SEICAV
Sociedad Española de Infecciones Cardiovasculares

Endocarditis Fúngica: Diagnóstico Microbiológico

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Málaga, 24 de octubre 2014

Endocarditis Fúngica: EPIDEMIOLOGÍA

Table 1 | Microbial aetiology of infective endocarditis by region*

Pathogen	Percentage of total cohort (*n* = 2,781)	Region (%)				*P* value for difference between regions
		North America (10 sites, *n* = 597)	South America (8 sites, *n* = 254)	Europe (22 sites, *n* = 1,213)	Rest of world‡ (18 sites, *n* = 717)	
Staphylococcus aureus	31	43	17	28	32	<0.001
Coagulase-negative *Staphylococcus*	11	12	7	13	9	0.005
Oral streptococci	17	9	26	16	23	<0.001
Streptococcus bovis	6	2	7	10	3	<0.001
Other streptococci	6	6	6	5	6	0.86
Enterococci	10	13	8	9	10	0.05
HACEK	2	0.3	2	2	2	0.02
Fungi or yeast	2	3	1	1	1	0.002
Polymicrobial	1	1	0.4	1	1	0.60
Culture negative	10	7	20	10	9	<0.001
Other	4	4	5	5	4	0.61

*Data from the ICE-PCS study conducted from June 2000 to September 2005.[1] ‡Including Australia, India, Israel, Lebanon, Malaysia, New Zealand, Singapore, South Africa, and Thailand. Abbreviation: HACEK, *Haemophilus* spp., *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp.

Werdan K, Nat Rev Cardiol 2014; 11: 35–50

Endocarditis Fúngica: EPIDEMIOLOGÍA

Table 1. Microbiologic Features of Native-Valve and Prosthetic-Valve Endocarditis.

Pathogen	Native-Valve Endocarditis				Prosthetic-Valve Endocarditis		
	Neonates	2 mo–15 yr of age	16–60 yr of age	>60 yr of age	Early (<60 days after procedure)	Intermediate (60 days–12 mo after procedure)	Late (>12 mo after procedure)
	approximate percentage of cases						
Streptococcus species	15–20	40–50	45–65	30–45	1	7–10	30–33
Staphylococcus aureus	40–50	22–27	30–40	25–30	20–24	10–15	15–20
Coagulase-negative staphylococci	8–12	4–7	4–8	3–5	30–35	30–35	10–12
Enterococcus species	<1	3–6	5–8	14–17	5–10	10–15	8–12
Gram-negative bacilli	8–12	4–6	4–10	5	10–15	2–4	4–7
Fungi	8–12	1–3	1–3	1–2	5–10	10–15	1
Culture-negative and HACEK organisms*	2–6	0–15	3–10	5	3–7	3–7	3–8
Diphtheroids	<1	<1	<1	<1	5–7	2–5	2–3
Polymicrobial	3–5	<1	1–2	1–3	2–4	4–7	3–7

Mylonakis E, NEJM 2001; 345: 1318

Microorganismos relacionados con EI y **hemocultivo negativo**

- Grupo HACEK
- *Bartonella spp*
- *Legionella spp.*
- *Coxiella burnetii*
- *Brucella melitensis*
- *Tropheryma whipplelii*
- *Neisseria gonorrhoeae*
- *Neisseria elongata*
- *Abiotrophia spp*
- *Gemella spp.*
- Bacilos Gram positivos
- Hongos

- *Mycobacterium spp.*
- *Mycoplasma spp*
- *Chlamydia spp*
- *Campylobacter fetus*
- *Pasteurella spp.*
- *Bordetella spp.*
- *Francisella tularensis*
- *Aeromonas hydrophila*
- *Yersinia enterocolitica*
- *Salmonella spp.*
- *Klebsiella spp.*
- *Serratia marcescens*
- *Streptobacillus moniliformis*
- …

EF: FOTO ACTUAL

- Muy infrecuente (2-4% total EI)
- Tres entidades:
  - EF válvula nativa
  - EF válvula protésica
  - EF dispositivo intracardíaco
- Última década: ↑ frecuencia

MAJOR ARTICLE

Fungal Endocarditis: Evidence in the World Literature, 1965–1995

M. E. Ellis,[1,2] H. Al-Abdely,[2] A. Sandridge,[3] W. Greer,[3] and W. Ventura[3]

[1]Faculty of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates; [2]King Faisal Specialist Hospital and Research Center, and [3]Biomedical Statistics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

We analyzed 270 cases of fungal endocarditis (FE) that occurred over 30 years. Vascular lines, non-cardiac surgery, immunocompromise and injection drug abuse are increasing risk factors. Delayed or mistaken diagnosis (82% of patients), long duration of symptoms before hospitalization (mean ± standard deviation, 32 ± 39 days) and extracardiac manifestations were characteristic. From 1988 onwards, 72% of patients were diagnosed preoperatively, compared with 43% before 1988 ($P = .0001$). The fungi most commonly isolated were *Candida albicans* (24% of patients), non-*albicans* species of *Candida* (24%), *Apergillus* species (24%), and *Histoplasma* species (6%); recently-emerged fungi accounted for 25% of cases. The mortality rate was 72%. Survival rates were better among patients who received combined surgical-antifungal treatment, were infected with *Candida*, and had univalvular involvement. Improvement in the survival rate (from <20% before 1974 to 41% currently) coincided with the introduction of echocardiography and with improved diagnostic acumen. Fungal endocarditis recurs in 30% of survivors. It is recommended that fungal endocarditis be diagnosed early through heightened diagnostic acumen; that patients be treated with combined lipid-based amphotericin B and early surgery; and that patients be followed up for ≥4 years while on prophylactic antifungal therapy.

Mortalidad EF x *Aspergillus*: 90%

Ellis M, CID 2001; 32: 50-62

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[1]Faculty of Medicine and Health Sciences, United Arab E
and Research Center, and [3]Biomedical Statistics, King

Timing diagnóstico (270 pts):

- **Pre Qx**: 128 (47%)
- **Peri Qx**: 40 (15%)
- **Post mortem**: 92 (34%)
- **Desconocido**: 10 (4%)

72%

43%

(P= 0,0001)

Ellis M, CID 2001; 32: 50-62

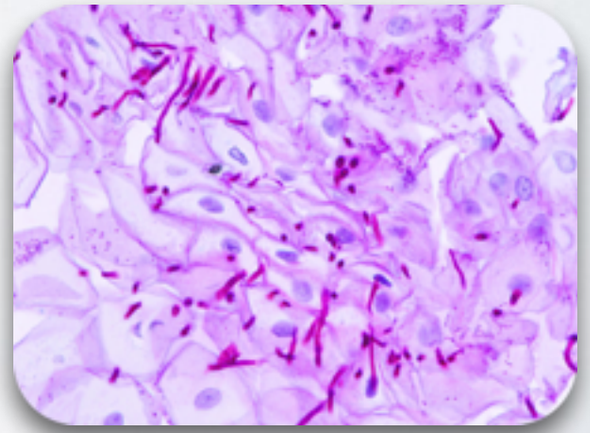
MAJOR ARTICLE

Fungal Endocarditis: Evidence in the World Literature, 1965–1995

Biomedical Statistics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Diagnóstico micológico (270 pts):

- **Hemocultivo**: 139/260 (S: 54%)
  - Pre Qx: 85%
  - Post Qx: 4%
  - Post mortem: 9%
- **Cultivo** vegetación: 143/197 (S: 73%)
- **Histología** vegetación: 173/185 (S: 95%)
- **Histología** émbolo arterial: 41/65 (S: 43%)
- **Serología**: 46/270 (S: 17%)



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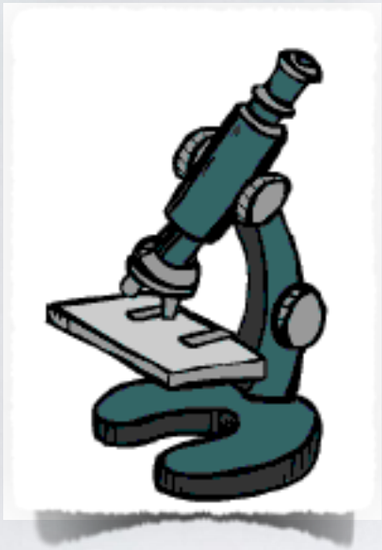
145 ptes con 3 técnicas diagnósticas

Table 5. Three-way correlations for mycologic diagnostic tests.

