



# Rational use of antifungals

## Lipid formulations

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Coordenador do SCIH do Hospital Evangélico do PR

### Conflitos de interesses

(últimos 2 anos)

(S=speaker; R=research; G=grants)

Teva (S), Novartis (SRG), Pfizer (S),  
Wieth (S), Bayer (S), MSD (SRG),  
Astellas (SR), United Medical (S),  
AstraZeneca (S), Sanofi (S)

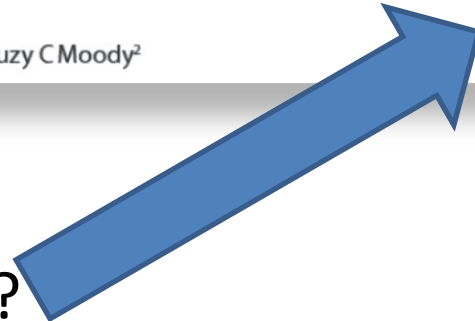


# Rational use of antifungals?

- We know **PERSPECTIVE**  
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- How can we maintain  
Mitigation of human-pathogenic fungi that exhibit resistance to medical agents: can clinical antifungal stewardship help?  
– Drugs  
– Ideal dose  
– Correct indication  
– Ideal choice  
– Decrease resistance?
- Local Antifungal Stewardship Program



d





# Steps for a LASP

- ★ – Group with a ID specialist, pharmacist and administrator support
- ★ – Develop local guidelines based on the local epidemiology and real condition for antifungal therapy and also supported by national or international guidelines
- ⊘ – Continuous education of healthcare staff (medical and pharmacist)
- ★ – Restriction formulary
- ★ – Bedside intervention of LASP with assistance group
- ★ – Evaluate periodically the consume of antifungal drugs
- ⊘ – Publication of data for all medical staff



# Aspergillus

Training should be the first step toward an antifungal stewardship program

Maricela Valerio<sup>a,c,\*</sup>, Patricia Muñoz<sup>a,c,d,e</sup>, Carmen Rodríguez-González<sup>b,c</sup>, María Sanjurjo<sup>b,c</sup>, Jesús Guinea<sup>a,c</sup>, Emilio Bouza<sup>a,c,d,e</sup>, on behalf the COMIC study group (Collaborative group on Mycosis)<sup>◇</sup>

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<sup>b</sup> Pharmacy Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain

<sup>c</sup> Instituto de Investigación Sanitaria del Hospital Gregorio Marañón, Madrid, Spain

<sup>d</sup> CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain

<sup>e</sup> Microbiology Department, School of Medicine, Universidad Complutense de Madrid, Spain

- *Aspergillus*:
  - 67% know how to indentify colonization from infection
  - 31% know the drug of choice
  - 36% know the treatment duration





## And in your hospital?

- ★ – Group with a ID specialist, pharmacist and administrator support
- ★ – Develop local guidelines based on the local epidemiology and real condition for antifungal therapy and also supported by national or international guidelines
- ⊘ – Continuous education of healthcare staff (medical and pharmacist)
- ★ – Restriction formulary
- ★ – Bedside intervention of LASP with assistance group
- ★ – Evaluate periodically the consume of antifungal drugs
- ⊘ – Publication of data for all medical staff

- Do the medical staff know the drug of choice, ideal dosage, empirical and specific therapies for invasive fungal infections?

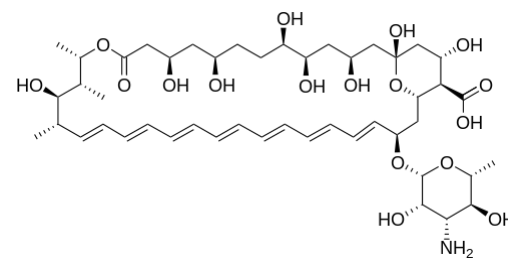
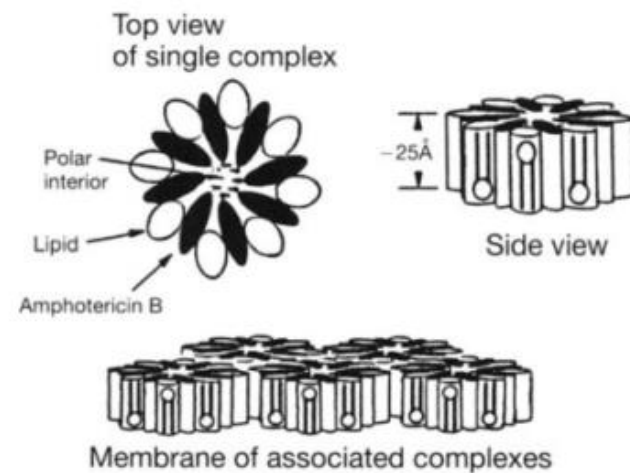
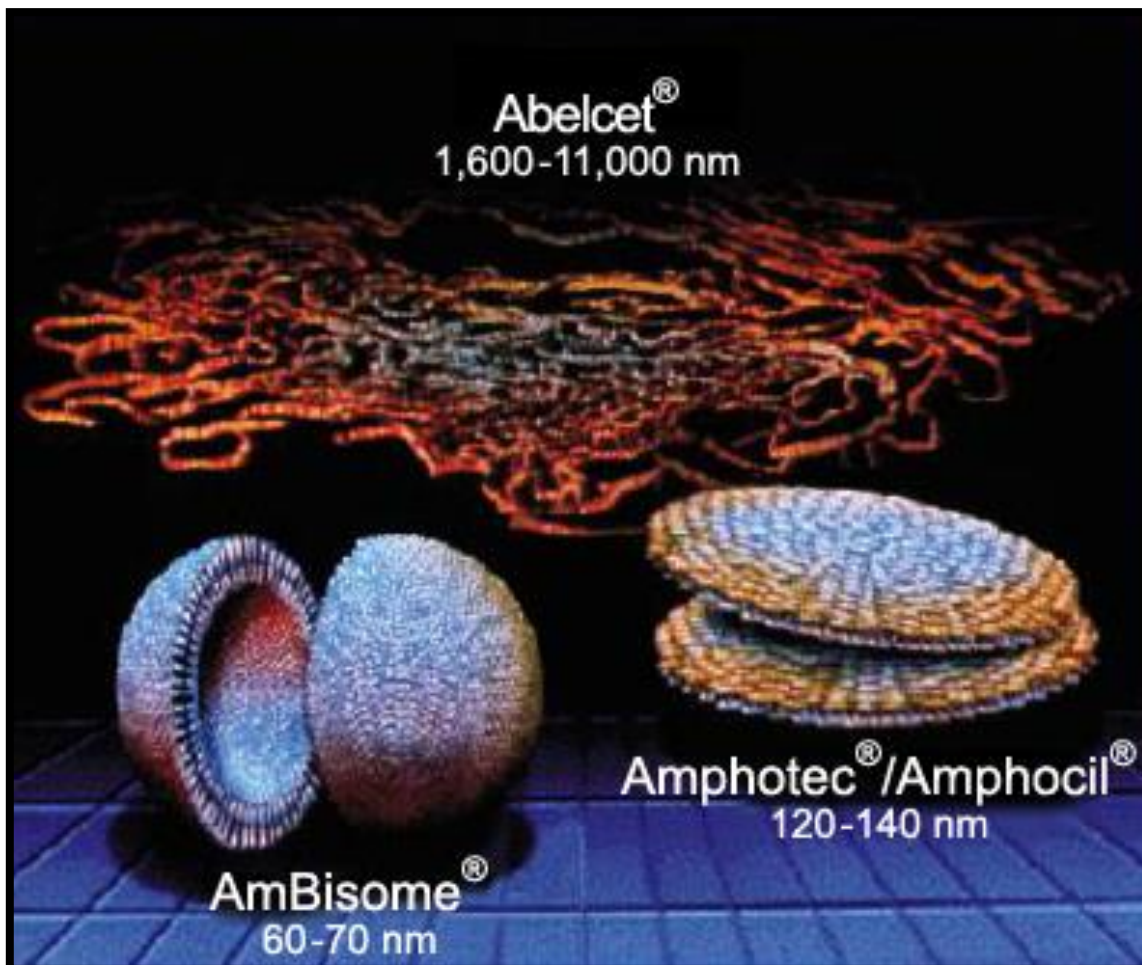




Neutropenic and endemic mycosis

**LET'S GO TO ...**





Fungal species	FLU	ITRA	POSA	VOR	AMB	Echinocandins <sup>a</sup>
<i>Aspergillus fumigatus</i>	—	+	+	+	+	+
<i>Aspergillus glaucus</i>	—	+	+	+	+	+
<i>Aspergillus terreus</i>	—	+/—	+	+	+/—	+
<i>Candida albicans</i>	+	+	+	+	+	+
<i>Candida krusei</i>	—	+/—	+	+	+/—	+
<i>Candida glabrata</i>	+/—	+/—	+/—	+/—	+	+
Other <i>Candida</i> species <sup>b</sup>	+	+	+	+	+	+/—
<i>Cryptococcus neoformans</i>	+	+	+	+	+	—
<i>Coccidioides</i> species	+	+	+	+	+	—
<i>Blastomyces dermatitidis</i>	+/—	+	+	+	+	—
<i>Histoplasma capsulatum</i>	+	+	+	+	+	—
<i>Fusarium</i> species	—	—	+/—	+/—	+/—	—
Zygomycetes	—	+/—	+	—	+	—
<i>Scedosporium apiospermum</i>	—	—	+	+	+/—	—
<i>Scedosporium prolificans</i>	—	—	—	—	—	—
<i>Trichosporon</i>	—	—	ND	+	+/—	—

