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Controle de Infecção e  
Epidemiologia Hospitalar  
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# Uso racional de antifúngicos EQUINOCANDINAS

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HSPE e ICHC-HC-FMUSP

# Introdução

Aumento da incidência de IFI últimas décadas



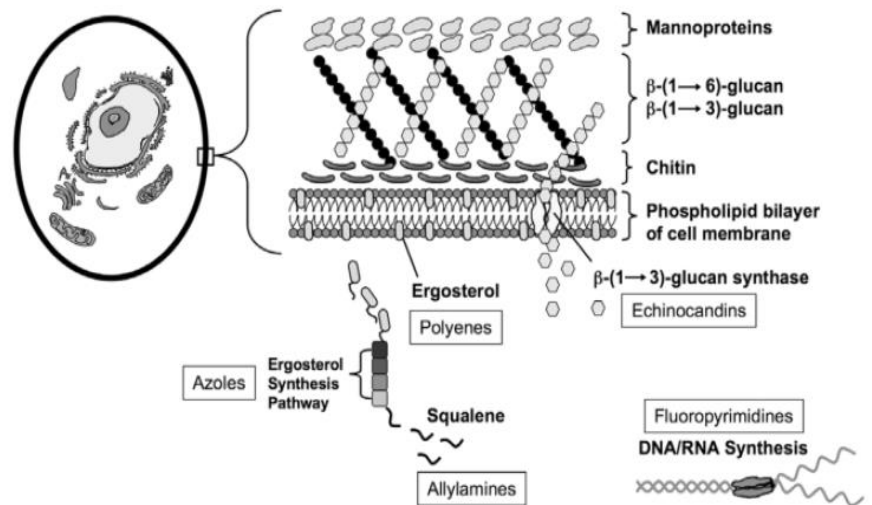
Anfotericina B e azólicos foram as únicas opções terapêuticas durante décadas

Incidência de reações relacionadas a infusão  
e nefrotoxicidade  
Emergência de espécies de *Candida* R  
azólicos

Necessidade de busca por outras opções  
terapêuticas

# Equinocandinas

- Nova classe de antifúngicos
- Inibição da B-1-3 glucana sintetase (parede celular)
- Baixa toxicidade
- Fungicida
- Uso exclusivamente EV

