Update on the Treatment of Invasive Fungal Infections for the Oncologist

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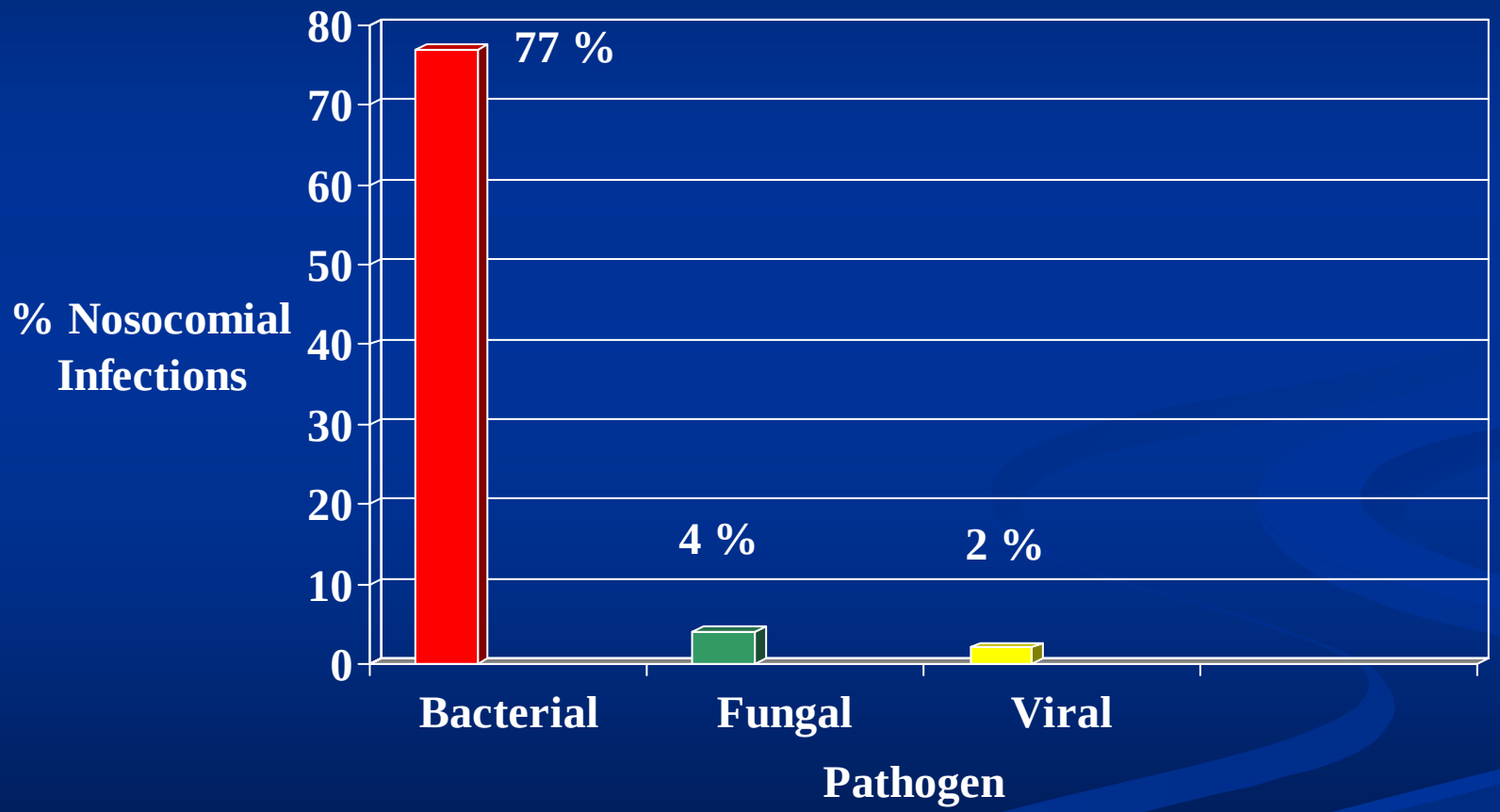
Epidemiology of Invasive Fungal Infections in Cancer Patients

Distribution of Nosocomial Pathogens in Cancer Patients



(Rotstein C et al. Infect Control Hosp Epidemiol 1988;9:13-19)

Epidemiology

- **Invasive fungal infections cause considerable morbidity & mortality in cancer patients particularly those with neutropenia.**

(Schwartz et al. Cancer 1984;53:411-419)
(Bodey et al. Eur J Clin Microbiol Infect Dis 1992;11:99-109)
(Bow et al. Clin Infect Dis 1995;21:361-369)

Gradation of Risk of Invasive Fungal Infection In Cancer Patients

Disease	Rates of Invasive Fungal Infection	
	1960s & 1970s[1]	1980s & 1990s
HSCT	20%-30%	21%-57%[2,3]
Acute Leukemia	20%-30%	19%-47%[4]
Lymphoma	10%-20%	NA
Solid Tumors	1%-5%	2%[5]

(1. Wingard JR, Leather HL. Oncology 2001;15:351-369. 2. De La Rosa GR, Champlin RE, Kontoiannis DP. Transpl Infect Dis 2002;4:3-9. 3. Wakayam M, Shibuay K, Ando T et al. Mycoses 2002;45:146-151. 4. Bow E. Br J Haematol 1998;101(suppl1):1-4. 5. Montesinos J, Sola C, Maroto P et al. Eur J Clin Microbiol Infect Dis 2001;20:569-572.)

Clinical Characteristics of Patients with IFIs

	No. of Patients (%)		
Characteristic	1989-93	1994-98	1999-2003
Median Age (range)	44 (15-87)	49 (2-83)	53 (19-77)
AML	60/147 (41)	41/85 (48)	30/82 (37)
ALL	23/147 (16)	16/85 (19)	17/82 (21)
CML	25/147 (17)	5/85 (6)	5/82 (6)
NHL	15/147 (10)	9/85 (11)	9/82 (11)
CLL	8/147 (5)	3/85 (4)	9/82 (11)
Myelodysplastic Syndrome	8/147 (5)	5/85 (6)	6/82 (7)
Other	8/147 (5)	6/85 (7)	5/82 (6)

(Chamilos G et al. Haematologica 2006;91:986-989)

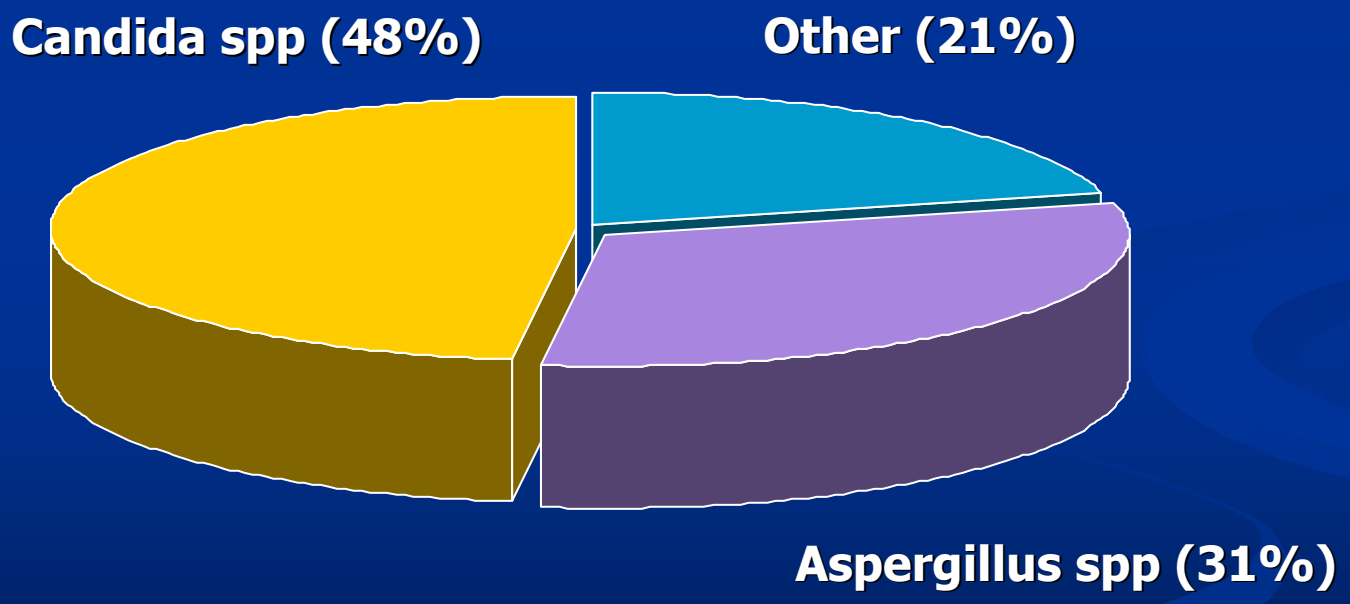
Epidemiology (cont'd)

- **High mortality from IFIs:**
  - **Mortality rates due to fungal infections in pt. with malignancies range from 6% - 60%**

(EORTC. Am J Med 1989;86:668-672)
(Guiot et al. Clin Infect Dis 1994;18:525-532)

