Εχινοκανδίνες

Νικόλαος Β. Σύψας, MD, FIDSA
Παθολόγος – Λοιμωξιολόγος
Καθηγητής
Ιατρική Σχολή ΕΚΠΑ
ΓΝΑ « Λαϊκό»

Περίγραμμα ομιλίας

- Ιστορικό ανακάλυψης των κανδινών
- Τρόπος δράσης
- Δραστικότητα έναντι των μυκήτων
- Αντοχή
- Δράση στο βιοφίλμ
- Φαρμακοκινητική / Φαρμακοδυναμική
- Κλινική πράξη
- Συμπεράσματα

Ανακάλυψη

- **Η ανάπτυξη φαρμάκων ικανών να αναστέλλουν τη σύνθεση της γλυκάνης, που είναι απαραίτητο συστατικό του κυτταρικού τοιχώματος των μυκήτων, αποτέλεσε ένα ορόσημο στην αντιμυκητιακή θεραπεία.**

- **Φυσικά προϊόντα**

Ανακάλυψη

Εχινοκανδίνη	Προϊόν ζύμωσης	Μύκητας
Καστοφουγκίνη (1985)	pneumocandin B_0	*Glarea lozoyensis*
Μικαφουγκίνη	hexapeptide FR901370	*Coleophoma empedra*
Ανιντουλαφουγκίνη	echinocandin B_0	*Aspergillus nidulans*

Ο μύκητας *Glarea lozoyensis* απομονώθηκε από τα νερά του ποταμού Lozoya κοντά στη Μαδρίτη

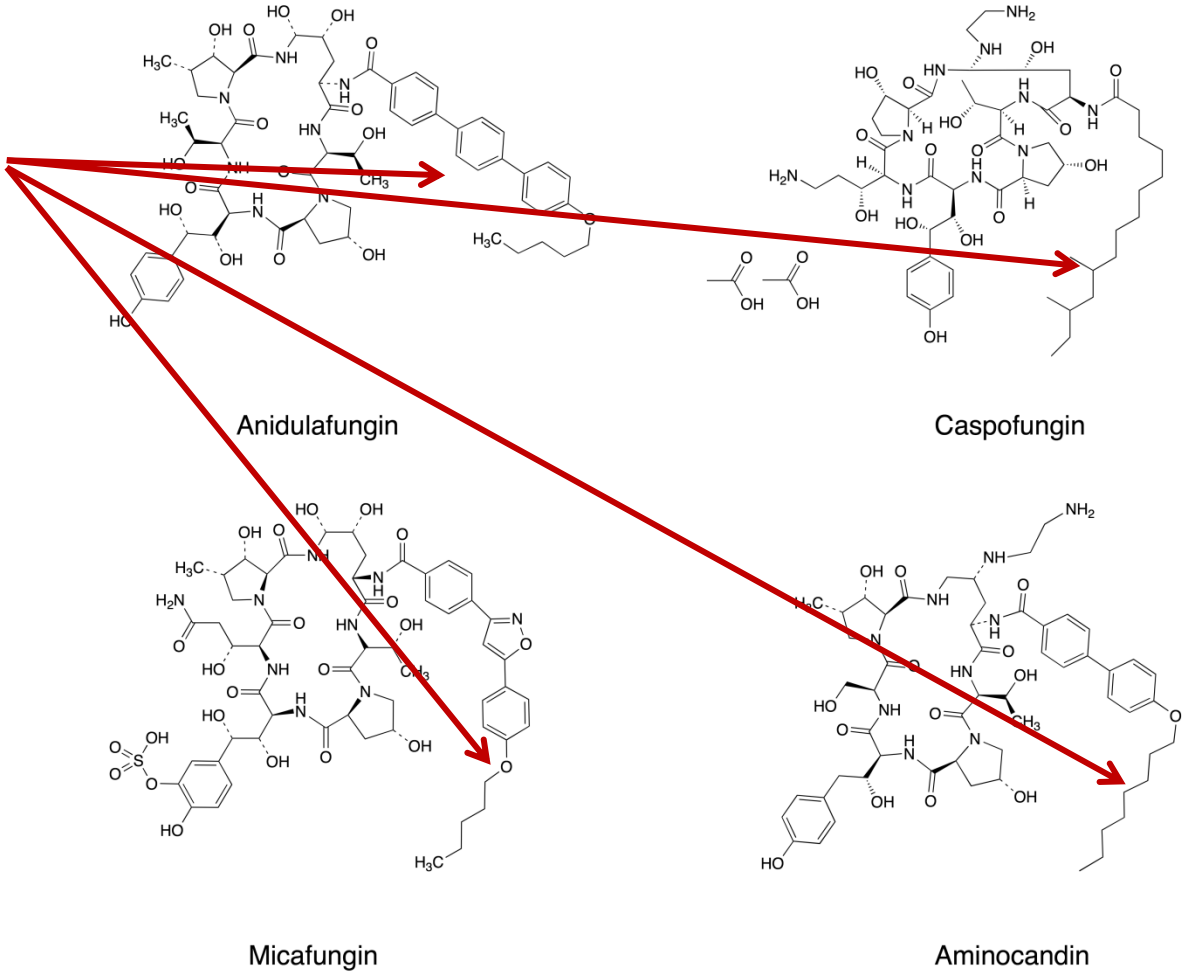
Ανακάλυψη

- **The first echinocandin**
  - **cilofungin**
- **Toxicity associated with a polyethylene glycol vehicle required to solubilize the drug for an intravenous administration**
- **The current group of echinocandins are semi-synthetic analogues**
  - **caspofungin**
  - **micafungin**
  - **anidulafungin**

Debono and Gordee, 1994; Hector, 1993.

Χημική Δομή

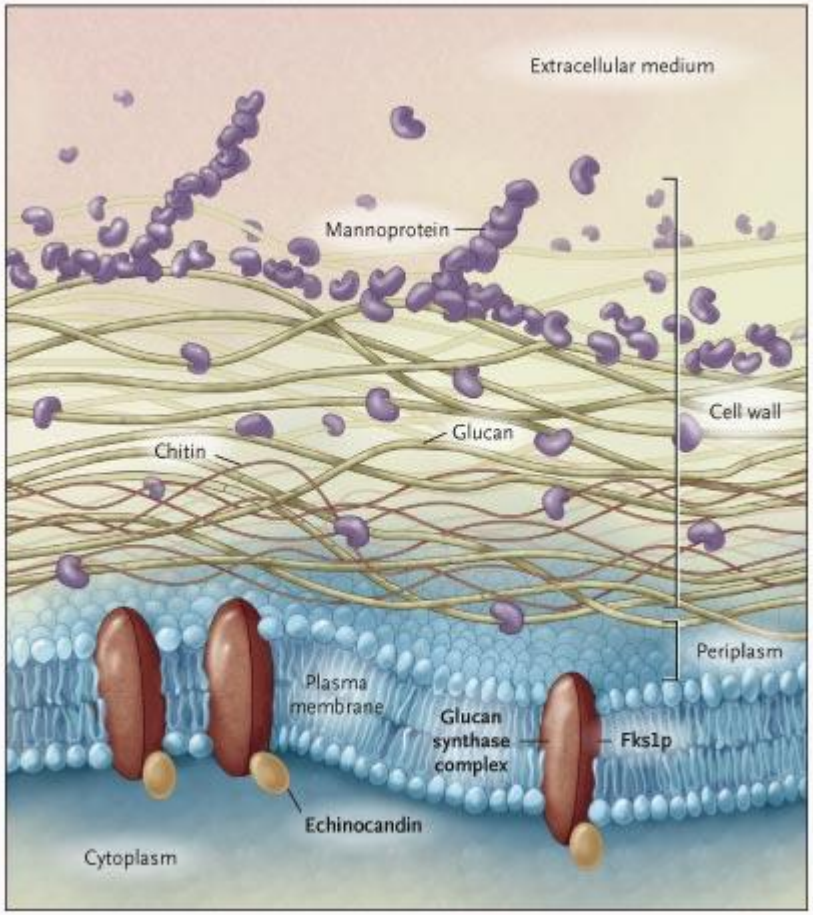
- Κυκλικά εξαπεπτίδια
- N-linked acyl lipid πλευρικές αλυσίδες
- επιτρέπουν την προσκόλληση του φαρμάκου στα φωσφολιπίδια της κυτταρικής μεμβράνης των μυκήτων

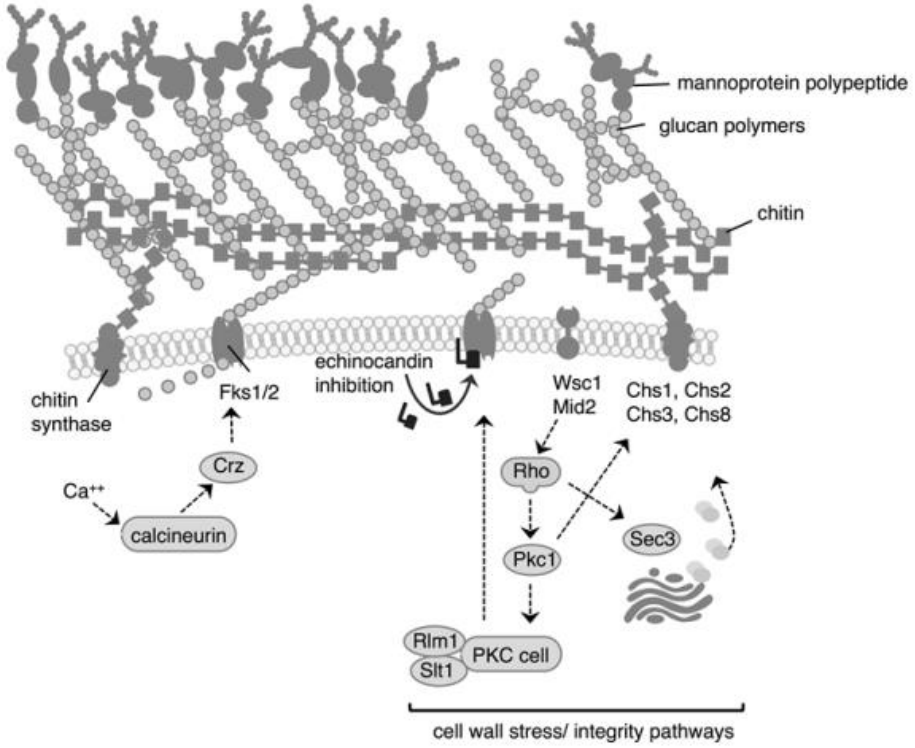


Τρόπος Δράσης

Εχινοκανδίνες

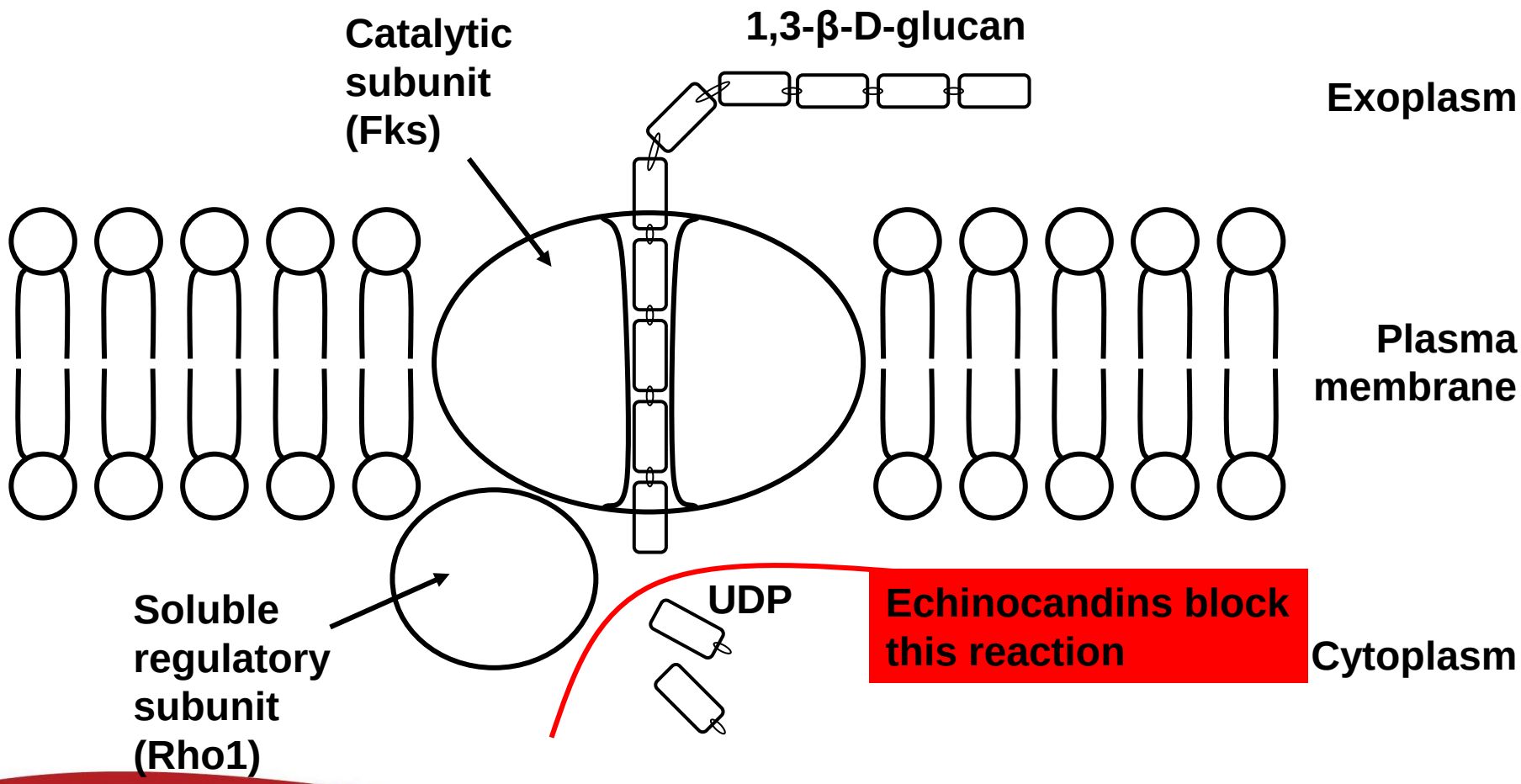
Αναστολή της συνθετάσης της γλυκάνης Ανοσοτροποποιητική Δράση