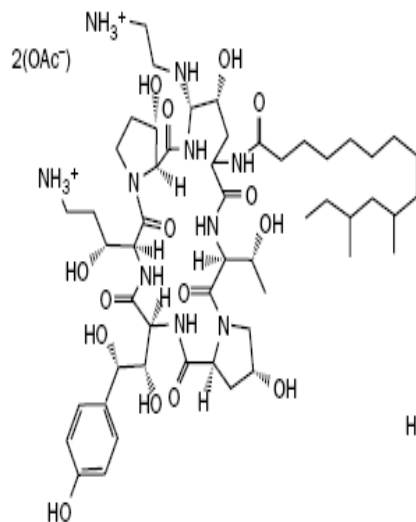


**Figure 1.** Targets of systemic antifungal agents

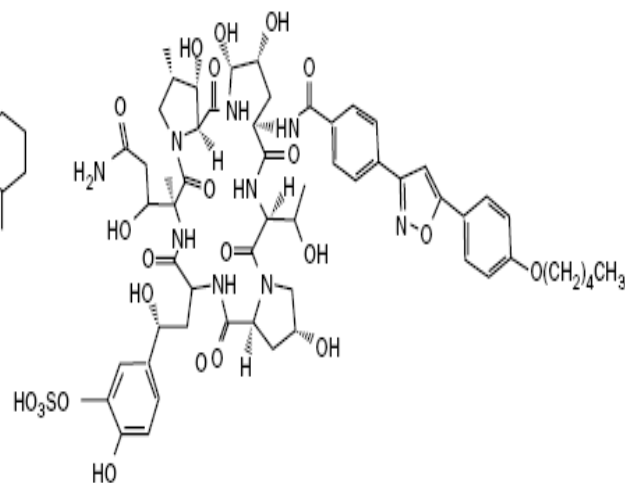
# Equinocandinas

NEW DRUG CLASSES

**Caspofungin**



**Micafungin**



**Anidulafungin**

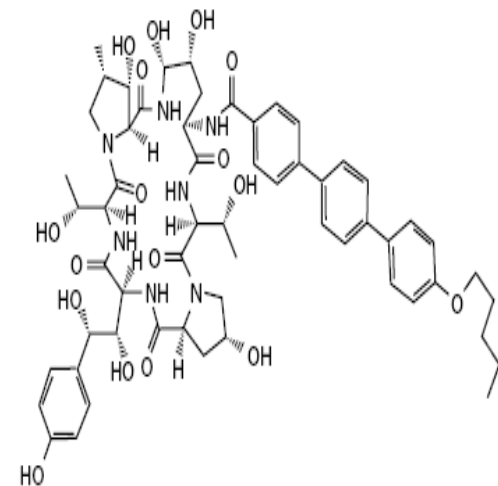


Figure 1: Chemical structures of caspofungin, micafungin, and anidulafungin

# Espectro de ação - Equinocandinas





Highly active	Very active	Some activity
<i>Candida albicans</i>	<i>Candida parapsilosis</i>	<i>Candida guilliermondii</i>
<i>Candida glabrata</i>	<i>Candida guilliermondii</i>	<i>Cryptococcus neoformans</i>
<i>Candida tropicalis</i>	<i>Aspergillus spp</i>	<i>Fusarium spp</i>
<i>Candida krusei</i>	<i>Aspergillus spp</i>	<i>Trichosporon spp</i>
<i>Candida kefyr</i>	<i>Aspergillus spp</i>	<i>Trichosporon spp</i>
<i>Pneumocystis carinii</i>	<i>Aspergillus spp</i>	<i>Trichosporon spp</i>

**MEDICAMENTOS DE PRIMEIRA LINHA  
TRATAMENTO DE CANDIDEMIA E CANDIDÍASE  
INVASIVA**

Highly active implies fungicidal activity and good in-vivo activity, Very active implies low minimum inhibitory concentrations. Some activity implies detectable activity, which might have therapeutic potential for man (in some cases in vitro). No activity implies no intrinsic activity. There are usually some differences between individual isolates within a species and there might be some differences between echinocandins. \*Only active against cyst form, and probably only useful for prophylaxis.

Table 3: Relative activity of the echinocandins

# Porquê ?

RCTs	Eficácia	Mortalidade 	Nefrotoxicidade	Referencia
Caspo x AMB-D	73 X 62%	34 X 30%	4 X 23% 	Mora-Duarte, 2002
Mica x AMB-L	74 x 69%	40 x 40%	2 x 6% 	Kuse, 2007
Mica x Caspo	87 x 87%	35 x 46%	----	Pappas, 2007
Anidula x Fluco	76 x 60% 	26 x 31%	----	Reboli, 2007

# Impact of Treatment Strategy on Outcomes in Patients with Candidemia and Other Forms of Invasive Candidiasis: A Patient-Level Quantitative Review of Randomized Trials

David R. Andes,<sup>1</sup> Nasia Safdar,<sup>1</sup> John W. Baddley,<sup>2</sup> Geoffrey Playford,<sup>6</sup> Annette C. Reboli,<sup>3</sup> John H. Rex,<sup>4</sup> Jack D. Sobel,<sup>5</sup> Peter G. Pappas,<sup>2</sup> and Bart Jan Kullberg<sup>7</sup> for the Mycoses Study Group<sup>a</sup>

**Table 3. Univariate Analysis of the Host, Disease, Organism, and Treatment Factors and Outcome in Patients With Invasive Candidiasis**

Variables	Alive (n = 1313)		Dead (n = 602)		P	Success (n = 1277)		Failure (n = 618)		P
	No.	%	No.	%		No.	%	No.	%	
Therapy					.001 <sup>a</sup>					.004 <sup>a</sup>
Amphotericin B	159	12.1	95	15.8		171	13.4	80	12.9	
Liposomal amphotericin B	146	11.1	72	12.0		143	11.2	75	12.1	
Fluconazole	171	13.0	100	16.6		151	11.8	110	17.8	
Voriconazole	164	12.5	90	15.0		162	12.7	87	14.1	
Anidulafungin	99	7.5	29	4.8		97	7.6	31	5.0	
Caspofungin	186	14.2	63	10.5		175	13.7	72	11.7	
Micafungin	388	30.0	153	25.4		378	29.6	163	26.4	
Polyene	305	23.2	167	27.7	<.001	314	24.6	155	25.1	.81
Triazole	335	25.5	190	31.6	.005	313	24.5	197	31.9	.0007
Echinocandin	673	51.3	245	40.7	<.001	650	50.9	266	43.0	.001



