Rational use of antibiotics

Echinocandins

&

Lipid formulation of amphoterin B

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Conflitos de interesses

(ultimos 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 kno

- How can d
  maintain
  - Drugs
  - Ideal d
  - Correct indication
  - Ideal choice
  - Decrease resistance?

- Local Antifungal Stewardship Program

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

Candida

Training should be the first step toward an antifungal stewardship program

Maricela Valerio[a,c,*], Patricia Muñoz[a,c,d,e], Carmen Rodríguez-González[b,c], María Sanjurjo[b,c], Jesús Guinea[a,c], Emilio Bouza[a,c,d,e], on behalf the COMIC study group (Collaborative group on Mycosis)[◊]

[a] *Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[b] *Pharmacy Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[c] *Instituto de Investigación Sanitaria del Hospital Gregorio Marañón, Madrid, Spain*
[d] *CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain*
[e] *Microbiology Department, School of Medicine, Universidad Complutense de Madrid, Spain*

- *Candida*:
  - 50% know how to differentiate colonization and infection
  - 17% know the resistance rate of fluconazol
  - 33% know the indication of prophylaxis
  - 23% know the indication of empirical antifungal therapy
  - 73% know which antifungal to use

Aspergillus

Training should be the first step toward an antifungal stewardship program

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[d] *CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain*
[e] *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 specifical therapies for invasive fungal infections?

- The next following concepts are based on medical literature considering the best level of evidence

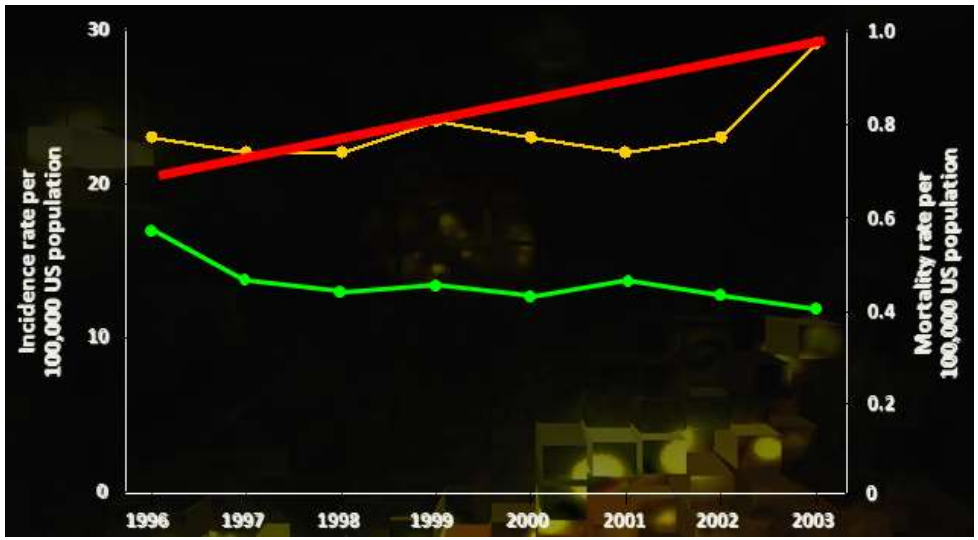
- Some data will be confronted with the current LASP in Hospital Universitario Evangelico de Curitiba
  - 660 beds (55 ICU)
  - Renal Tx
  - Trauma
  - Surgery
  - Burn

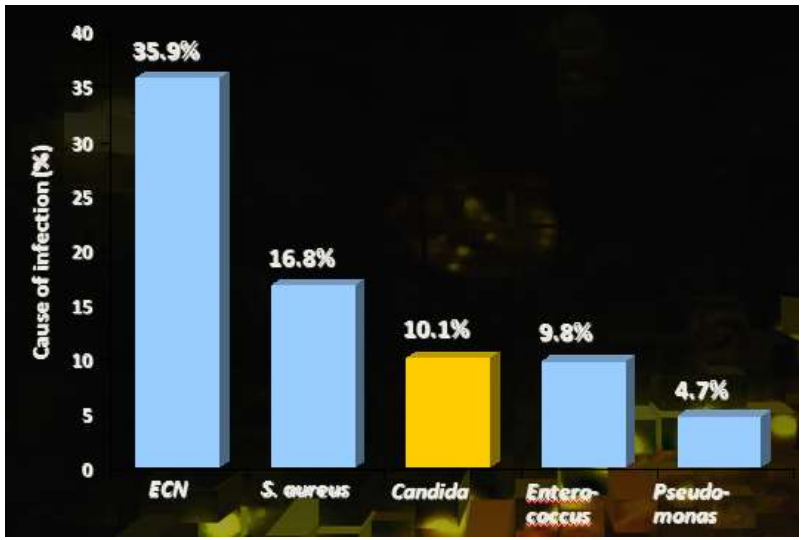
Candidemia

LET'S GO TO ECHINOCANDINS

Candidemia

- The best niche
- The most common presentation of invasive candidemia





Pfaller MA. CMR 2007

Wisplinghoff H . CID 2004

Pathogen	% BSI (rank)			Crude mortality (%)		
	Total (n = 2,447)	ICU (n = 1,196)	Non-ICU (n = 1,251)	Total (n = 971)	ICU (n = 656)	Non-ICU (n = 315)
S. aureus	15.4 (1)	12.8 (3)[a]	17.9 (1)	31.0	48.2	24.0
CoNS	13.8 (2)	16.6 (1)[a]	11.2 (3)	32.0	46.5	23.2
Klebsiella spp.	13.2 (3)	11.8 (4)[b]	14.5 (2)	34.7	55.2	24.8
Acineto			[a]		5.5	39.6
P. aeru					1.5	39.0
Enterob					1.4	17.1
Candid					5.9	53.4
Enteroc					4.2	36.2
Serratia					0.0	29.1
Proteus					1.1	30.0

Bacteria

Staphylococcus aureus
Klebsiella spp
Acinetobacter spp
E. coli
Enterobacter spp
Pseudomonas aeruginosa
Candida spp
Serratia spp
Outros

Marra A. J Clin Microbiol. 2011 Eggimann LID 2012

Mortality Map

Caggiano G. Mycoses 2009
Ruan S.Y. Clinical Microbiology and Infection (2008)
Vardakas K.Z. Clinical Microbiology and Infection (2009)
Klevay M.J. Diagnostic Microbiology and Infectious Disease (2008)

St-Germain G. Canadian Journal of Infectious Diseases and Medical Microbiology (2008)
Presterl E. Clinical Microbiology and Infection (2007)
Colombo A.L. Infection Control and Hospital Epidemiology (2007)
Al-Tawfiq J.A. International Journal of Infectious Diseases (2007)

Neutropenia, Corticoid use

High Apache

Delay or wrong Antifungal

Older

Longer hospitalization

The only one that can be modified

Vardakas K.Z. Clinical Microbiology and Infection (2009) Bassetti M. Diagnostic Microbiology and Infectious Disease (2007)
Tumbarello M. Journal of Clinical Microbiology (2007) Colombo A.L. Infection Control and Hospital Epidemiology (2007)

95% of delay

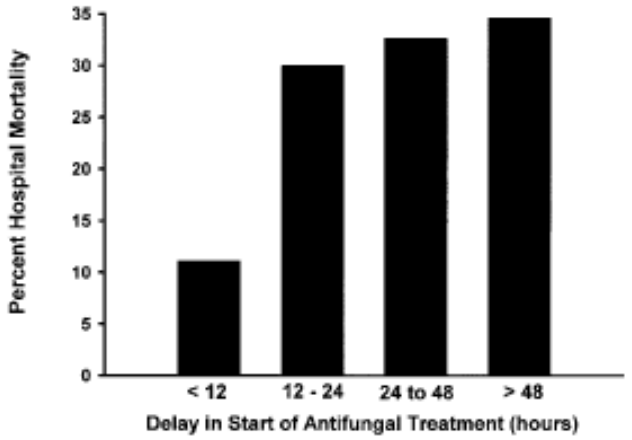
30% wrong dosage

BMC Infect Dis. 2010 Jun 3;10:150.
Micek ST, Kothari S, Shorr AF.

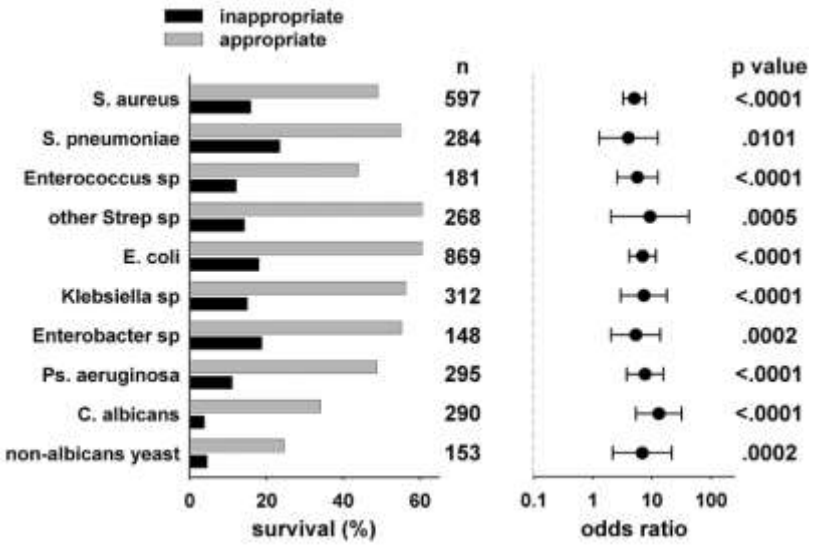
Antifungal therapy

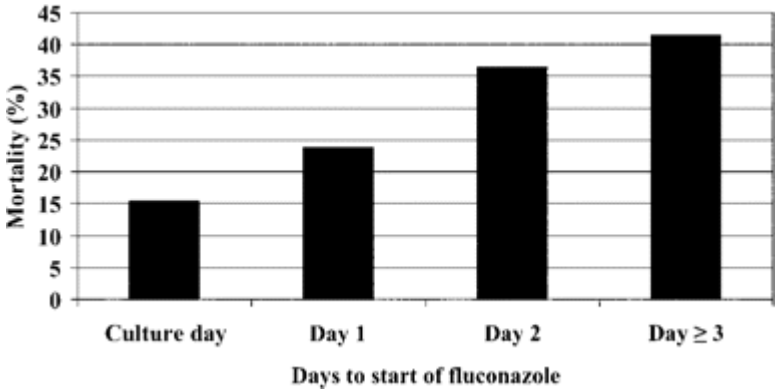
Must be empiric

Morrell 2005



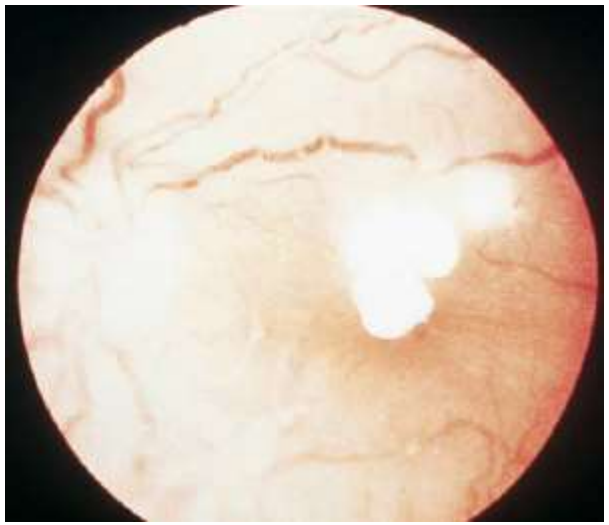
Kumar 2009





Garey 2006

Fever without a evident site of infection
Increased heart and breath rate
Embolic signs
Subcutaneous nodules
Retinal infiltrates



Sepsis

Diagnosis

- Blood Culture

Confirmed

- 1,3 beta-D-glucan
- Septifast – 6h
- PCR + ESM – 4h
  - Radical study
    - Europe and USA

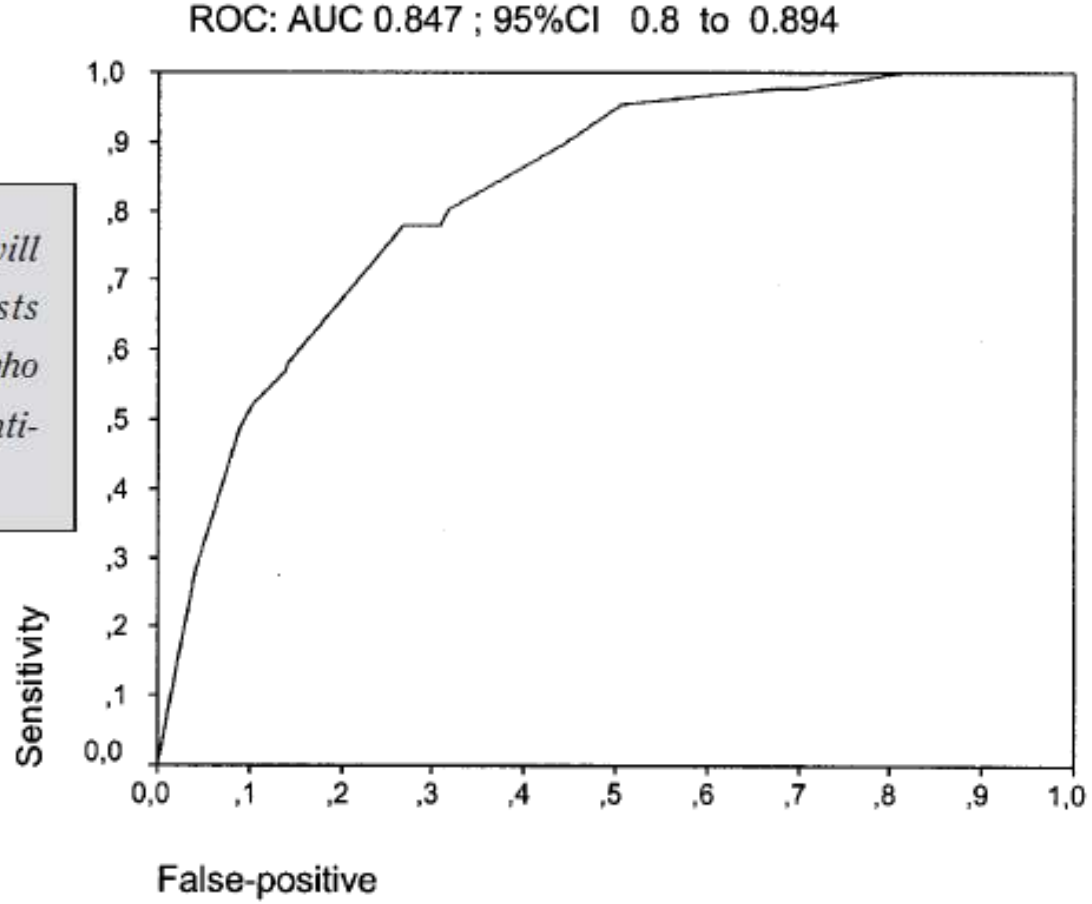
Probable (Pre-emptive)

Clinical parameters for pre-emptive therapy

Rule[a] (*n*=2,890)	Rule description	No. of patients selected by rule (% of total)	No. of cases selected by rule (% of total)	Infection rate among IC patients		Relative risk[b]	*p*-value[c]	Sensitivity	Specificity	PPV	NPV
				Not selected by rule (%)	Selected by rule (%)						
1 (*n*=2,889)	Any antibiotic use (day 1–3) AND CVC (day 1–3)	1,801 (62.3)	78 (88.6)	0.9	4.3	4.71 (2.45, 9.06)	<0.001	0.89	0.38	0.04	0.99
2 (*n*=2,879)	Any antibiotic use (day 1–3) AND CVC (day 1–3) AND at least one of the following additional risk factors: any surgery (day −7–0); immunosuppressive use (day −7–0); pancreatitis (day −7–0); TPN (day 1–3); any dialysis (day 1–3); steroid use (day −7–3)	916 (31.8)	58 (65.9)	1.5	6.3	4.14 (2.69, 6.39)	<0.001	0.66	0.69	0.06	0.98
3 (*n*=2,859)	Any antibiotic use (day 1–3) OR CVC (day 1–3) AND at least two of the following additional risk factors: any surgery (day −7–0); immunosuppressive use (day −7–0); pancreatitis (day −7–0); TPN (day 1–3); any dialysis (day 1–3); steroid use (day −7–3)	303 (10.6)	30 (34.1)	2.3	9.9	4.36 (2.85, 6.67)	<0.001	0.34	0.90	0.09	0.97

NNT = 13 – Should be considered

A score >2.5 will help intensivists select patients who will benefit from early anti-fungal administration.