Bennett J. N Engl J Med 2006;355:1154-1159

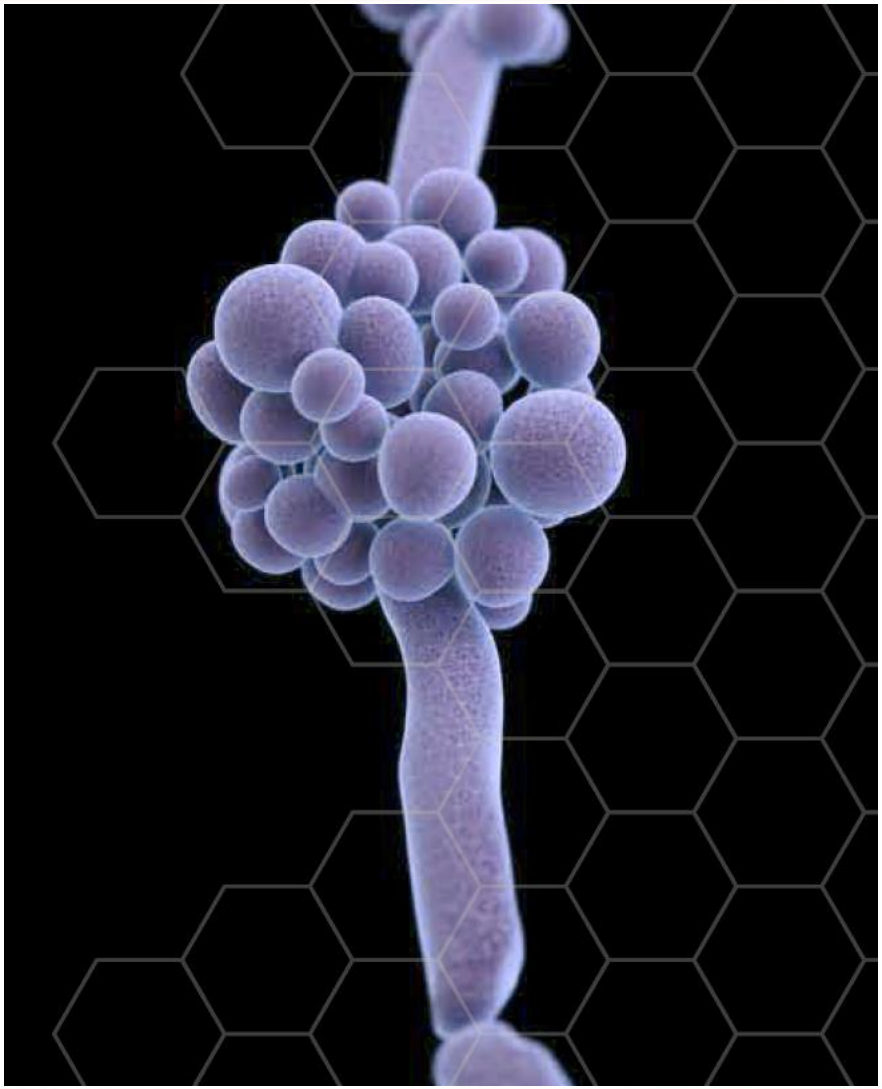
Structure of the 1,3-β-D-glucan synthase enzyme, revealing the site of action of micafungin



UDP = uridine diphosphate

Ζυμομύκητες (Κάντιντα)

- Οι γλυκάνες αποτελούν το 30-60% της μάζας του τοιχώματος
- Επομένως, η αναστολή της β-1,3-D-glucan συνθετάσης είναι θανατηφόρος για την κάντιντα, γιατί το κυτταρικό τοίχωμα χωρίς γλυκάνη δεν αντέχει στην αυξημένη ωσμωτική πίεση κατά την κυτταρική ανάπτυξη.

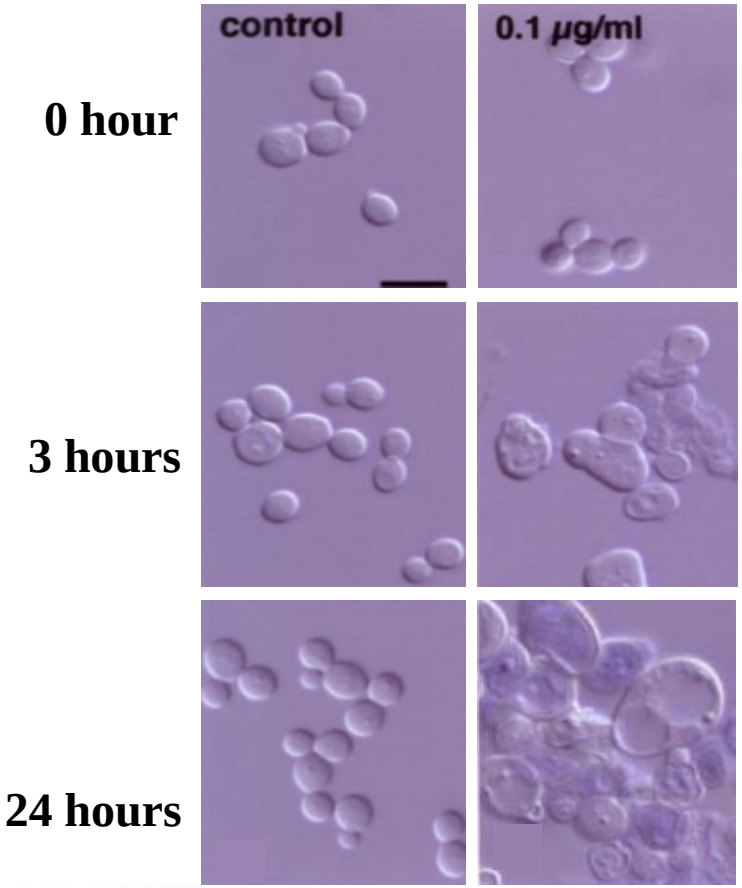


Τρόπος Δράσης

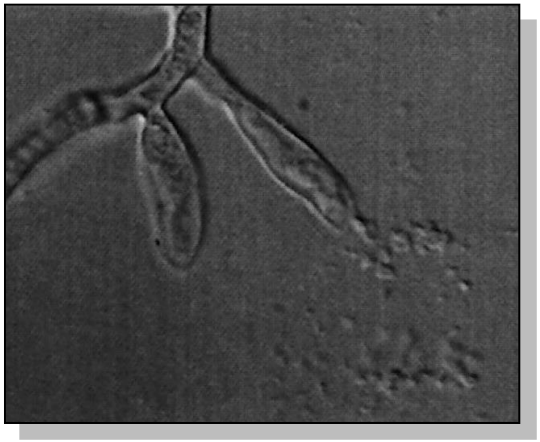
- **Νηματοειδείς μύκητες (Aspergillus fumigatus)**
  - **Η μεγάλη ποσότητα της γλυκάνης βρίσκεται στις κορυφές της υφής και στα σημεία των διακλαδώσεων.**
  - **Επομένως, η λύση αφορά μόνο αυτά τα σημεία και προκύπτουν δυσμορφικές, οιδηματώδης υφές που διατηρούν όμως εν ζωή τα υπόλοιπα τμήματά τους.**

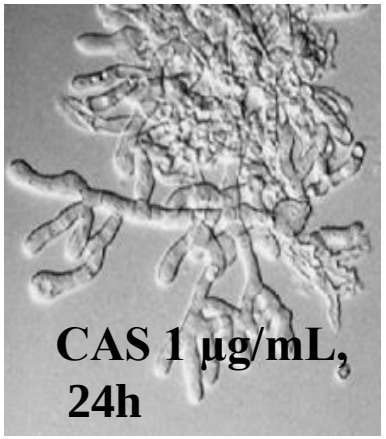
Candida Vs. Aspergillus Species
Differences In Patterns of Echinocandin Killing

C. albicans



A. fumigatus 293



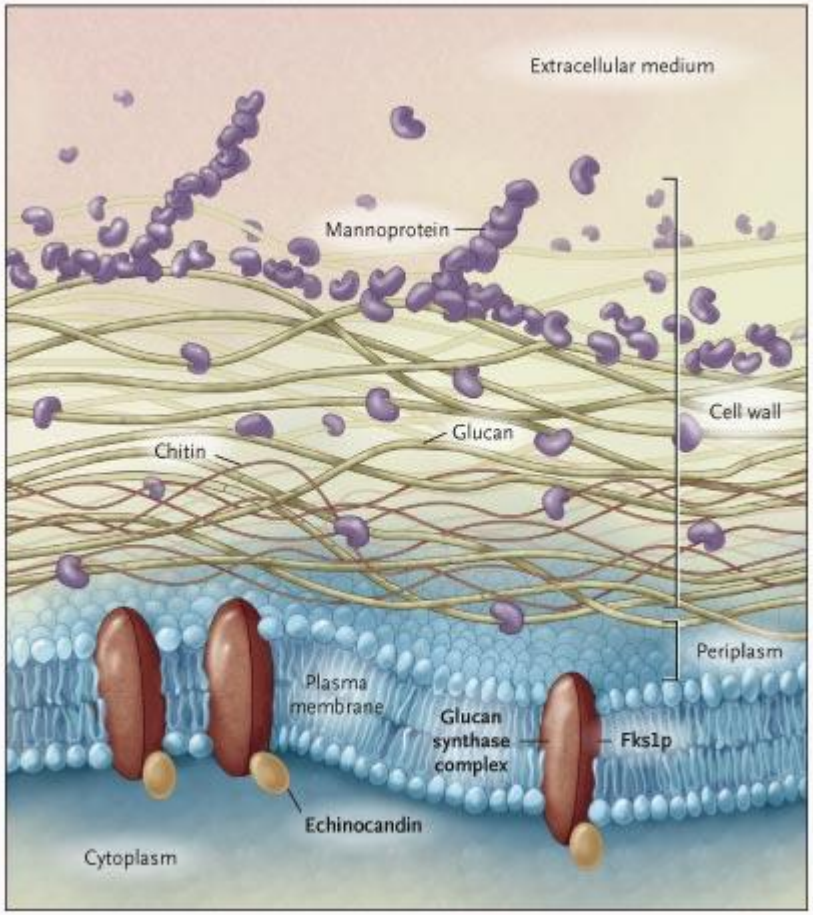


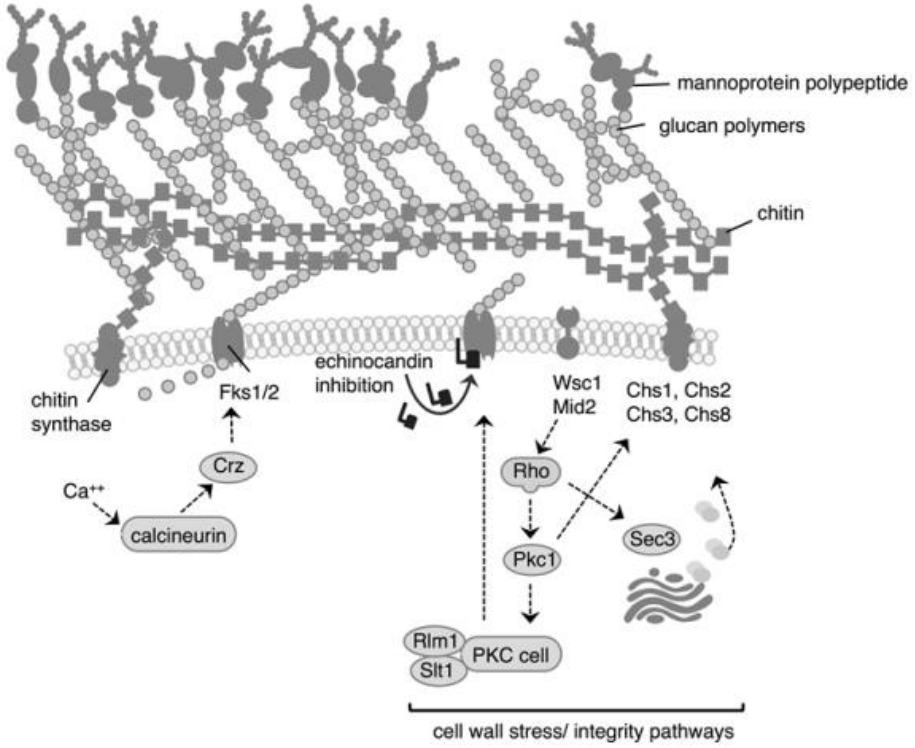
Nishiyama et al. J Electron Microscopy 2005;51:247-255
Bowman et al. *Antimicrob Agent Chemother* 2002;46:3001-12

Τρόπος Δράσης

- Echinocandins may possess an immunomodulatory mechanism of antifungal activity
- Under normal conditions, β-glucan epitopes are masked by cell constituents such as mannoproteins, rendering them less immunogenic to mammalian cells
  - Wheeler and Fink, 2006
- Exposure of *C. albicans* to sub-lethal echinocandin concentrations results in the “unmasking” of immunogenic β-glucan epitopes in vitro and in vivo enhancing host inflammatory responses against these fungi.