Aspergillus

Candida

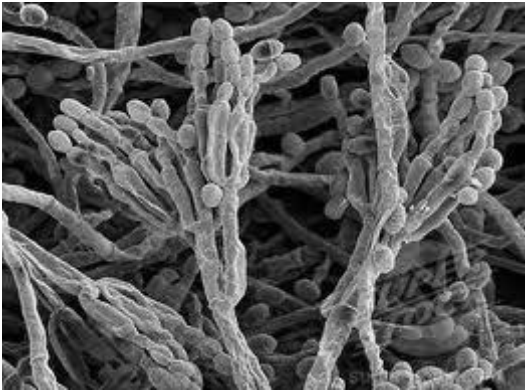
Endemic

Others

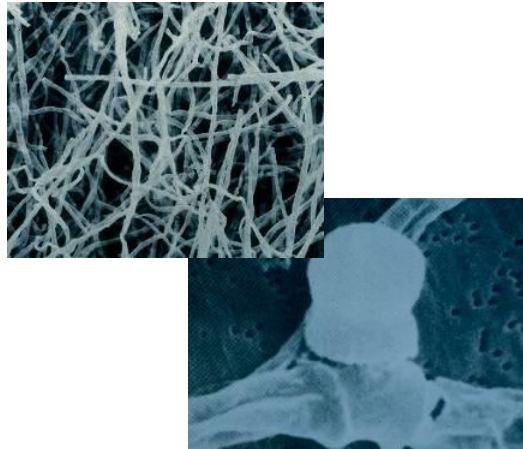




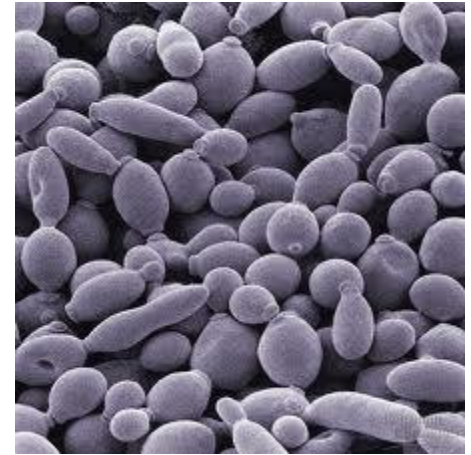
# Neutropenic



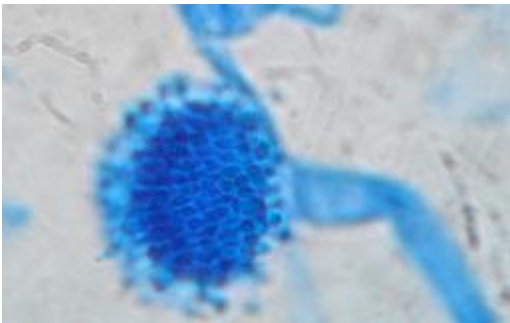
Molds



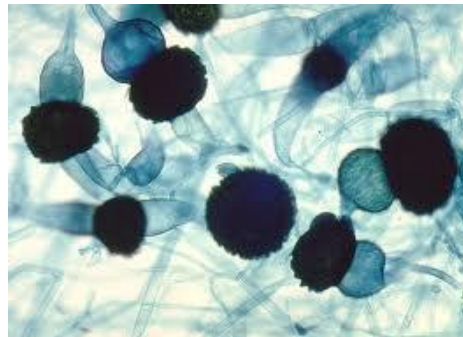
Dimorphic



Yeast



Aspergillus



Mucormycosis

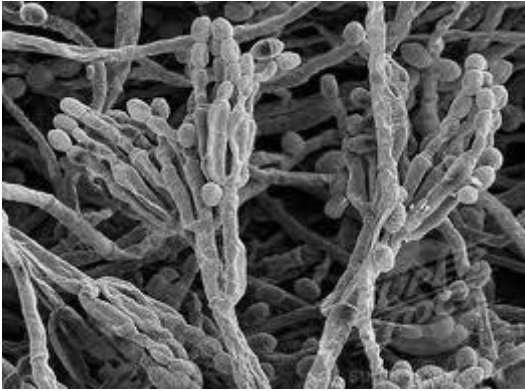


Fusarium

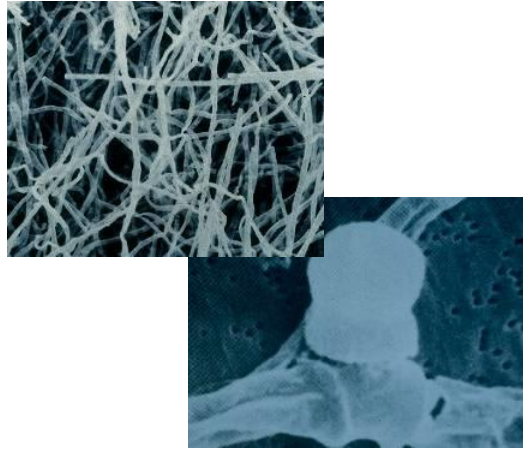




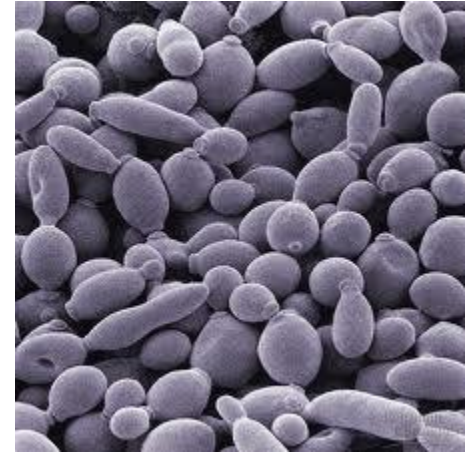
# Endemic



Molds



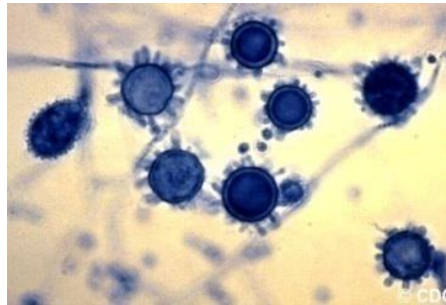
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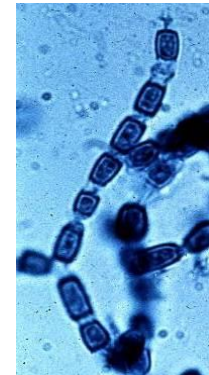
Yeast



Paracocci



Histoplasma

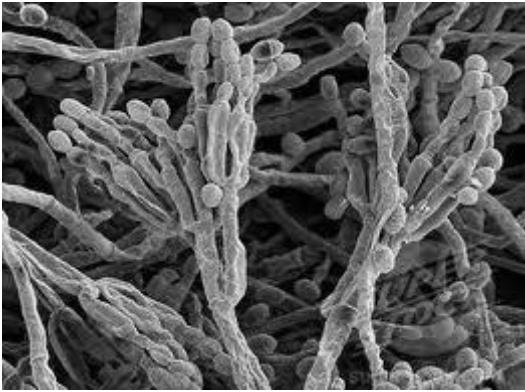


Coccidioides/Blasto

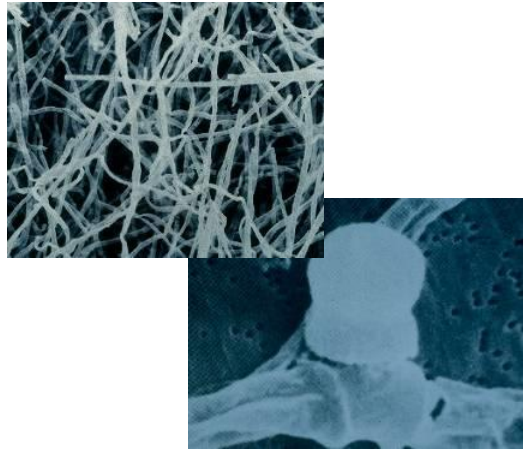




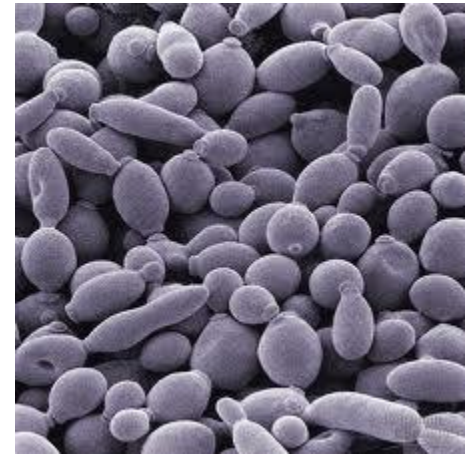
# Immunocompromised (HIV, ICU, Tx)



Molds



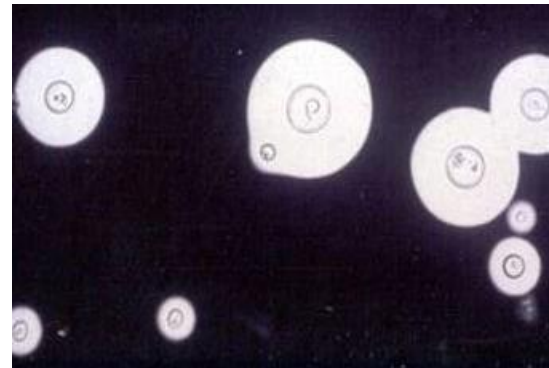
Dimorphic



Yeast



Candida



Cryptococcus





## Empirical antifungal against molds?

*Fus*

sp.

spp.

