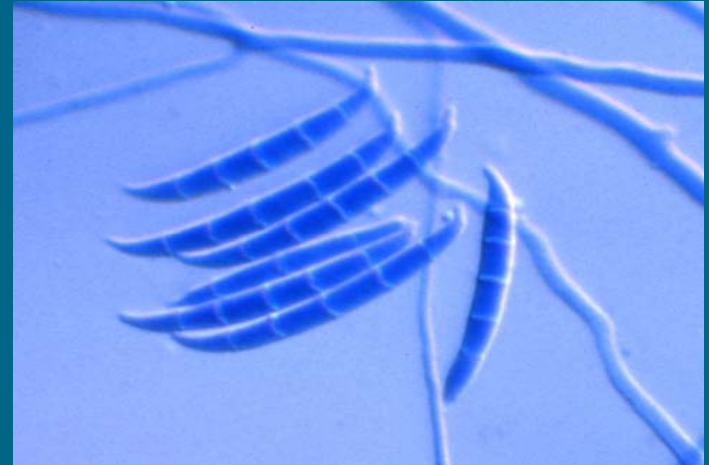
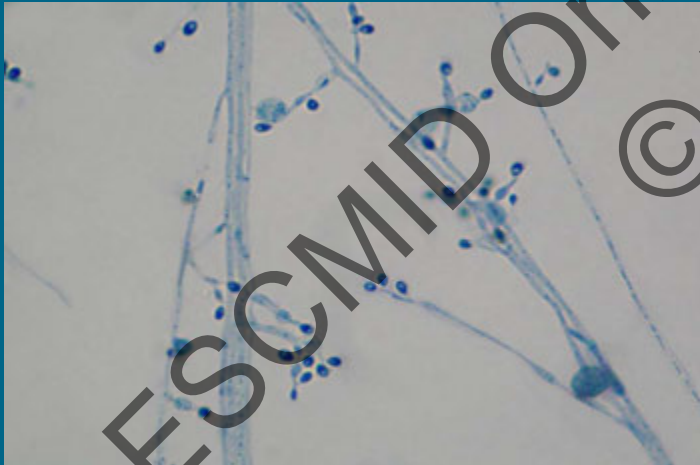




Instituto
de Salud
Carlos III

Polyenes and Echinocandins

Manuel Cuenca-Estrella
2011





Fungal Infections

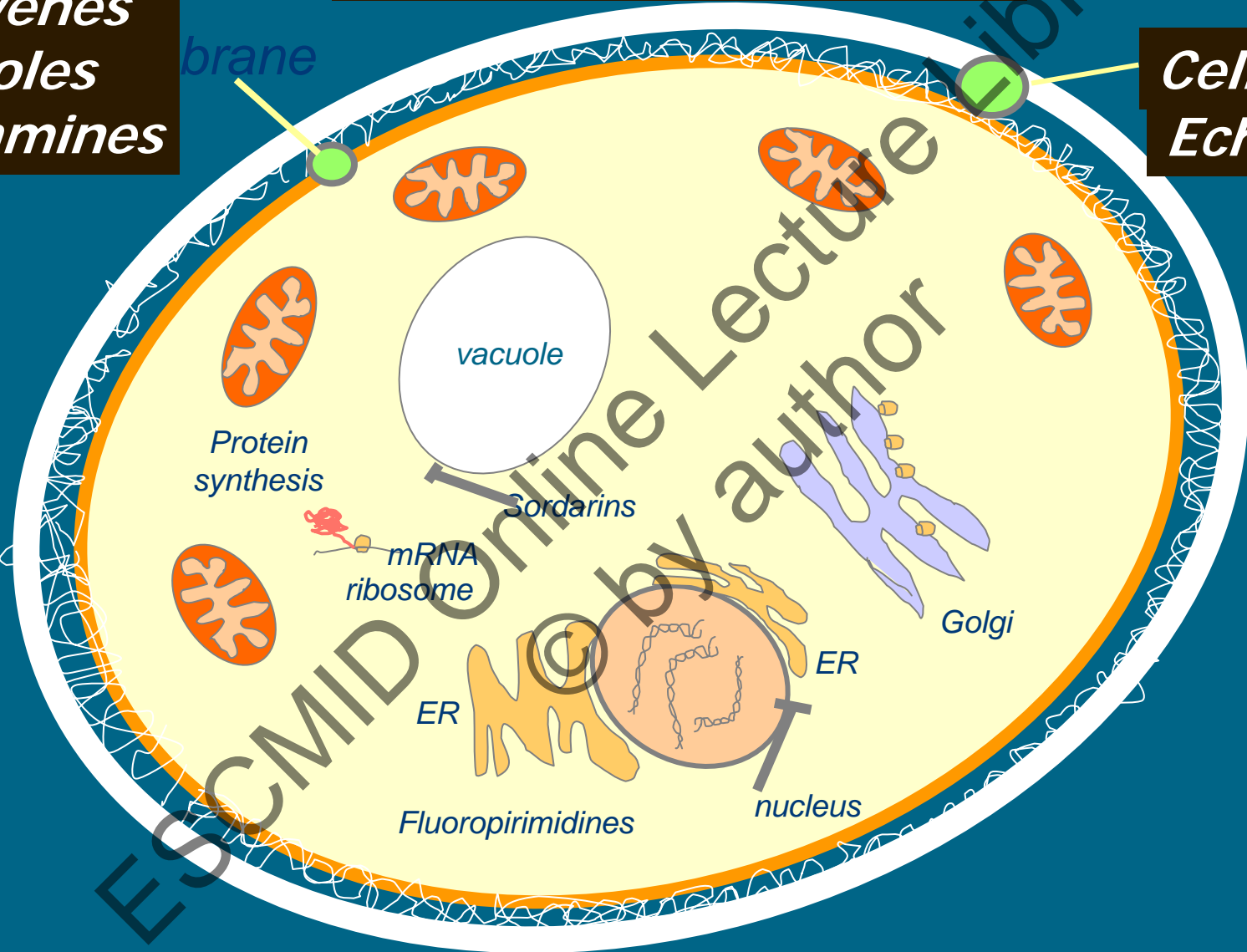
- *Aspergillus* and *Candida* spp. are still the most common causes of IFD
- Emerging pathogens: :
 - No reliable epidemiological data available
 - Ubiquitous species can infect any patient with predisposing factors



Fungal cell and antifungal targets

Polyenes
Azoles
Allylamines

Cell wall
Echinocandins



brane

Protein synthesis

vacuole

Sordarins

mRNA
ribosome

Golgi

ER

ER

nucleus

Fluoropyrimidines

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Current situation on

Conventional polyenes replaced with lipid formulations (liposomal)

-

- Candida

Voriconazole in Aspergillosis

- Mucor

Echinocandins in candidiasis, ; Fluconazole?

- Mucor

- Mucor

- Mucor

Posaconazole in prophylaxis

Combination therapy





Activity in vitro

Species	Antifungal						
	AMB	FC	FLC	ITC	VRC	POS	ECHIN
<i>Candida albicans</i>	S	S	S	S	S	S	S
<i>Candida parapsilosis</i>	S	S	S	S	S	S	S-I
<i>Candida tropicalis</i>	S	S	S	S	S	S	S
<i>Candida glabrata</i>	S	S	I-R	S-I-R	S-I-R	S-I-R	S
<i>Candida krusei</i>	S	R	R	S-I-R	S-I-R	S-I-R	S
<i>Candida guilliermondii</i>	S	S	I-R	S	S	S	S-I
<i>Candida lusitanae</i>	S	S	S	S	S	S	S
<i>Cryptococcus</i> spp.	S	S-I	S-I-R	S	S	S	R
<i>Trichosporon</i> spp.	S-I-R	R	I-R	S-I-R	S-I-R	S-I-R	R
Endemic mycosis	S	I-R	S	S	S	S	S-I
<i>Aspergillus fumigatus</i>	S	R	R	S	S	S	S
<i>Aspergillus flavus</i>	S	R	R	S	S	S	S
<i>Aspergillus terreus</i>	I-R	R	R	S	S	S	S
<i>Aspergillus niger</i>	S	R	R	S-I-R	S	S	S
<i>Fusarium</i> spp.	S-I-R	R	R	R	S-I-R	S-I-R	R
<i>Scedosporium</i> spp.	S-I-R	R	R	R	S-I-R	S-I-R	R
Mucorales	S-I-R	R	R	R	R	S-I-R	R



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. Sobel³

Clinical Infectious Diseases 2009;48:503–35

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}

Clinical Infectious Diseases 2008;46:327–60



Third European Conference on Infections in Leukemia ECIL3

Garden Beach Hotel, Juan-les Pins, France

September 25-26, 2009

Version April 13, 2009



EFISG

**ESCMID FUNGAL INFECTION
STUDY GROUP**

ESCMID Diagnostic & Management Guideline for Candida Diseases 2011

POLYENES

- Nystatin y pymaricin
 - Topical and oral solutions
- Amphotericin B
 - Safe for that time (c 1960). IV presentation
 - 70 % fever and chills
 - Doses: 0,3-1,5 mg/Kg
 - 3-5 g renal toxicity



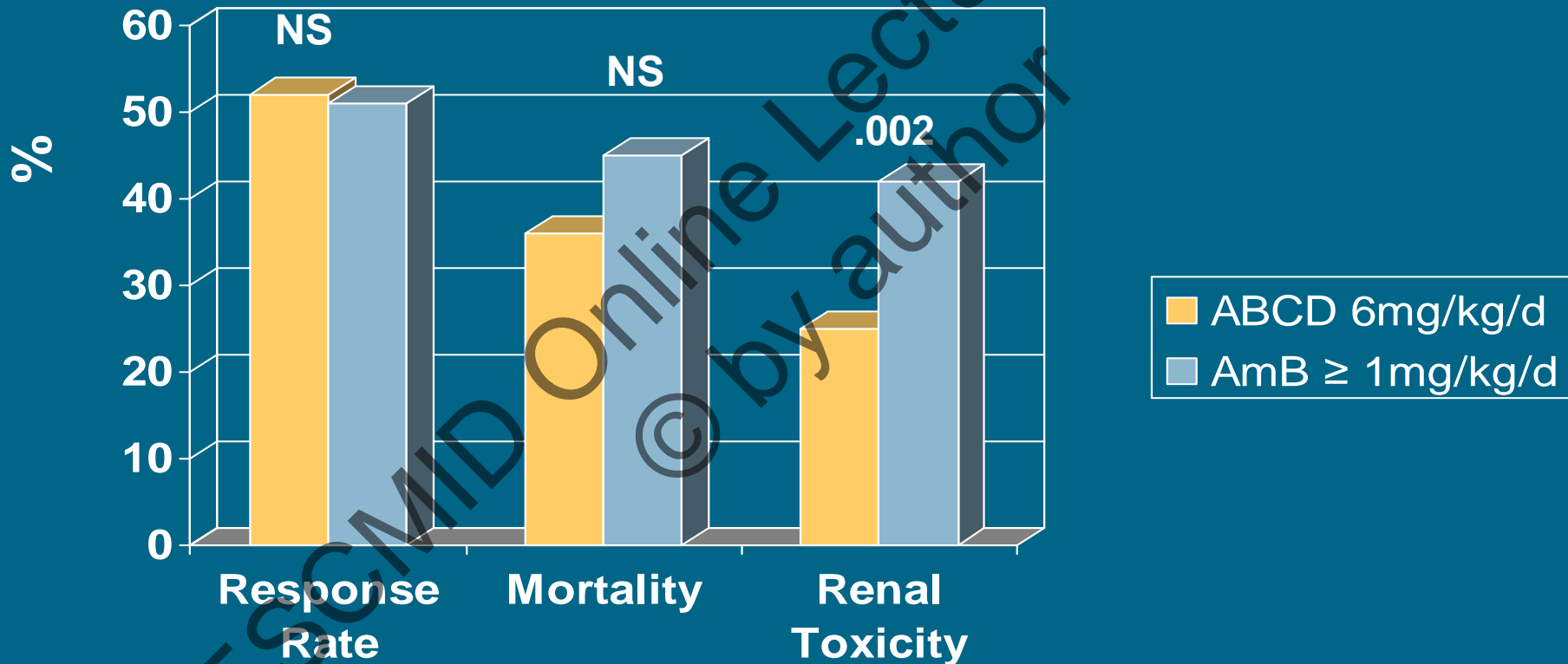
Lipid presentations

- Liposomal: Ambisome
- Lipid complex: Abelcet
- Colloidal dispersion: Amphocil
- Liposomal nystatin: Nyotran
 - Higher doses
 - Low administration effects
 - Safe, less toxicity
 - High cost
 - High efficacy??



