Current options of antifungal therapy in invasive candidiasis

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DEFINITION

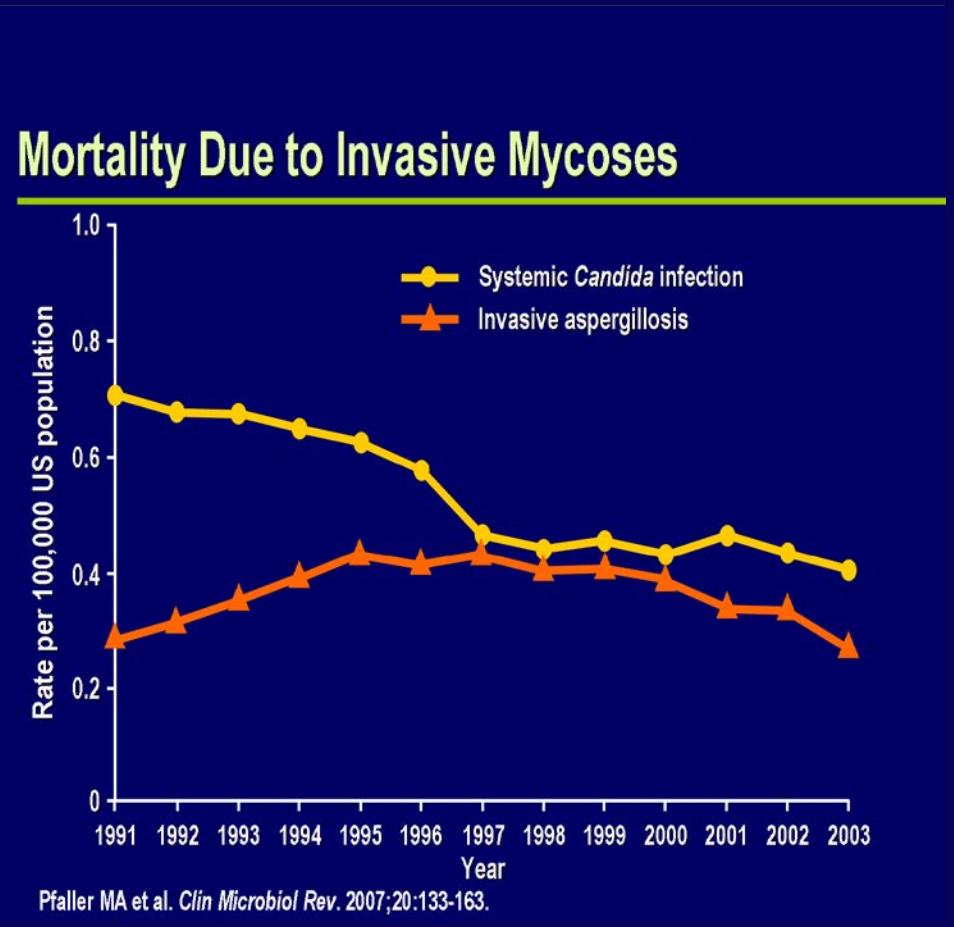
- One or more positive results on blood culture for Candida Spp or a positive culture from a normally sterile site

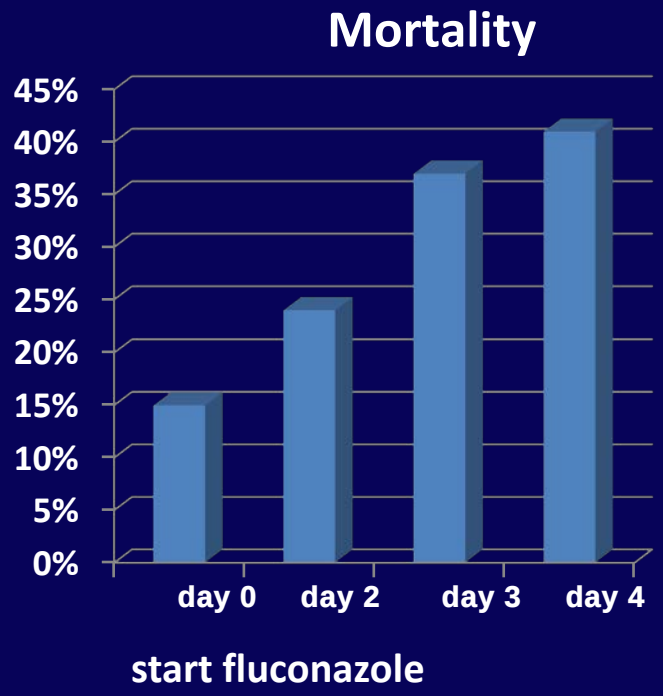
AND

- Clinical signs of infection

EPIDEMIOLOGICAL TRENDS

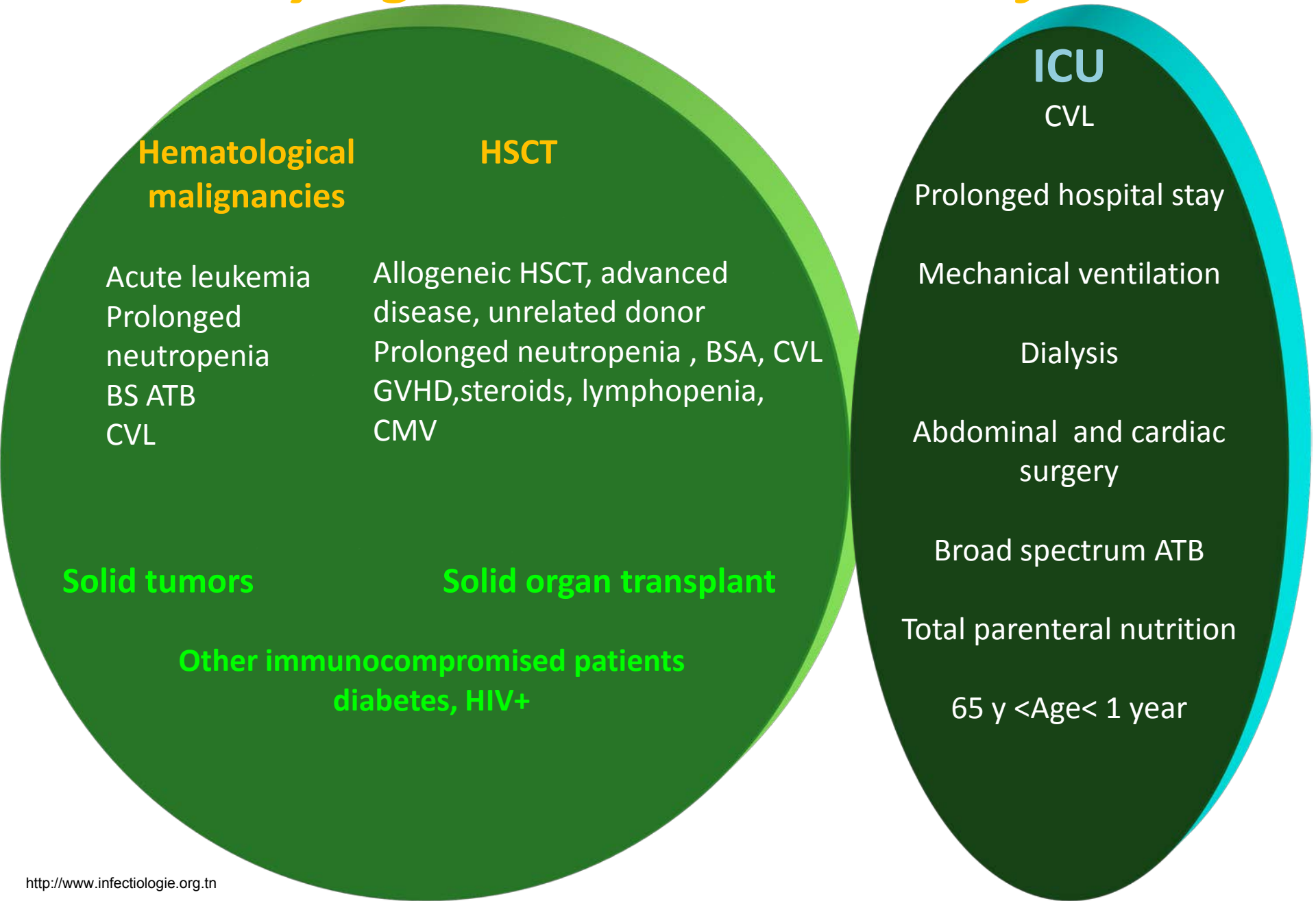
- Fourth leading cause of nosocomial BSI in the USA (8%-10% NBSI)
- 7000-28000 cases of nosocomial candidemia/year (Pfaller 2007).