Αναστολή της συνθετάσης της γλυκάνης Ανοσοτροποποιητική Δράση





Bennett J. N Engl J Med 2006;355:1154-1159

ΔΡΑΣΤΙΚΟΤΗΤΑ ΕΝΑΝΤΙ ΤΩΝ ΜΥΚΗΤΩΝ

ΕΧΙΝΟΚΑΝΔΙΝΕΣ

Ζυμομύκητες

	Aminocandin		**Anidulafungin**		**Caspofungin**		**Micafungin**	
Fungi	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC_{50} (mg/L)	MIC_{90} mg/L	MIC_{50} (mg/L	MIC_{90} mg/L	MIC_{50} mg/L	MIC_{90} mg/L
C. albicans	0.25	0.25	0.03	0.06	0.03	0.06	0.015	0.03
C. parapsilosis	1	2	0.25	1	0.25	1	1	2
C. glabrata	0.25	0.25	0.06	0.12	0.03	0.06	0.015	0.015
C. tropicalis	0.25	1	0.03	0.06	0.03	0.06	0.03	0.06
C. krusei	0.12	0.5	0.06	0.06	0.12	0.25	0.06	0.12
C. guillermondii	0.5	1	1	2	0.5	1	0.5	1
C. lusitaniae	-	-	0.5	0.5	0.25	0.5	0.12	0.25
C. kefyr	-	-	0.06	0.12	0.015	0.015	0.06	0.06
C. famata	-	-	1	2	0.25	1	0.5	1
C. neoformans	-	-	>16	>16	>16	>16	>16	>16

Pfaller et al., 2008

Ενδημικοί μύκητες

	Aminocandin		Anidulafungin		Caspofungin		Micafungin	
Fungi	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC_{50} (mg/L)	MIC_{90} mg/L	MIC_{50} (mg/L	MIC_{90} mg/L	MIC_{50} mg/L	MIC_{90} mg/L
	MIC range (mg/L)		MIC range (mg/L)		MIC range (mg/L)		MIC range (mg/L)	
H. capsulatum	-		1-8		0.5-32		64	
B. dermatitidis	-		0.5-8		0.5-8		>64	
C. immitis	-		>64		>64		>64	

Kohler et al., 2000
Nakai et al., 2003
Tawara et al., 2000

Υφομύκητες

	Aminocandin		Anidulafungin		Caspofungin		Micafungin	
Fungi	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC_{50} (mg/L)	MIC_{90} mg/L	MIC_{50} (mg/L	MIC_{90} mg/L	MIC_{50} mg/L	MIC_{90} mg/L
A. fumigatus	0.12-0.5		0.008-0.25		0.06-0.12		0.007-0.03	
A. terreus	-		0.03		0.12-2		0.004-0.007	
A. flavus	-		0.03-0.125		0.03-0.12		0.003-0.04	
A. niger	-		0.03-0.125		0.12-2		0.007-0.015	
F. solani	128-256		>16		>8		>8	
F. oxysporum	128-256		>16		>8		>8	
Mucorales	4-16		>16		>8		>8	
Absidia	4-16		>16		>8		>8	
Rhizopus	4-16		>16		>8		>8	
Scedosporium	4-8		>16		>8		>8	

Pfaller et al., 2008

Ελληνική εμπειρία

- ***Εχινοκανδίνες***
  - ***Η συνολική* MIC90 για τα 6 συχνότερα στελέχη *Candida* ήταν**
    - **0.03 g/ml - 0.5 g/ml**
- **Συνολικά, η MIC90 των εχινοκανδινών για την *C. parapsilosis ήταν* 2 g/ml**
- ***Συγκριτικά***
  - ***C. albicans (MIC range*, 0.06 to 0.25 g/ml)**
  - ***C. glabrata (MIC range, 0.12 to 1 g/ml)***
  - ***C. tropicalis (MIC range, 0.12 to 0.25 g/ml)***

Dimopoulos G, Velegraki A, Falagas ME. A 10-year survey of antifungal susceptibility of candidemia isolates from intensive care unit patients in Greece.
Antimicrob Agents Chemother. 2009;53:1242-4.

Αντοχή

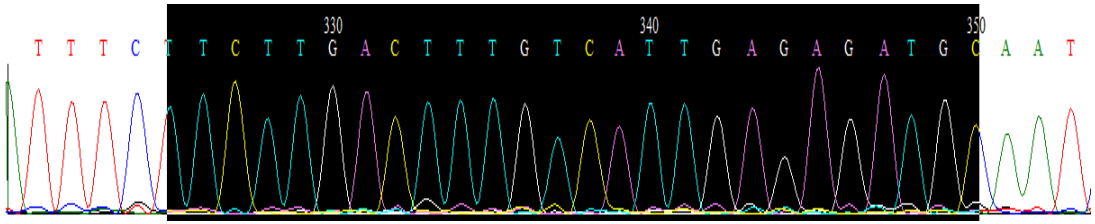
Εχινοκανδίνες

FKS1 sequencing of *Candida parapsilosis*

C. parapsilosis

- All strains presented the expected proline to alanine natural occurring mutation on the hot spot one region of the FKS1 gene
- No mutations on the hot spot one region of the FKS2 gene

Species	Strain ID	FKS1 HS1	
C. parapsilosis		TTCTTGACTTTGTCATTGAGAGATGCT	FLTLSLRD**A**

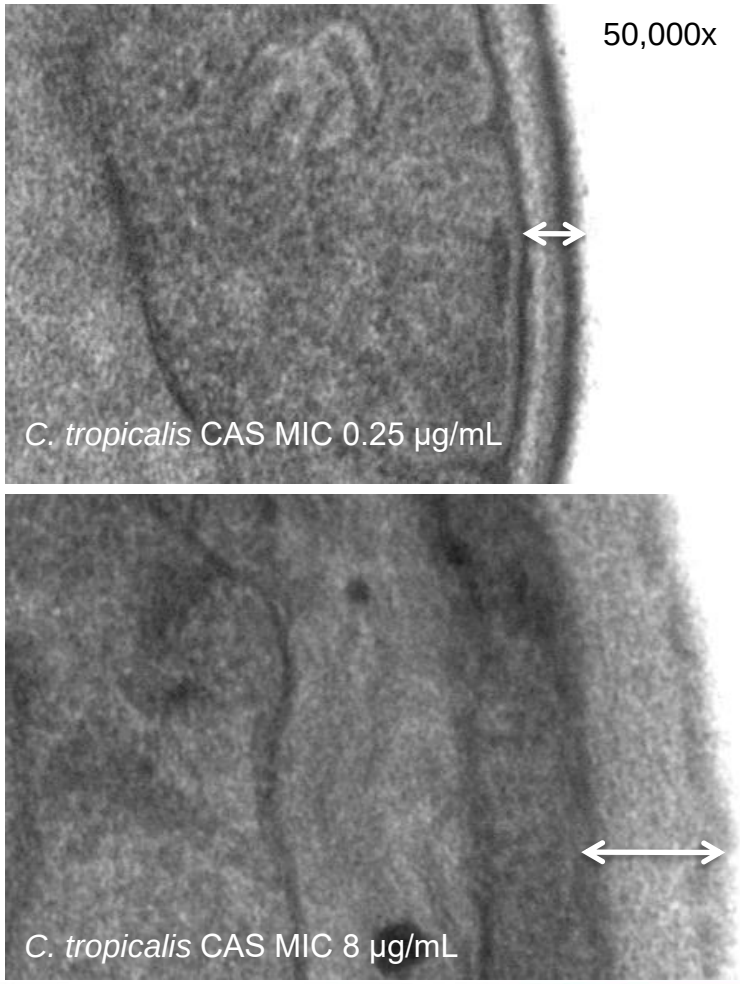


Gamaletsou MN, et al. ESCMID 2013, Berlin

Mechanisms of Resistance: Echinocandins

- **Point mutations in *FKS1*> FKS2 gene**
- ***FKS1* mutants require higher doses for efficacy in animals**
- **Decreased sensitivity of enzyme complex *in vitro***
- ***FKS1* mutants exhibit elevated MICs (4-8 *µ*g/mL) for all 3 echinocandins**

Cell wall remodeling with *FKS1* mutations



Park et al. *Antimicrob Agents Chemother*. 2005;49:3264-3273.
Perlin. *Drug Resist Updat*. 2007;10:121-130.

Example of acquired echinocandin resistance in *C.albicans* isolates recovered from a single patient

				Glucan synthesis	Mouse Model (Burden)
Isolate	Species	Fks1 Change	MIC (mg/L)	IC_{50} (ng/mL)	ED_{90} (mg/kg/day)
#1	C. albicans	None	0.5	0.56	< 0.06
#2	C. albicans	None	0.25	0.91	0.01
#3	C. albicans	S645F	> 8	162	1.09
#4	C. albicans		> 8	1997	9.98

Park et al., JAC 2005

Επιδημιολογία στο MDACC

	No. of patients (%)		
***Candida* species**	**1988–1992** **n=230**	**1993–2002** **n=281**	**2001-2007** **n=173**
C. albicans	79 (34)	38 (13)	41 (24)
Non-*albicans* species	139 (60)	227 (81)	129 (75)
C. glabrata	28 (12)	86 (31)	8 (5)
C. krusei	17 (7)	68 (24)	30 (17)
C. parapsilosis	33 (14)	39 (14)	42 (24)
C. tropicalis	53 (23)	27 (10)	37 (21)

Sipsas NV et al. Cancer 2009

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2011, p. 5358–5361 Vol. 55, No. 11
0066-4804/11/$12.00 doi:10.1128/AAC.00690-11

Prior Caspofungin Exposure in Patients with Hematological Malignancies Is a Risk Factor for Subsequent Fungemia Due to Decreased Susceptibility in *Candida* spp.: a Case-Control Study in Paris, France[▽]

Elodie Blanchard,[1,2,3] Olivier Lortholary,[4,5,6] Karine Boukris-Sitbon,[4,5] Marie Desnos-Ollivier,[4,5] Françoise Dromer,[4,5]* Didier Guillemot,[1,2,3]† and the French Mycosis Study Group

INSERM U 657, Paris, France[1]; Institut Pasteur, Pharmacoepidemiology and Infectious Diseases Unit, Paris, France[2]; Université Versailles Saint Quentin, Faculté de Médecine Paris Ile de France Ouest, EA 4499, Paris, France[3]; Institut Pasteur, Unité de Mycologie Moléculaire, Centre National de Référence Mycologie et Antifongiques, Paris, France[4]; CNRS URA 3012, Paris, France[5]; and Université Paris Descartes, Service des Maladies Infectieuses et Tropicales, Centre d'Infectiologie Necker-Pasteur, Hôpital Necker-Enfants Malades, APHP, Paris, France[6]

Received 18 May 2011/Returned for modification 16 June 2011/Accepted 9 August 2011

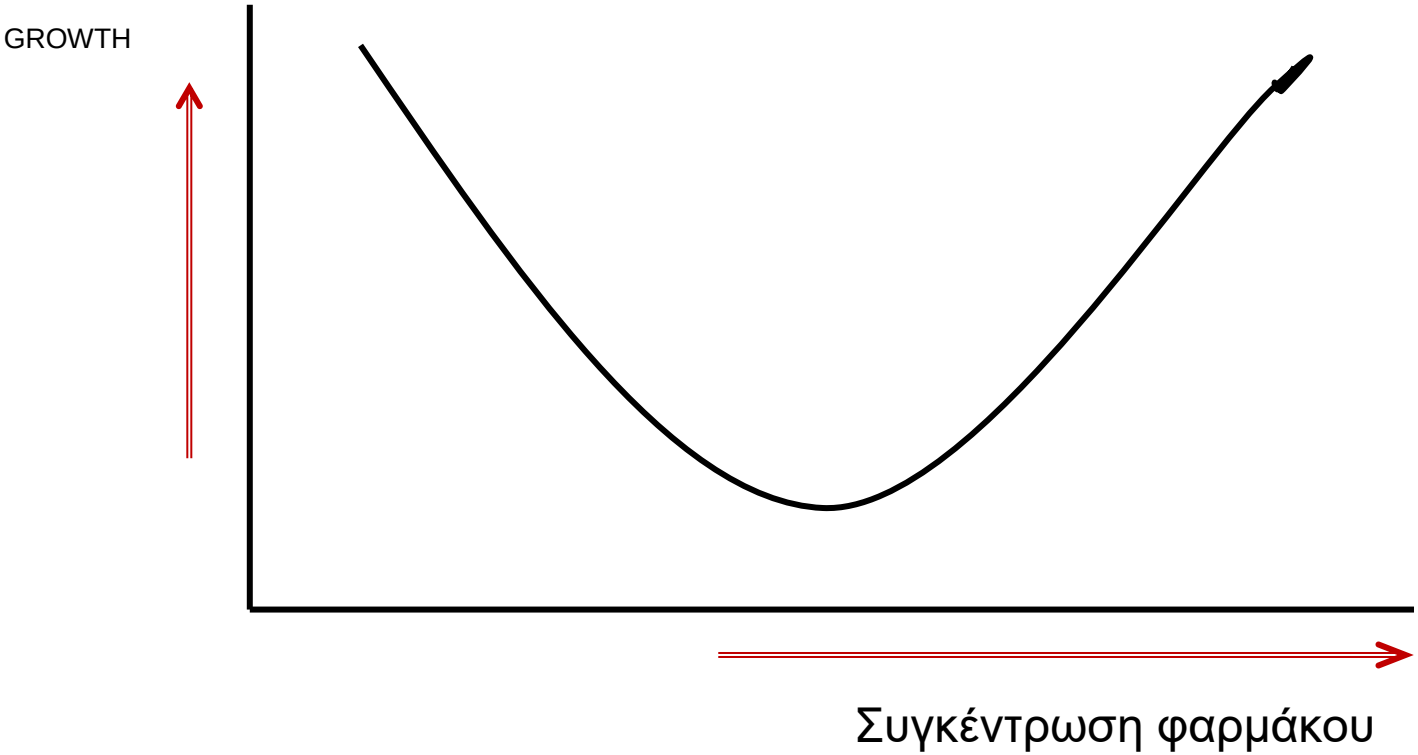
Characteristic or parameter	No. (%) among case group (n = 51) or values for group	No. (%) among control group (n = 102) or values for group	Univariate analysis			Multivariate analysis		
			OR	95% CI	P	OR	95% CI	P
Sex			1.71	0.87–3.36	0.12			
Male	34 (66.7)	54 (52.9)						
Female	17 (33.3)	48 (47.1)						
Age at fungemia					**0.005**			**0.015**
≤65 years	45 (88.2)	66 (64.7)	3.81	1.51–9.57		3.27	1.26–8.50	
>65 years	6 (11.8)	36 (35.3)	1			1		
Median length (days) of stay[b] (IQR) in treatment center	15 (28.0)	14 (25.1)	1.01	0.98–1.03	0.51			
Prior exposure to caspofungin (within 30 days)	14 (27.5)	6 (5.9)	6.31	2.06–19.33	**0.001**	5.25	1.68–16.35	**0.004**
Prior exposure to azole antifungal agent (within 30 days)	5 (9.8)	12 (7.9)	0.81	0.27–2.46	0.71			
Presence of hematological disease(s):					0.09			
Acute leukemia	24 (47.1)	35 (34.3)	2.62	1.06–6.46				
Lymphoma	17 (33.3)	31 (30.4)	2.10	0.79–5.59				
Other(s)	10 (19.6)	36 (35.3)	1					
Presence of cancer	1 (2.0)	5 (4.9)	0.36	0.04–3.36	0.36			
History of:								
Previous surgery (<30 days)	2 (3.9)	11 (10.8)	0.36	0.08–1.64	0.19			
Allogeneic HSCT	10 (19.6)	12 (11.8)	1.87	0.74–4.75	0.19			
Autologous HSCT	4 (7.8)	4 (3.9)	2.00	0.50–8.00	0.33			
GVHD	6 (11.8)	6 (5.9)	2.50	0.67–9.31	0.17			
Use of or exposure to:								
Immunosuppressive agents (including corticosteroids)	14 (27.5)	28 (27.5)	0.86	0.40–1.85	0.69			
Broad-spectrum antimicrobial agents	25 (49.0)	56 (54.9)	0.72	0.32–1.60	0.42			
Central venous catheter	46 (90.2)	87 (85.3)	1.60	0.54–4.72	0.39			
Indwelling venous catheter	11 (21.6)	28 (27.5)	0.70	0.30–1.63	0.41			
Arterial catheter	3 (5.9)	11 (10.8)	0.55	0.15–1.96	0.35			
Urinary probe	5 (9.8)	12 (11.8)	0.81	0.27–2.46	0.71			
Other foreign material	3 (5.9)	7 (6.9)	0.86	0.22–3.32	0.82			
Death before day 30	15 (29.4)	40 (39.2)						

[a] HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease. Values in boldface indicate statistical significance.
[b] Values are available for 18 patients in the case group and 41 patients in the control group admitted for inpatient treatment.