AmB lipid derivatives for invasive aspergillosis?

174 patients





AMPHO indications

- Invasive candidiasis fluconazole resistant
 - Alternative to echinocandins
 - Neutropenic patients (first line)
- Severe cryptococosis (plus flucytosine)
- Endemic mycosis (severe or IC)
 - Histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis,
- Aspergillosis, zygomycosis and other emerging mycosis
- Febrile neutropenia



AmbiLoad trial : overall response at EOT

Randomized multicenter double-blind trial
High vs. Conventional dosage during 14 days

N (%)	LAmB 3mg N=107	LAmB 10mg N=94
Overall Response at EOT	53 (50)	43 (46)
CR	1 (1)	2 (2)
PR	52 (49)	41 (44)
Unfavorable Response		
Stable	8 (7)	5 (5)
Failure	36 (34)	36 (38)
Not evaluable	10 (9)	10 (11)

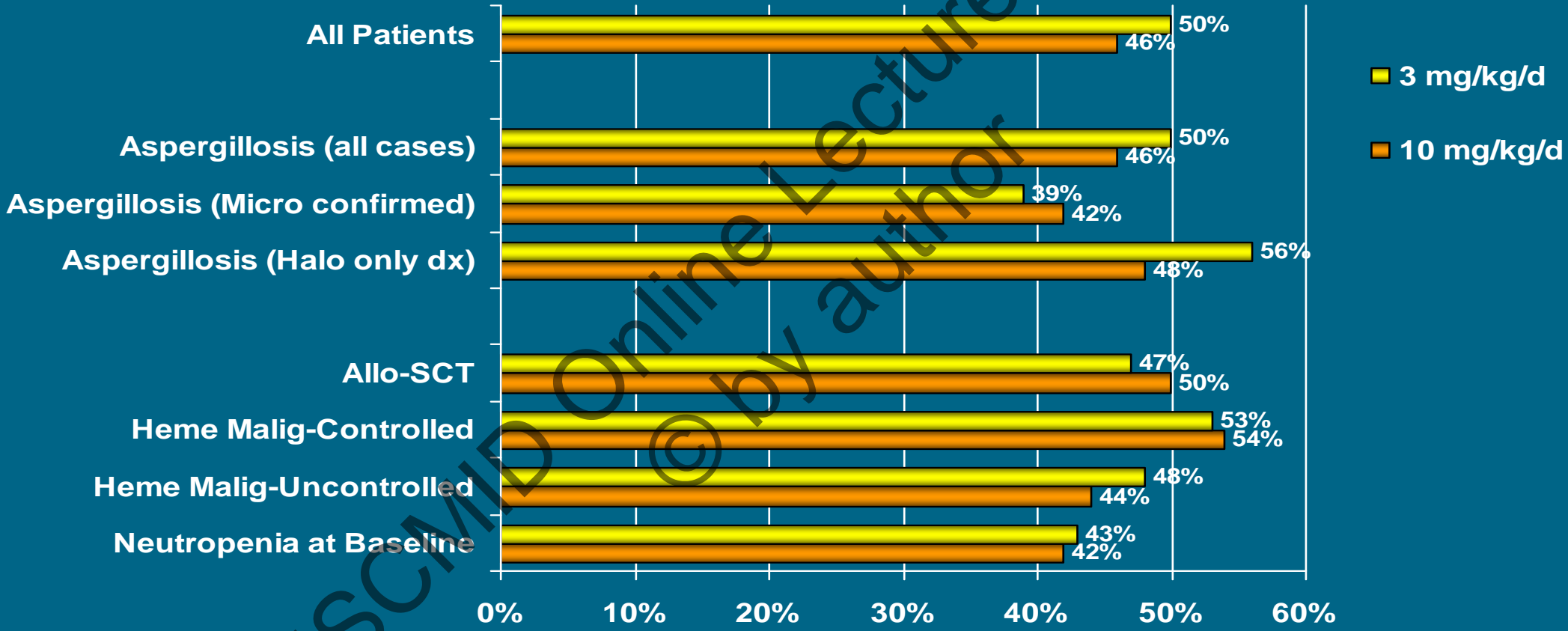
[MITT]

OA Cornely, et al. CID 2007; 44:1289-97



Favorable Overall Response

No differences are statistically significant





AmBiLoad Trial Laboratory Abnormalities

N (%)	AmBi-3mg N=115	AmBi-10mg N=111	P-value
Nephrotoxicity ¹	16/111 (14)	31/100 (31)	p<.01
Hypokalemia			
K ⁺ < 3.0 (gr 3)	18/113 (16)	32/106 (30)	p=.015
K ⁺ < 2.5 (gr 4)	3/113 (3)	4/106 (4)	NS
LFT abnormalities ²	18 (16)	16 (14)	NS

1. Serum creatinin > 2x baseline

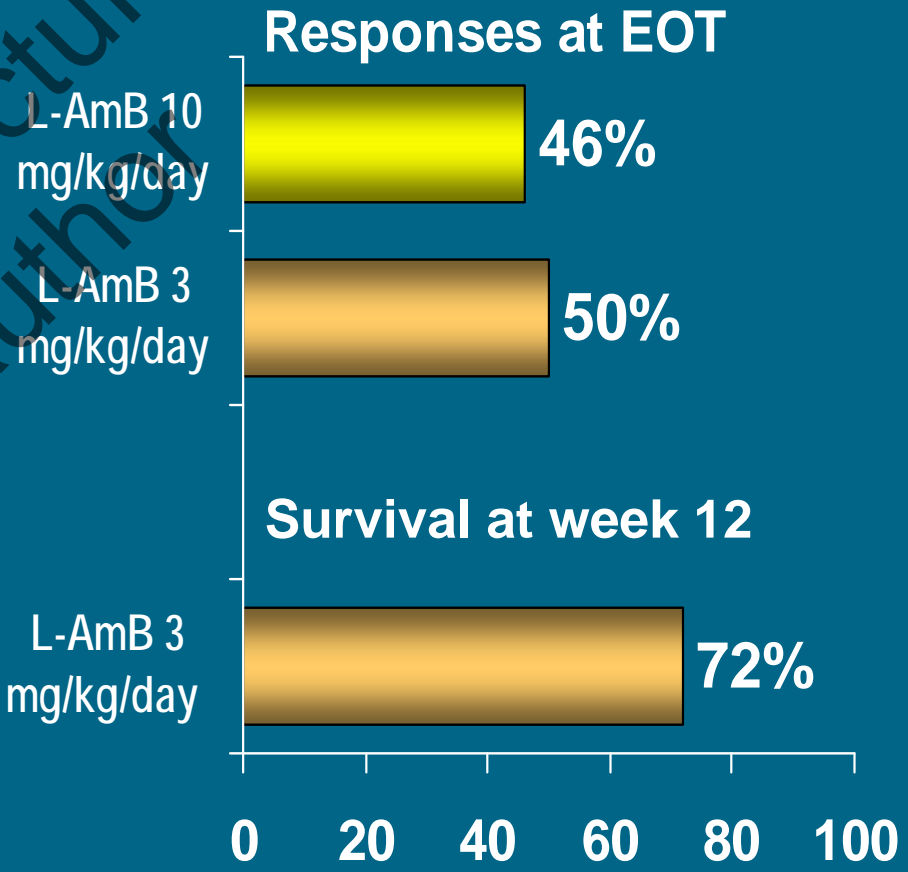
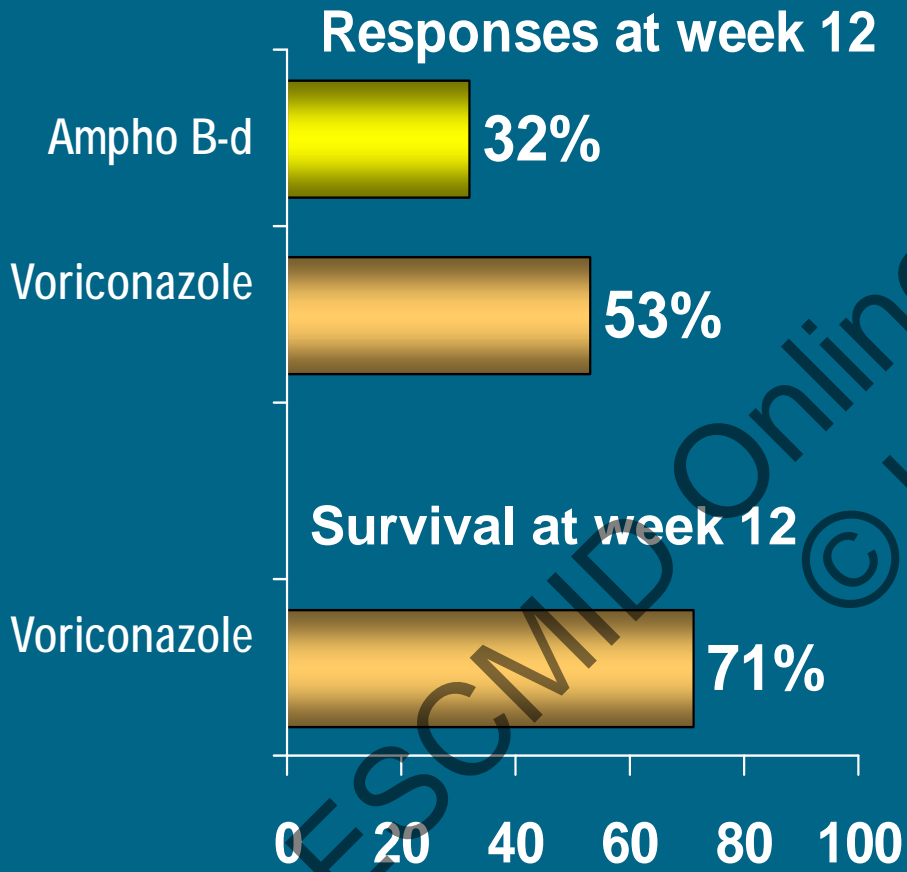
2. Treatment emergent grade 3 or 4 values of ALT, AST, alkaline phosphatase, or bilirubin



