Profilaxis antifúngica en el paciente pediátrico sometido a un trasplante de órgano sólido

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HUVH, BCN 26-03-2014

UPIIP: funcionamiento básico

Asistencia

Docencia (máster propio)

Investigación (grupo VHIR)

UAB
Universitat Autònoma de Barcelona

Vall d'Hebron
Institut de Recerca
VHIR

UPIIP: funcionamiento básico

Hospitalización: pacientes con IDP/VIH; infección comunitaria.

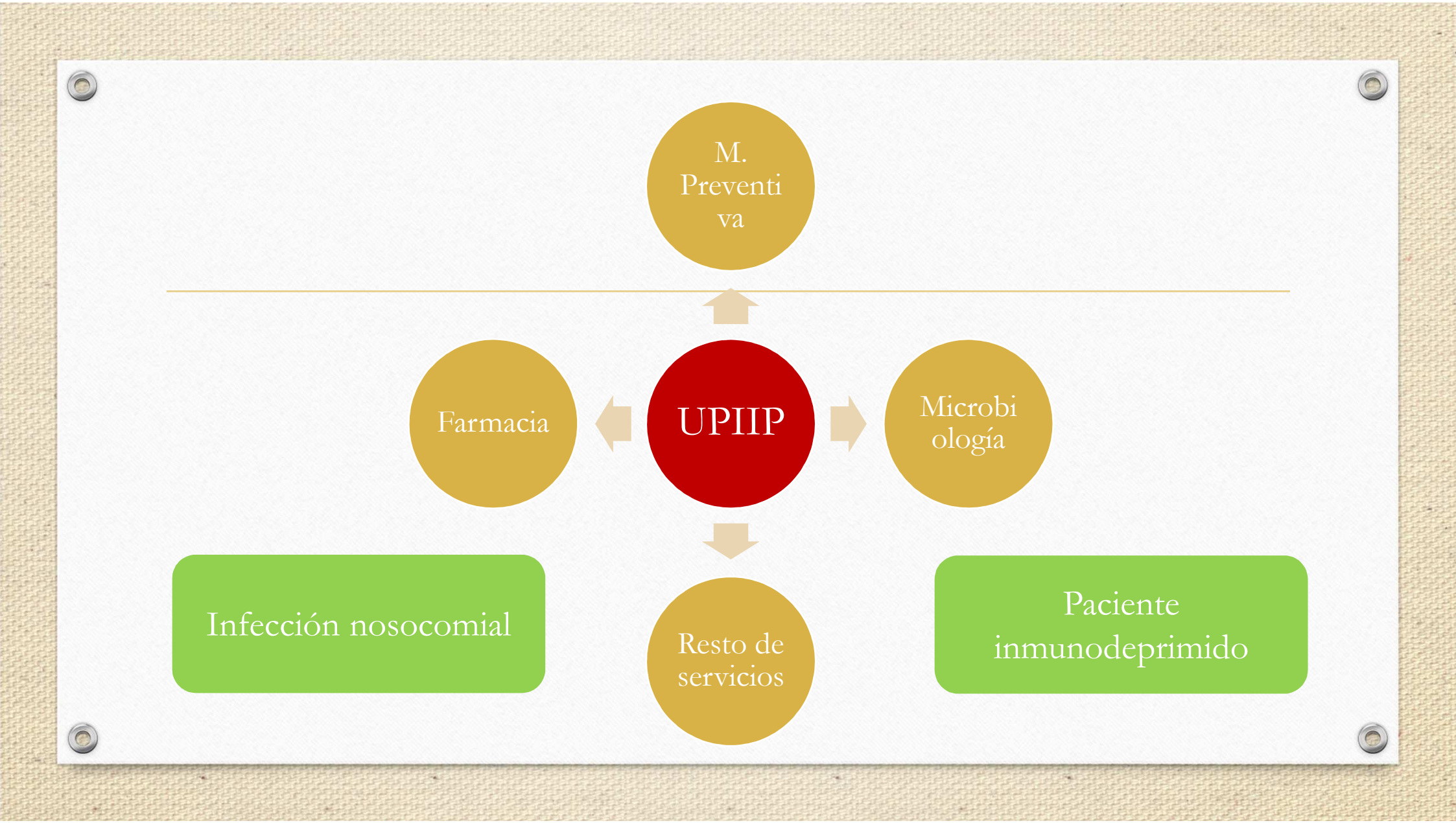
Consulta externa y Hospital de Día: pacientes con IDP/VIH; infección comunitaria; patología importada; transmisión vertical.

Consultoría – Infección nosocomial

Activa: H-O + TPH, UCIP, UCIN, **Tx. renal y cardíaco**.

A demanda: pediatría general, cirugía pediátrica, **Tx. pulmonar**.

No: Tx. hepático.


M. Preventiva
Farmacia
UPIIP
Microbiología
Infección nosocomial
Resto de servicios
Paciente inmunodeprimido

upiip

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Hospital Universitari Vall d'Hebron. Barcelona.

Infección fúngica en el TOS

Incidencia, características y factores de riesgo

Invited Review

Infections in Pediatric Solid Organ Transplant Recipients

Michael Green and Marian G. Michaels

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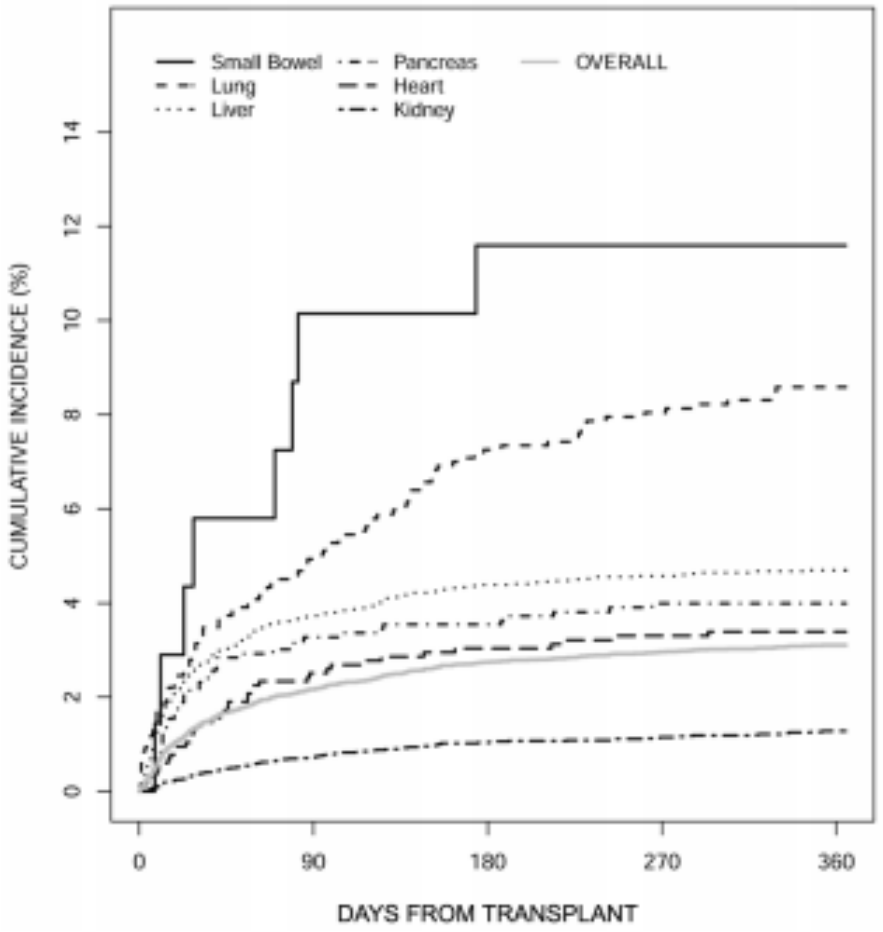
Infectious complications are an important cause of morbidity and mortality in children undergoing solid organ transplantation. Knowledge gained over the last 30 years provides a growing understanding of these infections. This review identifies risk factors for and timing of infections describes the common infectious syndromes and pathogens seen in children undergoing solid organ transplantation, and reviews preventive strategies.