# Guidelines

	Escolha	Nível de Evidencia	Alternativa	Nível Evidencia
Americano (1)	Fluconazol ou Equinocandina	A-1	AMB-D ou AMB-LF ou Voriconazol	A-1
Europeu (2)	Equinocandina	A-1	AMB-L ou Voriconazol	B-1
Brasileiro (3)	Equinocandina	A-1	Fluconazol	B-1

(1) Pappas, P et al. Infectious Diseases Society of America. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009.

(2) Cornely, OA et al. ESCMID Guideline for the Diagnosis and Management of *Candida* Diseases 2012: Non-Neutropenic Adult Patients. Clin Microbiol Inf 2012.

(3) Colombo AL, Guimaraes T, et al. Brazilian guidelines for the management of candidiasis - a joint meeting report of three medical societies. Braz J Infect Dis 2013.



# Considerando....

- Candidemia:

- Infecção grave, *life-threatening* particularmente em imunocomprometidos e críticos
- 4º patógeno causador de ICS geral
- 1,7 – 24 casos/100.000 hab/ano
- > 50% UTI
- Mortalidade de 20-50%
- Aumento tempestivo de candidas
- Aumento de custos diretos/paciente

**PORQUE NÃO UTILIZAR  
EQUINOCANDINAS ???**

- Candidemia causador de ICS geral, 6º em UTI
- Mortalidade de 61-85%
- Aumento de custos diretos/paciente

Neoh CF, Slavin M, et al. Echinocandins in the treatment of candidaemia and invasive candidiasis: clinical and economic perspectives. *Int J Antimicrobiol Agents*, 2014.

Colombo AL, Guimaraes T et al. Prognostic factors and historical trends in the epidemiology of candidemia in critically ill patients: an analysis of five multicenter studies sequentially conducted over a 9-year period.

*Intensive Care Med* 2014

# A resposta é: custo !!!

- Então temos que:
  - Otimizar o uso
  - Reduzir o custo
  - Manter a segurança

# Quais as evidências ?

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April 28, 2011

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## TREATMENT AND PROPHYLAXIS OF INVASIVE CANDIDIASIS WITH ANIDULAFUNGIN, CASPOFUNGIN AND MICAFUNGIN AND ITS IMPACT ON USE AND COSTS - REVIEW OF THE LITERATURE