*mella*

*S. apiospermum*

*P. variou*

*S. brevicaulis*

*S. prolificans*

*P. lilacinus*



# Empiric Vs preemptive

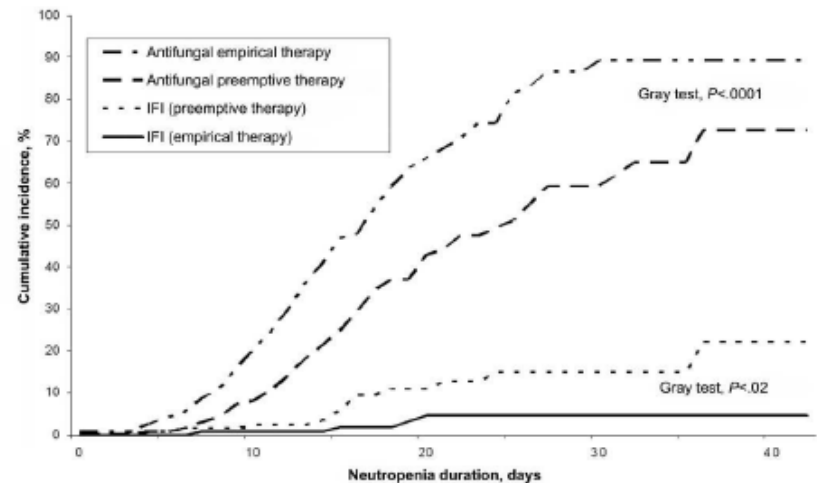
## Empirical versus Preemptive Antifungal Therapy for High-Risk, Febrile, Neutropenic Patients: A Randomized, Controlled Trial

Catherine Cordonnier,<sup>1</sup> Cécile Pautas,<sup>1</sup> Sébastien Maury,<sup>1</sup> Anne Vekhoff,<sup>4</sup> Hassan Farhat,<sup>11</sup> Felipe Suarez,<sup>5</sup> Nathalie Dhedin,<sup>6</sup> Françoise Isnard,<sup>7</sup> Lionel Ades,<sup>12</sup> Frédérique Kuhnowski,<sup>8</sup> Françoise Foulet,<sup>2</sup> Mathieu Kuentz,<sup>1</sup> Patrick Mais

- Empiric
  -
- Preemptive
  - Start if:
    - Positive culture
    - Thorax and sinuses CT
    - Diarrhea ou grade 3 mucositis
    - Galactomannan >0.5
    - Shock
    - Cutaneous suggestive lesions
    - Abdominal US
      - Abscess
    - Brain CT
      - Abscess
    - Neurological sign/symptoms

**Cost saving and rational**

- Empiric
  - Expensive
  - Less IFI
- Preemptive
  - Cost saving
  - More IFI
- No difference in mortality rate



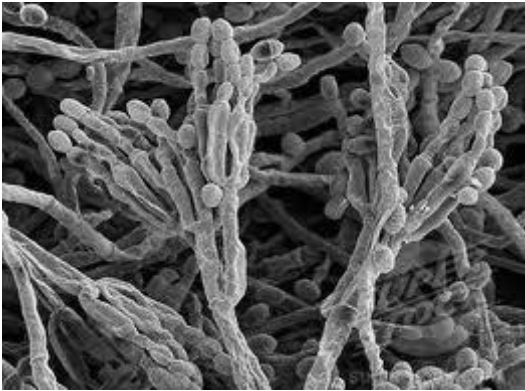
# What is the best empirical therapy in neutropenic persistent febrile patient

## European Conference on infections in leukaemia

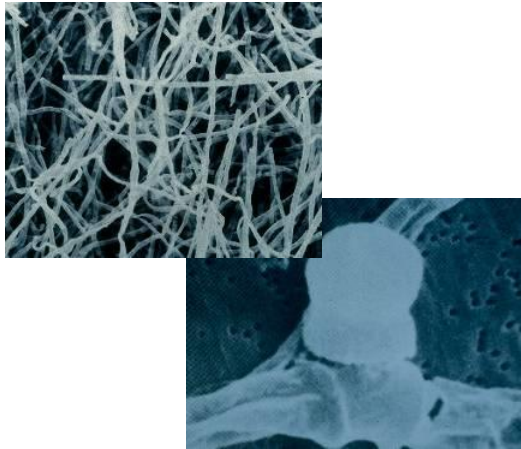
<i>Antifungal agent</i>	<i>Daily dose</i>	<i>Level of recommendation</i>	<i>CDC grading</i>	
			<i>Level of evidence for</i>	
			<i>Efficacy</i>	<i>Safety</i>
Liposomal amphotericin B	3 mg/kg	A <sup>a</sup>	I	I
Caspofungin	50 mg	A <sup>a,b</sup>	I	I
ABCD	4 mg/kg	B <sup>c</sup>	I	I
ABLC	5 mg/kg	B <sup>c</sup>	I	I
Itraconazole	200 mg i.v.	B <sup>b,e</sup>	I	I
Voriconazole	2 × 3 mg/kg i.v.	B <sup>b,d,e</sup>	I	I
<b><i>Micafungin</i></b>	<b><i>100 mg</i></b>	<b><i>B</i></b>	<b><i>II</i></b>	<b><i>II</i></b>
Amphotericin B deoxycholate	0.5–1 mg/kg	B <sup>c</sup> /D <sup>f</sup>	I	I
Fluconazole	400 mg i.v.	C <sup>b,e,g</sup>	I	I



# Neutropenic



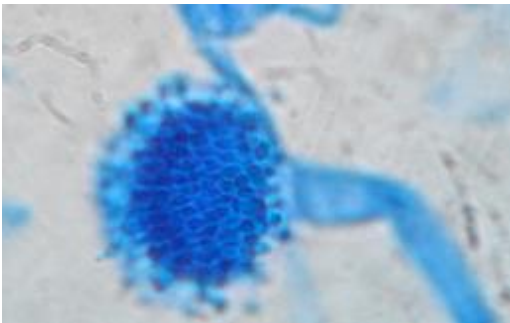
Molds



Dimorphic



Yeast



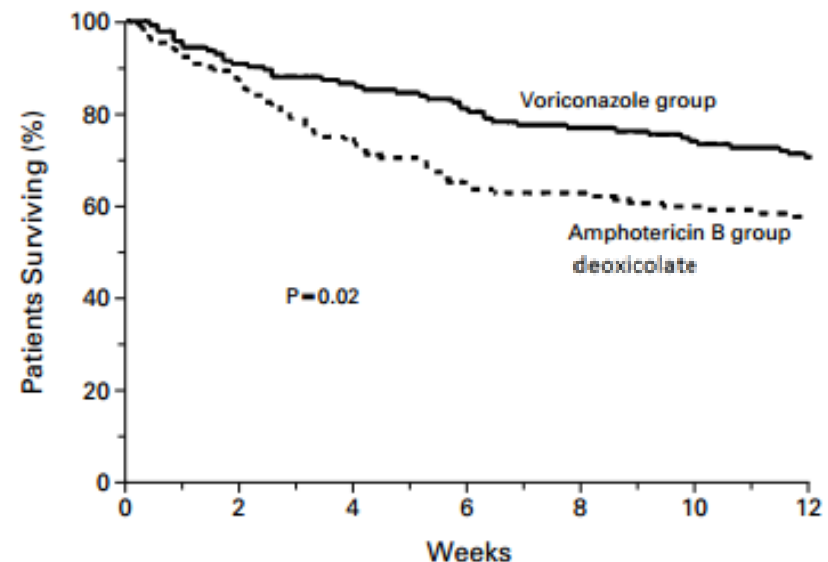
Aspergillus





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

- Voriconazole (AI)
  - Vorico vs ABD – 53% vs 32% (clinical response 12w)
  - Vorico vs ABD – 71% vs 58% (survival 12 w)
- AB Lipid 2<sup>a</sup>. choice (AI)
  - Resposta +/-40%
  - A. terreus resistente a AB
- Combined therapy not indicated
- Considered after failure or adverse effects of voriconazole







# Duration of the treatment

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

Thomas J. Walsh,<sup>1,a</sup> Elias J. Anaissie,<sup>2</sup> David W. Denning,<sup>13</sup> Raoul Herbrecht,<sup>14</sup> Dimitrios P. Kontoyia,<sup>15</sup> Kieren A. Marr,<sup>5</sup> Vicki A. Morrison,<sup>6,7</sup> Brahm H Segal,<sup>8</sup> William J. Steinbach,<sup>9</sup> David A. Stevens,<sup>10,11</sup> Jo-Anne van Burik,<sup>7</sup> John R. Wingard,<sup>12</sup> and Thomas F. Patterson<sup>4,a</sup>