B

Cutoff value	Sensitivity	False positive
1.055	.983	.653
1.509	.949	.495
1.963	.898	.426
2.069	.831	.312
2.074	.814	.301
2.528	.814	.259
2.982	.780	.231
3.026	.610	.132
3.093	.593	.130
3.547	.525	.092
4.001	.492	.077

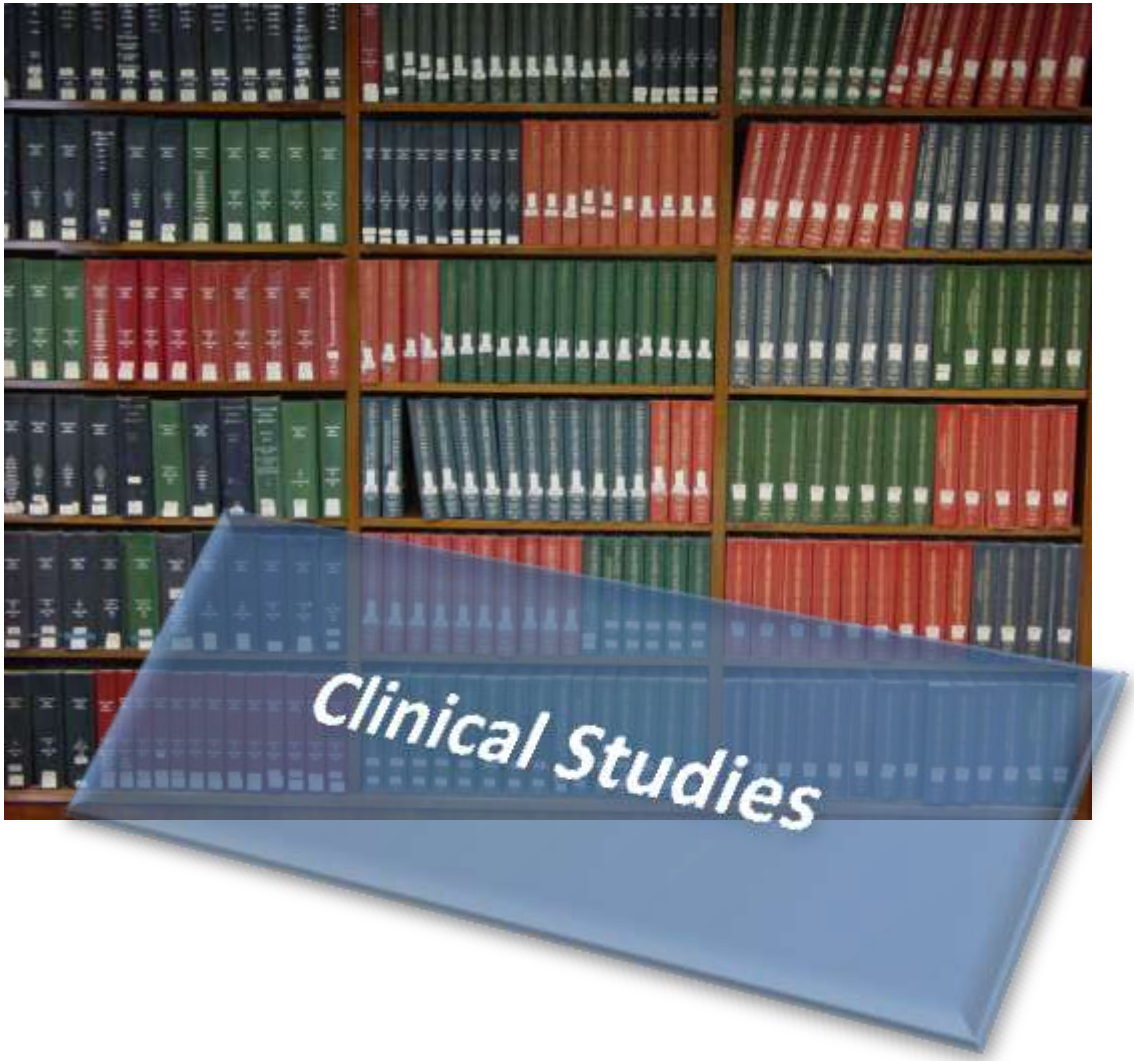
Empiric or pre-emptive

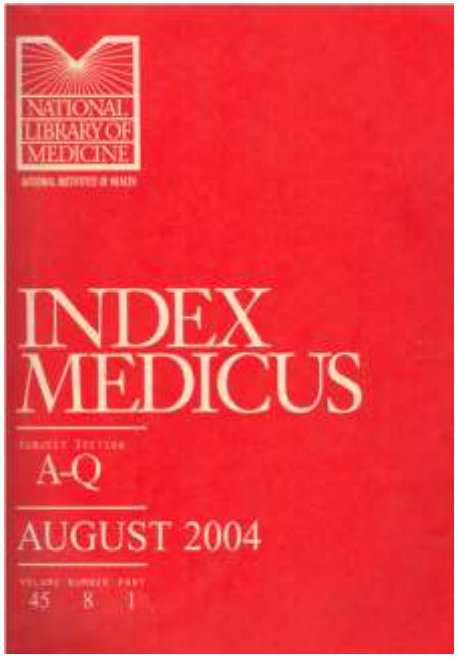
TABLE 4. Recommendations on fever-driven and diagnosis-driven therapy of candidaemia and invasive candidiasis

Population	Intention	Intervention	SoR	QoE	References
Empiric					
Pre-emptive					
Definitive					

APACHE, acute physiology and chronic health evaluation.
[a]The (1,3)-β-D-glucan tests have low specificity and sensitivity with false-positive results in the presence of haemodialysis, other fungal or bacterial infection, wound gauze, albumin or immunoglobulin infusion.

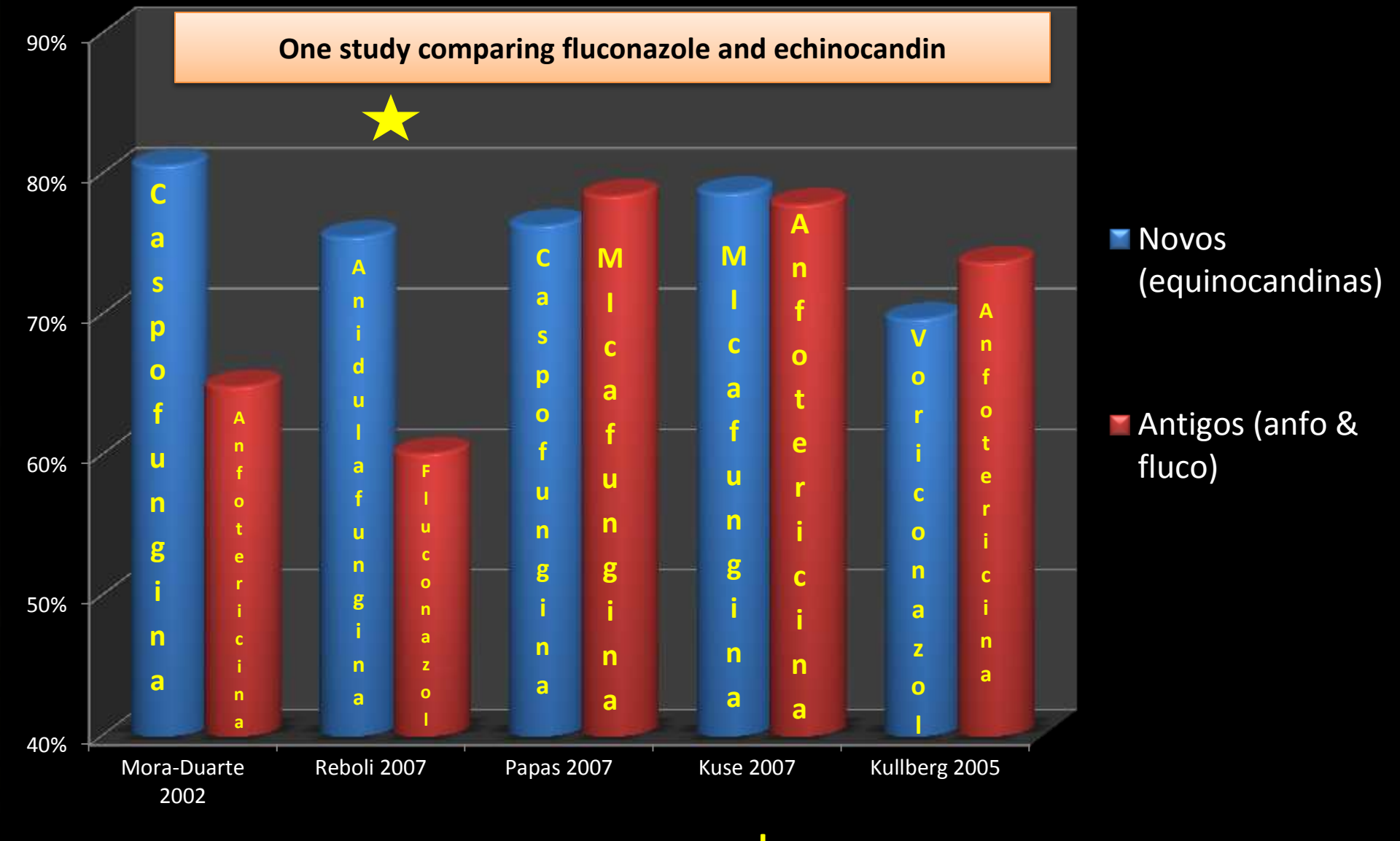
Grade	ESCMID EFISG
A	Strongly supports a recommendation for use
B	Moderately supports a recommendation for use
C	Marginally supports a recommendation for use
D	Supports a recommendation against use


Clinical Studies

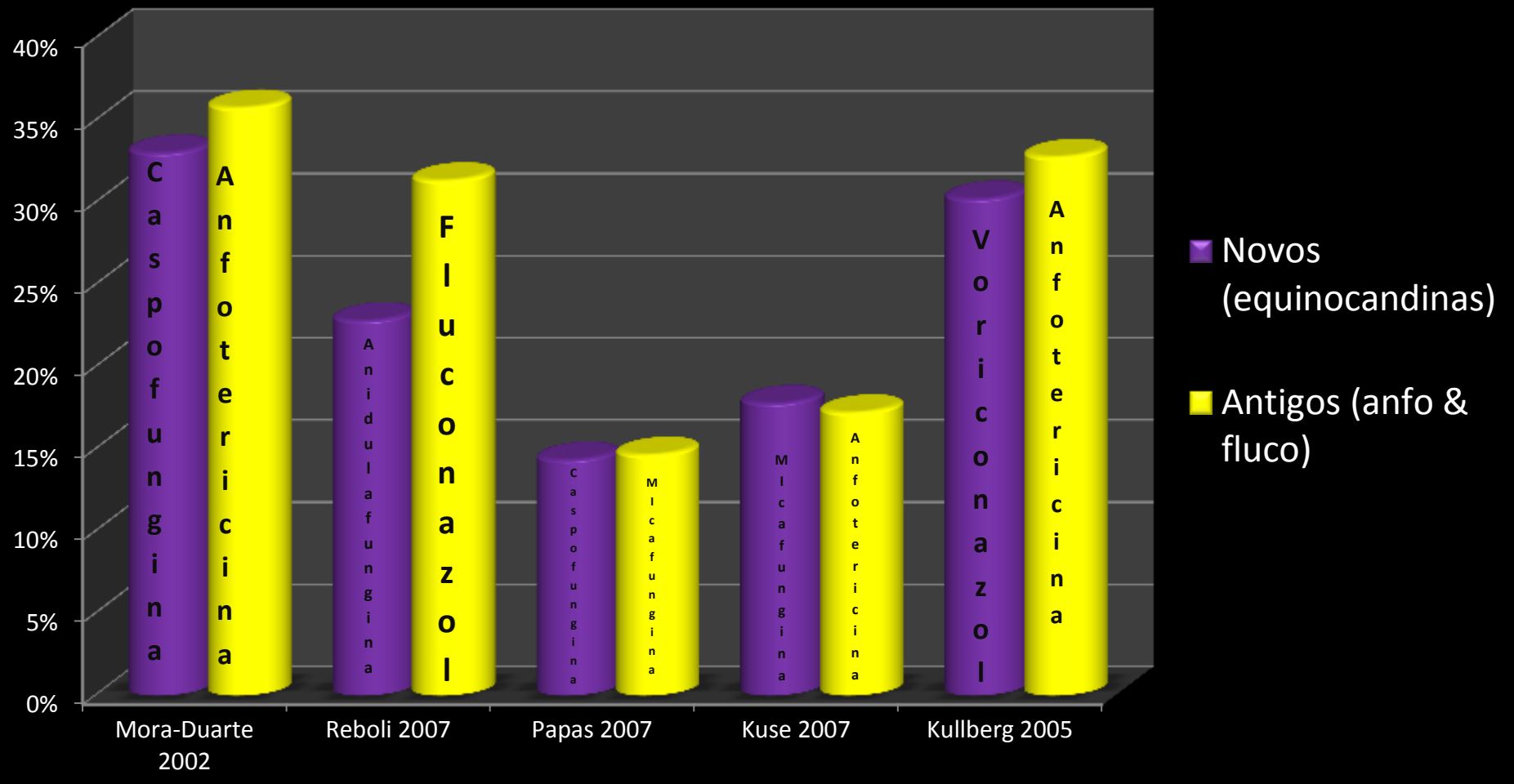

NATIONAL LIBRARY OF MEDICINE
INDEX MEDICUS
A-Q
AUGUST 2004
45 8 1


Prehistoric Googling

Clinical response



Mortality


40%
35%
30%
25%
20%
15%
10%
5%
0%
Caspofungina
Anfotericina
Anidulafungina
Fluconazol
Caspofungina
Micafungina
Micafungina
Anfotericina
Voriconazol
Anfotericina
Mora-Duarte 2002
Reboli 2007
Papas 2007
Kuse 2007
Kullberg 2005
Novos (equinocandinas)
Antigos (anfo & fluco)

Kett et al. Critical Care 2011, 15:R253
http://ccforum.com/content/15/5/R253

CRITICAL CARE

RESEARCH Open Access

Anidulafungin compared with fluconazole in severely ill patients with candidemia and other forms of invasive candidiasis: Support for the 2009 IDSA treatment guidelines for candidiasis

Daniel H Kett[1*], Andrew F Shorr[2], Annette C Reboli[3], Arlene L Reisman[4], Pinaki Biswas[5] and Haran T Schlamm[4]

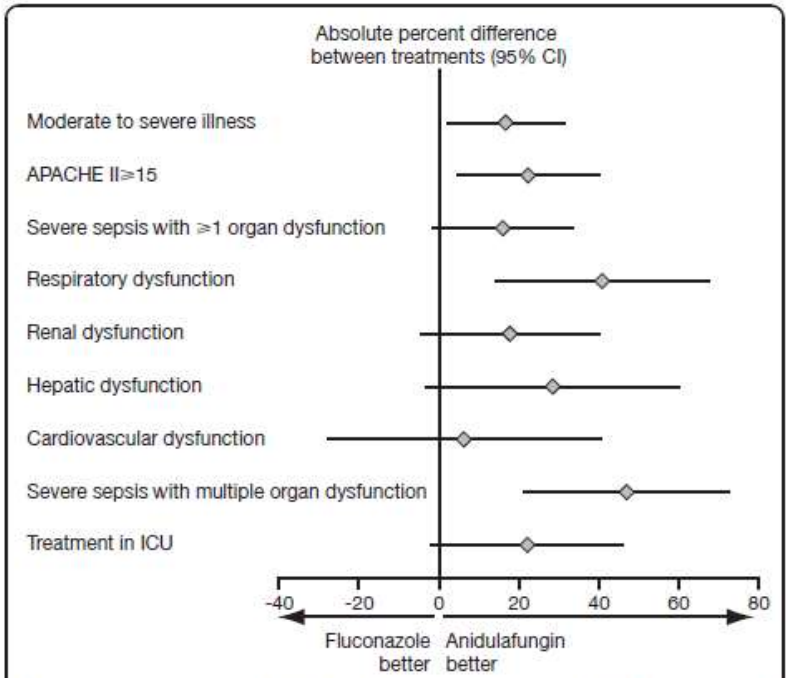


Figure 1 Difference in global response at end of treatment among severely ill patients and the various subpopulations.