Generalidades

- Menos frecuentes que las infecciones virales y bacterianas.
- Incidencia de infección fúngica dependiente del tipo de trasplante.
- Pulmón-corazón > higado > riñón.
- Predominio de *Candida* spp. Infección órgano trasplantado.
- *Aspergillus* spp y otros hongos filamentosos infrecuentes pero graves.
  - Excepciones: trasplante pulmonar > trasplante hepático.



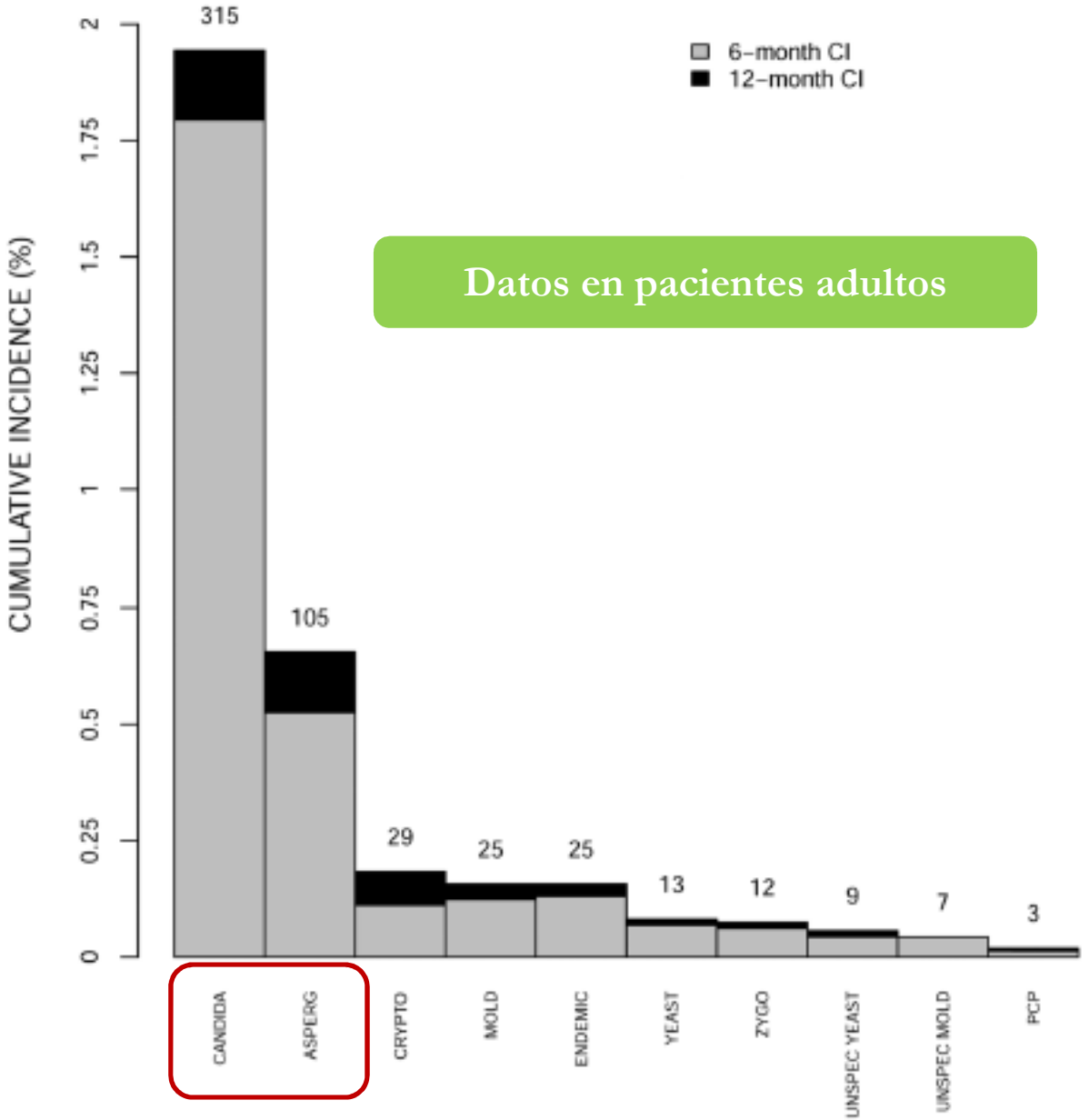
Invasive Fungal Infections among Organ Transplant Recipients: Results of the Transplant-Associated Infection Surveillance Network (TRANSNET)

Peter G. Pappas, Barbara D. Alexander, David R. Andes, Susan Hadley, Carol A. Kauffman, Alison Freifeld, Elias J. Anaissie, Lisa M. Brumble, Loreen Herwaldt, James Ito, Dimitrios P. Kontoyiannis, G. Marshall Lyon, Kieren A. Marr, Vicki A. Morrison, Benjamin J. Park, Thomas F. Patterson, Trish M. Perl, Robert A. Oster, Mindy G. Schuster, Randall Walker, Thomas J. Walsh, Kathleen A. Wannemuehler, and Tom M. Chiller[a]