Initial Therapy for Invasive Aspergillosis

Voriconazole vs AmB-d

AmBiLoad





Amphotericin B Lipid Complex Versus Liposomal Amphotericin B Monotherapy for Invasive Aspergillosis in Patients With Hematologic Malignancy

Ray Y. Hachem, MD

CANCER March 15, 2008 / Volume 112 / Number 6

- **Proven and probable aspergillosis**
- **157 L-Amb vs. 82 Amb-LC (first line and salvage therapies), several doses**
- **Similar response but higher toxicity with Amb-LC**

bjh research paper

Epidemiology and outcome of infections due to *Aspergillus terreus*: 10-year single centre experience

Cornelia Lass-Flörl,¹ Katharina Griff,¹
Astrid Mayr,¹ Andreas Petzer,² Günter
Gastl,² Hugo Bonatti,³ Martin Freund,⁴
Gabriele Kropshofer,⁵ Manfred P.
Dierich¹ and David Nachbaur²

*Departments of ¹Hygiene, Microbiology and Social
Medicine, ²Haematology and Oncology, ³Surgery,
⁴Radiology I, and ⁵Paediatrics, Medical University
of Innsbruck, Innsbruck, Austria*

Epidemiology and outcome of infections due to *Aspergillus terreus*: 10-year single centre experience

	<i>A. terreus</i>	Other species
Dissemination	63%	32%
CNS	31%	---
Skin	29%	---
AmB response	20%	47%

Epidemiology and outcome of infections due to *Aspergillus terreus*: 10-year single centre experience

	<i>A. terreus</i>	Other species
Dissemination	63%	32%
CNS	31%	---
Skin	29%	---
AmB response	20%	47%



Lung Transplantation

Nebulized AmBisome Prophylaxis dosing

- 25 mg of Liposomal Amphotericin B:
 - 30-60 d. Three times a week
 - Healing bronchial anastomoses
 - 2-6 month. Once a week
 - > 6 month. Once every 15 days
- In case of colonization: Three times a week



Monforte et al. J Heart Lung Transplant. 2009 Feb;28(2):170-5

Figure 3. Prophylaxis Mould Infection results Lung Transplant at Vall d'Hebron Hospital (1991-2004)

	n	<i>Candida</i> Mucositis n (%)	Mould Infection n (%)	Median (range) Time to Tx (mo)	Death Related to <i>Aspergillus</i> Infection, n (%)
No prophylaxis	13	8 (61.5 %)	7 (53.8 %) 3 IFI 2 UT - 2 T	11.6 (0.3-41)	3 (23.1%)
Nebulized CAB deoxycolate	280	0	17 (6%) 2 IFI 3 UT - 12 T	6 (0.5-27.6)	2 (0.7 %)
Nebulized Liposomal AB	40	0	1 (2.5%) 1 T		0

UT: upper tract
T: traqueobronquitis



Aerosolized Liposomal Amphotericin B for the Prevention of Invasive Pulmonary Aspergillosis during Prolonged Neutropenia: A Randomized, Placebo-Controlled Trial

Bart J. Rijnders,^{1,4} Jan J. Cornelissen,² Lennert Slobbe,³ Martin J. Becker,⁸ Jeanette K. Doorduyn,² Wim C. J. Hop,⁶ Elisabeth J. Ruijgrok,⁷ Bob Löwenberg,² Arnold Vulto,⁵ Pieterella J. Lugtenburg,² and Siem de Marie⁴

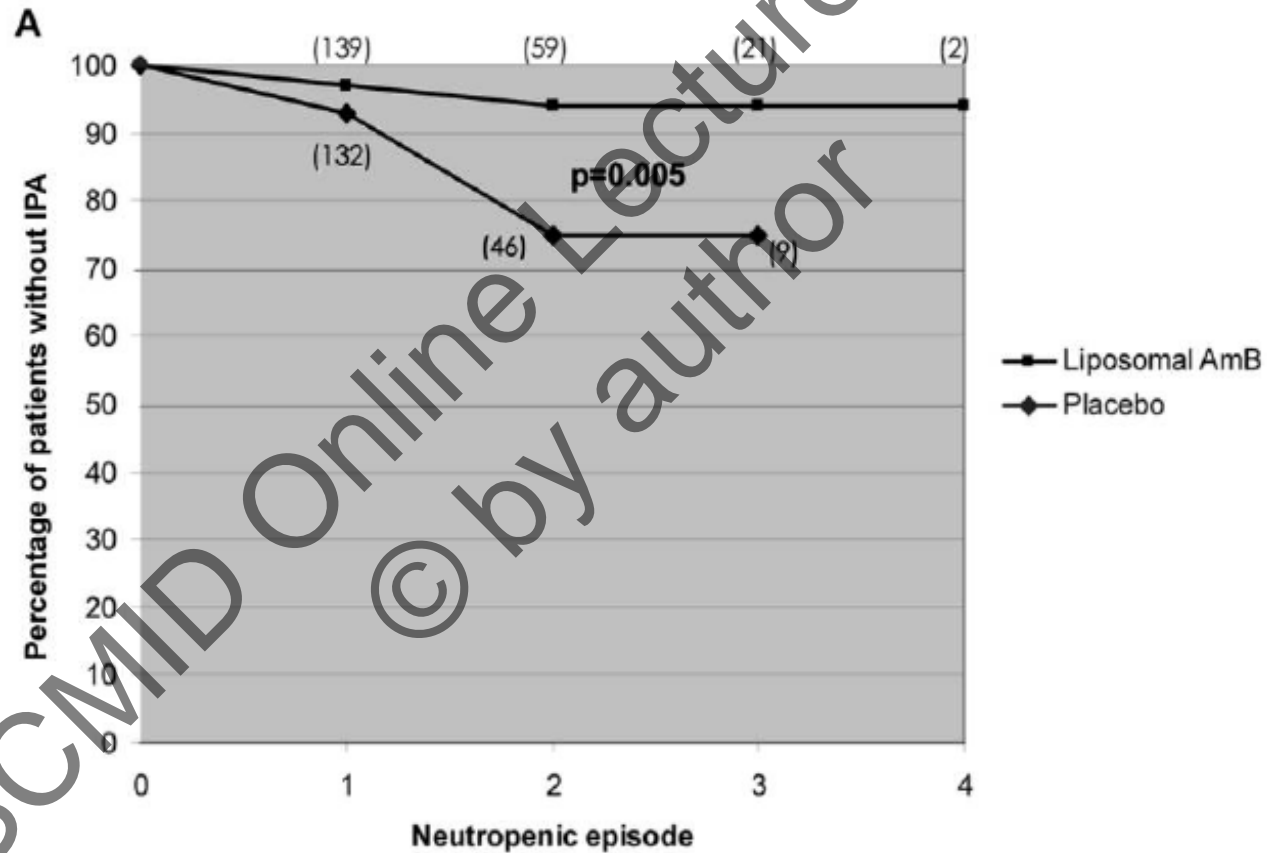
Clinical Infectious Diseases 2008;46:1401-8

- **271 patients were studied during 407 neutropenic episodes.**
- **18 of 132 patients in the placebo group developed IPA**
- **6 of 139 patients in the liposomal amphotericin B group**
- **5-mg/mL nebulization for 30 min per day on 2 consecutive days a week**



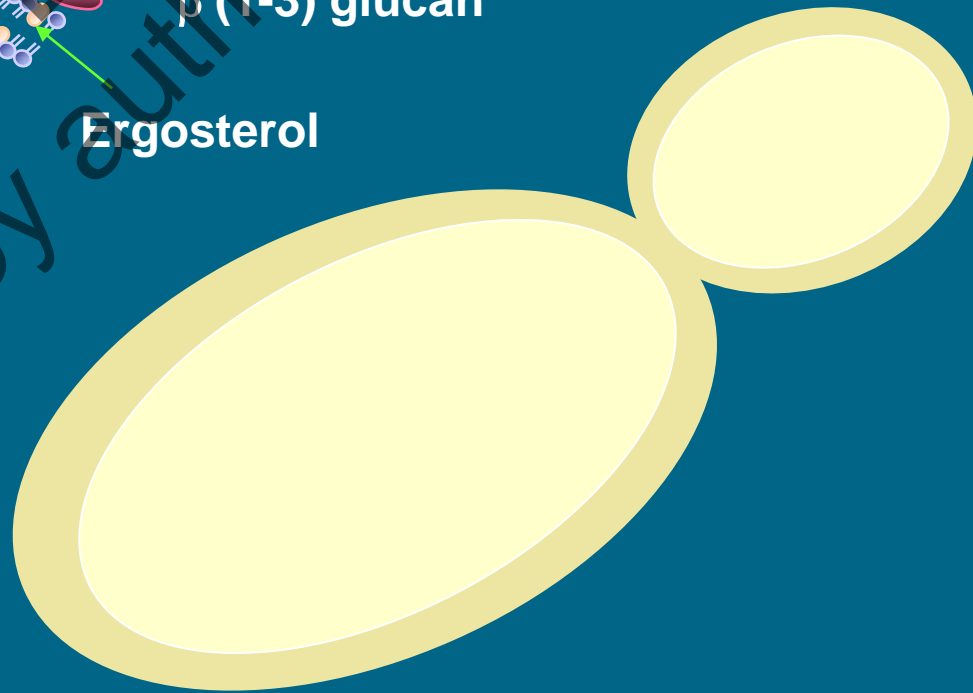
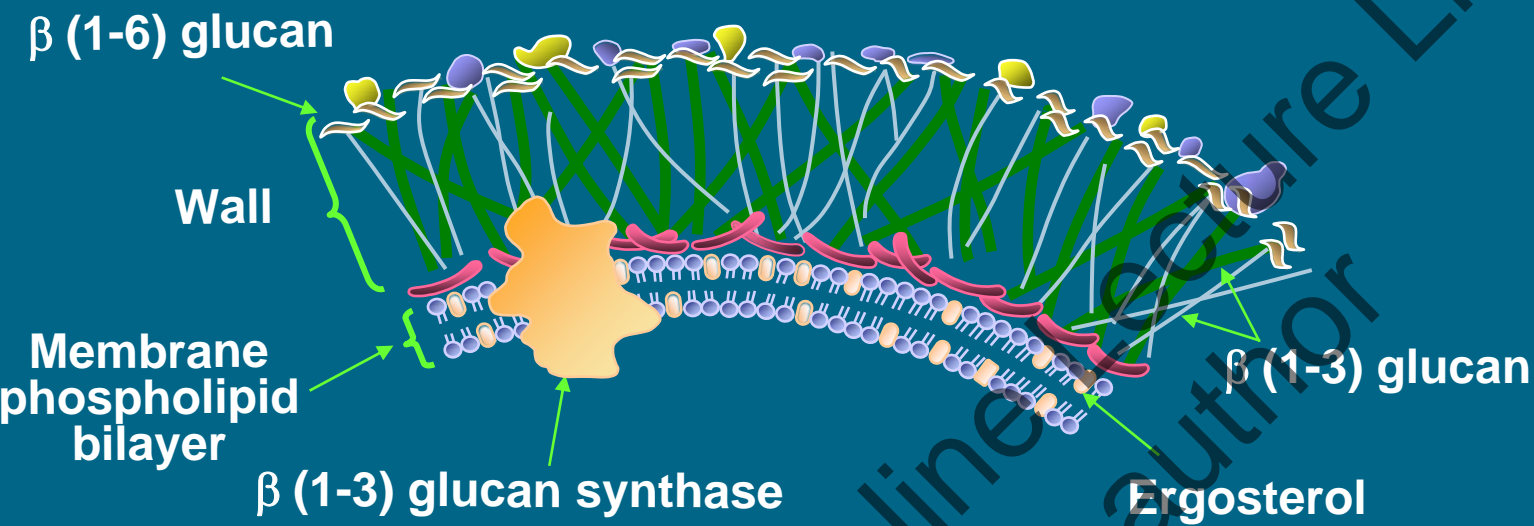
Aerosolized Liposomal Amphotericin B for the Prevention of Invasive Pulmonary Aspergillosis during Prolonged Neutropenia: A Randomized, Placebo-Controlled Trial