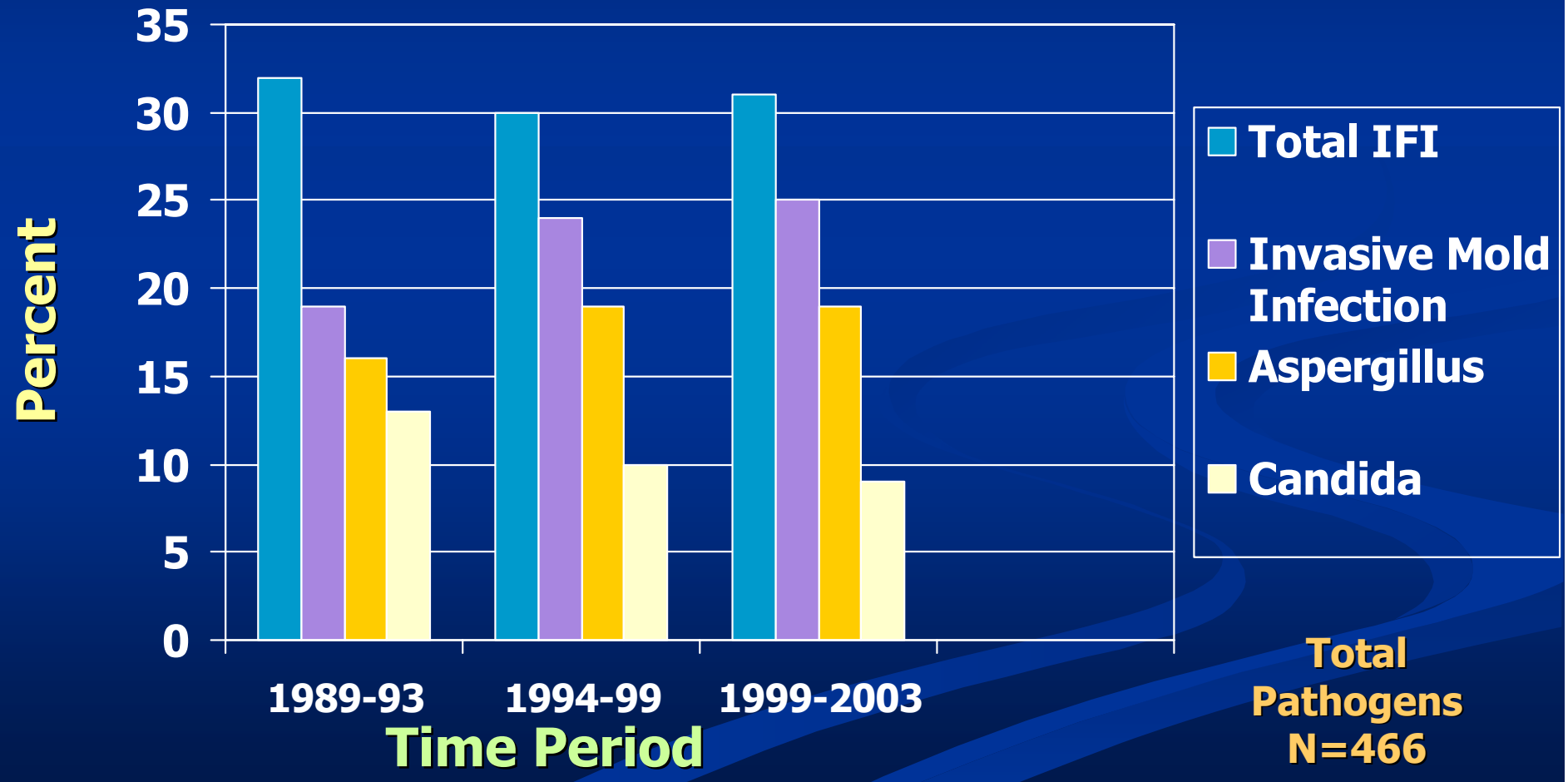
Pathogenic Fungi

Etiology of Fungal Infection in Cancer Patients



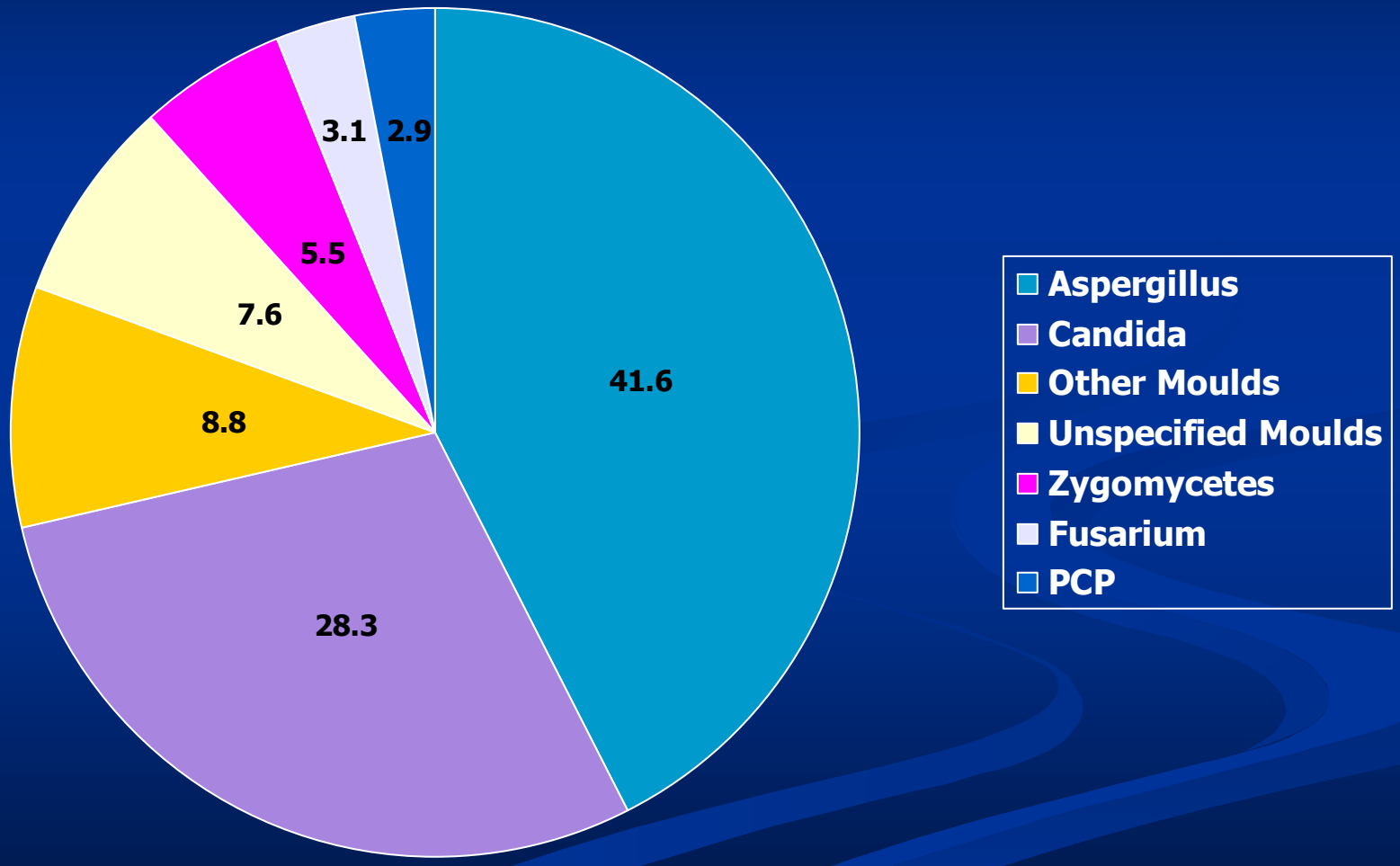
(Data from Walsh et al. Rev Infect Dis. 1991;Bodey et al. Eur J Clin Microbiol Infect Dis. 1992; Vazquez et al. J Infect Dis. 1993; Pannuti et al. Cancer. 1992; Anaisse et al. Rev Infect Dis. 1989; Morrison et al. Am J Med. 1994)

Prevalence of IFIs in Hematological Malignancies: Autopsy Study 1989-93, 1994-98 & 1999-2003 - MD Anderson



