Dilema en el manejo de las IFIs
Rol del tratamiento combinado

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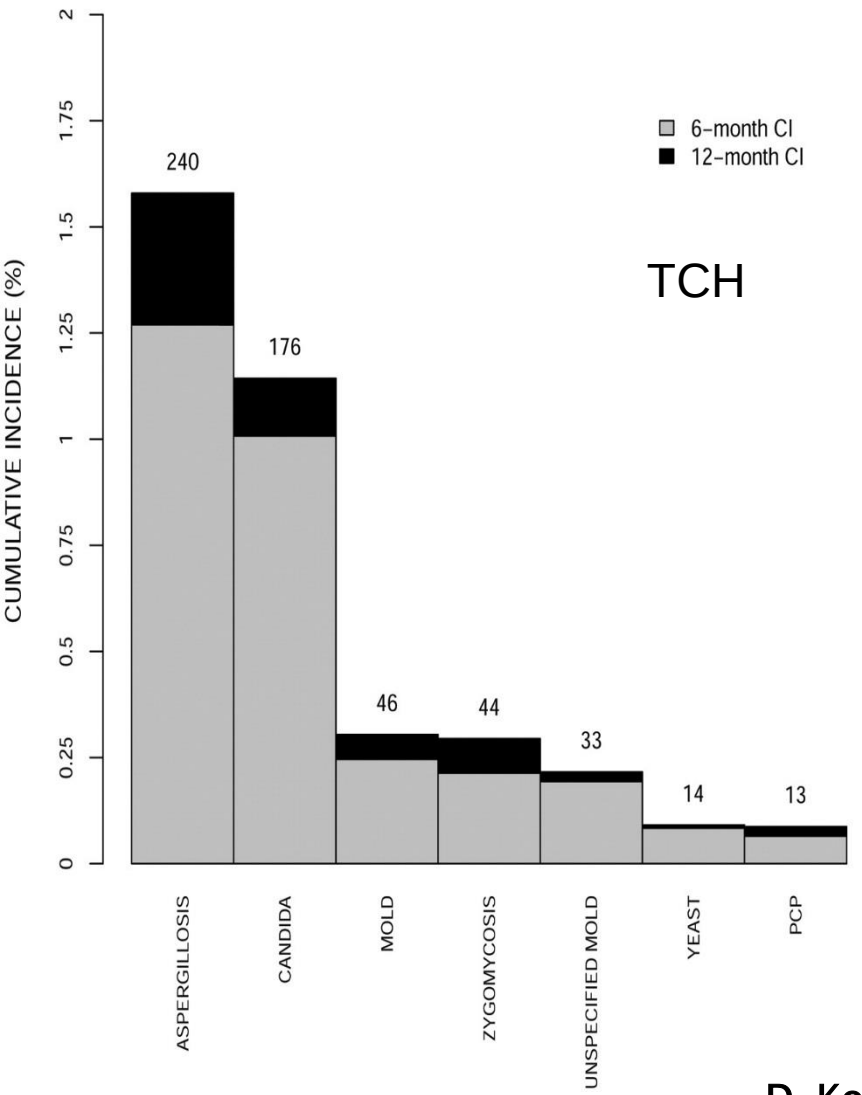
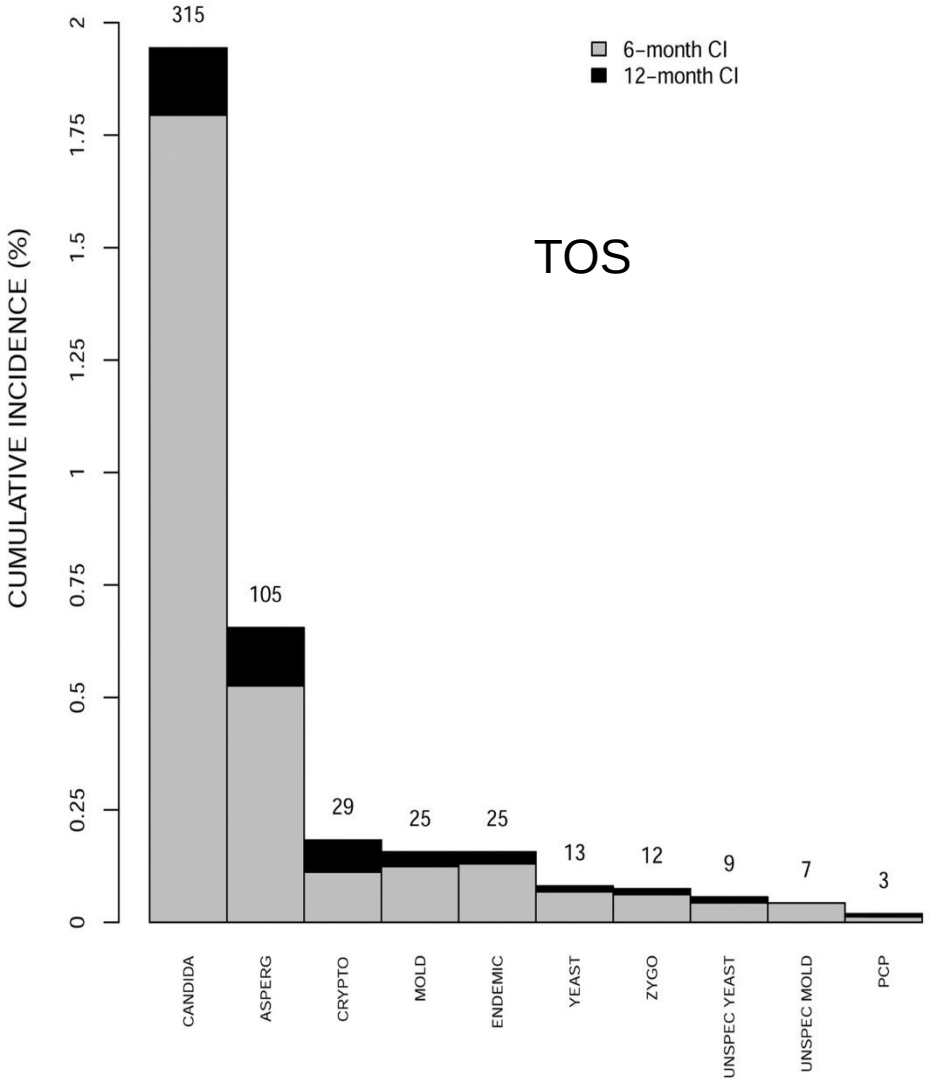
Conflictos de interés:

Gador – Astellas
MSD

Incidencia – TRANSNET USA 2001-10

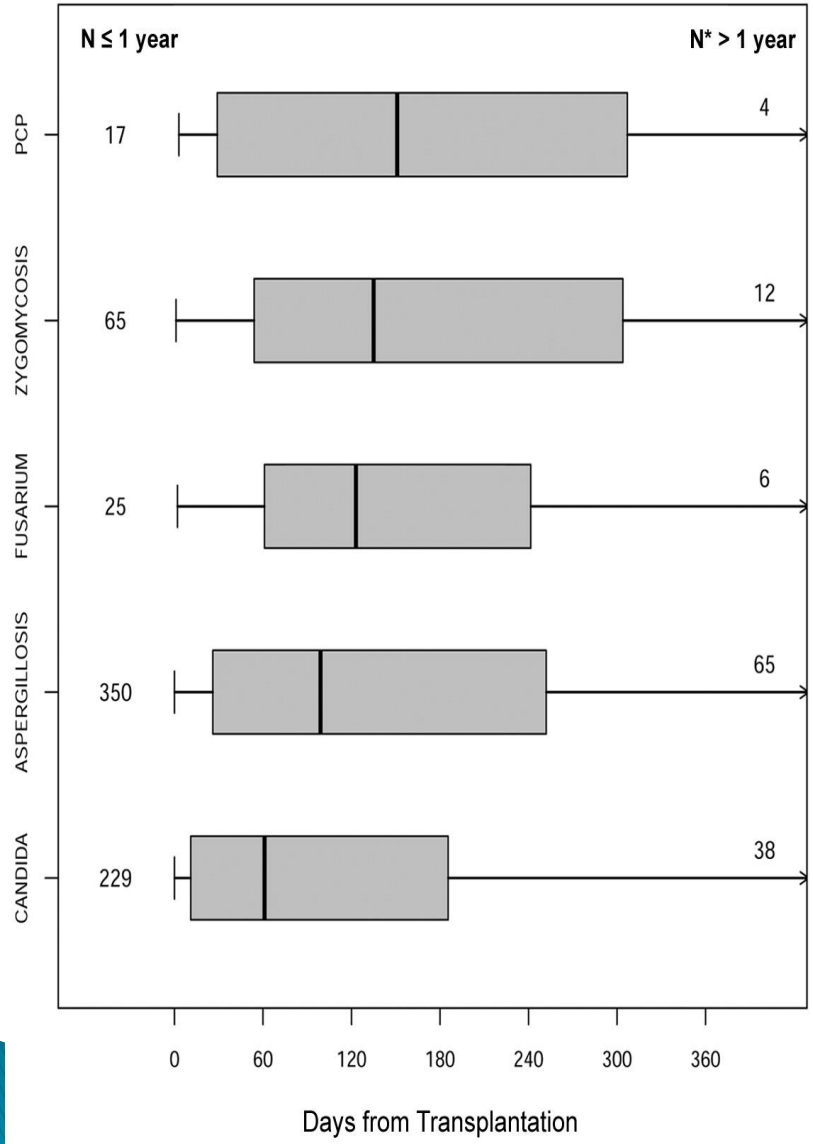




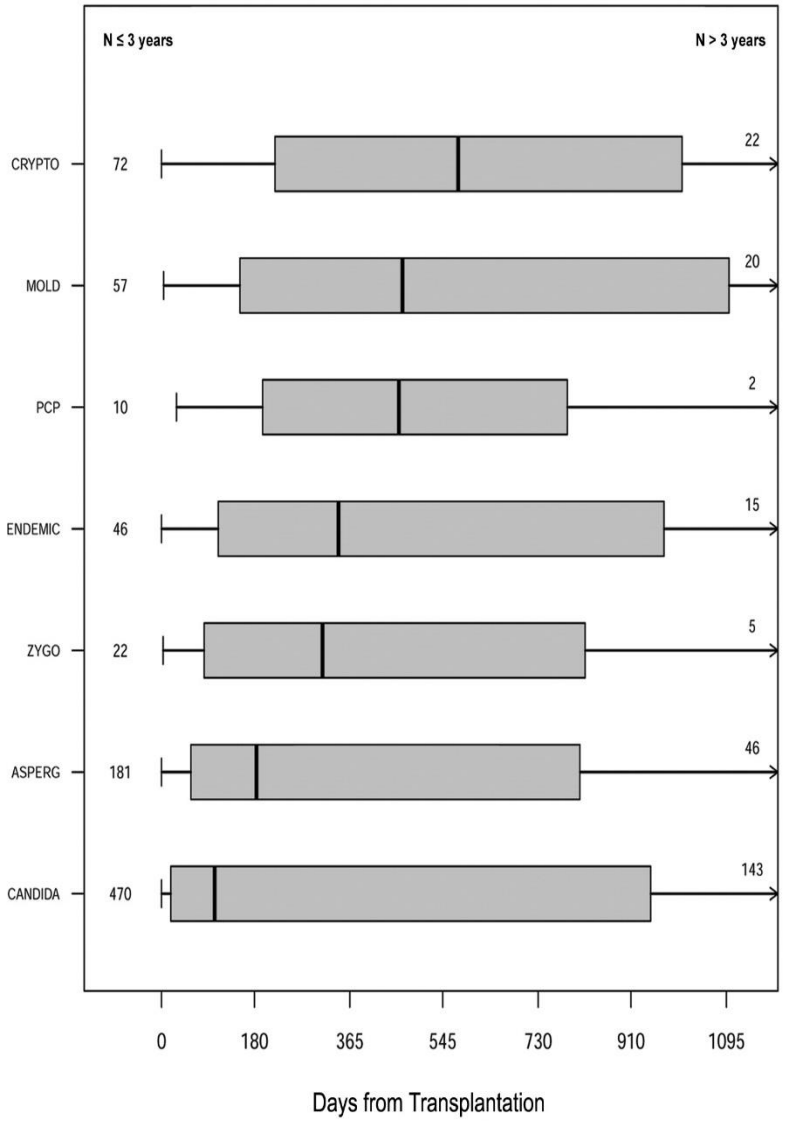
D. Kontoyiannis et al., CID 2010, 50: 1091–1100