Bart J. Rijnders,^{1,4} Jan J. Cornelissen,² Lennert Slobbe,³ Martin J. Becker,⁸ Jeanette K. Doorduyn,² Wim C. J. Hop,⁶ Elisabeth J. Ruijgrok,⁷ Bob Löwenberg,² Arnold Vulto,⁵ Pieterella J. Lugtenburg,² and Siem de Marie⁴





Candins. Mechanism



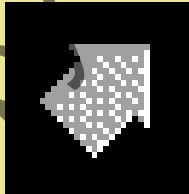
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ECHINOCANDIN

ABC

Azole



FCZ

MDR1

Alterations in FSK1 protein



1,3-BETA-GLUCAN

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Activity in vitro

Species	Antifungal						
	AMB	FC	FLC	ITC	VRC	POS	ECHIN
<i>Candida albicans</i>	S	S	S	S	S	S	S
<i>Candida parapsilosis</i>	S	S	S	S	S	S	S-I
<i>Candida tropicalis</i>	S	S	S	S	S	S	S
<i>Candida glabrata</i>	S	S	I-R	S-I-R	S-I-R	S-I-R	S
<i>Candida krusei</i>	S	R	R	S-I-R	S-I-R	S-I-R	S
<i>Candida guilliermondii</i>	S	S	I-R	S	S	S	S-I
<i>Candida lusitanae</i>	S	S	S	S	S	S	S
<i>Cryptococcus</i> spp.	S	S-I	S-I-R	S	S	S	R
<i>Trichosporon</i> spp.	S-I-R	R	I-R	S-I-R	S-I-R	S-I-R	R
Endemic mycosis	S	I-R	S	S	S	S	S-I
<i>Aspergillus fumigatus</i>	S	R	R	S	S	S	S
<i>Aspergillus flavus</i>	S	R	R	S	S	S	S
<i>Aspergillus terreus</i>	I-R	R	R	S	S	S	S
<i>Aspergillus niger</i>	S	R	R	S-I-R	S	S	S
<i>Fusarium</i> spp.	S-I-R	R	R	R	S-I-R	S-I-R	R
<i>Scedosporium</i> spp.	S-I-R	R	R	R	S-I-R	S-I-R	R
Mucorales	S-I-R	R	R	R	R	S-I-R	R



Caspofungin in refractory IA

Favorable responses (n=37)

All patients

≥ 1 dose received

45% = 37 pts /83 [5% CR, 40% PR]

Treatment >7 days

56.1 % = 37 pts/66 [6% CR, 50% PR]

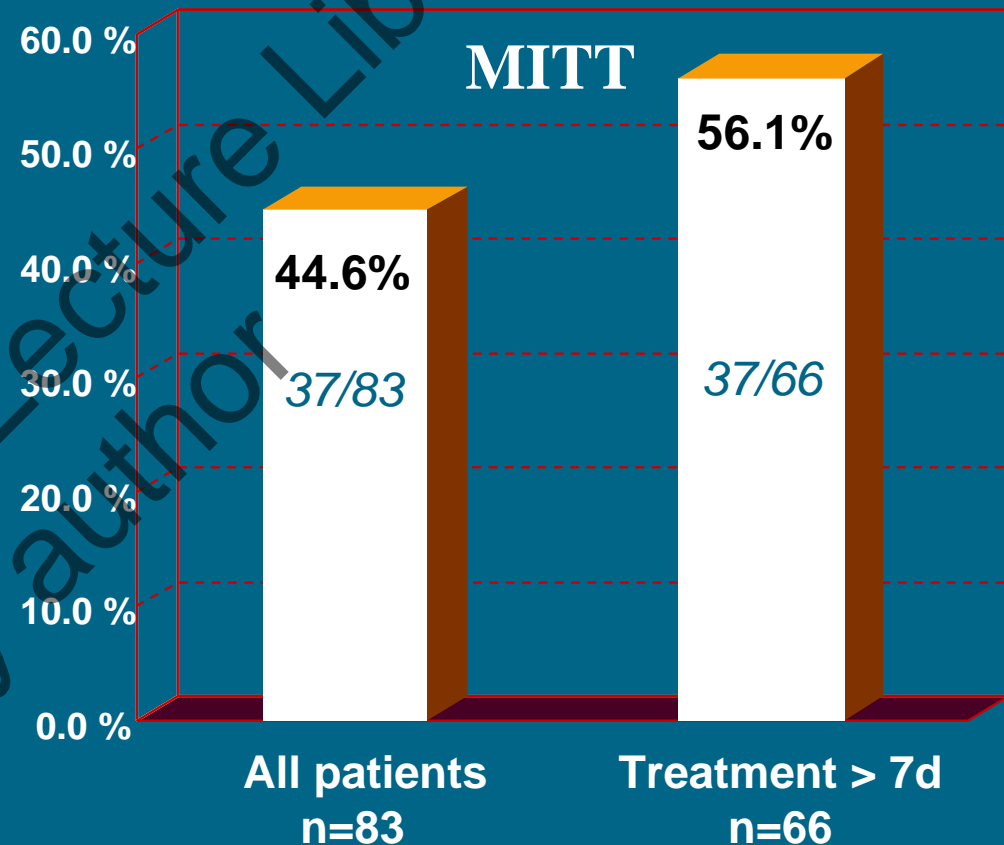
Relapse

3/37

W4 after end of therapy

One relapse confirmed

Only one patient previously treated by VCZ

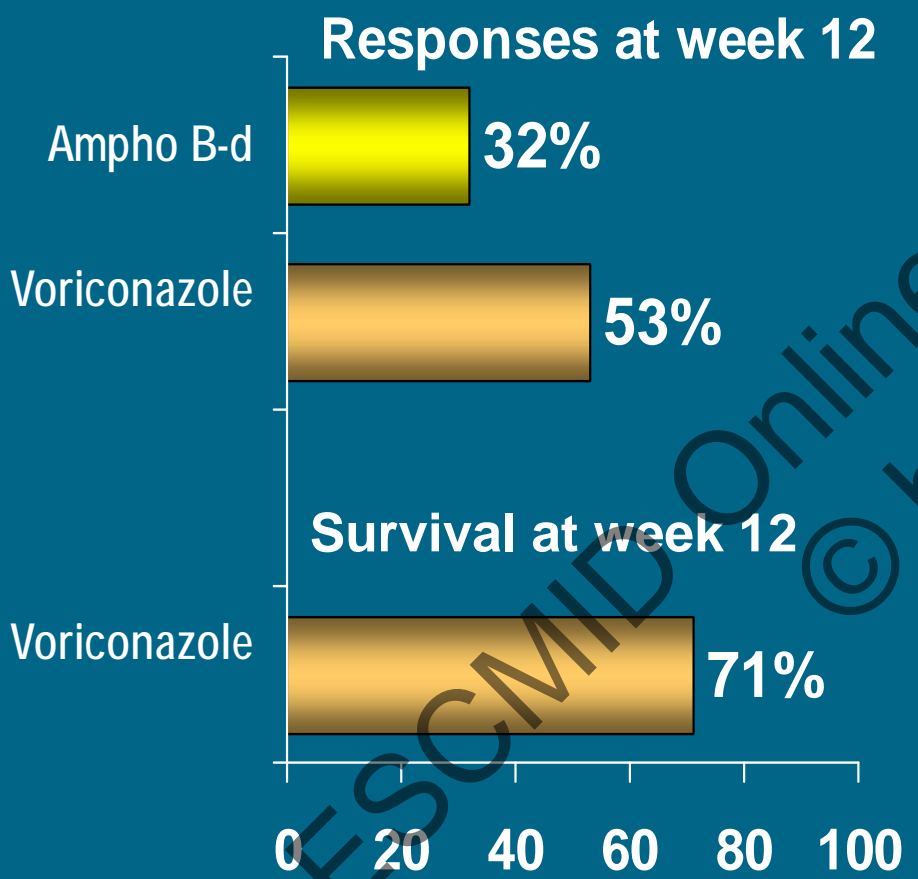


- Multicenter, non comparative, open trial
- 86 % refractory cases
- 77.1 % : IPA
- 73 % : Hematological malignancy
- 22.9 % : Neutropenic

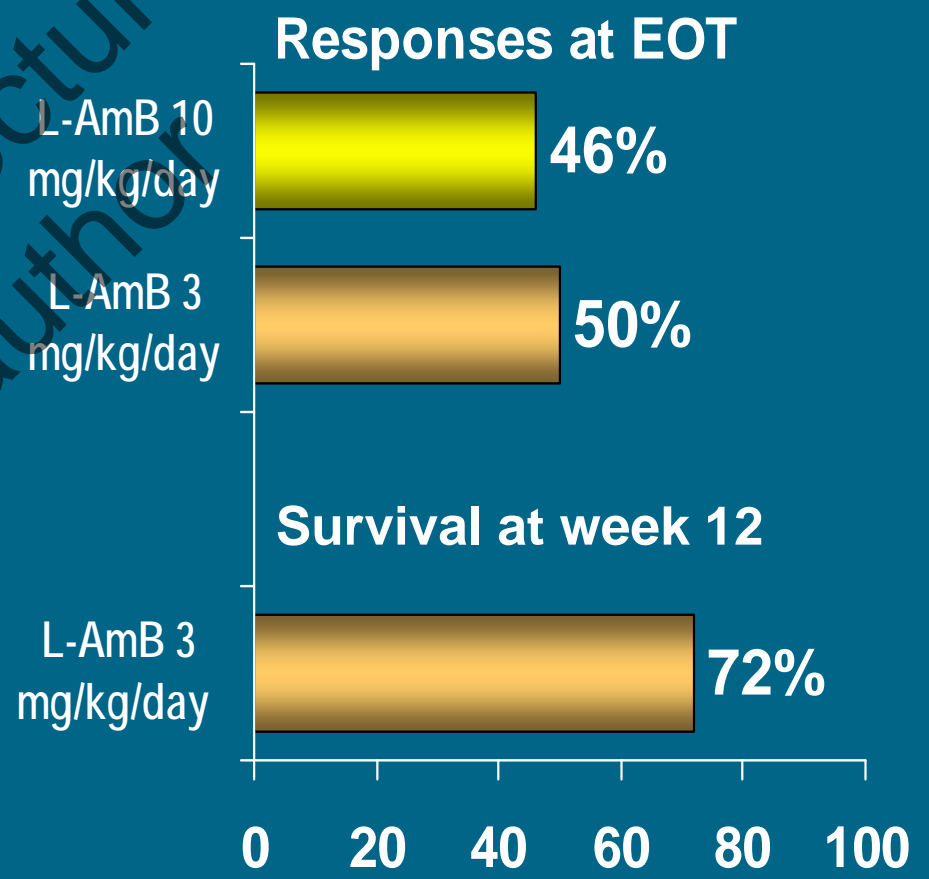


Initial Therapy for Invasive Aspergillosis

Voriconazole vs. AmB-d



AmBiLoad





Initial Therapy for Invasive Aspergillosis

Viscoli et al. JAC 2010

Initial therapy with 70/50 mg/d

33% response at 12 weeks

53% survival rate at 12 weeks



The New England Journal of Medicine

**COMPARISON OF CASPOFUNGIN AND AMPHOTERICIN B
FOR INVASIVE CANDIDIASIS**

JORGE MORA-DUARTE, M.D., ROBERT BETTS, M.D., COLEMAN ROTSTEIN, M.D., ARNALDO LOPES COLOMBO, M.D.,
LUIS THOMPSON-MOYA, M.D., JUANITA SMETANA, B.S., ROBERT LUPINACCI, M.S., CAROLE SABLE, M.D.,
NICHOLAS KARTSONIS, M.D., AND JOHN PERFECT, M.D., FOR THE CASPOFUNGIN INVASIVE CANDIDIASIS STUDY GROUP*