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# Introdução

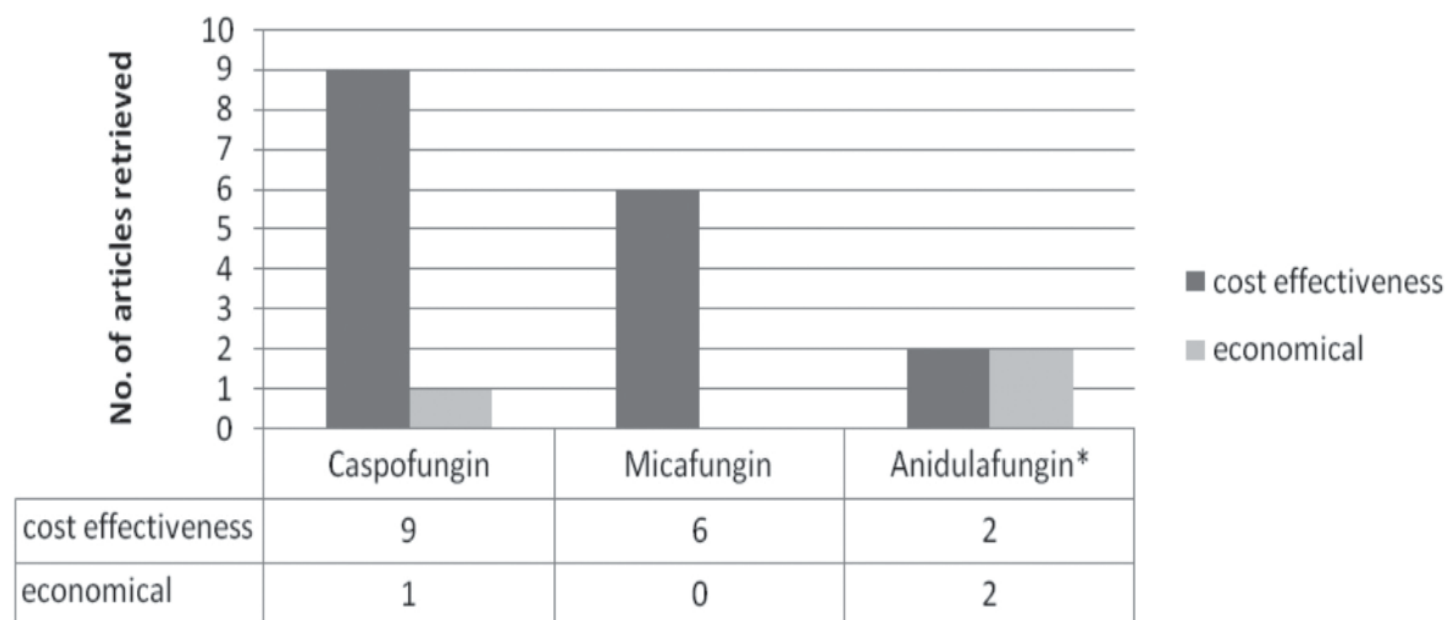
- Custos do paciente com candidemia:
  - 8.252 a 16.595 libras
  - 34.123 a 44.536 dólares
- Para saber se a terapia antifúngica é uma opção economicamente adequada:
  - Direcionador de custos
  - Tempo de hospitalização
  - Custo de aquisição do medicamento

# Métodos

- Revisão da literatura
- Investigar evidências disponíveis de custo-efetividade
- Estratégias antifúngicas de equinocandinas em:
  - Candidíase invasiva comprovada
  - Suspeita de infecção fúngica
  - Profilaxia
- Custos:
  - Duração da terapia
  - Ajuste da terapia após disponibilidade de resultados microbiológicos
  - Custo da aquisição do medicamento
  - Início precoce do tratamento
  - Complicações renais e hepáticas
  - Sucesso terapêutico

# Resultados

## Search findings on "cost effectiveness" and "economical"



*Fig. 1.* Results of the literature search for cost-effectiveness of echinocandins. \* Analyses for anidulafungin as poster presentations, one article in press.

21 artigos

# Resultados

*Table 1.* Summary of potential economic effects of the echinocandins. X = potential reduction of total treatment cost vs. more traditional antifungals.

Parameter/agent	Caspofungin	Micafungin	Anidulafungin
cost-effectiveness in invasive candidiasis/candidemia	X	X	X
cost-effectiveness in suspected infections	X	X	
Lowering the incidence of IRF	X	X	X
cost-effectiveness in prophylaxis		X	

*Table 2.* General aspects of C/IC-therapy. Proven cost-effective strategies in the Management of C/IC.

De-escalation of initial therapy after microbiological differentiation
Regular clinical audits of antifungals utilization and regular updates of treatment algorithms
Appropriate (early and right-dosed) effective antifungal therapy



# Limitações

- N pequeno
- Dados de estudos clínicos
- Anidulafungina = modelos de farmacoeconomia
- Padrões de resistência não foram analisados
- Se incidência de *Candida* R fluconazol > 25 % => equinocandina deve ser considerada com terapia empírica inicial custo-efetiva

# Candidemia in the intensive care unit: analysis of direct treatment costs and clinical outcome in patients treated with echinocandins or fluconazole

S. M. Heimann • O. A. Cornely • H. Wisplinghoff • M. Kochanek • D. Stippel •  
S. A. Padosch • G. Langebartels • H. Reuter • M. Reiner • A. Vierzig • H. Seifert •  
M. J. G. T. Vehreschild • J. Glossmann • B. Franke • J. J. Vehreschild