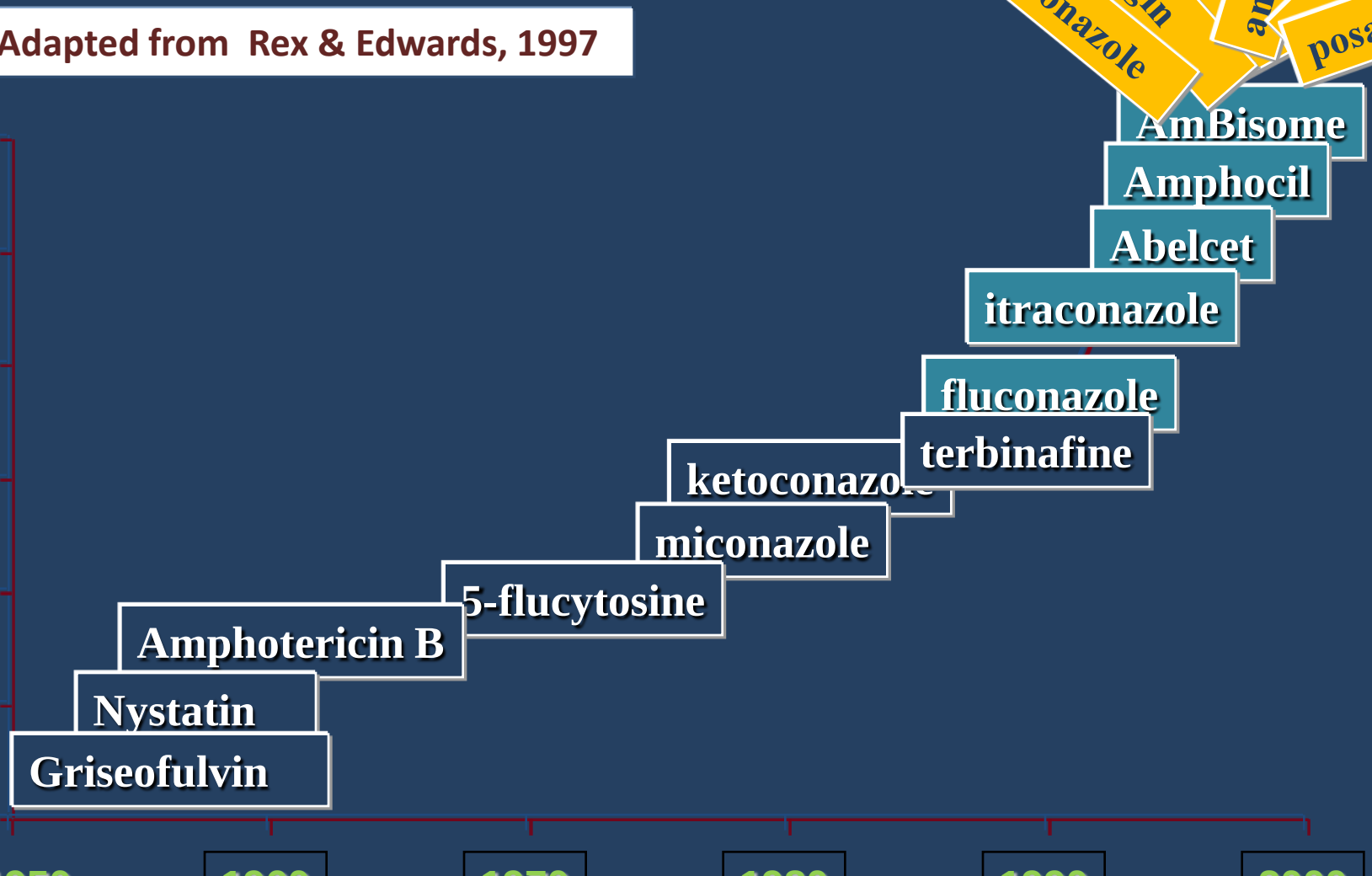
Garey et al. Clin Infect Dis 2006; 43:25-31

Underlying conditions and risk factors



PACE OF DEVELOPMENT OF NEW ANTIFUNGAL AGENTS

Adapted from Rex & Edwards, 1997



	PROS	CONS
AmB-d	Broad spectrum Fungicidal++++ Low cost	**Nephrotoxicity+++** Related infusion AEs+++
LFAmB	Broad spectrum Better tolerated Less nephrotoxic Higher doses	High cost+++ Low delivery in urinary tract
Fluconazole	Oral and IV Oral bioavailibility>90% Excellent CNS and vitreous diffusion Low cost	Drug-drug interactions, Coverage gaps *(kruzei and glabrata)* Abnormal hepatic tests
Voriconazole	Oral and IV Broad spectrum Oral bioavailibility>90% Excellent CNS and vitreous diffusion	Drug-drug interactions, visual disturbances, abnormal hepatic tests, hypokalemia Coverage gaps(*glabrata*)
Candins	Broad spectrum Fungicidal Excellent safety profile	High cost+++ Coverage gaps (*parapsilosis)*

Clinical trials in IC

- Heterogeneous populations
- Very few hematologic patients included
- Different timing of response assessment
- Different primary endpoints

FLUCONAZOLE versus AmB-d

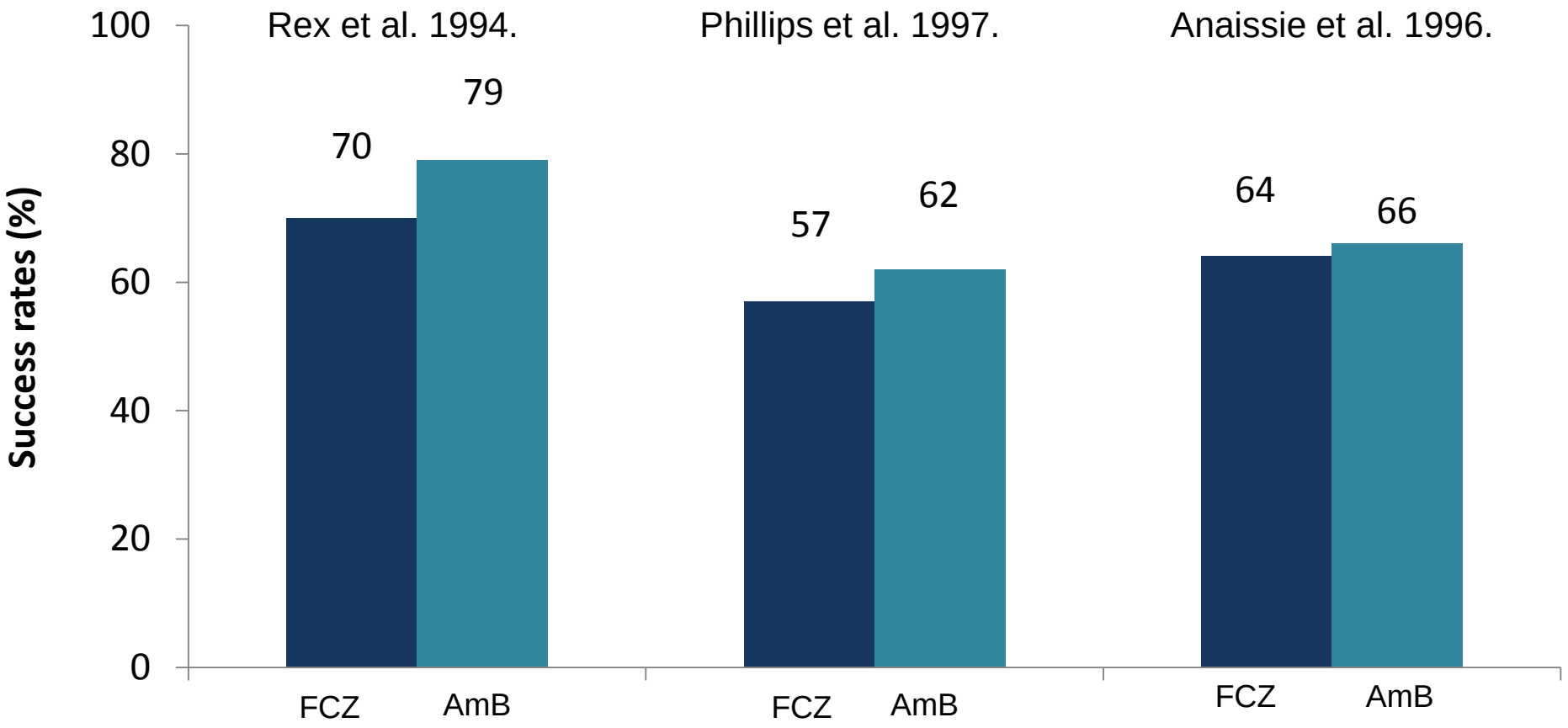
Randomized Clinical Trials

Fluconazole versus Amphotericin B in non neutropenic

3 Randomized studies

Reference	Infection population	Antifungal (number of evaluable patients)	Timing of response assessment
Rex. NEJM 1994 Prospective randomized study	**documented IC** Non hematologic cancers, renal failure, GI disease No neutropenic patients	**Fluco 400 mg (103)** **AmB-d 0.5-0.6mg/kg (103)**	**EOT, 2, 6 and 12 w after EOT**
Anaissie. CID 1996 Prospective randomized study	**Documented or presumed IC** Cancer, other diseases, leukemia and BMT Neutropenic (25%)	**Fluco 400 mg (75)** 16 neutropenic **AmB-d (67) 25-50mg/d 0.67 mg /kg if neutropenia** 20 neutropenic	**2 days, 5 days and EOT**
Philips. Eur J Clin Microbiol. Infect Dis 1997	**Candidemia** GI disease, diabetes, Kc, renal failure	**Fluco 800 mg D1 (42) 400** **AmB-d 0.6 mg/kg (42)**	**EOT**