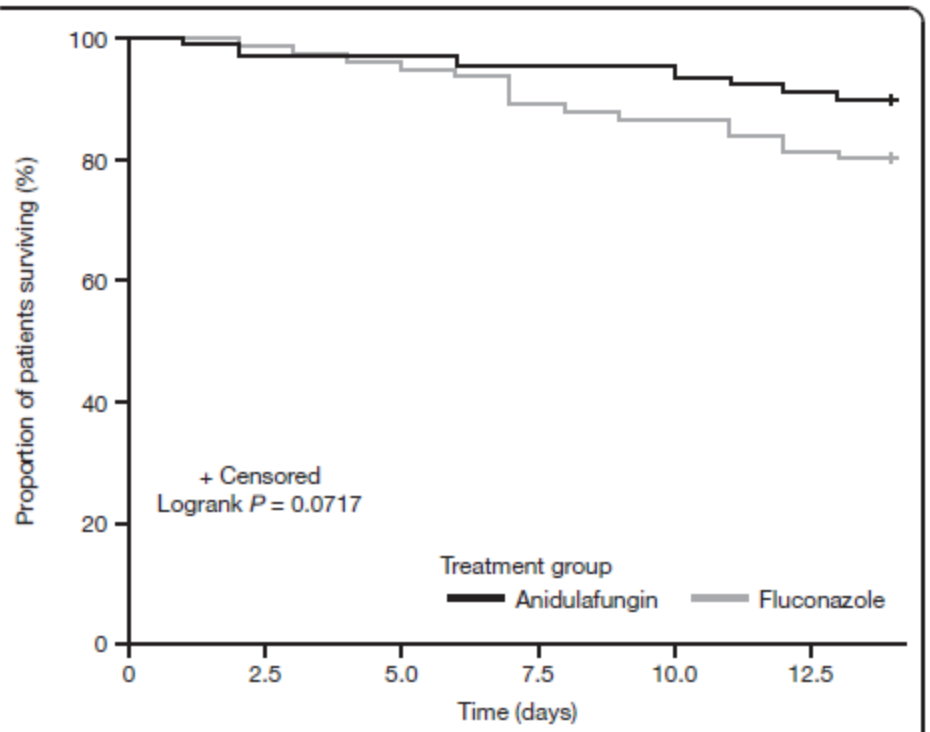


Figure 2 Kaplan-Meier analysis of survival to 14 days among severely ill patients with candidemia.

pos-hoc study of Anidulafungine vs Fluconazole APACHE >15

	IDSA [9]	ECIL-4 (for overall population) [10]	EFISG (ESCMID) [11]	DMYKG/PEG [12]
Indication for antifungal therapy	• All pts with *Candida*-positive blood culture	• All pts with *Candida*-positive blood culture	• All pts with *Candida*-positive blood culture	• All pts with *Candida*-positive blood culture
Preferred first line therapy	• EC or FLC	• EC or L-AMB or FLC or VORI	• EC	• EC or FLC • L-AMB alternative in critically ill pts
Criteria for choice of drug	• EC: moderately to severely ill, recent azole exposure • FLC: less severely ill	• FLC and VORI: avoid after azole prophylaxis • FLC: avoid if severely ill	• Only EC as recommended first line therapy	• FLC: avoid after azole prophylaxis and in critically ill pts
Duration of therapy	• 2 weeks after documented clearance of *Candida* from bloodstream AND • resolution of symptoms	• 14 d after last positive blood culture AND • resolution of signs and symptoms	• 14 d after end of candidaemia	• 14 d after first negative blood culture AND • complete resolution of all signs and symptoms attributable to

Echinocandin

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www.elsevier.es/reviberoammicol

Special Article

Guideline

Recommendations for the management of candidemia in adults in Latin America

Marcio Nucci[a,m,*], Luis Thompson-Moya[b,m], Manuel Guzman-Blanco[c,m], Iris Nora Tiraboschi[d,m], Jorge Alberto Cortes[e,m], Juan Echevarría[f,m], Jose Sifuentes[g,m], Jeanette Zurita[h,m], María E. Santolaya[i,m], Tito Alvarado Matute[j,m], Flavio de Queiroz Telles[k,m], Arnaldo Lopes Colombo[l,m]

Brazilian guidelines for the management of candidiasis: a joint meeting report of three medical societies – Sociedade Brasileira de Infectologia, Sociedade Paulista de Infectologia, Sociedade Brasileira de Medicina Tropical

Echinocandins: are they all the same?

Mukherjee PK, Sheehan D, Puzniak L, Schlamm H, Ghannoum MA.

Center for Medical Mycology and Mycology Reference Laboratory, Department of Dermatology, University Hospitals Case Medical Center and Case Western Reserve University, Cleveland, Ohio 44106, USA.

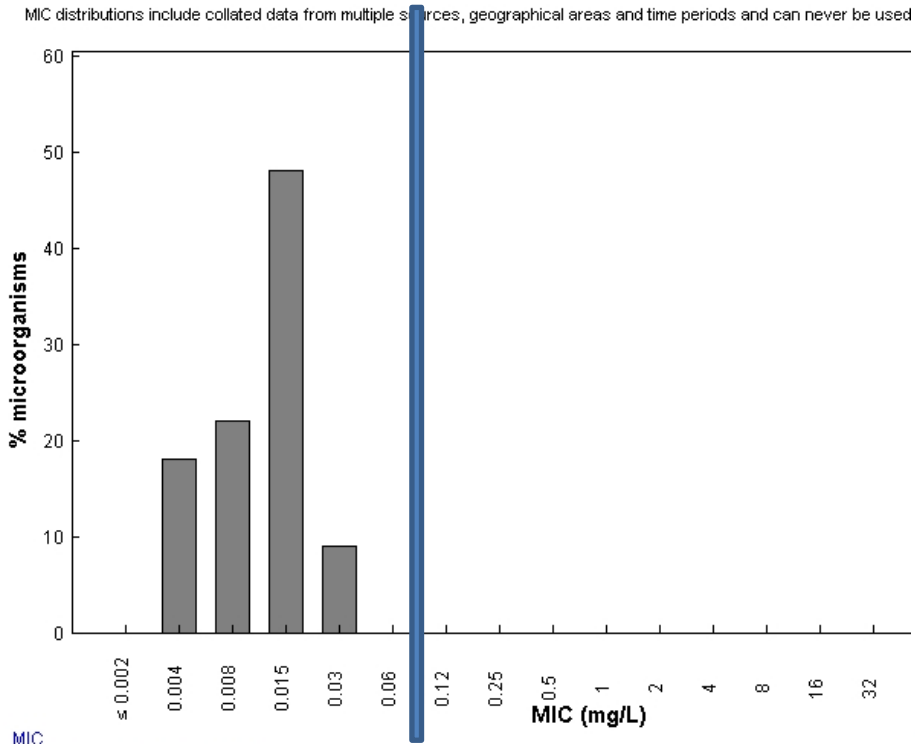
Organism	Caspofungin	Micafungin	Anidulafungin
***Candida* species**	**MIC_{50}, MIC_{90}**	**MIC_{50}, MIC_{90}**	**MIC_{50}, MIC_{90} (range)**
C. albicans	0.03, 0.06	0.015, 0.03	0.03, 0.06 (0.03–0.25)
C. glabrata	0.03, 0.06	0.015, 0.015	0.06, 0.12 (0.03–1)
C. tropicalis	0.03, 0.06	0.03, 0.06	0.03, 0.06 (0.06–2)
C. krusei	0.12, 0.25	0.06, 0.12	0.06, 0.06 (0.12–1)
C. parapsilosis	0.25, 1	1, 2	2, 2 (0.12 to >2)
C. guilliermondii	0.5, 1	0.5, 1	1, 2 (1–4)
C. lustitaniae	0.25, 0.5	0.06, 0.12	0.5, 0.5 (0.125–2)
C. dubliniensis	–, 0.5	–, 0.03	–, 0.06

3:38

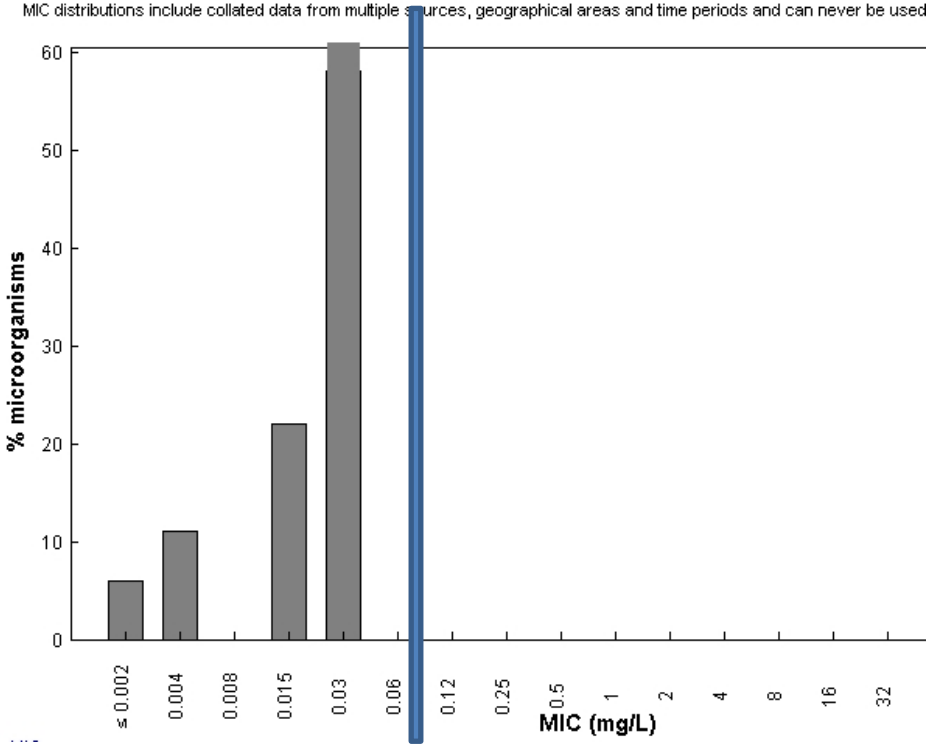
Variable	Caspofungin	Micafungin	Anidulafungin
C_{max} (mg/L) [50 mg single dose]	7.64	4.95	2.07–3.5
Bioavailability (%)	<10	<10	2–7
$t_{½}$ (h)	9–11	11–17	24–26
Vd (L/kg)	0.14	0.22–0.24	0.5
AUC (mg • h/L)	87.9–114.8	111.3	44.4–53
Protein binding (%)	96–97	99.8	>99
Metabolism	Slow peptide hydrolysis, N-acetylation and spontane degradation to inactive proc	Catechol-*O*-methyltransferase	Not metabolized cal degradation to tabolites
Cl_T	0.15		
Fraction excreted unchanged in urine (%)	1.4		
Elimination	35% faeces, 41% urine, 1.4% as unchanged drug	40% faeces, <15% urine	Primarily faeces (<10% as intact drug), 1% urine
CSF penetration (% plasma)	Low	Low	<0.1%
Dose adjustment in renal insufficiency	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed
Dose adjustment in geriatric patients	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed
Dose adjustment in hepatic insufficiency	Child-Pugh 5–6: none Child-Pugh 7–9: significant increase in AUC; reduce maintenance dose to 35 mg/day Child-Pugh >9: no data	Child-Pugh 7–9: C_{max} not altered, AUC significantly decreased compared with healthy subjects	No dose adjustment needed in patients with mild, moderate or severe hepatic dysfunction

PK EC = AUC/MIC

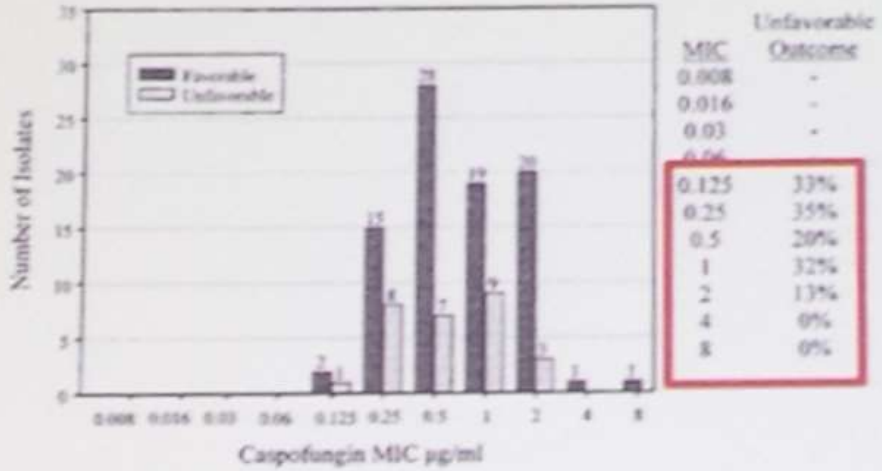
Micafungin / Candida albicans EUCAST
International MIC Distribution - Reference Database 2014-10-01



Anidulafungin / Candida albicans EUCAST
International MIC Distribution - Reference Database 2014-10-01



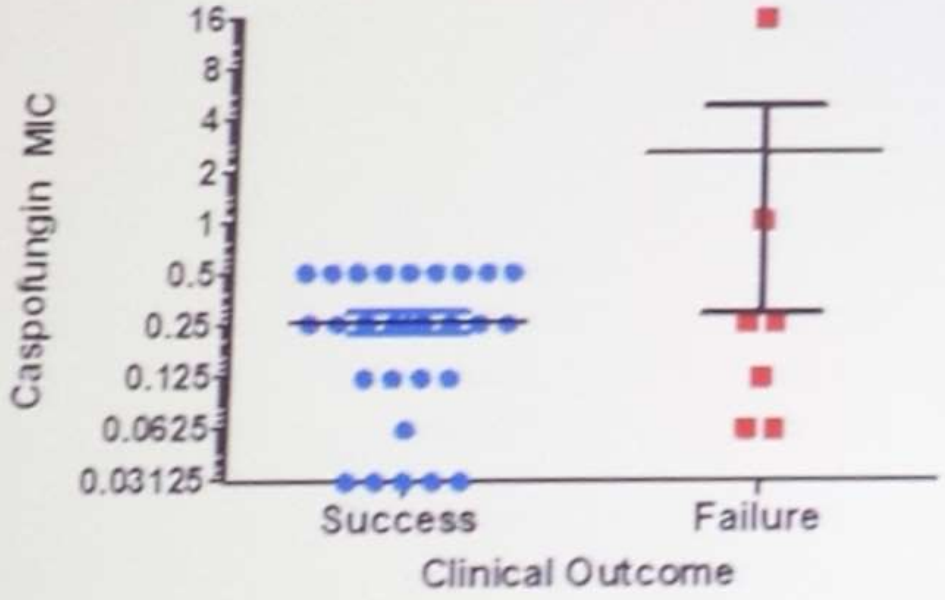
Is there clinical relevance?