P. Pappas et al., CID 2010, 50: 1101-1111

Incidencia – TRANSNET USA 2001-10



TCH



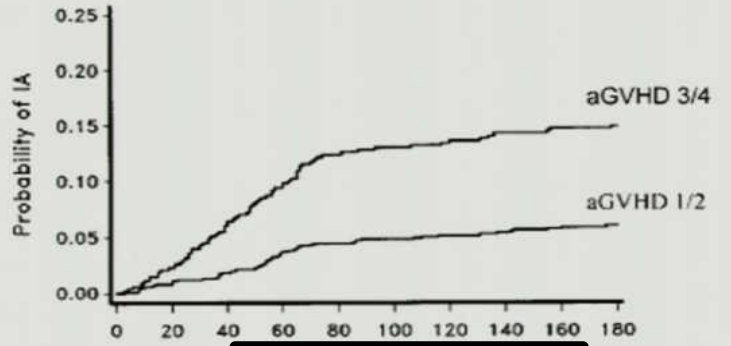
TOS

Incidencia según la enfermedad hematológica

Malignancy	Incidence IFI	Incidence Molds	Incidence Yeasts
AML	12 %	7.9 %	4.4 %
ALL	6.5 %	4.3 %	2.2 %
Allogeneic HSCT	7.8 %	6.7 %	1.1 %
CML	2.5 %	2.3 %	0.2 %
CLL	0.5 %	0.4 %	0.1 %
NHL	1.6 %	0.9 %	0.7 %
HD	0.7 %	0.35 %	0.35 %
MM	0.5 %	0.3 %	0.2 %
Autologous HSCT	1.2 %	0.4 %	0.8 %

≤2%

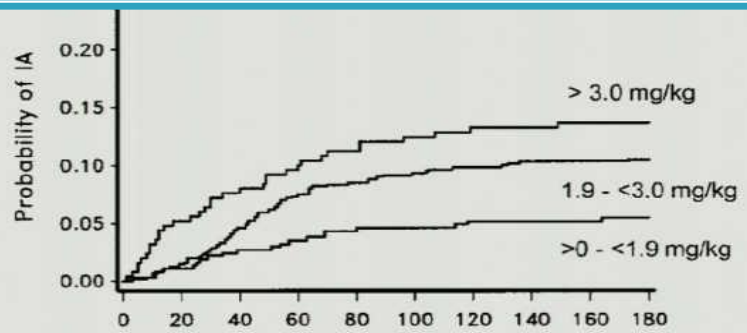
EICH e incidencia de AI



Días post EICH

Marr KA et al. Blood 2002; 100: 4358-66.

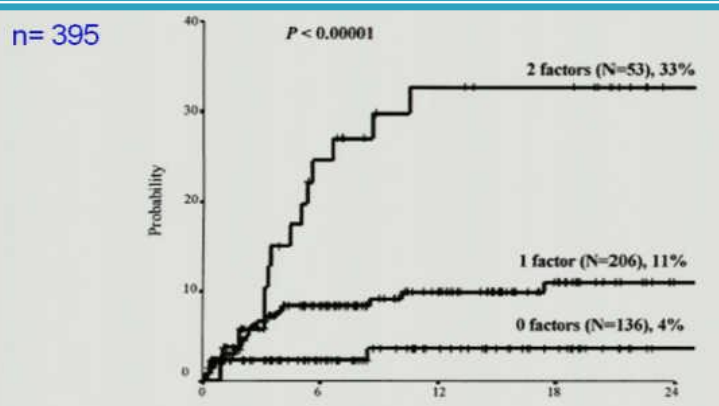
Impacto de la dosis de esteroides y AI



Días post adm. dosis max. esteroides

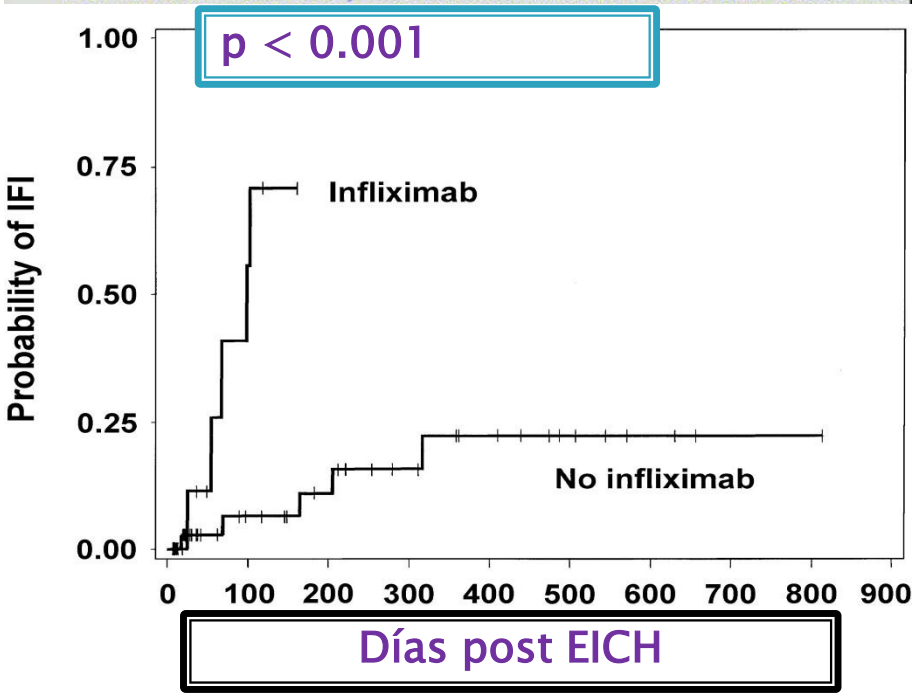
Marr KA et al. Blood 2002; 100: 4358-66. Mikulska M et al. BMT 2009: 1-10.