Table 3 Overview of cost distribution among groups

Cost parameter (€), mean (95% CI)	Group				<i>p</i> -Value*
	Echinocandins, <i>N</i> =41	% of overall direct costs	Fluconazole, <i>N</i> =64	% of overall direct costs	
Directs costs					
ICU treatment	20,338 (12,893–27,883)	53.5	11,932 (8,016–15,849)	53.4	0.110
General ward treatment	7,957 (4,117–11,597)	20.9	4,641 (2,772–6,510)	20.8	0.595
Antifungals	3,775 (2,582–4,968)	9.9	1,758 (983–2,533)	7.8	<b>&lt;0.001</b>
Antibacterials	1,501 (1,072–1,929)	3.9	1,236 (929–1,543)	5.5	0.234
Antivirals	25 (–4–53)	<1.0	32 (3–61)	<1.0	1.000
Diagnostic measures	1,114 (778–1,449)	2.9	664 (515–814)	2.9	<b>0.011</b>
Radiographic findings	913 (615–1,211)	2.4	553 (427–680)	2.4	0.067
Laboratory tests	2,423 (1,618–3,227)	6.3	1,487 (1,119–1,855)	6.6	0.074
Overall costs					
Direct costs	37,995 (26,614–49,376)	100.0	22,305 (16,817–27,793)	100.0	<b>0.012</b>
Costs per day					
Direct costs	1,158 (1,036–1,280)		927 (828–1,026)		<b>0.001</b>

CI confidence interval; ICU intensive care unit

\*Non-parametric Mann–Whitney *U*-test for independent groups

# Anidulafungina x Fluconazol em candidemia

Anidula (127) versus Fluco (118)

Anidula (200 mg → 100 mg IV/d)

Versus

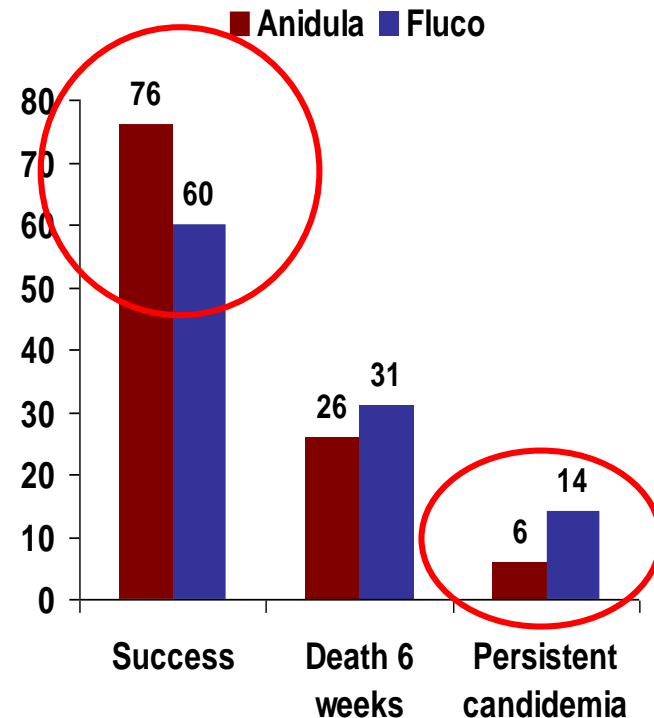
fluco (400 mg/d IV) ≥10d → fluco VO,

Se paciente estável

**Exclusão:** Ins hepática e *C Krusei*

APACHE II score:

15 (Anidula) x 14,4 (Fluco)



**p=0.01**

**p=0.03**

*Reboli et al. NEJM 2007; 356:2472-82*

# Echinocandins in the treatment of candidaemia and invasive candidiasis: clinical and economic perspectives

Chin Fen Neoh<sup>a,b</sup>, Monica Slavin<sup>c</sup>, Sharon C.-A. Chen<sup>d</sup>, Kay Stewart<sup>b</sup>, David C.M. Kong<sup>b,\*</sup>

**Table 2**

Economic studies for targeted treatment of candidaemia and invasive candidiasis (n=16).