Eagle-effect

- **A paradoxical tolerance to echinocandin activity in *Candida* species may be seen at higher drug concentrations**
  - **Hector, 1993**
- **The phenomena is usually evident *in vitro* by normal susceptibility patterns at low MICs , but then paradoxically at high levels of growth at higher drug concentrations (> 16 mg/L)**
- **More common with caspofungin**
  - **Chamilos et al., 2007; Perlin, 2007**
- **Paradoxical growth is not related to FKS1 mutations**
  - **Stevens et al., 2005**

EAGLE EFFECT



Eagle-effect

- **This paradoxical phenotype *in vitro* has been difficult to document *in vivo***
  - **Clemons et al., 2006**
- **Therefore, the clinical significance of this tolerance effect outside laboratory testing remains unknown.**

Νέα breakpoints

Table 1. Interpretive Guidelines for *In Vitro* Susceptibility Testing of *Candida* spp. and Echinocandins[1]

Antifungal Agent	Species	MIC Range (µg/mL)		
		S	I[a]	R
Anidulafungin[b]	*C. albicans*	≤0.25	0.5	≥1
	C. glabrata	≤0.12	0.25	≥0.5
	C. tropicalis	≤0.25	0.5	≥1
	C. krusei	≤0.25	0.5	≥1
	C. parapsilosis	≤2	4	≥8
	C. guilliermondii	≤2	4	≥8

Pfaller MA, et al. CLSI Subcommittee for Antifungal Testing. Clinical breakpoints for the echinocandins and *Candida* revisited: integration of molecular, clinical, and microbiological data to arrive at species-specific interpretive criteria. Drug Resist Update 2011;14:164-176.

Ποια είναι η κλινική σημασία των MICs και των Breakpoints

Μικρή σε ουδετεροπενικούς ασθενείς με αιματολογικές κακοήθειες

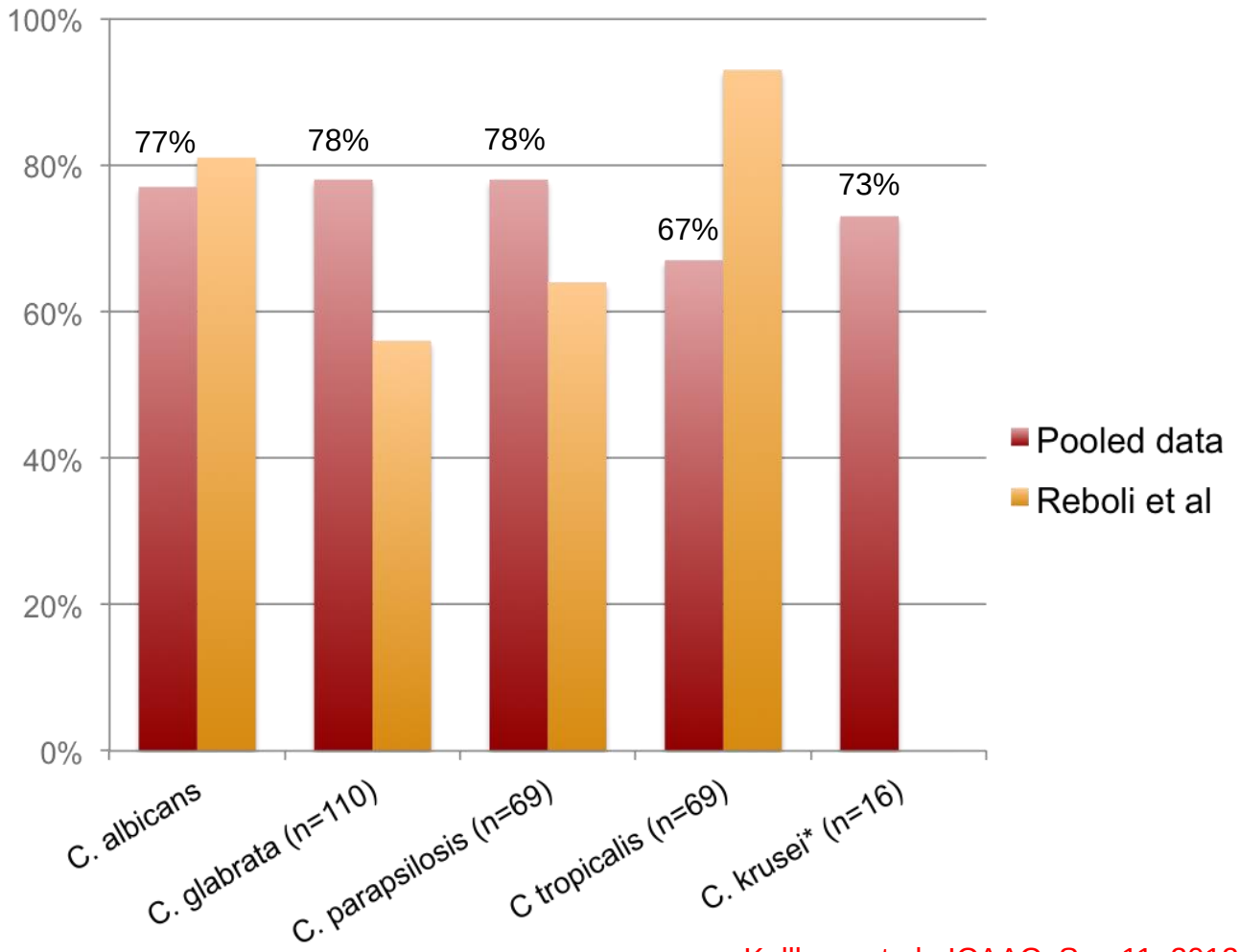
MLC/MIC ratios of seven *C. parapsilosis* isolates with MICs ≤ 1 µg/ml to all echinocandins.

Patient #	Antifungal at the time of BTC	MLC / MIC		
		Caspofungin	Anindulafungin	Micafungin
3	Amphotericin B	2	2	2
5	Amphotericin B - Voriconazole	8	8	8
9	Posaconazole	2	2	2
10	Fluconazole	16	16	2
11	Posaconazole	4	1	1
14	Posaconazole	1	2	2
18	Amphotericin B	8	8	2

Gamaletsou MN, et al. ESCMID 2013, Berlin

Efficacy of Anidulafungin in 504 Patients with Invasive Candidiasis Response by pathogen (EOivT)

C. albicans	256
C. glabrata	110
C. parapsilosis	69
C. tropicalis	69
C. krusei	16



Kullberg et al., ICAAC, Sep 11, 2012
Reboli et al., N Engl J Med 2007

**C. krusei* infections were excluded from the anidulafungin vs. fluconazole trial*

Δράση στα βιοϋμένια
Biofilms

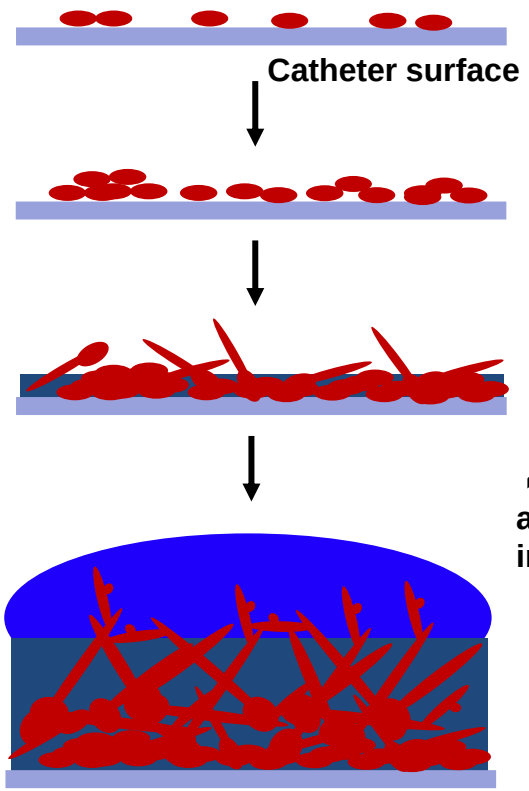
Εχινοκανδίνες

Δράση στα βιοϋμένια

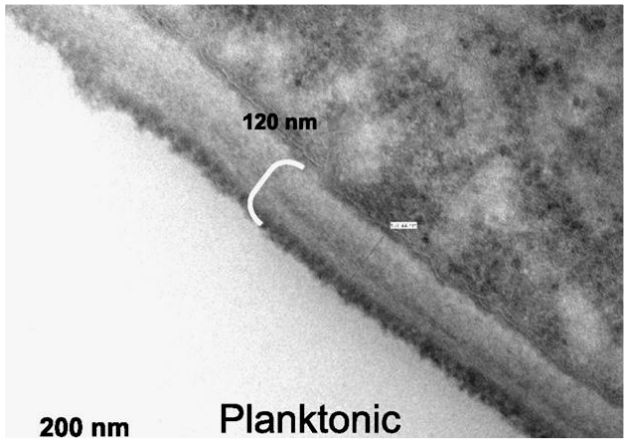
- **Echinocandins are unique among currently-available systemic antifungal agents in their capacity to retain activity against biofilm-embedded *Candida* species.**
- **Under biofilm-like conditions, the MIC values for amphotericin B and fluconazole may increase by 10 to 1000-fold**
  - **Kuhn et al., 2002; Ramage et al., 2002.**
- **MIC values for the echinocandins, with inoculum reductions of >99% for biofilm-embedded *C. albicans***
  - **Kuhn et al., 2002; Ramage et al., 2002.**

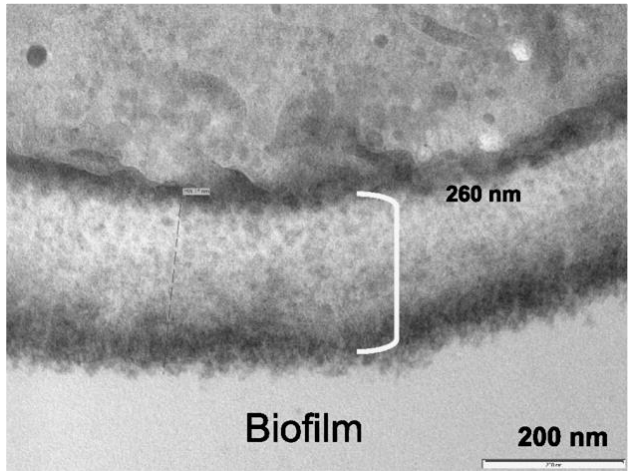
Antifungal Resistance in Biofilms Is Associated with Increased β-Glucan

Mechanism of Biofilm formation



↑ β–glucan in cell wall and biofilm milieu directly inhibits fluconazole activity

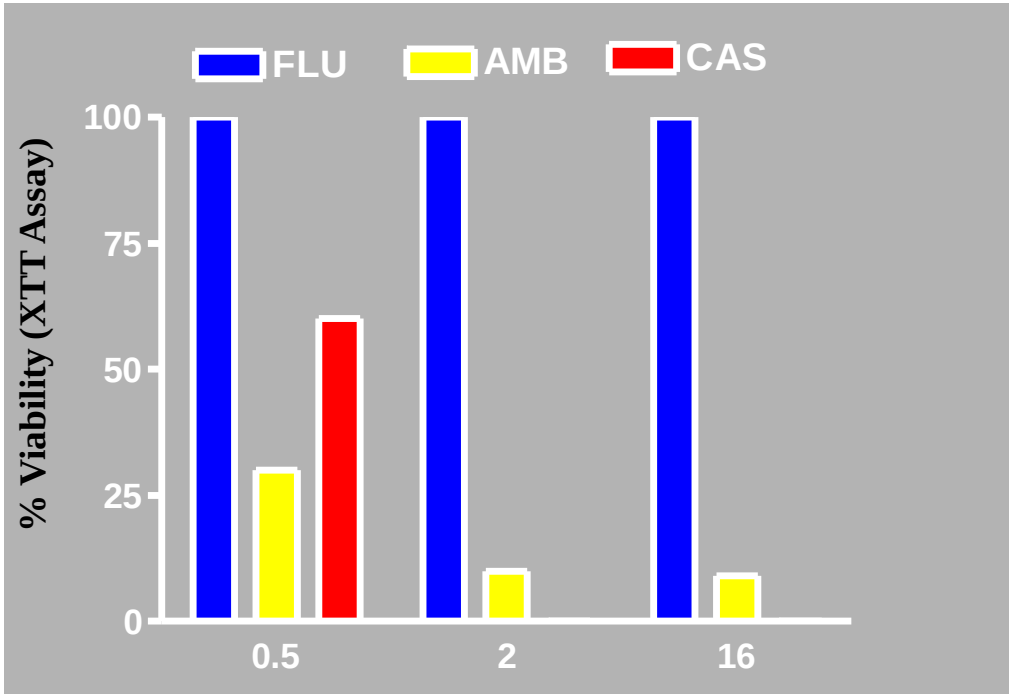




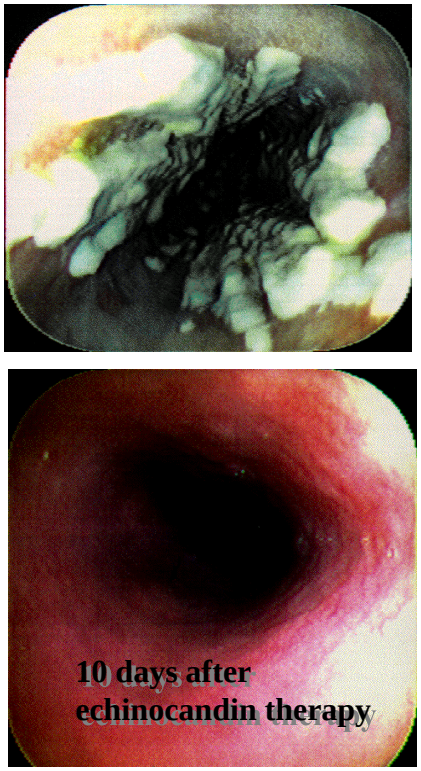
Ramage et al. Chapter 12. *Mol Principals of Fungal Pathogenesis*. ASM Press. 2006
Nett et al. Antimicrob Agent Chemother 2007;51:510-20.