N Engl J Med, Vol. 347, No. 25 · December 19, 2002



Caspofungin in candidemia

Global response at end of IV therapy

Randomized multicenter double-blind trial Non-neutropenic & neutropenic patients

Analysis	Caspofungin 70/50 mg n/m (%)	Amphotericin B 0.6-1.0 mg/kg n/m (%)	Estimated difference % (95.6% CI)
MITT (n=244)	80/109 (73.4)	71/115 (61.7)	12.7% (-0.7- 26.0) (p=0.09)
Evaluable patients	71/88 (80.7)	63/97 (64.9)	15.4% (1.1- 29.7) (p=0.03)



COMPARISON OF CASPOFUNGIN AND AMPHOTERICIN B FOR INVASIVE CANDIDIASIS

Species	N	GM MIC
<i>C albicans</i>	133 (25 FLZ R)	0.08
<i>C parapsilosis</i>	58	0.69

FAILURE OR RELAPSE

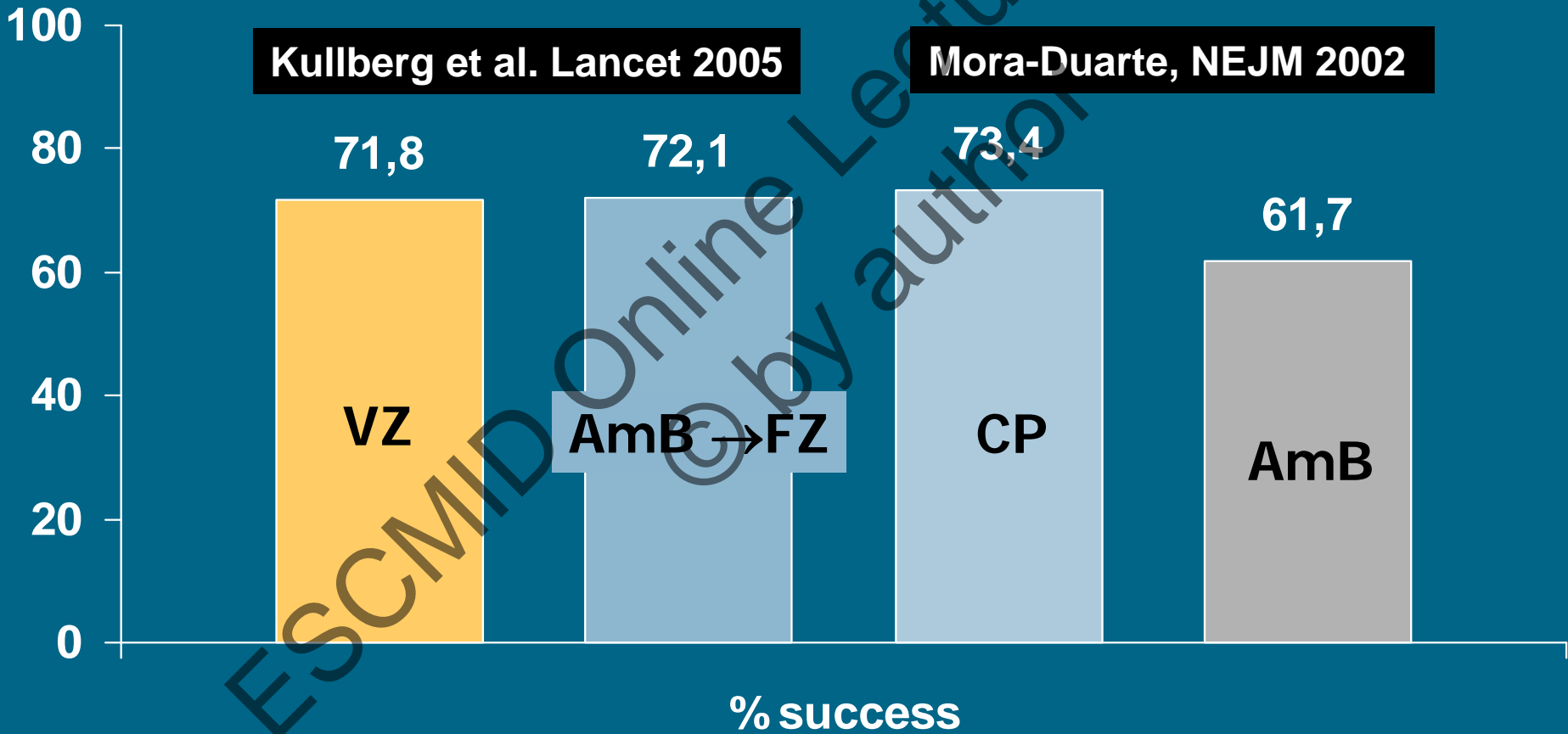
CASPOFUNGIN (N= 109) AMPHOTERICIN B (N= 115)


no. (%)

Failure at end of therapy	29 (26.6)	44 (38.3)
Persistently positive cultures	9 (8.3)	10 (8.7)*
<i>Candida albicans</i>	3	8
<i>C. glabrata</i>	1	0
<i>C. krusei</i>	0	1
<i>C. parapsilosis</i>	5†	0
<i>C. albicans</i> and <i>C. lusitaniae</i>	0	1



Response at End of Treatment (MITT Population)





A Multicenter, Double-Blind Trial of a High-Dose Caspofungin Treatment Regimen versus a Standard Caspofungin Treatment Regimen for Adult Patients with Invasive Candidiasis

Robert F. Betts,¹ Marcio Nucci,⁷ Deepak Talwar,⁹ Marcelo Gareca,² Flavio Queiroz-Telles,⁸ Roger J. Bedimo,⁵ Raoul Herbrecht,¹⁰ Guillermo Ruiz-Palacios,¹¹ Jo-Anne H. Young,⁴ John W. Baddley,⁶ Kim M. Strohmaier,³ Kimberly A. Tucker,³ Arlene F. Taylor,³ and Nicholas A. Kurtzman,³ for the Caspofungin High-Dose Study Group^a

Clinical Infectious Diseases 2009; 48:1676–84

50 mg/d tras 70 mg/d, un día vs. 150 mg/d

104 pat vs. 100 pat invasive candidiasis (7-8% neutropenia)

Response: 71,6% vs. 77,9%. Mortality similar but response *C. parapsilosis* 61% vs. 81%

Toxicity: 1, 9% vs. 3% (flebitis, hepatic alterations)



The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 30, 2004

VOL. 351 NO. 14

Caspofungin versus Liposomal Amphotericin B
for Empirical Antifungal Therapy in Patients
with Persistent Fever and Neutropenia

Thomas J. Walsh, M.D., Hedy Tepler, M.D., Gerald R. Donowitz, M.D., Johan A. Maertens, M.D.,
Lindsey R. Baden, M.D., Anna Dmoszynska, M.D., Ph.D., Oliver A. Cornely, M.D., Michael R. Bourque, M.S.,
Robert J. Lupinacci, M.S., Carole A. Sable, M.D., and Ben E. dePauw, M.D., Ph.D.



Table 2. Outcomes of Empirical Antifungal Therapy.*

End Point	Caspofungin (N=556)	Liposomal Amphotericin B (N=539)	Difference (CI) [†] <i>percentage points</i>	P Value
Overall favorable response				
Adjusted for strata — no. of patients (%)	190 (33.9)	181 (33.7)	0.2 (-5.6 to 6.0)	
Not adjusted for strata — no. of patients (%)	190 (34.2)	181 (33.6)	—‡	
Observed, according to risk category — no. of patients/total no. (%)				
High risk	63/146 (43.2)	46/122 (37.7)	5.4 (-6.3 to 17.2)	
Low risk	127/410 (31.0)	135/417 (32.4)	-1.4 (-7.7 to 4.9)	
Antifungal prophylaxis	105/313 (33.5)	100/304 (32.9)		
No antifungal prophylaxis	85/243 (35.0)	81/235 (34.5)		
Observed components of primary end point				
Successful treatment of baseline fungal infection — no. of patients/ no. with infection	14/27 (51.9)	7/27 (25.9)	25.9 (0.9 to 51.0)	0.04
Absence of breakthrough fungal infection — no. of patients/total no.	527 (94.8)	515 (95.5)	-0.8 (-3.3 to 1.8)	0.56
Survival for ≥7 days after completion of study therapy — no. of patients/ total no. [§]	515 (92.6)	481 (89.2)	3.4 (0.0 to 6.8)	0.05
Resolution of fever in setting of neutropenia — no. of patients/total no.	229 (41.2)	223 (41.4)	-0.2 (-6.0 to 5.6)	0.95
Study therapy discontinued prematurely because of toxicity or lack of efficacy — no. of patients/total no.				
No	499 (89.7)	461 (85.5)	4.2 (0.3 to 8.1)	0.03
Yes				
Lack of efficacy [¶]	30 (5.4)	34 (6.3)	-0.9 (-3.7 to 1.9)	
Drug toxicity	27 (4.9)	44 (8.2)	-3.3 (-6.2 to -0.4)	

