Tratamiento antifúngico en el paciente pediátrico sometido a un trasplante de órgano sólido

P. Soler-Palacín

Unitat de Patologia Infecciosa i Immunodeficiències de Pediatria. Hospital Universitari Vall d'Hebron. Institut de Recerca Vall d'Hebron. Universitat Autònoma de Barcelona. Barcelona.

Madrid, 29-10-2015

Infección Fúngica en Pediatría

Conflicto de intereses:

El ponente de la presente comunicación declara la ausencia de conflicto de intereses

Nota legal:

Dado el carácter y la finalidad exclusivamente docente y eminentemente ilustrativa de las explicaciones en clase de esta presentación, el autor se acoge al artículo 32 de la Ley de propiedad intelectual vigente, respecto al uso parcial de obras ajenas tal como imágenes, gráficos u otro material contenido en las diferentes diapositivas.

Todas las imágenes presentadas se incluyen como citas necesarias para ilustrar las explicaciones de esta clase.

"Imprescindibles" para el tratamiento de la IFI

A. Conocer características y situación clínica del paciente

B. Conocer el contexto epidemiológico

C. Tener claro el objetivo del tratamiento

D. Conocer la metodología del tratamiento: recomendaciones terapéuticas

Conocer al paciente

"Although children and adults are similarly vulnerable to invasive fungal infections, important differences between these two patient groups have to be considered."

Expert Rev. Anti Infect. Ther. 9(3), 275–278 (2011)

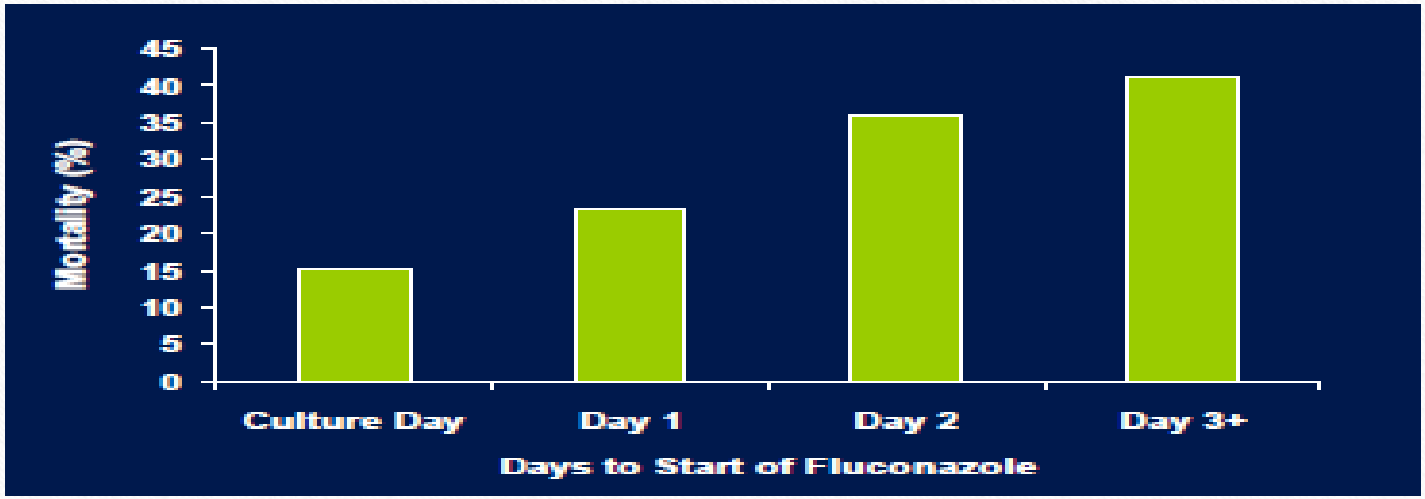
Conocer el contexto

- CI y AI: IFIs más frecuentes (además de *P. jirovecii*).
- Patología de base, interacciones y toxicidad acumulada.
- Papel de la profilaxis previa.
- Emergencia nuevos géneros/especies fúngicas.
- Emergencia cepas resistentes a azoles y candinas.