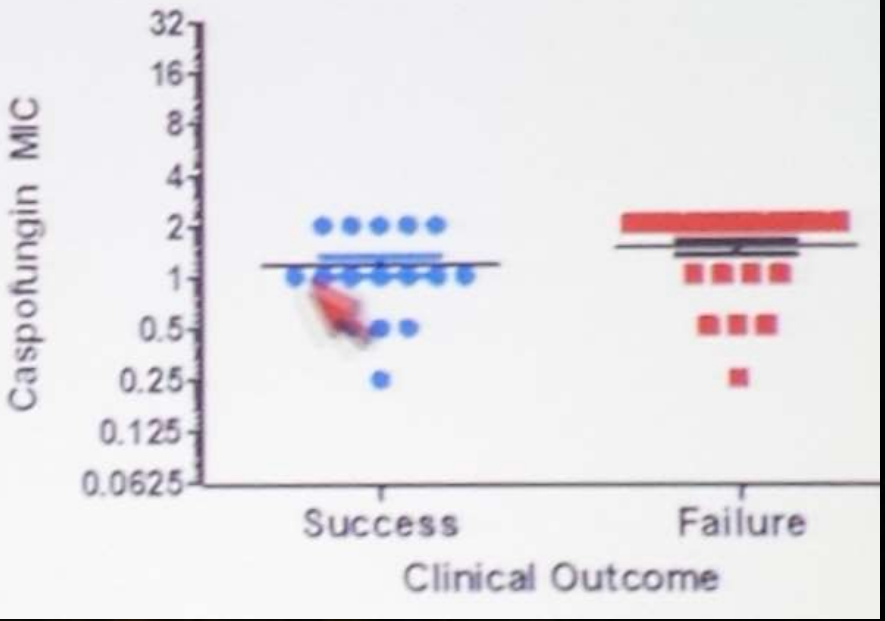
MIC	Unfavorable Outcome
0.008	-
0.016	-
0.03	-
0.125	33%
0.25	35%
0.5	20%
1	32%
2	13%
4	0%
8	0%

Kartsonis *AAC* 2005

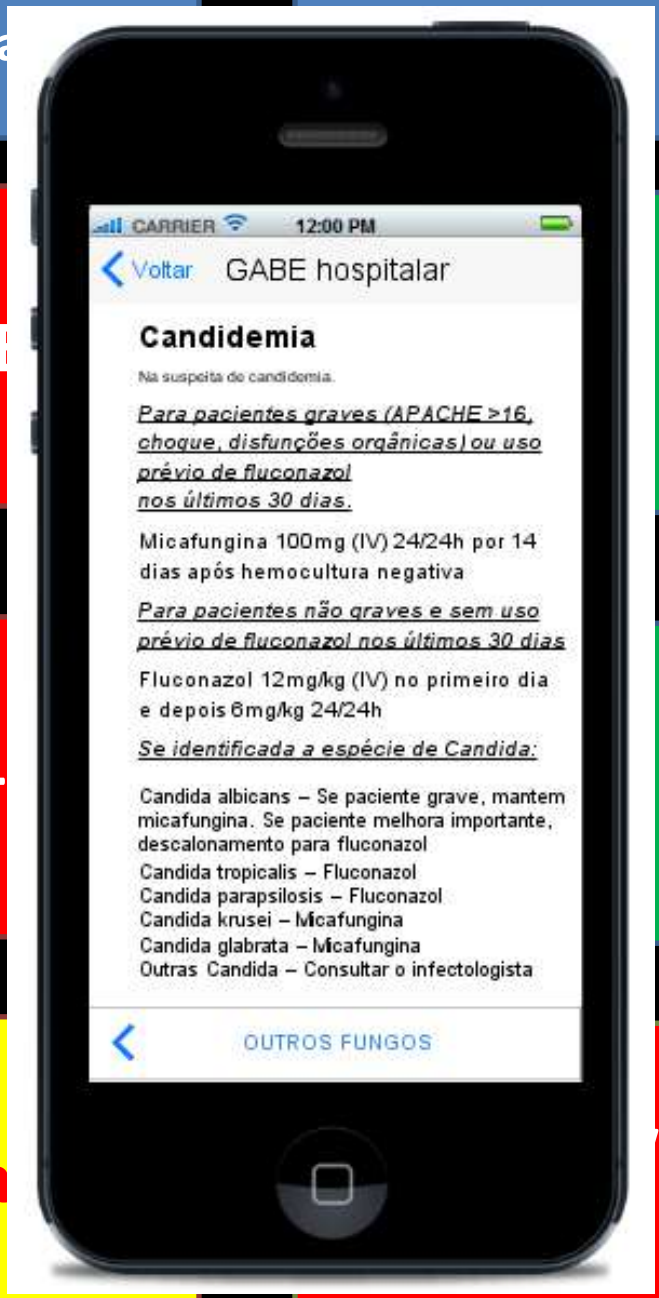
C. albicans, krusei, tropicalis



C. parapsilosis



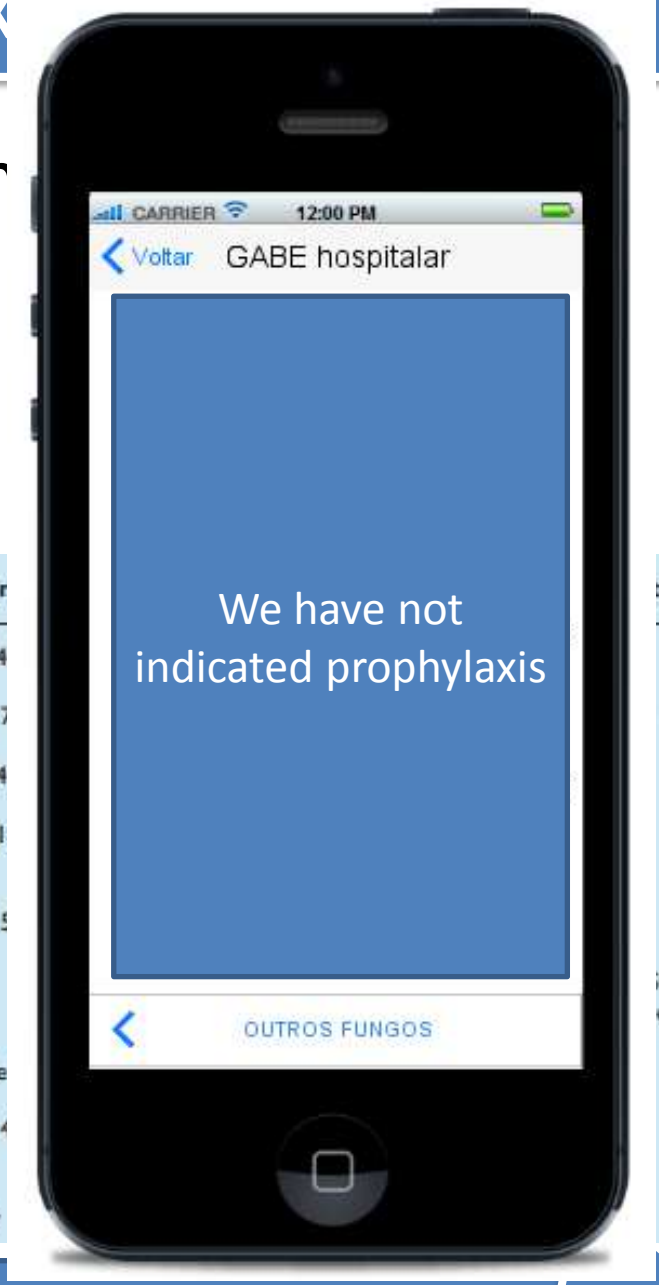
	Caspofungin	Anidula
Loading dose	YES	YE
Price	+++	+
Other	Child B/C	Gen



Prophylax

- Fluconazole is established (6r
  - Not for echinocandin

Population	Intention	Intervention
Recent abdominal surgery AND recurrent gastrointestinal perforations or anastomotic leakages	To prevent intraabdominal *Candida* infection	Fluconazole 4 Caspofungin 7
Critically ill surgical patients with an expected length of ICU stay ≥3 day	To delay the time to fungal infection	Fluconazole 4
Ventilated for 48 h and expected to be ventilated for another ≥72 h	To prevent invasive candidiasis/candidaemia	Fluconazole 1
Ventilated, hospitalized for ≥3 day, received antibiotics, CVC, and ≥1 of: parenteral nutrition, dialysis, major surgery, pancreatitis, systemic steroids, immunosuppression	To prevent invasive candidiasis/candidaemia	Caspofungin 5
Surgical ICU patients	To prevent invasive candidiasis/candidaemia	Ketoconazole
Critically ill patients with risk factors for invasive candidiasis/candidaemia	To prevent invasive candidiasis/candidaemia	Itraconazole 4
Surgical ICU with catabolism	To prevent invasive candidiasis/candidaemia	Nystatin 4 Mio IU/day



Rational use of echi

- Non-neutropenic patients
  - Positive blood culture
    - Always (echinocandin or fluconazole)
  - Biomarker (b-d-glucan)
    - Weak
  - Candida score
    - Not established by some guidelines (E
      - Latin America – Well discussed but witl
    - Easy at bedside for decision
      - Sepsis + risk factors
      - NNT=13
  - Fever in ICU
    - Not indicated

Empirical therapy

- IDSA

Fluco for mild disease

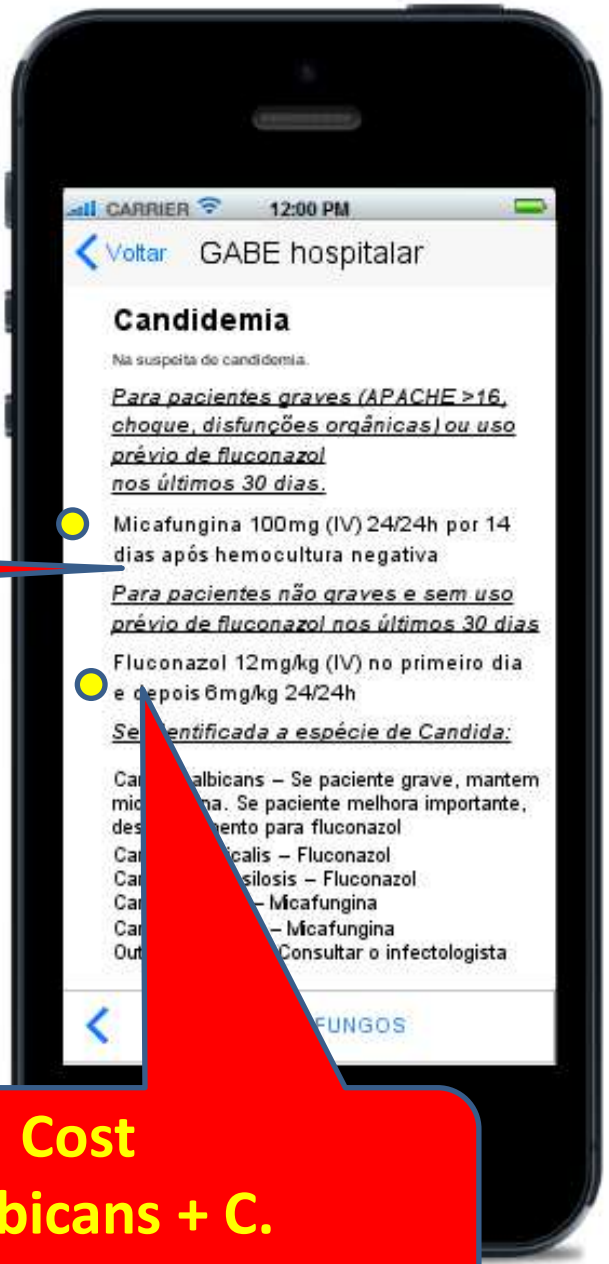
- Moderate to severe

Why micafungin?

Cost
NO loading dose

Why fluconazole?

ness of empiric
d disease



Cost
C. albicans + C. parapsilosis> >85%

De-scalation therapy

- Change echinocandin to fluconazole
  - Consideration for oral therapy
    - Early discharge
  - Low cost
  - Avoid exposure to echinocandins?

Candida species

CALL ID
others

C. albicans

C. guilhermondi

Amphotericina

C. lusitanae

C. tropicalis

C. krusei

Fluconazole

C. glabrata

C. parapsilosis

Echinocandins

Med Mycol. 2012 Jul 5. [Epub ahead of print]

Candida glabrata: an emerging pathogen in Brazilian tertiary care hospitals.

Colombo AL, Garnica M, Aranha Camargo LF, Da Cunha CA, Bandeira AC, Borghi D, Campos T, Senna AL, Valias Didier ME, Dias VC, Nucci M

*Universidade Federal de São Paulo, São Paulo.

Abstract

Candida glabrata is an infrequent cause of candidemia in Brazilian public hospitals. We investigated putative differences in the epidemiology

Candida tropicalis: its prevalence, pathogenicity and increasing resistance to fluconazole

Rajendra J. Kothavade,[1] M. M. Kura,[2] Arvind G. Valand[3] and M. H. Panthaki[4]

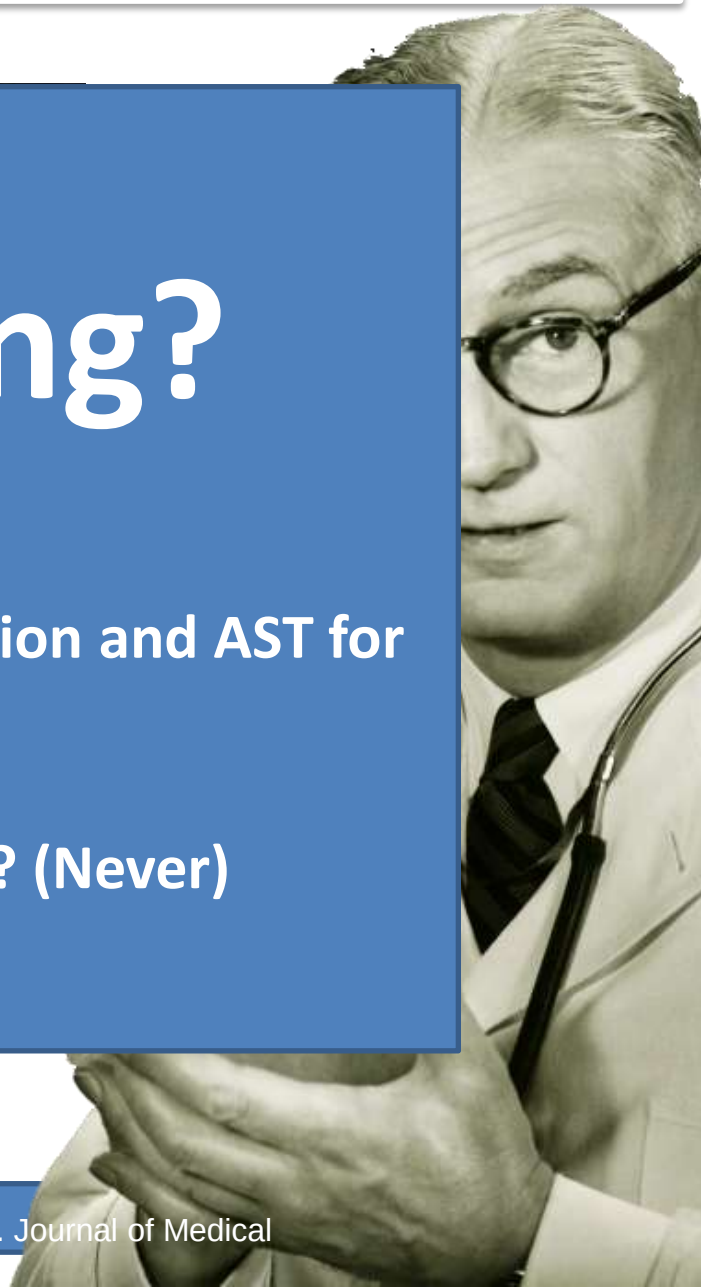
Identification of species

Is it cost saving?