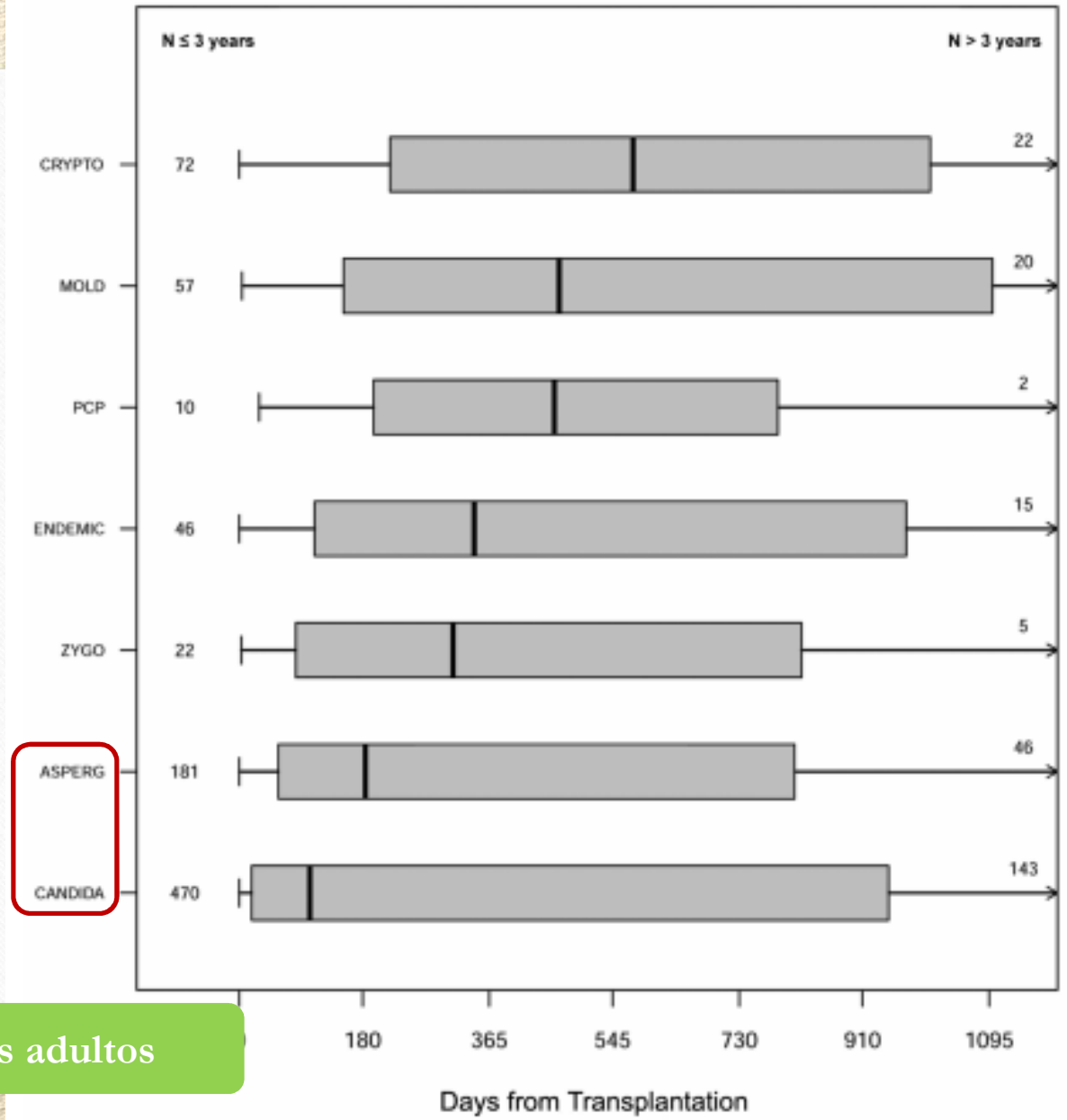
N= 16.808

(4% pediátricos)

Datos en pacientes adultos



Datos en pacientes adultos



Datos en pacientes adultos

Table 1
Incidence of invasive fungal infection (IFI), predominant fungal pathogens in solid organ transplant (SOT) recipients and risk factors for a high probability of invasive aspergillosis (IA)

Type of transplant	Incidence of IFI (%)	Usual aetiological agent (s)	Variables predicting higher risk of IA	Mortality of IA (%)
Renal	0–20	76–95% *Candida* (mainly UTIs), 0–25% *Aspergillus*	Graft failure requiring haemodialysis, high level and prolonged duration of corticosteroids	77
Heart	5–20	70–90% *Aspergillus*, 8–25% *Candida*	Isolation of *Aspergillus* spp. in respiratory tract cultures, re-operation, post-transplant haemodialysis, CMV disease	78
Liver	5–40	35–90% *Candida*, 9–45% *Aspergillus*	Re-transplantation, renal failure (particularly requiring renal replacement therapy), fulminant hepatic failure as an indication for transplantation, primary allograft failure, high transfusion requirements, use of monoclonal antibodies	87
Lung/heart–lung	10–45	43–72% *Candida*, 25–50% *Aspergillus*	Single lung transplant, CMV infection, rejection and augmented immunosuppression, bronchitis obliterans, *Aspergillus* colonisation, acquired hypogammaglobulinaemia, presence of bronchial stents, reperfusion injury, airway ischaemia	68
Pancreas (+ kidney)	10–40	>90% *Candida*, 0–3% *Aspergillus*	Similar factors to liver and kidney transplant, graft loss (vascular graft thrombosis, post-reperfusion pancreatitis), enteric drainage, alemtuzumab-containing immunosuppressive regimen	100
Small bowel	30–60	80–100% *Candida*, 0–5% *Aspergillus*	Not clearly determined, similar factors to others intra-abdominal SOT recipients: graft rejection/dysfunction, enhanced immunosuppression, anastomotic disruption, multivisceral transplant	66

UIT, urinary tract infection; CMV, cytomegalovirus.

Datos en pacientes adultos

Table 2. Risk Factors for IFIs in SOT Recipients

	Specific Risk Factors for IFIs in SOT		
	Candida	*Aspergillus*	Other Mold
Liver	Prolonged or repeat operation Retransplantation *Candida* colonization Choledocojejunostomy High transfusion requirement	Retransplantation Renal failure and renal replacement therapy Pretransplantation acute liver failure Reoperation Use of monoclonal antibodies	*Zygomycosis* Renal failure Rejection and augmented immunosuppression Corticosteroid usage Exposure to antifungals not active against zygomycetes (ie, voriconazole) Poorly controlled diabetes mellitus Prolonged neutropenia Iron chelation with deferoxamine *Fusariosis* Prolonged neutropenia Impaired macrophage function
Lung	Broad spectrum antibiotics and duration of antibiotic use Central venous catheters Renal replacement therapy	Pretransplantation or posttransplantation *Aspergillus* colonization Early airway ischemia Anastomotic dehiscence Single lung transplant CMV infection Rejection and augmented immunosuppression Acquired hypogammaglobulinemia (IgG <400 mg/dL)	
Heart	Broad spectrum antibiotics and duration of antibiotic use Central venous catheters Renal replacement therapy	Isolation of *Aspergillus* in respiratory tract cultures Reoperation CMV infection Posttransplantation hemodialysis Existence of an episode of IA in the program 2 months before or after heart transplantation	
Pancreas	Enteric drainage Vascular thrombosis Postperfusion pancreatitis		
Small bowel	Graft rejection/dysfunction Anastomotic disruption Abdominal reoperation Multivisceral transplantation		

Abbreviations: CMV, cytomegalovirus; Ig, immunoglobulin.

Datos en pacientes adultos

J Heart Lung Transplant. 2008 June ; 27(6): 655–661.

INCREASED MORTALITY AFTER PULMONARY FUNGAL INFECTION WITHIN THE FIRST YEAR AFTER PEDIATRIC LUNG TRANSPLANTATION

LA Danziger-Isakov[1], S Worley[2], S Arrigain[2], P Aurora[3], M Ballmann[4], D Boyer[5], C Conrad[6], I Eichler[7], O Elidemir[8], S Goldfarb[9], GB Mallory[8], MG Michaels[10], P Michelson[10], PJ Mogayzel[11], D Parakininkas[12], M Solomon[13], G Visner[5], S Sweet[14], and A Faro[14]

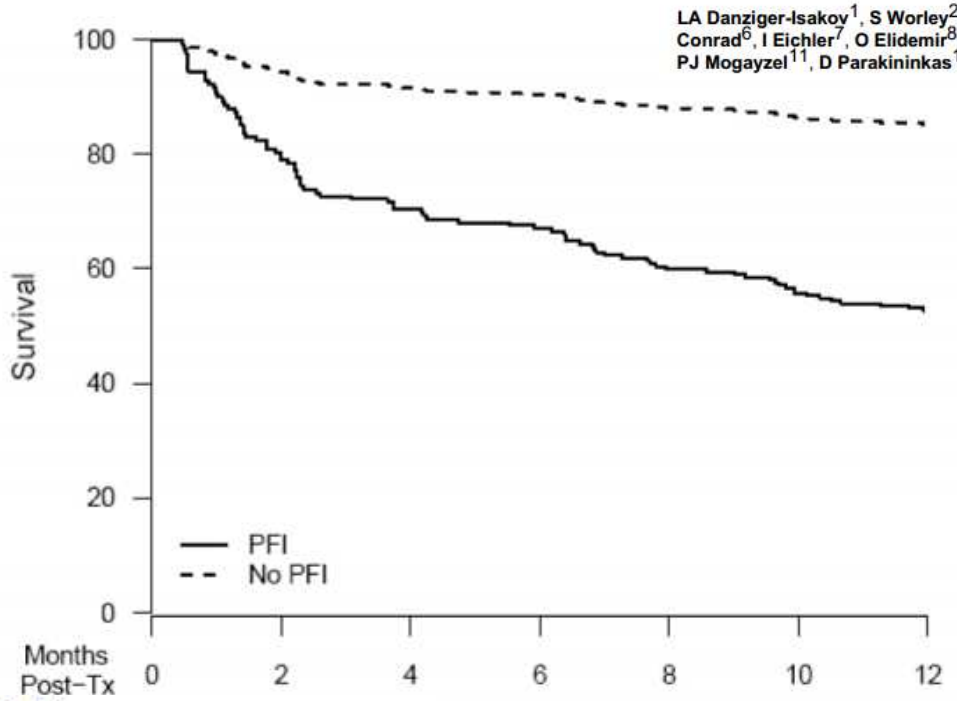


TABLE 1

Identified organisms from *Proven and Probable Pulmonary Fungal Infections*

SITE	All organisms	Candida species	Aspergillus species	Other
Pulmonary (Total)	*62*	*10*	*39*	*13*
Proven	*20*	*8*	*11*	*1*
Probable	*42*	*2*[•]	*28*	*12*