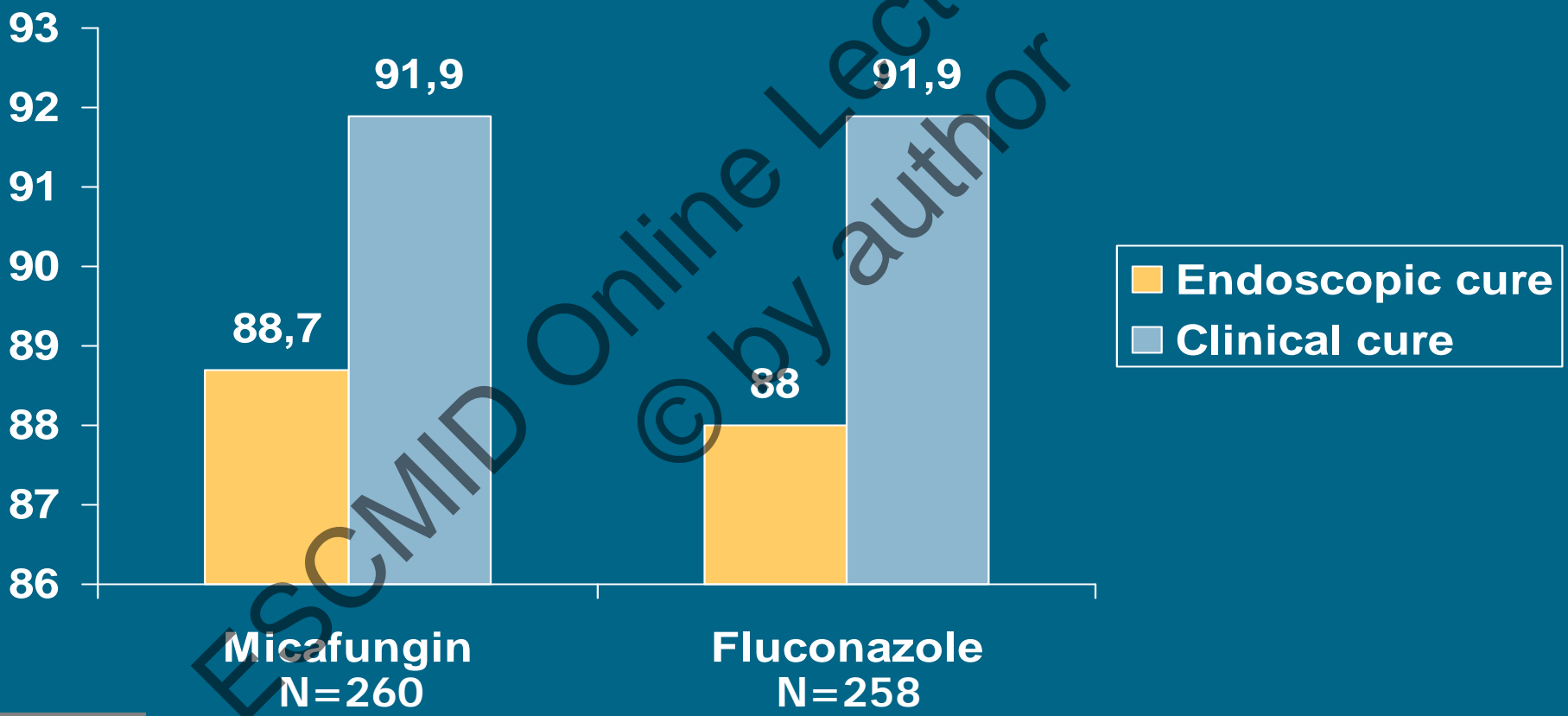
Micafungin

- Esophageal candidiasis
- Prophylaxis in neutropenia after SCT
- Invasive candidiasis
- Aspergillosis*
- Febrile neutropenia*
- Other prophylaxis*



Mica & oesophageal candidosis

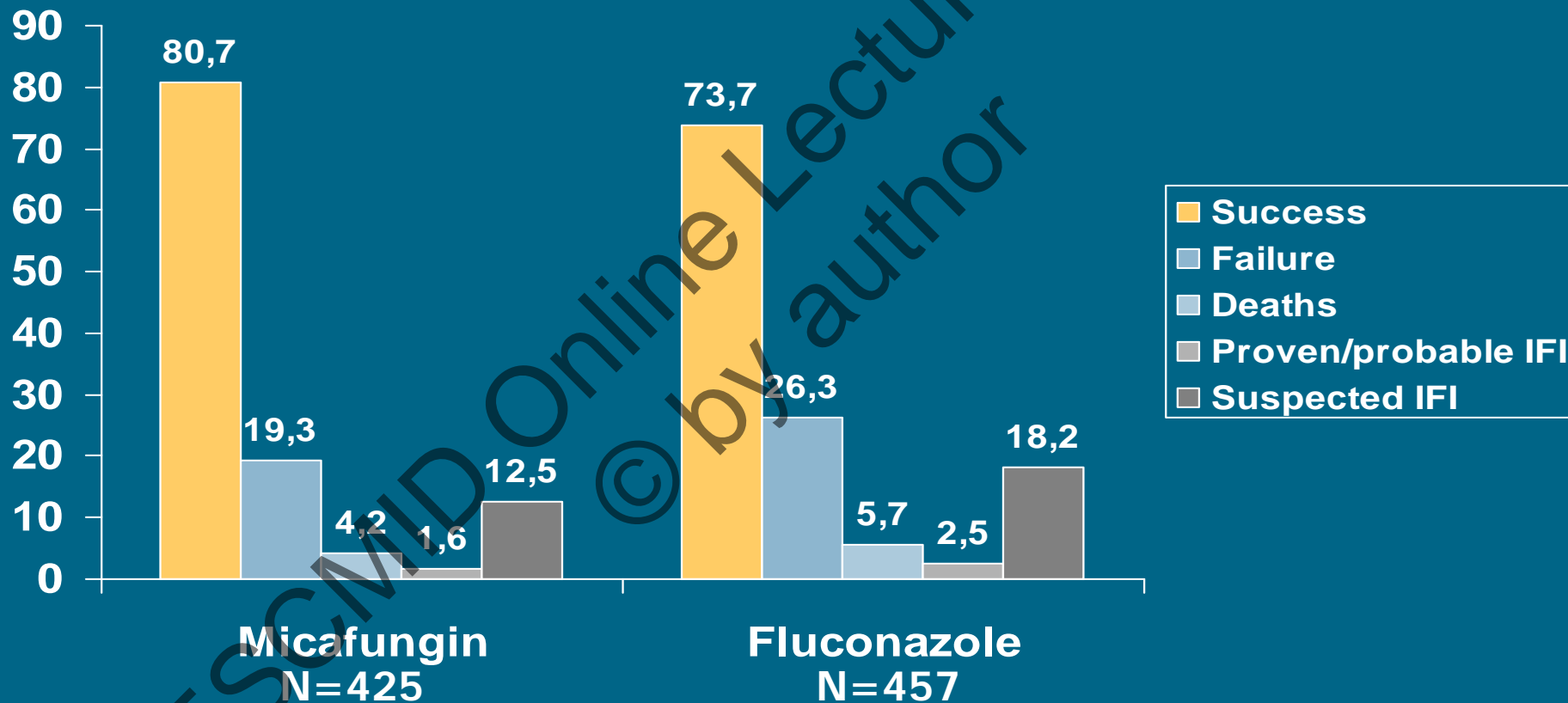
Micafungin 150/mg/day vs Fluconazole 200 mg/day





Mica & Prophylaxis in BMT

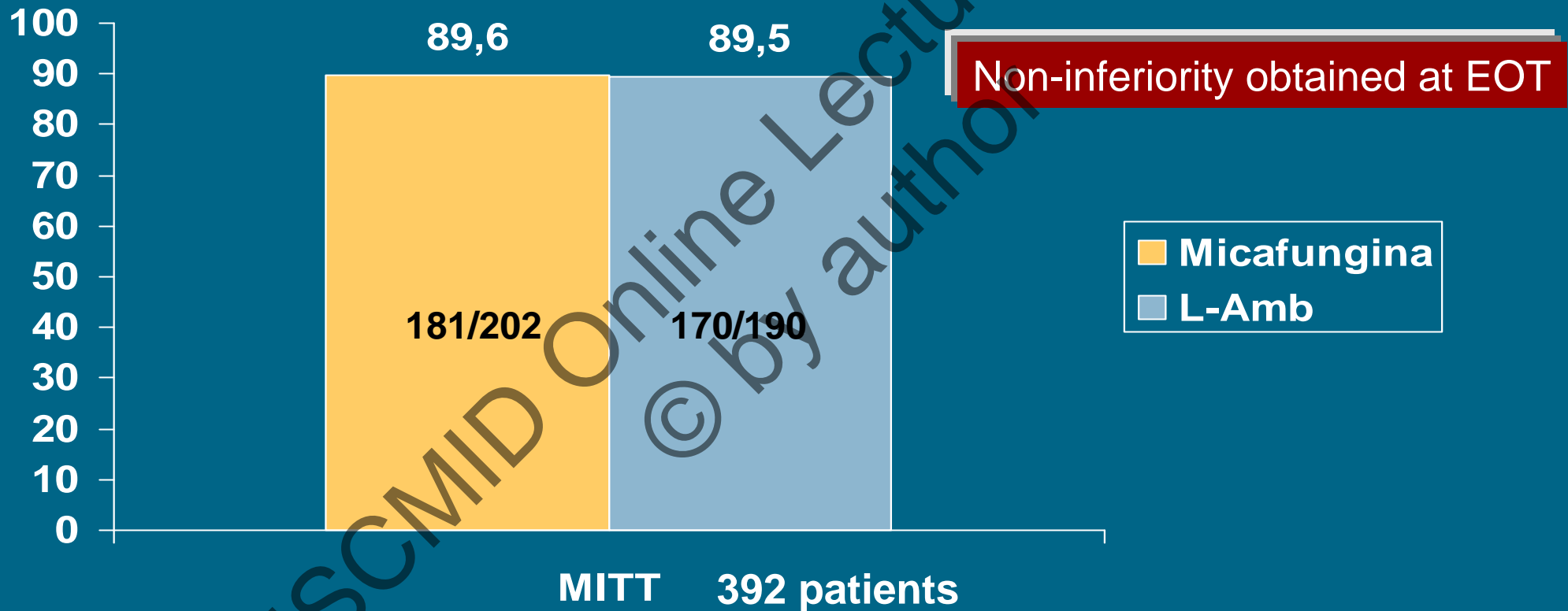
Micafungin 50/mg/day vs Fluconazole 400 mg/day