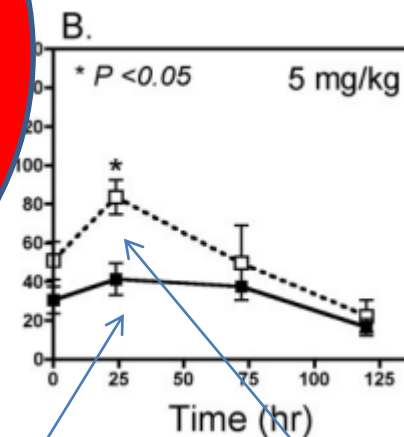
**Cost saving**

- 6 to 12 weeks or neutrophils 'recovery, absence of lesions in the CT
- Low levels of galactomannan, decrease lesions on CT, clinical response
- Restart prophylaxis if neutropenia



# Comparative Analysis of Amphotericin B Lipid Complex and Liposomal Amphotericin B Kinetics of Lung Fungal Clearance in a Murine Model of Acute Aspergillus Fungus Infection

- ABLC (Lipid complex) vs
- ABL (liposomal)

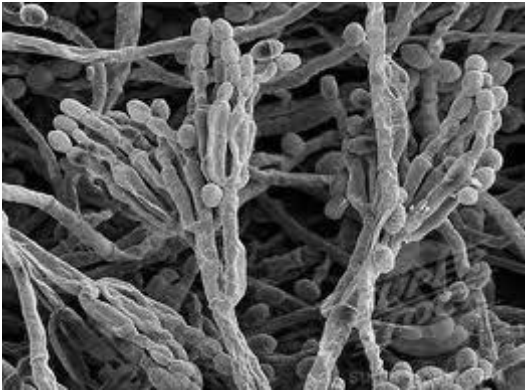


ABLC

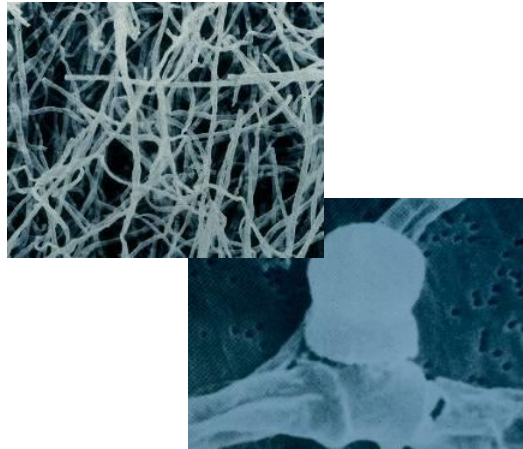
Ambisome



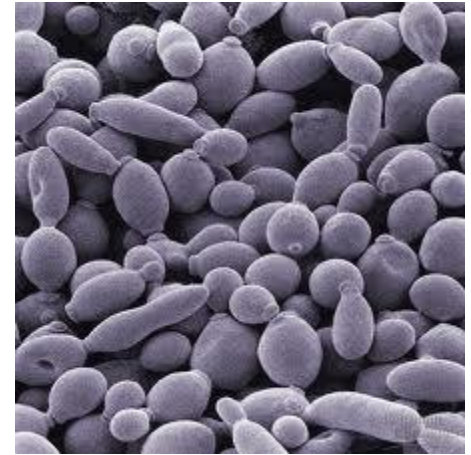
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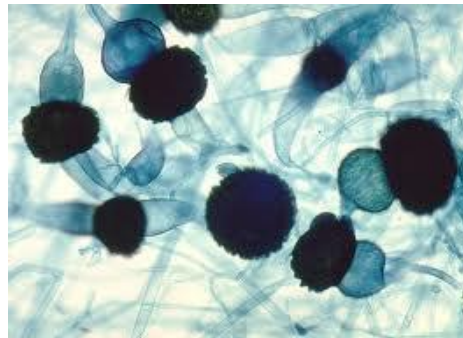
Molds



Dimorphic



Yeast



Mucormycosis





# And about mucormycosis?

No RCT

ESCMID guidelines

Amphotericin is the drug of choice

Population	Intention	Intervention	SoR	QoE
Any	To increase survival rates	Surgical debridement	A	llu
Any	To cure and to increase survival rates	Surgical debridement in addition to antifungal treatment	A	llu
Immunocompromised Any	To increase survival rates To cure and to increase survival rates	Immediate treatment initiation Amphotericin B, liposomal $\geq 5$ mg/kg <sup>a</sup>	A A	llu llu
CNS	To cure	Amphotericin B, liposomal 10 mg/kg, initial 28 days <sup>a</sup>	A	ll
Any, except CNS	To cure	Amphotericin B, lipid complex 5 mg/kg <sup>a</sup>	B	llu



Murine models suggest that liposomal amphotericin B is more effective than the deoxycholate formulation against mucormycosis [124], and that liposomal amphotericin B and amphotericin B lipid complex have dose-dependent [125]. Actually the liposomal formulation achieved higher lung concentrations than the deoxycholate formulation liposomal amphotericin B

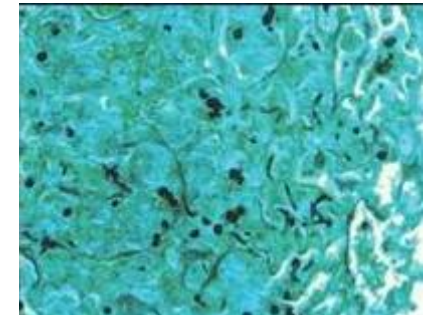
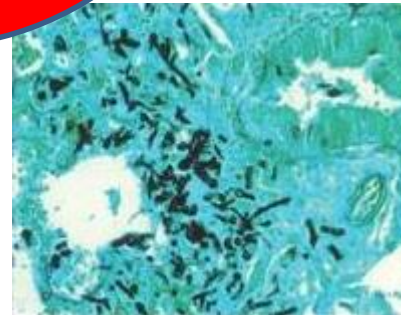
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2010, p. 1298–1304  
0066-4804/10/\$12.00 doi:10.1128/AAC.01222-09  
Copyright © 2010, American Society for Microbiology. All Rights Reserved.

#### Comparative Pharmacodynamics of Amphotericin B Complex and Liposomal Amphotericin B in a Murine Model of Pulmonary Mucormycosis

Russell E. Lewis,<sup>1,2\*</sup> Nathan D. Albert,<sup>2</sup> Guangling Liao,<sup>1</sup> Jinfa Wang,<sup>1</sup> Randall A. Prince,<sup>1,2</sup> and Dimitrios P. Kontoyiannis<sup>1,2</sup>

