

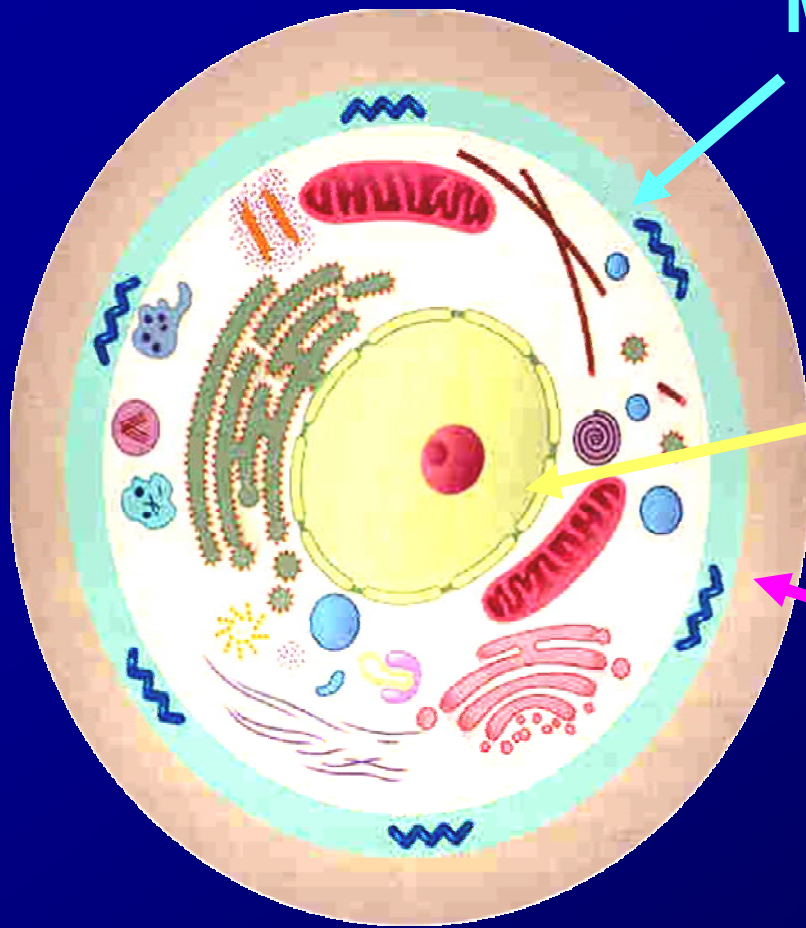


Equinocandinas

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Diana de Acción de los Antifúngicos



Membrana celular

- **Polienos:** anfotericina B, Anfotericinas lipídicas
- **Azoles:** ketoconazol, itraconazol, fluconazol

Triazoles 2^a generación:

- Voriconazol
- Posaconazol

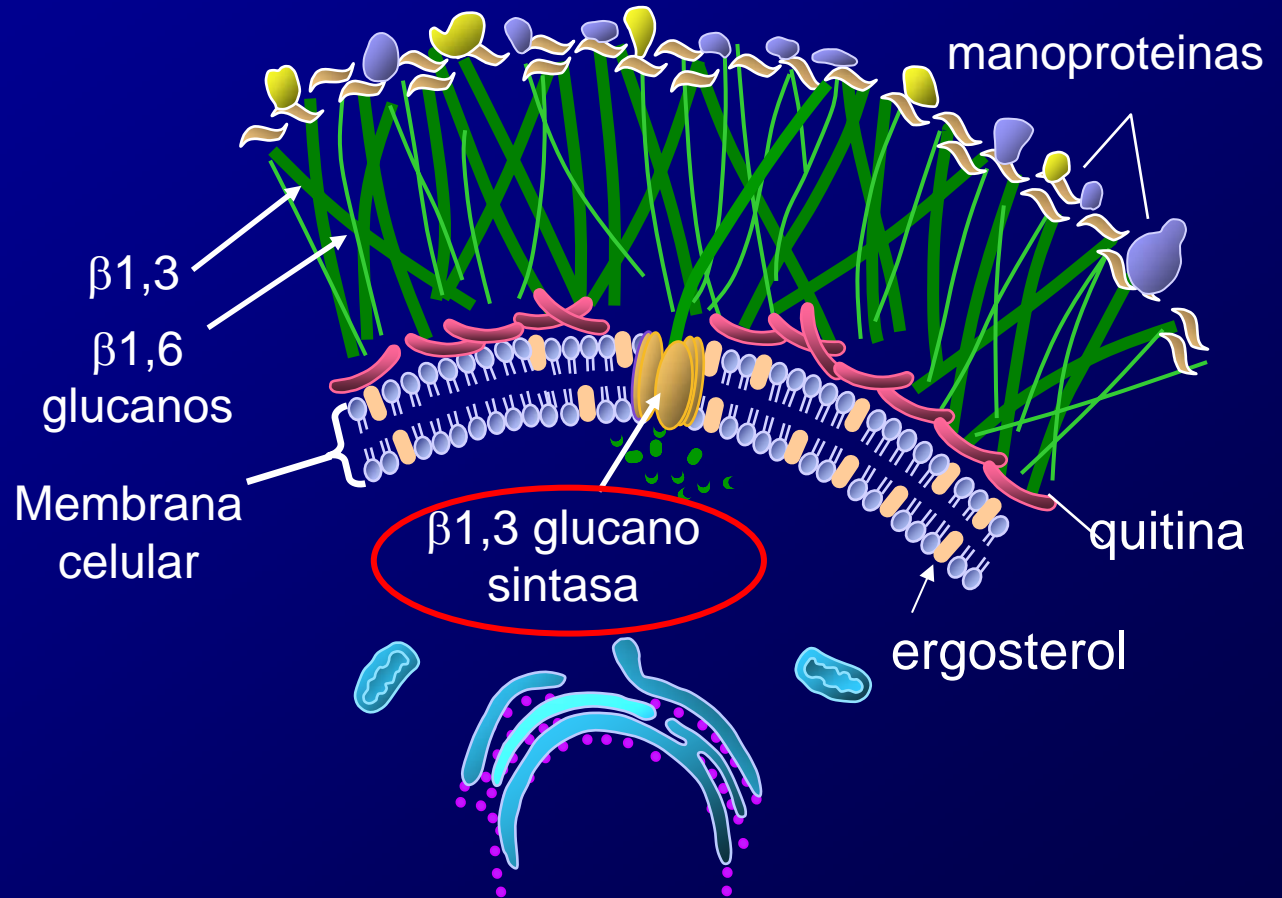
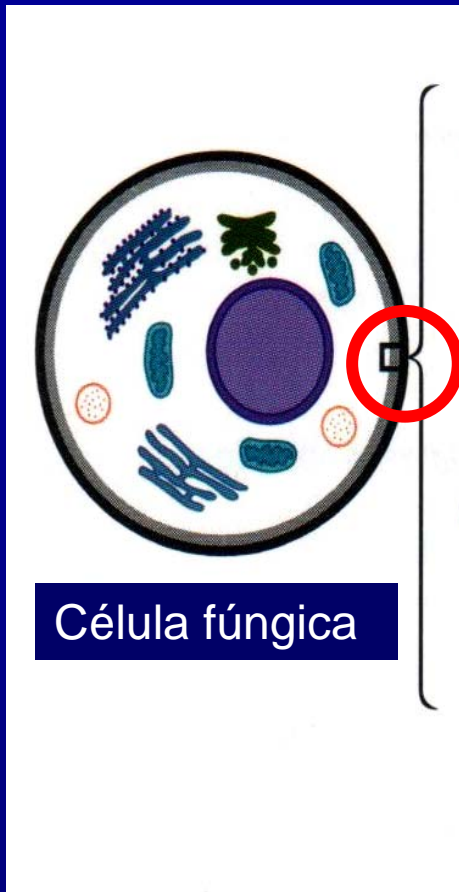
Síntesis DNA/RNA:

- 5-Fluorocitosina

Pared celular:

- **Candinas:**
 - Caspofungina
 - Micafungina
 - Anidulafungina

Pared celular fúngica



Equinocandinas

Mecanismo de acción

- Antifúngicos lipopéptidos que interfieren con la síntesis de la pared celular fúngica inhibiendo la β -(1,3)-D-glucano sintasa (también la (1,6)- β)
- Pérdida del glucano produce una fragilidad osmótica de la pared celular
- Células humanas carecen de β -(1,3) D-glucano: actividad selectiva sobre las células fúngicas
- **Actividad frente al biofilm producido por *Candida*, a diferencia de los azoles**