Factores de riesgo e incidencia IFI en TCH alogénico



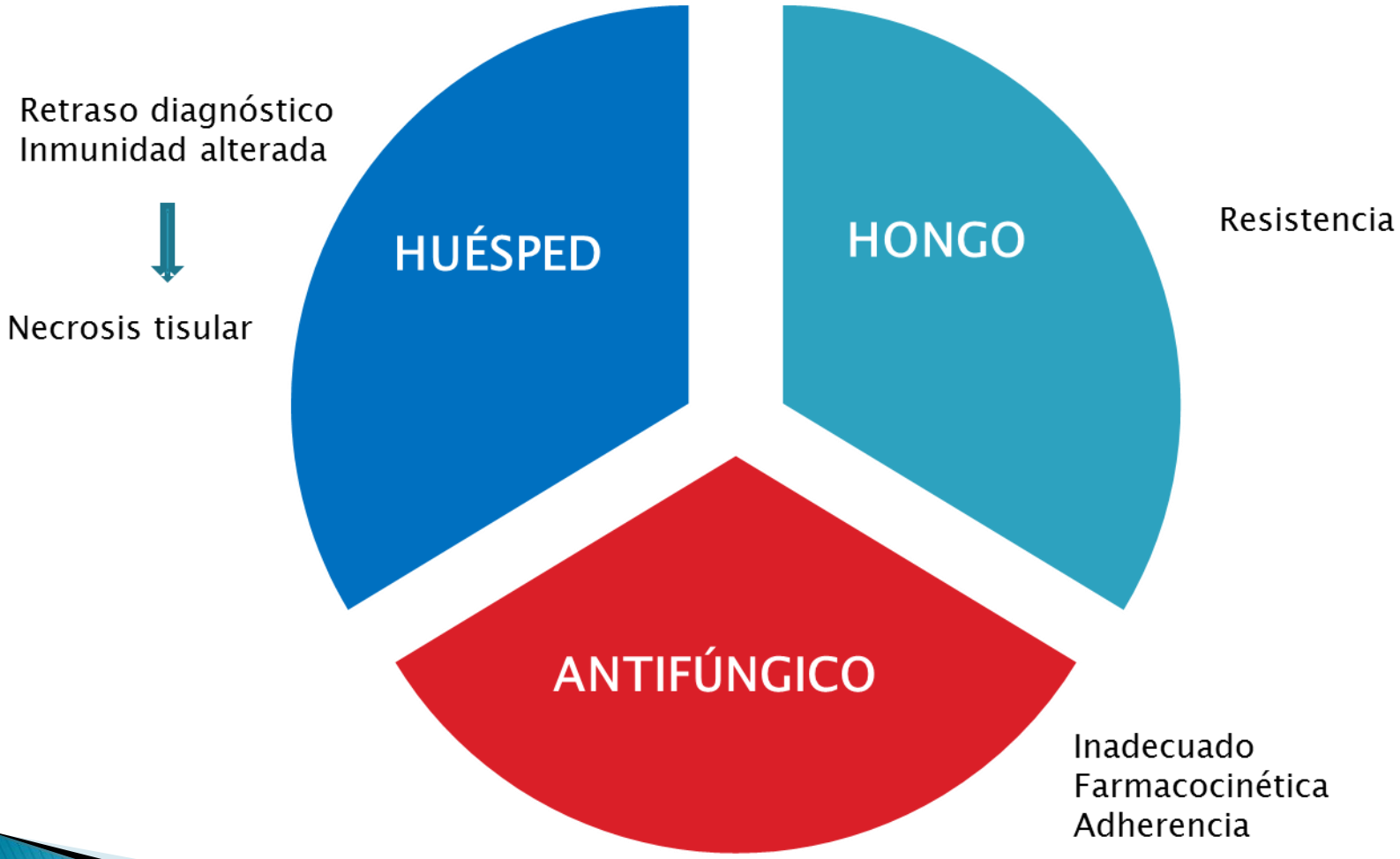
FR: EICH y esteroides

Martino R et al. BJH 2002.



Días post EICH

Porque falla la terapia antifúngica?



Mortalidad en IFIs

Estudio	Población	Mortalidad atribuible (12 semanas)
Upton 2007	405 TCH (94% alo) AI	78% (1990-2001) 55% (2002-04) P<0.01
Pagano 2007	3228 TCH (39% alo)	72% alo 35% auto 72% AI y 50% Candida
Pagano 2010	152 LMA AI	27%
Baddley 2010	642 AI TCH y TOS	49% 58% TCH y 34% TOS P<0.01

Candidiasis

SENTRY: distribución candidemias 2008 – 2010

Species	% of isolates by species and geographic region (n^b)				
	Asia-Pacific (51)	Latin America (348)	Europe (750)	North America (936)	Total (2,085)
C. albicans	56.9	43.6	55.2	43.4	48.41
C. glabrata	13.7	5.2	15.7	23.5	18.0
C. parapsilosis	13.7	25.6	13.7	17.1	17.2
C. tropicalis	11.7	17.0	7.3	10.5	10.5
C. krusei	2.0	1.4	2.5	1.6	1.9
C. lusitaniae	0.0	0.9	1.2	2.2	1.6
C. dubliniensis	0.0	0.3	0.8	1.0	0.8
C. guilliermondii	0.0	1.7	0.1	0.1	0.4
Misc.[a]	2.0	1.6	1.7	0.6	1.2

J Clin Microbiol 2011; 49: 396

Candidemia 2015 HIBA

	Total (138)	R Fluconazol	Total Muertes 45 (33%)
C albicans	63 (46%)	2 (3%)	20 (32%)
C glabrata	40 (29%)	40 (100%)	18 (45%)
C parapsilosis	18 (13%)	0	3 (17%)
C krusei	8 (5.5%)	8 (100%)	4 (50%)
C tropicalis	8 (5.5%)	2 (25%)	0
C kefyr	1 (1%)	1 (100%)	0

75 (54%)

R Fluconazol: 51/75 (68%)

Valledor A. SADI 2015

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Candidiasis

	Overall population	Hematologic patients
Antifungal therapy		
Micafungin[a]	A I	A II
Anidulafungin	A I	A II[b]
Caspofungin	A I	A II
Liposomal amphotericin B	A I	A II
Amphotericin B lipid complex	B II	B II
Amphotericin B colloidal dispersion	B II	B II
Amphotericin B deoxycholate[c]	C I	C II
Fluconazole[d,e]	A I	C III
Voriconazole[d]	A I	B II
Catheter removal[f]	A II	B II

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Candidiasis

Candida species	Overall population		Hematologic patients	
C. albicans	Echinocandins[a]	A I	Echinocandins	A II
	Fluconazole[b]	A I	Fluconazole	C III
	Liposomal amphotericin B	A I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	A II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	A II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. glabrata	Echinocandins[a]	A I	Echinocandins	A II
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. krusei	Echinocandins[a]	A II	Echinocandins[a]	A III
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
Oral stepdown	Voriconazole	B I	Voriconazole	C III
C. parapsilosis	Fluconazole	A II	Fluconazole	A III
	Echinocandins[c]	B II	Echinocandins	B III

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Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David R. Andes,[3] Cornelius J. Clancy,[4] Kieren A. Marr,[5] Luis Ostrosky-Zeichner,[6] Annette C. Reboli,[7] Mindy G. Schuster,[8] Jose A. Vazquez,[9] Thomas J. Walsh,[10] Theoklis E. Zaoutis,[11] and Jack D. Sobel[12]