Parapsilosis -> fluconazole
1 echinocandin treatment => 70 identification and AST for yeasts

1 parapsilosis / 69 non-parapsilosis ? (Never)

– MIC



Sheppard D.C. Journal of Clinical Microbiology (2008) Metwally L. Journal of Medical

In resume

- How can I improve the use echinocandins in the ICU?
  - Increase the pre-emptive therapy
    - Biomarkers (BDG, mannan)
    - PCR, Maldi-Tof, Septifast
  - Avoid vicious prescriptions of fluconazole for severe patients in the ICU
  - Add “clinical scores of candidemia” in the routine like other severeness scores (APACHE, SOFA, MODS)

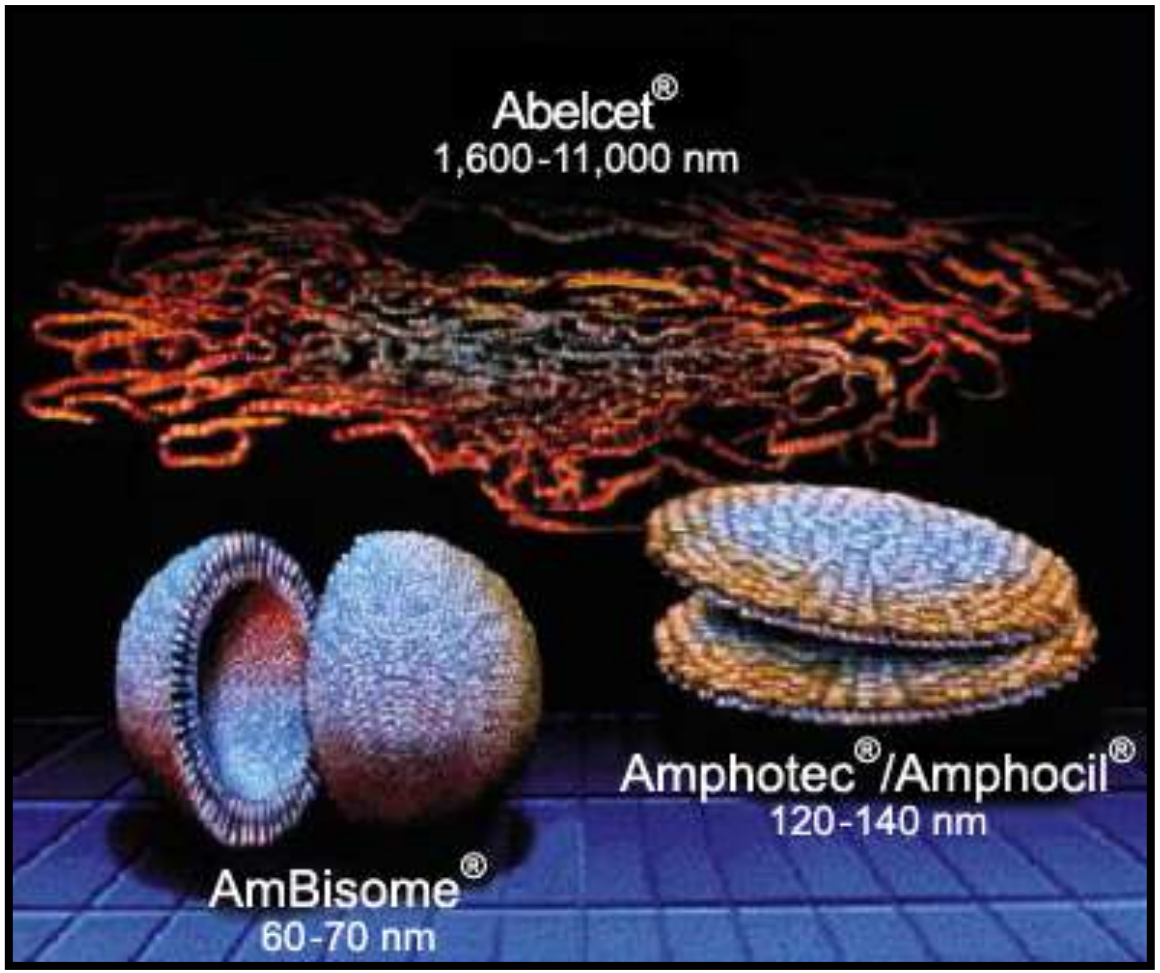
What is the best echinocandin?

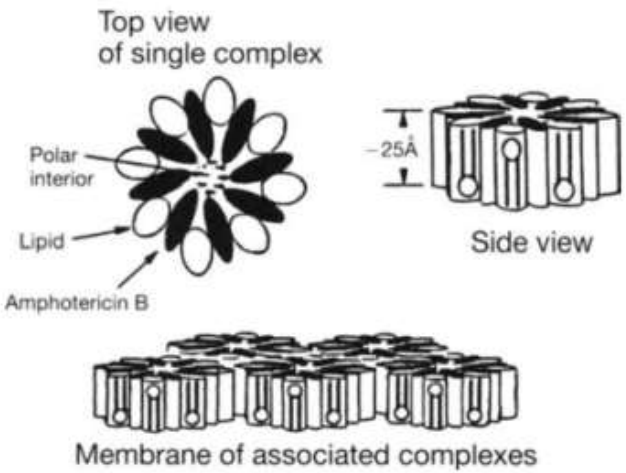
- The most affordable for you hospital

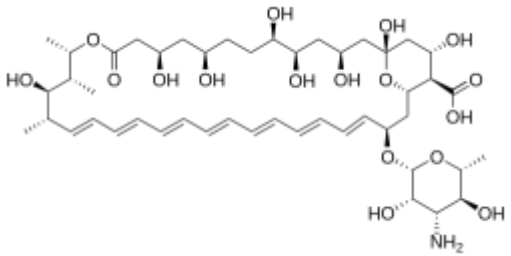
- In Brazil
  - in public hospitals, the cost is the main point of the decision
  - In private hospital, the reimburment can be a advantage.

Neutropenic and endemic mycosis

LET'S GO TO LIPID FORMULATION OF AMPHOTERICIN B


Abelcet®
1,600-11,000 nm
Amphotec®/Amphocil®
120-140 nm
AmBisome®
60-70 nm


Top view
of single complex
Polar
interior
Lipid
Amphotericin B
~25Å
Side view
Membrane of associated complexes



Fungal species	FLU	ITRA	POSA	VOR	AMB	Echinocandins[a]
Aspergillus fumigatus	–	+	+	+	+	+
Aspergillus flavus	–	+	+	+	+	+
Aspergillus terreus	–	+/–	+	+	+/–	+
Candida albicans	+	+	+	+	+	+
Candida krusei	–	+/–	+	+	+/–	+
Candida glabrata	+/–	+/–	+/–	+/–	+	+
Other *Candida* species[b]	+	+	+	+	+	+/–
Cryptococcus neoformans	+	+	+	+	+	–
Coccidioides species	+	+	+	+	+	–
Blastomyces dermatitidis	+/–	+	+	+	+	–
Histoplasma capsulatum	+	+	+	+	+	–
Fusarium species	–	–	+/–	+/–	+/–	–
Zygomycetes	–	+/–	+	–	+	–
Scedosporium apiospermum	–	–	+	+	+/–	–
Scedosporium prolificans	–	–	–	–	–	–
Trichosporon	–	–	ND	+	+/–	–

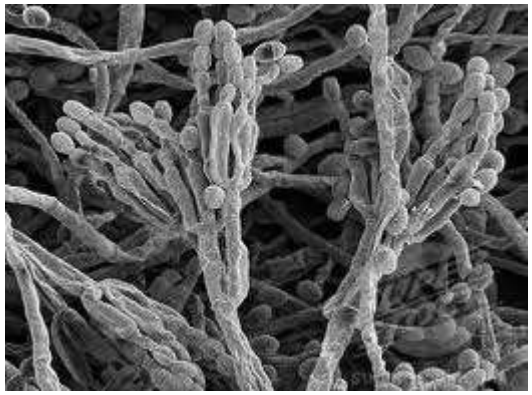
Aspergillus

Candida

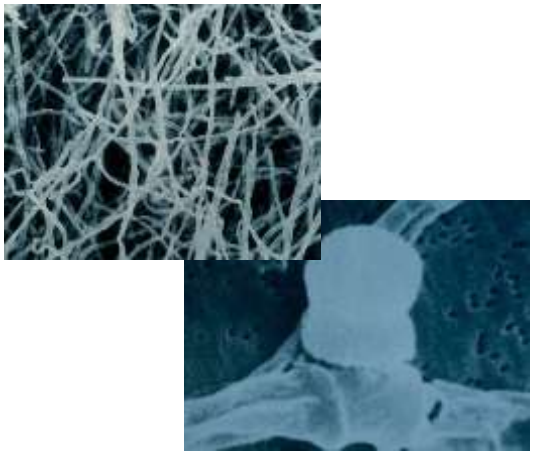
Endemicos

Outros

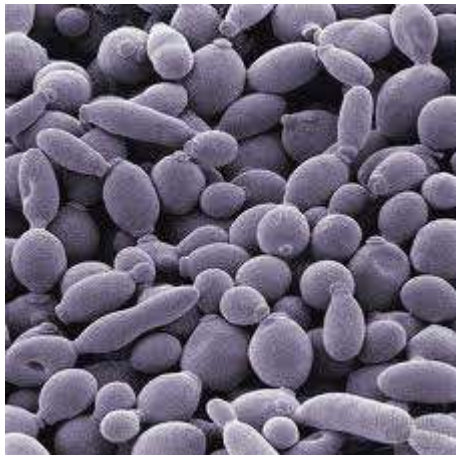
Neutropenic



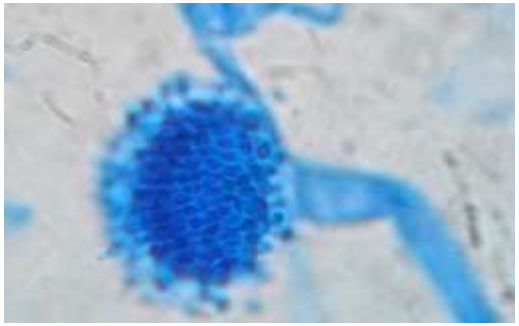
Filamentosos



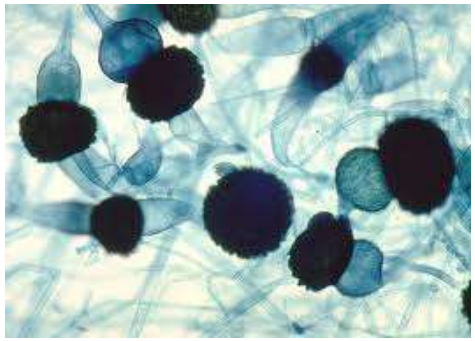
Dimorfos



Leveduriformes



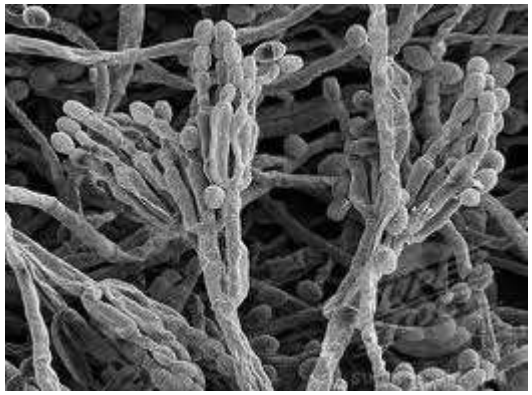
Aspergillus



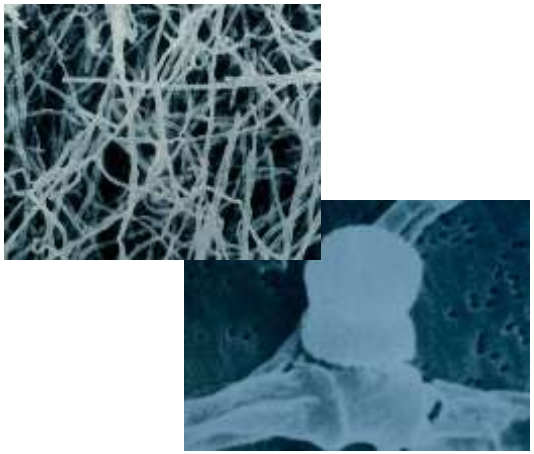
Fungos da mucormicose

Fusarium

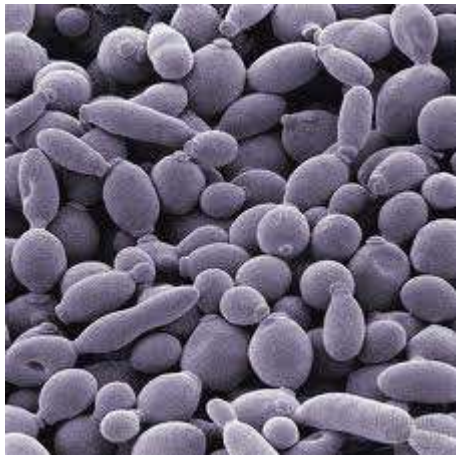
Endemic



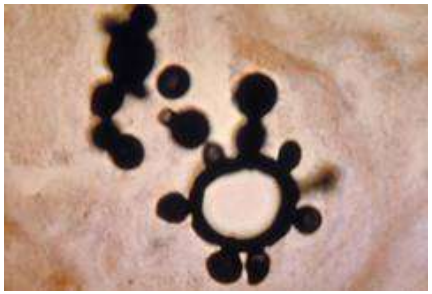
Filamentosos



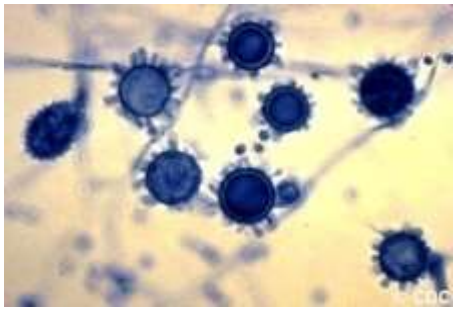
Dimorfos



Leveduriformes



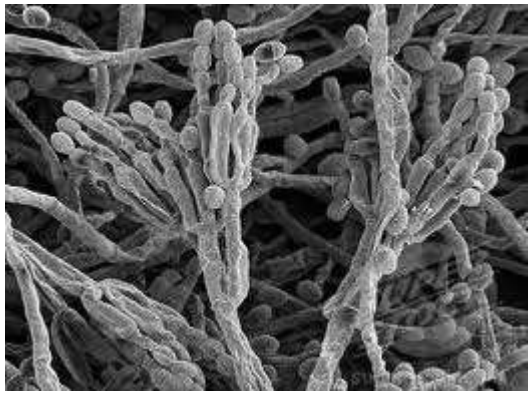
Paracocci



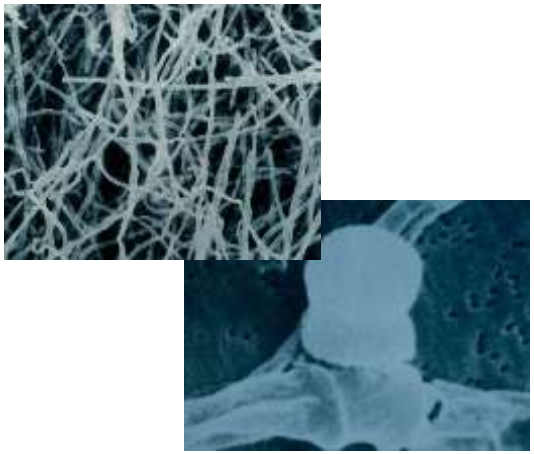
Histoplasma

Coccicioides/Blasto

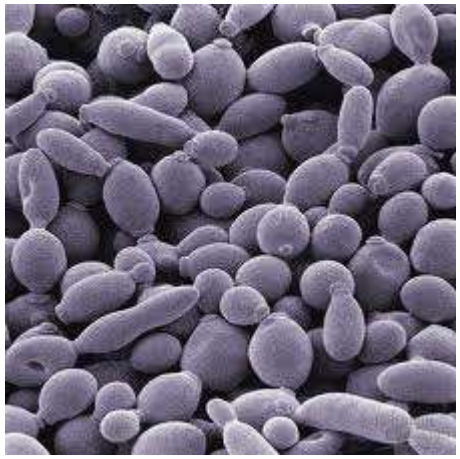
Immunocompromised (HIV, ICU, Tx)



Filamentosos

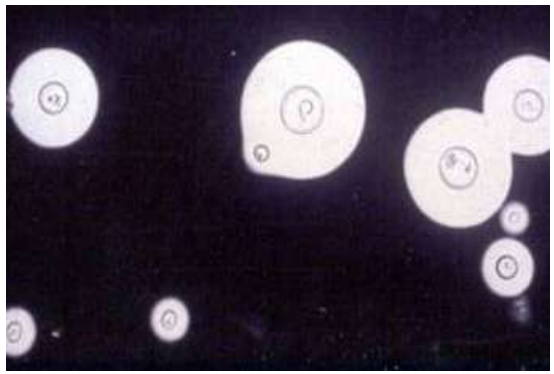


Dimorfos



Leveduriformes

Candida



Cryptococcus

Approach to the Classification of Medically Important Moulds
Segal B, Bow EJ, Menichetti F: Infect Dis Clin N Am 2002;16:935-64

Empirical antifungal against molds?

Fus

*p.

*spp.

*.