Equinocandinas

Fármacos aprobados

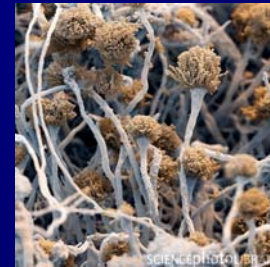
- Caspofungina (*Candidas*®, MSD) (2001)
- Micafungina (*Mycamine*®, Astellas Pharma) (2005)
- Anidulafungina (*Ecalta*®, Pfizer) (2006)

Equinocandinas

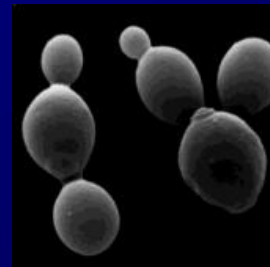
Espectro de Actividad Antifúngica

● Hongos con β -(1,3)-D-Glucano:

● *Aspergillus* spp.



● *Candida* spp.



● No activas sobre zigomicetos ni *Cryptococcus neoformans*

Equinocandinas

Mecanismo de acción

● *CANDIDA*: Efecto fungicida:

- Cambios en la integridad de la pared
- Pérdida de resistencia mecánica

● *ASPERGILLUS*: Efecto fungistático:

- Inhibición de la síntesis de la pared celular
- Reducción del crecimiento

Equinocandinas

Espectro de Actividad Antifúngica

Marcada:

Candida albicans
Candida glabrata
Candida tropicalis
Candida krusei
Candida kefyr
Pneumocystis jiroveci

● CMI <0,5 mg/L, con actividad fungicida y buena actividad in vivo

Menos potente:

Candida parapsilosis
Candida guilliermondii
Candida lusitanae
Aspergillus fumigatus
Aspergillus flavus
Aspergillus terreus

● CMI 0,5-2 mg/L. Sin actividad fungicida frente a *Aspergillus*

Escasa:

Coccidioides immitis
B. dermatididis
Scedosporium spp
Paecilomyces variotii
H. capsulatum

● Actividad detectable, potencialmente terapéutica combinadas con otros AF

Penicillium, *Bipolaris*, *Pseudallescheria*, *Wangiella*: actividad prometedora in vitro

Equinocandinas

Espectro de Actividad Antifúngica

■ *No activos:*

- *Cryptococcus neoformans*
- *Zygomycetos*
- *Trichosporon* sp.
- *Fusarium* sp
- *Scedosporium prolificans*

Distribución de las especies de *Candida* por sensibilidad *in vitro* a equinocandinas

Quindós, Rev Iberoam Micol 2009

Sensibles

Insensibles

Candida albicans

Candida parapsilosis

Candida dubliniensis

Candida glabrata

Candida krusei

Candida quilliermondii

Candida lusitaniae

Candida tropicalis

0,03 0,06 0,125 0,25 0,5 1 2 4 8 16 $\mu\text{g/ml}$

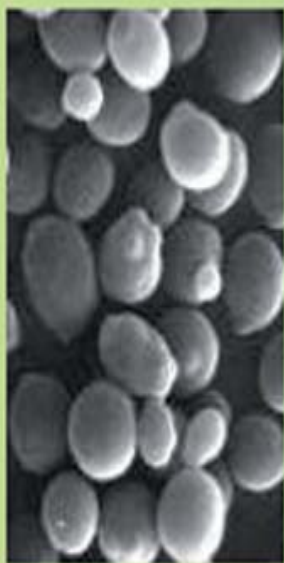


Table I. Echinocandin activity against common *Candida* and *Aspergillus* species^[23,24,42-45]

Organism	Caspofungin	Micafungin	Anidulafungin
<i>Candida</i> species	MIC₅₀, MIC₉₀	MIC₅₀, MIC₉₀	MIC₅₀, MIC₉₀ (range)
<i>C. albicans</i>	0.03, 0.06	0.015, 0.03	0.03, 0.06 (0.03–0.25)
<i>C. glabrata</i>	0.03, 0.06	0.015, 0.015	0.06, 0.12 (0.03–1)
<i>C. tropicalis</i>	0.03, 0.06	0.03, 0.06	0.03, 0.06 (0.06–2)
<i>C. krusei</i>	0.12, 0.25	0.06, 0.12	0.06, 0.06 (0.12–1)
<i>C. parapsilosis</i>	0.25, 1	1, 2	2, 2 (0.12 to >2)
<i>C. guilliermondii</i>	0.5, 1	0.5, 1	1, 2 (1–4)
<i>C. lusitanae</i>	0.25, 0.5	0.06, 0.12	0.5, 0.5 (0.125–2)
<i>C. dubliniensis</i>	–, 0.5	–, 0.03	–, 0.06
<i>Aspergillus</i> species	MEC₉₀^a (range)	MEC₉₀^a (range)	MEC₉₀^a (range)
<i>A. fumigatus</i>	0.12 (0.007–1)	0.03 (0.007–0.25)	0.03 (0.007–0.12)
<i>A. flavus</i>	0.06 (0.007–1)	0.015 (0.007–1)	0.015 (0.007–0.25)
<i>A. terreus</i>	0.03 (0.007–2)	0.015 (0.007–0.25)	0.015 (0.007–0.5)