Tener claro el objetivo del tratamiento

Importancia del tratamiento precoz

- Mortalidad directamente asociada al retraso en el inicio del tratamiento

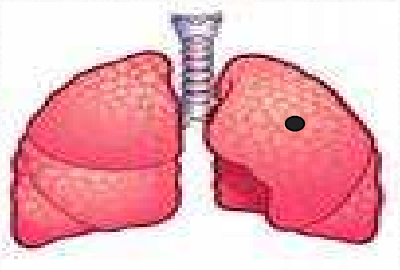


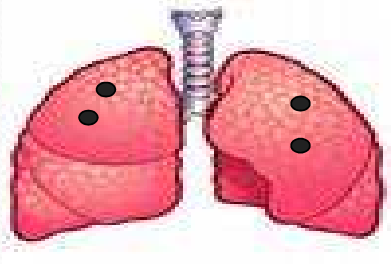
Garey KW, et al. *Clin Infect Dis* 2006;43:25-31.

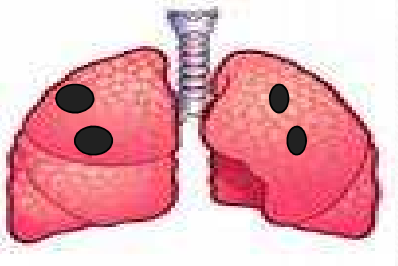
Tener claro el objetivo del tratamiento
Estrategias terapéuticas

Profilaxis | T. empírico | T. anticipado | T. dirigido

> eficacia/< toxicidad







Riesgo IFI

IFI posible

- Clínica
- TC
- Micro

IFI Probable/ Probada

DNAemia precede al GM una media de 49 días

Tener claro el objetivo del tratamiento
Tto anticipado: micología positiva +/- signos clínicos de IFI

- 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

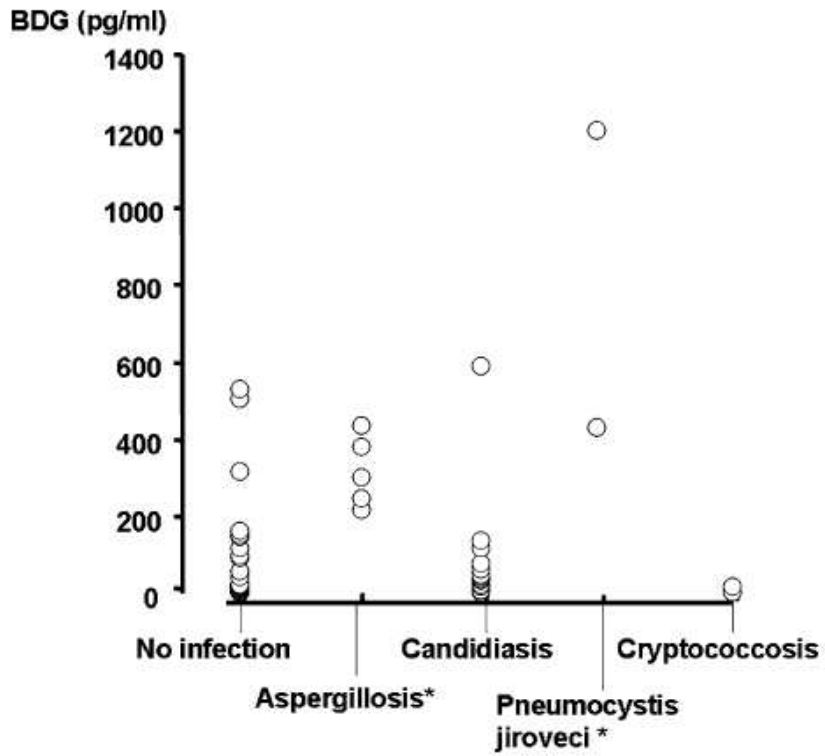


Figure 3. The distribution of maximum (1 → 3) β-D-glucan (BDG) level before treatment stratified by the fungal species. *<0.05 to those without infection.