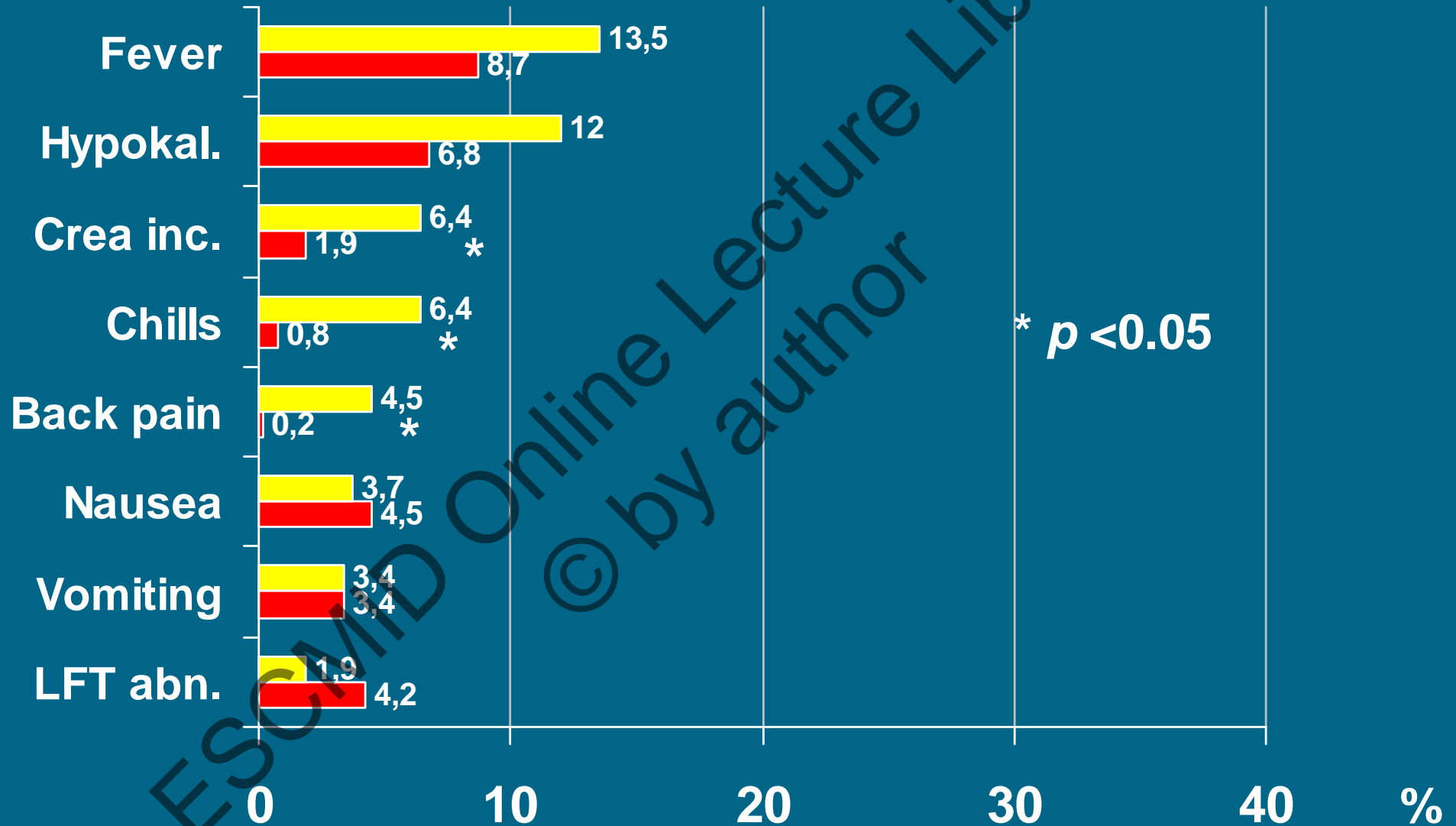
Micafungin and invasive candidosis

Randomised multicenter double-blind non-inferiority phase III trial
non-neutropenic & neutropenic patients





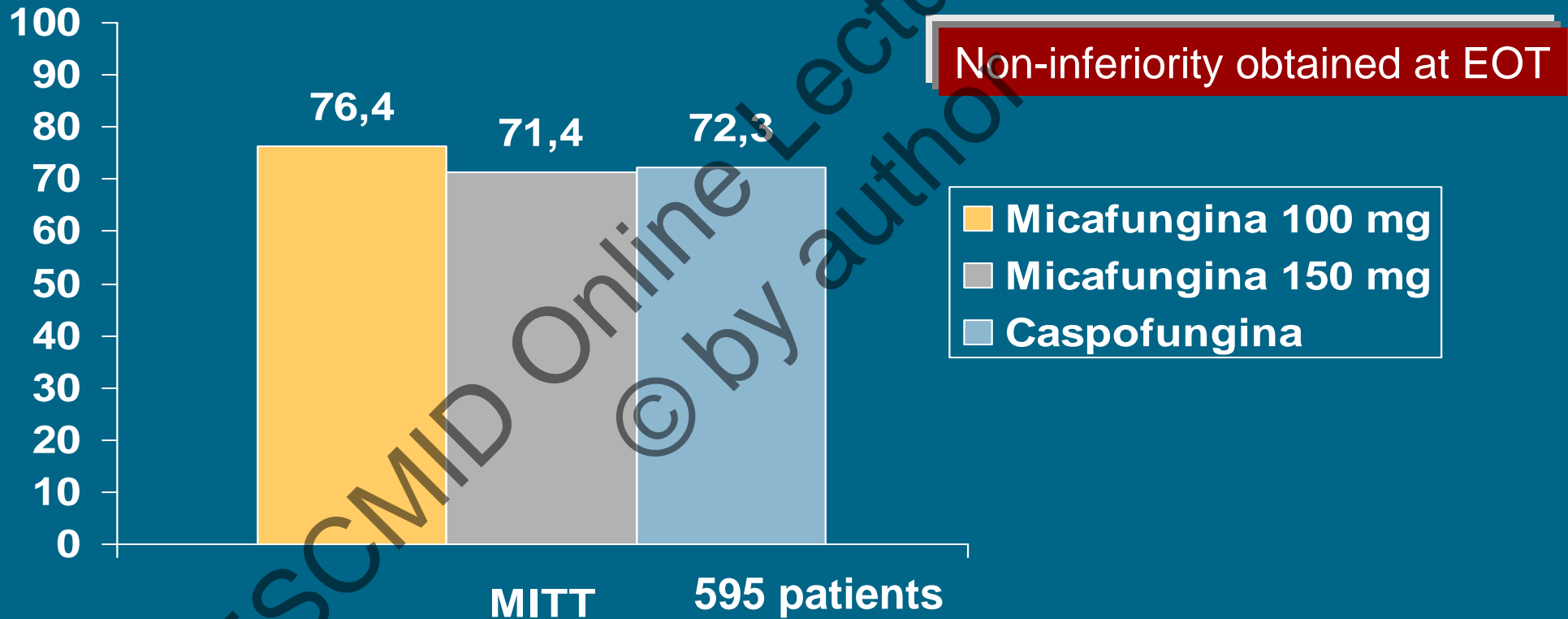
MC related adverse events





Micafungin vs Caspofungina in Candidemia and invasive candidosis

Randomised multicenter double-blind non-inferiority phase III trial





Queiroz-Telles F. et al. Pediatr Infect Dis J. 2008 Sep;27(9):820-6.

Micafungin versus liposomal amphotericin B for pediatric patients with invasive candidiasis: substudy of a randomized double-blind trial.

50 pt L-AMB and 48 pt MICA

19 neonates

35/48 (72.9%) patients treated with MICA and 38/50 (76.0%) patients treated with L-AMB

Discontinuation in MICA group (2/52, 3.8%) and L-AMB group (9/54, 16.7%)



Anidulafungin

- Candidemia
- Esophageal candidiasis
- Peritonitis and abscesses
- Prophylaxis?
- Aspergillosis?

ESCMID Online Lecture Library
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Anidulafungin in candidemia & invasive candidosis

- Randomized, double-blind, multicenter, non inferiority, phase III
- anidulafungin IV 200 mg load 100 mg /d
- fluconazole IV 800 mg load; 400 mg /d
 - ± fluconazole 400 mg/d oral after D 10

Characteristics		Anid N=127 n (%)	Flu N=118 n (%)
Apache II	≤ 20	101 (79.5)	98 (83.1)
	> 20	26 (20.5)	20 (16.9)
	Mean	15.0	14.4
Neutrophils	> 500	124 (97.6)	114 (96.6)
	≤ 500	3 (2.4)	4 (3.4)
Type of infection	candidemia	116 (91.3)	103 (87.3)



Primary Endpoint

Global response at end of iv therapy

Response (MITT)	Treatment Group		Treatment Difference (%)	95% CI
	Anid N = 127	Flu N = 118		
Success, n (%)	96 (75.6)	71 (60.2)	15.42	3.9-27
Failure, n (%)	31 (24.4)	47 (39.8)		

EOT Phase 2, 100 mg Global Success, MITT pop: 69.2%



Anidulafungin in candidemia & invasive candidosis

Candida Pathogen	Successful Microbiologic Response			Successful Global Response†		
	Anidulafungin Group	Fluconazole Group	P Value	Anidulafungin Group	Fluconazole Group	P Value
	no. of isolates/total no. (%)			no. of patients/total no. (%)		
<i>Candida albicans</i>	77/81 (95)	57/70 (81)	0.01	60/74 (81)	38/61 (62)	0.02
<i>C. glabrata</i>	15/20 (75)	18/30 (60)	0.37	9/16 (56)	11/22 (50)	0.75
<i>C. parapsilosis</i>	9/13 (69)	14/16 (88)	0.36	7/11 (64)	10/12 (83)	0.37
<i>C. tropicalis</i>	13/15 (87)	7/11 (64)	0.35	13/14 (93)	4/8 (50)	0.04
Other candida species	5/6 (83)	3/3 (100)	1.00	3/4 (75)	2/3 (67)	1.00
All candida species	119/135 (88)	99/130 (76)	0.02	92/119 (77)	65/106 (61)	0.01