[1]University of Alabama at Birmingham; [2]Veterans Affairs Ann Arbor Healthcare System and University of Michigan Medical School, Ann Arbor; [3]University of Wisconsin, Madison; [4]University of Pittsburgh, Pennsylvania; [5]Johns Hopkins University School of Medicine, Baltimore, Maryland; [6]University of Texas Health Science Center, Houston; [7]Cooper Medical School of Rowan University, Camden, New Jersey; [8]University of Pennsylvania, Philadelphia; [9]Georgia Regents University, Augusta; [10]Weill Cornell Medical Center and Cornell University, New York, New York; [11]Children's Hospital of Pennsylvania, Philadelphia; and [12]Harper University Hospital and Wayne State University, Detroit, Michigan

Antifúngico	Fuerza Recomendación	Calidad Evidencia
Equinocandinas	Fuerte	Moderada
ANFO – L	Fuerte	Moderada
Fluconazol	Débil	Baja
Voriconazol	Débil	Baja

C Kruzei

Equinocandinas ANFO – L Voriconazol	Fuerte	Baja

CID 2015

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Candidiasis Hepatoesplénica

Antifúngico	Fuerza Recomendación	Calidad Evidencia
ANFO – L Equinocandinas	Fuerte	Baja

CID 2015

Candida auris

- Mortalidad 59%

- Resistencia:

Fluconazol	93%
Voriconazol	54%
Anfotericina	54%
Equinocandinas	7%
> 2 clases	41%

CID 2017; 64: 134
Rev Iberoam Micol 2017; 34: 23
MMWR 2016; 44: 1234

Aspergilosis

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

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Aspergilosis: Primera linea

	Grade	Comments
Voriconazole[a]	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole[a] + anidulafungin	C I	
Other combinations	C III	
Recommendation against use Amphotericin B deoxycholate	A I	Less effective and more toxic

Monitoring of serum levels is indicated. In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have not been graded.

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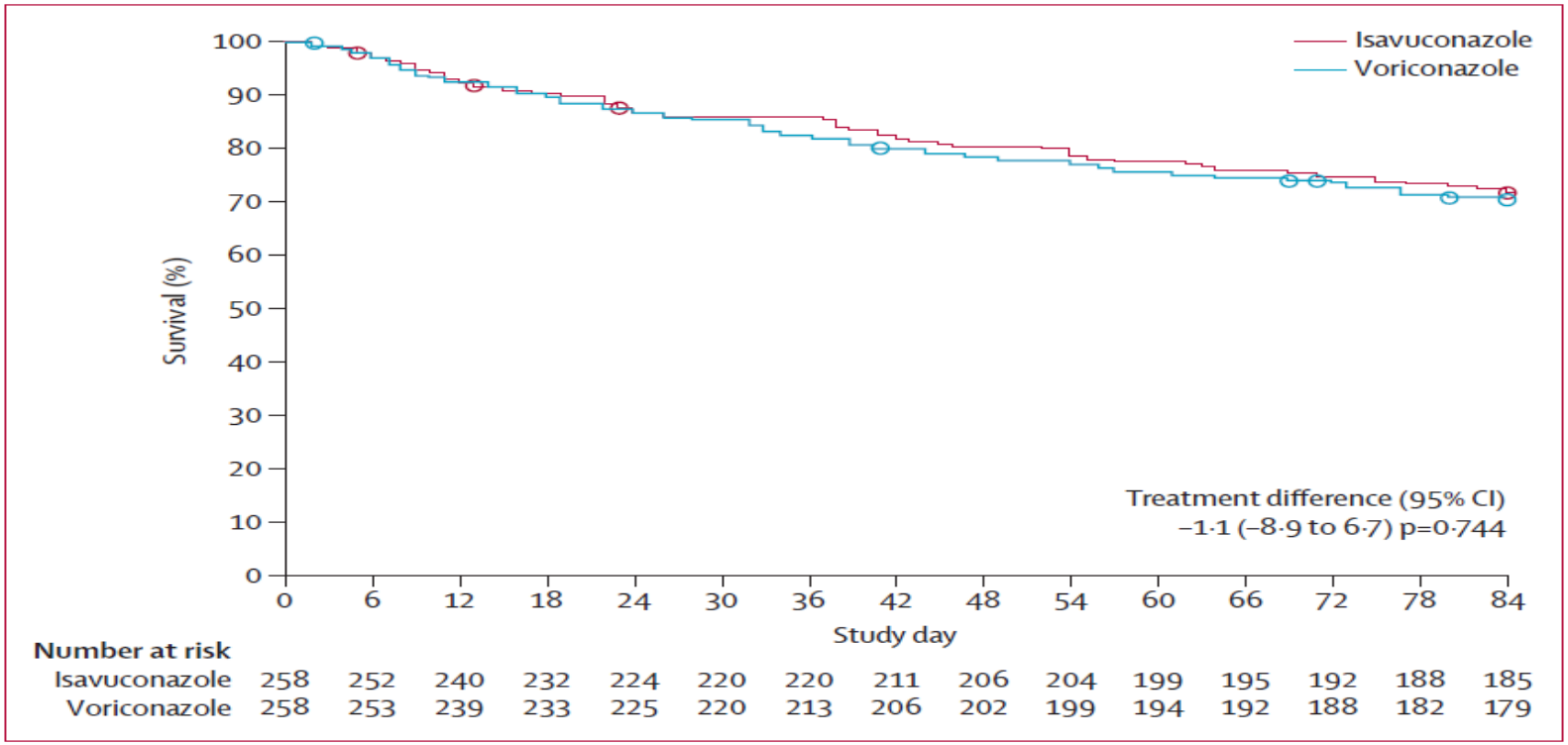
Isavuconazole versus voriconazole for primary treatmen of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial

Johan A Maertens, Issam I Raad, Kieren A Marr, Thomas F Patterson, Dimitrios P Kontoyiannis, Oliver A Cornely, Eric J Bow, Galia Rahav, Dionysios Neofytos, Mickael Aoun, John W Baddley, Michael Giladi, Werner J Heinz, Raoul Herbrecht, William Hope, Meinolf Karthaus, Dong-Gun Lee, Olivier Lortholary, Vicki A Morrison, Ilana Oren, Dominik Selleslag, Shmuel Shoham, George R Thompson III, Misun Lee, Rochelle M Maher, Anne-Hortense Schmitt-Hoffmann, Bernhardt Zeiher, Andrew J Ullmann