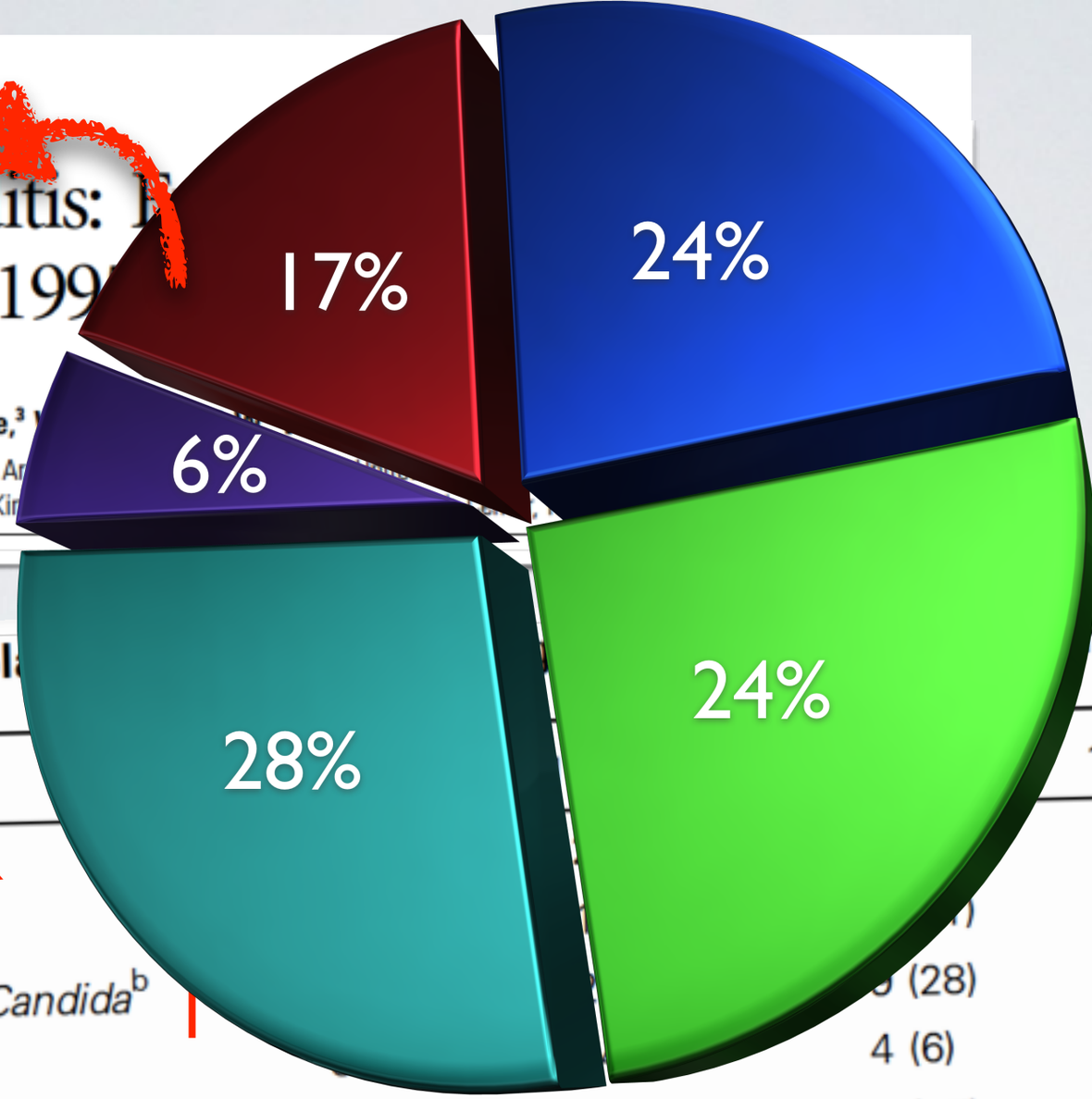
Patient group (*n*)	Blood culture	Culture of cardiac vegetation	Histologic examination of valve
1 (44)	+	+	+
2 (21)	47,6%	80,7%	83,5%
3 (4)	+		
4 (56)	–	+	+
5 (17)	–	+	–
6 (2)	–	–	–

NOTE. +, Fungus positively identified; –, no fungus identified.



Ellis M, CID 2001; 32: 50-62

	n
Paecilomyces spp	6
Mucor spp	3
Trichosporon spp	4
C neoformans	3



- *Aspergillus spp*
- *C albicans*
- *C no-albicans*
- *Histoplasma*
- *Otros*

Table 6. Pathogens isol… esults were published.

Pathogen(s)				1988–1995	Total
Aspergillus species[a]				14 (24)	66 (24)
Candida albicans				14 (24)	66 (24)
Non-*albicans* species of *Candida*[b]			(28)	16 (28)	76 (28)
Histoplasma			4 (6)	1 (2)	15 (6)
Other[c]	5 (8)	12 (15)	17 (25)	13 (22)	47 (17)
Total	64 (100)	80 (100)	68 (100)	58 (100)	270 (100)
Ratio of:					
Non-*albicans* species of *Candida* to *C. albicans*	0.75	1.4	1.4	1.1	1.2
Aspergillus to *Candida*	0.5	0.5	0.4	0.5	0.5

C. parapsilosis: 12,2% (23% levaduras, 43% no-albicans)

A. fumigatus: 9,2% (38% *Aspergillus*)

Ellis M, CID 2001; 32: 50-62

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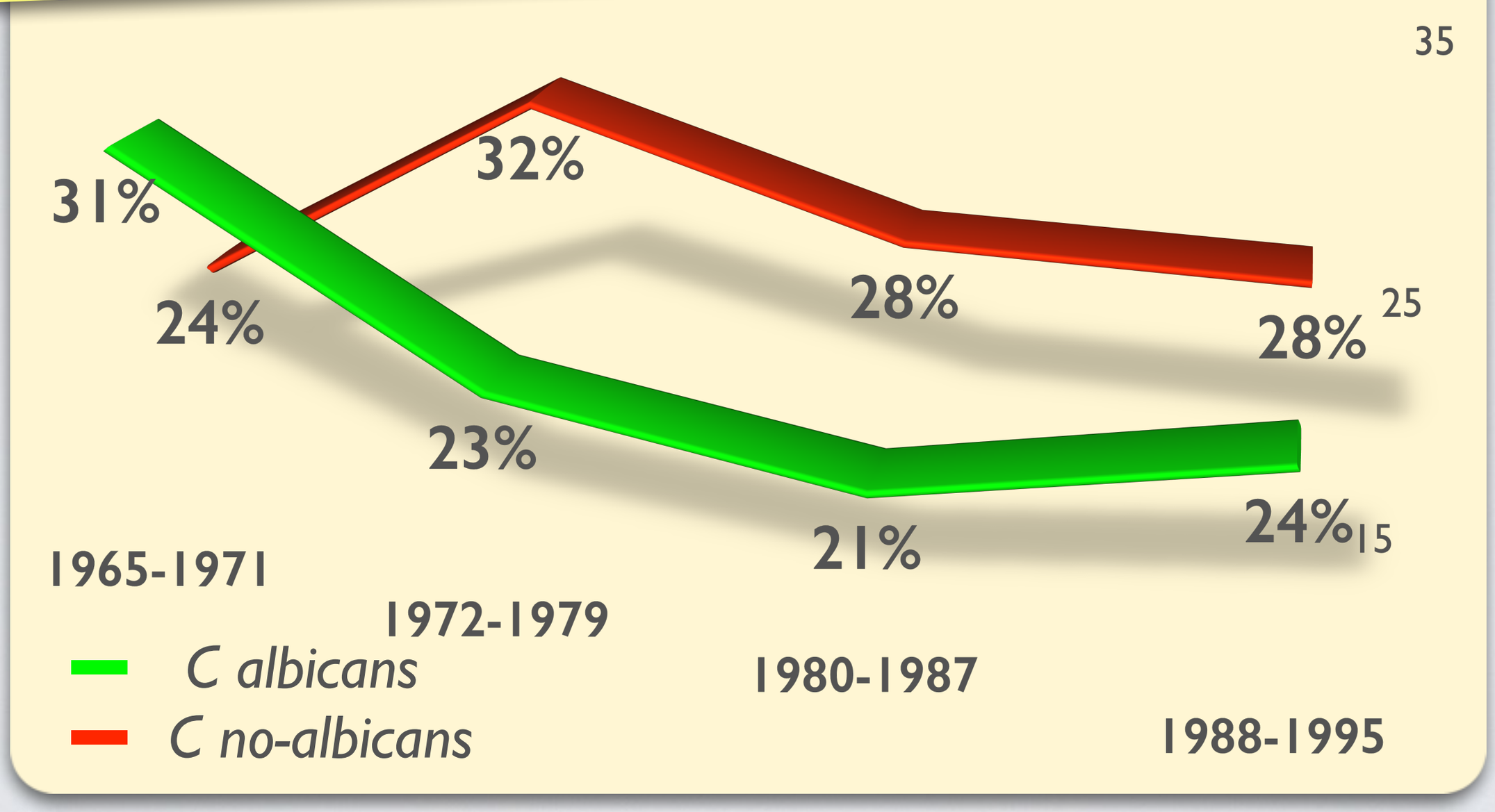
Evolución temporal aislamientos de *Candida*



Ellis M, CID 2001; 32: 50-62

¿QUÉ HERRAMIENTAS DISPONEMOS PARA DIAGNOSTICAR UNA EF?

¿PODEMOS HACER ALGO MÁS...?

¿...O HACER ALGO MEJOR?