a MEC₉₀ values and MEC₉₀ range values were from Pfaller et al.^[45] and Antachopoulos et al.^[44]

MEC=minimum effective concentration; **MIC₅₀**=minimum inhibitory concentration at which the growth of 50% of the isolates tested were inhibited; **MIC₉₀**=minimum inhibitory concentration at which 90% of isolates tested were inhibited; – indicates not available.

In vitro resistance profiles of 3 echinocandins and 4 triazoles tested against *Candida* spp., *C. neoformans*, and *A. fumigatus* isolates from the SENTRY Antimicrobial Surveillance Program for 2009

Pfaller, Diagn Microbiol Infect Dis 2011

Organism (no. tested)	Antimicrobial agent	MIC ($\mu\text{g/mL}$) ^a			% Resistant
		Range	50%	90%	
<i>C. albicans</i> (422)	Anidulafungin	≤ 0.001 to 4	0.03	0.06	0.0
	Caspofungin	0.06 to 1	0.25	0.5	0.2
	Micafungin	0.015 to 2	0.03	0.06	0.0
	Fluconazole	≤ 0.5 to 4	≤ 0.5	≤ 0.5	0.0
	Itraconazole	≤ 0.015 to 1	0.03	0.06	0.2
	Posaconazole	≤ 0.06 to 1	≤ 0.06	0.12	0.0
	Voriconazole	≤ 0.06 to 0.25	≤ 0.06	≤ 0.06	0.0
<i>C. glabrata</i> (159)	Anidulafungin	0.004 to 2	0.12	0.12	1.9
	Caspofungin	0.06 to 2	0.25	0.5	2.5
	Micafungin	0.015 to 0.5	0.03	0.06	0.6

In vitro resistance profiles of 3 echinocandins and 4 triazoles tested against *Candida* spp., *C. neoformans*, and *A. fumigatus* isolates from the SENTRY Antimicrobial Surveillance Program for 2009

Pfaller, Diagn Microbiol Infect Dis 2011

		Rango	CMI 50	CMI 90	% Resist.
<i>C. tropicalis</i> (93)	Anidulafungin	0.008 to 1	0.03	0.06	1.1
	Caspofungin	0.06 to 0.5	0.25	0.25	0.0
	Micafungin	0.015 to 0.5	0.06	0.06	1.1
	Fluconazole	≤0.5 to >64	≤0.5	1	3.2
	Itraconazole	0.03 to >2	0.12	0.25	3.2
	Posaconazole	≤0.06 to >8	0.12	0.25	1.1
	Voriconazole	≤0.06 to >8	≤0.06	0.25	1.1
<i>C. parapsilosis</i> (162)	Anidulafungin	0.12 to 4	2	2	0.0
	Caspofungin	0.25 to 4	1	1	0.0
	Micafungin	0.03 to 4	1	2	0.0