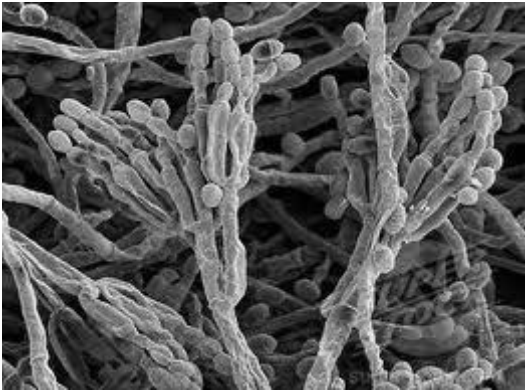
ABL

ABLC

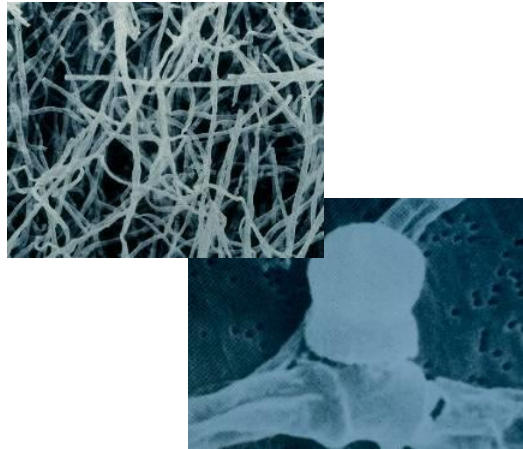




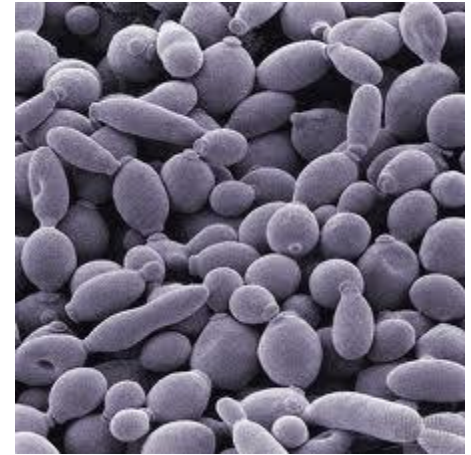
# Neutropenic



Molds



Dimorphic



Yeast



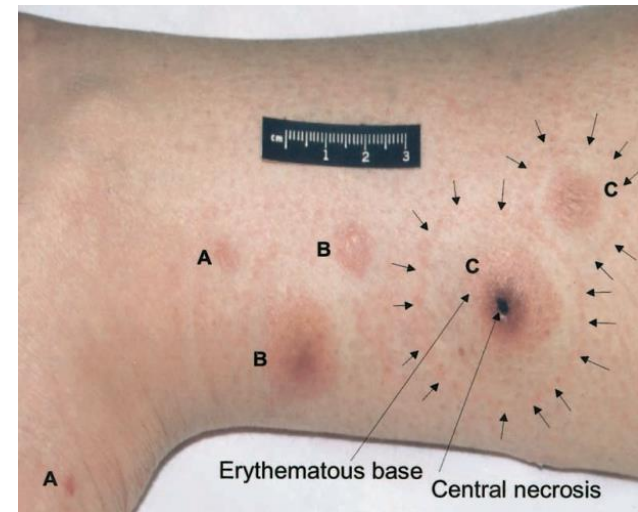
Fusarium





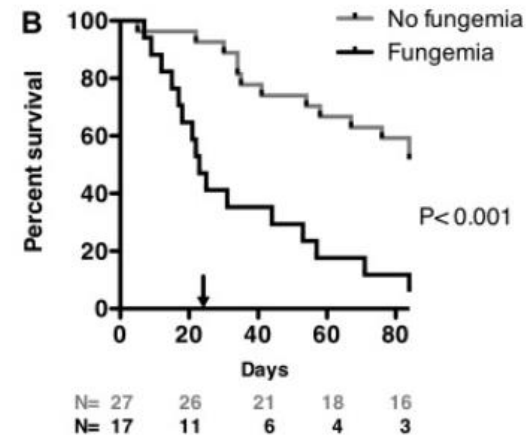
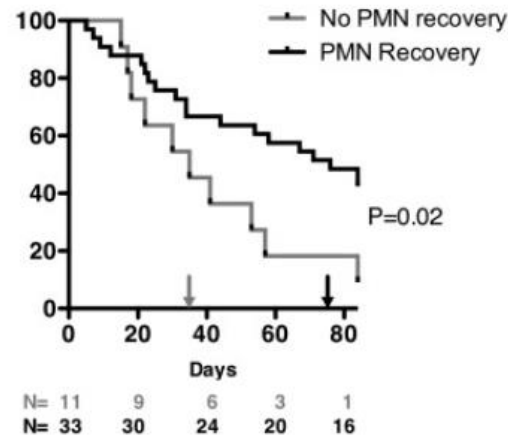
# Fusarium

Fungal species	FLU	ITRA	POSA	VOR	AMB	Echinocandins <sup>a</sup>
<i>Histoplasma capsulatum</i>	+	+	+	+	+	+/-
<i>Fusarium</i> species	-	-	+/-	+/-	+/-	-
Zygomycetes	-	+/-	+	-	+	-





# Fusarium



- **Mortality 50 to 80%**
  - Associated with fungemia and duration of neutropenia
- **Treatment choices**
  - *F. solani* and *F. verticillioides*
    - Lipid formulation of Amphotericin B
  - Other species of *Fusarium*
    - ABLC or ABL
    - Voriconazole





# ESCMID guidelines

Population	Intention	SoR	QoE	Comment	References
Immunocompromised patients	First-line treatment				
	Voriconazole	A	II,t,r	Therapeutic drug monitoring required Response rate was associated with underlying condition and infection site	<a href="#">[23, 24, 60, 196, 197]</a>
	Liposomal amphotericin B	B	II,t,r	Fungi may be resistant to amphotericin B	<a href="#">[4, 198, 199]</a>
	Amphotericin B lipid complex	C	III	Limited case reports	<a href="#">[200]</a>
	Amphotericin B deoxycholate	D	II,t,u	Fungi often resistant to amphotericin B Breakthrough infections may occur Excessive toxicity	<a href="#">[4, 198, 199]</a>
	Any echinocandin	D	III	Intrinsically resistant	<a href="#">[21]</a>

- No RCT



# What is the best lipid formulation?

- **REDUCE COSTS WITH PATIENT SAFETY**



# Dosage < 5mg/kg (1mg/kg/d)

## Clinical Report

Chemotherapy

Chemotherapy 1999;45:205-212

### **Low-Dose Amphotericin B Lipid Complex for the Treatment of Persistent Fever of Unknown Origin in Patients with Hematologic Malignancies and Prolonged Neutropenia**

Rodrigo Martino Maricel Subirá Andreu Domingo-Albós<sup>†</sup>  
Anna Sureda Salut Brunet Jordi Sierra

- 1mg/kg

*Journal of Antimicrobial Chemotherapy* (1999) **44**, 569-572

JAC

**Amphotericin B lipid complex at 3 mg/kg/day for treatment of invasive fungal infections in adults with haematological malignancies**

- 3mg/kg

Rodrigo Martino\*, Maricel Subirá, Anna Sureda and Jorge Sierra



# Is there any difference?

- And about safety (kidney toxicity?)

## Drug-Induced Nephrotoxicity Caused by Amphotericin B Lipid Complex and Liposomal Amphotericin B

### *A Review and Meta-Analysis*

*Amar Safdar, MD, Jonathan Ma, PhD, Fouzi Saliba, MD, Bertrand Dupont, MD, John R. Wingard, MD,  
Ray Y. Hachem, MD, Gloria N. Mattiuzzi, MD, Pranatharthi H. Chandrasekar, MD,  
Dimitrios P. Kontoyiannis, MD, Kenneth V. Rolston, MD, Thomas J. Walsh, MD,  
Richard E. Champlin, MD, and Issam I. Raad, MD*

- 2010



Study First Author Year (ref.)	Study Type (Yr)	Mean/Median Age ( $\pm$ SD, yr), Patient Population	ABLC No. Patients, Mean Daily Dose, Duration ( $\pm$ SD)	L-AmB No. Patients, Mean Daily Dose, Duration ( $\pm$ SD)	Nephrotoxicity* ABLC vs. L-AmB (P Value)
Wingard 2000 <sup>34</sup>	Randomized, double-blind, multicenter (1997–1998)	Mean age: 42.0 $\pm$ 20.4, minimum age: $\geq$ 2 yr; Hematologic malignancies: 42%, HSCT: 49%	n = 78 5 mg/kg 8 d	n = 166 3–5 mg/kg 8 d	42.3% vs. 14.5% (p $\leq$ 0.01)
Fleming† 2001 <sup>9</sup>	Randomized, double-blind, single-center (1997)	Median age: 57 (ABLC), 59 (L-AmB) AML/MDS: 65%, ALL: 15%, CML/CLL: 11%	n = 40 3 mg/kg 10 d	n = 36 4 mg/kg 15 d	40% vs. 28% (p = 0.26)
Cannon 2001 <sup>4</sup>	Retrospective and prospective, observational (1996–1999)	Mean age: 50 (ABLC), 55 (L-AmB), minimum age: $\geq$ 4 yr; Cancer: $\sim$ 73%, HSCT: $\sim$ 24%, non-hemodialysis	n = 46 5.3 mg/kg 15 d	n = 21 4.8 mg/kg 16 d	4.3% vs. 19% (p = NS)
McKechnie 2003 <sup>21</sup> (Abstract)	Retrospective and prospective, observational, multicenter (NA)	Mean age: NA, minimum age: $\geq$ 2 yr; Hematologic malignancies: $\sim$ 65%, HSCT: $\sim$ 26%, non-hemodialysis	n = 150 4 mg/kg 16 d	n = 104 3.3 mg/kg 19 d	13.6% vs. 12.7% (p = NS)
Mattiuzzi 2004 <sup>20</sup>	Prospective with historical controls (1997–2000)	Median age: 65 (ABLC), 63 (L-AmB), minimum age: $\geq$ 15 yr; AML: 60%, MDS: 40%	n = 131 2.5 mg/kg 17 d	n = 70 3 mg/kg 14 d	12.2% vs. 20% (p = NS)
Malani 2005 <sup>18</sup>	Retrospective (1997–2002)	Mean age: 40.5 $\pm$ 21.8, minimum age: $\geq$ 2 mo; Hematologic malignancies: $\sim$ 49%, HSCT: $\sim$ 27%, renal insufficiency: $\sim$ 21%	n = 31 4.5 mg/kg 38 d	n = 41 4 mg/kg 31 d	45% vs. 32% (p = 0.36)
Saliba‡ 2006 <sup>28</sup> (Abstract)	Prospective, multicenter (2003–2004)	Mean age: 49.6 $\pm$ 14; Neutropenic: 44%	n = 60 [37] 4.8 mg/kg 13.5 $\pm$ 8 d	n = 28 [19] 3.3 mg/kg 15.0 $\pm$ 11 d	23.3% vs. 7.1% (p = 0.067) [10.8% vs. 5.3%] [p = 0.067]
Hachem§ 2008 <sup>11</sup>	Retrospective, single-center (1993–2005)	Mean age: 46.5 $\pm$ 14.3 (ABLC), 48.1 $\pm$ 15.1 (L-AmB); Acute leukemia: $\sim$ 50%, chronic leukemia: $\sim$ 20%, lymphoma: $\sim$ 22%, myeloma: $\sim$ 4%	n = 52 [30] 5–10 mg/kg 12.9 $\pm$ 9.8 d	n = 106 [51] 5–10 mg/kg 13.6 $\pm$ 14.4 d	21.2% vs. 2.8% p < 0.001 [10% vs. 5.9%] [p = 0.67]



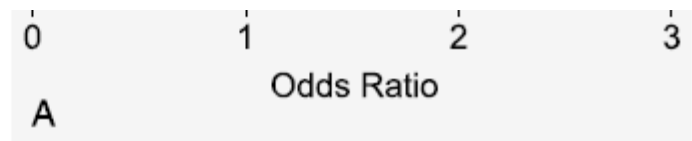
- Wingard showed different consistence other studies
- No difference about the nephrotoxicity?