J Antimicrob Chemother 2012; **67**: 269–289
doi:10.1093/jac/dkr450 Advance Access publication 14 November 2011

Journal of Antimicrobial Chemotherapy

Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the Working Party of the British Society for Antimicrobial Chemotherapy

F. Kate Gould[1]*, David W. Denning[2], Tom S. J. Elliott[3], Juliet Foweraker[4], John D. Perry[1], Bernard D. Prendergast[5], Jonathan A. T. Sandoe[6], Michael J. Spry[1] and Richard W. Watkin[7]

Recomendaciones DIAGNÓSTICO

Hemocultivos

- Previos al tto **[B]**
- 3 sets en <6 h, volumen adecuado, vía periférica **[C]**
- Incubación >7 d no necesaria **[B]**

A: estudios aleatorizados, meta-análisis ensayos aleatorizados. **B:** datos observaciones, estudios no aleatorizados. **C:** opinión expertos, consensos de trabajo

Gould K, JAC 2012; 67: 269

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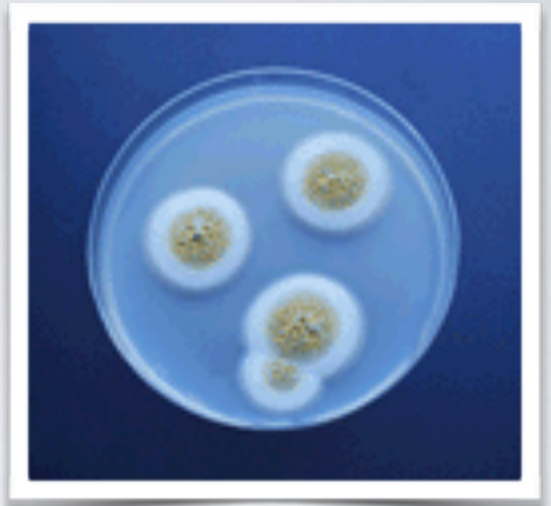
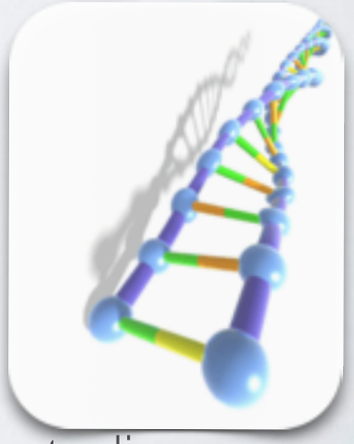


Recomendaciones DIAGNÓSTICO

Otras técnicas diagnósticas

- Detección Ag o Ac **no** recomendada por falta de evidencia
- Cultivo y examen histológico del tejido valvular o vegetaciones **[B]**
- Detección ADN (PCR) en válvula o vegetaciones **[B]**



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Recomendaciones MONITORIZACIÓN TRATAMIENTO

- Hemocultivos control (primeras 2 semanas)
- Niveles antifúngico (azoles)
- Técnicas imagen (tamaño vegetación)
- Biomarcadores (pre y durante tto): Ag, BG, PCR

A: estudios aleatorizados, meta-análisis ensayos aleatorizados. **B:** datos observaciones, estudios no aleatorizados. **C:** opinión expertos, consensos de trabajo

CURRENT OPINION

Fungal endocarditis

Daniela Tacke[a,*], Philipp Koehler[a,*], and Oliver A. Cornely[a,b,c]

15 casos publicados

Table 1. Current case reports, a literature based review of 2012–2013

Author/Ref.	Age/sex	Pathogen	Clinical findings	Predisposing conditions	Cardiac involvement	Complications	Pathogen detection	Surgical treatment	Antifungal treatment	Treatment duration	Outcome
Attia et al. [4■]	60/f	Aspergillus fumigatus	Reduced general condition, pancytopenia	CLL, BMI 17.5, chemotherapy + SCT, immunosuppression	Vegetation with filling defect, obliteration of LVOT	Endophthalmitis, cerebral embolism, bilateral lung nodules	Bronchoscopic specimen	Incomplete excision of fungal mass	Pre and post: VORI + LAmB i.v.	Approx. 2 m	Recovery, died 4 m later
Card and Lolland [5■]	41/f	Candida albicans	Pain with numbness of lower extremities, evidence of limb threatening ischaemia, leukocytosis, anaemia	i.v. drug use, mycotic valve aneurysm, AVR, postsurgical endocarditis; factor V Leiden, DVT	Fungal mass in descending aorta	Ischaemia due to superinfected thrombosis	Tissue culture (DVT)	Aortoiliac and femoroiliac thrombectomy	Post: VORI + MICA i.v.	Unknown	Unknown
Grunberg et al. [6]	62/m	Candida albicans	Fever, dyspnoea, chest pressure	ICD, hepatitis C, diabetes, congestive heart failure	Vegetation anchored entirely to ICD	Infiltrate in upper right lung	B.c.	Removal of fungal mass and ICD, replacement after 6 w.	Pre: FLU i.v. Post: FLU p.o.	12 w	Recovery
Ribeiro et al. [7■]	50/m	Candida albicans	Asthenia, fever, headache, anaemia abdominal pain, pain with numbness of lower extremities, splenomegaly, diastolic murmur	Hepatitis C, i.v. drug use	Fungal mass at aortic valve – systolic dysfunction	Evidence of limb threatening ischaemia, acute renal failure, cerebral infarctions, hydroureteronephrosis caused by aneurysm of the right common iliac artery, multiple pseudoaneurysms, muscular abscesses	B.c., specimen of aortic valve, thrombus (DVT)	AVR + crossover bypasses	Pre: AmB i.v. Post: none, due to hepatotoxicity	Unknown	Death – cardiac arrest due to multiple infarctions, celiac trunk embolism, vegetation on aortic prosthesis. Candida albicans in b.c. shortly before death
Toscini et al. [8]	75/f	Candida albicans	Fever	Pacemaker	Complete obstruction of vena cava superior, large vegetations adherent to atrial lead	None	B.c.	PM removal; 10 days later implantation of a new device	Pre: 1. FLU i.v. Pre + post: 2. MICA i.v.	Approx. 70 d	Recovery
Gilani and Barr [9]	62/m	Candida parapsilosis	Confusion, rigors, knee pain, fever	Knee replacement, diabetes, AVR and aortic root replacement; Candida parapsilosis endocarditis	Mid ascending aorta graft filling defect (CT angiogram)	Cranial septic emboli and multiple ischaemic infarcts, cerebritis	B.c.	None	1. FLU i.v. 2. AmB + FLUCYT i.v.	12 w	Recovery
Mvondo et al. [3]	44/f	Candida parapsilosis	Fever, odynophagia, cough, chest pain	AVR	No fungal mass in echo	None	B.c.	AVR	1. CASPO i.v. 2. FLU p.o.	Approx. 2 y	Recovery
Pelemi et al. [10]	23/f	Candida parapsilosis	Fever, hepatomegaly, petechial skin rash, leukopenia, anaemia	None	Vegetation at aortic valve	None	B.c., surgical specimen	AVR	Pre: 1. FLU 2. LAmB i.v. Post: LAmB + FLU i.v. later p.o.	Approx. 5 m	Recovery
Uchida et al. [11■]	66/m	Candida parapsilosis	Systolic murmur, leukocytosis	Unspecified	Pulmonary valve vegetations	Pulmonary embolism	B.c.	Pulmonary leaflets together with vegetations were resected first, valve replacement 2 y later	PreAmB i.v. + postAmB i.v.	12 w	Recovery
Wollner et al. [12■■]	72/m	Candida parapsilosis	Fever, fatigue, anaemia, later dyspnoea, septic shock and acute liver failure	AVR and CABG	F18-FDG PET-CT: tracer uptake near prosthetic aortic valve	Septic retrosternal abscess spreading to the hip joint	B.c., sputum, urine	None	1. CASPO i.v. 2. FLU i.v. 3. VORI + AmB i.v. 4. FLU p.o. lifelong	Approx. 7 w	Recovery
Jajoo et al. [13■]	Term neonate/m	Candida tropicalis	Nonvigorous at birth, hepatomegaly, rash, icterus, leukocytosis, anaemia	None	Right-sided echogenic masses	Additional echogenic masses in gall bladder	B.c.	None	1. AmB 2. LAmB + FLU i.v. 3. FLU p.o.	Approx. 2.5 y	Recovery
De Rosa et al. [14]	65/f	Candida glabrata	Fever, weight loss	A + MVR 30 y ago; MVR for endocarditis 10 y ago; tricuspid valve replacement 6 y ago, HCV; C. glabrata candidaemia	Vegetations at tricuspid valve	lung hemorrhagic lesion	B.c.	Yes (but unspecified)	Pre: 1. LAmB i.v. 2. ANIDU i.v. Post: 3. ANIDU 4. VORI p.o.	ANIDU 6 w, VORI unspecified	Unspecified (11 m later no relapse)
Doveson and Woods [15■■]	30/m	Lodderomyces elongisporus	Fever, oedema localized to left ankle region, systolic murmur	i.v. drug use (heroin), bicuspid aortic valve with combined stenosis and insufficiency	Bulky lesions at both leaflet margins of aortic valve	Cerebral embolic lesions; multifocal osteomyelitis left foot	B.c.	AVR	Pre: 1. CASPO i.v. 2. FLUCYT + AmB i.v. Post: 3. FLUCYT + AmB i.v. 4. VORI p.o.	Approx. 13 m	Recovery
Esnakula et al. [16■■]	44/m	Fusarium solani	Fever, diarrhoea, later dyspnoea and intubation, leukocytosis	AIDS, hepatitis C, CVC, haemodialysis, corticosteroids	Right atrial thrombus	Diffuse bilateral infiltrates with areas of consolidation	B.c.	None	AmB i.v.	Unspecified	Death (DIC)
Patel et al. [17■■]	50/f	Exophiala dermatitidis	Weakness, fatigability, swollen and tender left wrist, dry cough, anaemia	Renal transplant	Systolic and diastolic murmur, cardiomegaly, vegetation over aortic valve with regurgitation	None	B.c., surgical specimen	Bioprosthetic AVR	1. FLU i.v. 2. VORI i.v.	6 m	Recovery