Lancet 2016; 387: 760

Annals of Internal Medicine ORIGINAL RESEARCH

Combination Antifungal Therapy for Invasive Aspergillosis

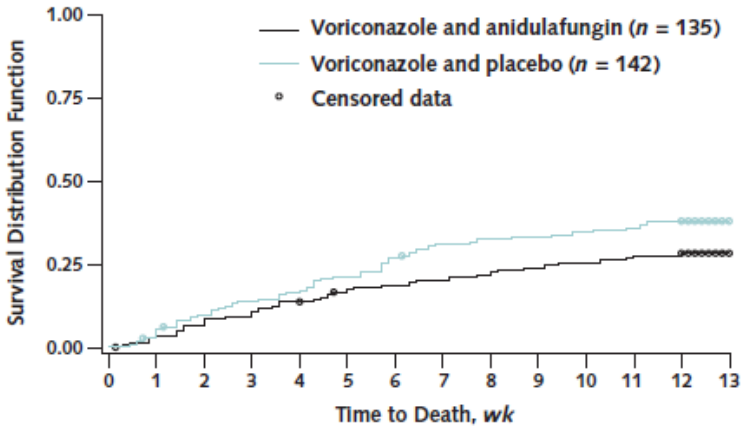
A Randomized Trial

Kieren A. Marr, MD; Haran T. Schlamm, MD; Raoul Herbrecht, MD; Scott T. Rottinghaus, MD; Eric J. Bow, MD, MSc; Oliver A. Cornely, MD; Werner J. Heinz, MD; Shyla Jagannatha, PhD; Liang Piu Koh, MBBS; Dimitrios P. Kontoyiannis, MD; Dong-Gun Lee, MD; Marcio Nucci, MD; Peter G. Pappas, MD; Monica A. Slavin, MD; Flavio Queiroz-Telles, MD, PhD; Dominik Selleslag, MD; Thomas J. Walsh, MD; John R. Wingard, MD; and Johan A. Maertens, MD, PhD

Randomizaron 459 pacientes
Voriconazol vs Voriconazol + Anidulafungina

Mortalidad 12 semanas (n=277)
Combo 19.3% (26/135)
Monoterapia 27.5% (39/142)

Figure 2. Cumulative incidence of death in the modified intention-to-treat population.



Log-rank, $P = 0.086$.

Ann Intern Med. 2015;162:81-89.

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Aspergilosis: Tratamiento de salvatage

	Grade	Comments
Liposomal amphotericin B	B II	No data on voriconazole failure
Amphotericin B lipid complex	B II	No data on voriconazole failure
Caspofungin	B II	No data on voriconazole failure
Itraconazole	C III	Insufficient data
Posaconazole[a]	B II	No data on voriconazole failure
Voriconazole[a]	B II	If not used in first-line
Combination	B II	Various studies and conflicting results

[a]Monitoring of serum levels is indicated, especially if posaconazole oral suspension is used.

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Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Thomas F. Patterson,[1,a] George R. Thompson III,[2] David W. Denning,[3] Jay A. Fishman,[4] Susan Hadley,[5] Raoul Herbrecht,[6] Dimitrios P. Kontoyiannis,[7] Kieren A. Marr,[8] Vicki A. Morrison,[9] M. Hong Nguyen,[10] Brahm H. Segal,[11] William J. Steinbach,[12] David A. Stevens,[13] Thomas J. Walsh,[14] John R. Wingard,[15] Jo-Anne H. Young,[16] and John E. Bennett[17,a]

Aspergilosis

Condition	Primary	Alternative	Comments
Invasive syndromes of *Aspergillus*			
IPA	Voriconazole (6 mg/kg IV every 12 h for 1 d, followed by 4 mg/kg IV every 12 h; oral therapy can be used at 200–300 mg every 12 h or weight based dosing on a mg/kg basis); see text for pediatric dosing	Primary: Liposomal AmB (3–5 mg/kg/day IV), isavuconazole 200 mg every 8 h for 6 doses, then 200 mg daily Salvage: ABLC (5 mg/kg/day IV), caspofungin (70 mg/day IV × 1, then 50 mg/day IV thereafter), micafungin (100–150 mg/day IV), posaconazole (oral suspension: 200 mg TID; tablet: 300 mg BID on day 1, then 300 mg daily, IV: 300 mg BID on day 1, then 300 mg daily, itraconazole suspension (200 mg PO every 12 h)	Primary combination therapy is not routinely recommended; addition of another agent or switch to another drug class for salvage therapy may be considered in individual patients; dosage in pediatric patients for voriconazole and for caspofungin is different than that of adults; limited clinical experience is reported with anidulafungin; dosage of posaconazole in pediatric patients has not been defined
Empiric and preemptive antifungal therapy	For empiric antifungal therapy, Liposomal AmB (3 mg/kg/day IV), caspofungin (70 mg day 1 IV and 50 mg/day IV thereafter), micafungin (100 mg day), voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral therapy can be used at 200–300 mg every 12 h or 3–4 mg/kg q 12 h)		Preemptive therapy is a logical extension of empiric antifungal therapy in defining a high-risk population with evidence of invasive fungal infection (eg, pulmonary infiltrate or positive GM assay result)

CID 2016

Aspergilosis Tratamiento combinado

- No hay evidencia de inicio
- Mayor toxicidad y costos
- Estudios retrospectivos
- Ni SECURE (Anidula+Vori) ni Raad (Vori+Caspo)

Maertens Lancet 2016; 387: 760
Raad Int J Antim Ag 2015; 42: 283

- Falla:
- Posa + Caspo (no tiene comparador)
- Altas dosis de ANFO –L + Caspo
- Azoles o ANFO + EQ

Lellek Mycosis 2011; 54:39
Walsh CID 2008; 46: 327
Kontoyiannis Cancer 2003; 98: 292
Cornley CID 2007; 44: 1289
De Paw CID 2008: 46: 1813
Patterson CID 2016; 63(4): 1
Panackal Int J Inf Dis 2014 28:80

Mucormicosis

Mucor, Rhizopus, Rhizomucor, Apophysomyces

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Mucormicosis: Primera linea

	Grade	Comments
Management includes antifungal therapy, surgery and control of underlying conditions	A II	Multidisciplinary approach is required
Antifungal therapy		
Amphotericin B deoxycholate	C II	
Liposomal amphotericin B	B II	Daily dose: 5 mg/kg. Liposomal amphotericin B should be preferred in CNS infection and/or renal failure
Amphotericin B lipid complex	B II	
Amphotericin B colloidal dispersion	C II	
Posaconazole	C III	No data to support its use as first-line treatment. Alternative when amphotericin B formulations are absolutely contraindicated.
Combination therapy	C III	
Control of underlying condition	A II	Includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive thera
Surgery		
Rhino-orbito-cerebral infection	A II	
Soft tissue infection	A II	
Localized pulmonary lesion	B III	
Disseminated infection	C III	Surgery should be considered on a case by case basis, using a multi-disciplinary approach
Hyperbaric oxygen	C III	
Recommendation against use		
Combination with deferasirox	A II	

CNS: central nervous system.