[•] Candida species recovered in same culture as Aspergillus probable episode.

ant recipients with and without PFI

SPECIAL FOCUS | Invasive pediatric fungal infections

Review

www.expert-reviews.com/toc/eri/9/3

EXPERT REVIEWS

Invasive *Candida* infections in solid organ transplant recipient children

Expert Rev. Anti Infect. Ther. 9(3), 317–324 (2011)

Key issues

- Invasive fungal infections cause significant morbidity and mortality in solid organ transplant recipient children.
- Among fungal infections, *Candida* species are the most common pathogens isolated with high mortality rates. *Candida albicans* remains the most common species in transplant recipients, but there is a shift towards non-albicans *Candida* species.
- The epidemiology and clinical manifestations of invasive candidiasis in solid organ recipients varies with the type of organ transplant and liver transplant recipients have the highest rate of *Candida* infections.
- Guidelines for adults are usually used in the treatment and prophylaxis of invasive candidiasis in children.
- Large multicenter, randomized controlled studies evaluating risk factors, diagnosis, prophylaxis and treatment strategies for *Candida* infections in organ transplant recipient children are needed.

Vall d'Hebron Hospitals

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Hospital Universitari Vall d'Hebron. Barcelona.

¿Pre-emptive therapy?

Papel del galactomanano

Otros marcadores

Pre-emptive therapy

- Muchos menos datos que para profilaxis.
- Pacientes habitualmente no neutropénicos.
- Datos aislados en trasplante hepático con galactomanan y β-D-glucano.
- Papel del galactomanano en BAL en Tx. Pulmonar.
- ¿Possible utilidad en pacientes de alto riesgo a pesar de profilaxis?

Preemptive Treatment of Fungal Infection Based on Plasma (1 → 3)β-D-Glucan Levels after Liver Transplantation

N. Akamatsu, Y. Sugawara, J. Kaneko, S. Tamura, M. Makuuchi

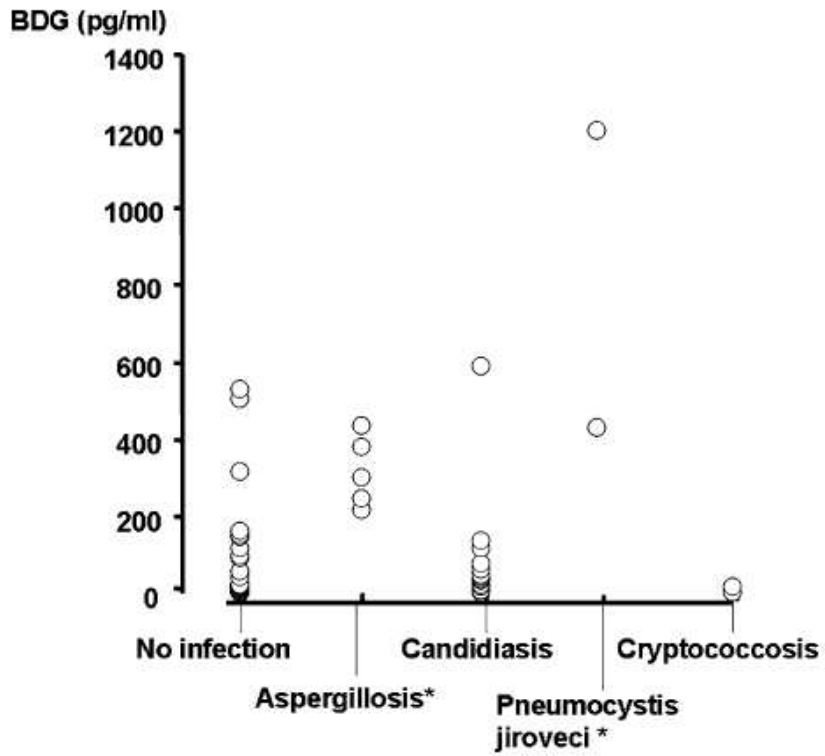


Figure 3. The distribution of maximum (1 → 3) β-D-glucan (BDG) level before treatment stratified by the fungal species. *<0.05 to those without infection.

Sensibilidad: 58%
Especificidad: 83%
VPP: 35%
VPN: 93%
PLR: 3,41
NLR: 1,978

Datos en pacientes adultos

TABLE 2. Characteristics of the aspergillus antigen sandwich-EIA test in this study

		95% CI
Sensitivity	55.6%	22.7–84.7
Specificity	93.9%	78.4–98.9
Positive predictive value	71.4%	30.3–94.9
Negative predictive value	88.6%	72.3–96.3
LR+	9.17	2.12–39.66
LR−	0.47	0.22–1.01

The results of the *Aspergillus* antigen detection using a sandwich-ELISA in serum in the group of case and control patients are shown in this figure. Confidence intervals for LR were calculated using Taylor's method.

Abbreviations used in table: LR+, likelihood ratio for a positive test; LR−, likelihood ratio for negative test.

Table 2 . Characteristics of the aspergillus antigen sandwich-EIA test in this studyThe results of the Aspergillus antigen detection using a sandwich-ELISA in serum in the group of case and control patients are shown in this figure. Confidence intervals for LR were calculated using Taylor's method.Abbreviations used in table: LR+, likelihood ratio for a positive test; LR-, likelihood ratio for negative test.

ASPERGILLUS ANTIGENEMIA SANDWICH-ENZYME IMMUNOASSAY TEST AS A SERODIAGNOSTIC METHOD FOR INVASIVE ASPERGILLOSIS IN LIVER TRANSPLANT RECIPIENTS1.

Fortun, J; Martin-Davila, P; Alvarez, M; Sanchez-Sousa, A; Quereda, C; Navas, E; Barcena, R; Vicente, E; Candelas, A; Honrubia, A; Nuno, J; Pintado, V; Moreno, S

Transplantation. 71(1):145-149, January 15, 2001.

Datos en pacientes adultos

TABLE 3. False-positive galactomannan results in the bronchoalveolar lavage fluid in 31 lung transplant recipients

Patient	GM index	Disease status	Colonizing species			Pipe-tazo	Dialysis
			Aspergillus	*Penicillium*	*Candida*		
1	0.5	Surveillance	—	—	Yes	—	—
2	0.5	Surveillance	—	—	Yes	—	—
3	0.5	Possible IA	—	—	Yes	—	—
4	0.5	Surveillance	—	—	Yes	—	—
5	0.5	Possible IA	—	—	Yes	—	—
6	0.5	Surveillance	—	—	Yes	—	—
7	0.5	Surveillance	—	—	—	—	—
8	0.5	*Aspergillus* colonization	*A. flavus*	—	Yes		
9	0.6	*Aspergillus* colonization	*A. fumigatus*	—	Yes	—	—
10	0.6	Surveillance	—	—	Yes	—	—
11	0.6	*Aspergillus* colonization	*A. fumigatus* and *A. niger*	—	—	—	—
12	0.7	*Aspergillus* colonization	*A. fumigatus*	—	Yes	—	—
13	0.7	Possible IA	—	—	Yes	—	Yes
14	0.7	Surveillance	—	—	—	Yes	—
15	0.7	Surveillance	—	—	Yes	—	
16	0.7	*Aspergillus* colonization	*A. fumigatus*	Yes	Yes	—	
17	0.8	*Aspergillus* colonization	*A. niger*	Yes	Yes	—	
18	0.8	Possible IA	—	—	Yes	—	
19	0.8	Possible IA	—	—	Yes	—	
20	0.9	Surveillance	—	—	Yes	—	
21	0.9	*Aspergillus* colonization	*A. fumigatus*	—	Yes	—	
22	1.0	Possible IA	—	—	—	—	
23	1.2	*Aspergillus* colonization	*A. fumigatus*	—	Yes	—	
24	1.3	Surveillance	—	—	—	—	
25	1.3	Surveillance	—	—	Yes	—	
26	1.4	*Aspergillus* colonization	*A. fumigatus*	—	—	—	
27	1.9	*Aspergillus* colonization	*A. niger*	Yes	—	—	
28	1.9	*Aspergillus* colonization	*A. niger*	—	Yes	—	
29	2.0	Surveillance	—	—	Yes	—	
30	2.2	Possible IA	—	—	Yes	Yes	—
31	7.3	*Aspergillus* colonization	*A. fumigatus*	—	—	—	—