Tacke D, Curr Opin Infect Dis 2013, 26:501

EF: REVISIÓN LITERATURA 2012-2013

15 casos publicados

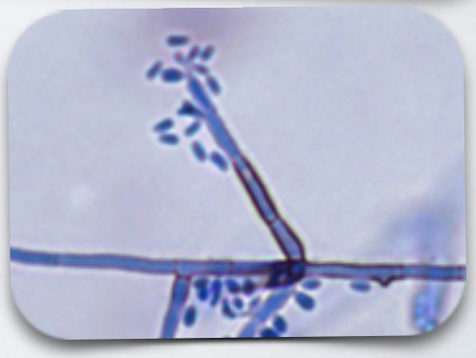
Levaduras (12):

- *C. parapsilosis* (5)
- *C. albicans* (4)
- *C. tropicalis*
- *C. glabrata*
- *Lodderomyces elongisporus*

H. filamentosos (3):

- *Fusarium solani*
- *Aspergillus fumigatus*
- *Exophiala dermatitidis*

Mortalidad 12,5%:
C. albicans, F. solani



Tacke D, Curr Opin Infect Dis 2013, 26:501

EF: REVISIÓN LITERATURA 2012-2013

Factores predisponentes

- ADVP
- Dispositivos biomédicos:
  - Catéter
  - Marcapasos
  - DAI
  - Prótesis valvulares

- Inmunosupresión:
  - TOS
  - TPH
  - Quimioterapia
- Antibióticos amplio espectro
- Enfermedad de base:
  - Diabetes
  - Malnutrición

Tacke D, Curr Opin Infect Dis 2013, 26:501

EF: REVISIÓN LITERATURA 2012-2013

Valor diagnóstico de las MUESTRAS clínicas

Candida spp.

- Hemocultivo
  - >90% sensibilidad
- Cultivo válvula/ vegetación/émbolo
- Técnicas alternativas:
  - Beta-glucano
  - ADN

Aspergillus spp.

- Hemocultivo:
  - <10% sensibilidad
- Cultivo válvula/vegetación
- Técnicas alternativas:
  - Galactomanano
  - Beta-glucano
  - ADN

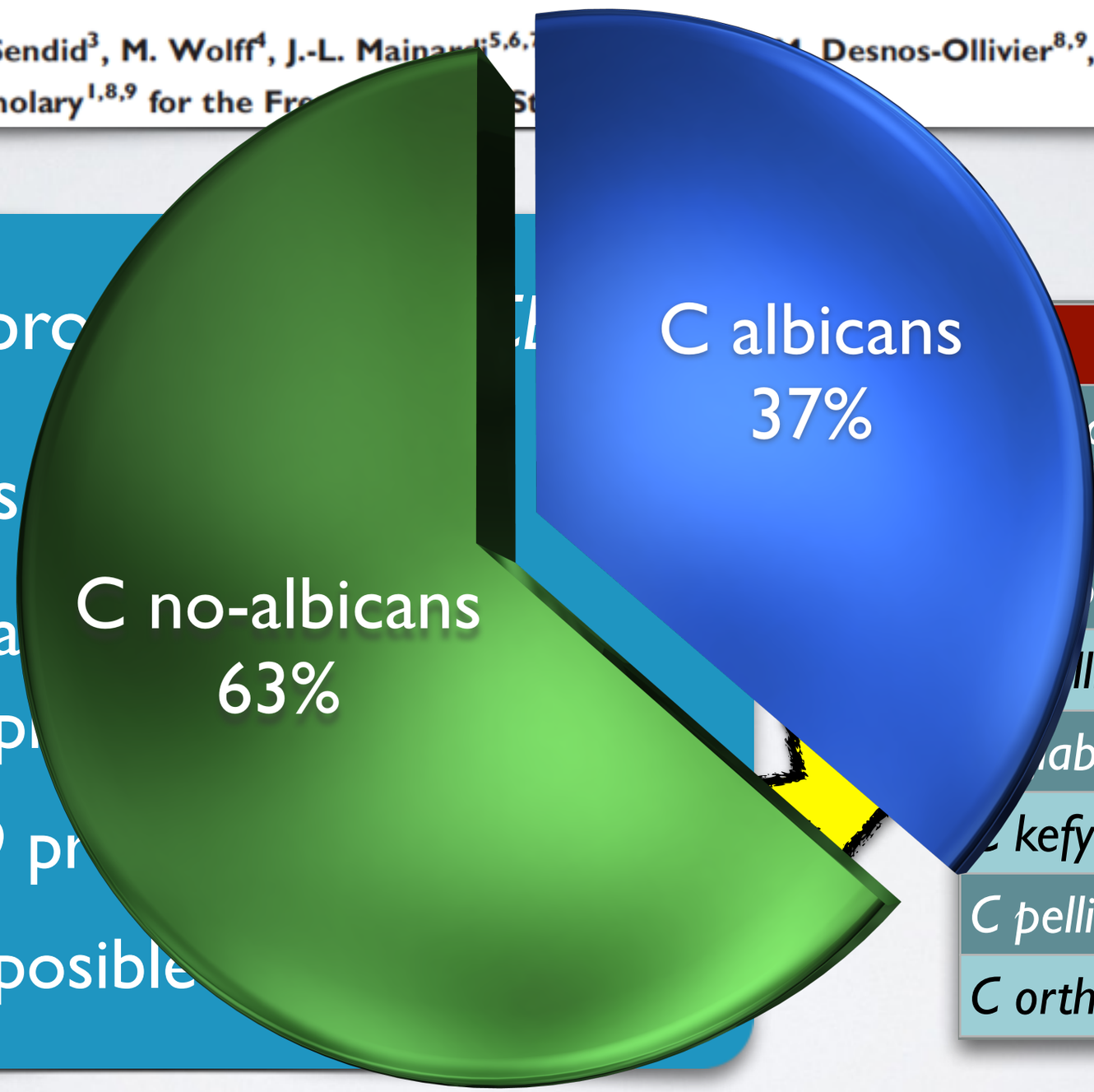
Tacke D, Curr Opin Infect Dis 2013, 26:501

ORIGINAL ARTICLE MYCOLOGY

Diagnosis, management and outcome of *Candida* endocarditis

A. Lefort[1]*, L. Chartier[2], B. Sendid[3], M. Wolff[4], J.-L. Mainardi[5,6,7] … Desnos-Ollivier[8,9], A. Fontanet[2,10], S. Bretagne[8,9,11] and O. Lortholary[1,8,9] for the Fr… St…

- Estudio pro… /…
- 27 meses
- 20 hospita…
  - 30 epi…
    - ☑ 29 pr…
    - ☑ 1 posible…



	n
…cans	11
…psilosis	9
…icalis	3
…lliermondii	2
…abrata	2
…kefyr	1
C pellicullosa	1
C orthopsilosis	1

Lefort A, CMID 2012; 18: E-99

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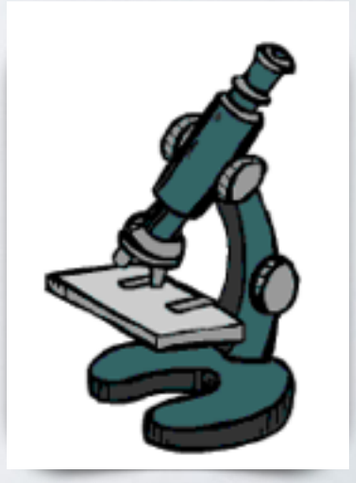
A. Lefort[1]*, L. Chartier[2], B. Sendid[3], M. Wolff[4], J.-L. Mainardi[5,6,7], I. Podglajen[5], M. Desnos-Ollivier[8,9], A. Fontanet[2,10], S. Bretagne[8,9,11] and O. Lortholary[1,8,9] for the French Mycosis Study Group†

- Hemocultivos +: 28/30 (93%)
- Hemocultivos -: 2/30 (7%)
- Cirugía valvular: 12 ptes
  - Cultivo +: 9/12 (75%)
  - Microscopía +: 6/8 (75%)
  - PCR +: 4/6 (67%)



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ORIGINAL ARTICLE MYCOLOGY

Diagnosis, management and outcome of *Candida* endocarditis

A. Lefort[1]*, L. Chartier[2], B. Sendid[3], M. Wolff[4], J.-L. Mainardi[5,6,7], I. Podglajen[5], M. Desnos-Ollivier[8,9], A. Fontanet[2,10], S. Bretagne[8,9,11] and O. Lortholary[1,8,9] for the French