All 8 studies  
Hachem primary population  
All 8 studies



### Meta-Analysis: ABLC vs. L-AMB Nephrotoxicity

amphotericin B becomes increasingly important in patients requiring broad-spectrum antifungal therapy. Our meta-analysis raises questions about the previously known relative nephrotoxicity of ABLC or L-AmB. In addition, no conclusive differences in response and outcome have been reported in patients with invasive fungal infections treated with ABLC or L-AmB. Therefore, cumulative evidence suggests that ABLC or L-AmB can be administered to immunocompromised individuals for the treatment or prophylaxis of invasive mycoses, with comparable efficacy and safety.



# ABLC is more used in USA than ABL in the treatment of Invasive aspergillosis (278 hospitals)

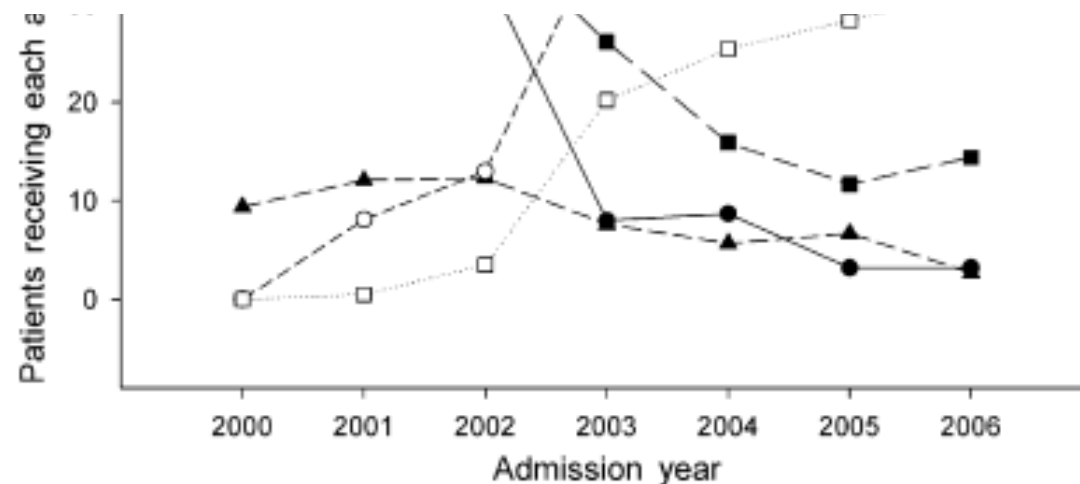


## Hospital costs and outcomes among intravenous antifungal therapies for patients with invasive aspergillosis in the United States

Aryun Kim,<sup>1</sup> David P. Nicolau<sup>1,2</sup> and Joseph L. Kuti<sup>1</sup>

<sup>1</sup>Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, CT, USA and <sup>2</sup>Division of Infectious Diseases, Hartford Hospital, Hartford, CT, USA

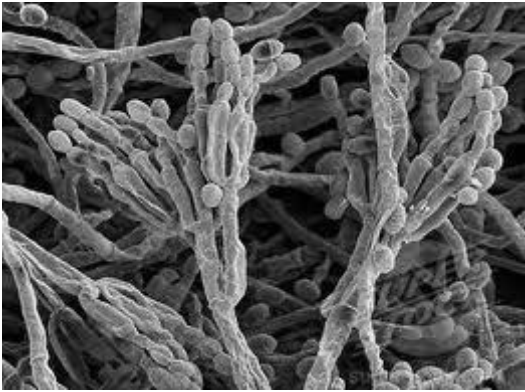
several co-morbidities. Finally, initial treatment with ABLC, caspofungin and voriconazole was independently associated with shorter hospital LOS.



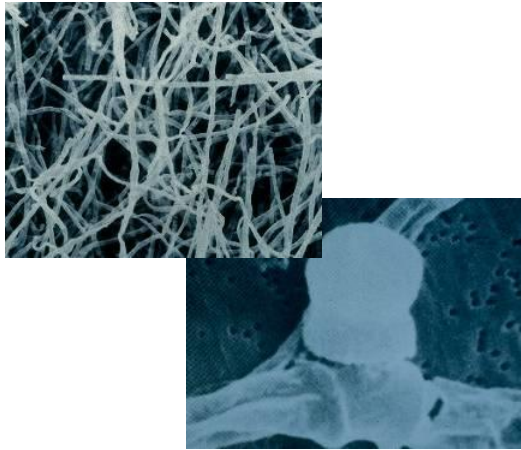




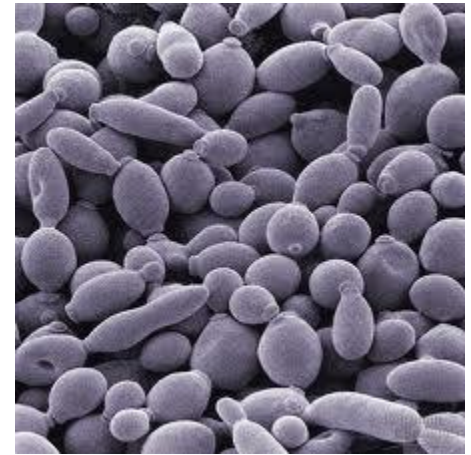
# Immunocompromised (HIV, ICU, Tx)



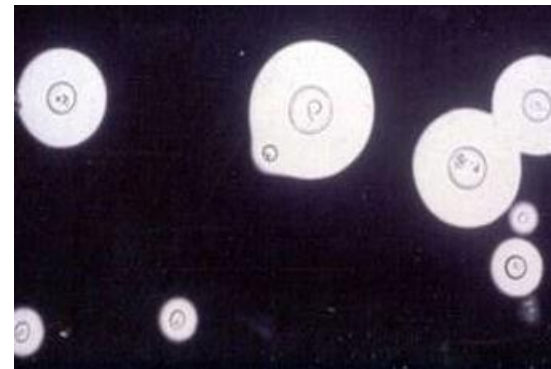
Molds



Dimorphic



Yeast



Cryptococcus







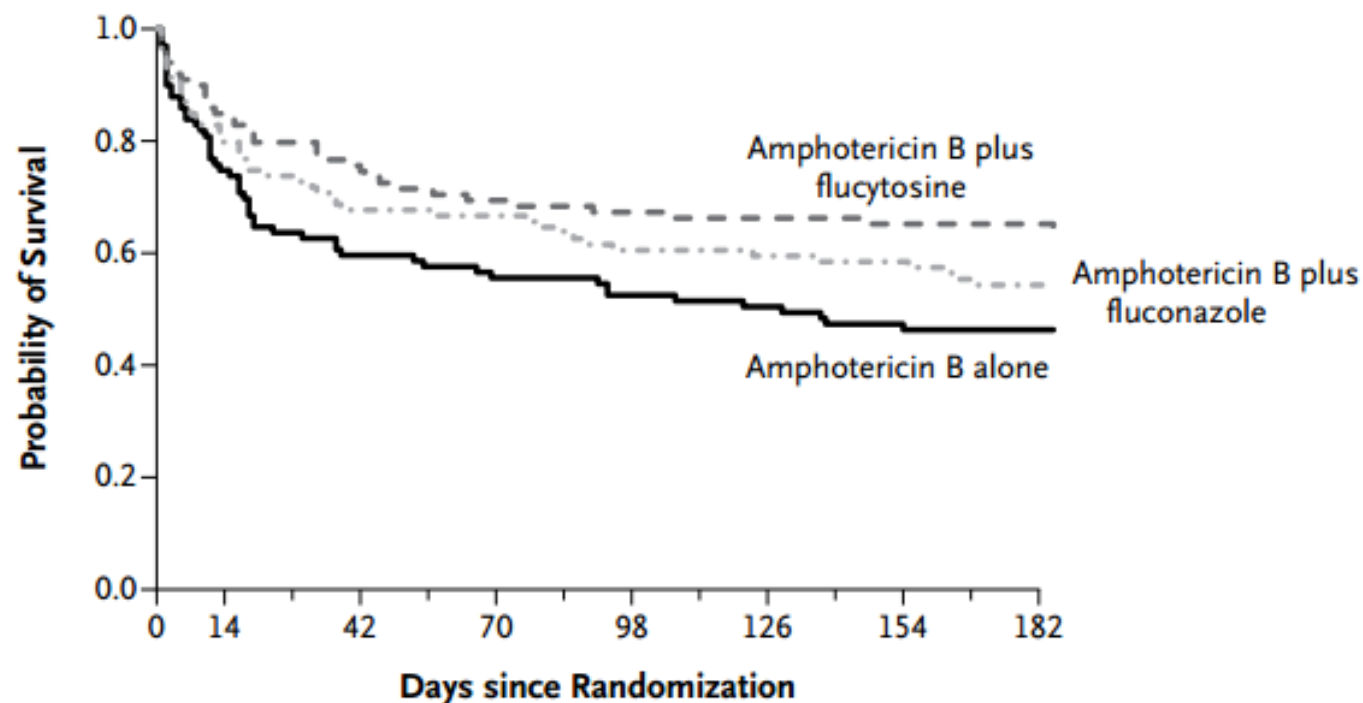
**Table 2. Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Human Immunodeficiency Virus–Infected Individuals**