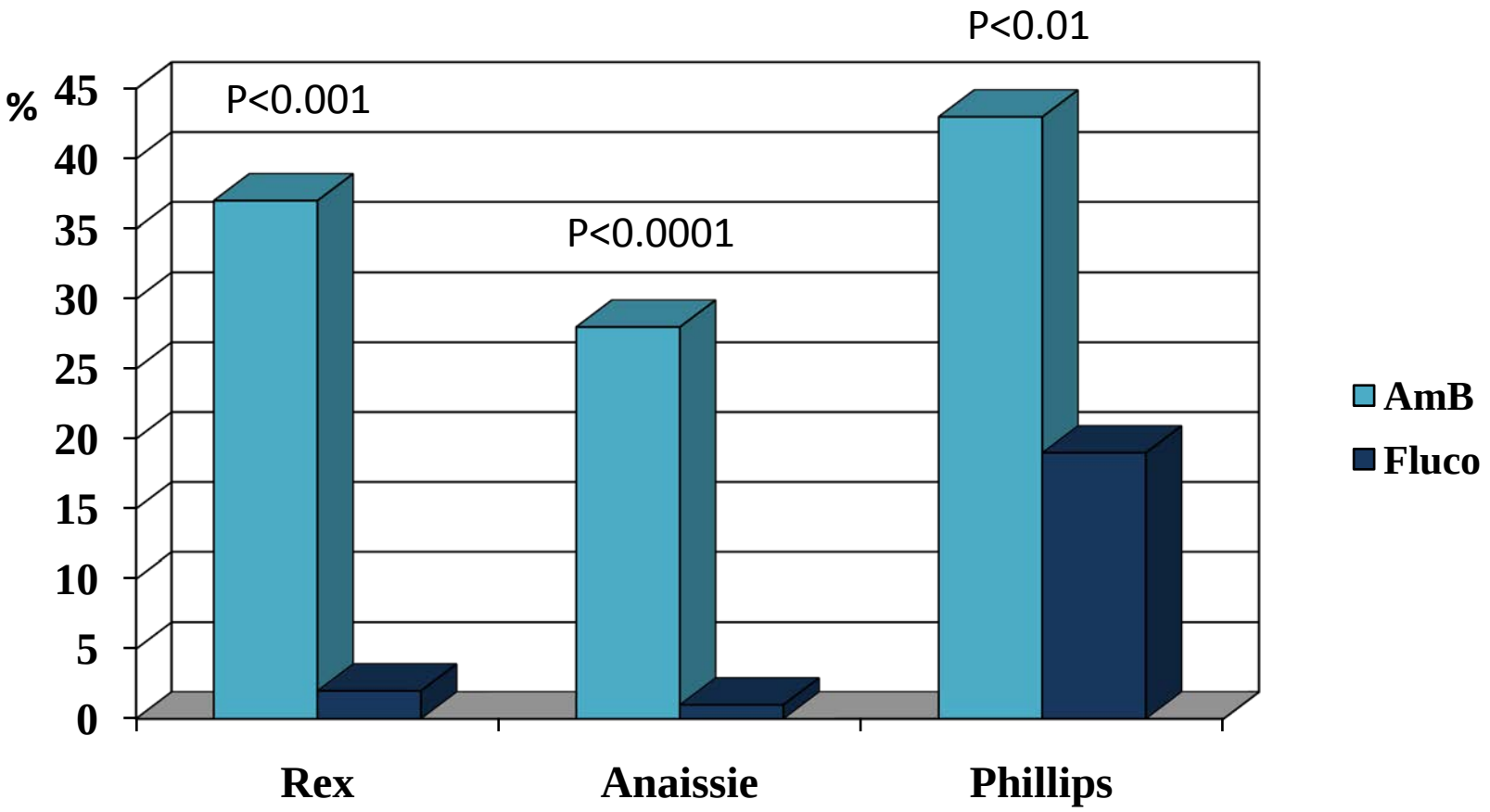
Fluconazole response in clinical trials



No differences as related to site infection or pathogen, no differences in survival

Rex et al. *NEJM* 1994. Phillips et al. *Eur J Clin Microbiol Infect Dis* 1997. Rex et al. *Clin Infect Dis*. 2003.

AmB vs Fluconazole : Renal toxicity (%)



Fluconazole for IC in neutropenic patients

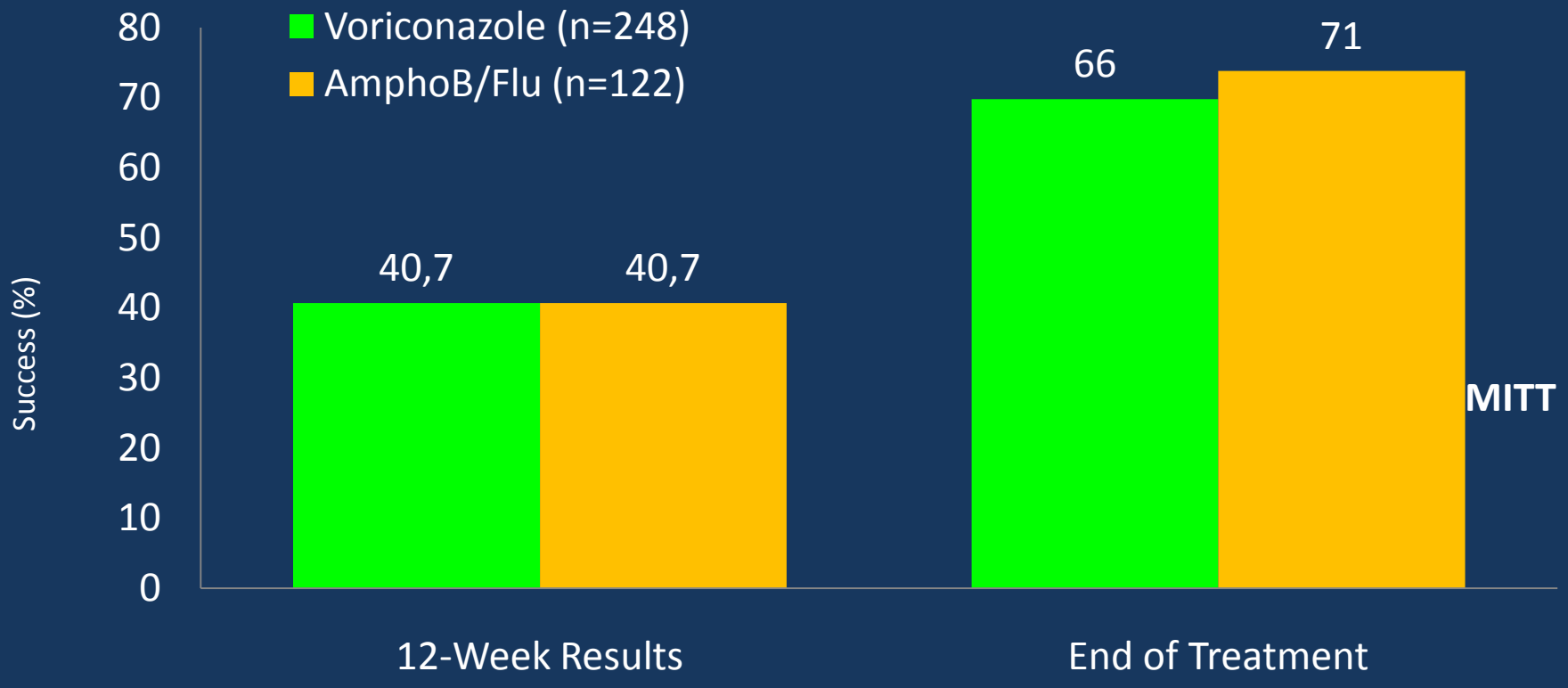
- Lack of randomized studies
- One retrospective study Fluconazole vs AmB (Anaissie, Am J Med. 1998; 104: 238-239)
  - 476 patients (217 neutropenic- 257 non neutropenic)
  - Number of neutropenic patients who received FCZ or AmB not stated

	Neutropenic	Non neutropenic
Cure (%)	44%	72%
Overall 3 month mortality	63%	43%

Voriconazole for Candidemia in non neutropenic patients

AmB-d 3-7 days then fluconazole vs voriconazole IV>3 Days then PO

422pts (ICU, abdominal and non abdominal surgery, mechanical ventilation)- 96% of patients had candidemia only



Fewer serious adverse events (46% vs 57%) and cases of renal toxicities (8% vs 21%) in the voriconazole arm

Kullberg BJ et al Lancet 2005, 366:1435-1442

Lipid Amphotericin B Formulations

Liposomal AmB (Ambisome®)

Lipid- Complex (Abelcet®)

Colloidal dispersion (Amphocil®- Amphotec®)

- Only one RCT in non neutropenic patients with IC (L-AmB vs micafungin)