Echinocandin Activity vs. Biofilm-Embedded *Candida*

Antifungal Killing vs. Biofilm-Embedded *Candida* spp.



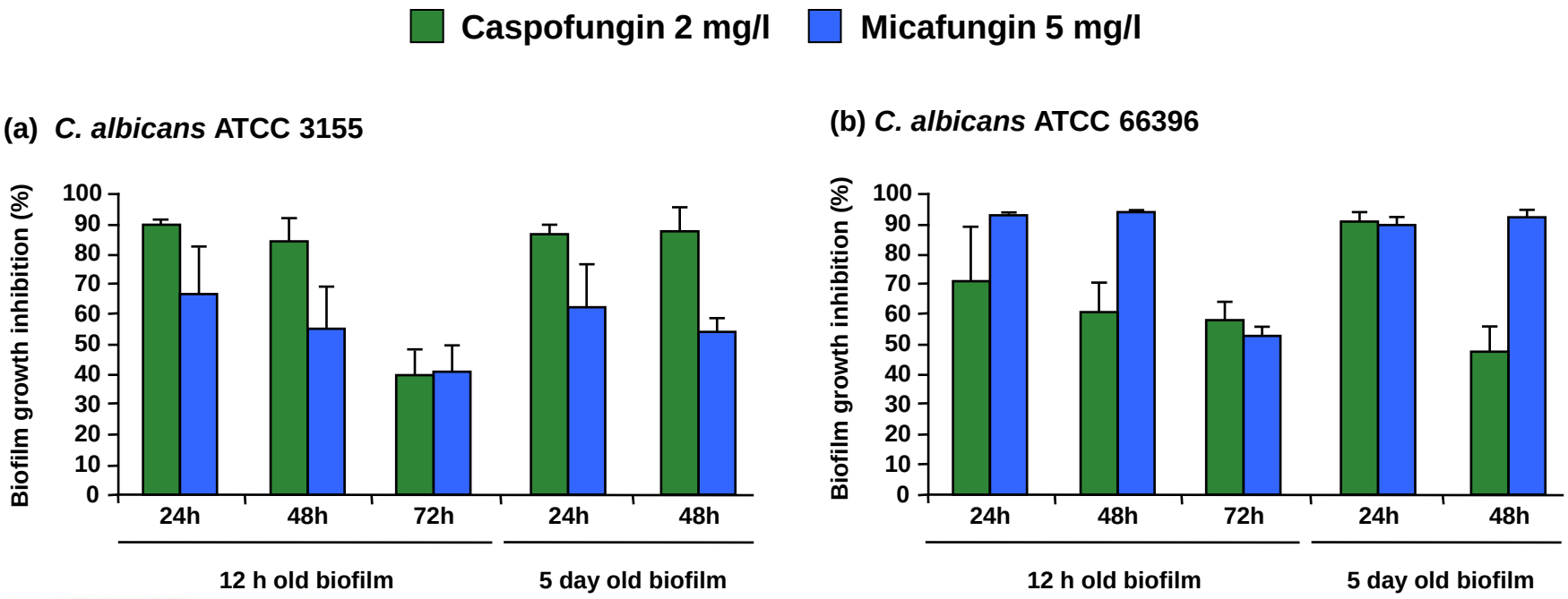
Echinocandin response in azole-refractory esophagitis



Ramage et al. *Antimicrob Agent Chemother* 2002;46:3634

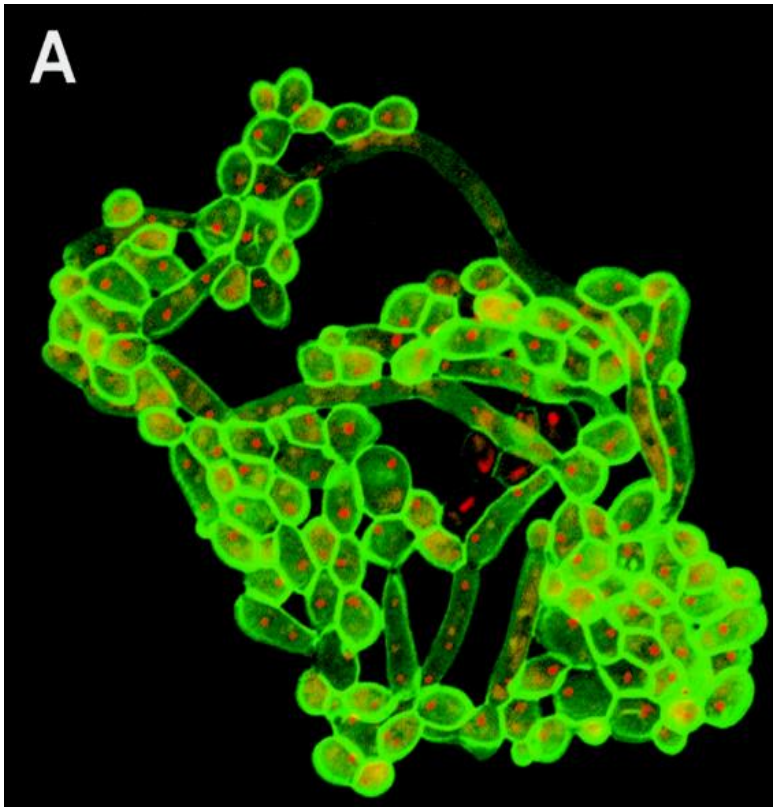
Echinicandin activity against biofilms

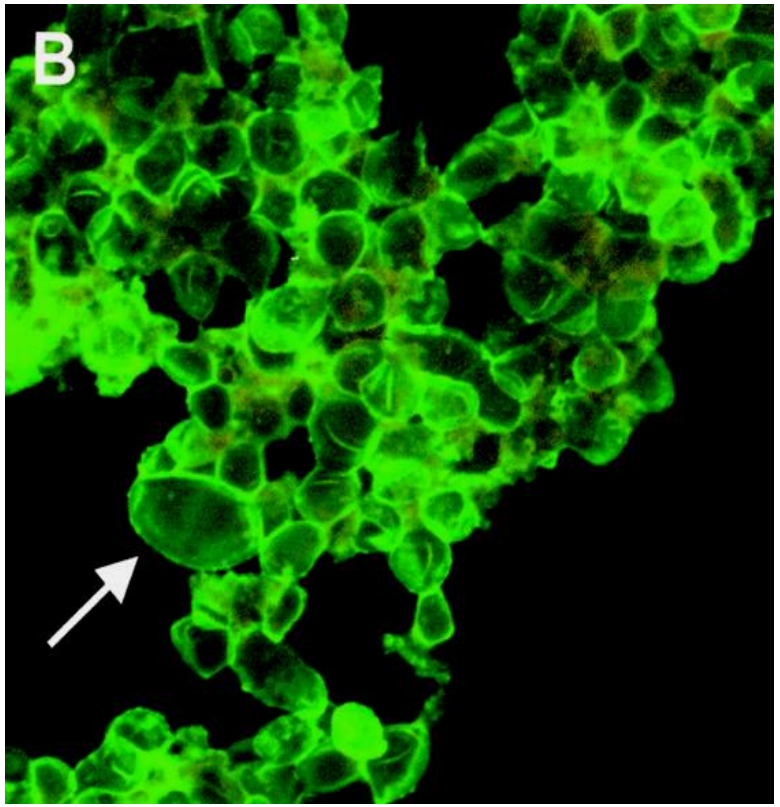
- **Echinocandins showed excellent activity against both intermediate- and mature-phase biofilms of two separate *Candida albicans* strains:**
  - **ATCC 3153**
  - **ATCC 66396**



Cateau E, *et al. J Antimicrob Chemother* 2008; **62:**153–5

Echinocandins Are Fungicidal Versus *Candida* Species And Exhibit Activity Against Biofilm-embedded Organisms





Kuhn et al. *Antimicrob Agent Chemother.* 2002;46:1773-80

Hallmark characteristic of biofilms: resistance to antifungal agents

- **Azoles were not active against biofilms[1]**
- **Lipid amphotericin B formulations and echinocandins exhibited activity against biofilms[1,2]**

Drug	Planktonic MIC_{50} (µg/mL)	Biofilm MIC_{50} (µg/mL)
Amphotericin B	0.25	4
Nystatin	1	16
Chlorhexidine	8	8
Terbinafine	32	128
Fluconazole	0.25	>256
Voriconazole	8	>256
Liposomal amphotericin B	0.06	0.25
Lipid complex nystatin	0.06	16
Amphotericin B lipid complex	0.06	0.25
Caspofungin	0.125	0.5
Micafungin	0.001	0.5
Anidulafungin*	≤0.03	≤0.03

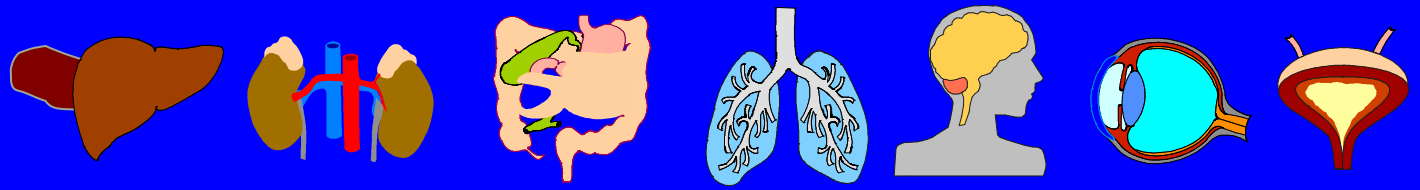
MIC_{50}, minimum drug concentration causing 50% growth inhibition compared to control

1. Kuhn DM, et al. Antimicrob Agents Chemother 2002;46:1773–80;
2. Jacobson MJ, et al. Antimicrob Agents Chemother 2008;52:2242–3*

Φαρμακοκινητική / φαρμακοδυναμική

Αλληλεπιδράσεις

Φαρμακοκινητική των ΑΜ: Κατανομή του φαρμάκου



	Ήπαρ/ Σπλήν	Νεφρός	Έντερο / Χολή	Πνεύμων	ΚΝΣ/ ΕΝΥ	Οφθαλμός	Ουροποιητικό
AmB	+	+	+	+	-	–	-
5FC	+	+	+	+	+	+	+
FLU	+	+	+	+	+	+	+
ITR	+	+	+	+	-	–	-
VOR	+	+	+	+	+	+	–
POS	+	+	+	+	-	–	–
Echino	+	+	+	+	-	–	–

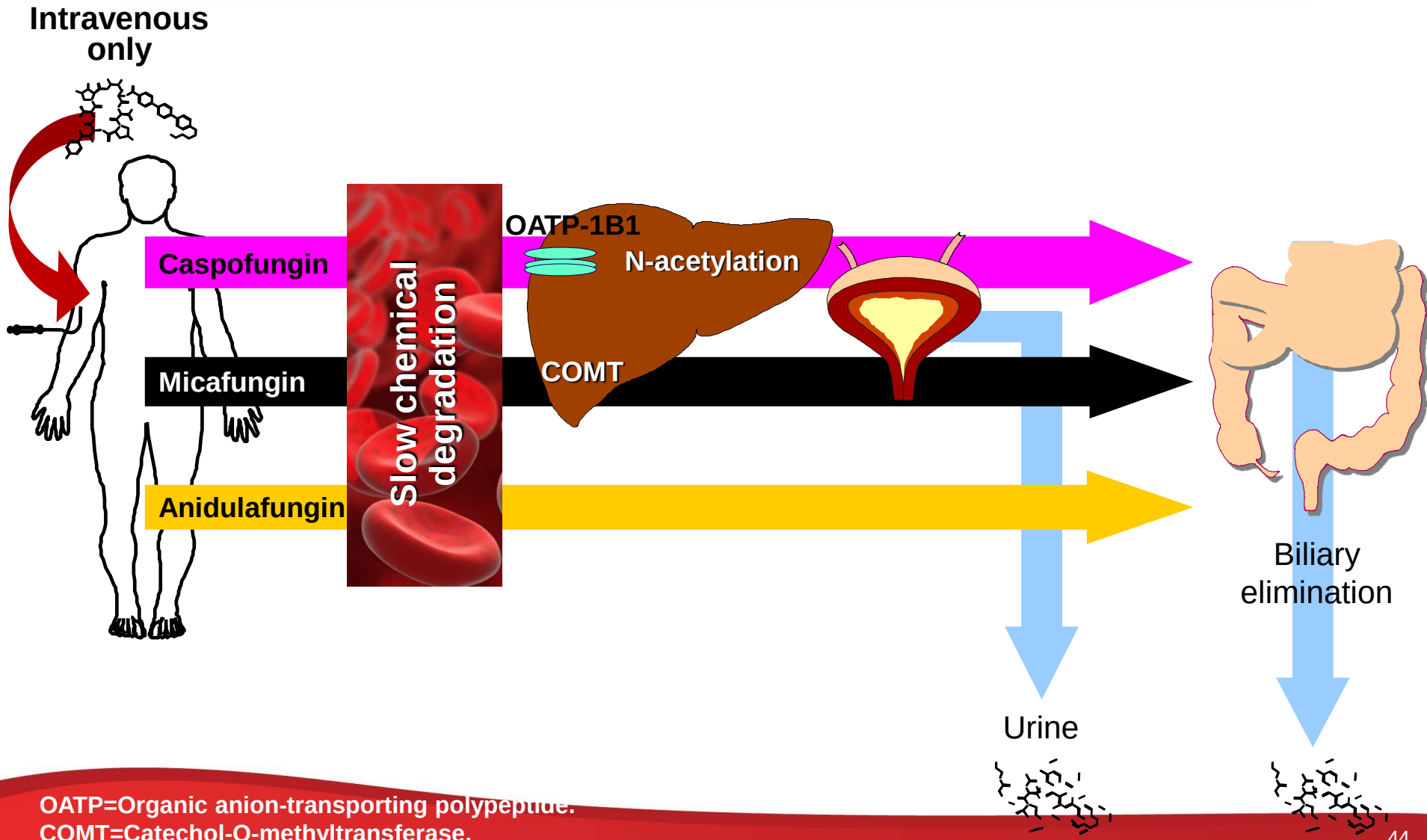
+ ≥50% of serum concentrations
– <10% of serum concentrations

Groll AH et al. *Advances in Pharmacol.* 1998;44:343.