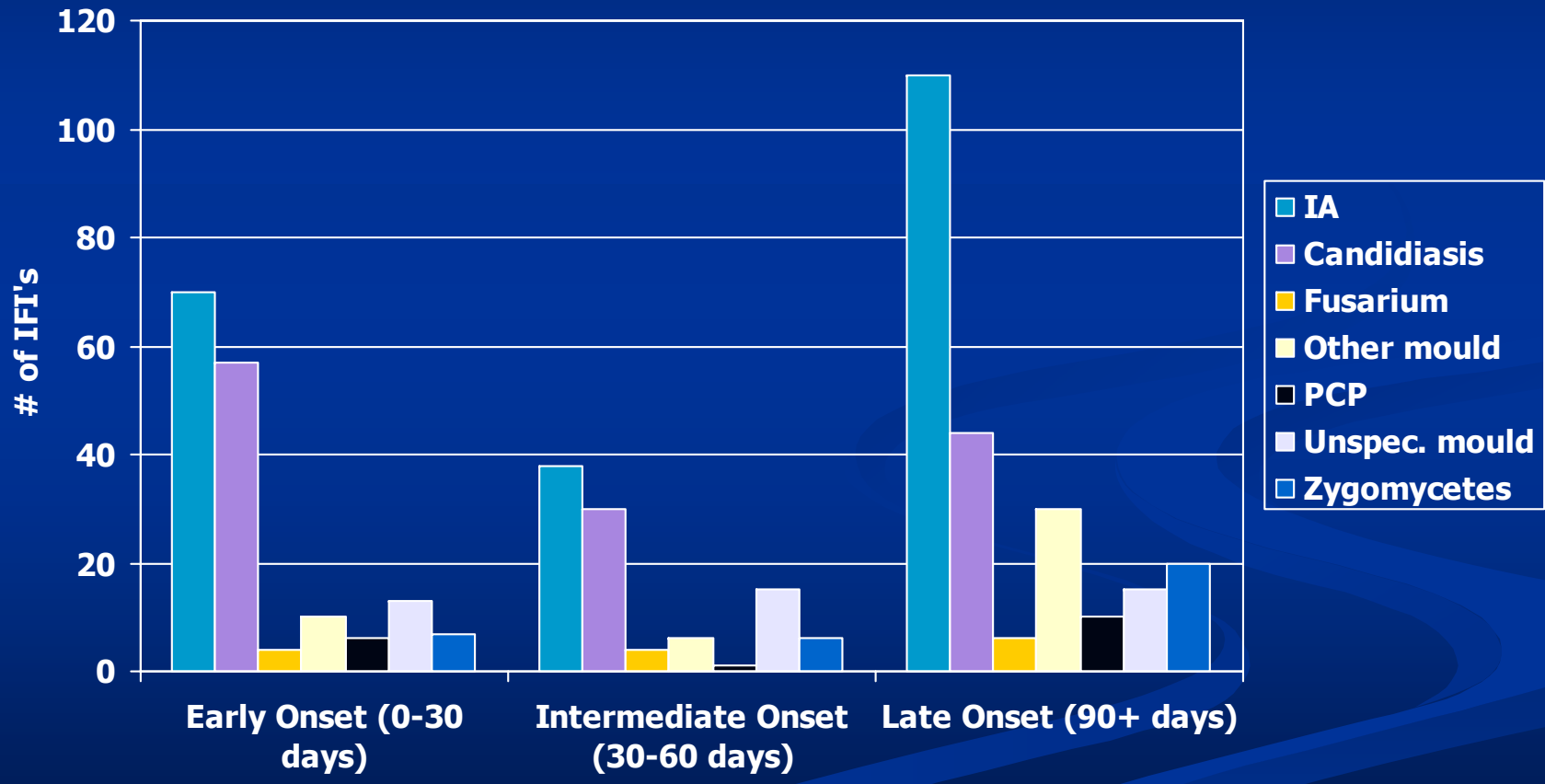
(Chamilos G et al. Haematologica 2006;91:986-989)

IFI's in HSCTs



(Pappas PG. FOFI 2005)

Time to Onset of IFI for HSCTs



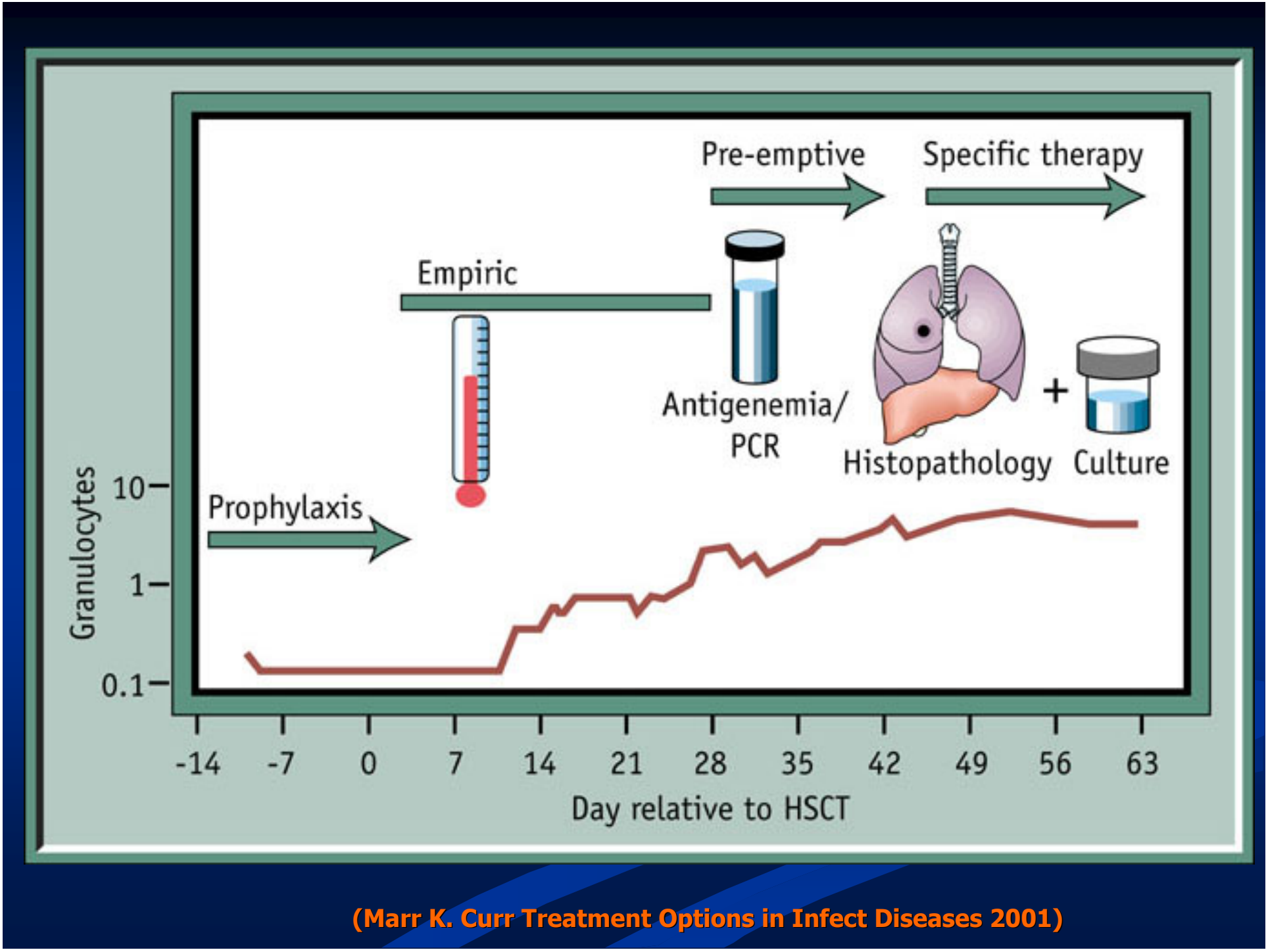
(PG Pappas: Transplant Associated Infection Surveillance Network)

Origin of Pathogenic Fungi

Origin of Fungal Pathogens

- ***Candida spp.***
  - **Endogenous organisms – normal commensals of skin, GI tract & GU tract**
- ***Aspergillus spp.***
  - **Ubiquitous in environment**
  - **Inhaled**

Strategies for Treatment of Invasive Fungal Infections in Cancer Patients



(Marr K. Curr Treatment Options in Infect Diseases 2001)

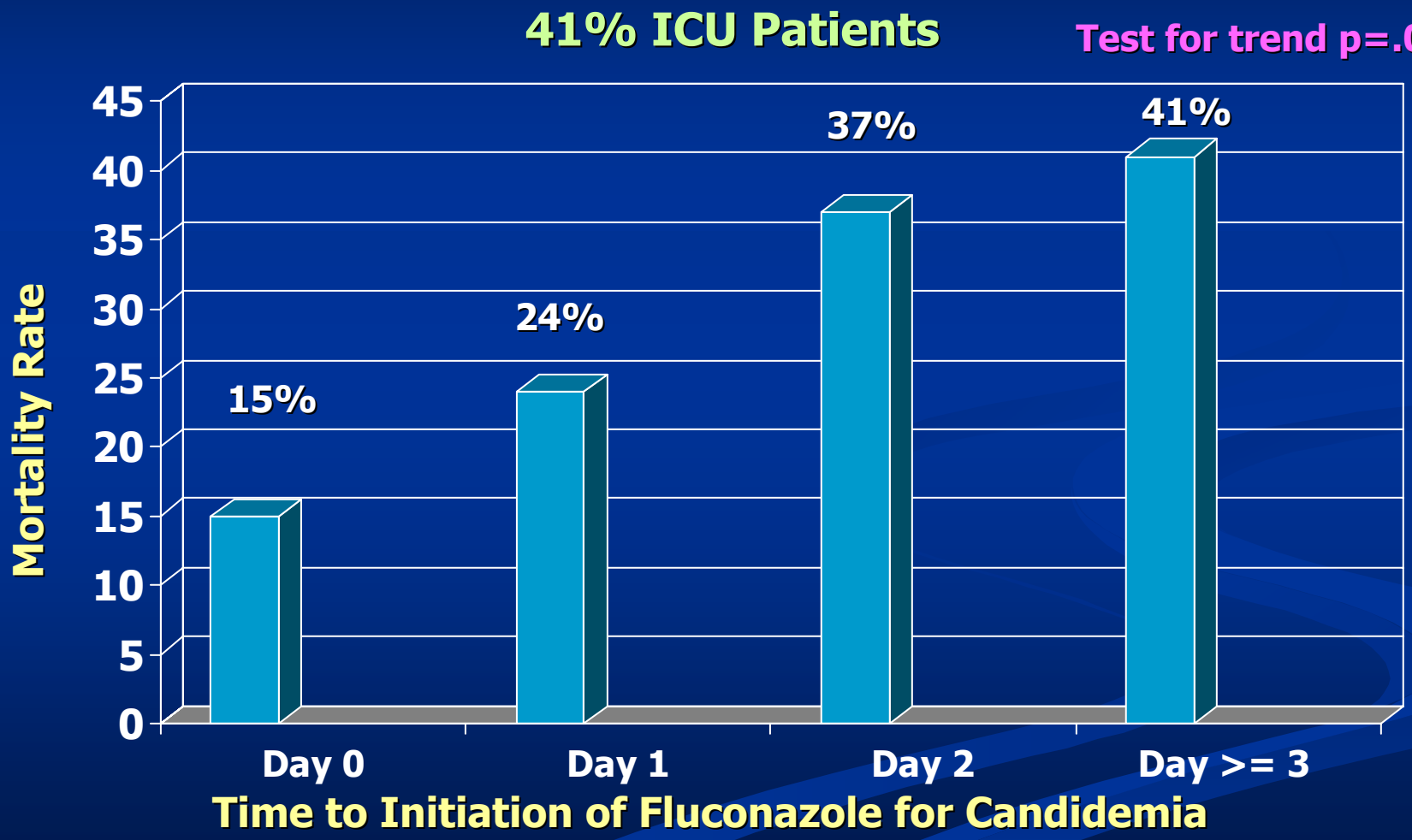
Treatment for Candidemia/Invasive Candidiasis and Invasive Aspergillosis