*mella

S. prolificans

P. lilacinus

Empiric Vs preemptive

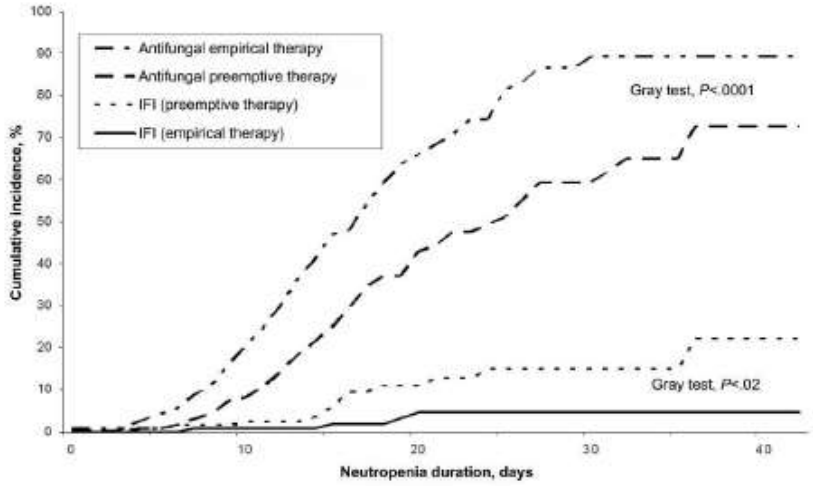
Empirical versus Preemptive Antifungal Therapy for High-Risk, Febrile, Neutropenic Patients: A Randomized, Controlled Trial

Catherine Cordonnier,[1] Cécile Pautas,[1] Sébastien Maury,[1] Anne Vekhoff,[4] Hassan Farhat,[11] Felipe Suarez,[5] Nathalie Dhédin,[6] Francoise Isnard,[7] Lionel Ades,[12] Frédérique Kuhnowski,[8] Francoise Foulet,[2] Mathieu Kuentz,[1] Patrick Mais

- Em
  - —
- Preemptive
  - Start if:
    - Positive culture
    - Thorax and sinuses CT
    - Diarrheia ou grade 3 mucositis
    - Galactomannan >0.5
    - Shock
    - Cutaenous suggestive lesions
    - Abdome US
      - Abscess
    - Brain CT
      - Abscess
    - Neurological sign/symtoms

Cost saving and rational

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

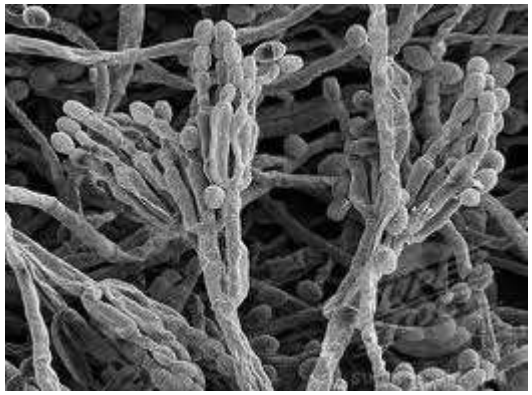


What is the best empirical therapy in neutropenic persistent febrile patient

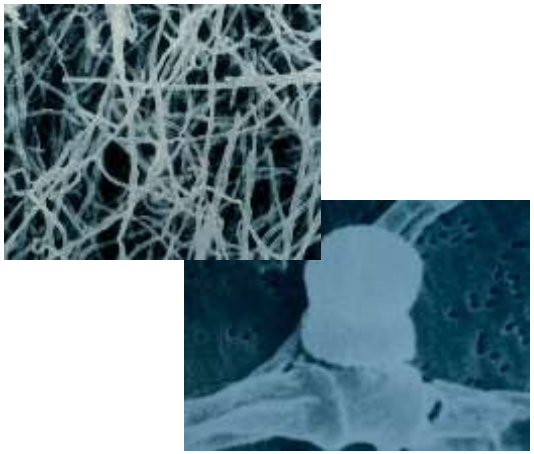
European Conference on infections in leukaemia

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

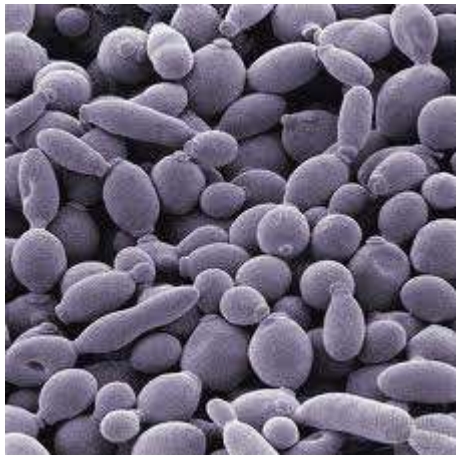
Neutropenic



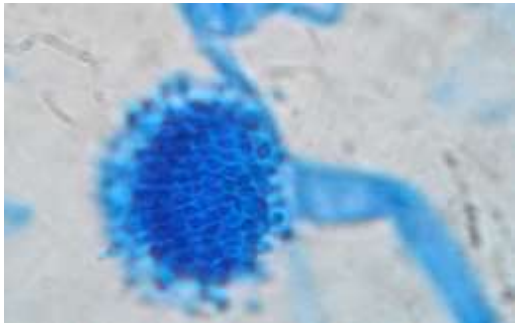
Filamentosos



Dimorfos



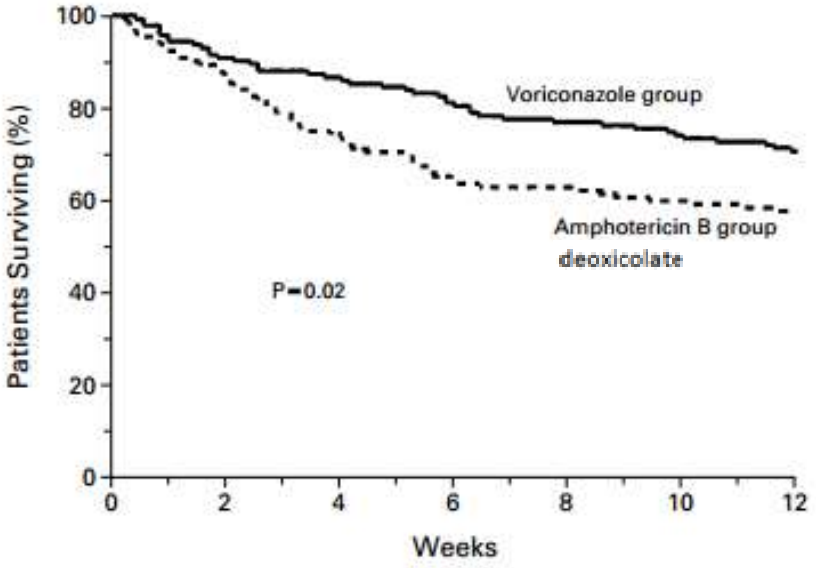
Leveduriformes



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 2ª. choice (AI)
  - Resposta +/-40%
  - A. terreus resistente a AB
- Combined therapy not indicated
- Considered after failure or adverse effects of voriconazole



Walsh TJ, Pappas P, Winston DJ, et al. N Engl J Med 2002; 346:225–34.

Duration of the treatment

Treatment of Aspergillosis: Clinical Practic
Guidelines of the Infectious Diseases Socie
of America

Thomas J. Walsh,[1,a] Elias J. Anaissie,[2] David W. Denning,[13] Raoul Herbrecht,[14] Dimitrios P. Kontoyia
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]

Cost saving

- 6 to 12 weeks or neutrophils 'r overy, absence of lesions in the CT
- Low levels of galactomannan

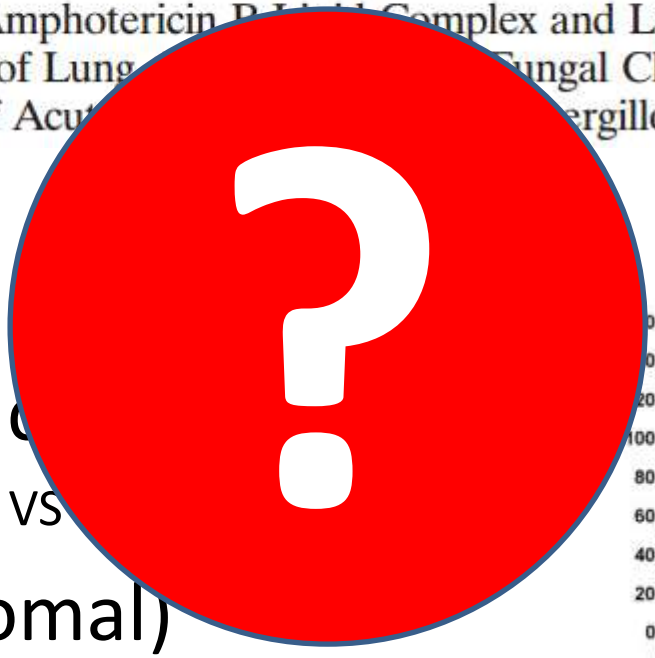
- Restart prophylaxis if neutropenia

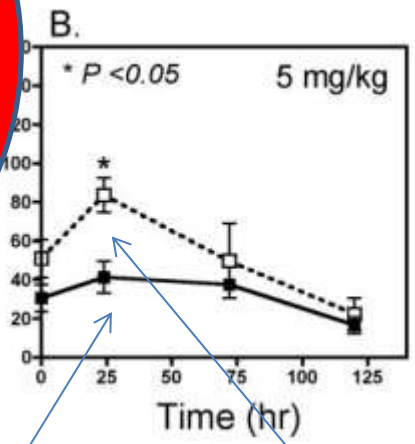
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2007, p. 1253–1258
0066-4804/07/$08.00+0 doi:10.1128/AAC.01449-06

Vol. 51, No. 4

Comparative Analysis of Amphotericin B Lipid Complex and Liposomal Amphotericin B Kinetics of Lung Fungal Clearance in a Murine Model of Acute Aspergillosis

- ABLC (Lipid c
  vs
- ABL (lipossomal)



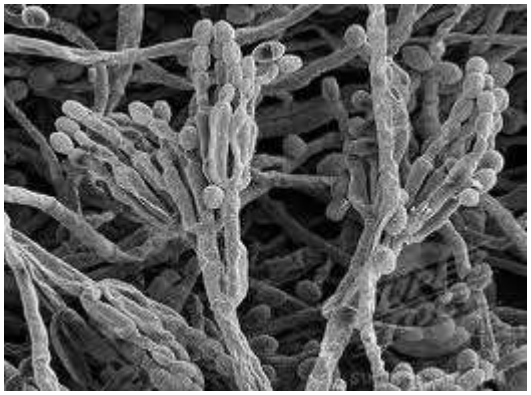


ABCL

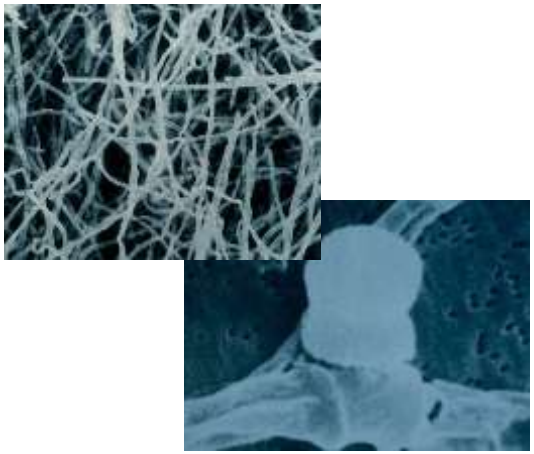
Ambisome

Lewis RE. Antimicrob Agents Chemother. 2007 Apr;51(4):1253-8

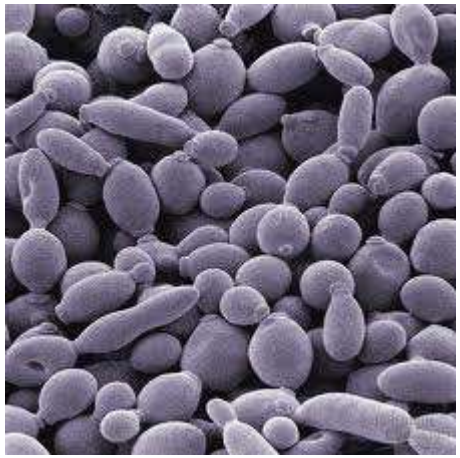
Neutropenic



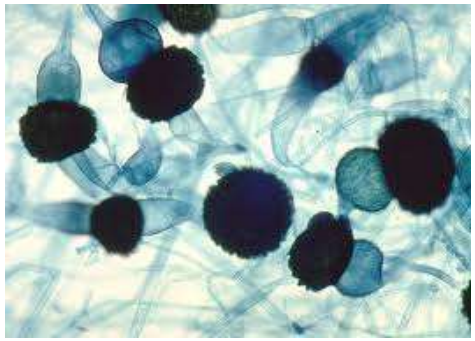
Filamentosos



Dimorfos



Leveduriformes



Fungos da mucormicose

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	IIu
Any	To cure and to increase survival rates	Surgical debridement in addition to antifungal treatment	A	IIu
Immunocompromised	To increase survival rates	Immediate treatment initiation	A	IIu
Any	To cure and to increase survival rates	Amphotericin B, liposomal ≥5 mg/kg[a]	A	IIu
CNS	To cure	Amphotericin B, liposomal 10 mg/kg, initial 28 days[a]	A	II
Any, except CNS	To cure	Amphotericin B, lipid complex 5 mg/kg[a]	B	IIu

Murine models suggest that liposomal amphotericin B is more effective than the deoxycholate formulation against mucormycosis [124], and th amphotericin B and amphotericin B lipid e-dependent [125]. Actually the lip ned higher lung concentrations nce than liposomal amphoteri

?

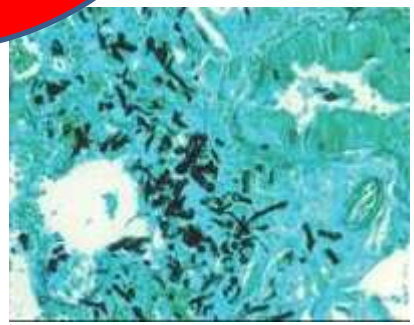
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2010, p. 1298–1304
0066-4804/10/$12.00 doi:10.1128/AAC.01222-09

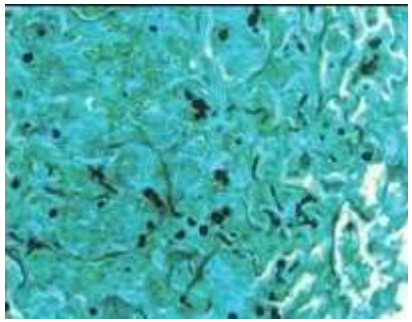
Comparative Pharmacodynamics of
Complex and Liposomal Amphoteri
Model of Pulmonary Mucormy

Russell E. Lewis,[1,2]* Nathan D. Albert,[2] Guangling Liao,[1] Jing
Randall A. Prince,[1,2] and Dimitrios P. Kontoyiannis[1,2]