Diagnosis of Invasive Aspergillosis in Lung Transplant Recipients by Detection of Galactomannan in the Bronchoalveolar Lavage Fluid

Alessandro C. Pasqualotto,[1,2,3,6] Melissa O. Xavier,[1] Letícia B. Sánchez,[4] Clarice D. A. de Oliveira Costa,[4] Sadi M. Schio,[4] Spencer M. Camargo,[4] Jose J. Camargo,[4] Teresa C. T. Sukiennik,[2] and Luiz Carlos Severo[1,3,5]

TABLE 4. Performance of Platelia *Aspergillus* EIA in BAL samples of lung transplant recipients using distinct cutoff values

Cutoff value	Sensitivity (%)	Specificity (%)	LR (+)	LR (−)	PPV[a] (%)	NPV[a] (%)
0.5	100	40.4	1.68	—	20.5	100
0.7	100	61.5	2.60	—	28.6	100
1.0	100	80.8	5.20	—	44.4	100
1.4	100	88.5	8.67	—	57.1	100
1.5	100	90.4	10.40	—	61.5	100
2.0	87.5	94.2	15.17	0.13	70.0	98.0
2.2	75.0	96.2	19.50	0.26	75.0	96.2

[a] Based on a pretest probability of 13.3% (prevalence of invasive aspergillosis observed in this study).
BAL, bronchoalveolar lavage fluid; EIA, enzyme-linked immunoassay; LR, likelihood ratio; +, positive; −, negative; PPV, positive predictive value; NPV, negative predictive value.

Datos en pacientes adultos

Profilaxis antifúngica

Profilaxis antifúngica

- Ha demostrado disminuir la mortalidad asociada a IFI pero no mortalidad global.
- La mejor profilaxis es el control de los factores de riesgo asociados.
- No indicación universal.
  - Indicada de forma rutinaria en trasplante pulmonar.
  - Indicada en casos seleccionados de trasplante hepático y cardíaco.
  - No indicada en trasplante renal.
- No existen guías para el paciente pediátrico. Se adaptan de las recomendaciones (débiles) en el paciente adulto.

Profilaxis antifúngica

- En todos los casos, profilaxis frente a *P. jirovecii*.
- La cobertura dependerá de los hongos implicados con más frecuencia.
- Atención:
  - Interacciones con IS (azoles).
  - Efectos secundarios de los antifúngicos.
  - Disfunción hepática y renal en algunos casos.
  - Datos disponibles en pediatría.

Profilaxis de neumonía por *Pneumocystis jiroveci* en niños y adultos sometidos a trasplante de órganos sólidos y de precursores hematopoyéticos

M. Pilar Gambra y Teresa Bidart

2011

Recomendación Nº 2: Profilaxis para neumonía por *P. jiroveci* en trasplante de órganos sólidos y precursores hematopoyéticos

- Se debe administrar a todos los receptores de TOS y TPH (A1)
- Terapia de elección: cotrimoxazol (A1)
  - Adultos: 80/400 mg/día de trimetoprim/sulfametoxazol, 3 veces/semana en días alternos (A1)
  - Niños: 5/20 mg/kg/día de trimetoprim/sufametoxazol dividido en 2 dosis, tres días consecutivos cada semana (A2)
- Inicio de profilaxis: En TOS día 7-14 post-trasplante, en TPH, luego del implante (C3)
- Duración de la profilaxis: En TOS 6 meses, excepto en trasplante de pulmón e hígado, que se recomienda un año. En TPH, 6 meses post-implante, prolongar en pacientes que persistan con terapia inmunosupresora, EICH crónica, rechazo y LTCD4 < 200/mm³ (B2)
- Alternativa: En caso de reacción adversa grave a cotrimoxazol, se recomienda dapsona por sobre pentamidina aerosolizada (B2). Atavacuona ha mostrado buena tolerancia en pacientes con TPH autólogo (C2)

6/9

1/5

0/2

0/1

Table 1. Key antifungal prophylaxis trials in solid organ transplant recipients.

Study (year)	Design	Population	Prophylaxis	IFI risk (%)	Comments	Ref.
Liver						
Tollemar *et al.* (1995)	Prospective, randomized	LTRs	LAmB vs placebo	0 vs 16	No difference observed in 30-day survival	[19]
Winston *et al.* (1999)	Prospective, randomized	LTRs	Fluc vs placebo	6 vs 23	Deaths attributed to IFIs reduced by Fluc (from 13 to 2%)	[21]
Biancofiore *et al.* (2002)	Prospective, randomized	LTRs	Sequential LAmB and Itra vs Fluc and Itra vs placebo	24 vs 23 vs 29	No observed difference in low-risk patient population	[23]
Sharpe *et al.* (2003)	Prospective, randomized	LTRs	Itra vs placebo	4 vs 24	Rates included superficial infections, no proven IFIs	[24]
Winston and Busuttil (2002)	Prospective, randomized	LTRs	Itra vs Fluc	7 vs 3	More adverse events in Itra recipients	[25]
Singh *et al.* (2001)	Prospective, interventional	LTRs with RRT post-transplant	LAmB	0 vs 36 (HC)	Unique high-risk population benefited	[26]
Pappas *et al.* (2006)	Prospective, observational	Low-risk LTRs	None	3.6	Low incidence of IFIs in low-risk population	[27]
Hadley *et al.* (2009)	Prospective, randomized	High-risk LTRs	LAmB vs Fluc	17	Low enrollment precluded comparison LAmB to Fluc	[28]
Castroagudin *et al.* (2005)	Prospective, interventional	High-risk LTRs	LAmB	9.5	Some criteria used to define high risk not validated	[29]
Fortún *et al.* (2009)	Prospective, interventional	High-risk LTRs	Caspofungin	2.8	Only published evaluation of an echinocandin	[32]
Lung						
Minari *et al.* (2002)	Retrospective	LuTRs	Sequential AmB and Itra vs no prophylaxis	4.9 vs 18.2	Early trial demonstrating benefit of universal antifungal prophylaxis in LuTRs	[35]
Borro *et al.* (2008)	Retrospective	LuTRs	Aerosolized LAmB	1.7	Lipid formulation well tolerated; no comparator group	[45]
Husain *et al.* (2006)	Retrospective	LuTRs	Vori vs Fluc or Itra and AmB	1.5 vs 23	Incidence of non-*Aspergillus* fungal infection and hepatotoxicity higher in Vori group	[46]
Monforte *et al.* (2001)	Retrospective	LuTRs	AmB vs no prophylaxis	22.7 vs 72.7	AmB efficacious (OR: 0.13; $p < 0.05$); well tolerated	[48]
Drew *et al.* (2004)	Prospective, randomized	LuTRs	Aerosolized LAmB vs AmB	14.3 vs 11.8	28 (LAmB) vs 42% (AmB) experienced adverse events	[49]
Heart						
Reichenspurner *et al.* (1997)	Retrospective	HTRs, LuTRs, HLTRs	AmB vs no prophylaxis	8 vs 20	Variable patient population and duration of prophylaxis	[50]
Muñoz *et al.* (2004)	Retrospective	HTRs	Itra	3 vs 11 (HC)	IFIs included *Aspergillus*, *Scedosporium*	[51]
Kidney						
Albano *et al.* (2009)	Retrospective	KTRs	None	0.10	GI tract perforat… harvesting impli…	

AmB: Amphotericin B; Fluc: Fluconazole; HC: Historical control; HLTR: Heart–lung transplant recipient; HTR: Heart transplan… Itra: Itraconazole; KTR: Kidney transplant recipient; LAmB: Liposomal amphotericin B; LTR: Liver transplant recipient; LuTR: L… transplant recipient; RRT: Renal replacement therapy; SBTR: Small bowel transplant recipient; Vori: Voriconazole.