Treatment of Candidemia/ Invasive Candidiasis

Two Key Principles of Treatment

- Hit Early
- Hit Right

Mortality Rates with Delay in Therapy for Candidemia



(Garey KW et al. CID 2006;43:25-31)

Increased Hospital Mortality with Inadequate Antimicrobial Therapy for Candidemia

- Bloodstream infection-related mortality rate higher for patients receiving inadequate antimicrobial therapy 29.9% vs. 11.9% with adequate antimicrobial therapy ($p<.001$).

- Multiple logistic regression analysis showed that: *Candida spp.* associated with inadequate therapy (AOR 51.86, 95% CI 24.57 to 109.49, $p<.001$).

(Ibrahim EH et al. Chest 2000;118:146-155)

2008 IDSA Guidelines for the Treatment of Candidemia/Invasive Candidiasis

- **Non-Neutropenic patients - Clinically stable and no recent azole exposure:**
  - **Fluconazole 800mg then 400 mg daily IV/po (preferred) or an echinocandin (Anidulafungin 200mg IV then 100 mg IV daily, Caspofungin 70 mg then 50 mg IV daily or Micafungin 100 mg IV daily) [A-I].**
  - **Transition from an echinocandin to fluconazole for fluconazole susceptible organisms & patients clinically stable [A-II].**

IDSA2008 Guidelines for the Treatment of Candidemia/Invasive Candidiasis (Cont'd)

- For *C. glabrata* an echinocandin is preferred. Transition to fluconazole or voriconazole should not be done unless isolate susceptible. If fluconazole used initially and patient improved and cultures negative then continue with fluconazole [B-III].

- For *C. parapsilosis* fluconazole is preferred. If an echinocandin used and patient improved with negative cultures can continue with echinocandin [B-III].

- AmB 0.5 to 1.0 mg/kg/d IV or LF-AmB 3-5 mg/kg/d IV are alternatives if there is intolerance or limited availability of other antifungals [A-I].

IDSA2008 Guidelines for the Treatment of Candidemia/Invasive Candidiasis (Cont'd)

- **Voriconazole** is effective for candidemia but offers little advantage over fluconazole except for step down therapy for *C. krusei* and voriconazole-susceptible *C. glabrata*.
- Removal of IV catheters recommended.
- Duration of therapy 2 weeks after last positive blood culture and resolution of symptoms.

IDSA2008 Guidelines for the Treatment of Candidemia/Invasive Candidiasis (Cont'd)

- **Non-neutropenic patients - moderately severe to severely ill and recent azole exposure:**
  - **Echinocandin (Anidulafungin 200mg IV → 100 mg daily IV, Caspofungin 70mg IV → 50 mg daily IV or Micafungin 100 mg daily IV)**

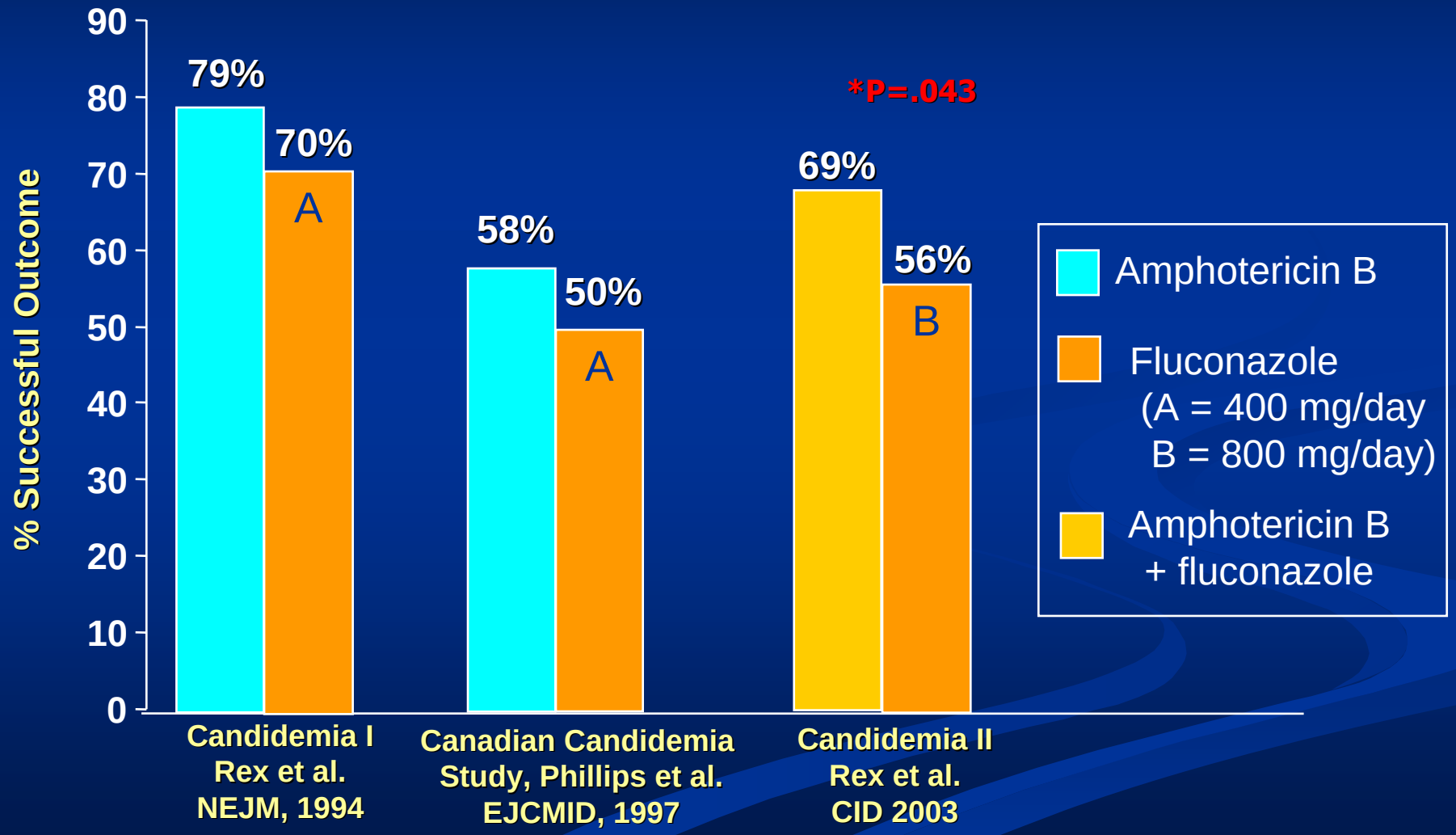
IDSA2008 Guidelines for the Treatment of Candidemia/Invasive Candidiasis (Cont'd)

- **Candidemia in neutropenic patients:**
  - **Echinocandin (Anidulafungin 200 mg → 100 mg daily IV, Caspofungin 70 mg → 50 mg daily IV or Micafungin 100 mg daily IV) or LF-AmB 3-5 mg/kg/d IV [A-II].**
  - **For less critically ill patients, fluconazole 800mg → 400 mg daily is alternative. Voriconazole may be used in situations where additional mould coverage is desired [B-III].**