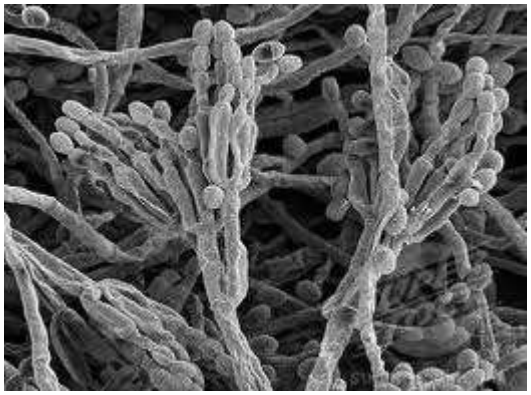
ABL

ABLC

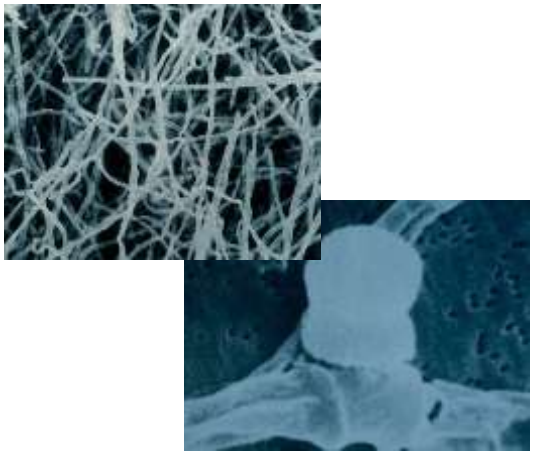




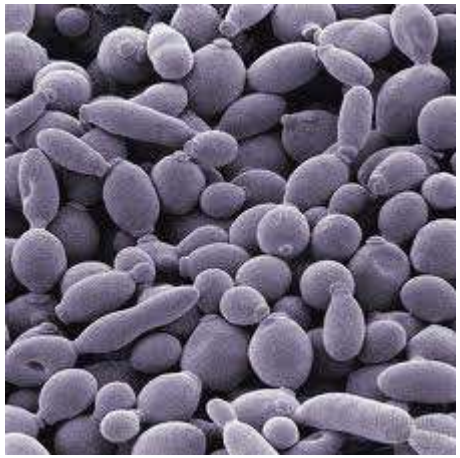
Neutropenic



Filamentosos



Dimorfos



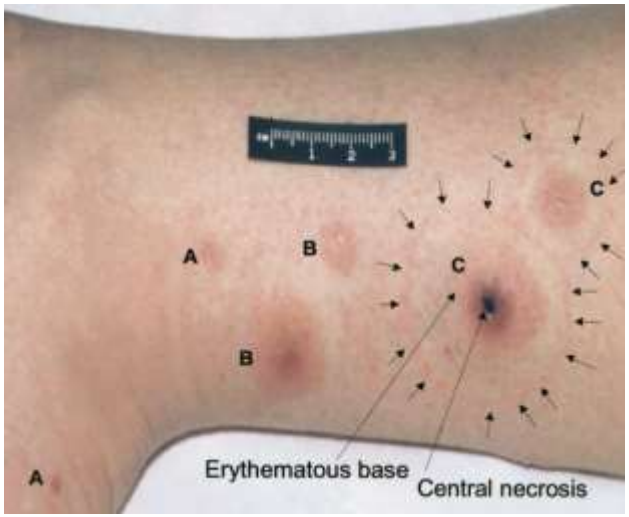
Leveduriformes

Fusarium

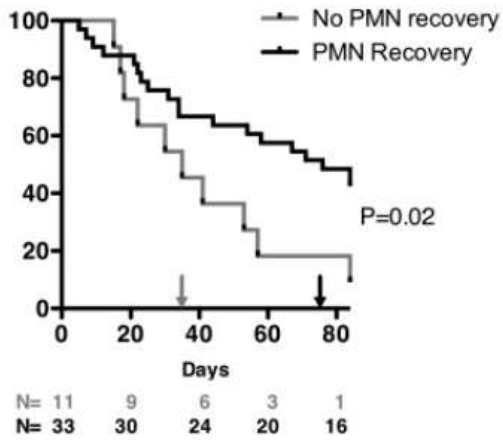
Fusariose

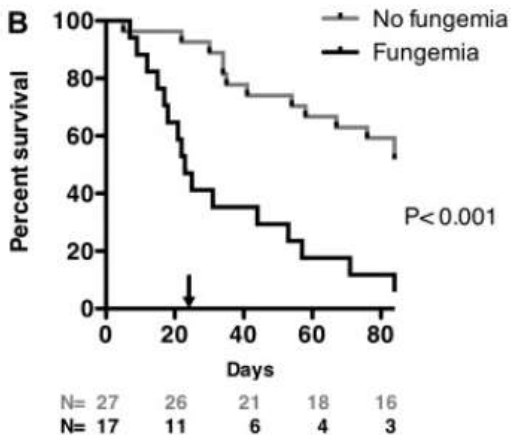
Fungal species	FLU	ITRA	POSA	VOR	AMB	Echinocandins[a]
Histoplasma capsulatum	+	+	+	+	+	–
Fusarium species	–	–	+/–	+/–	+/–	–
Zygomycetes	–	+/–	+	–	+	–

+/-



Fusariose





- **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

Nucci, CMR. 2011

ESCMID guidelines

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

- No RCT

What is the best lipid formulation?

- **REDUCE COSTS WITH PATIENT SAFETY**

Doses < 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†
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

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

- 3mg/kg

Is there any difference?

- And about safety (kidney toxicity?)

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

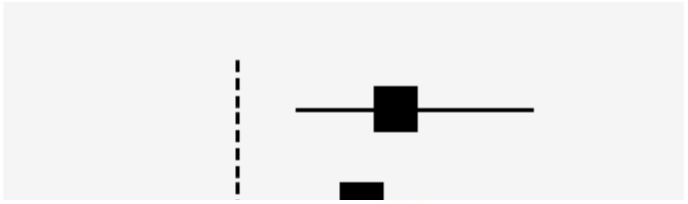
A Review and Meta-Analysis

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

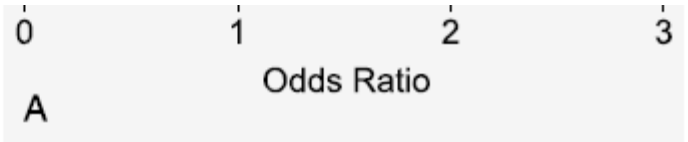
Study First Author Year (ref.)	Study Type (Yr)	Mean/Median Age (±SD, yr), Patient Population	ABLC No. Patients, Mean Daily Dose, Duration (±SD)	L-AmB No. Patients, Mean Daily Dose, Duration (±SD)	Nephrotoxicity* ABLC vs. L-AmB (P Value)
Wingard 2000[34]	Randomized, double-blind, multicenter (1997–1998)	Mean age: 42.0 ± 20.4, minimum age: ≥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 ≤ 0.01)
Fleming† 2001[9]	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[4]	Retrospective and prospective, observational (1996–1999)	Mean age: 50 (ABLC), 55 (L-AmB), minimum age: ≥4 yr; Cancer: ~73%, HSCT: ~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[21] (Abstract)	Retrospective and prospective, observational, multicenter (NA)	Mean age: NA, minimum age: ≥2 yr; Hematologic malignancies: ~65%, HSCT: ~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[20]	Prospective with historical controls (1997–2000)	Median age: 65 (ABLC), 63 (L-AmB), minimum age: ≥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[18]	Retrospective (1997–2002)	Mean age: 40.5 ± 21.8, minimum age: ≥2 mo; Hematologic malignancies: ~49%, HSCT: ~27%, renal insufficiency: ~21%	n = 31 4.5 mg/kg 38 d	n = 41 4 mg/kg 31 d	45% vs. 32% (p = 0.36)
Saliba‡ 2006[28] (Abstract)	Prospective, multicenter (2003–2004)	Mean age: 49.6 ± 14; Neutropenic: 44%	n = 60 [37] 4.8 mg/kg 13.5 ± 8 d	n = 28 [19] 3.3 mg/kg 15.0 ± 11 d	23.3% vs. 7.1% (p = 0.067) [10.8% vs. 5.3%] [p = 0.067]
Hachem§ 2008[11]	Retrospective, single-center (1993–2005)	Mean age: 46.5 ± 14.3 (ABLC), 48.1 ± 15.1 (L-AmB); Acute leukemia: ~50%, chronic leukemia: ~20%, lymphoma: ~22%, myeloma: ~4%	n = 52 [30] 5–10 mg/kg 12.9 ± 9.8 d	n = 106 [51] 5–10 mg/kg 13.6 ± 14.4 d	21.2% vs. 2.8% p < 0.001 [10% vs. 5.9%] [p = 0.67]

- Wingard showed different consistance other studi
- No differen about the neprotoxicity?



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)

mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

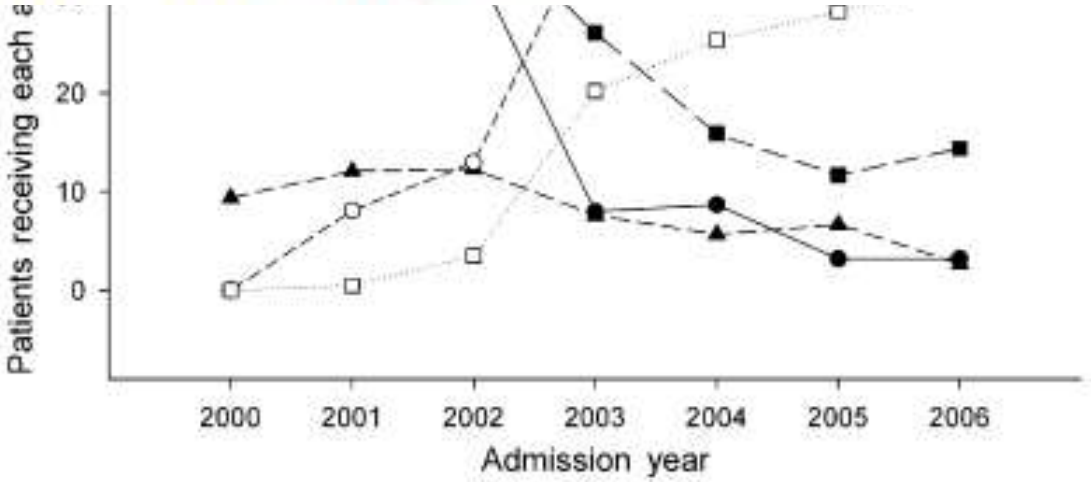
Original article

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

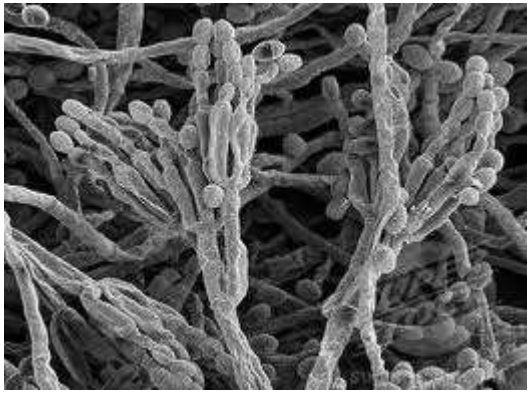
Aryun Kim,[1] David P. Nicolau[1,2] and Joseph L. Kuti[1]

[1]*Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, CT, USA and* [2]*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)



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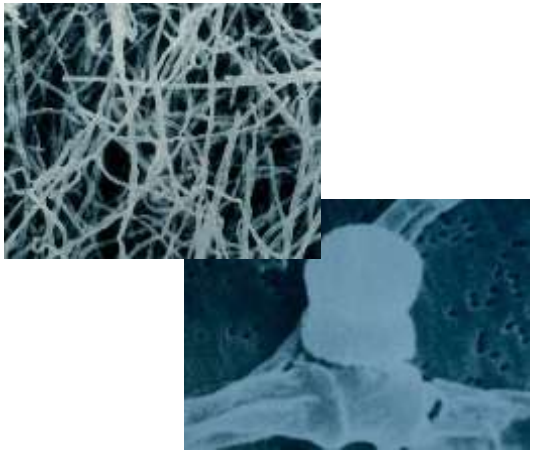

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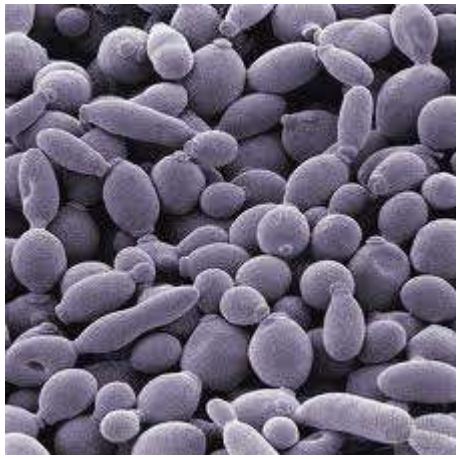
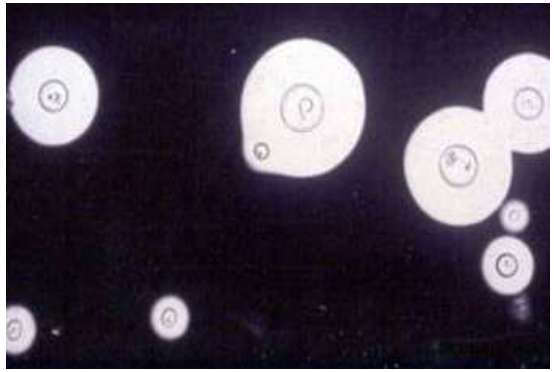


Leveduriformes



Cryptococcus

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

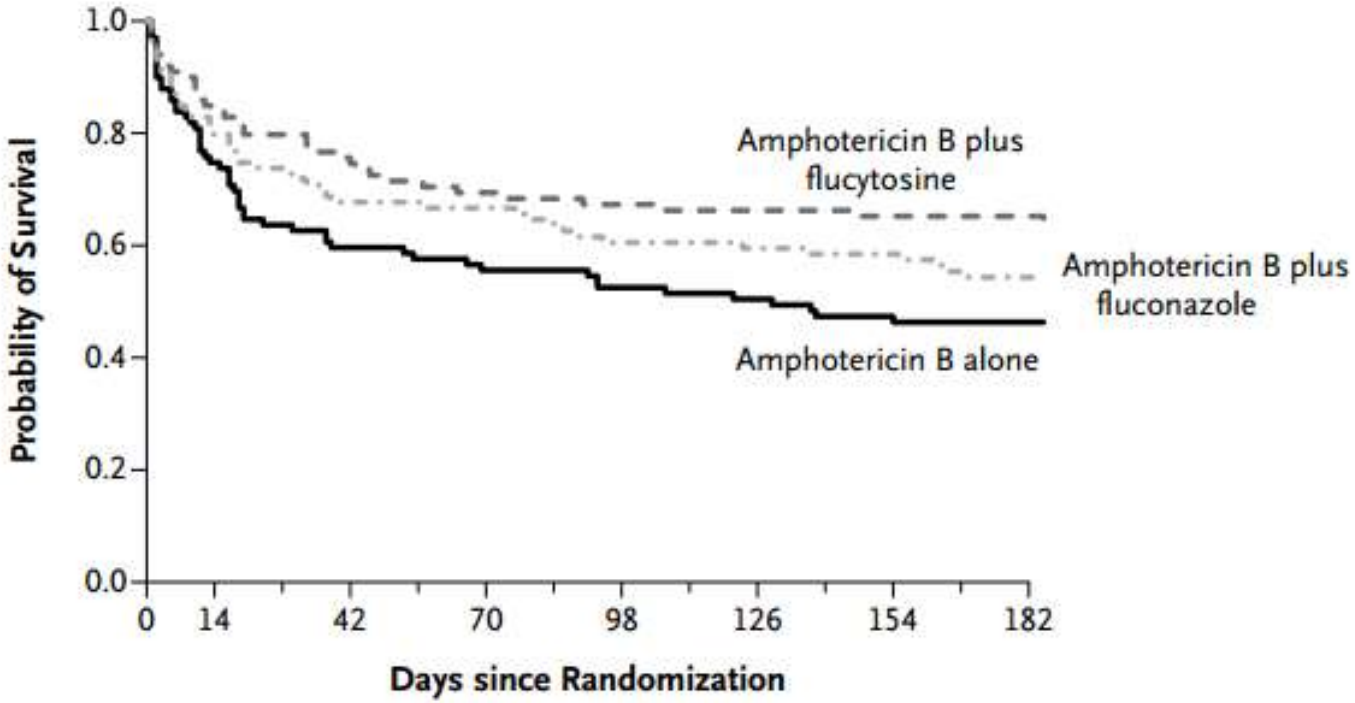
Regimen	Duration	Evidence
Induction therapy		
AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)[a]	2 weeks	A-I
Liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, with renal function concerns) plus flucytosine (100 mg/kg per day)[a]	2 weeks	B-II
AmBd (0.7–1.0 mg/kg per day) or 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[b]		
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)[a]	≥1 year[c]	A-I
Alternatives for maintenance therapy[b]		
Itraconazole (400 mg per day)[d]	≥1 year[c]	C-I
AmBd (1 mg/kg per week)[d]	≥1 year[c]	C-I