Regimen	Duration	Evidence
Induction therapy		
AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day) <sup>a</sup>	2 weeks	A-I
Liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, with renal function concerns) plus flucytosine (100 mg/kg per day) <sup>a</sup>	2 weeks	B-II
AmBd (0.7–1.0 mg/kg per day) or liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, for flucytosine-intolerant patients)	4–6 weeks	B-II
Alternatives for induction therapy <sup>b</sup>		
AmBd plus fluconazole	...	B-I
Fluconazole plus flucytosine	...	B-II
Fluconazole	...	B-II
Itraconazole	...	C-II
Consolidation therapy: fluconazole (400 mg per day)	8 weeks	A-I
Maintenance therapy: fluconazole (200 mg per day) <sup>a</sup>	≥1 year <sup>c</sup>	A-I
Alternatives for maintenance therapy <sup>b</sup>		
Itraconazole (400 mg per day) <sup>d</sup>	≥1 year <sup>c</sup>	C-I
AmBd (1 mg/kg per week) <sup>d</sup>	≥1 year <sup>c</sup>	C-I

## ORIGINAL ARTICLE

Combination Antifungal Therapy  
for Cryptococcal Meningitis

N ENGL J MED 368;14 NEJM.ORG APRIL 4, 2013



## No. at Risk

Amphotericin B alone	99	74	59	54	51	49	46	30
Amphotericin B plus flucytosine	100	84	73	67	64	63	62	46
Amphotericin B plus fluconazole	99	79	67	65	59	58	57	39



# Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America

**Table 4. Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Non-Human Immunodeficiency Virus-Infected and Nontransplant Patients**

Regimen	Duration	Evidence
Induction therapy		
AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)	≥4 weeks <sup>a,b</sup>	B-II
AmBd (0.7–1.0 mg/kg per day) <sup>c</sup>	≥6 weeks <sup>a,b</sup>	B-II
Liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day) combined with flucytosine, if possible <sup>d</sup>	≥4 weeks <sup>a,b</sup>	B-III
AmBd (0.7 mg/kg per day) plus flucytosine (100 mg/kg per day) <sup>e</sup>	2 weeks	B-II
Consolidation therapy: fluconazole (400–800 mg per day) <sup>f</sup>	8 weeks	B-III
Maintenance therapy: fluconazole (200 mg per day) <sup>b</sup>	6–12 months	B-III