Φαρμακοκινητική / φαρμακοδυναμική

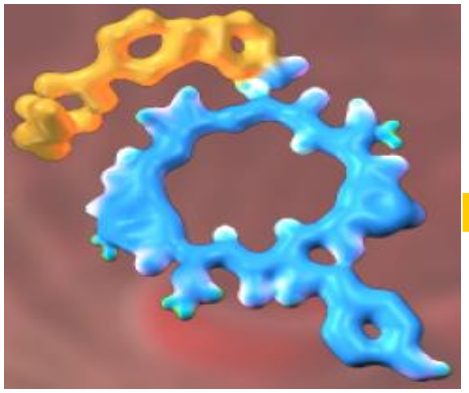
Variable	Anidulafungin[a] 200/100	Caspofungin[b] 70/50	Micafungin[c] 100
C_{max} (50 mg dose)	8.6	14.03	10.1
Bioavailability	2-7%	minimal	minimal
$t_{1/2\beta}$ (hours)	24-26	9-11	11-17
Vd (L/kg)	0.50	0.14	0.22-0.24
AUC (mg•h/L)	11.8	87.9-114.8	111.30
Protein binding (%)	84	96-97	99.8
Metabolism	Not metabolized; undergoes slow chemical degradation to inactive metabolites	Slow peptide hydrolysis and N-acetylation, with some spontaneous degradation to peptide product	Metabolized by catechol-O-methytransferase and to a lesser extent, CYP1A2, 2B6, 2C and 3A4
Cl (total) (ml/min/kg)	0.26	0.15	0.19
Fraction urine excretion	<1%	1.40%	0.70%
CSF penetration (% of plasma)	< 0.1%	< 0.1%	< 0.1%

Μεταβολισμός και απέκκριση

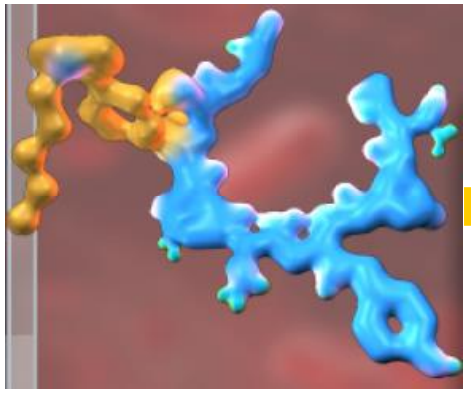


OATP=Organic anion-transporting polypeptide.
COMT=Catechol-O-methyltransferase.

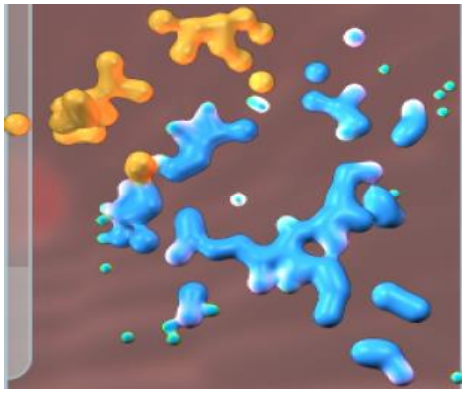
Η Ανιντουλαφουγκίνη υφίσταται βραδεία χημική αποδόμηση σε φυσιολογικές συνθήκες



Ενεργό Μόριο

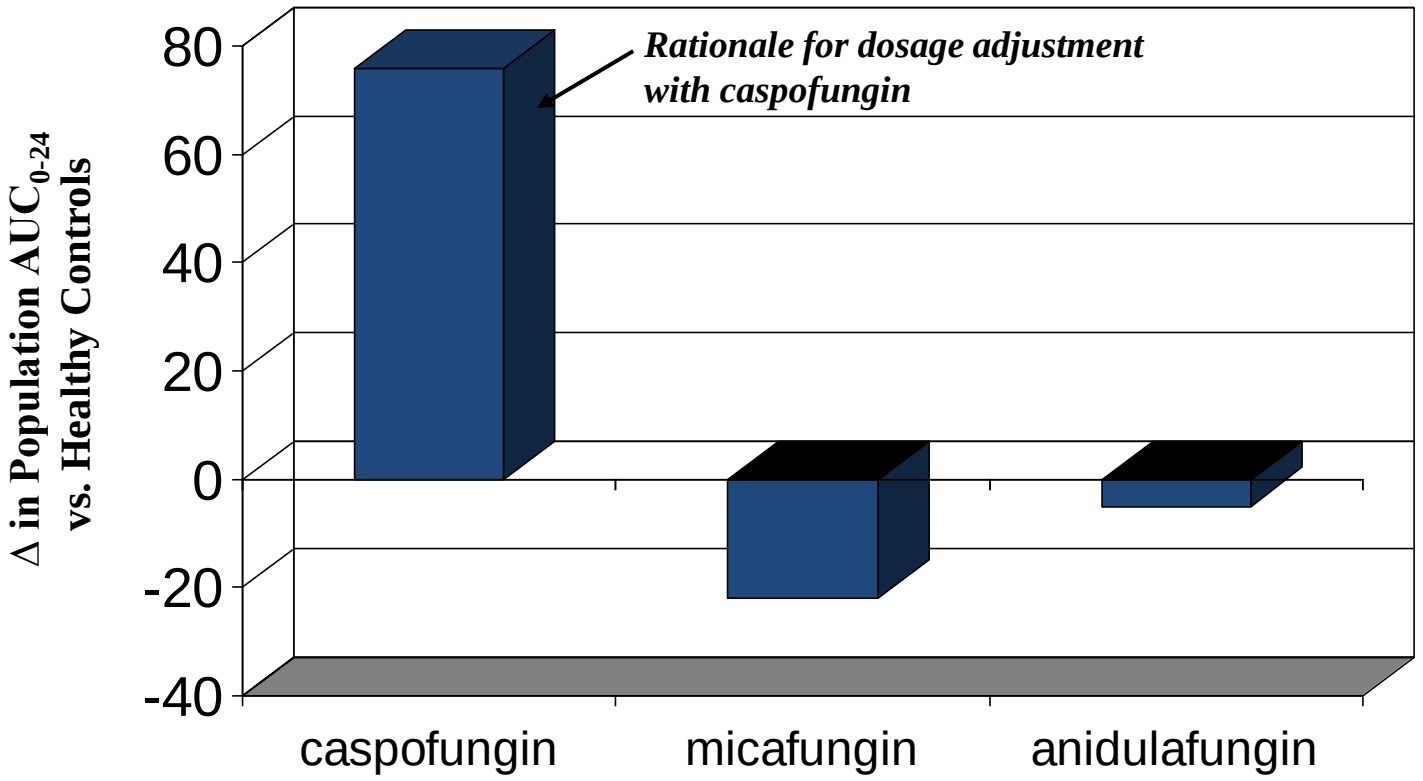


Η αλυσίδα ανοίγει φυσιολογικά 37°C και pH 7.4



Το ανενεργό ανοικτό πεπτίδιο διασπάται σε πεπτιδικά προϊόντα αποδόμησης που αποβάλλονται με τα κόπρανα

Echinocandin Pharmacokinetics In Hepatic Dysfunction (Child-pugh Score 7-9): Clinical Significance?



Stone et al. *Antimicrobial Agents Chemother* 2002; 46:739.
Hebart et al. *J Clin Pharmacokin* 2005;45:1145-52.
www.FDA.gov accessed 5-15-06

Προσαρμογή δόσης

Variable	Anidulafungin 200/100	Caspofungin 70/50	Micafungin 100
Dosage adjustment in renal insufficiency	No adjustment necessary	No adjustment necessary	No adjustment necessary
Dosage adjustment in hepatic insufficiency	No adjustment necessary	Child-Pugh 5-6: none; Child-Pugh 7-9, significant increases in AUC, consider reducing maintenance dose to 35 mg/day; Child Pugh >9: no data	Child-Pugh 7-9, C_{max} and Cl not significantly altered but AUC decreased compared to healthy subjects

Φαρμακευτικές αλληλεπιδράσεις των εχινοκανδινών

Anidulafungin 200/100	Caspofungin 70/50	Micafungin 100
Anidulafungin AUC decreased ~ 20% by cyclosporin	Concomitant cyclosporin increases caspofungin AUC by 35% Enzyme inducers (rifampin, efavirenz, nevirapine, phenytoin, dexamethasone, carbamazepine) reduce caspofungin AUC by 15-30% Caspofungin reduces tacrolimus AUC by 20%	Micafungin increases the AUC of sirolimus and decreases the clearance of cyclosporin by 16% Micafungin increases the AUC of nifedipine by 18%

Κλινική Πράξη

Κάντιντα

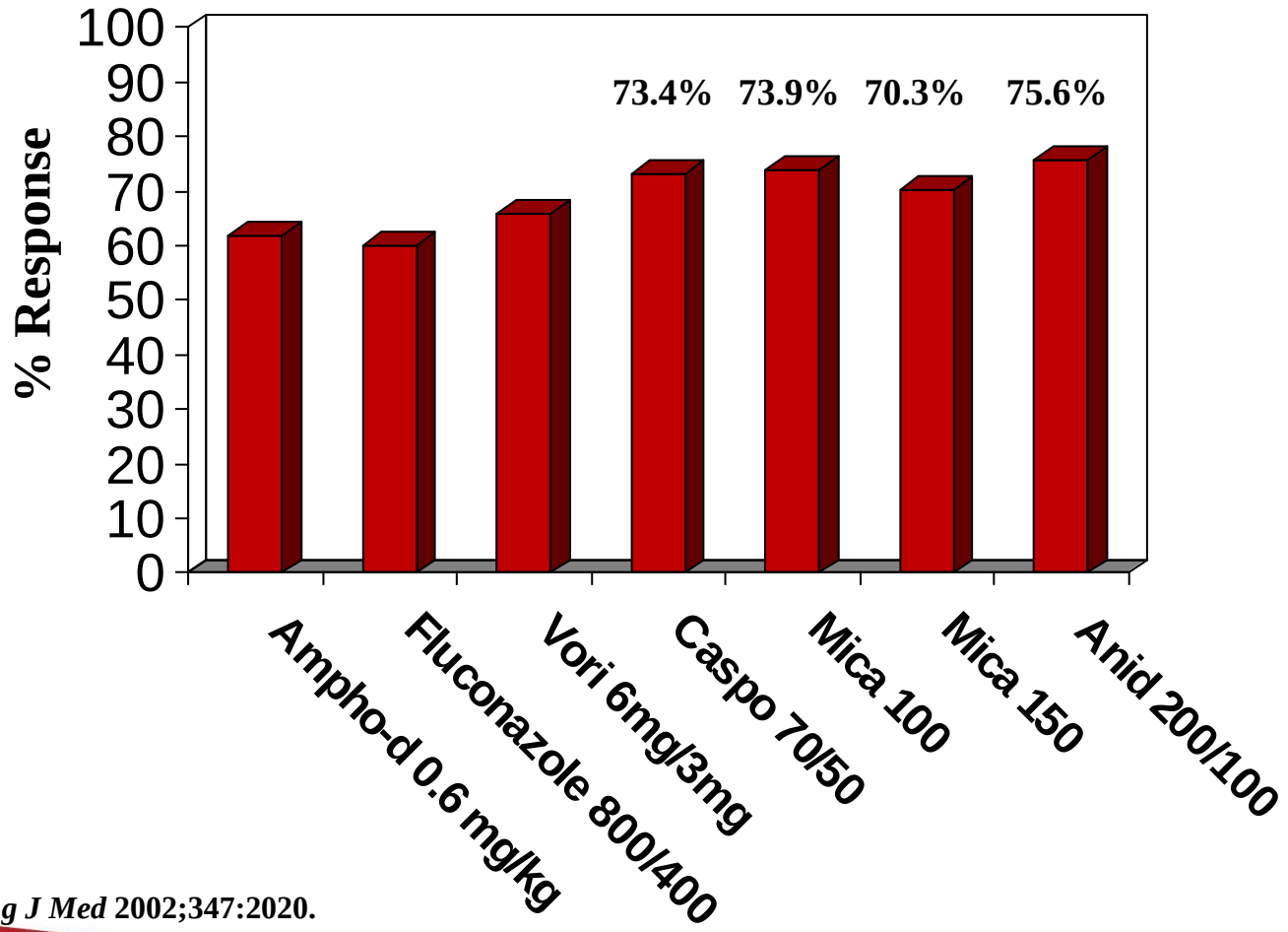
Κλινικές μελέτες εχινοκανδινών στην καντινταιμία

Study	Design	Success rate (cured + improved)
Mora-Duarte et al, 2002	Caspofungin vs. amphotericin B	73% vs. 62% * p = ns
Betts et al, 2006	Micafungin vs. caspofungin	74% (100 mg) 70% (150 mg) vs. 71% * p = ns
Kuse et al, 2007	Micafungin vs. liposomal amphotericin B	74% vs. 70% * p = ns
Reboli et al, 2005	Anidulafungin vs. fluconazole	76% vs. 60% ** p < o.o5

Mora-Duarte J et al. *N Engl J Med*. 2002;347:2020-2029.
Betts RF et al. 2006.
Kuse E-R et al. *Lancet*. 2007;369:1519-1527.
Reboli AC et al. *N Engl J Med.* 2007;356:2472-2482.