The NEW ENGLAND JOURNAL of MEDICINE

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

Clin
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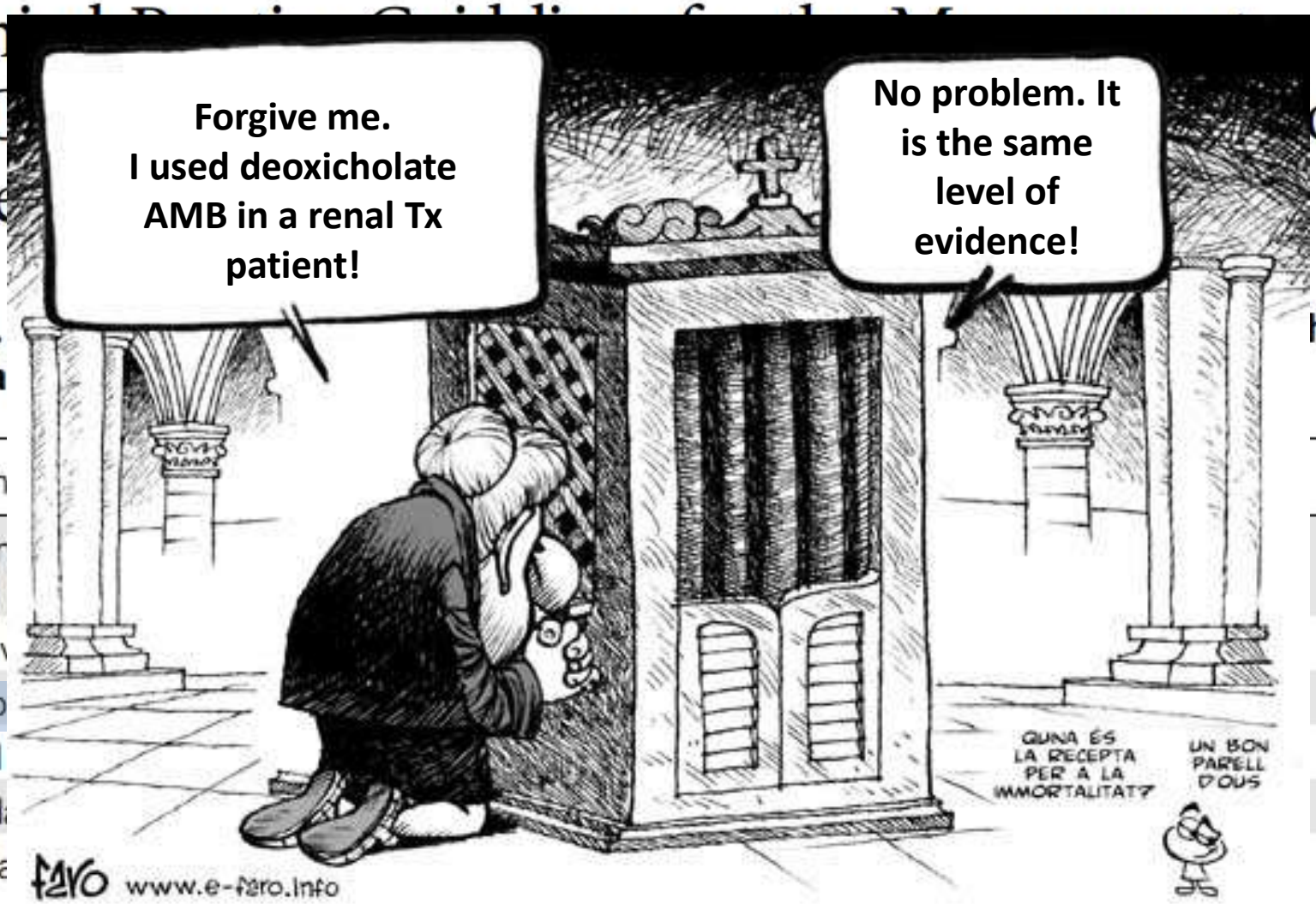
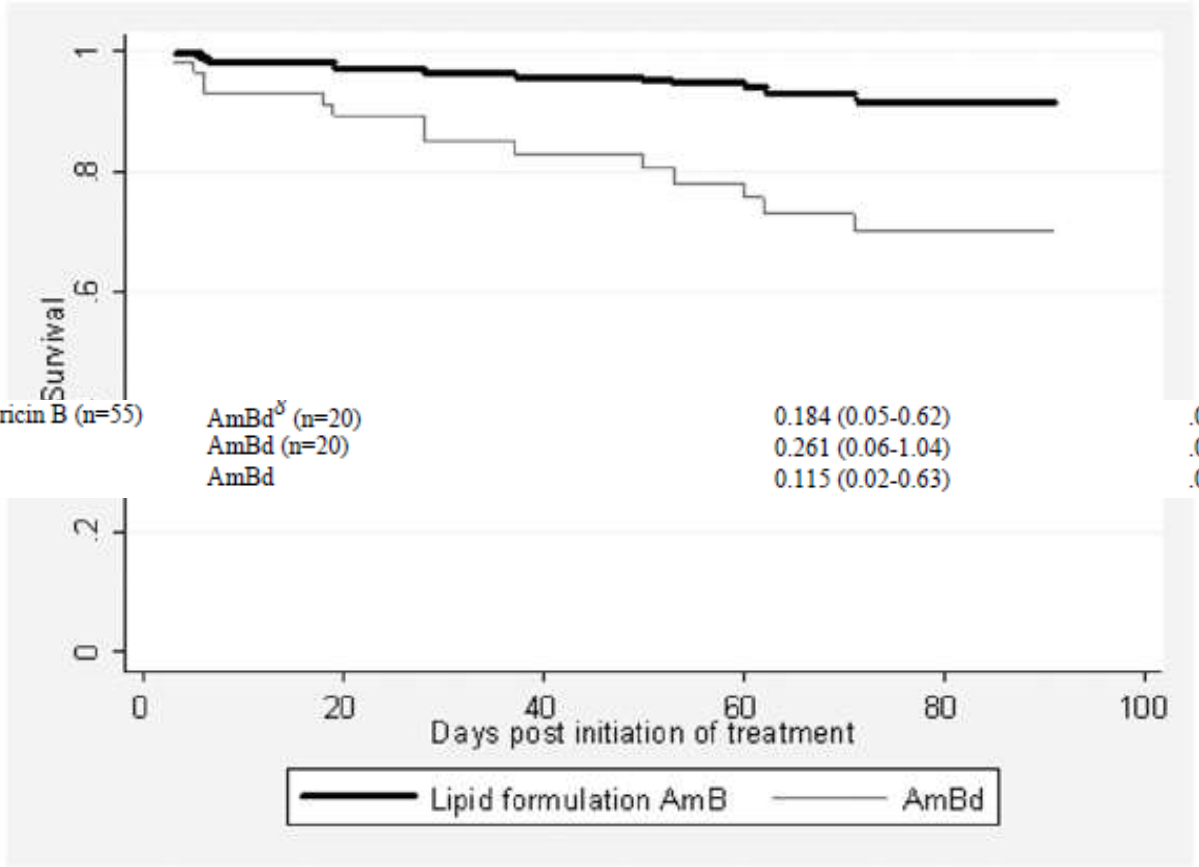
Table 3.
Transpla
halitis in

Regimen	Evidence
Induction	
ABLC	B-III
Alternati	
Liposo	B-III
AmBd	B-III
Consolid	B-III
Maintena	B-III



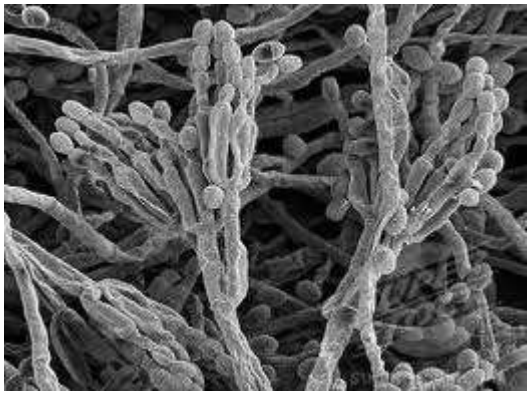
- Neurocriptococose em Tx órgãos



Lipid formulations of amphotericin B (n=55)	AmBd[δ] (n=20)	0.184 (0.05-0.62)	.007	0.11 (0.02-0.57)
L-AmB[9] (n=26)	AmBd (n=20)	0.261 (0.06-1.04)	.058	
ABLC[10] (n=29)	AmBd	0.115 (0.02-0.63)	.012	

Sun et al, Clin Infect Dis. 2009 December 1; 49(11): 1721–1728

Endemic



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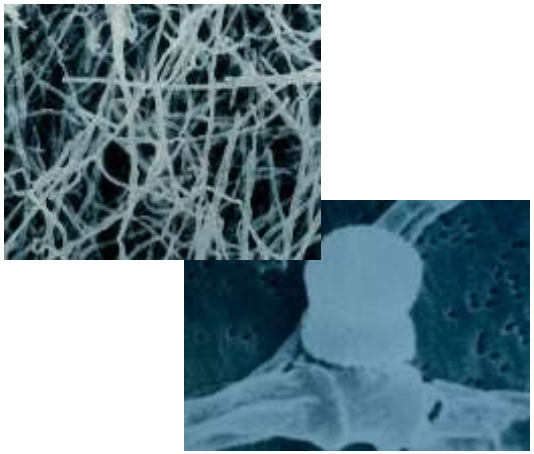

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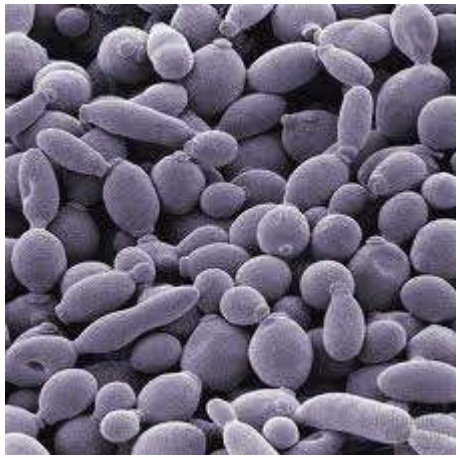
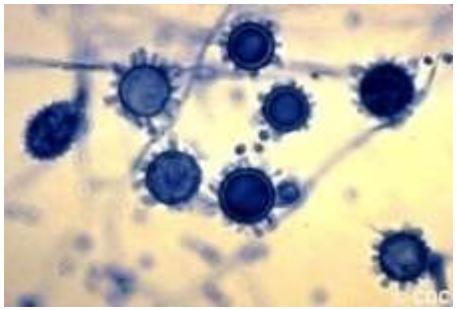


Leveduriformes



Histoplasma

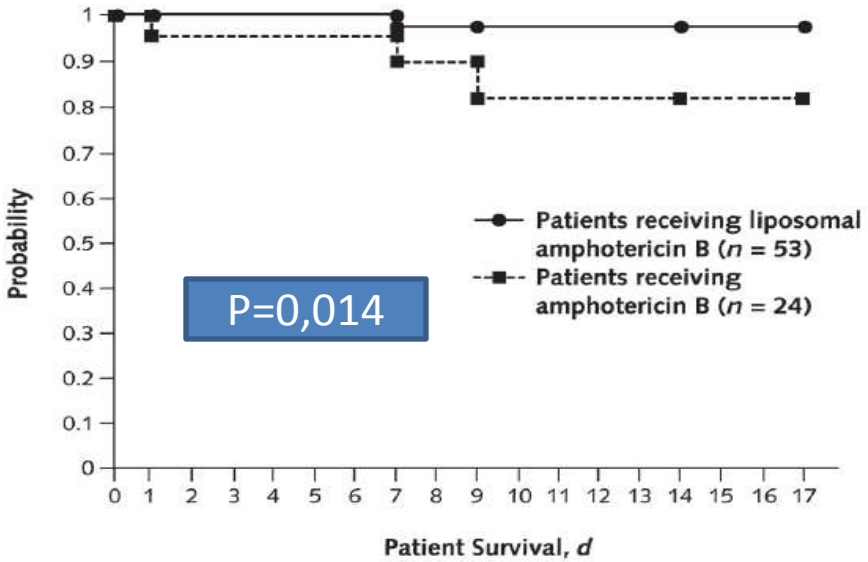
Histoplasmosis – IDSA 2007

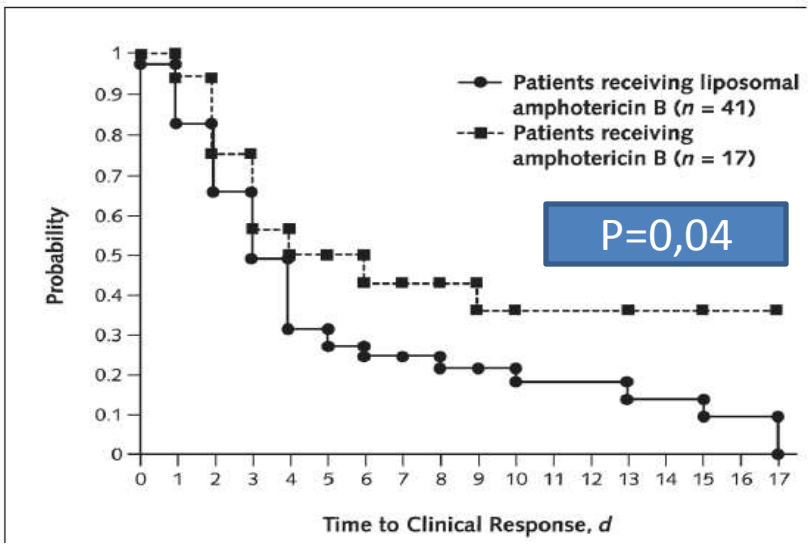
Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007 Update by the Infectious Diseases Society of America

- Pulmonar
  - FLAB (A
  - ABD (AI
- SNC
  - FLAB (BI
- Dissemina
  - ABL (AI)

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] 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





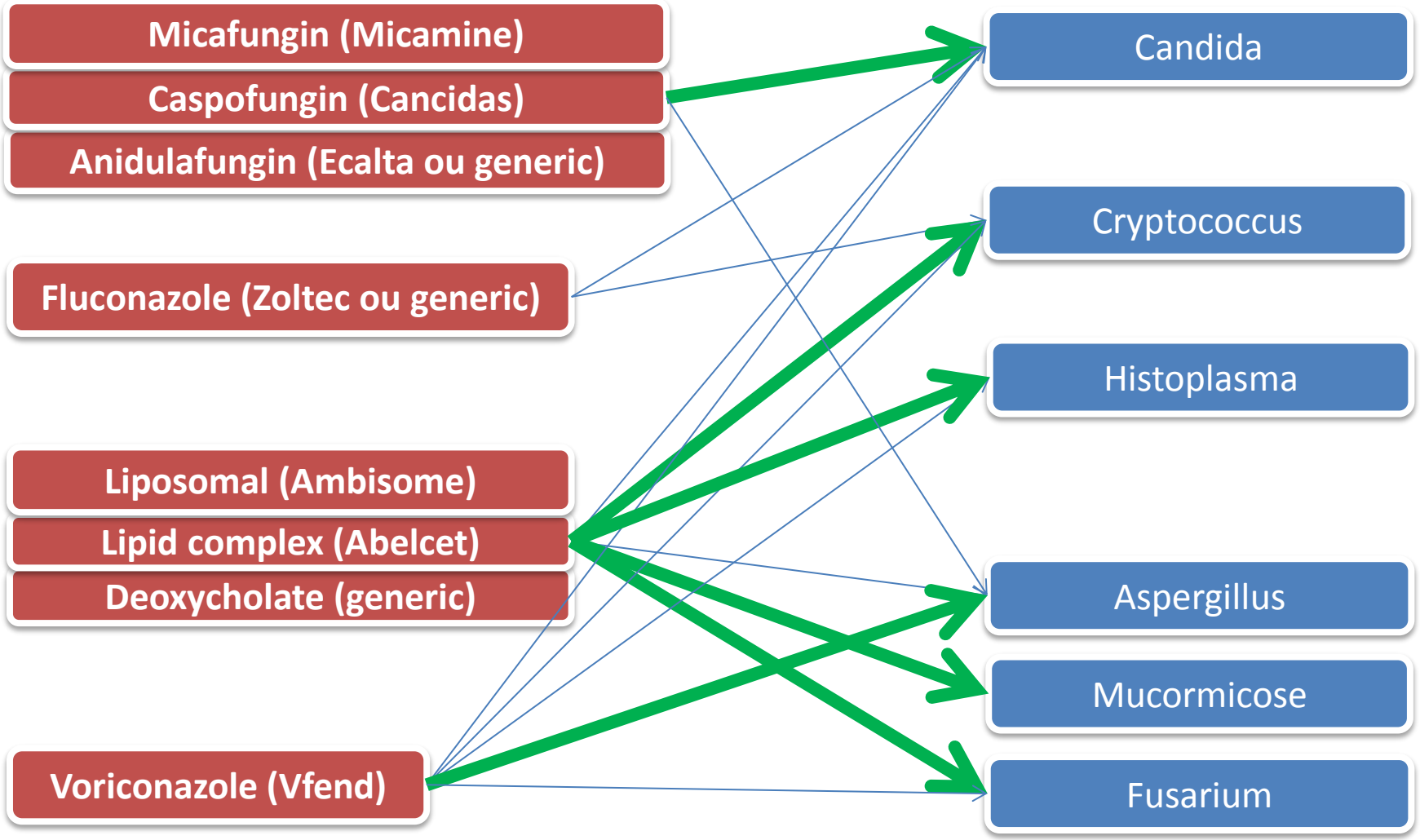
Infusion toxicity = (25%) ABL vs (63%) ABD (P = 0.002)
Renal failure = (9%) ABL vs (37%) ABD (*P* = 0.003).

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

Johnson PC et al, Ann Inter Med 137:105-109, 2002

Antifungal review



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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