Author (year, country)	Type of analysis (study design)	Year of costing, currency	Perspective (time frame)	Comparisons	Outcome measure(s)	Economic findings	Conclusion
Dranitsaris et al. [77] (1998, Canada)	Cost analysis (chart review)	1997, CAN\$	Hospital (6 months)	CAMB vs. fluconazole	Cost/patient	CAN\$2370 (CAMB) vs. CAN\$3578 (fluconazole) (P=0.001)	CAMB is cost saving
Wingard et al. [81] (2005, USA)	Cost analysis (hypothetical cohort)	2003, US\$	Hospital (1 week to a few months)	CAMB vs. caspofungin	Cost/patient	US\$6349.37 (CAMB) vs. US\$5590.77 (caspofungin)	Caspofungin is cost saving
Rotstein et al. [79] (2008, Canada)	Cost effectiveness (decision analytical model)	2005, CAN\$	Hospital (14 weeks)	CAMB vs. voriconazole	(i) Cost/patient; (ii) Incremental cost/survivor; (iii) Incremental cost/toxicity avoided	(i) CAN\$69,368 (CAMB) vs. CAN\$70,489 (voriconazole); (ii) CAN\$17,739/survivor; (iii) CAN\$9298/toxicity avoided	Voriconazole is cost effective
Earnshaw et al. [71] (2007, USA) <sup>a</sup>	Cost effectiveness (decision analytical model)	US\$ <sup>b</sup>	Hospital (unknown)	Anidulafungin vs. fluconazole	(i) Cost/patient; (ii) Incremental cost/treatment success	(i) US\$73,000 (anidulafungin) vs. US\$81,000 (fluconazole) (ii) Value not reported	Anidulafungin is cost effective
Reboli et al. [72] (2009, USA) <sup>a</sup>	Cost analysis (chart review)	US\$ <sup>b</sup>	Hospital (13 weeks)	Anidulafungin vs. fluconazole	(i) Cost/patient (adjudication); (ii) Cost/patient (regression)	(i) US\$44,781 (anidulafungin) vs. US\$42,558 (fluconazole) (P=0.70); (ii) US\$47,658 (anidulafungin) vs. US\$44,977 (fluconazole) (P=0.66)	Insignificant cost difference between both comparators
Grau et al. [73] (2009, Spain) <sup>a</sup>	Cost effectiveness (decision analytical model)	2007, €	Hospital (unknown)	Anidulafungin vs. fluconazole	(i) Cost/patient; (ii) Incremental cost/treatment success	(i) €37,240 (anidulafungin) vs. €37,327 (fluconazole); (ii) Value not reported	Anidulafungin is cost effective
Reboli et al. [82] (2011, USA)	Cost analysis (chart review)	2008, US\$	Hospital (13 weeks)	Anidulafungin vs. fluconazole	(i) Cost/patient (whole cohort); (ii) Cost/patient (ICU cohort); (iii) Adjusted incremental cost/survivor	(i) US\$58,555 (anidulafungin) vs. US\$55,875 (fluconazole) (P=0.73); (ii) US\$80,594 (anidulafungin) vs. US\$95,631 (fluconazole) (P=0.38); (iii) US\$231/survived patient (P=0.98)	Insignificant cost differences between both comparators in whole cohort and ICU cohort
Neoh et al. [83] (2011, Australia)	Cost effectiveness (decision analytical model)	2010, AU\$	Hospital (8 weeks)	Anidulafungin vs. fluconazole	(i) Cost/patient; (ii) Incremental cost/LY saved	(i) AU\$74,587 (anidulafungin) vs. AU\$60,945 (fluconazole); (ii) AU\$22,003/LY saved	Anidulafungin is cost effective
Cornely et al. [78] (2008, Germany)	Cost effectiveness (decision analytical model)	2006, €	Hospital (14–20 weeks)	Micafungin vs. LAMB	(i) Cost/patient; (ii) Cost/treatment success	(i) €43,243 (micafungin) vs. €49,216 (LAMB); (ii) €81,779 (micafungin) vs. €100,280 (LAMB)	Micafungin is more cost effective than LAMB
Park et al. [74] (2008, UK) <sup>a</sup>	Cost effectiveness (decision analytical model)	£ <sup>b</sup>	Hospital (14–20 weeks)	Micafungin vs. LAMB	(i) Cost/patient; (ii) Cost/treatment success	(i) £26,838 (micafungin) vs. £29,549 (LAMB); (ii) £50,755 (micafungin) vs. £60,197 (LAMB)	Micafungin is more cost effective than LAMB
Viale et al. [75] (2008, Italy) <sup>a</sup>	Cost effectiveness (decision analytical model)	€ <sup>b</sup>	Hospital (14–20 weeks)	Micafungin vs. LAMB	(i) Cost/patient; (ii) Cost/treatment success	(i) €28,668 (micafungin) vs. €40,760 (LAMB); (ii) €54,215 (micafungin) vs. €83,035 (LAMB)	Micafungin is more cost effective than LAMB