Treatment Success in Invasive Candidiasis

End of IV Therapy (ITT/MITT Analysis)



Mora-Duarte et al. *N Eng J Med* 2002;347:2020.
Kullberg et al. Lancet 2005;366:1435.
Reboli et al. ICAAC 2005; LB Abstract M-718.
Betts et al ICAAC 2006; LB Abstract M-1308a

Κλινική Πράξη

Ασπέργιλλος

Current first-line Treatment Guidelines: IA

Drugs	IDSA[1]	UK[2]	ECIL[3]	DGHO[4]	Australia[5]
AmB DC	D	D	D	EII	Alternative
AmB-LS	AI	AI	BI	AII	Alternative
ABLC			BII		
ABCD			D		
Itraconazole			CIII		
Posaconazole					
Voriconazole	AI	AI	AI	AI	Recommended
Caspofungin			CII		
Micafungin					
Combination	Not recommended	Discouraged	Discouraged	CIII	No supportive evidence

1. Walsh TJ, et al. Clin Infect Dis 2008;46:327–60.
2. Prentice AG, et al. http://www.bcshguidelines.com/documents/fungal_infection_bcsh_2008.pdf
3. Maertens J et al. Bone Marrow Transplantation 2011; 46:709–18
4. Bohme A et al. Ann Hematol 2009;88:97–110
5. Thursky KA, et al. Intern Med J 2008;38:496–520

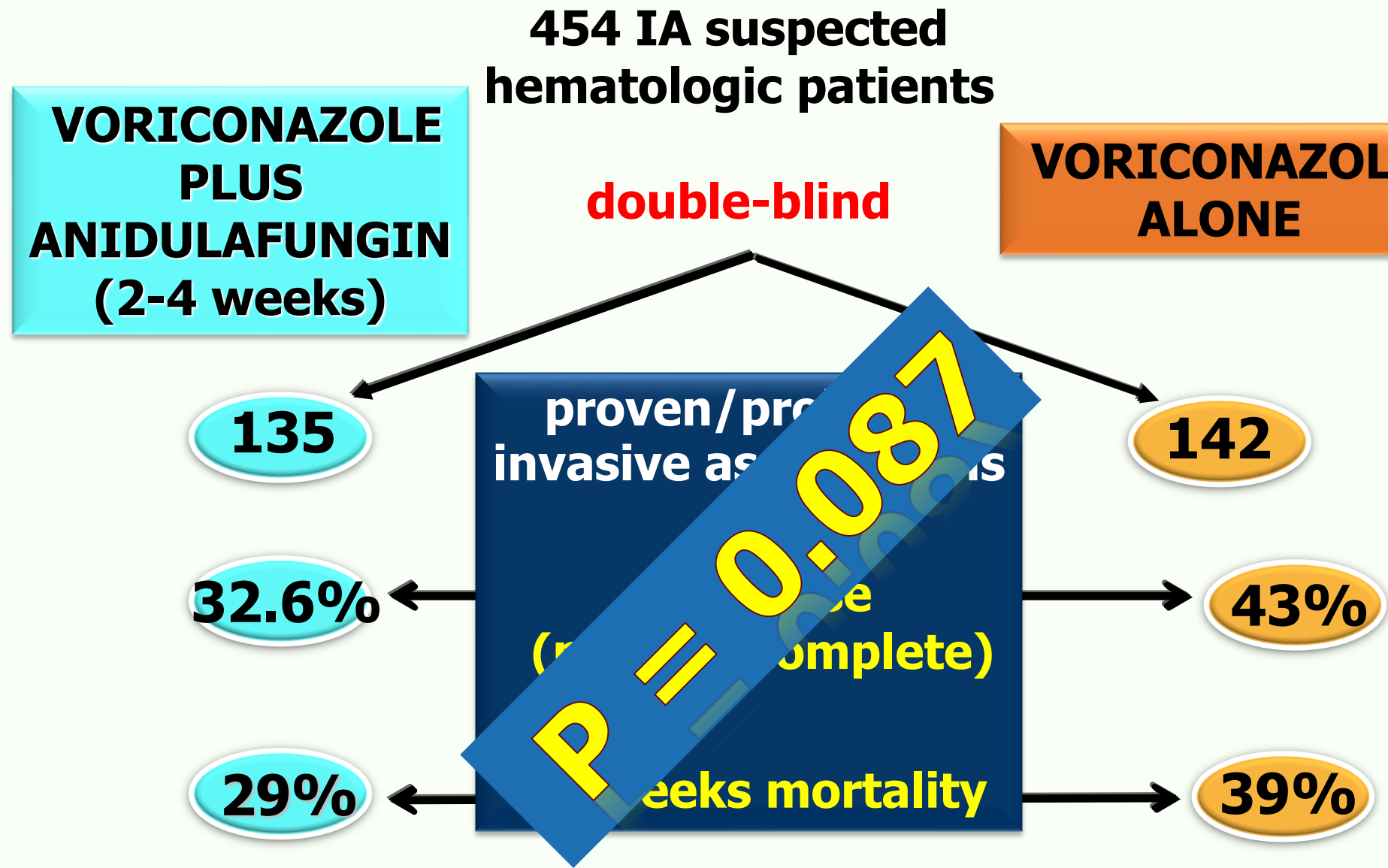
Invasive pulmonary aspergillosis
Combination therapy

- **First line**
  - **Not recommended** **D-III**
- **Salvage**
  - **Caspofungin + Lipid AMB** **C-II**
  - **Caspofungin + Voriconazole** **C-II**
  - **AMB (any formulation) and –azole** **no data**

ECIL 3, 2009

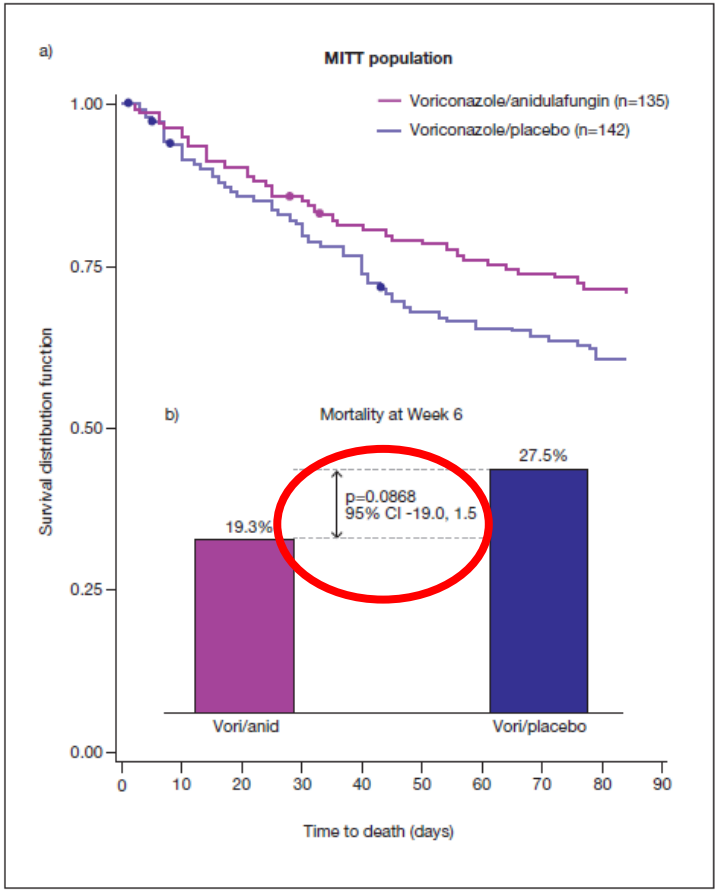
VORICONAZOLE ALONE OR IN COMBINATION WITH ANIDULAFUNGIN AGAINST ASPERGIILLOSIS

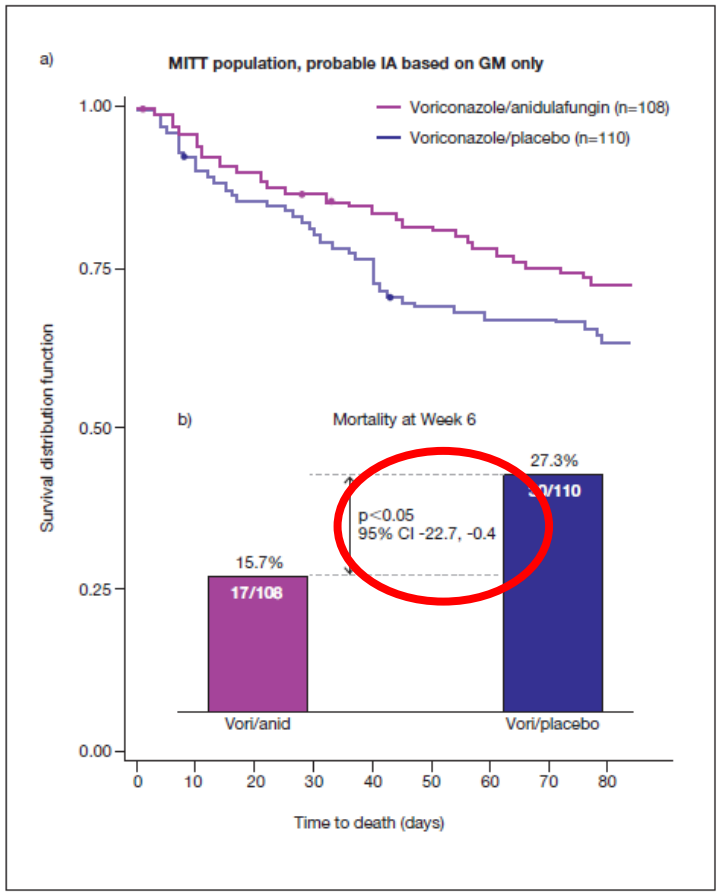
Marr et al. ECCMID 2012; Abstr #LB2812 2012



A randomised, double-blind study of combination antifungal therapy with voriconazole and anidulafungin versus voriconazole monotherapy for primary treatment of invasive aspergillosis

Kieren A. Marr,[1] Haran Schlamm,[2] Scott T. Rottinghaus,[2] Shyla Jagannatha,[2] Eric J. Bow,[3] John R. Wingard,[4] Peter Pappas,[5] Raoul Herbrecht,[6] Thomas J. Walsh,[7] Johan Maertens[8] and the Mycoses Study Group

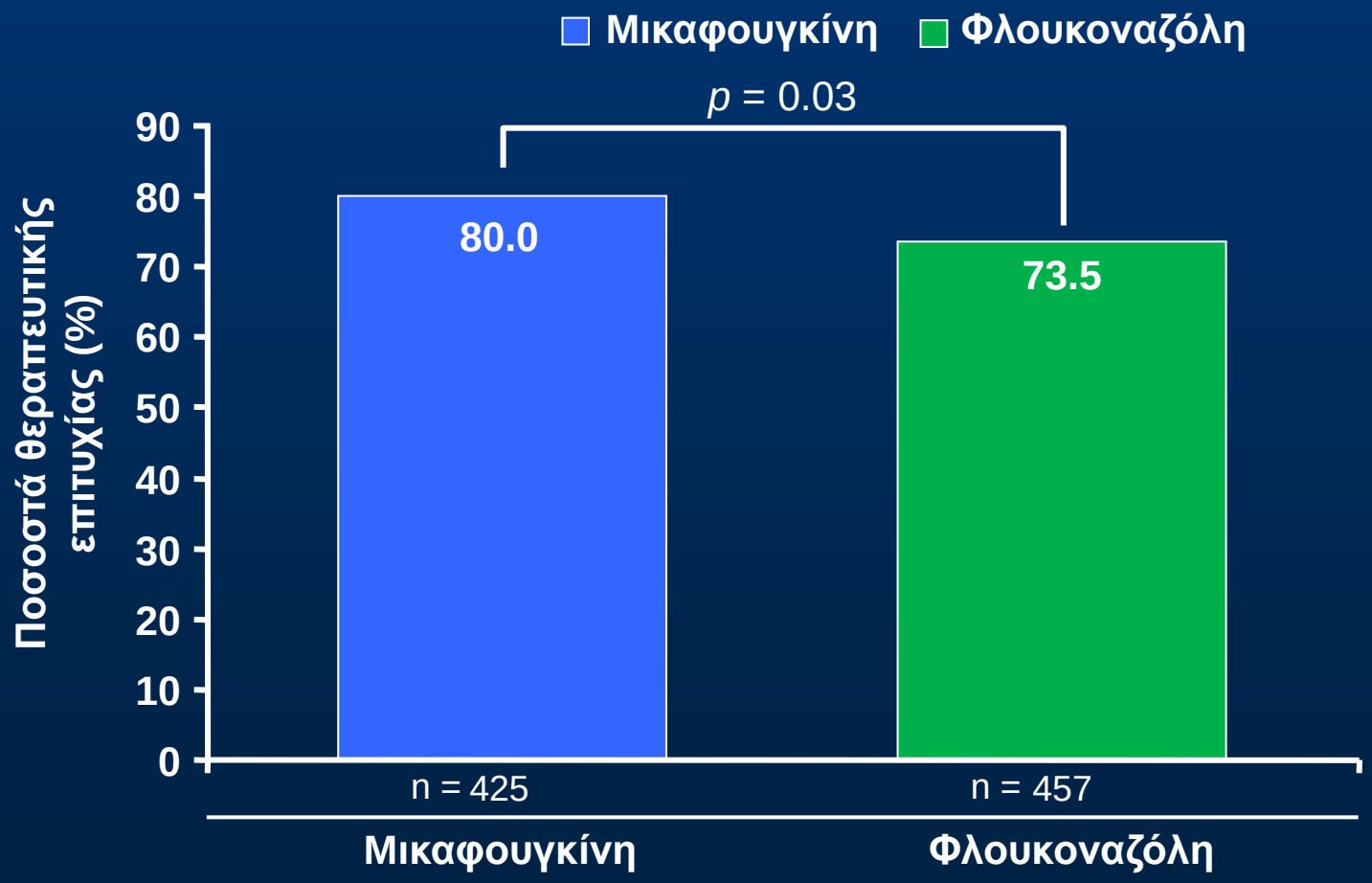




Κλινική Πράξη

Προφύλαξη σε αιματολογικούς ασθενείς υψηλού κινδύνου

Μικαφουγκίνη *vs.* φλουκοναζόλη σε αλλογενείς και αυτόλογους HSCT ασθενείς: Συνολικά ποσοστά θεραπευτικής επιτυχίας



van Burik JA, *et al*. *Clin Infect Dis* 2004; **39:** 1407–16.