Diagnóstico alternativo al cultivo

- ADN sangre (Septifast) +: 5/12 (42%)
  - 2 *C parapsilosis*, 2 *C tropicalis*, 1 *C albicans*
- Man/anti-Man +: 15/18 (83%)
- Beta-glucano +: 18/18 (100%)
- Man/anti-Man 2+ consecutivos: 13/18 (81%)
- Beta-glucano 2+ consecutivos: 16/18 (88%)

Lefort A, CMID 2012; 18: E-99

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Beta-glucano:

- Niveles séricos > altos en EF por *C parapsilosis* complex, *C tropicalis* y *C guilliermondii* que por *C albicans* (p<0,002)
- 15/18 ptes niveles altos a las 3 sem post-dtico
- Sin relación con la evolución

Lefort A, CMID 2012; 18: E-99

Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry

William J. Steinbach [a,b,*], Kieren A. Marr [c], Elias J. Anaissie [d], Nkechi Azie [e], Shun-Ping Quan [e], Herwig-Ulf Meier-Kriesche [e], Senu Apewokin [d], David L. Horn [f]

- Estudio prospectivo (2004-2008)
- 25 hospitales EEUU y Canadá
- 960 pacientes
- 1117 aislamientos *Aspergillus*
- Supervivencia 12 semanas: 64%

- *A. fumigatus*: 73%
- *A. flavus*: 10%
- *A. niger*: 9%
- *A terreus*: 4%

Steinbach W, J Infect 2012; 65: 453

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Table 5 Infection site by *Aspergillus* spp.

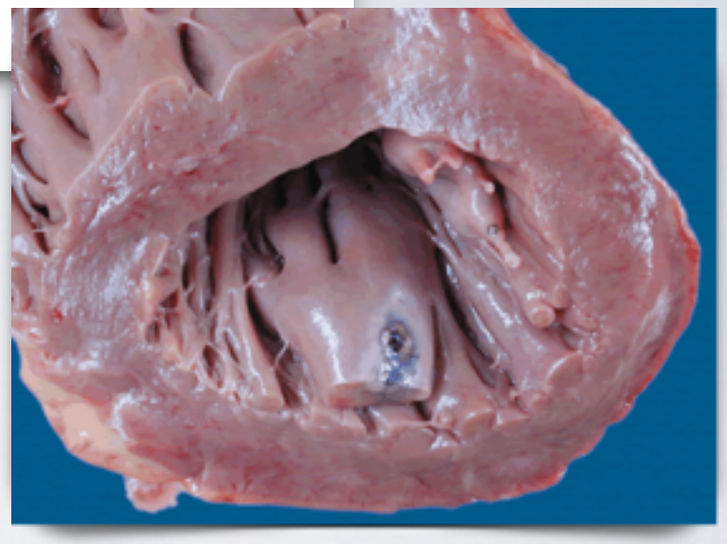
Infection site	*A. fumigatus*	*A. flavus*	*A. niger*	*A. terreus*	Other[a]	Unspecified	Total
Lung	466	46	56	31	23	222	867
Tracheobronchial	39	6	2	1	3	3	57
Sinus	18	11	3	1	2	10	47
Skin and soft tissue	18	7	4		3	5	40
Central nervous system	19	1	2			1	23
Blood	4	1	1			15	21
Abdominal	9	3	1			5	18
Skeleton	11	3				2	16
Heart	6		1			7	14
Orbital	2	1			1		5
Endophthalmitis	1						1
Other	3	1			2		8
Total	596	80	70	33	34	270	1117

[a] Includes *A. versicolor* (23), *A. ustus* (6), *A. nidulans* (3),

Endocarditis: 1,3% de las AI

Steinbach W, J Infect 2012; 65: 453

Aspergillus endocarditis in the era of new antifungals: Major role for antigen detection☆

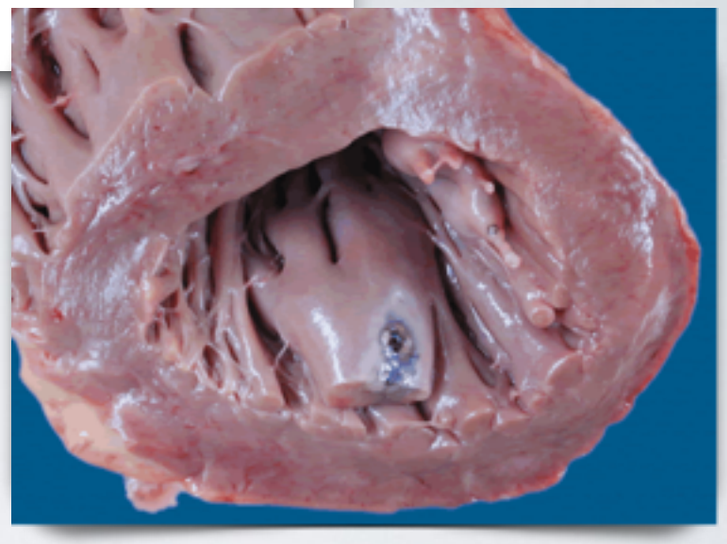


- Estudio prospectivo *MYCENDO*
- 6 años (2005-2011)
- 20 hospitales franceses:
  - 8 episodios EF por *Aspergillus*:
    - ☑ 7 probadas
    - ☑ 1 posible

- **Diagnóstico:**
  - ✱ Criterios Duke
  - ✱ Cultivos
  - ✱ Galactomanano
  - ✱ Beta-glucano
  - ✱ ADN (suero/válvula)

Riviere S, J Infect 2013; 67: 85

Aspergillus endocarditis in the era of new antifungals: Major role for antigen detection☆



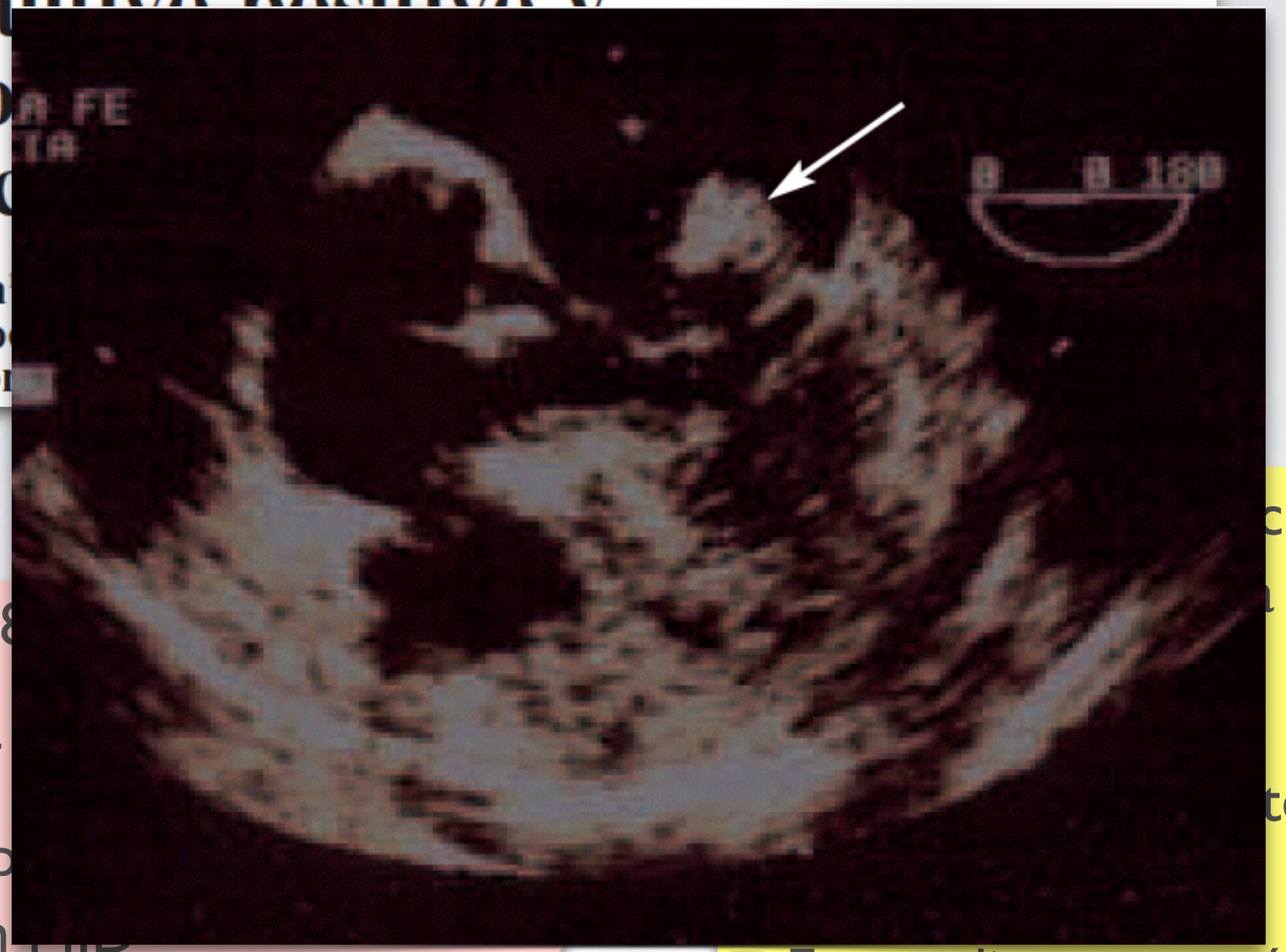
- Cultivos micológicos:
  - Hemocultivo +: 1/8
  - Válvula +: 6/6
- Detección de antígenos:
  - Beta-glucano +: 4/4
  - GM +: 6/6 (4 pre HC+)
- Detección ADN:
  - Válvula: 2/2
  - Suero: 2/2 (1 con HC-)