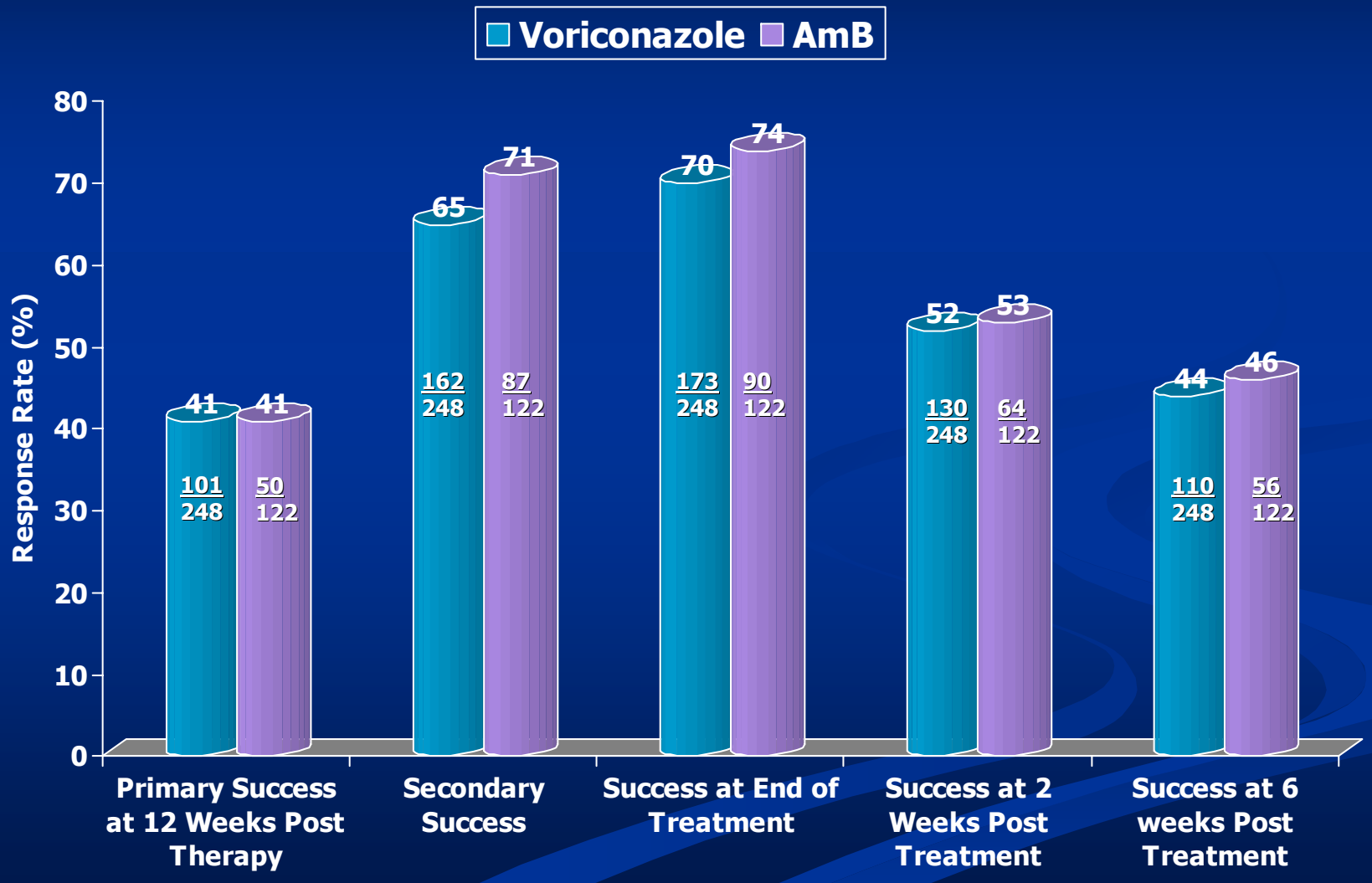
IDSA2008 Guidelines for the Treatment of Candidemia/Invasive Candidiasis (Cont'd)

- **Candidemia in neutropenic patients (cont'd):**
  - For *C. glabrata*, an echinocandin or LF-AmB is preferred. If patients are improved on fluconazole or voriconazole and blood cultures are negative, they can be continued [B-III].
  - For *C. parapsilosis* infections, fluconazole or LF-AmB is preferred [B-III].
  - For *C. krusei*, an echinocandin or voriconazole is preferred [B-III].

Efficacy Results in Candidemia in Non-neutropenic Patients

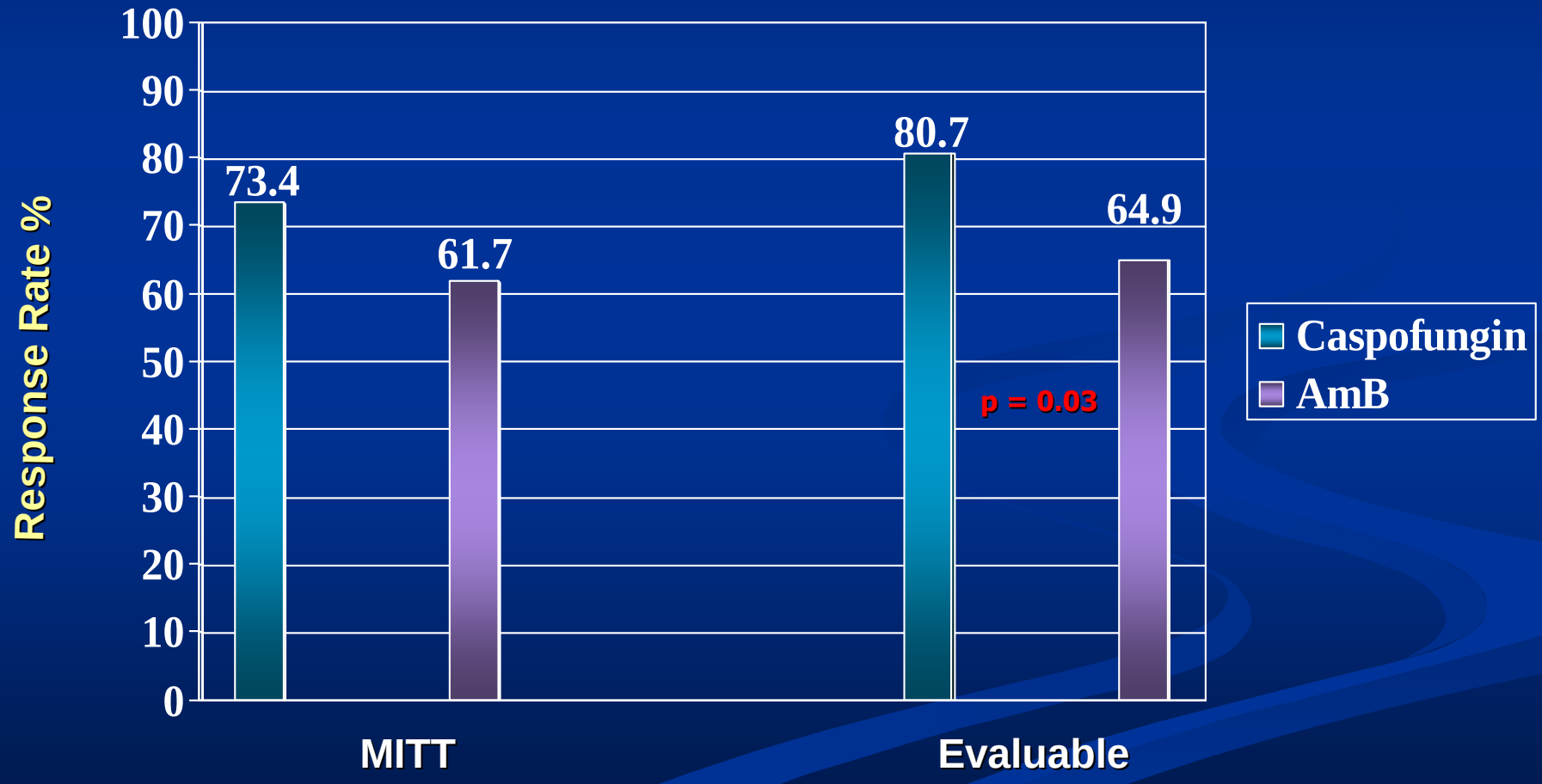


Response Rates
Voriconazole vs. AmB for Candidemia



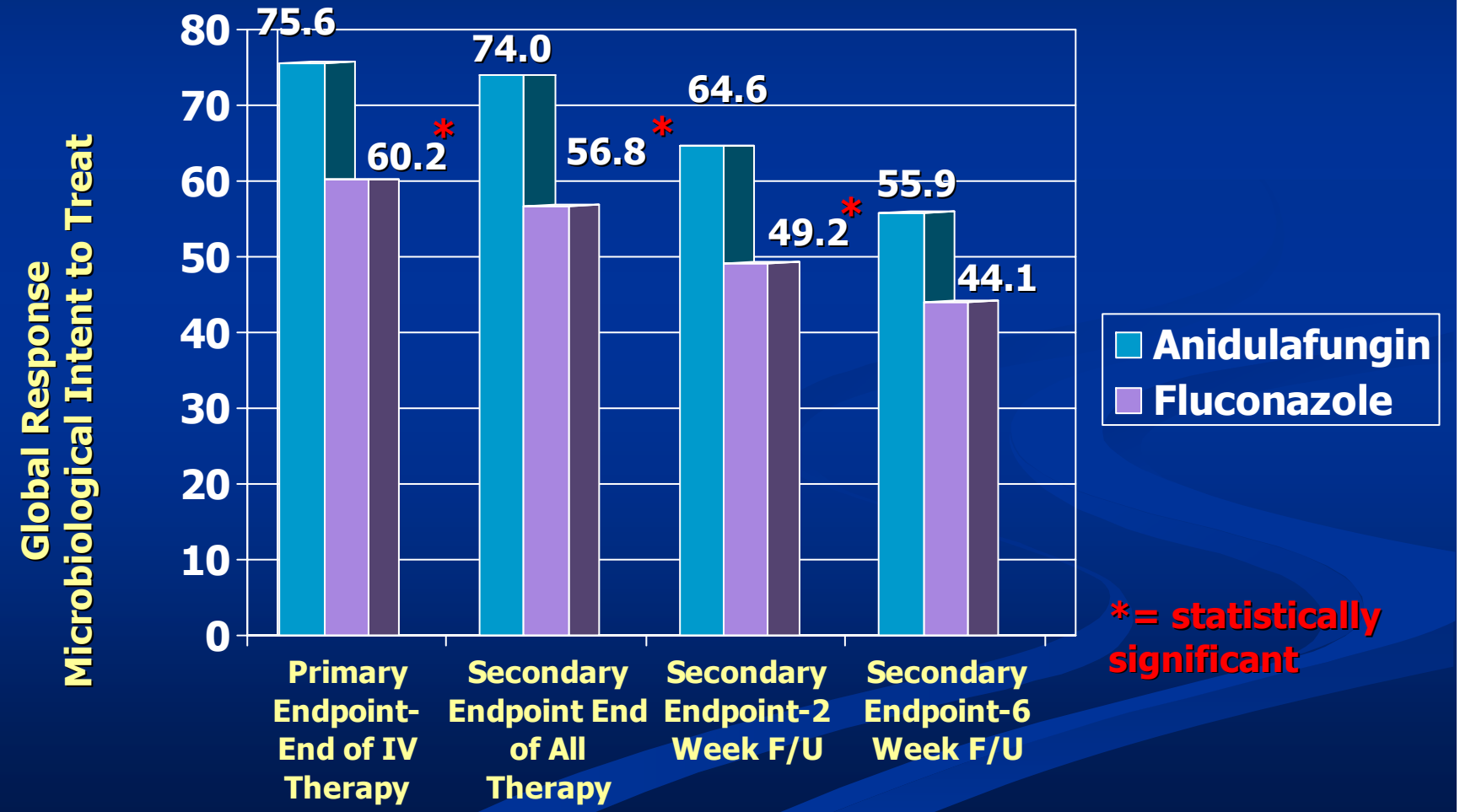
(Kullberg BJ et al. Lancet 2005;366:1435-1442)