- Few data on the treatment of IC with LFAmB in neutropenic patients

Lipid formulations of AmB in IC

Study	Study design/ underlying condition	Antifungal	Total/ Neutropenic patients (n)	No of success (%) Total/neutropenic
Noskin. CID 1998; 26: 461	Review of 5 phase I-II trials BMT , HM , SOT, Solid tumors, others	ABCD 3.9 mg/kg (median dose)	148/88 evaluable 18* 49°	53% 39%* vs 79%** 47%° vs 62%°°
Ito. CID 2005; 40 (supp6): S384	Registry (n=979) Invasive candidiasis haematological malignancies or HSCT (n= 124)	AmB lipid complex	979/124 HM+HSCT° not stated*	61%/49% Albicans=non albicans

*Neutropenic patients
° Bone marrow recipients

**non-neutropenic patients
°° non transplanted patients

Lipid formulations of AmB in IC of neutropenic patients

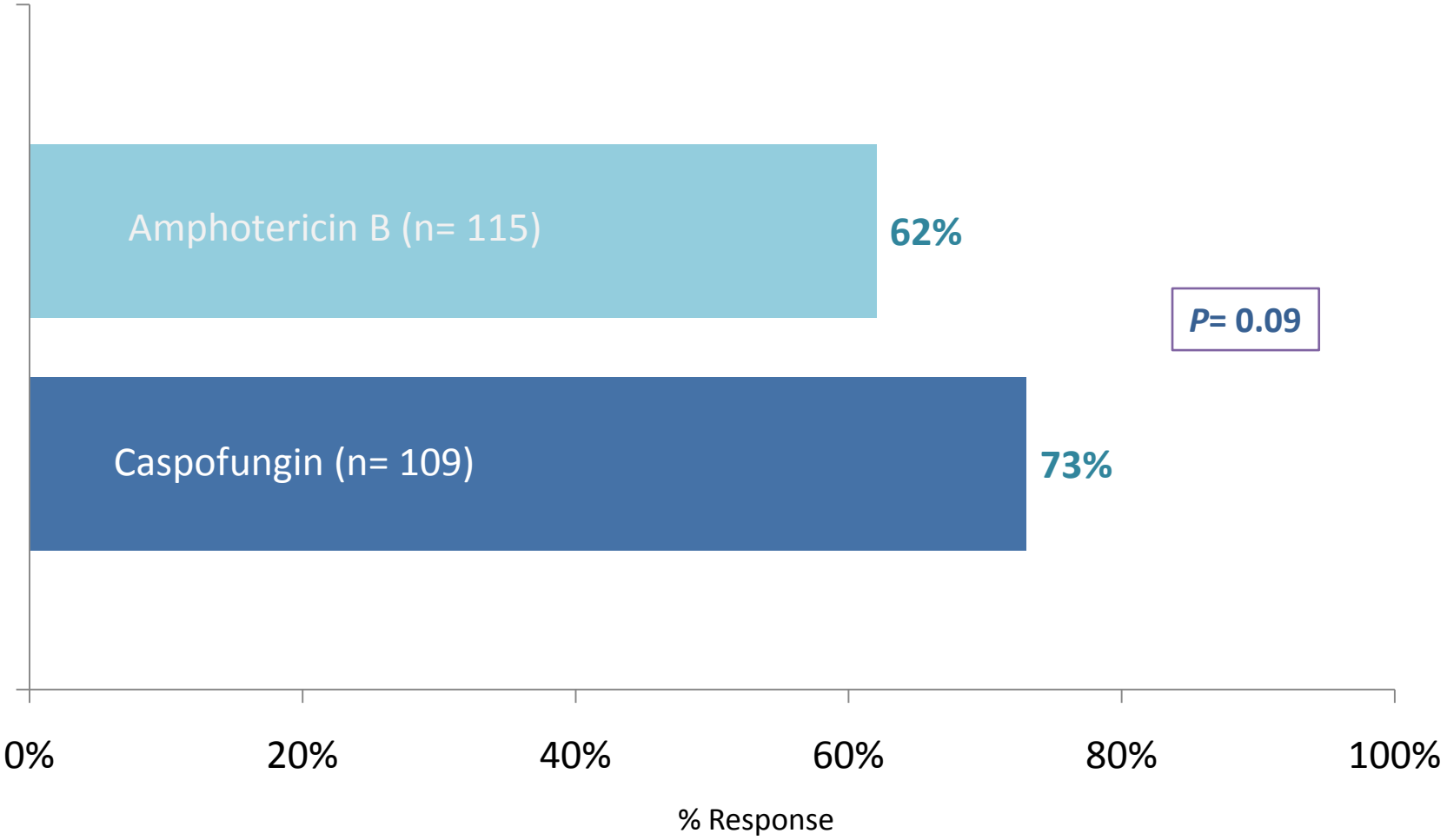
Study	Study design/ population	Antifungal	No of success (%)
Walsh. NEJM 2004	Prospective double blind randomized multinational Patients with persistent fever and neutropenia Invasive candidiasis 24 pts	Caspofungin 70mg D1, 50 mg daily	8/12 (66.7)
		Liposomal AmB 3mg/kg	5/12 (41.7)
Leenders. Br J Haematol 1998; 103: 205	**Open randomized study of documentd or suspected IFI in neutropenic patients**	**Liposomal AmB 5mg/kg 5 documented candidemia**	**3/5**
		AmB-D 1mg/kg 2 documented candidemia	**0/2**

Echinocandins in IC
4 Randomized Clinical Trials

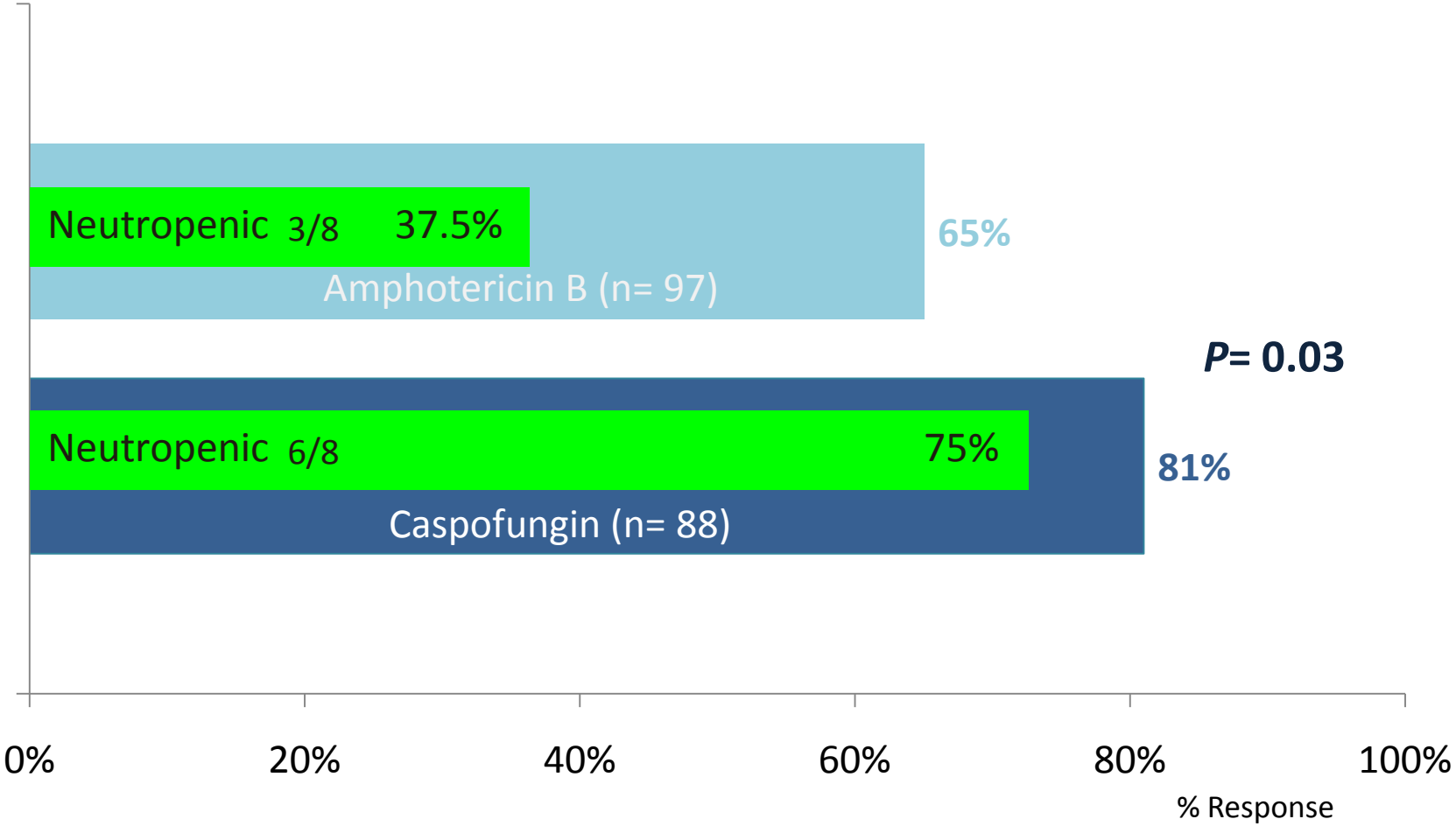
Few neutropenic patients

Reference	Infection Underlying condition	Antifungal (Number of patients)	Timing of response assessment
1/ Mora- Duarte NEJM 2002 Multicenter double blind trial	IC Diabetes mellitus, active leukemia or lymphoma, renal failure, HIV infection Neutropenia 24 pts (11%)	Caspofungin70 mg D1 50 mg daily (114/109 MITT) AmB-d 0.6-0.7mg/kg 0.7-1mg/kg if neutropenia (125/115 MITT)	End of IV therapy 6-8-week period after the EOT