IDSA 2011

	Ποιοί	Ποιο ΑΜ	Σχόλια
Προφύλαξη έναντι διηθητικής καντιντίασης	• allogeneic HSCT recipients • intensive remission-induction or salvage-induction chemotherapy for acute leukemia • (A-I).	Fluconazole, itraconazole, voriconazole, posaconazole, micafungin, caspofungin	

Clinical Infectious Diseases 2011;52:427–431

IDSA 2011

	Ποιοί	Ποιο ΑΜ	Εναλλακτικά
Προφύλαξη έναντι διηθητικής ασπεργίλλωσης	Ασθενείς με ΟΜΛ και MDS (1st induction) HSCT (GVHD και ουδετεροπενία)	•**Ποσακοναζόλη** (200 mg κάθε 8 ώρες)	•**Ιτρακοναζόλη** (200 mg κάθε 12 ώρες IV για 2 μέρες, ακολούθως 200 mg κάθε 24 ώρες IV) ή ιτρακοναζόλη (200 mg PO κάθε 12 ώρες); •**Μικαφουγκίνη** (50 mg/ημέρα)

Clinical Infectious Diseases 2011;52:427–431

Incidence Density of Invasive Fungal Infections during Primary Antifungal Prophylaxis in Newly Diagnosed Acute Myeloid Leukemia in a Tertiary Cancer Center, 2009 - 2011

Marisa Z. R. Gomes,[a,b] Victor E. Mulanovich,[a] Y. Jiang,[a] Russell E. Lewis,[a*] Dimitrios P. Kontoyiannis[a]

Outcome	Echinocandin PAP (per 1000 prophylaxis-days, [95% CI])	Anti-*Aspergillus* azole PAP (per 1000 prophylaxis-days, [95% CI])	*P*-value
During 120-day study period			
Overall IFIs	8.1 (4.64–13.20)	2.3 (1.21–3.90)	**<0.001**
Documented IFIs	7.1 (3.88–11.93)	1.1 (0.3 –2.29)	**<0.0001**
Mold documented IFIs	4.6 (2.08–8.67)	1.1 (0.38–2.29)	**<0.01**
Yeast IFIs	2.0 (0.54–5.20)	0	**<0.01**
Definite IFIs	4.1 (1.75–8.01)	0.18 (0.02–9.78)	**<0.001**
Probable "invasive aspergillosis"	3.0 (1.11–6.63)	0.7 (0.19–1.80)	**0.045**
Presumed IFIs	1.0 (0.11–3.67)	1.2 (0.49–2.53)	0.61
EATs	4.1 (1.75–8.0)	2.8 (1.60–4.56)	0.39
During 42-day study period			
Documented IFI	8.6 (4.28–15.37)	2.4 (0.77–5.60)	**0.03**

IFIs, invasive fungal infections; EATs, empirical antifungal therapies; PAP, primary antifungal prophylaxis

152 patients with AML received AF prophylaxis during remission-induction chemotherapy

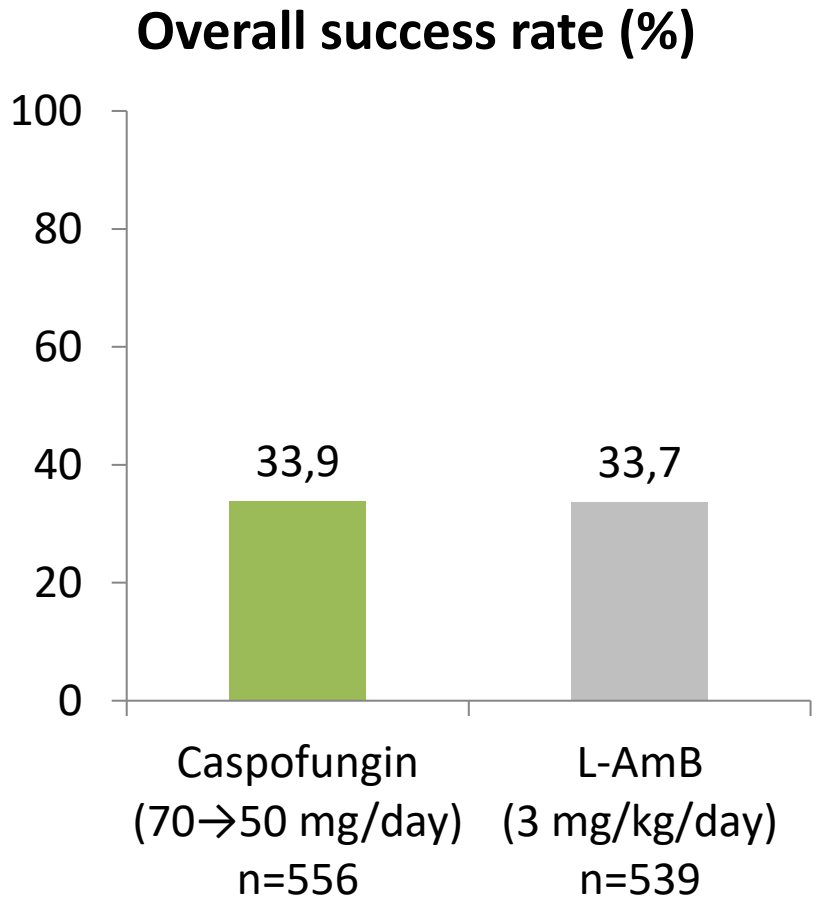
Antimicrob Agents Chemother. 2014 Mar 3

Κλινική Πράξη

Εμπειρική αγωγή σε ουδετεροπενικούς ασθενείς

Εμπειρική αγωγή – Καστοφουγκίνη

- 1,095 patients in primary efficacy analysis (MITT population)
- Components of composite endpoint: (caspofungin vs L-AmB)
  - Treatment of baseline fungal infection
    51.9% vs 25.9% (p=0.04)
  - No breakthrough fungal infections
    94.8% vs 95.5% (p=ns)
  - Survival for 7 days after EOT
    92.6% vs 89.2% (p=0.05)
  - Resolution of fever during the period of neutropenia
    41.2% vs 41.4% (p=ns)
  - Premature discontinuations
    10.3% vs 14.5% (p=0.03)



Εμπειρική αγωγή – Μικαφουγκίνη

Study	Patients	Initial micafungin dose	Micafungin dose escalation allowed? (max dose)	Success rate
Yanada 2006	18	50 mg/day	Yes (300 mg/day)	77.8%
Toubai 2007	23	50–300 mg/day	No	73.9%
Tamura 2009	51	50–150 mg/day	Yes (300 mg/day)	86.3%
Kubiak 2010	174	100 mg/day	No	81.0%
Park 2010	47	100 mg/day	No	61.7%
Goto 2010	53	150 mg/day	Yes (300 mg/day)	69.8%
Yamaguchi 2011	119	50–300 mg/day	Yes (not specified)	79.0%/39.5%*
Yoshida 2012	388	50–150 mg/day	Yes (300 mg/day)	65.3%
Ráčil 2013	73	100 mg/day	No	84.5%/64.8%*
Kobayashi 2013	25	1–3 mg/kg/day	Yes (6 mg/kg/day)	56.7%
Mizuno 2013	78	150 mg/day	No	60.3%

IDSA 2008

	Πρωταρχικώς	Εναλλακτικώς	Σχόλια
«Empirical» και «preemptive» αντιμυκητιασική θεραπεία	L-AMB (3 mg/kg/ημέρα ενδοφλεβίως), caspofungin itraconazole voriconazole AI		«Preemptive» θεραπεία σε υψηλού κινδύνου ασθενείς με απόδειξη ΣΜ (π.χ., διήθηση πνεύμονα ή θετικό αποτέλεσμα γαλακτομαννάνης)

Clin Inf Dis 2008; 46: 327–60.

ECIL-4 guidelines
Empirical antifungal therapy

Antifungal agent	Daily dose	Level of recommendation
Liposomal AmB	3 mg/kg	A-I
Caspofungin	50 mg	A-I
AmB colloidal dispersion	4 mg/kg	B-I
AmB lipid complex	5 mg/kg	B-I
Itraconazole	200 mg IV	B-I
Voriconazole	2 × 3 mg/kg IV	B-I
Micafungin	100 mg	B-II
AmB deoxycholate	0.5–1 mg/kg	B-I/D-I
Fluconazole	400 mg IV	C-I

Maertens J, et al. Bone Marrow Transplant 2011;46:709–18

Εγκεκριμένες ενδείξεις και δόσεις

	Caspofungin	**Micafungin**	**Anidulafungin**
Indications	• Invasive candidiasis • Esophageal candidiasis •empiric therapy in febrile neutropenic patients •Refractory aspergillosis	• Esophageal candidiasis • Invasive candidiasis • Prophylaxis of *Candida* infections in HSCT	• Esophageal candidiasis • Candidemia in non-neutropenic patients
Dosing	70 mg day#1, then 50 mg/day thereafter Increase to 70 mg daily for sub-optimal clinical response	Esophageal candidiasis: 150 mg/day HSCT prophylaxis: 50 mg/day Candidemia: 100 mg/day: *C. albicans*	Candidemia 200 mg day#1 then 100 mg/day

Pediatric patients

- Caspofungin is approved in pediatric patients 12 months to 17 years of age. The safety and efficacy of caspofungin have not been sufficiently studied in clinical trials involving neonates and infants <12 months of age. Caution is advised when treating this age group.
- Micafungin is indicated in children of all ages for the treatment of invasive candidiasis and prophylaxis of Candida infection in patients undergoing allogeneic HSCT or patients who are expected to have neutropenia (ANC <500/µL) for ≥10 days

Pediatric dosing

- **Dosing studies completed to date for all three of the echinocandins in the pediatric population,**
  - **Caspofungin: 50 mg/m^2 rather than 1 mg/kg**
  - **Micafungin: dosage adjustment needed at ≤ 8 years**
  - **Anidulafungin: no dosage adjustment needed**

Εγκυμοσύνη

- **There are no adequate well-controlled studies of anidulafungin, caspofungin, or micafungin in pregnant women**
- **It is not known whether anidulafungin, caspofungin, or micafungin are excreted in human breast milk.**

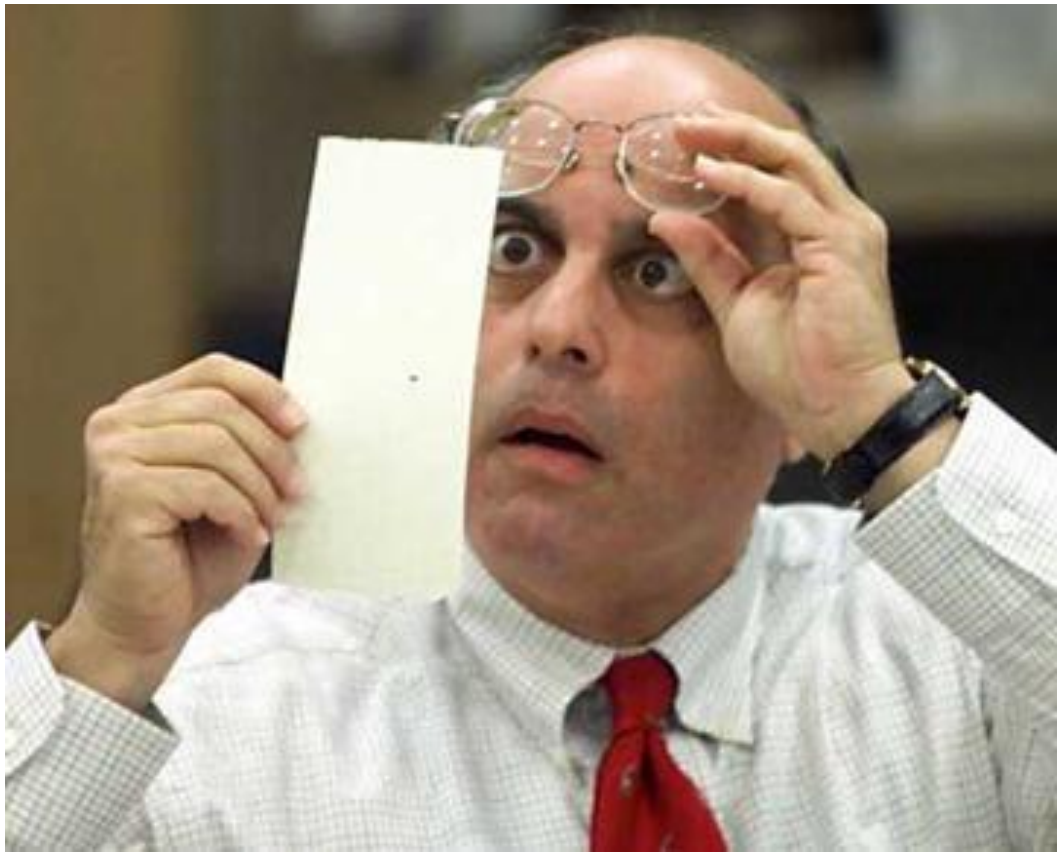
Intravitreal treatment

- **Intravitreal caspofungin (100 µg/ 0.1 mL)**
  - **Kusbeci et al., 2007**
- **Intravitreal micafungin (15 µg/ 0.06 mL)**
  - **Harrison et al., 2005**
- **effective and safe in rabbit models of Candida and Aspergillus endophthalmitis.**
- **Anidulafungin may be a less ideal echinocandin due to the alcohol vehicle required for solubilization**
- **Sufficient clinical experience is lacking**
  - **Khan et al., 2007**

Ποια εχινοκανδίνη;

- Αποτελεσματικότητα
- Τοπική επιδημιολογία
- Φάσμα
- Αντοχή
- Ασφάλεια / ανοχή
- Αλληλεπιδράσεις
- Προσαρμογή δόσης σε ηπατική / νεφρική λειτουργία
- Κλινικές μελέτες

Κόστος



Echinocandins-Ideal Antifungals For Canidiasis?

Advantages

- **Excellent in vivo *Candida* efficacy**
- **No cross resistance among azole-resistant *Candida* species**
- **Predictable pharmacokinetic profile**
- **Excellent safety at efficacious doses**
- **Low theoretical risk of drug interactions or antagonism of other antifungals**

Disadvantages

- **Notable holes in spectrum for other yeasts (e.g., *Trichosporon*, *Cryptococcus*)**
- **No oral formulation**
- **Not distributed in anatomically priveleged sites (e.g.,CNS, eye)**