# Conclusão

- Expansão do armamentário antifúngicos
  - Tratamento de candidemia e candidíase invasiva
- Equinocandinas
  - 1ª linha
  - Eficácia clínica
  - Segurança
  - **Alto preço**
- Baseado em dados da literatura
  - Tratamento com equinocandina é “cost-effective” or “cost-saving” comparado com poliênicos ou azólicos (devido aos efeitos colaterais)
- Estudos de farmacoeconomia existem mas são limitados e existem variações nos desenhos e na qualidade da metodologia empregada

# Equinocandinas – Indicações de uso

## Dirigido

- Candidemia em pacientes com isolamento de espécies de *Candida* resistentes ao fluconazol (*C. krusei* e *C. glabrata*)

## Empírico

- Infecções suspeitas de candidemia em pacientes com uso prévio de azólicos E/OU fatores de risco para disfunção renal

# Custos

- Caspofungina
  - Frasco de 50 mg R\$ 600,43
  - Frasco de 70 mg R\$ 789,00
- Anidulafungina
  - Frasco de 100 mg R\$ 376,84 = hospital público R\$ 293,00
  - Frasco de 100 mg genérico R\$ 196,00 = hospital público R\$ 96,55
- Micafungina
  - Frasco de 100 mg R\$ 197,00
  - Frasco de 50 mg R\$ 106,00



# Como compramos

- ANIDULAFUNGINA 100MG, PÓ LIOFILIZADO PARA SOLUÇÃO INJETÁVEL INTRAVENOSA, AMPOLA OU FRASCO
- ACETATO DE CASHEIRIN, PÓ LIOFILIZADO PARA SOLUÇÃO INJETÁVEL INTRAVENOSA, AMPOLA OU FRASCO
- MICAFUNGINA 100MG, PÓ LIOFILIZADO PARA SOLUÇÃO INJETÁVEL INTRAVENOSA, FRASCO-AMPOLA
- VÍDEO DEBATE - ANEXO II. PROPOSTA DE EQUIVALÊNCIA 1:1:1

**E GANHA A MAIS BARATA !!!**

# Controle de ATM

- ATM de uso restrito => CCIH
- **Qualidade assistencial**
- Desenvolvimento de resistência
- **Custos**

## Resistance to echinocandins comes at a cost

### The impact of *FKS1* hotspot mutations on *Candida albicans* fitness and virulence

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# Resistência

Mutação FKS 1 confere resistência a equinocandina

Thus, restricting echinocandin use should allow susceptible strains to replace less fit *fks1* mutants, limiting the potential of echinocandin-resistant strains to spread within hospitals and the community (Andersson et al., Nat Rev Microbiol 2010).

# OBRIGADA

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INSCREVA-SE NO:

# INFECTO 2015

Gramado - 26 a 29 de agosto

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Realização:

Gerenciamento:

SBI - Sociedade Brasileira de Infectologia - 1980

SRGI - Sociedade Rio-Grandense de Infectologia

CCM Worldwide Medical Congresses

The poster features a central graphic of a stylized white figure with a circular head, surrounded by a ring of colorful dots. To the right, there are three small images: a night view of a building with a clock tower, an interior view of a room with a fireplace and chandelier, and a silhouette of a building against a sunset sky.