- **Mortalidad (62,5%):**
  - Mejoras Qx y soporte
  - Dtco precoz: Ag y PCR
  - Tto prolongado VCZ

Riviere S, J Infect 2013; 67: 85

Endocarditis por *Aspergillus fumigatus* en válvula nativa con hemocu
galacto
de un c

Javier Pemán
Marisa Cresp
Emilia Cantór



- Varón, 58
- EPOC +
- Ingresa p
  dolor en

cción
+ infartos

teria

- Ecocardio transtorácica: vegetación mitral

Pemán J, Rev Iberoam Micol 2007; 24: 157

Endocarditis por *Aspergillus fumigatus* en válvula nativa con hemocultivo positivo y galactomanano negativo. Descripción de un caso y revisión de la literatura

- Cirugía valvular urgente
- Implante prótesis metálica
- Envío a AP y Microbiología de vegetación y válvula

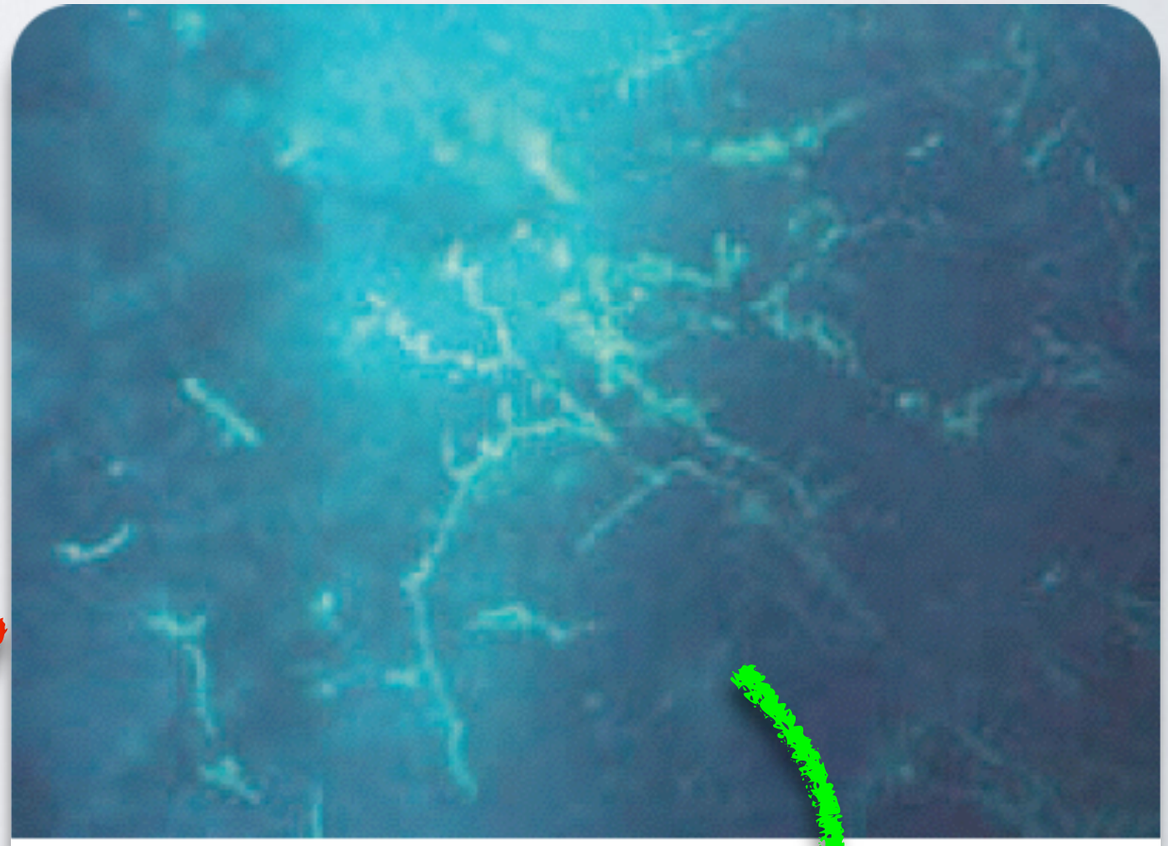


Figura 2. Examen microscópico directo de la vegetación mediante la tinción con blanco de calcoflúor donde se observan estructuras tabicadas y ramificadas compatibles con un hongo filamentoso (x200).

Pemán J, Rev Iberoam Micol 2007; 24: 157

Voriconazol iv

Endocarditis por *Aspergillus fumigatus* en válvula nativa con hemocultivo positivo y galactomanano negativo. Descripción de un caso y revisión de la literatura

- Cultivo vegetación: *A. fumigatus*
- AP vegetación: hifas tabicadas y ramificadas
- Hemocultivo (2/2): *A. fumigatus*
- GM suero (2/2): ID < 0,5

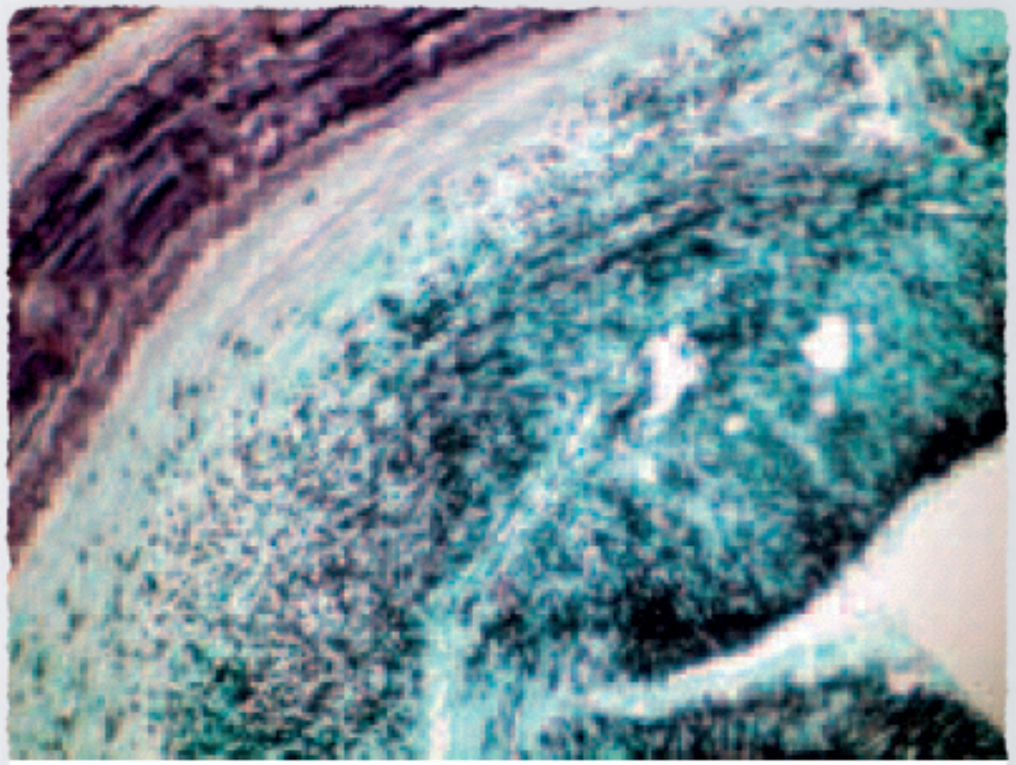


Figura 3. Examen histopatológico de la biopsia valvular mediante la tinción de Gomori-Grocott. Se aprecian abundantes hifas tabicadas y ramificadas en ángulo agudo (x200).

- Mala evolución
- +10 d: VCZ+caspofungina
- +45 d: exitus

Pemán J, Rev Iberoam Micol 2007; 24: 157

Endocarditis por *Aspergillus fumigatus* en válvula nativa con hemocultivo positivo y galactomanano negativo. Descripción de un caso y revisión de la literatura

Tabla. Resumen de los tres casos de endocarditis fúngica por *Aspergillus* con hemocultivo positivo.