CASPOFUNGIN VS. AmB for Candidemia: End of IV Antifungal Therapy



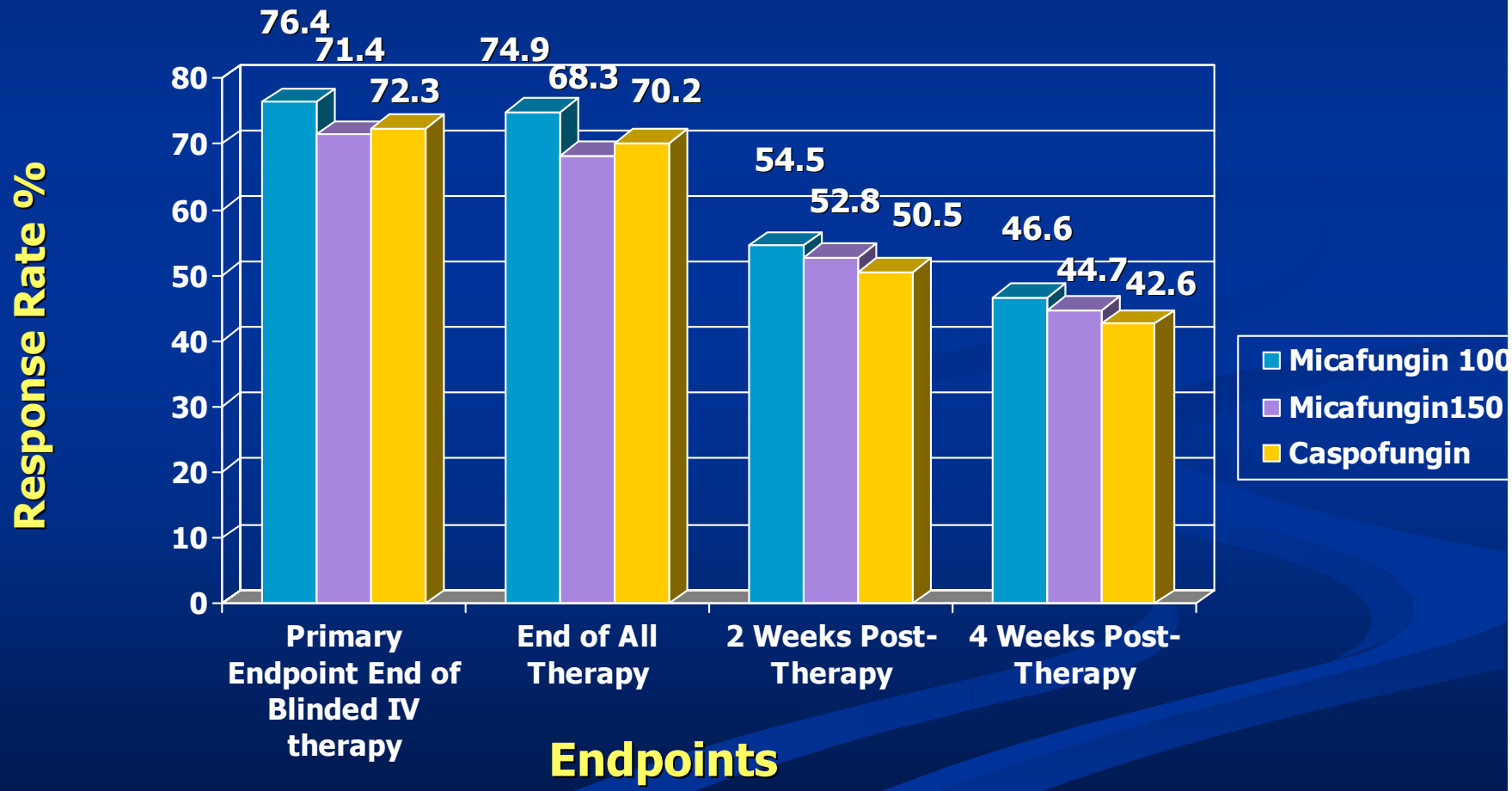
(Mora-Duarte J et al. NEJM 2002;347:2020-2029)

Anidulafungin vs. Fluconazole for Candidemia and Invasive Candidiasis



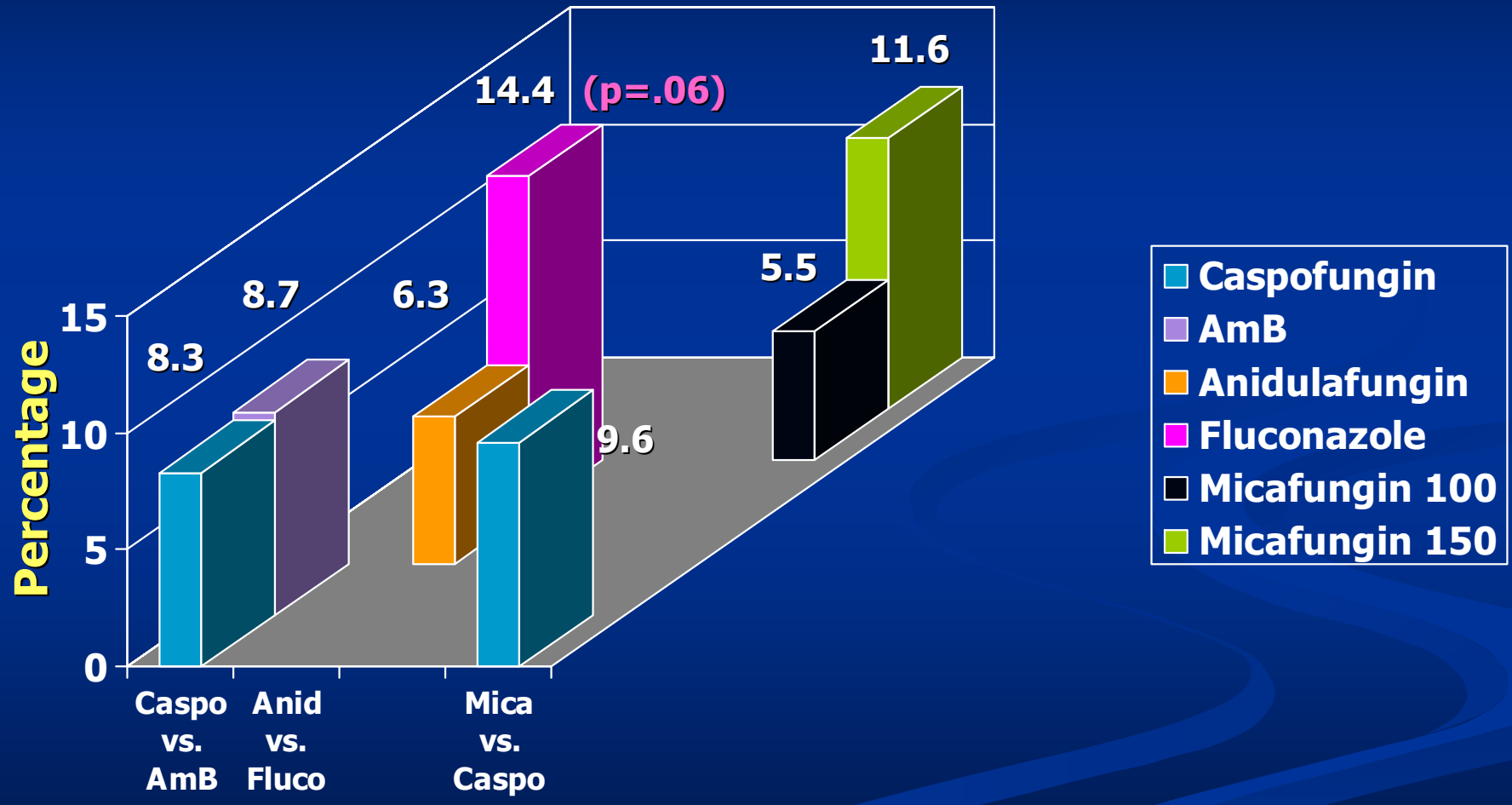
(Reboli AC, Rotstein C, Pappas P, et al. N Engl J Med 2007;356:2472-2482)

Response Rates of Micafungin vs. Caspofungin for Candidemia/Invasive Candidiasis



(Pappas P, Rotstein C, Betts RF et al. CID 2007;45:883-893)

