolongado

Sin embargo



- Lo que acabo de recomendar NO está basado en datos con gran evidencia científica
- La mortalidad continúa siendo superior a la de las endocarditis no fúngicas
- Sería necesario realizar estudios multicéntricos al menos para identificar los pacientes que pueden ser curados sin cirugía, o para ver si las cándidas son mejores que AMB-L, pero

doubt is not a
pleasant condition,
but certainty
is absurd

Muchas gracias !!

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Thank you very much

 **Grupos de Apoyo al Manejo
de la Endocarditis Infecciosa
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