Caspofungin vs AmB-d
Efficacy at EOIVT (MITT analysis, primary analysis)



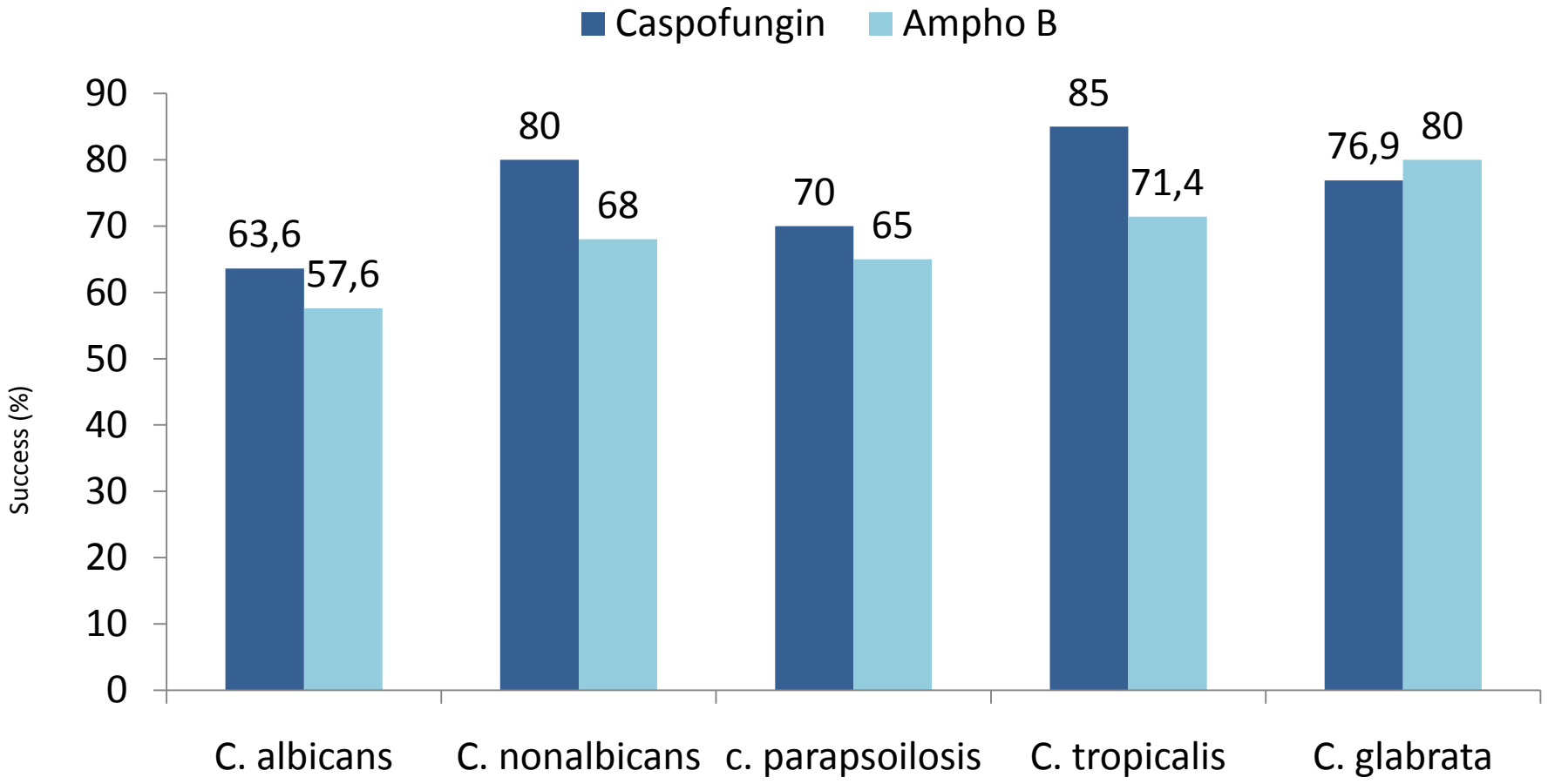
Caspofungin vs AmB-d
(Secondary Analysis, patients who met criteria for evaluation)



Mortality rates due to invasive *Candida* infection were 4.4% for caspofungin and 7.2% for amphotericin B (*P*=NS).