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

Recomendaciones terapéuticas

Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David Andes,[4] Daniel K. Benjamin, Jr.,[5] Thierry F. Calandra,[11] John E. Edwards, Jr.,[6] Scott G. Filler,[6] John F. Fisher,[7] Bart-Jan Kullberg,[12] Luis Ostrosky-Zeichner,[8] Annette C. Reboli,[9] John H. Rex,[13] Thomas J. Walsh,[10] and Jack D. Sobel[3]

An Pediatr (Barc). 2011;xxx(xx):xxx.e1—xxx.e17

ANALES DE PEDIATRÍA

www.elsevier.es/anpediatr

ASOCIACIÓN ESPAÑOLA DE PEDIATRÍA

Recomendaciones de la Sociedad Española de Infectología Pediátrica sobre diagnóstico y tratamiento de la candidiasis invasiva

C. Figueras[a,*], C. Díaz de Heredia[b], J.J. García[c], M. Navarro[d], J. Ruiz-Contreras[e], R. Rossich[f], J. Rumbao[g], M.A. Frick[a] y E.M. Rosselló[h], en representación del grupo de estudio de la Infección Fúngica Invasiva de la Sociedad Española de Infectología Pediátrica (SEIP)◊

- Priorización equinocandinas (paciente grave / interacciones / Px azoles)
- Fluconazol: - en candidiasis diseminada
  - en tratamiento de continuación
  - pielonefritis candidiásica
- AMB-L +/- flucitosina en afectación SNC o EI.

Caspo: > 12 m
Mica: 0-18 a
Anidula: > 18 a

Espectro de actividad

Table 1. Antifungal spectrum of activity against common fungi.

Organism	Antifungal agent								
	AmB[a]	Flu	Itr	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
Aspergillus species	+	−	+	+	+	+	+	+	−
A. flavus	±	−	+	+	+	+	+	+	−
A. fumigatus	+	−	+	+	+	+	+	+	−
A. niger	+	−	±	+	+	+	+	+	−
A. terreus	−	−	+	+	+	+	+	+	−
Candida species	+	+	+	+	+	+	+	+	+
C. albicans	+	+	+	+	+	+	+	+	+
C. glabrata	+	±	±	+	+	+	+	+	+
C. krusei	+	−	±	+	+	+	+	+	±
C. lusitaniae	−	+	+	+	+	+	+	+	+
C. parapsilosis	+	+	+	+	+	±	±	±	+
C. tropicalis	+	+	+	+	+	+	+	+	+
Cryptococcus neoformans	+	+	+	+	+	−	−	−	+
Coccidioides species	+	+	+	+	+	±[b]	±[b]	±[b]	−
Blastomyces	+	+	+	+	+	±[b]	±[b]	±[b]	−
Histoplasma species	+	+	+	+	+	±[b]	±[b]	±[b]	−
Fusarium species	±	−	−	+	+	−	−	−	−
Scedosporium apiospermum	±	−	±	+	+	−	−	−	−
Scedosporium prolificans	−	−	−	±	±	−	−	−	−
Zygomycetes	±	−	−	−	+	−	−	−	−

Farmacocinética

Table 2. Comparative pharmacokinetics of the antifungal agents.

	Antifungal agent											
Pharmacokinetic parameter	AmB	ABCD	ABLC	LAB	Flu	Itr[a]	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
Oral bioavailability, %	<5	<5	<5	<5	95	50	96	ND	<5	<5	<5	80
Food effect	NA	NA	NA	NA	NE	ES	ES	Food	NA	NA	NA	NE
Distribution												
Total C_{max} μg/mL	0.5–2	4	131	0.1	0.7	11	4.6	7.8	0.83	0.27	0.24	80
AUC, mg × h/L	17	43	14	555	400	29.2	20.3	8.9	99[b]	119	158[b]	62
Protein binding, %	>95	>95	>95	>95	10	99.8	58	99	84	97	99	4
CSF penetration, %	0–4	<5	<5	<5	>60	<10	60	NR	<5	<5	<5	75
Vitreal penetration, %	0–38[c,d]	0–38[c,d]	0–38[c,d]	0–38[c,d]	28–75[c,d]	10[c]	38[c]	26[c,d]	0[d]	0[c]	<1[d]	49[d]
Urine penetration, %[e]	3–20	<5	<5	4.5	90	1–10	<2	<2	<2	<2	<2	90
Metabolism	Minor Hep	Unk	Unk	Unk	Minor Hep	Hep	Hep	Hep	None	Hep	Hep	Minor intestinal
Elimination	Feces	Unk	Unk	Unk	Urine	Hep	Renal	Feces	Feces	Urine	Feces	Renal
Half-life, h	50	30	173	100–153	31	24	6	25	26	30	15	3–6