Edad / sexo	Válvula afectada	Especie aislada	Factores de riesgo/ Enfermedad de base	Cuadro clínicoi	Tratamiento antifúngico	Tratamiento quirúrgico	Hemo-cultivos + / −	Evolución	Referencia
60 / ♀	Mitral	*A. terreus*	Leucemia linfoblástica aguda	Fiebre, disnea, FA, SS válvula mitral, embolismo aórtico	Anfotericina B	Sí	7 / [illegible]	[illegible]	[21]
67 / ♂	Mitral	*A. fumigatus*	Sin factores de riesgo para aspergilosis invasora / bronquiectasias	Cefalea, abscesos cerebrales, embolismo ocular y en MSI	Anfotericina B	Sí	1 / 2	*Exitus*	[8]
58 / ♂	Mitral	*A. fumigatus*	Ciclos discontinuos de corticoterapia / bronquitis crónica	Amaurosis fugaz, embolismo en MMII	Voriconazol + caspofungina	Sí	2 / 2	*Exitus*	Hospital Univ La Fe

FA: fibrilación auricular; SS: shock séptico; MSI: miembro superior

crecimiento en las muestras de sangre sembradas e incuba-
das en los caldos enriquecidos con tripticasa de soja. En el
tercer caso, en ningún momento los sistemas automáticos
de detección dieron señal positiva de crecimiento; sin em-
bargo, al observar visualmente las botellas, siete de ellas
mostraban crecimiento macroscópico de un hongo fila-
mentoso [21]. Esta circunstancia demuestra la escasa sen-

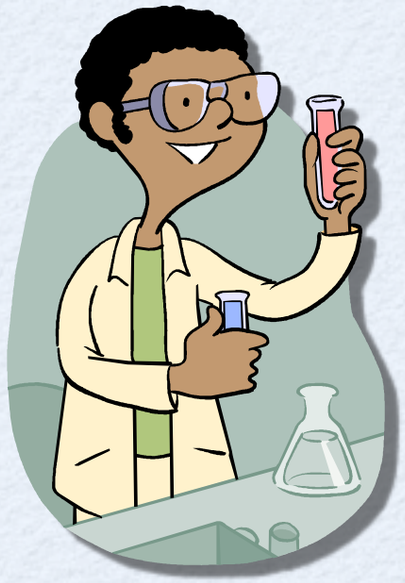
Peman J, Rev Iberoam Micol 2007; 24: 157

Sistemas automatizados de hemocultivo

Tiempo incubación:

NO crecimiento

- 5-7 días → 21 días
- Final incubación:
  - ¡¡¡ Examen macroscópico !!! + Subcultivo ciego



MÉTODOS DIAGNÓSTICOS en ENDOCARDITIS FÚNGICA

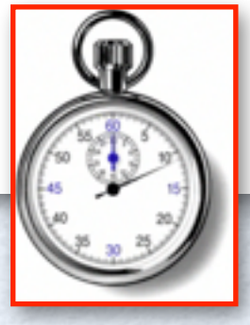
... el PASADO

... ¿¿¿ y el FUTURO ???

... el PRESENTE

MALDI-TOF "directo" de hemocultivo

Direct MALDI-TOF Mass Spectrometry Assay of Blood Culture Broths for Rapid Identification of *Candida* Species Causing Bloodstream Infections: an Observational Study in Two Large Microbiology Laboratories



30'

We evaluated the reliability of the Bruker Daltonik's MALDI Biotyper system in species-level identification of yeasts directly from blood culture bottles. Identification results were concordant with those of the conventional culture-based method for 95.9% of *Candida albicans* (187/195) and 86.5% of non-*albicans Candida* species (128/148). Results were available in 30 min (median), suggesting that this approach is a reliable, time-saving tool for routine identification of *Candida* species causing bloodstream infection.

In conclusion, our study confirms that the Bruker Biotyper system is one of the more promising alternatives proposed to accelerate species-level ID of yeast isolates. Furthermore, almost 80% of our positive BCs were reported positive ≤24 h after sample entry (median time, 16 h). Consequently, with direct Bruker Biotyper assay of BC broth, physicians can realistically expect (in many cases) to receive species-level ID data for *Candida* isolates causing BSI within 24 h after the BC is drawn, a prospect that is unthinkable with conventional culture-based phenotypic testing.

Spanu T. J Clin Microbiol 2012; 50:176–9

PCR + nanopartículas + RM

3 h

RESEARCH ARTICLE

DIAGNOSTICS

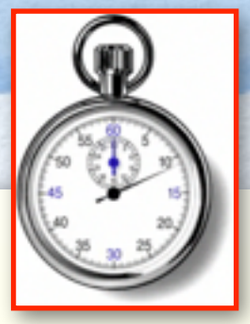
T2 Magnetic Resonance Enables Nanoparticle-Mediated Rapid Detection of Candidemia in Whole Blood

Detecta 1 ufc/mL de *Candida* spp en sangre en < 3 h !!!

Candida spp. cause both local and disseminated infections in immunocompromised patients. Bloodstream infections of *Candida* spp., known as "candidemia," are associated with a high mortality rate (40%), which is mainly attributed to the long diagnostic time required by blood culture. We introduce a diagnostic platform based on T2 magnetic resonance (T2MR), which is capable of sensitive and rapid detection of fungal targets in whole blood. In our approach, blood-compatible polymerase chain reaction is followed by hybridization of the amplified pathogen DNA to capture probe–decorated nanoparticles. Hybridization yields nanoparticle microclusters that cause large changes in the sample's T2MR signal. With this T2MR-based method, *Candida* spp. can be detected directly in whole blood, thus eliminating the need for analyte purification. Using a small, portable T2MR detection device, we were able to rapidly, accurately, and reproducibly detect five *Candida* species within human whole blood with a limit of detection of 1 colony-forming unit/ml and a time to result of <3 hours. Spiked blood samples showed 98% positive agreement and 100% negative agreement between T2MR and blood culture. Additionally, performance of the assay was evaluated on 21 blinded clinical specimens collected serially. This study shows that the nanoparticle- and T2MR-based detection method is rapid and amenable to automation and offers clinicians the opportunity to detect and identify multiple human pathogens within hours of sample collection.

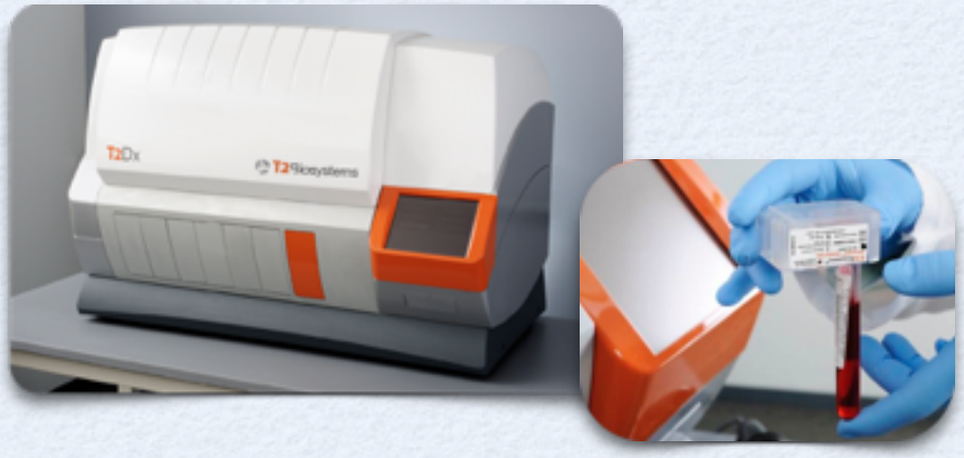
Neely LA. Science Trans Med 2013; 5:182ra54

PCR + RM + nanopartículas



3 h

- Detección directa de *Candida* en sangre completa
- 5 especies de *Candida* *(C. albicans, C. tropicalis, C. krusei, C. parapsilosis, C. glabrata)*
- Límite de detección 1 ufc/ml
- Evaluación en muestras de sangre inoculadas con *Candida*
- Concordancia: 98% (cultivos positivos); 100% (cultivos negativos)
- Sistema comercializado, detector portátil de sobremesa
- Tiempo: 3 h
- Manejo: 2 minutos
- Rápido, automatizado, fácil