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Mucormicosis: segunda linea

	Grade	Comments
Salvage therapy		
Management includes antifungal therapy, control of underlying disease and surgery	A II	
Posaconazole	B II	
Combination of lipid amphotericin B and caspofungin	B III	
Combination of lipid amphotericin B and posaconazole	B III	
Maintenance therapy		
Posaconazole	B III	Overlap of a few days with first-line therapy to obtain appropriate serum levels. Monitoring of serum levels might be indicated[a]

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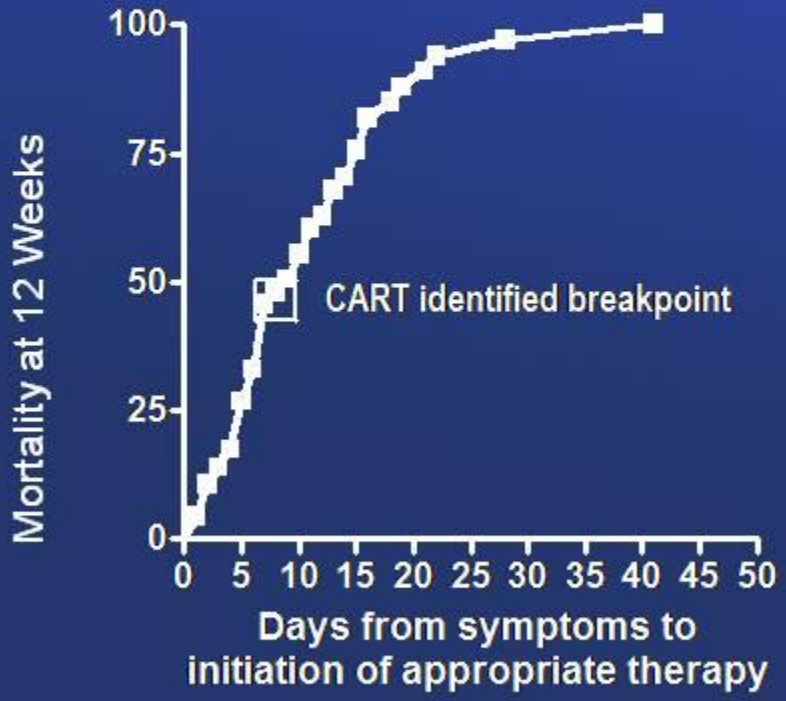
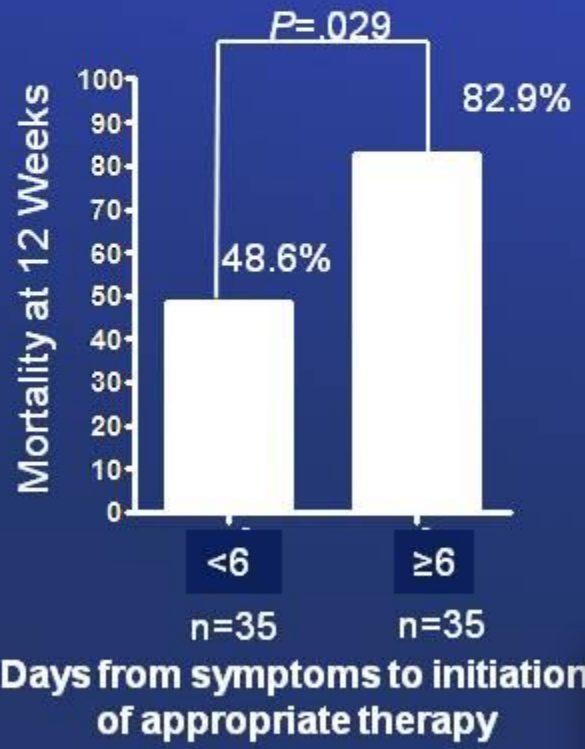
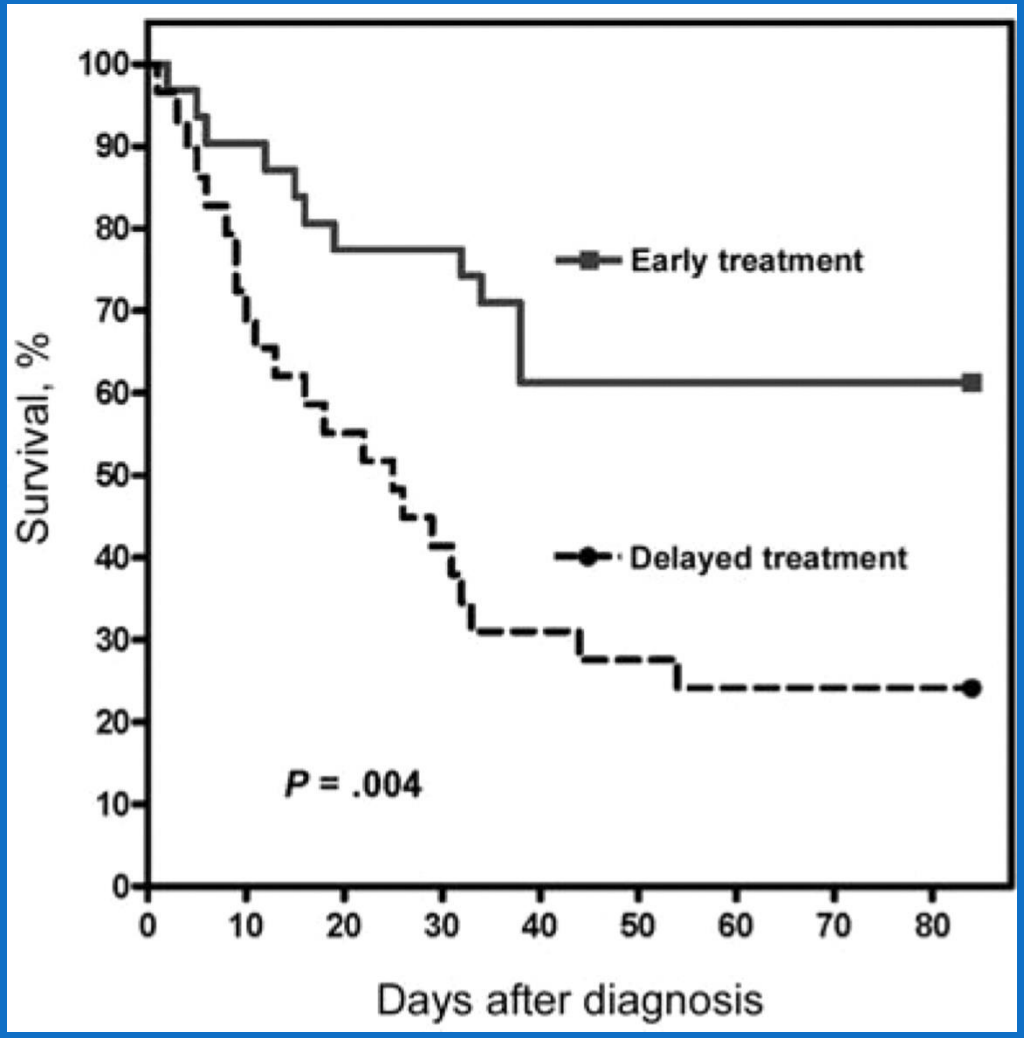
Treatment Delays and Outcome of Invasive Zygomycosis in 70 Patients