Farmacocinética equinocandinas

Cuadro 4. PERFIL FARMACOLÓGICO EQUINOCANDINAS

	Caspofungina	Micafungina	Anidulafungina
Vía de administración y dosis	IV Dosis carga: 70 mg/día el primer día, seguida por 50 mg/día.	IV No requiere dosis carga. 50-150 mg/dia. (*)	IV Dosis carga: 150-200 mg/dia el primer día, seguida por 75-100 mg/día. (*)
Biodisponibilidad oral	<10 %	<10 %	2-7 %
Vida media	9-11 h	11-17 h	24-26 h
Unión proteínas	97 %	99,8 %	84 %
Metabolismo	Metabolismo hepático lento no enzimático por hidrolisis de péptidos y N acetilación a metabolitos inactivos. No interviene CIT P 450	Metabolismo hepático por Arilsulfatasas, catechol-O-methyl-transferase, y en menor grado CYP3A	No se metaboliza, degradación en plasma a productos inactivos
Eliminación	35 % heces, 41% orina.	40 % heces <15 % orina	Principalmente en heces 1% en orina
Concentración LCR	Baja	Baja	<0,1 %
Ajuste de dosis en insuficiencia renal	No	No	No
Ajuste dosis en insuficiencia hepática	Child-Pugh A: no ajuste Child-Pugh B: reducir dosis Child-Pugh C: no datos	No requiere ajuste en disfuncion moderada. Severa: no datos	No requiere ningún tipo de ajuste
Categoría embarazo	C	C	C

(*) Dosis utilizadas en diferentes estudios clínicos. Estas dosis pueden variar dependiendo de la indicación clínica.

Drugs 2011; 71 (1)

Toxicidad

Table 6. Comparative toxicities of antifungal agents.

	Antifungal agent											
Type of toxicity	AmB	ABCD	ABLC	LAB	Flu	Itr	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
Hepatic	++	++	++	++	+	+	+	+	+	+	+	++
Nephrotic	++++	+++	+++	++	–	–	–	–	–	–	–	–
Hematologic	+	+	+	+	NR	NR	NR	NR	NR	+	+	+++
Infusion-related	+++	+++	+++	++	–	–	–	NA	+	+	+	NA
Electrolyte abnormalities[a]	+++	++	++	++	NR	+	+	NR	+	+	NR	+

NOTE. Plus signs indicate degree of toxicity: +, mild; ++, moderate; and +++, severe. ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; AmB, amphotericin B; Flu, fluconazole; Itr, itraconazole; LAB, liposomal amphotericin B; NA, data not available because of a lack of formulation; NR, not reported; Pos, posaconazole; Vor, voriconazole. Data are derived from [5, 37, 41, 45, 47, 51, 52, 54, 58, 70, 111–118].

[a] Includes hypokalemia and hypomagnesemia.

Requerimiento ajuste dosis por disfunción orgánica

Table 3. Suggested dose modifications for antifungal agents, by type of organ dysfunction.

Type of organ dysfunction	Antifungal agent											
	AmB	ABCD	ABLC	LAB	Flu	Itr	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
Hepatic	None	None	None	None	None	None	Decrease dose for mild-to-moderate cirrhosis	None	None	Decrease dose for moderate insufficiency	None	None
Renal	None	None	None	None	Decrease dose	Caution with iv preparation for ClCr <30 mL/min	Caution with iv preparation for ClCr <50 mL/min	None	None	None	None	Decrease dose

NOTE. ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; AmB, amphotericin B; ClCr, creatinine clearance; Flu, fluconazole; Itr, itraconazole; LAB, liposomal amphotericin B; Pos, posaconazole; Vor, voriconazole. Data are derived from [37, 41, 45, 47, 54, 80, 81, 90, 92].

Interacciones farmacológicas

- Caspofungina
  - Disminuye AUC para tacrolimus en 20%, C_{Max} 16%
  - Ciclosporina incrementa AUC caspo en 35% - ojo PFHs
  - Usar dosis de 70 mg/día si recive al tiempo un inductor de P450 e.g.
    fenitoína, dexametasona, rifampicina, carbamacepina
- Micafungina
  - Incrementa AUC de sirolimus en 21% : monitorear
  - Incrementa AUC de nifedipina en 18%, C_{Max} en 41%
- Anidulafungina
  - Degradación en torrente sanguíneo – órgano independiente
  - ¿Incrementa AUC de anidulafungina con ciclosporina?