Datos en pacientes adultos

Table 2. Recommendations for antifungal prophylaxis in solid organ transplantation.

Organ	Predominant pathogen(s)	Antifungal agent(s)	Duration
Liver	*Candida* and *Aspergillus*	Lipid preparation of AmB or Fluc for high-risk patients	1–4 weeks
Lung	*Aspergillus*	Itra or Vori; lipid AmB with or without aerosolized AmB	1–6 months
Heart	*Candida* and *Aspergillus*	None indicated	N/A
Kidney	*Candida*	None indicated	N/A
Pancreas	*Candida*	Fluc for high-risk patients	1–4 weeks
Small bowel	*Candida*	Fluc or lipid preparation of AmB	1–4 weeks

AmB: Amphotericin B preparation; Fluc: Fluconazole; Itra: Itraconazole; N/A: Not applicable; Vori: Voriconazole.

Datos en pacientes adultos

Profilaxis antifúngica en niños y adultos sometidos a trasplante de órganos sólidos y de precursores hematopoyéticos

Ricardo Rabagliati y M. Elena Santolaya

2012

Recomendación Nº 1 (b):
Profilaxis antifúngica en trasplante pulmonar

Uso universal. Alternativas:

- Itraconazol 200 mg/día vo (suspensión), con o sin anfotericina liposomal nebulizada en la fase inicial (C2)
- Anfotericina liposomal nebulizada (C3)
- Voriconazol 200 mg c/ 12 h vo (C2)
- No hay recomendación especifica en pediatría

Recomendación Nº 1 (a):
Profilaxis antifúngica en trasplante hepático

Uso sólo en casos seleccionados por factores de riesgo. Alternativas:

- Fluconazol (A1)
  - Adultos: 400 mg/día
  - Niños: 6-8 mg/kg/día
- Si existe riesgo de aspergilosis
  - Anfotericina B 15 mg/día iv (C2)
  - Anfotericina liposomal 50 mg/día iv (C2)
  - Caspofungina 70 mg carga inicial luego 50 mg/día iv (C2)
  - Ninguno de los tres está validado en pediatría como profilaxis

Recomendación Nº 1 (c):
Profilaxis antifúngica en trasplante cardiaco

Uso en casos seleccionados por factores de riesgo:

- Itraconazol 200 - 400 mg/día vo (suspensión) (C2)
- No hay recomendación especifica en pediatría

Prophylaxis With Caspofungin for Invasive Fungal Infections in High-Risk Liver Transplant Recipients

Jesus Fortún,[1,11] Pilar Martín-Dávila,[1] Miguel Montejo,[2] Patricia Muñoz,[3] José M. Cisneros,[4] Antonio Ramos,[5] Cesar Aragón,[6] Marino Blanes,[7] Rafael San Juan,[8] Joan Gavaldá,[9] and Pedro Llinares,[10] GESITRA Study Group

of caspofungin prophylaxis

Event	No. (%) patients
IFI	2/71 (2.8%)
Surgical infection by *Mucor* spp, 41 d after ending a course of 21 d of caspofungin	1
Surgical infection by *Candida albicans*, 19 d after ending a course of 21 d of caspofungin[a]	1
Suspension of caspofungin administration by clinical adverse events	0
Suspension of caspofungin administration by laboratory adverse events	6 (8.4%)
Favorable response (MITT analysis) (primary objective)	63/71 (88.7%)
Favorable response (EP analysis) (secondary objective)	
Absence of invasive Fungal infection (IFI)	54/56 (96.45%)
Absence of invasive aspergillosis (IA)	56/56 (100%)
Safety analysis (toxicity grade III)[b] (secondary analysis)[c]	
At day +3 of caspofungin administration	49/70 (70%)
At day +10 of caspofungin administration	39/68 (57.3%)
At the end of caspofungin administration	33/65 (50.7%)[d]
Two weeks after stopping caspofungin administration (safety visit)	24/65 (36.9%)[d]
Safety analysis (toxicity grade IV)[b] (secondary analysis)[c]	
At day +3 of caspofungin administration	21/70 (30%)
At day +10 of caspofungin administration	20/68 (29.4%)
At the end of caspofungin administration	18/65 (27.7%)[e]
Two weeks after stopping caspofungin administration (safety visit)	10/65 (15.4%)[e]

Datos en pacientes adultos

LIVER TRANSPLANTATION 18:680-685, 2012

ORIGINAL ARTICLE

Safety of Anidulafungin in Solid Organ Transplant Recipients

J.M. Aguado,[1] E. Varo,[2] P. Usetti,[3] J.C. Pozo,[4] A. Moreno,[5] M. Catalán,[1] O. Len,[6] M. Blanes,[7] A. Solé,[7] P. Muñoz,[8] M. Montejo,[9] and the TOSCANA Study Group

[1]12 de Octubre University Hospital, Madrid, Spain; [2]Central University Hospital, Santiago de Compostela, Spain; [3]Puerta de Hierro University Hospital, Madrid, Spain; [4]Reina Sofía University Hospital, Córdoba, Spain; [5]Hospital Clínic, Barcelona, Spain; [6]Vall d'Hebron University Hospital, Barcelona, Spain; [7]La Fe University Hospital, Valencia, Spain; [8]Gregorio Marañón University Hospital, Madrid, Spain; and [9]Cruces University Hospital, Bilbao, Spain

Anidulafungin was started at a mean of 359 days (range = 0-4638 days) after transplantation. The mean duration of treatment was 16.6 days (range = 2-61 days). Thirty-nine patients (45.3%) received anidulafungin for more than 14 days, 28 (32.6%) received anidulafungin for 7 to 14 days, and 19 patients (22.1%) received less than 7 days of treatment. The indications for anidulafungin therapy were prophylaxis against IFIs in 62 high-risk patients (72%) and the treatment of IFIs (probable or proven) in 24 patients (28%). Anidulafungin prophylaxis was administered for at least 7 days. The duration of treat-