<i>C. krusei</i> (16)	Anidulafungin	0.015 to 0.12	0.06	0.12	0.0
	Caspofungin	0.25 to 1	0.5	1	12.5
	Micafungin	0.06 to 0.25	0.12	0.25	0.0
	Itraconazole	0.25 to 2	0.5	1	43.8
	Posaconazole	0.25 to 1	0.5	1	0.0
	Voriconazole	0.25 to 1	0.5	1	0.0
<i>Candida</i> spp. (32) ^c	Anidulafungin	0.015 to 4	0.25	2	NA
	Caspofungin	0.12 to 2	0.5	1	NA
	Micafungin	0.03 to 1	0.25	1	NA
	Fluconazole	≤0.5 to >64	1	4	6.3
	Itraconazole	0.03 to 1	0.25	0.5	9.4
	Posaconazole	≤0.06 to 1	0.12	1	0.0
<i>C. neoformans</i> (31)	Voriconazole	≤0.06 to 2	≤0.06	0.25	0.0
	Fluconazole	1 to 16	4	8	NA
	Itraconazole	≤0.015 to 0.5	0.12	0.25	NA
	Posaconazole	≤0.06 to 0.5	0.25	0.25	NA
	Voriconazole	≤0.06 to 0.25	≤0.06	0.12	NA
	<i>A. fumigatus</i> (40)	Anidulafungin ^d	≤0.001 to 0.015	0.004	0.008
Caspofungin ^d		≤0.008 to 0.25	0.25	0.25	NA
Micafungin ^d		≤0.008 to 0.015	≤0.008	≤0.008	NA
Itraconazole		0.5 to 1	0.5	1	0.0
Posaconazole		0.25 to 0.5	0.25	0.5	0.0
Voriconazole		0.25 to 0.5	0.25	0.5	0.0

Caspofungin: Analysis of MICs and Treatment Outcomes

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2005, p. 3616–3623
0066-4804/05/\$08.00+0 doi:10.1128/AAC.49.9.3616–3623.2005
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Vol. 49, No. 9

Caspofungin Susceptibility Testing of Isolates from Patients with Esophageal Candidiasis or Invasive Candidiasis: Relationship of MIC to Treatment Outcome

Nicholas Kartsonis,* John Killar, Lori Mixson, Chao-Min Hoe, Carole Sable, Kenneth Bartizal, and Mary Motyl

Merck Research Laboratories, West Point, Pennsylvania

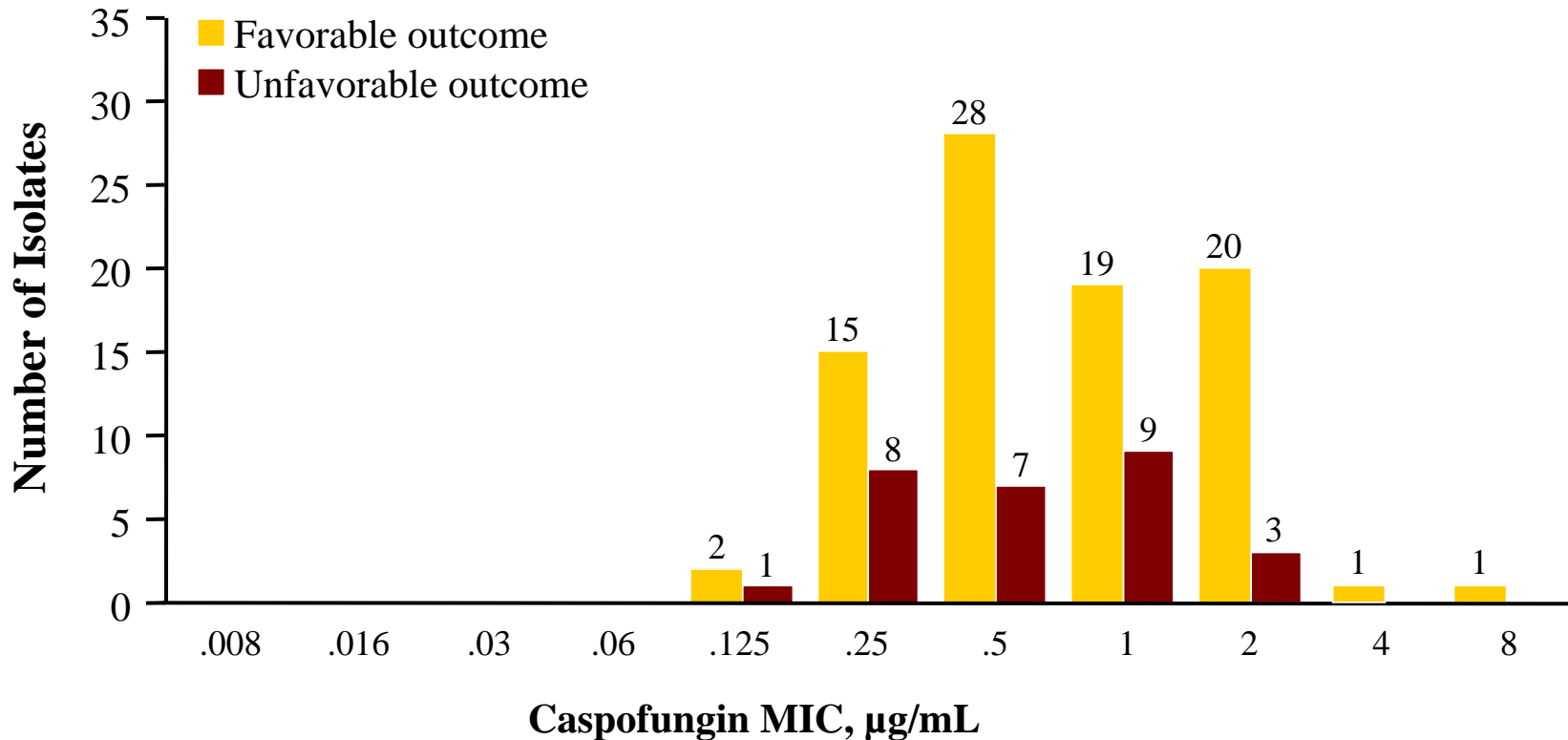
Received 12 April 2005/Returned for modification 16 May 2005/Accepted 28 June 2005