Morris MI. Echinocandins in the management of invasive fungal infections. Part 1.

Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America

Thomas J. Walsh,[1,a] Elias J. Anaissie,[2] David W. Denning,[13] Raoul Herbrecht,[14] Dimitrios P. Kontoyiannis,[3] Kieren A. Marr,[5] Vicki A. Morrison,[6,7] Brahm H Segal,[8] William J. Steinbach,[9] David A. Stevens,[10,11] Jo-Anne van Burik,[7] John R. Wingard,[12] and Thomas F. Patterson[4,a]

Table 2. Summary of recommendations for the treatment of aspergillosis.

Condition	Therapy[a]		Comments
	Primary	Alternative[b]	
Invasive pulmonary aspergillosis	Voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h)	L-AMB (3–5 mg/kg/day IV), ABLC (5 mg/kg/day IV), caspofungin (70 mg day 1 IV and 50 mg/day IV thereafter), micafungin (IV 100–150 mg/day; dose not established[c]), posaconazole (200 mg QID initially, then 400 mg BID PO after stabilization of disease[d]), itraconazole (dosage depends upon formulation)[e]	Primary combination therapy is not routinely recommended based on lack of clinical data; 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 is 5–7 mg/kg IV every 12 h and for caspofungin is 50 mg/m²/day; limited clinical experience is reported with anidulafungin; dosage of posaconazole in pediatric patients has not been defined; indications for surgical intervention are outlined in table 3

- Voriconazol: 1ª línea. AMB-L alternativa (IFFI no aspergilar)
- Terapia combinada no recomendada
- Indicaciones Q bien definidas

Table 2
Recommendations for antifungal therapy of proven or probable invasive aspergillosis in pediatric patients with cancer or hematopoietic stem-cell transplantation.
Traitement curatif des aspergilloses invasives de l'enfant atteint de cancer ou traité par allogreffe de cellules souches hématopoïétiques.

Agent	Dose	Level of evidence	Comments
First line			
Voriconazole	If ≤ 14 years of age and weight ≤ 50 kg: 8 mg/kg/12 h (D1: 9 mg/kg) IV or 9 mg/kg/12 h PO If ≥ 15 years of age and/or and weight ≥ 50 kg: 4 mg/kg/12 h (D1: 6 mg/kg) IV or 200 mg/12 h PO	A-I	Monitoring of recommended plasmatic trough level (target 1.0–5.0 mg/l) Preferred treatment in case of central nervous system involvement Discuss another therapeutic class in case of IA occurring while treated azoles
Liposomal amphotericin B	3 mg/kg/24 h IV	B-I	
Amphotericin B lipid complex	5 mg/kg/24 h IV	B-I	
In combination with echinocandin + polyene or triazole		C-III	
Second line			
Voriconazole	Idem first line	A-I	Not approved if < 2 years of age Option to choose as 2nd line for voriconazole naive patients Monitoring of recommended plasmatic trough level (target: 1.0–5.0 mg/l)
Liposomal amphotericin B	Idem first line	B-I	Preferred treatment in case of failure of or intolerance to voriconazole
Caspofungin	50 mg/m^2/24 h IV (D1: 70 mg/m^2)	A-II	
Amphotericin B lipid complex	Idem first line	B-II	
In combination with echinocandin + polyene or triazole		C-II	
Itraconazole	If ≥ 2 years of age: 2.5 mg/kg/12 h PO	–	Monitoring of recommended plasmatic trough level (target: ≥ 0.5 mg/l)
Posaconazole	If ≥ 13 years of age: 800 mg/day in 2 or 4 intakes PO	–	Monitoring of recommended plasmatic trough level (target: ≥ 0.7–1.5 mg/l)
Micafungin	2–4 mg/kg/24 h IV (100–200 mg/24 h if weight ≥ 50 kg)	–	

Adapted from Groll et al. [32].
PO: per os; IV: intravenous.

Frange P, et al. An update on pediatric invasive aspergillosis. Med Mal Infect (2015).

Espectro de actividad

Table 1. Antifungal spectrum of activity against common fungi.