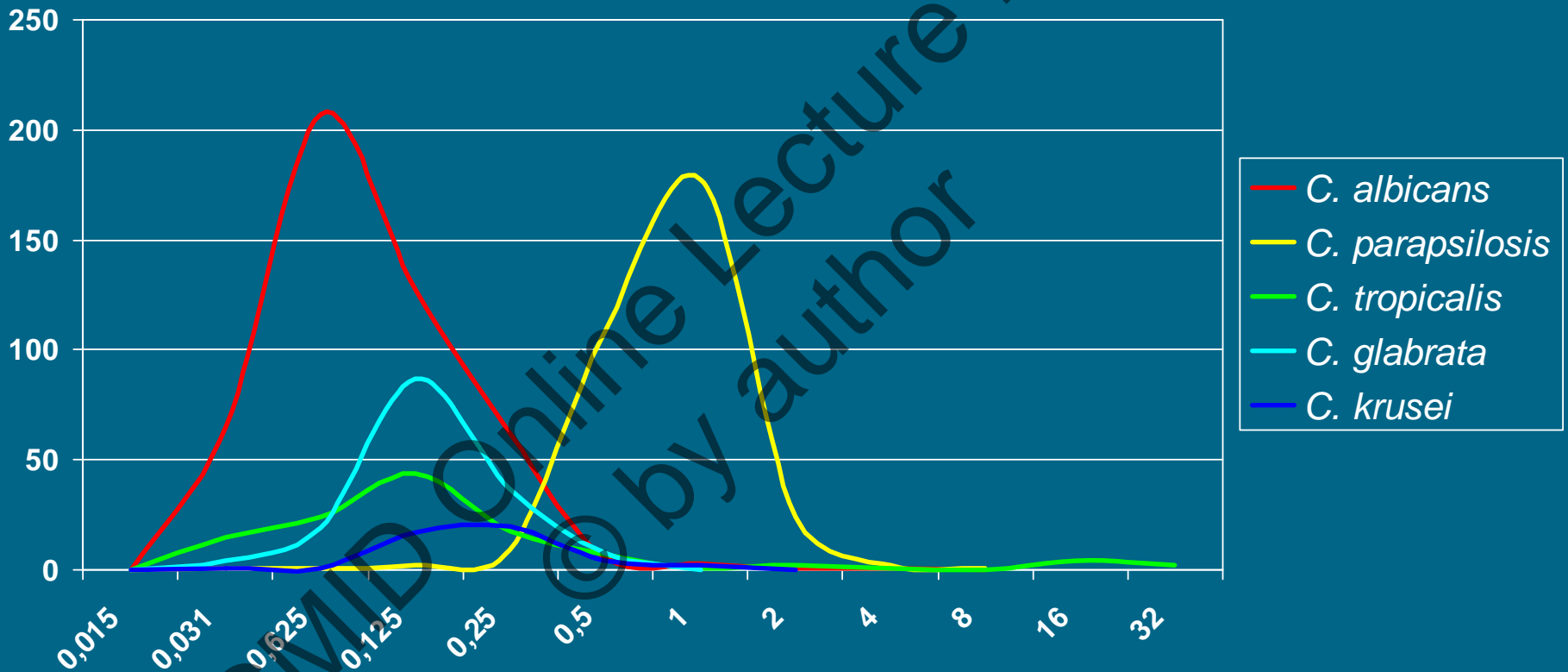


Nek breakpoints values by CLSI and EUCAST

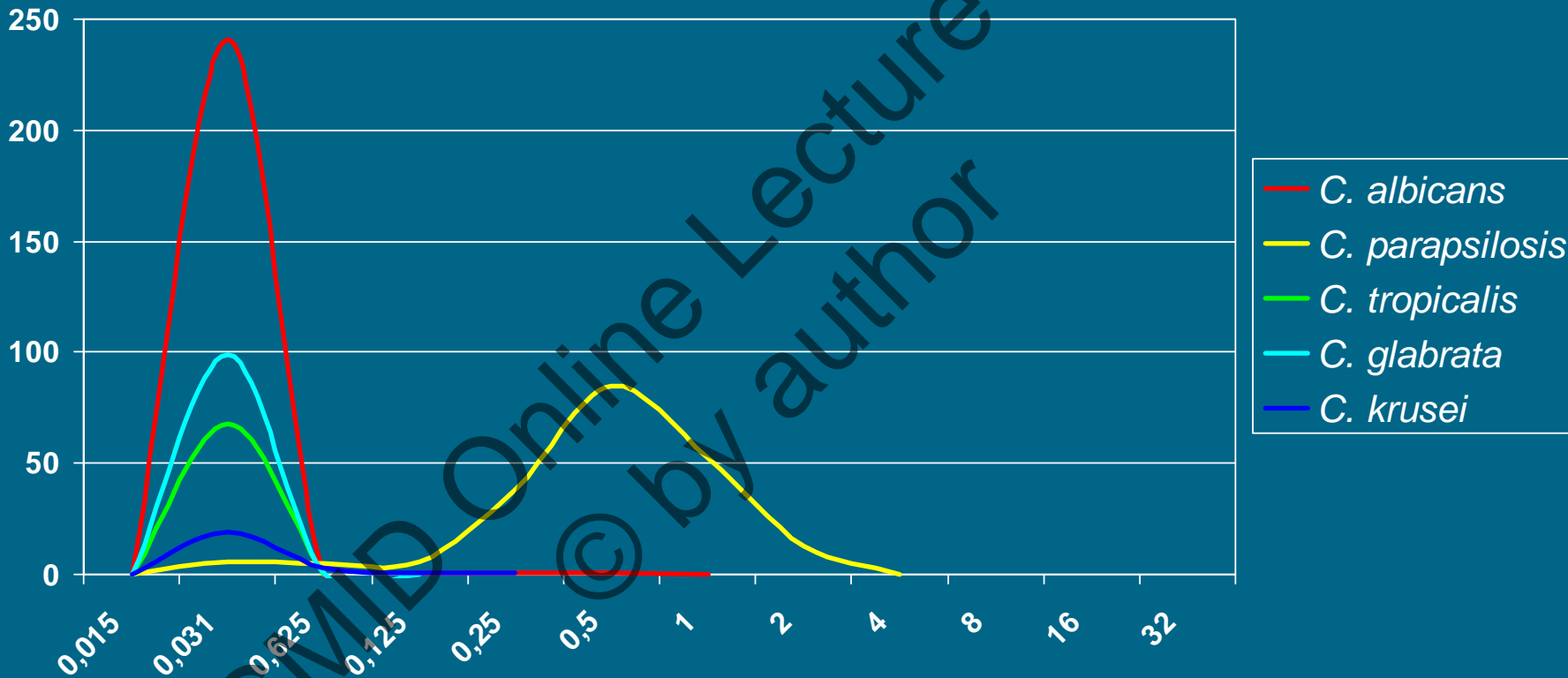
Sensible	Intermed./resistant
≤ 0,12-0,25 mg/L	???

ESCMID Online Lecture
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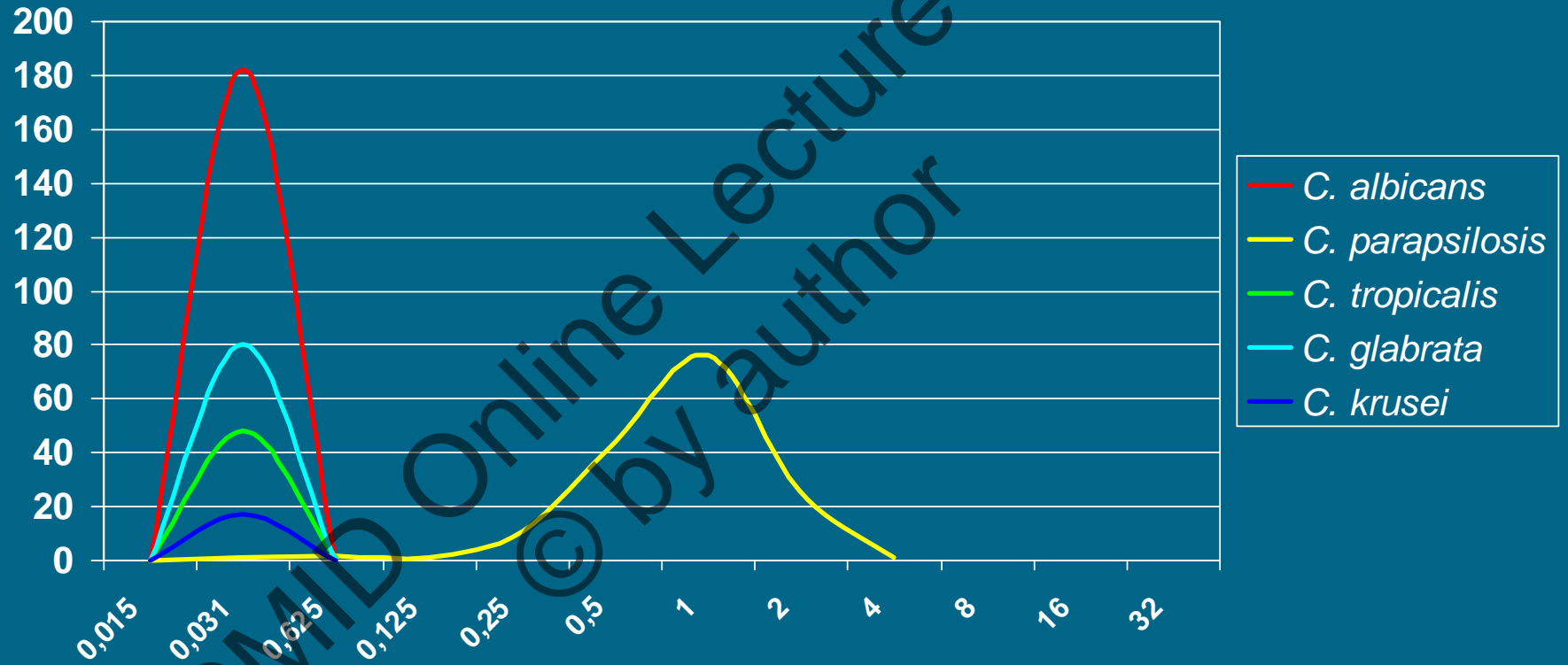
MIC wildtype distribution of caspofungin



MIC wildtype distribution of micafungin



MIC wildtype distribution of anidulafungin





Resistance to echinocandins

Substitutions of amino acids in regions (*hot-spots*)
Fks, encoding major subunit of glucan-synthetase

Described in several *Candida* spp.

A naturally occurring proline-to-alanine amino acid change in Fks1p in Candida parapsilosis, Candida orthopsilosis, and Candida metapsilosis accounts for reduced echinocandin susceptibility. (Garcia-Effron et al. AAC 2008)

Cross resistance to echinocandins

**COMPARISON OF CASPOFUNGIN AND AMPHOTERICIN B
FOR INVASIVE CANDIDIASIS**

JORGE MORA-DUARTE, M.D., ROBERT BETTS, M.D., COLEMAN ROTSTEIN, M.D., ARNALDO LOPES COLOMBO, M.D.,
LUIS THOMPSON-MOYA, M.D., JUANITA SMIETANA, B.S., ROBERT LUPINACCI, M.S., CAROLE SABLE, M.D.,
NICHOLAS KARTSONIS, M.D., AND JOHN PERFECT, M.D., FOR THE CASPOFUNGIN INVASIVE CANDIDIASIS STUDY GROUP*

**TABLE 5. TREATMENT FAILURES AND RELAPSES
(MODIFIED INTENTION-TO-TREAT ANALYSIS).**

FAILURE OR RELAPSE	CASPOFUNGIN (N= 109)	AMPHOTERICIN B (N= 115)
	no. (%)	
Failure at end of therapy	29 (26.6)	44 (38.3)
Persistently positive cultures	9 (8.3)	10 (8.7)*
<i>Candida albicans</i>	3	8
<i>C. glabrata</i>	1	0
<i>C. krusei</i>	0	1
<i>C. parapsilosis</i>	5†	0
<i>C. albicans</i> and <i>C. lusitaniae</i>	0	1

A Multicenter, Double-Blind Trial of a High-Dose Caspofungin Treatment Regimen versus a Standard Caspofungin Treatment Regimen for Adult Patients with Invasive Candidiasis

Robert F. Betts,¹ Marcio Nucci,⁷ Deepak Talwar,⁹ Marcelo Gareca,² Flavio Queiroz-Telles,⁸ Roger J. Bedimo,⁵ Raoul Herbrecht,¹⁰ Guillermo Ruiz-Palacios,¹¹ Jo-Anne H. Young,⁴ John W. Baddley,⁶ Kim M. Strohmaier,³ Kimberly A. Tucker,³ Arlene F. Taylor,³ and Nicholas A. Kartsonis,³ for the Caspofungin High-Dose Study Group^a

Clinical Infectious Diseases 2009; 48:1676–84

50 mg/d tras 70 mg/d, un día vs. 150 mg/d

104 pat vs. 100 pat invasive candidiasis (7-8% neutropenia)

Response: 71,6% vs. 77,9%. Mortality similar but response *C. parapsilosis* 61% vs. 81%

Toxicity: 1, 9% vs. 3% (flebitis, hepatic alterations)



Micafungin and invasive candidosis

	Micafungin		Liposomal amphotericin B	
	Number of patients ^a	Number of patients with mycological persistence (%)	Number of patients ^a	Number of patients with mycological persistence (%)
Any <i>Candida</i> spp	194	18 (9%)	174	16 (9%)
<i>Candida albicans</i>	85	9 (11%)	79	8 (11%)
Non- <i>albicans</i> <i>Candida</i> spp	120	11 (9%)	107	9 (8%)
<i>C tropicalis</i>	49	1 (2%)	45	2 (4%)
<i>C parapsilosis</i>	35	5 (14%)	29	3 (10%)
<i>C glabrata</i>	22	3 (14%)	15	3 (20%)
<i>C krusei</i>	6	1 (17%)	5	1 (20%)
<i>C guilliermondii</i>	7	0	4	0
<i>C lusitaniae</i>	1	0	6	0
<i>C rugosa</i>	1	1	4	0
<i>C kefyr</i>	1	0	1	0
<i>C famata</i>	0	"	1	0
<i>C dubliniensis</i>	1	0	1	0
More than one <i>Candida</i> spp	15	2 (13%)	11	1 (9%)

Kuse et al. Lancet 2007; 369: 1519-27

Anidulafungin in candidemia & invasive candidosis

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All candida species	119/135 (88)	99/130 (76)	0.02	92/119 (77)	65/106 (61)	0.01