The caspofungin clinical trial database offers an opportunity to assess susceptibility results for *Candida* pathogens obtained from patients with candidiasis and allows for correlations between efficacy outcomes and MICs. *Candida* isolates have been identified from patients enrolled in four studies of esophageal candidiasis and two studies of invasive candidiasis. The MICs of caspofungin for all baseline isolates were measured at a central laboratory using NCCLS criteria (document M-27A); MICs for caspofungin were defined as the lowest concentration inhibiting prominent growth at 24 h. MICs were then compared to clinical and microbiological outcomes across all studies. MICs for caspofungin ranged from 0.008 to 2.0 $\mu\text{g/ml}$ for the majority (~96%) of *Candida* species. MICs were highest (>2 $\mu\text{g/ml}$) for patients with esophageal candidiasis and lowest (<1 $\mu\text{g/ml}$) for patients with invasive candidiasis. Additionally, no correlation was identified between MIC and outcome for specific *Candida* species.

Sólo 3 aislados con CMI>2

"Patients with isolates for which the MICs were highest (>2 $\mu\text{g/ml}$) had better outcomes than patients with isolates for which the MICs were lower (<1 $\mu\text{g/ml}$). Additionally, no correlation between MIC and outcome was identified for specific *Candida* species."

Lack of Correlation of Caspofungin MICs to Clinical Outcome: MITT Population*



*Patients with invasive candidiasis.

MITT = modified intention-to-treat.

Adapted from Kartsonis N et al. *Antimicrob Agents Chemother.* 2005;49:3616–3623.

Actividad in vitro de 5 antifúngicos sistémicos sobre *A. fumigatus*

Antifungal drug	MIC ₅₀ , µg/mL	MIC ₉₀ , µg/mL
Anidulafungin	≤0.03	≤0.03
Amphotericin B	0.5	1
Caspofungin ^a	0.06	0.25
Itraconazole	0.06	0.12
Voriconazole	≤0.03	0.12

^a Expressed as minimal effective concentration (MEC).

Distribución y metabolismo de equinocandinas: tabla comparativa

Eschenauer, Ther Clinics Risk Management 2007

	Caspo	Mica	Anidula
Metabolismo y excreción	Hepático	Hepático	No hepático (degradación química)
Vida ½ (h)	12-14	12-18	25
Interacciones	↓ Ciclosporina, ↑ rifampicina, ↑ EFV, NVP, CBZ, DXM, FNT ↑ tacrolimus	Monitorizar ciclosporina. Vigilar nifedipina	Ninguna significativa ¡Ojo alcohol!

Table IV. Drug interactions with the echinocandins^[11-13,138-142]

Drug	Caspofungin	Micafungin	Anidulafungin
CYP/P-glycoprotein interactions	Poor substrate for CYP Not an inhibitor of CYP Not a substrate/inhibitor of P-glycoprotein	Substrate for CYP3A4 Weak inhibitor CYP3A4 Not a substrate/inhibitor of P-glycoprotein	Not a substrate, inducer, inhibitor of CYP
Tacrolimus	AUC, peak and 12-hour concentrations of tacrolimus are decreased by ~20%	No significant effect on tacrolimus	No significant effect on tacrolimus
Sirolimus	No data	Increases AUC of sirolimus by 12%	No data
Ciclosporin	35% increase in the AUC of caspofungin	Decreases clearance of ciclosporin by 16%	22% increase in AUC of anidulafungin; dose adjustment not required
Rifampicin	Decreases steady-state plasma caspofungin concentrations	No significant effect on micafungin	No significant effect on anidulafungin
Voriconazole	No data	No significant effect on micafungin	No significant effect on anidulafungin
Nefidipine	No data	Increases the AUC and C _{max} of nifedipine by 18% and 43%, respectively	No data

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum concentration; **CYP** = cytochrome P450.