Organism	Antifungal agent								
	AmB[a]	Flu	Itr	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
Aspergillus species	+	−	+	+	+	+	+	+	−
A. flavus	±	−	+	+	+	+	+	+	−
A. fumigatus	+	−	+	+	+	+	+	+	−
A. niger	+	−	±	+	+	+	+	+	−
A. terreus	−	−	+	+	+	+	+	+	−
Candida species	+	+	+	+	+	+	+	+	+
C. albicans	+	+	+	+	+	+	+	+	+
C. glabrata	+	±	±	+	+	+	+	+	+
C. krusei	+	−	±	+	+	+	+	+	±
C. lusitaniae	−	+	+	+	+	+	+	+	+
C. parapsilosis	+	+	+	+	+	±	±	±	+
C. tropicalis	+	+	+	+	+	+	+	+	+
Cryptococcus neoformans	+	+	+	+	+	−	−	−	+
Coccidioides species	+	+	+	+	+	±[b]	±[b]	±[b]	−
Blastomyces	+	+	+	+	+	±[b]	±[b]	±[b]	−
Histoplasma species	+	+	+	+	+	±[b]	±[b]	±[b]	−
Fusarium species	±	−	−	+	+	−	−	−	−
Scedosporium apiospermum	±	−	±	+	+	−	−	−	−
Scedosporium prolificans	−	−	−	±	±	−	−	−	−
Zygomycetes	±	−	−	−	+	−	−	−	−

Farmacocinética

Table 2. Comparative pharmacokinetics of the antifungal agents.

	Antifungal agent											
Pharmacokinetic parameter	AmB	ABCD	ABLC	LAB	Flu	Itr[a]	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
Oral bioavailability, %	<5	<5	<5	<5	95	50	96	ND	<5	<5	<5	80
Food effect	NA	NA	NA	NA	NE	ES	ES	Food	NA	NA	NA	NE
Distribution												
Total C_{max} μg/mL	0.5–2	4	131	0.1	0.7	11	4.6	7.8	0.83	0.27	0.24	80
AUC, mg × h/L	17	43	14	555	400	29.2	20.3	8.9	99[b]	119	158[b]	62
Protein binding, %	>95	>95	>95	>95	10	99.8	58	99	84	97	99	4
CSF penetration, %	0–4	<5	<5	<5	>60	<10	60	NR	<5	<5	<5	75
Vitreal penetration, %	0–38[c,d]	0–38[c,d]	0–38[c,d]	0–38[c,d]	28–75[c,d]	10[c]	38[c]	26[c,d]	0[d]	0[c]	<1[d]	49[d]
Urine penetration, %[e]	3–20	<5	<5	4.5	90	1–10	<2	<2	<2	<2	<2	90
Metabolism	Minor Hep	Unk	Unk	Unk	Minor Hep	Hep	Hep	Hep	None	Hep	Hep	Minor intestinal
Elimination	Feces	Unk	Unk	Unk	Urine	Hep	Renal	Feces	Feces	Urine	Feces	Renal
Half-life, h	50	30	173	100–153	31	24	6	25	26	30	15	3–6

Toxicidad

Table 6. Comparative toxicities of antifungal agents.

	Antifungal agent											
Type of toxicity	AmB	ABCD	ABLC	LAB	Flu	Itr	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
Hepatic	++	++	++	++	+	+	+	+	+	+	+	++
Nephrotic	++++	+++	+++	++	–	–	–	–	–	–	–	–
Hematologic	+	+	+	+	NR	NR	NR	NR	NR	+	+	+++
Infusion-related	+++	+++	+++	++	–	–	–	NA	+	+	+	NA
Electrolyte abnormalities[a]	+++	++	++	++	NR	+	+	NR	+	+	NR	+

NOTE. Plus signs indicate degree of toxicity: +, mild; ++, moderate; and +++, severe. ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; AmB, amphotericin B; Flu, fluconazole; Itr, itraconazole; LAB, liposomal amphotericin B; NA, data not available because of a lack of formulation; NR, not reported; Pos, posaconazole; Vor, voriconazole. Data are derived from [5, 37, 41, 45, 47, 51, 52, 54, 58, 70, 111–118].

[a] Includes hypokalemia and hypomagnesemia.

Toxicidad a largo plazo mal conocida (VCZ y cancer piel)

Requerimiento ajuste dosis por disfunción orgánica

Table 3. Suggested dose modifications for antifungal agents, by type of organ dysfunction.