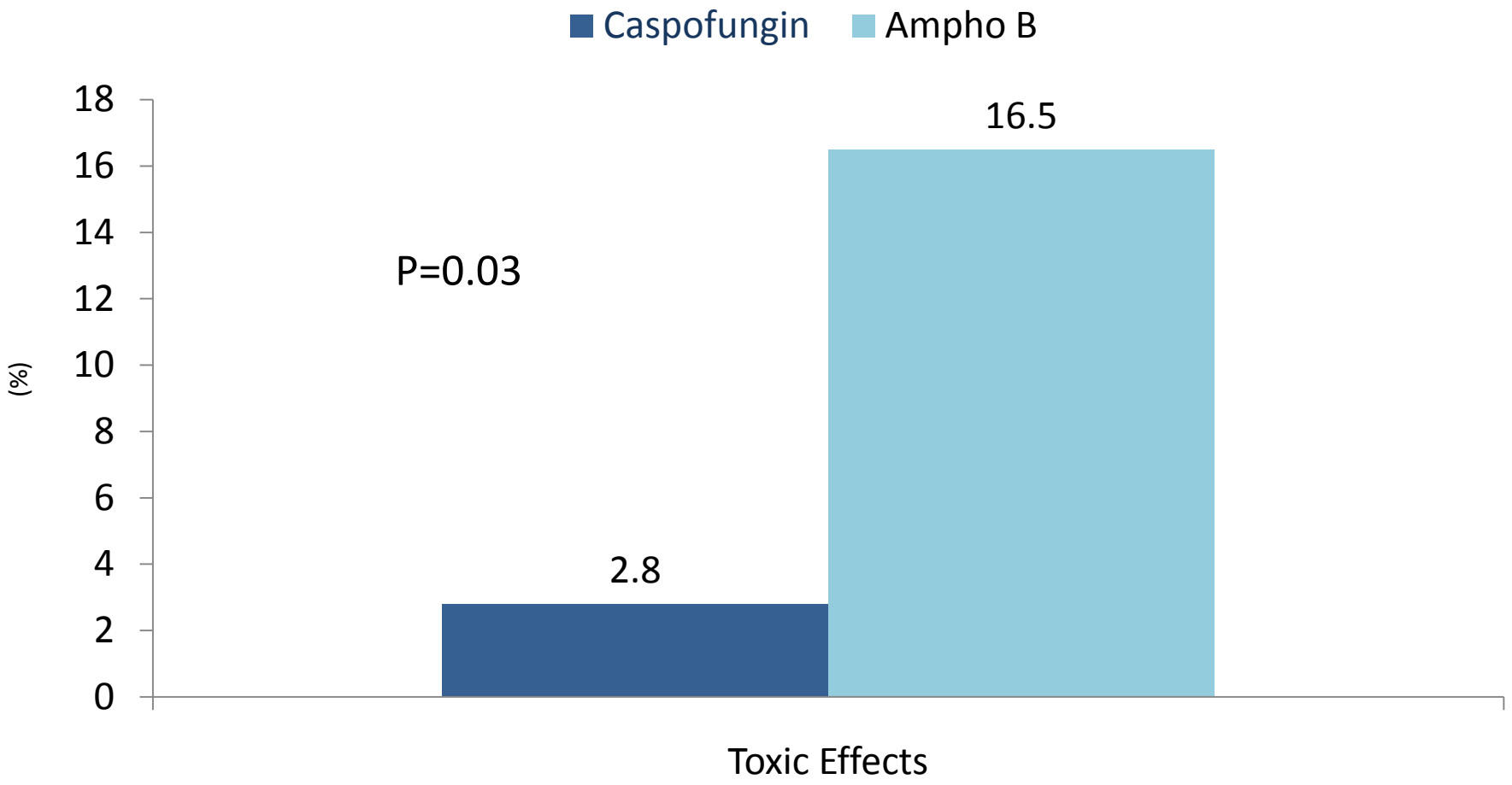
Caspofungin vs AmB-d

Success Rates per Pathogen



Mayo-Pypaert et al. *N Engl J Med.* 2002;347:2020–2029

Caspofungin vs AmB-d
Toxic Effects Requiring Change in Therapy



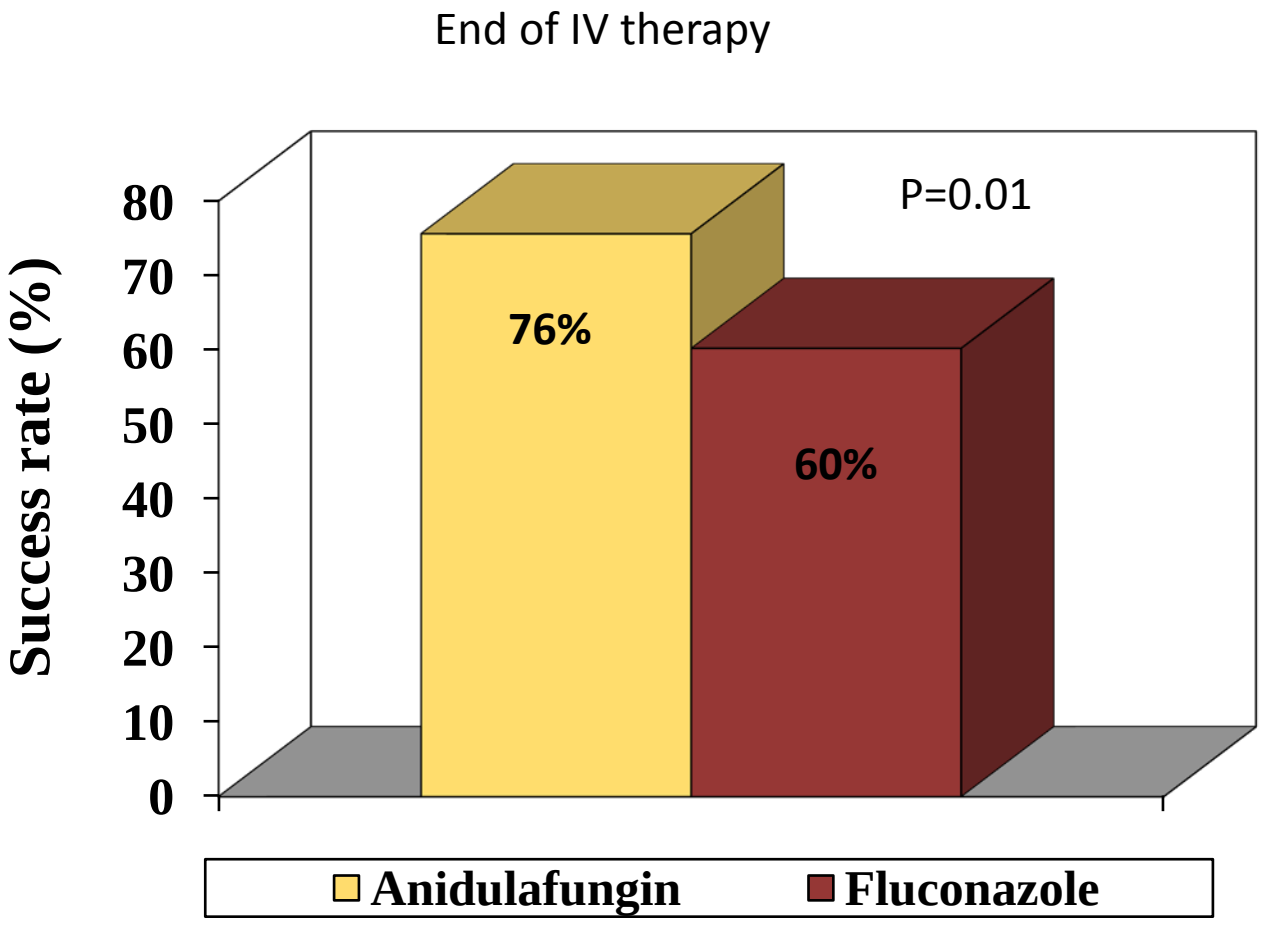
Maertens J, et al. *N Engl J Med.* 2002;347:2020–2029

Reference	Infection Underlying condition	Antifungal Number of patients	Timing of response assessment
1/ Duarte NEJM 2002 Multicenter double blind trial	Diabetes mellitus, active leukemia or lymphoma, renal failure, HIV infection Neutropenia 24 pts (11%)	Caspofungin70 mg D1 50 mg daily AmB-d 0.6-0.7mg/kg 0.7-1mg/kg if neutropenia	EOIVT 6-8 w after therapy
2/ Reboli . NEJM 2007 Multicenter double blind trial	Invasive candidiasis (89% candidemia only) solid tumor, recent surgery, pancreatitis, diabetes, renal failure, bacterial sepsis Neutropenia (5%)	Anidulafungin 200 mg D1 100mg daily 127 MITT Fluconazole 800 mg D1 400 mg daily 118 MITT	End of IV therapy End of all study therapy 2 and 6 w after the EOT

Anidulafungin vs Fluconazole

No differences in mortality rates 23% vs 33% (p=0.13)
Similar safety profile
Possible center effect

Conclusion: anidulafungin is non inferior to fluconazole for the primary TTT of the candidemic form of invasive candidiasis



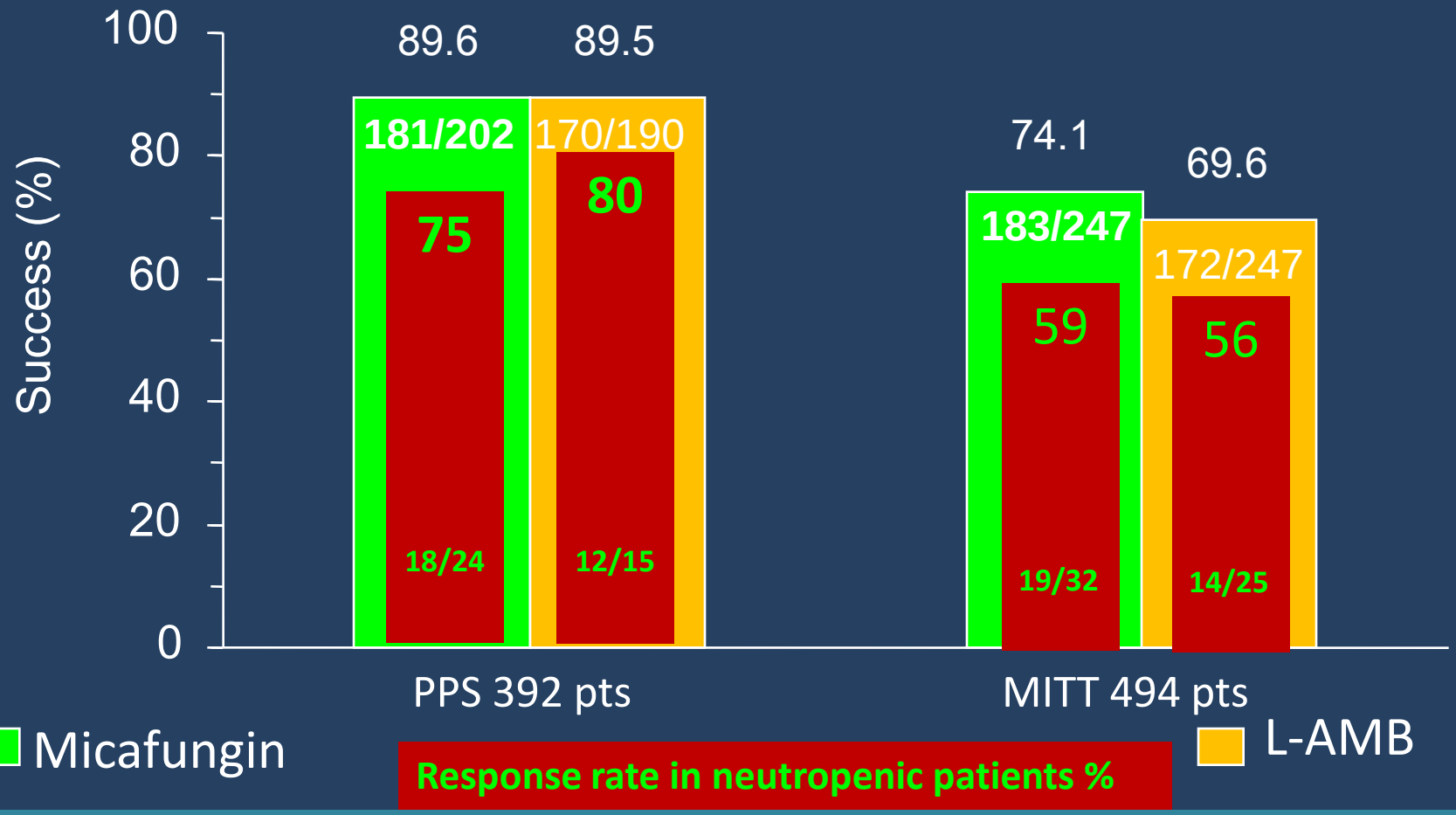
Reboli et al. *NEJM* 2007.