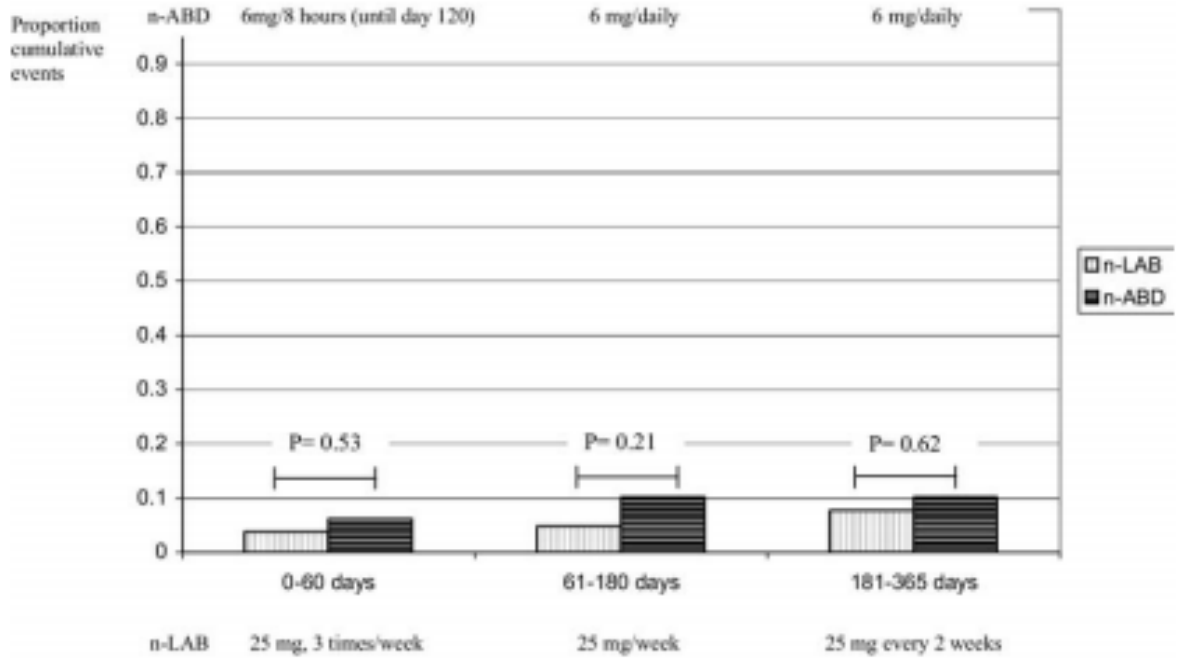
TABLE 3. Evolution of Tacrolimus Blood Levels During Anidulafungin Therapy

	Tacrolimus Blood Level (ng/mL)					
	Baseline (n = 19)	Day 2 (n = 17)	Day 4 (n = 17)	Day 7 (n = 15)	Day 10 (n = 15)	Day 14 (n = 15)
Mean ± standard deviation	10.97 ± 5.30	9.00 ± 4.68	9.40 ± 6.93	9.45 ± 5.73	8.35 ± 3.80	9.89 ± 4.88
Median (interquartile interval)	9.60 (6.50-15.60)	7.30 (5.70-9.60)	6.10 (5.20-13.60)	9.60 (3.50-14.20)	8.60 (6.50-10.70)	9.30 (6.00-12.20)

Datos en pacientes adultos

Feasibility, tolerability, and outcomes of nebulized liposomal amphotericin B for *Aspergillus* infection prevention in lung transplantation

Víctor Monforte, MD,[a,f] Piedad Ussetti, MD,[b] Joan Gavaldà, MD,[c] Carles Bravo, MD,[a,f] Rosalia Laporta, MD,[b] Oscar Len, MD,[c] Cristina López García-Gallo, MD,[b] Lluís Tenorio, MD,[d] Joan Solé, MD,[e] and Antonio Román, MD[a,f]



Datos en pacientes adultos

Aerosolized Liposomal Amphotericin B:
A Potential Prophylaxis of Invasive Pulmonary Aspergillosis in Immunocompromised Patients

Harutai Kamalaporn, MD,[1]* Kitty Leung, BSc,[2] Mark Nagel, BSc,[3] Saranya Kittanakom, PhD,[4] Battista Calvieri, PhD,[5] Reinhart A.F. Reithmeier, PhD,[4] and Allan L. Coates, MD[6]

Summary. Background: Aerosolized liposomal Amphotericin B may reduce the incidence of invasive pulmonary Aspergillosis in adults with chemotherapy-induced prolonged neutropenia with less nephrotoxicity. The breath-actuated AeroEclipse® BAN nebulizer is very efficient and minimizes environmental drug contamination since no aerosol is produced, unless the patient is inspiring through the device. Our aim is to develop an appropriate delivery system suitable for children that does not disrupt the liposomes due to the shear forces in nebulization. Methods: This is an in vitro experimental study in vitro. Six ml of 4 mg/ml liposomal Amphotericin B solution (AmBisome®; Astellas Pharma Inc., Markham, Ontario, CA) was nebulized with the breath-actuated nebulizer (AeroEclipse®; Trudell Medical International, Canada) and captured by the glass liquid impinger. Sodium dodecyl sulfate was used as detergent to disrupt the liposomes in control samples. Gel filtration, electron microscopy, and high performance liquid chromatography (HPLC) were used to compare the size and shape of the liposomes, and amount of the drug before and after nebulization. The aerosol particle size was obtained by the laser diffraction. Results: After nebulization, 97.5% of amphotericin B was captured by the liquid impinger and detected by HPLC. Gel filtration and electron microscopy demonstrated that the drug remained in its liposomal configuration after nebulization. The mass median diameter (MMD) was 3.7 μm and 66% of aerosol particles were less than 5 μm in diameter. Conclusions: We demonstrated that liposomal Amphotericin B can be nebulized successfully without disrupting the liposomes and minimize drug loss by using the breath-actuated nebulizer. **Pediatr Pulmonol.** © 2013 Wiley Periodicals, Inc.

Key words: aerosolized liposomal amphotericin B; invasive pulmonary Aspergillosis; breath-actuated nebulizer; AeroEclipse.

Funding source: none reported.

upiip

Unitat de Patologia Infecciosa i Immunodeficiències de Pediatria.
Hospital Universitari Vall d'Hebron. Barcelona.

Situación en nuestro centro

Procediments d'alta complexitat

Apostem per una nova medicina dirigida cap a la frontera del coneixement. Una medicina que, des de la comprensió del funcionament de les biomolècules i els processos biològics sigui capaç d'introduir intervencions innovadores, per tal de potenciar el desenvolupament d'una societat més sana i solidària

1.500
tractaments de radioteràpia

588
intervencions de cirurgia cardiaca extracorpòria

200
intervencions de cirurgia robòtica

60
consultes de teleICTUS

30
consultes de cardiologia pediàtrica a distància

Trasplantaments d'adults
82 Còrnia
46 Hepàtic
54 Moll d'os
46 Pulmonar
95 Renal

Trasplantaments infantils
7 Cor
9 Hepàtic
25 Moll d'os
3 Pulmonar
10 Renal

Año 2012

Trasplantaments d'adults
82 Còrnia
46 Hepàtic
54 Moll d'os
46 Pulmonar
95 Renal

Trasplantaments infantils
7 Cor
9 Hepàtic
25 Moll d'os
3 Pulmonar
10 Renal

PROFILAXI ANTIINFECCIOSA
EN EL TRASPLANTAMENT CARDIAC PEDIÀTRIC

Unitat de Patologia Infecciosa i Immunodeficiències de Pediatria; Servei de Cardiologia Pediàtrica; Servei de Cures Intensives Pediàtriques, Servei de Farmàcia i Servei de Microbiologia. Hospital Universitari Vall d'Hebron. Barcelona. Àrea Maternoinfantil.

Setembre 2012

PROFILAXIS ANTIINFECCIOSA

EN EL TRASPLANTE RENAL PEDIÁTRICO

le Patología Infecciosa i Immunodeficiències de Pediatria, Servei de
ía Pediátrica, Servei de Farmàcia Pediàtrica, Servei de Microbiologia i
Unitat de Cures Intensives Pediàtriques.

Juny 2012

¿Trasplante pulmonar 2013-2014?.....

- Ajuste de dosis: de nuevo, se deberá tener presente que en el momento del trasplante estos pacientes suelen presentar un FG < 10 y ajustar la dosis según corresponde.
- En caso de toxicidad/alergia a TMP-SMX, la alternativa para la profilaxis es la pentamidina IV/nebulizada según la edad del paciente *(ver protocolo correspondiente: www.upiip.com)*.

b) Otras infecciones fúngicas.