Persistence of Invasive Candida Infections with Echinocandins



1. Mora-Duarte J et al. N Engl J Med 2002;347:2020-2029
2. Reboli AC, Rotstein C, Pappas P et al. NEJM 2007;356:2472-2482
3. Pappas P, Rotstein C, Betts RF et al. CID 2007;45:883-893

Empiric Antifungal Therapy for Candidiasis in Neutropenic Patients

IDSA2008 Guidelines for the Treatment of Candidemia/Invasive Candidiasis (Cont'd)

- **Empiric treatment for suspected invasive candidiasis in neutropenic patients:**
  - **LF-AmB 3-5 mg/kg daily IV, Caspofungin 70 mg → 50 mg daily IV or Voriconazole 6 mg/kg q12h IV X2 then 3 mg/kg q12h IV followed by 200 mg bid po.**
  - **Fluconazole 800 mg load then 400 mg daily or Itraconazole 200 mg bid are alternatives.**
  - **AmB use is discouraged due to the risk of nephrotoxicity.**
  - **Azoles should not be used for empiric therapy if they have been used as prophylaxis in patients**

Review: Empiric Antifungal Therapy in Febrile Neutropenia: A Meta-Analysis of Randomized Controlled Trials

Comparison: LF AmB vs Conventional AmB – Including patients with suspected infection

Outcome: Survival

Study or sub-category	LF AmB n/N	Conventional AmB n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Moreau 1992	16/16	16/16			not estimable
Caillot 1994	18/19	18/20		2.80	2.00 (0.17, 24.07)
Pascual 1995	7/7	8/8			Not estimable
Schoffski 1998	23/27	18/24		8.76	1.92 (0.47, 7.83)
White 1998	82/98	82/95		27.56	0.81 (0.37, 1.80)
Walsh 1999	318/343	308/344		60.88	1.49 (0.87, 2.54)
Total	510	507		100.00	1.30 (0.86, 1.97)

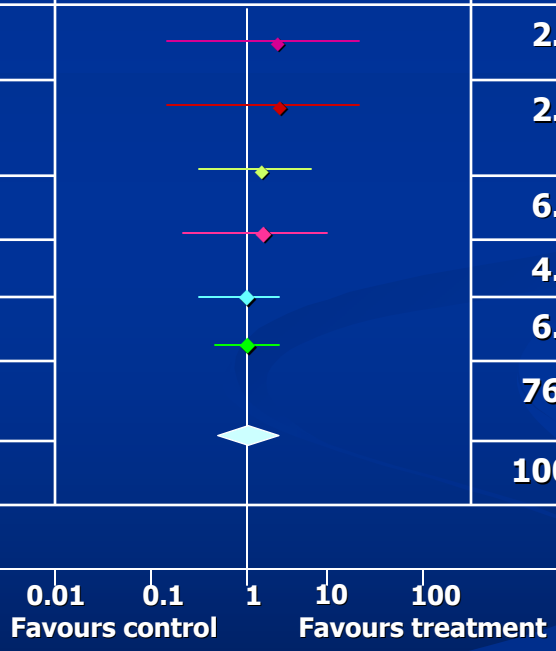
Total (95% CI)
Total events: 464 (LF AmB) 450 (Conventional AmB)
Test for heterogeneity: $Chi^2 = 2.00$, df=3 (P=0.57), $I^2 = 0\%$
Test for overall effect: Z=1.23 (P=0.22)

Review: Empiric Antifungal Therapy in Febrile Neutropenia: A Meta-Analysis of Randomized Controlled Trials

Comparison: LF AmB vs Conventional AmB – Including patients with suspected infection

Outcome: Avoidance of Fungal Breakthrough Infections

Study or sub-category	LF AmB n/N	Conventional AmB n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Moreau 1992	15/16	14/16		2.93	2.14 (0.17, 26.33)
Caillot 1994	18/19	18/20		2.98	2.00 (0.17, 24.07)
Prentice	227/231	98/100		6.29	1.16 (0.17, 24.07)
Schoffski 1998	25/27	22/24		4.43	1.14 (0.15, 8.76)
White 1998	95/98	92/95		6.99	1.03 (0.20, 5.25)
Walsh 1999	309/343	307/344		76.38	1.10 (0.67, 1.79)
Total	734	599		100.00	1.14 (0.74, 1.75)



Total (95% CI)
Total events: 689 (LF AmB) 551 (Conventional AmB)
Test for heterogeneity: Chi^2 =0.48, df=5 (P=0.99), I^2=0%
Test for overall effect: Z=0.59 (P=0.55)

Review: Empiric Antifungal Therapy in Febrile Neutropenia: A Meta-Analysis of Randomized Controlled Trials

Comparison: LF AmB vs Conventional AmB – Including patients with suspected infection

Outcome: Renal Toxicity (Creatinine > 1.5 x Baseline)

Study or sub-category	LF AmB n/N	Conventional AmB n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Moreau 1992	2/16	9/16		11.81	0.11 (0.02, 0.66)
Schoffski 1998	2/27	0/27		4.63	4.80 (0.22, 105.22)
White 1998	20/102	51/99		36.54	0.23 (0.31, 0.58)
Walsh 1999	101/343	170/344		47.02	0.43 (0.31, 0.58)
Total	488	483		100.00	0.32 (0.16, 0.65)

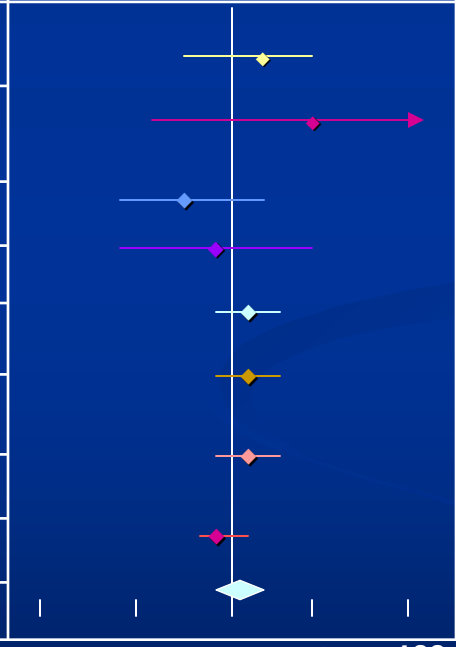
Total (95% CI)
Total events: 125 (LF AmB), 230 (Conventional AmB)
Test for heterogeneity: Chi^2 =7.43, df= 3 (P=0.06), I^2=59.6%
Test for overall effect: Z=3.17 (P=0.002)

Review: Empiric Antifungal Therapy in Febrile Neutropenia: A Meta-Analysis of Randomized Controlled Trials

Comparison: Azoles vs. AmB compounds– Including patients with suspected sites of infection

Outcome: Survival

Study or sub-category	Azole n/N	AmB n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Walsh 1991	27/32	25/32		6.60	1.51 (0.42, 5.38)
Marie 1993	65/65	64/66		1.19	5.08 (0.24, 107.83)
Ellis 1995	8/16	19/25		5.93	0.32 (0.08, 1.21)
Viscoli 1996	53/56	54/56		3.27	0.65 (0.11, 4.07)
Malik 1998	38/52	32/48		13.62	1.36 (0.58, 3.20)
Winston 2000	145/158	142/159		16.92	1.34 (0.63, 2.85)
Boogaerts 2001	160/179	156/181		22.78	1.35 (0.71, 2.55)
Walsh 2002	382/415	397/422		29.69	0.73 (0.43, 1.25)
Total	973	989		100.00	1.03 (0.74, 1.44)



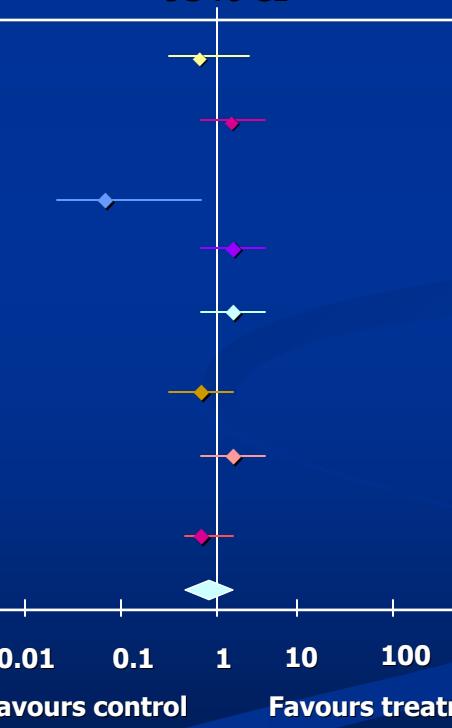
Total (95% CI)
Total events: 878 (Azole), 889 (AmB)
Test for heterogeneity: Chi^2 =7.74, df=7 (P=0.36), I^2=9.5%
Test for overall effect: Z=0.17 (P=0.86)

Review: Empiric Antifungal Therapy in Febrile Neutropenia: A Meta-Analysis of Randomized Controlled Trials

Comparison: Azoles vs. AmB compounds– Including patients with suspected sites of infection