Reference	Infection Underlying condition	Antifungal Number of patients	Timing of response assessment
1/ Duarte NEJM 2002 Multicenter double blind trial	Diabetes mellitus, active leukemia or lymphoma, renal failure, HIV infection Neutropenia 24 pts (11%)	Caspofungin70 mg D1 50 mg daily AmB-d 0.6-0.7mg/kg 0.7-1mg/kg if neutropenia	
2/ Reboli . NEJM 2007	**Invasive candidiasis** solid tumor, **recent surgery,** pancreatitis, diabetes, renal failure, bacterial sepsis Neutropenia (5%)	Anidulafungin 200 mg D1 100mg daily Fluconazole 800 mg D1 400 mg daily	
3/ Kuse. The Lancet 2007 Multicenter non inferiority double blind trial	Candidemia/Invasive candidiasis Hematological disorder, solid tumor, transplant, pancreatitis, diabetes, renal failure Neutropenia (6%)	Micafungin 100 mg (>40 kg) 2mg/kg (≤ 40 kg) 264/247 MITT Liposomal AmB 3mg/kg 267/247 MITT	EOT

Micafungin vs L-AmB

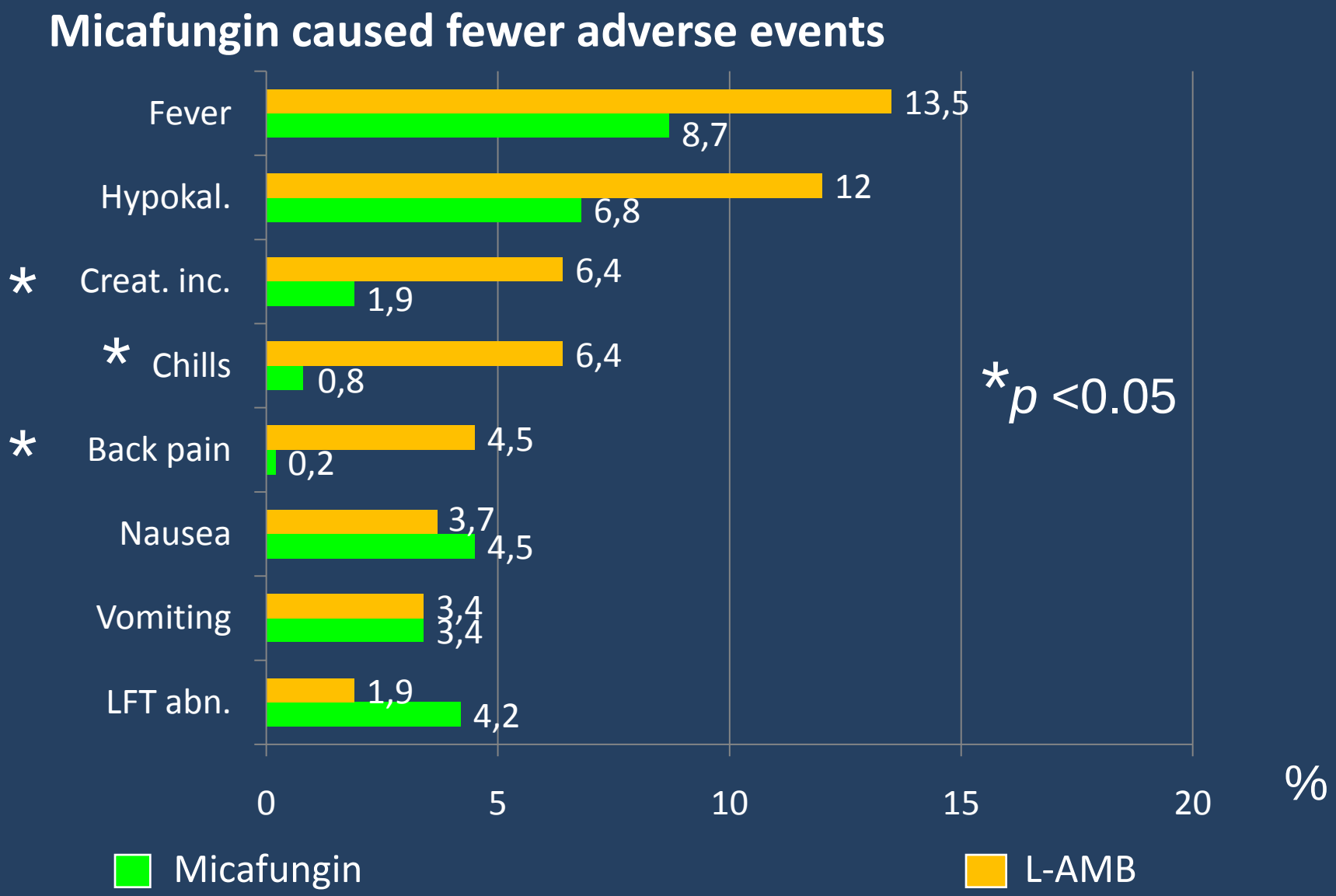
1/Micafungin was as effective as L-AmB as first line treatment of candidemia and IC

2/Efficacy was independent of the candida spp, primary site of infection, neutropenic status and APACHE II score



Kuse et al. *Lancet* 2007.

Micafungin vs L-AmB- adverse events



Kuse et al. *Lancet* 2007.

Reference	Infection Underlying condition	Antifungal	Number of patients
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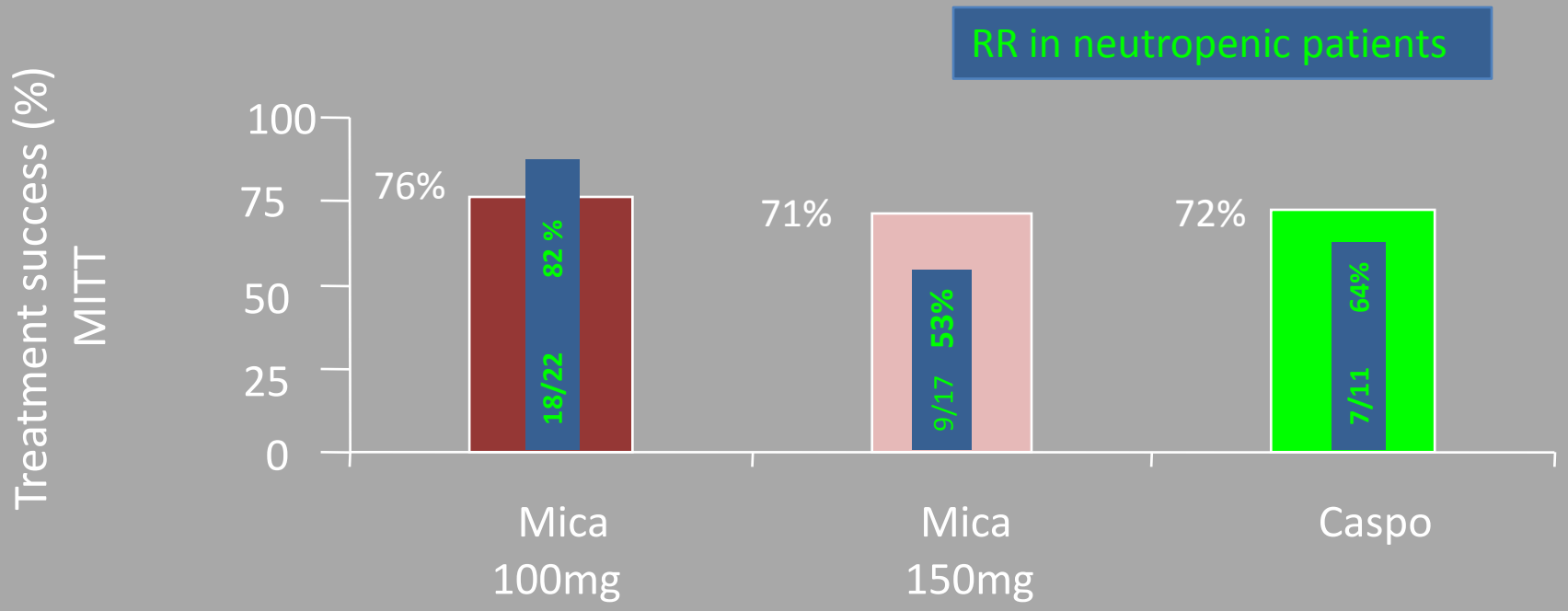
		Fluconazole 800 mg D1 400 mg daily	118 MITT
3/ Kuse. The Lancet 2007	**Candidemia/Invasive candidiasis** Hematological disorder, solid tumor, transplant, pancreatitis, diabetes, renal failure Neutropenia (6%)	Micafungin 100 mg (>40 kg) 2mg/kg (≤ 40 kg)	264/247 MITT
		Liposomal AmB 3mg/kg	267/247 MITT
4/ Pappas. CID 2007 Multicenter double blind trial	**Candidemia 85%/Invasive candidiasis** **Diabetes mellitus,chemotherapy, recent surgery, hemodialysis, pancreatitis, renal failure, hepatic failure and HSCT** **Neutropenia (9%)**	**Micafungin 100 mg** **191**	**EOT**
		Micafungin 150 mg **199**	
		Caspofungin70 mg D1 **then 50 mg daily** **188**	

Micafungin vs caspofungin in candidemia/IC

No significant differences in treatment success at EoT,
mortality, relapsing/emergent infections, or AEs.
Similar efficacy for *C.albicans* and non albicans accross the 3 arms



Micafungin 100mg/d and 150mg/d equivalent to standard dose caspofungin for candidemia/IC.