# Clinical Practice Guidelines for the Treatment of Chronic Hepatitis B

**Table 3.**  
**Transplantation**

Regimen

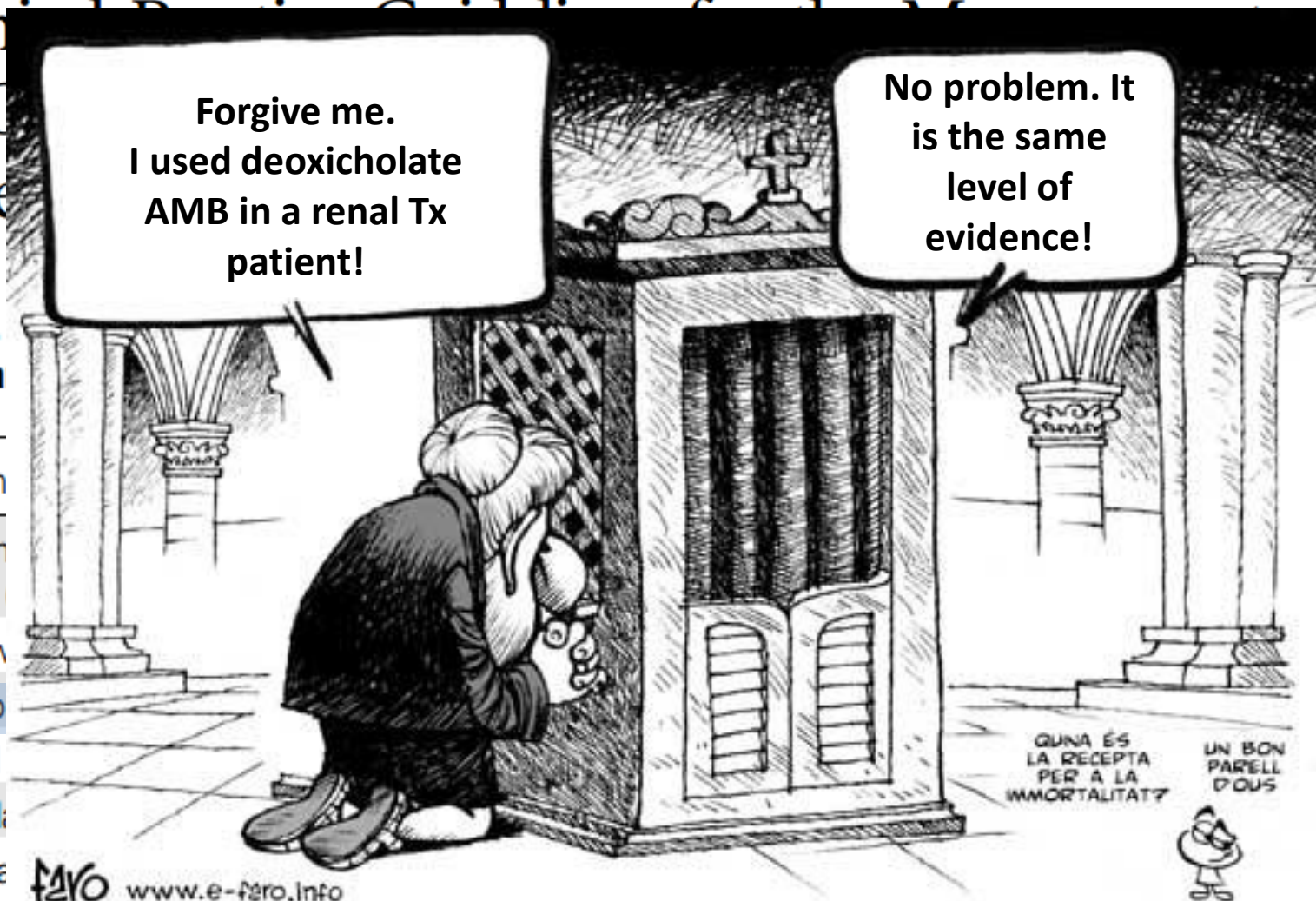
Induction  
ABLC

Alternative  
Liposol

AmBd

Consolidation

Maintenance



OUS

halitis in

Evidence

B-III

B-III

B-III

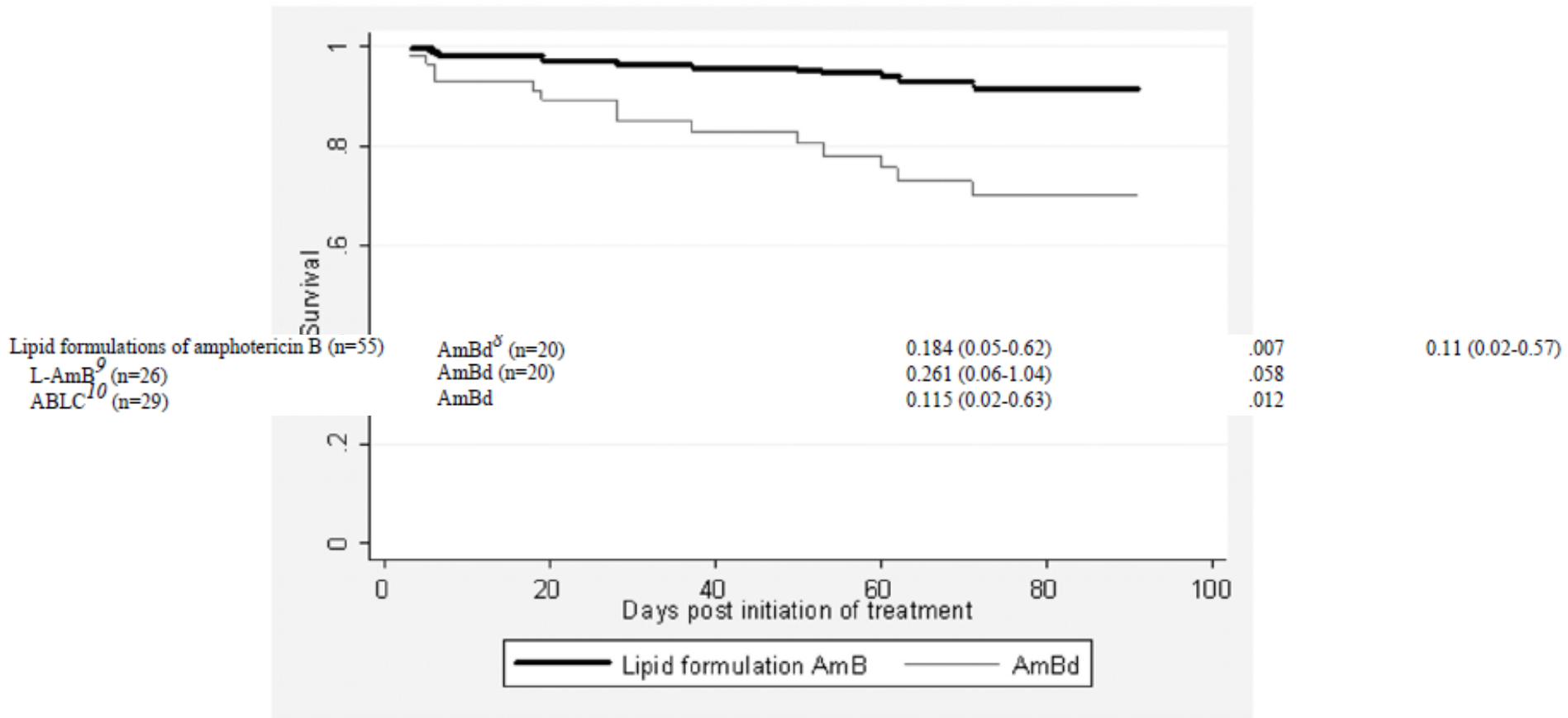
B-III

B-III



- Neurocryptococcosis solid organ Tx

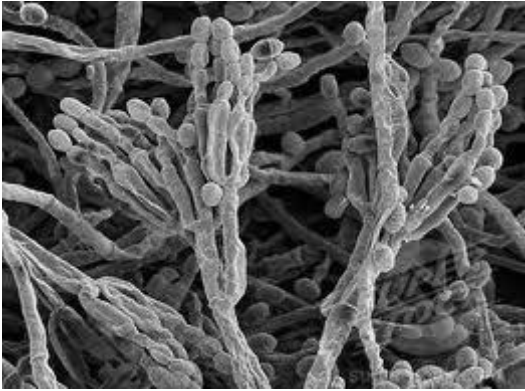
Page 10



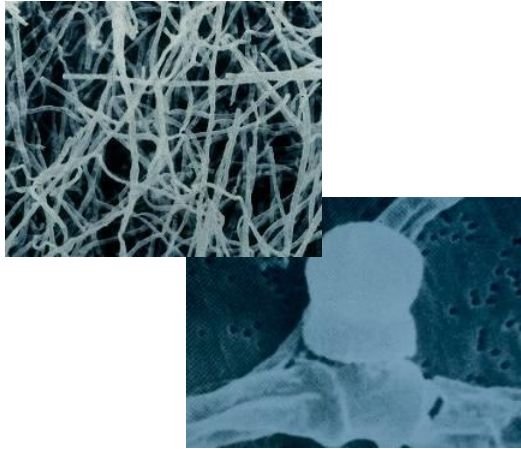




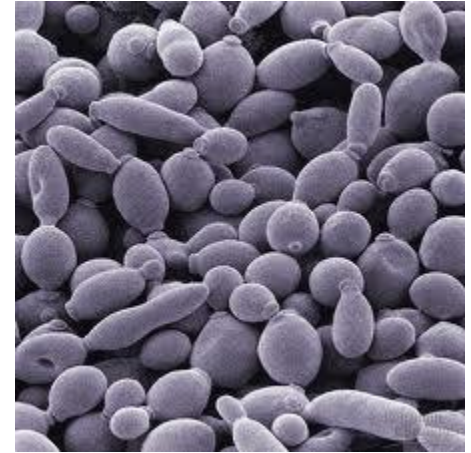
# Endemic



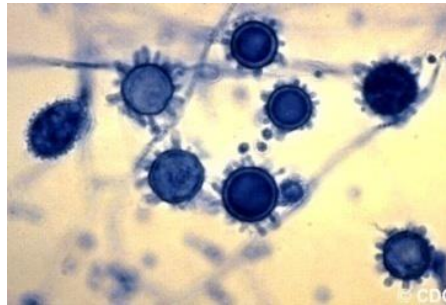
Molds



Dimorphic



Yeast



Histoplasma





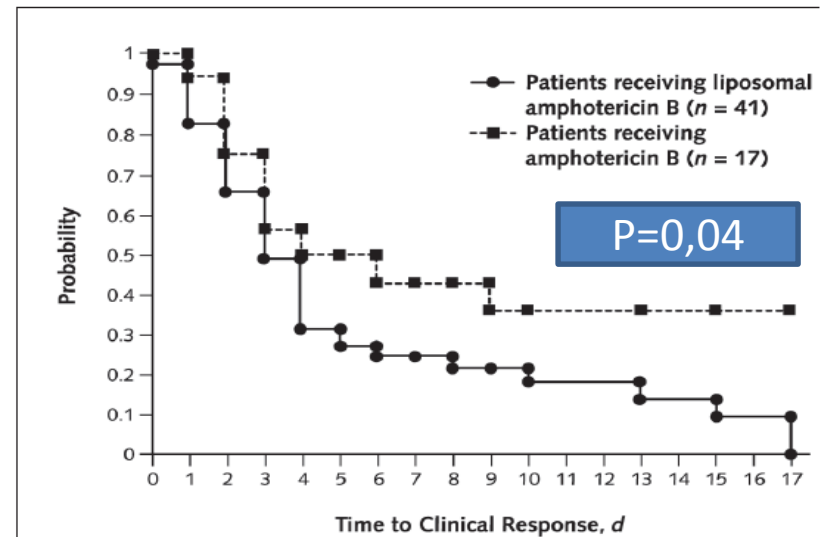
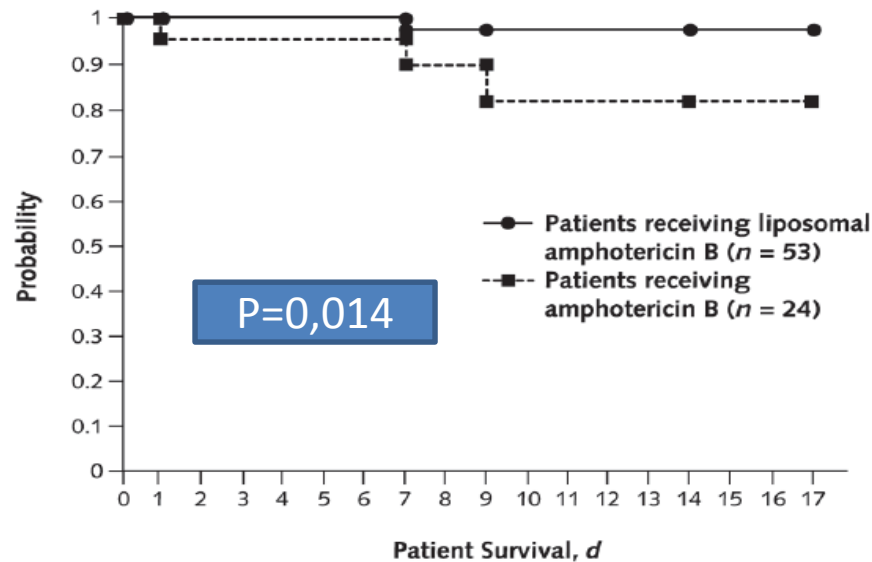
# Histoplasmosis – IDSA 2007

## Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007 Update by the Infectious Diseases Society of America

- Severe Pulmonary  
– FLAB  
– ABD  
severe pulmonary or disseminated forms of histoplasmosis. A multicenter, randomized, blinded clinical trial demonstrated a higher response rate (88% vs. 64%) and lower mortality rate (2% vs. 13%) in patients who had AIDS and progressive disseminated histoplasmosis and who were treated with liposomal amphotericin B than among recipients of amphotericin B deoxycholate, respectively [8]. Amphotericin B lipid complex has also been used successfully for treatment of histoplasmosis [9]
- Central  
– FLAB
- Dissem  
– ABL (and may be preferred by some because of lower cost. Amphotericin B deoxycholate is the least expensive formulation and is a reasonable alternative to the lipid formulations for patients



# Histoplasmosis – IDSA 2007



Infusion toxicity = (25%) ABL vs (63%) ABD ( $P = 0.002$ )

Renal failure = (9%) ABL vs (37%) ABD ( $P = 0.003$ ).

Protocol therapy was discontinued because of toxicity in one patient in the liposomal amphotericin B treatment group and two patients in the amphotericin B treatment group ( $P = 0.19$ ).

**Disseminated histoplasmosis in HIV infected patients**





# Antifungal review

Micafungin (Micamine)

Caspofungin (Cancidas)

Anidulafungin (Ecalta ou generic)

Fluconazole (Zoltec ou generic)

Liposomal (Ambisome)

Lipid complex (Abelcet)

Deoxycholate (generic)

Voriconazole (Vfend)

Candida

Cryptococcus

Histoplasma

Aspergillus

Mucormycosis

Fusarium





# Main point of Amphotericin in Brazil

- Neglected Hospital Disease (NHD)
- Cost-effectiveness study (in Brazil)
  - Renal failure vs mortality
- Reimbursement for ideal indications of Lipid formulation
- New drugs?



**SAVE US!**

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