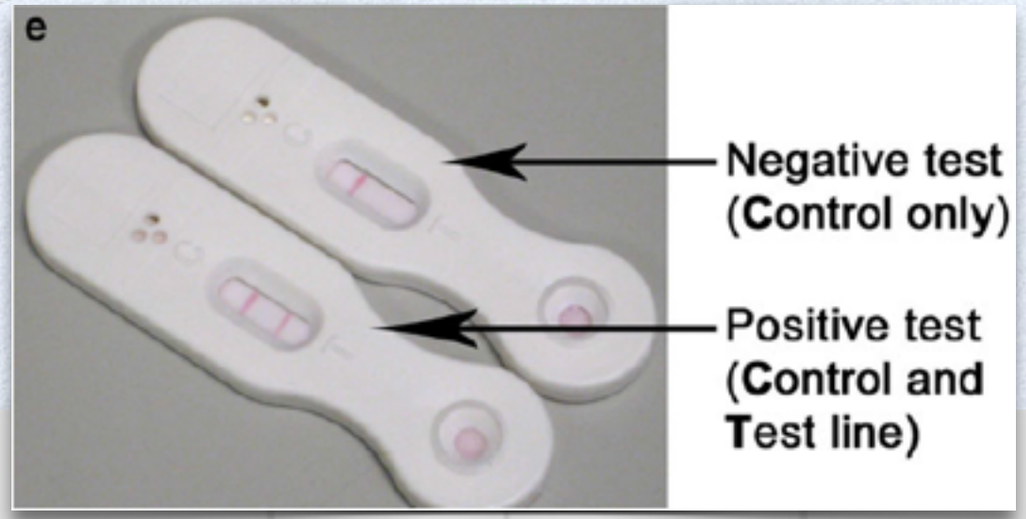


Neely LA. Science Trans Med 2013; 5:182ra54

Aspergillus Lateral-Flow Device

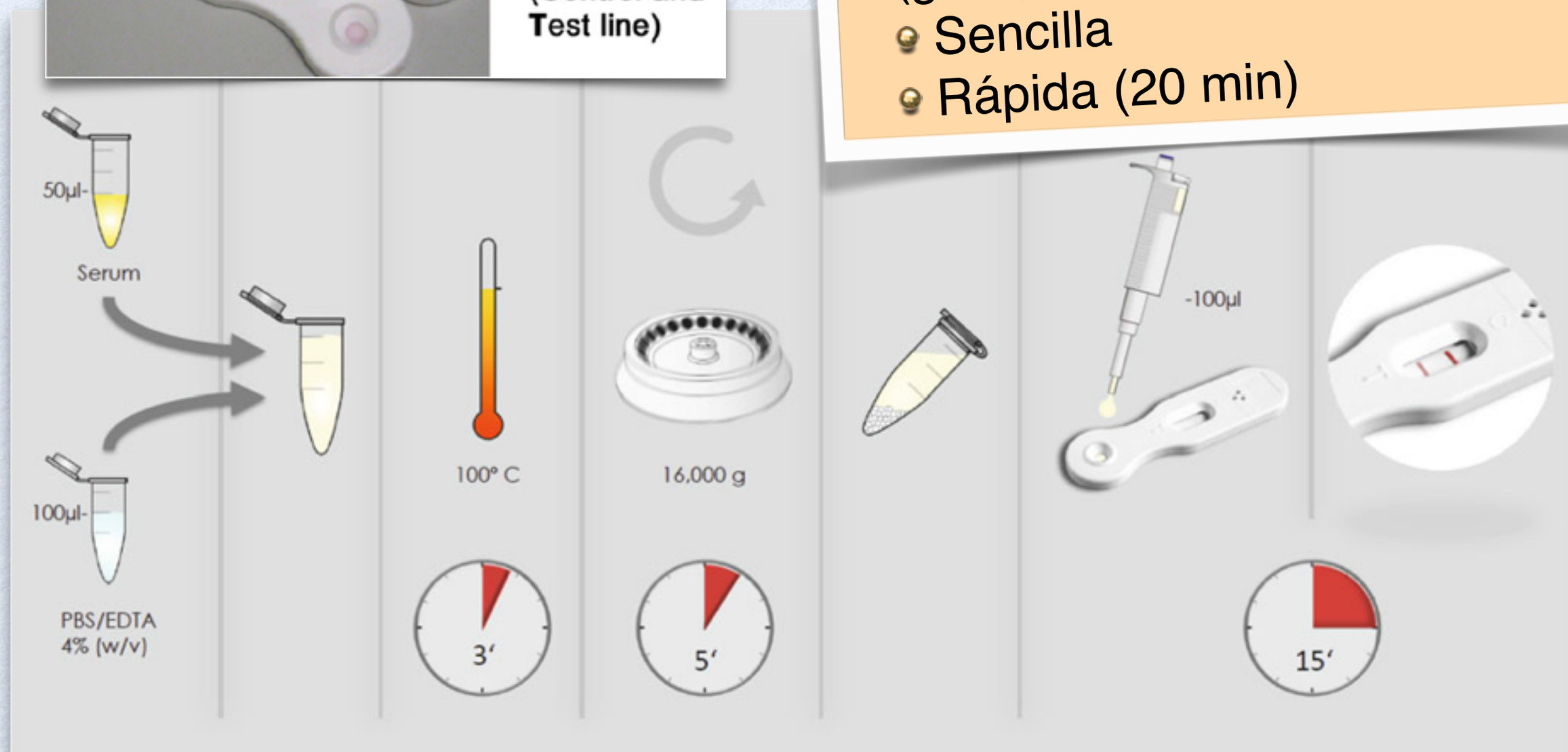
20’

Isca Diagnostics



Inmunocromatografía:

- Ac monoclonal JF5 (glicoproteínas extracelulares)
- Sencilla
- Rápida (20 min)



Aspergillus Lateral-Flow Device

20'

Comparison of a novel *Aspergillus* lateral-flow device and the Platelia® galactomannan assay for the diagnosis of invasive aspergillosis following haematopoietic stem cell transplantation

Held J et al. Infection 2013; 41:1163

		Sens	Esp	VPP	VPN
1 suero	LFD	40%	87%	25%	93%
	GM	40%	89%	29%	93%

101 pacientes TPH

Conclusions If used as a screening test (one positive serum required for test positivity) or to rule out IFD, the *Aspergillus*-LFD has shown a comparable diagnostic performance to the GM-EIA. However, if the results have to

Aspergillus Lateral-Flow Device

20'

Comparison of Lateral Flow Technology and Galactomannan and (1→3)-β-D-Glucan Assays for Detection of Invasive Pulmonary Aspergillosis[▽]

We compared a lateral flow device to galactomannan and (1→3)-β-D-glucan assays to detect invasive aspergillosis in an established guinea pig model of pulmonary disease. The lateral flow device became positive earlier (day 3) than the (1→3)-β-D-glucan and galactomannan assays (day 5), with all samples positive by each assay on day 7.

TABLE 1. Comparison of the lateral flow device and galactomannan and (1→3)-β-D-glucan assays

Assay and result	No. of positive results/no. tested				
	1 h	Day 3 (sensitivity)	Day 5 (sensitivity)	Day 7 (sensitivity)	Uninfected (specificity)
Lateral flow device positive	0/5	12/25 (48%)	14/17 (82%)	6/6 (100%)	0/10 (100%)
β-Glucan of >80 pg/ml	0/5	0/25 (0%)	4/17 (23%)	6/6 (100%)	2/10 (80%)
Galactomannan index of >0.5	1/5	1/25 (4%)	10/17 (59%)	6/6 (100%)	0/10 (100%)

Winderhold N. Clin Vacc Immunol 2009; 16:1844

Ácidos nucleicos

FilmArray™ (BioFire DX)

Screening de 24 patógenos causales de Sepsis en 1 hora

Sangre total (>4ml)

Líquidos estériles (máx. disponible hasta 10 ml)

Incubación (12h)
***según volumen muestra**

Extracción+Amplificación+Detección HRM (1h)

El 90% de las infecciones bacterianas y candidiásicas graves son debidas a:

Gram + Bacteria *Staphylococcus*	**Gram - Bacteria**	**Fungi**	**Antibiotic Resistance***
Staphylococcus aureus	*Enterobacteriaceae*	*Candida albicans*	*mecA*
Streptococcus	*Enterobacter cloacae complex*	*Candida glabrata*	*vanA / vanB*
Streptococcus agalactiae	*Escherichia coli*	*Candida krusei*	*KPC*
Streptococcus pyogenes	*Klebsiella oxytoca*	*Candida parapsilosis*	
Streptococcus pneumoniae	*Klebsiella pneumoniae*	*Candida tropicalis*	
Enterococcus	*Serratia*		
Listeria monocytogenes	*Proteus*		
	Acinetobacter baumannii		
	Haemophilus influenzae		
	Neisseria meningitidis		
	Pseudomonas aeruginosa		

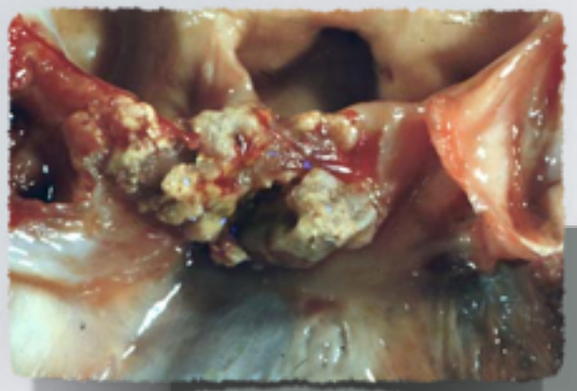
Resumiendo…

La **rentabilidad de las técnicas** microbiológicas para el diagnóstico de la endocarditis fúngica es **diferente** según el **patógeno** responsable y la **muestra clínica** analizada

		Levaduras (*Candida*)	Mohos (*Aspergillus*)
Sangre	Hemocultivo	😃😃😃😃	😟/😃
	PCR tr	😃	😃
Suero	Beta-glucano	😃😃	😃😃
	Man/anti-Man	😃😃	
	Galactomanano		😃😃

Resumiendo...

La **rentabilidad de las técnicas** microbiológicas para el diagnóstico de la endocarditis fúngica es **diferente** según el **patógeno** responsable y la **muestra clínica** analizada



		Levaduras (*Candida*)	Mohos (*Aspergillus*)
Tejidos: · vegetación · válvula · émbolos	Microscopía directa	😃😃😃	😃😃😃
	Cultivo	😃😃😃	😃😃😃
	Histopatología	😃😃😃	😃😃😃
	Inmunohistoquímica	😃	😃😃
	ADN	😃😃	😃😃


¡¡ Muchas gracias !!