Chamilos G et al. *Clin Infect Dis.* 2008;47:503–509.

Kaplan-Meier probability of survival after the diagnosis of zygomycosis, according to the timing of initiation of amphotericin B–based treatment (P=.004, by log-rank test).



Chamilos G et al. Clin Infect Dis. 2008;47:503-509

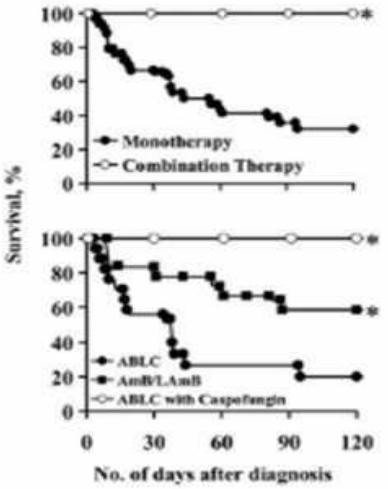
Mucormicosis

- ANFO-L + Caspo

83%DBT
34% OH
10% TOS

Combination of AmB-Caspofungin

- Bicentric retrospective study (41 proven cases, 1994-2006)
  - rhino-orbital (n=21), rhino-orbito-cérébral (n=20)
  - 24 cultures + (19 *Rhizopus sp.*)
- ATF treatments:
  - AmB: n=15
  - ABLC (5 mg/kg/d): n=22; 5 + CAS
  - LAmB (5 mg/kg/d): n=4; 2 + CAS
- Success = survival d30 after hosp:
- Success in 54% of patients:
  - Monotherapy =45%
  - Bitherapy= 100%
  - ABLC=37% vs.AmB/ Lamb= 72%



Reed C, CID 2008

Mucormicosis

- Monoterapia versus combinación (106 p)
- Mortalidad a 6 semanas: no hubo DS (p=0.85)
- Monoterapia 44% ANFO-L
- Combinación: ANFO-L + Posa 27%
  ANFO-L + EQ 46%
  ANFO-L + Posa o EQ 27%

Factores de mal pronóstico:

Admisión en UTI y Linfopenia

Factores de buen pronóstico:

Diagnóstico temprano y reconstitución inmune

Kyvernitakis Clin Microb and Inf 2016

Fusarium

Fusarium

- F. solani complex (50%) oxysporum (20%)
- Resistencia in vitro y relevancia clínica incierta
- Mortalidad elevada 75%
- Tratamiento combinado de inicio:
  - Vori +ANF-L
  - ANF-L + Caspo

Liu Med Mycol 2011; 49: 872
Spader Mycoses 2011; 54:131
Spelberg JAC 2006; 58: 973

Lomentospora (Scedosporium) prolificans

ANF-L + Mica

ANF-L + Vori

Yustes AAC 2002; 46: 3323
Rodriiguez AAC 2009; 53: 2153

Scopulariopsis brevicaulis

VORI + Caspo

Tortorano Clin Microb Inf 2014; 20:27
Baddley J Clin Microb 2000; 38: 395
Peti Lancet Inf Dis 2011; 11: 416

Inmunomodulación

- GCSF*: Recomendación débil – Bajo nivel de evidencia
- Transfusión de granulocitos**: 0.6 x 10^9 gran/kg
  Recomendación débil – Bajo nivel de evidencia
- IFNγ***: Fuerte recomendación – Alto nivel de evidencia

*Lyman J Clin Oncol 2010; 28: 2914. Smith J Clin Oncol 2006; 24: 3187. Crawford J Nat Comp Canc Netw 2013; 11: 1266 Kuderer J Clin Oncol 2007; 25: 3158

** Bensinger Blood 1993; 81: 1883. Hubel Transfusion 2002; 42:1414. Price Blood 2000; 95: 3302. Price Blood 2015; 126:2153

*** Hebart Bllod 2002; 100: 4521. NEJM 1991; 324:509

Conclusiones I

Candidiasis:

- No evidencia tratamiento combinado
- Inciar Equinocandinas o ANFO-L (AI)
- Deescalar

Conclusiones II

Aspergilosis:

- No evidencia de tratamiento combinado
- Iniciar: Voriconazol o Isavuconazol (AI)
  Anfotericina-L (BI)
- Falla: no evidencia de combo
- Recomendación (sin poder estadístico):

ANFO-L + Caspo / Azol + ANFO-l ó Equinocandinas

Conclusiones III

Mucormicosis:

- Inicio precoz – Cirugía
- No evdencia de tratamiento combinado
- ANFO – L (AI) altas dosis
- EVITAR Anfo desoxicolato y Deferasirox (AI)
- Falla: no evidencia de combo
- Recomendación (sin poder estadístico):
- ANF-L + Caspo ó Posa

Conclusiones IV

Hongos de alta resistencia

- Fusarium:
  Vori + ANF-L

- Lomentospora (Scedosporium) prolificans:
  ANFO-L + Mica ó Vori

- Scopulariopsis spp:
  Vori + Caspo

Muchas Gracias!

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