Distribución y metabolismo de equinocandinas: tabla comparativa

Eschenauer, Ther Clinics Risk Management 2007

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Distribución y metabolismo de equinocandinas: tabla comparativa

Eschenauer, Ther Clinics Risk Management 2007

	Caspo	Mica	Anidula
Eliminación	35% heces, 41% orina	40% heces, <15% orina	Heces, 1% orina
Penetración en SNC y ojo	Baja	Baja	<1%
Ajuste dosis en I. renal	No	No	No
Ajuste dosis en I. hepática	Child-Pugh 5-6: No Child-Pugh 7-9: 35 mg Child-Pugh >9: no datos	Child-Pugh 7-9: no necesaria Child-Pugh >9: no datos	No precisa

Equinocandinas

Efectos adversos más frecuentes

- *Fiebre*
- *Diarrea*
- *Aumento enzimas hepáticas y FA*
- *Hipopotasemia*
- *Reacciones infusionales*
- *Flebitis/tromboflebitis*

Safety Profile of the Echinocandins: Contraindications, Warnings, and Precautions

	Caspofungin	Micafungin	Anidulafungin
Contraindications Hypersensitivity to any component of the product	Yes	Yes	Yes
Warnings Serious hypersensitivity	No	Yes	No
Precautions Hepatic effects	+ (Evaluate risk/benefit when using with cyclosporine)	+ (Isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure reported)	+ (Isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure reported)
Renal effects	-	+ (Elevation in blood urea nitrogen and creatinine; isolated cases of significant renal dysfunction or acute renal failure reported)	-
Hematologic effects	-	+ (Acute intravascular hemolysis, hemoglobinuria, isolated cases of significant hemolysis and hemolytic anemia reported)	-
Pregnancy	Category C	Category C	Category C

Equinocandinas: experiencia clínica

Uso clínico comparativo

	Caspofungina	Micafungina	Anidulafungina
Candidemia / CI	Tan eficaz como AMB*	Tan eficaz como AMB-L*	Más eficaz que FLU*
Esofagitis <i>Candida</i>	Tan eficaz como FLU*	Tan eficaz como FLU*	Tan eficaz como FLU*
Aspergilosis	Eficaz en terapia rescate	Eficaz en terapia rescate	ND
Neutropenia febril	Tan eficaz como AMB-L*	ND	ND
Profilaxis en TPH		Más eficaz que FLU*	

* Datos procedentes de Ensayos Clínicos (EC) aleatorizados

ND: sin datos de Ensayos Clínicos; TPH= Trasplante de progenitores hematopoyéticos

Equinocandinas

Indicaciones aprobadas por la FDA y EMEA

	Caspofungina	Micafungina	Anidulafungina
Candidemia	Jul / 2003	Ene / 2008	Feb / 2006
Candidiasis invasora	Jul / 2003	Abril 2008, adultos y niños	Feb / 2006, adultos no neutropénicos
Esofagitis <i>Candida</i>	Sep / 2002	Mar / 2005	Feb / 2006
Neutropenia febril	Feb / 2005		
Rescate AI	Ene / 2001		
Profilaxis CI en TPH		Mar / 2005 adultos y niños	

AI: aspergilosis invasora; CI: candidiasis invasora;
TPH: trasplante progenitores hematopoyéticos

Caspofungina vs micafungina en candidiasis invasora

Table 3. Treatment success for the modified intent-to-treat population.