Pappas et al. CID 2007.

Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

IDSA

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. Sobel[3]

ECIL1

EJC SUPPLEMENTS 5 (2007) 49–59

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ELSEVIER

Treatment of invasive *Candida* and invasive *Aspergillus* infections in adult haematological patients ☆

Raoul Herbrecht[a,*], *Ursula Flückiger*[b], *Bertrand Gachot*[c], *Patricia Ribaud*[d], *Anne Thiebaut*[e], *Catherine Cordonnier*[f]

IDSA Grading System

ECIL
CDC Grading System

Strength of recommendations	
A	Strong evidence for efficacy and substantial clinical benefit: Strongly recommended
B	Strong or moderate evidence for efficacy, but only limited clinical benefit: Generally recommended
C	Insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (e.g. drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches: Optional
D	Moderate evidence against efficacy or for adverse outcome: Generally not recommended
E	Strong evidence against efficacy or of adverse outcome: Never recommended

Limits of the recommendations in hematology patients

- The majority of patients included in the large trials for candidemia were intensive care patients and not hematology patients

- Lack of adequately powered randomized contolled Trials (RCT) of treatment of candidemia in neutropenic patients and lack of sufficient power for proper statistical comparison within the hematology population

- The level of recommendation and the quality of evidence are lower in the hematology population. In the same trial, a drug may have been graded AI in the whole population and BII for the neutropenic patient

Criteria of choice of AFT before specie identification

- Severity of illness
- Presence or no of neutropenia
- Recent azoles exposure
- Evidence of involvement of CNS, cardiac valves and/or visceral organs

IDSA
ECIL

- Local epidemiology
- Renal function
- Use of concomitant nephrotoxic drugs

Before specie identification

IDSA guidelines
ECIL guidelines

	Non neutropenia Non HM or neutropenia	Neutropenia Hematological malignancies and neutropenia
Echinocandin	**A-I** **AIII** (if moderately severe to severe illness or recent azole exposure) **A-I**	**A-II** (A-III for anidulafungin) **B-II**
Ambisome	**A-I** (if intolerance or a limited availibility of other antifungals) **A-I**	**A-II** **B-II**
Other LFAmB	**A-I** (if intolerance or a limited availibility of other antifungals) **AII**	**A-II** **B-II**
AmB- d	**A-I** (if intolerance or a limited availibility of other antifungals)	
Fluconazole	**A-I** **A-III** (if less critical illness and no recent azole exposure) **A-I**	**B-III** (if less critical illness and no recent azole exposure) **C-III**
Voriconazole	**A-I** **A-I**	**B-III** (If no recent azole exposure and if additional mold coverage desired) **B-II**

Treatment of IC in non neutropenic patients

After specie identification

Transition from echinocandin to fluconazole

- Isolates likely to be susceptible and clinically stable patient A-II

Glabrata: **echinocandin** B-III

Transition to FCZ or VCZ only if confirmed susceptibility B-III

If initially FCZ or VCZ, continue if clinical improvement and FU culture results negative B-III

Kruzei: **VCZ** as step-down oral ttt B-III

Parapsilosis: **fluconazole** B-III

If initially echinocandin, continue if clinical improvement and FU culture results negative B-III

Treatment Guidelines for Candidiasis • CID 2009:48 (1 March)

Treatment of IC in neutropenic patients
After specie identification

Glabrata: echinocandin is preferred B-III

If initially FCZ or VCZ, continue if clinical improvement and FU culture results negative BIII

Parapsilosis: fluconazole or LFAmB preferred B-III

If initially echinocandin, continue if clinical improvement and FU culture results negative B-III

Kruzei: echinocandin, LFAmB or VCZ BIII

Treatment Guidelines for Candidiasis • CID 2009:48 (1 March)

Catheter removal Guidelines

- Intravenous catheter removal is strongly recommended in non neutropenic patients with candidemia A-II

- Intravenous catheter removal if possible should be considered in neutropenic patients B-III

IDSA guidelines

Duration of therapy

Two weeks

- After documented clearance of Candida from the bloodstream

AND

- Resolution of symptoms attributable to candidemia

AND

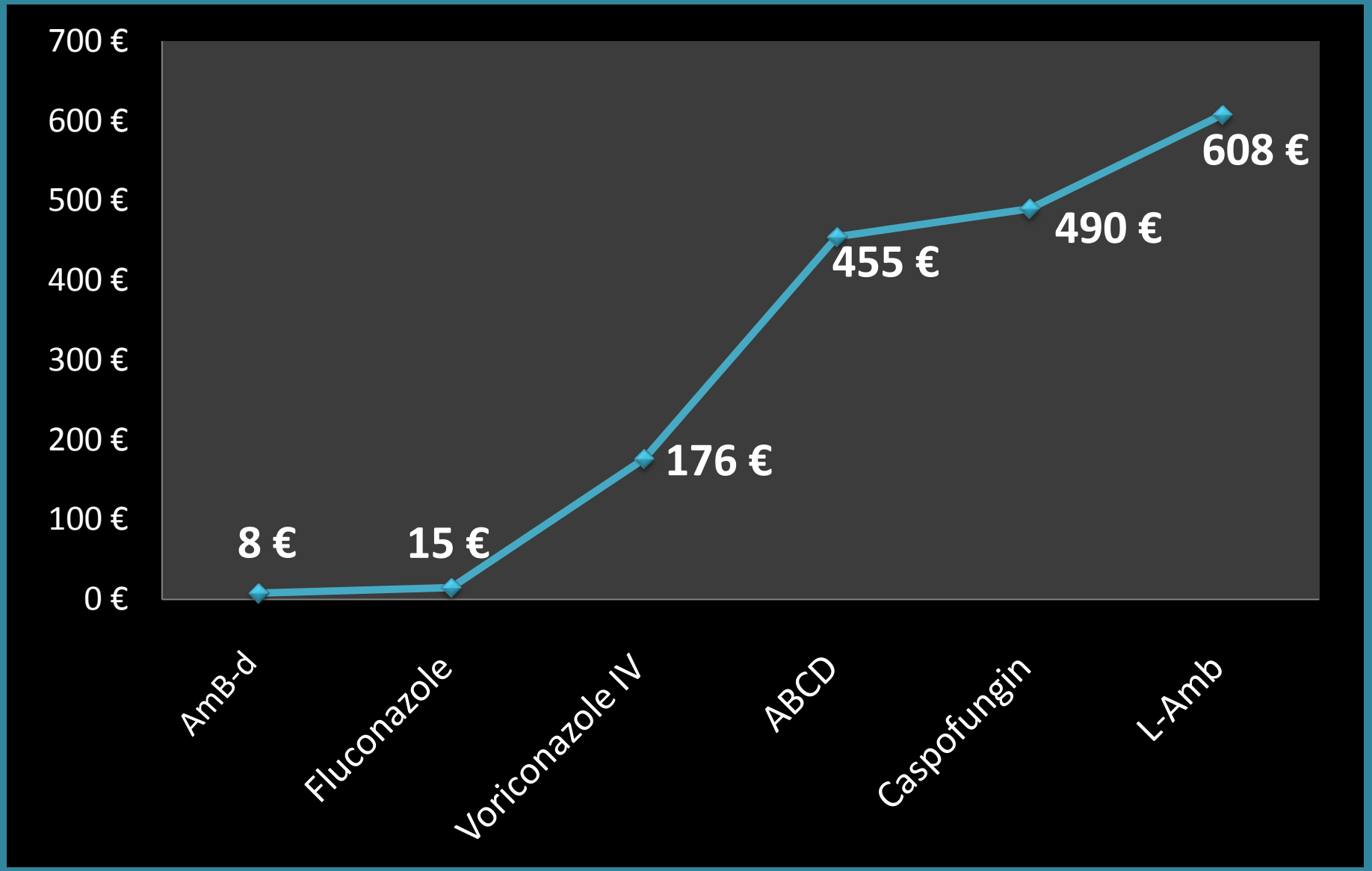
- Resolution of neutropenia

In the absence of metastatic complications **(A-III)**

Duration of therapy in metastatic localizaions

- **Endocarditis:**
  - **AFT maintained 6 weeks after valve replacement**
  - **Long term suppression (FCZ) if no valve replacement**
- **Pericarditis: several months**
- **Osteomyelitis: 6-12 months**
- **Septic arthritis: 6 weeks**
- **Endophtalmitis: 4-6 weeks**
- **CNS: several weeks and until signs, CSF and Rx abnormalities have resolved**

Daily cost


700 €
600 €
500 €
400 €
300 €
200 €
100 €
0 €
8 €
15 €
176 €
455 €
490 €
608 €
AmB-d
Fluconazole
Voriconazole IV
ABCD
Caspofungin
L-Amb

CONCLUSION

- Guidelines are very useful to guide physician decision (applied in 73% of patients in North America)

- In countries with limited resources, the cost or the non availability of some new drugs may preclude applying the guidelines.

- AmB-d can be used instead of candins or LFAmB in selected patients (normal renal function, no more than 1 associated nephrotoxic drug)

- Need of sensitive and specific biological tools for early diagnosis to reduce mortality