Type of organ dysfunction	Antifungal agent											
	AmB	ABCD	ABLC	LAB	Flu	Itr	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
Hepatic	None	None	None	None	None	None	Decrease dose for mild-to-moderate cirrhosis	None	None	Decrease dose for moderate insufficiency	None	None
Renal	None	None	None	None	Decrease dose	Caution with iv preparation for ClCr <30 mL/min	Caution with iv preparation for ClCr <50 mL/min	None	None	None	None	Decrease dose

NOTE. ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; AmB, amphotericin B; ClCr, creatinine clearance; Flu, fluconazole; Itr, itraconazole; LAB, liposomal amphotericin B; Pos, posaconazole; Vor, voriconazole. Data are derived from [37, 41, 45, 47, 54, 80, 81, 90, 92].

Interacciones farmacológicas

TABLA 6. Principales interacciones medicamentosas de voriconazol

Tipo de interacción	Recomendación
El fármaco disminuye los niveles de voriconazol	
Carbamacepina	Contraindicado
Rifampicina	Contraindicado
Barbitúricos de acción prolongada	Contraindicado
Voriconazol incrementa las concentraciones del fármaco	
Astemizol	Contraindicado
Cisaprida	Contraindicado
Ciclosporina	Reducir dosis a la mitad y monitorizar niveles
Alcaloides ergotamínicos	Contraindicado
Omeprazol	Reducir dosis a la mitad
Quinidina	Contraindicado
Sirolimus	Contraindicado
Tacrolimus	Reducir la dosis dos tercios y monitorizar las concentraciones
Terfenadina	Contraindicado
Warfarina	Monitorizar el tiempo de protrombina
El fármaco disminuye los valores de voriconazol y voriconazol incrementa concentraciones del otro fármaco	
Rifabutina	Contraindicado
Fenitoína	Doblar dosis de voriconazol y monitorizar niveles de fenitoína
Voriconazol probablemente incrementa los valores del fármaco	
Estatinas	Monitorizar los efectos de los fármacos y considerar una reducción en las dosis cuando se añade voriconazol
Alacaloides de la VINCA	
Sulfonilureas	
Bloqueantes de los canales del calcio	
Benzodiacepinas	

Monitorización de concentraciones plasmáticas de los antifúngicos

TABLE 4. Tentative recommendations for monitoring of blood levels during antifungal therapy

Drug	Indication	Time of first measurement after start of therapy (days)	Target blood concn[a] (μg/ml) for:	
			Efficacy	Safety
Flucytosine	Routine during first wk of therapy, renal insufficiency, lacking response to therapy	3–5	Peak of >20	Peak of <50
Itraconazole	Routine during first wk of therapy, lacking response, gastrointestinal dysfunction, comedication	4–7	For prophylaxis, trough of >0.5; for therapy, trough of >1 to 2	NA
Voriconazole	Lacking response; gastrointestinal dysfunction; comedication; children; intravenous-to-oral switch; severe hepatopathy; unexplained neurological symptoms/signs	4–7	For prophylaxis, trough of >0.5; for therapy, trough of >1 to 2	Trough of <6
Posaconazole	Lacking response; gastrointestinal dysfunction, therapy with proton pump inhibitors; comedication	4–7	For prophylaxis, trough of >0.5; for therapy, trough of >0.5 to 1.5	NA

[a] Total or bound and unbound drug concentrations. NA, not applicable.

¡Muchas gracias!

www.upiip.com

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

Ann Intern Med. 2015;162:81-89. doi:10.7326/M13-2508 www.annals.org
For author affiliations, see end of text.

rections (2). In this study, the paradox was that the global response at 6 weeks was lower in the group of patients who received the combination of voriconazole and anidulafungin compared with voriconazole monotherapy. By analyzing the individual components of the global response assessments, we discovered that a large proportion of patients in the combination therapy group were not evaluable by the DRC at week 6 because they survived but did not have computed tomography performed within the study visit window. In contrast, a relatively large proportion of patients in the monotherapy group died before that time point. We

We conclude that treatment of IA with the combination of voriconazole and anidulafungin was associated with a nonsignificant but clinically meaningful survival benefit in patients with HM or HCT. Further clinical studies are necessary to confirm differences in mortality and to define the population with the greatest potential benefits of combination antifungal therapy.