- No recomendada de forma rutinaria.

CASE REPORT/CAS CLINIQUE

Invasive fungal infections in renal transplant recipients: About 11 cases

Mycoses invasives chez les greffés rénaux : à propos de 11 cas

H. Trabelsi [a], S. Néji [a], H. Sellami [a], S. Yaich [b], F. Cheikhrouhou [a], R. Guidara [a], K. Charffedine [b], F. Makni [a], J. Hachicha [b], A. Ayadi [a,*]

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			Biology	Treatment	Evolution
		ateral ltrates	Blood culture: *C. glabrata*	–	Dead
			Blood culture: *C. tropicalis* Urine: *C. krusei*	–	Digestive bleeding Diffuse intravascular coagulation Dead
		and	3 sputums: *A. terreus* Aspergillus antigen (galactomannan): 2.25 Sputum and Serum PCR: (+)	Voriconazole: 400 mg × 2/d (1day) then 200 mg × 2/d: (6 months)	Favorable
4	Fever Cough Dyspnoea Expectorations	Thoracic radiography: bilateral focal pulmonary areas + excavations Chest CT: alveolar condensation	BAL/sputums: *A. flavus* Aspergillus antigen (galactomannan): 1.5 Serum, BAL and sputum PCR: (+)	AMB: 80 mg (10 days) then Voriconazole: 1 bottle × 2/d (10 days)	Septic shock Respiratory distress Dead
5	Headache resistant to symptomatic treatment Neurological signs: bilateral ptosis + facial paralysis + ophtalmoplegia	Brain MRI: multiples lesions in hypersignal T2—weighted signals in the white sitting at the two frontal lobes and around the aqueduc of Sylvius	CSF culture: *C. neoformans* *C. neoformans* circulating antigen: 1/100	AMB: 10 mg (1 day) then 50 mg/d (3 days) then FLZ: 200 mg/d (7 months)	Pulmonary embolus Dead
6	Fever Headache Dysarthria	Brain CT and MRI-angiography: normal	CSF + blood culture + urines *C. neoformans* *C. neoformans* circulating antigen: 1/10	AMB: 10 mg (1 day) then 0.7 mg/kg/d (6 weeks) then FLZ: 400 mg (4 weeks) then FLZ: 100 mg/d (11 months)	Favorable
7	Fever Expectoration Respiratory distress	Thoracic radiography: bilateral alveolar and interstitial opacities	Sputum PCR: *P. jiroveci* DIF: (–) Colorations: (–)	Cotrimoxazole: 6 tablets/d	Dead
8	Degradation of general state Respiratory distress	Thoracic radiography: diffuse interstitial syndrome Chest CT: shadow of ground glass density and bilateral pleurisy	BAL and sputum PCR: *P. jiroveci* DIF: (–) Colorations: (–)	Cotrimoxazole: 4 tablets × 4/d	Dead
9	Respiratory distress	Thoracic radiography: bilateral alveolar opacities	Sputum PCR: *P. jiroveci*	Cotrimoxazole: 5 tablets/d	Septic shock Dead
10	Fever Respiratory distress	Thoracic radiography: bilateral alveolar and interstitial opacities	Sputum PCR: *P. jiroveci* DIF: (–) Colorations: (–)	Cotrimoxazole: 4 tablets × 3/d	Dead
11	Fever Purulent rhinorrhea Headache Left facial swelling	Craniofacial scanner: maxillary, ethmoidal and sphenoidal sinusitis	2 sinusal biopsy: *Rhizopus oryzae*	Incomplete surgical resection AMB: 0.5 mg/kg/d (6 weeks)	Consciousness disorder Unknown evolution

CT: computerized tomography; PCR: polymerase chain reaction; BAL: bronchoalveolar lavage; MRI: resonance magnetic imaging; AMB: amphotericin B; CSF: cerebrospinal fluid; FLZ: fluconazole; DIF: direct immunofluorescence.

Así, tras revisar los datos disponibles en la literatura y en base a la experiencia en nuestro centro, siguiendo las últimas recomendaciones en el trasplante cardíaco, realizaríamos las siguientes indicaciones de profilaxis antifúngica para hongos filamentosos:

1. En pacientes con los siguientes factores de riesgo:
    a. Pacientes menores de 1 año,
    b. Viremia o enfermedad por CMV,
    c. Reintervención cardíaca reciente (durante el mismo ingreso),
    d. Aislamiento de *Aspergillus* spp en el lavado broncoalveolar u otro cultivo respiratorio.
2. En ausencia de factores de riesgo **no** se recomienda profilaxis para *Aspergillus* spp. de forma rutinaria.

Aspergillus spp.	ABL IV hasta extubación Pasar posteriormente a ABL nebulizada (24mg/6ml)	1 mg/Kg/día 24 mg: - Primer mes: 3 veces/sem - Hasta los 3 – 6 meses: 1 vez/sem	En caso de factores de riesgo para infección por *Aspergillus* spp.: 3 meses Prolongar en caso de persistencia de factores de riesgo o 6 meses en los casos de rechazo
Pneumocystis jirovecii	Cotrimoxazol IV o VO Si alergia/toxicidad: Pentamidina IV o nebulizada	150 mg/m2/día cada 24h (máx 320 mg TMP/día) Ver procotolo correspondiente en www.upiip.com	6 meses postrasplante Si intensificación de tratamiento inmunosupresor por rechazo agudo: durante todo periodo de tratamiento y los 3 meses posteriores

Trasplante pulmonar

- Anfotericina B inhalada/instilada: 6 mg/8h en niños > 20 kg, y 4 mg/8h en < 20 kg. A partir de los cuatro meses una dosis diaria.
- Alternativa: Anfotericina B liposomal: 24 mg 1 vez/día 3 veces por semana el primer mes, 1 vez a la semana hasta los 4 meses y posteriormente 1 vez cada 2 semanas. No iniciar mientras el paciente esté con ventilación mecánica.
- Anfotericina B liposomal iv en todos los pacientes colonizados por hongos filamentosos (*Aspergillus*, *Scedosporium*, etc). Se iniciará en quirófano, antes de la intervención 3 mg/kg. Se continuará en UCIP: 5 mg/kg/día si la función renal es normal. Se suspenderá a los 10-14 días una vez comprobada la negatividad de los cultivos postoperatorios. En pacientes con fibrosis quística colonizados previamente por *Scedosporium* la pauta debe ser consultada específicamente.

Pneumocystis carinii:

- Cotrimoxazol 5 mg/kg/24h. Se inicia durante la primera semana una vez comprobada la tolerancia oral. En alérgicos a cotrimoxazol: pentamidina en aerosol 300 mg/mes (en mayores de 5 años).

Trasplante hepático

- Anidulafungina (3 mg el primer día y 1,5 mg los siguientes) si el paciente cumple alguno de los siguientes criterios:
  - Disfunción renal previa.
  - Trasplante parcial (ya sea donante vivo o *split*).
  - Insuficiencia hepática aguda.
  - Cierre diferido de la laparotomía.

- Duración: tres días o hasta cierre de la laparotomía.

Conclusiones y propuestas

- Profilaxis establecida para *P. jirovecii*.
- Otras infecciones fúngicas poco frecuentes pero potencialmente muy graves.
- *Candida* spp > *Aspergillus* spp > resto.
- Pulmón > hígado > resto.
- No profilaxis universal, limitada a pacientes de alto riesgo.
- Escasos datos en el paciente pediátrico.
- Limitaciones en su aplicación por interacciones y efectos adversos.

Conclusiones y propuestas

- Revisión de las infecciones fúngicas de los pacientes pediátricos sometidos a TOS.
- ¿Proyecto coordinado para 2014?
- UPIIP-Microbiología-Servicios implicados

¡Muchas gracias!

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