Pappas, Clin Infec Dis 2007

Variable	Micafungin arms		Caspofungin arm (n = 188)
	100 mg arm (n = 191)	150 mg arm (n = 199)	
Duration of therapy, median days (range) ^a	14 (1.0–61.0)	14 (1.0–56.0)	14 (1.0–43.0)
Treatment success ^b			
Investigators	146 (76.4)	142 (71.4)	136 (72.3)
Data review panel	139 (72.8)	139 (69.8)	133 (70.7)
Clinical success			
Overall	167 (87.4)	174 (87.4)	164 (87.2)
Candidemic ^c			
Complete response	128/163 (78.5)	136/168 (81.0)	123/161(76.4)
Partial response	15/163 (9.2)	12/168 (7.1)	21/161 (13.0)
Noncandidemic			
Complete response	14/28 (50.0)	17/30 (56.7)	15/26 (57.7)
Partial response	10/28 (35.7)	9/30 (30.0)	5/26 (19.2)
Mycological success	169 (88.5)	166 (83.4)	158 (84.0)

^a Number of days from first dose day of blinded study drug to last dose day of either blinded study drug or protocol-defined oral fluconazole, whichever was later.

^b Concordance between the investigators' assessments and the data review panel's assessment was 92.2%.

^c Includes patients without candidemia but with *Candida* species recovered from culture of a normally sterile site.

Table 4 Adult dosing of echinocandins (Krause, Reinhardt, et al 2004; Cancidas PI 2005; Mycamine PI 2005; Reboli et al 2005; Ruhnke et al 2005; Eraxis PI 2006) *Therapeutics and Clinical Risk Management 2007:3(1) 71–97*

Indication	Dosage		
	Caspofungin (Cancidas®)	Micafungin (Mycamine®)	Anidulafungin (Eraxis®)
FDA approval (year)	January 2001	March 2005	February 2006
Empirical therapy for presumed fungal infections in febrile, neutropenic patients	70 mg LD 50 mg daily MD	-	-
Treatment of candidemia and the following <i>Candida</i> infections: intra-abdominal abscesses, peritonitis, and pleural space infections	70 mg LD 50 mg daily MD	100 mg daily MD*	200 mg LD 100 mg daily MD
Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies	70 mg LD 50 mg daily MD	-	-
Treatment of patients with esophageal candidiasis	50 mg daily MD	150 mg daily MD	100 mg LD 50 mg daily MD
Prophylaxis of <i>Candida</i> infections in patients undergoing HSCT	-	50 mg daily MD	-

Note: *dosage used in clinical trial, however, not an FDA-approved dosage or indication

Abbreviations: FDA, Food and Drug Administration; LD, loading dose; MD, maintenance dose; HSCT, hematopoietic stem cell transplantation.

Table 3 Echinocandin-containing combination antifungal therapy (in vitro and animal data) (Johnson et al 2004)

Caspofungin	<i>Candida</i> spp.	In vitro combination with fluconazole yielded generally indifferent results, and showed potential benefit in an animal study.
	<i>Aspergillus</i> spp.	In vitro and animal combination with AmB and triazoles generally synergistic. Antagonism not seen. AmB + caspofungin + flucytosine shown to be synergistic against all tested isolates in vitro (Dannaoui et al 2004). Sulfmethoxazole combination synergistic in 29/31 isolates in vitro (Yekutieli et al 2004).
	Mucormycosis	Combination with AmB showed survival benefit in animal model (Spellberg et al 2005).
Micafungin	<i>Aspergillus</i> spp.	In in vitro and animal models, the combination of AmB and triazole antifungals was generally synergistic, and significantly decreased the EC ₉₀ of voriconazole against <i>A. fumigatus</i> and <i>A. terreus</i> , but not <i>A. flavus</i> (Heyn et al 2005; Lewis and Kontoyiannis 2005).
	<i>Candida</i> spp.	Voriconazole combination indifferent in 97% of isolates, most likely due to already low MICs with micafungin (Heyn et al 2005). Combination with amphotericin B required to eradicate <i>C. glabrata</i> infection in immunosuppressed mice (Olson et al 2005).
	<i>Scedosporium</i> spp. and <i>Fusarium solani</i>	Combination with voriconazole synergistic in 64% of isolates. Antagonism not noted (Heyn et al 2005).
Anidulafungin	<i>Aspergillus</i> spp.	In vitro combination with AmB was antagonistic in 5/26 strains. Combination with itraconazole + voriconazole generally showed synergy (Philip et al 2005).
	<i>Candida</i> spp.	In vitro combination with AmB, itraconazole, ketoconazole, itraconazole, and 5-fluorocytosine generally showed additivity or indifference. Antagonism noted in all strains of <i>C. tropicalis</i> with combination of ketoconazole and anidulafungin (Karlowsky et al 2006).

Gracias