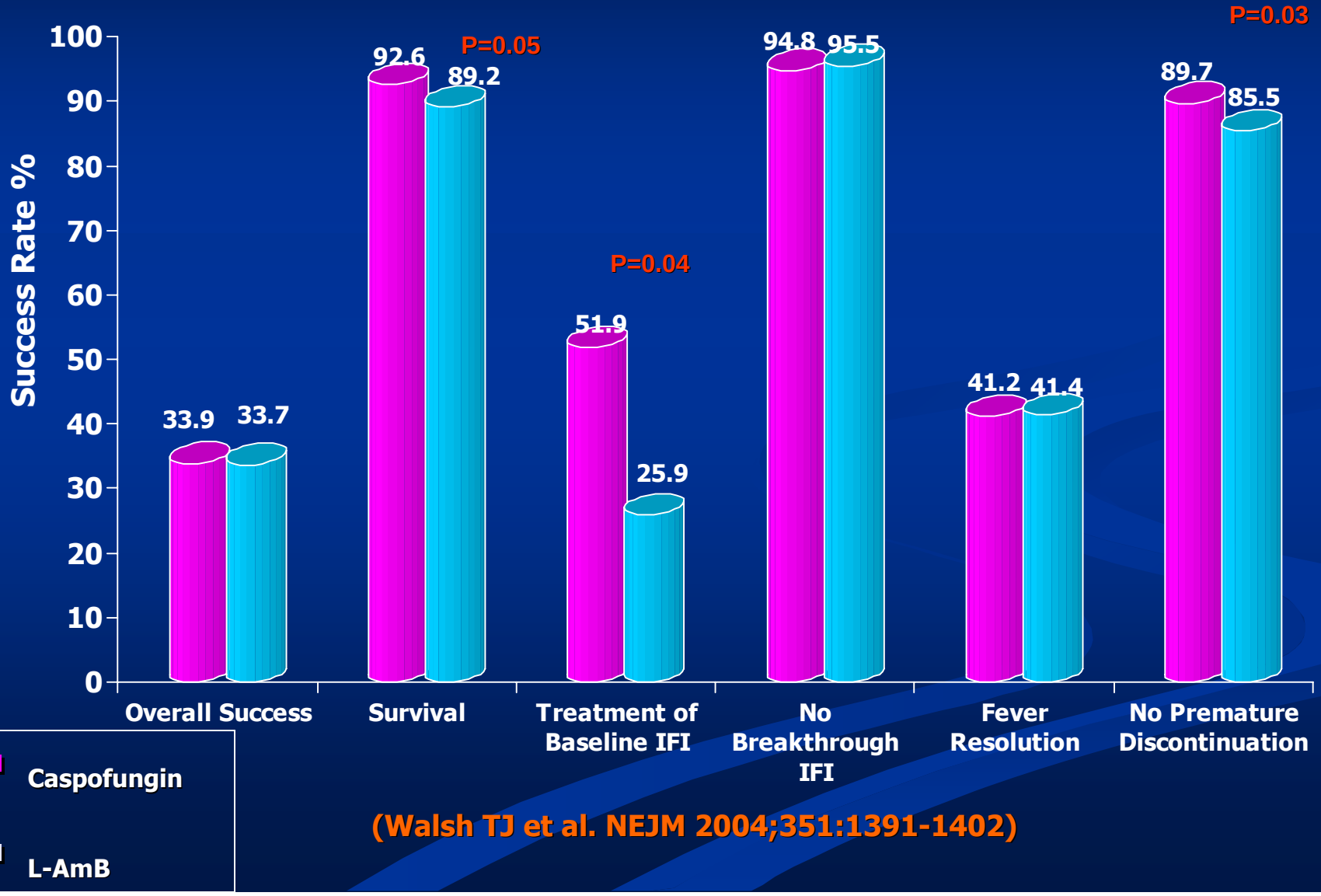
Outcome: Defervescence

Study or sub-category	Azole n/N	AmB n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Fainstein 1987	40/60	52/69		10.01	0.65 (0.30, 1.41)
Marie 1993	42/65	41/66		11.12	1.11 (0.55, 2.27)
Ellis 1995	8/16	21/25		3.52	0.19 (0.04, 0.81)
Viscoli 1996	42/56	37/56		9.08	1.54 (0.68, 3.50)
Malik 1998	29/52	22/48		12.04	0.60 (0.30, 1.16)
Winston 2000	133/158	143/159		18.51	1.16 (0.73, 1.84)
Boogaerts 2001	131/179	127/181		18.51	1.16 (0.73, 1.84)
Walsh 2002	135/415	154/422		26.12	0.84 (0.63, 1.12)
Total	1001	1026		100.00	0.91 (0.68, 1.21)



Total (95% CI)
Total events: 560 (Azole), 597 (AmB)
Test for heterogeneity: Chi^2 =11.50, df=7 (P=0.12), I^2=39.1%
Test for overall effect: Z=0.63 (P=0.53)

Caspofungin vs. L-AmB for Empiric Antifungal Therapy in Patients with Persistent Neutropenia



(Walsh TJ et al. NEJM 2004;351:1391-1402)

Prophylaxis

IDSA2008 Guidelines for the Treatment of Candidemia/Invasive Candidiasis (Cont'd)

- **Antifungal prohylaxis for invasive candidiasis in chemotherapy induced neutropenia and HSCT:**
  - **Fluconazole 400mg daily [A-I] or Posaconazole 200 mg tid [A-I] or Caspofungin 50 mg daily IV [B-II] are recommended.**
  - **For neutropenia in HSCT, Fluconazole 400 mg po daily, Posaconazole 200 mg po tid or Micafungin 50 mg daily IV are recommended [A-I].**

Azole Antifungal Prophylaxis

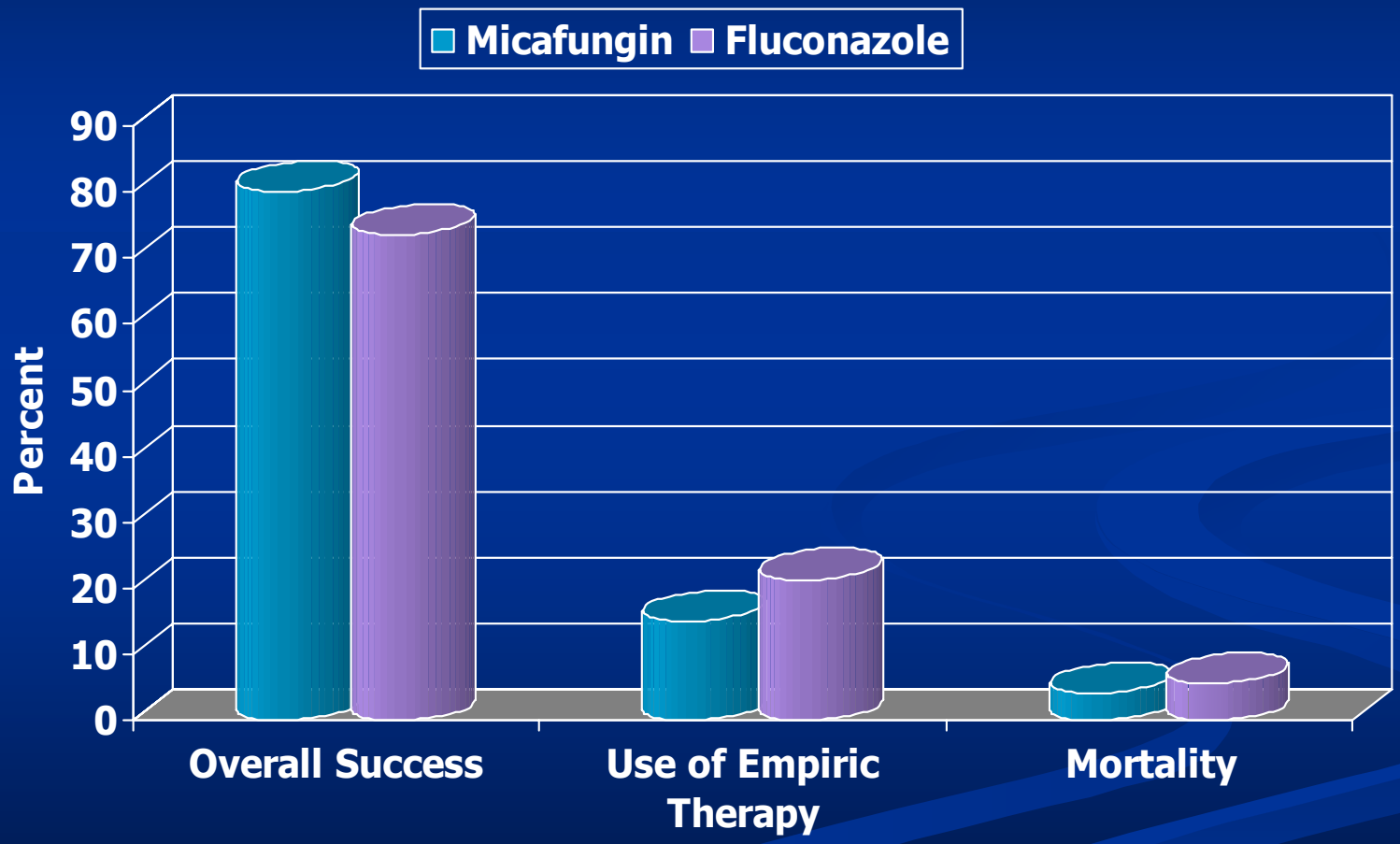
Meta-analysis, 38 trials, n=7014

Endpoint	Odds Ratio*	RRR/NNT
Need for AF Rx	0.57	19%, 10
Superficial infxn	0.29	61%, 12
Proven IFI	0.44	56%, 22
Fungal mortality	0.58	47%, 52
Overall mortality	0.87	-

* All favour study agent (prophylaxis) $p<0.05$

(Bow EJ et al, Cancer 2002;94:3230-46)

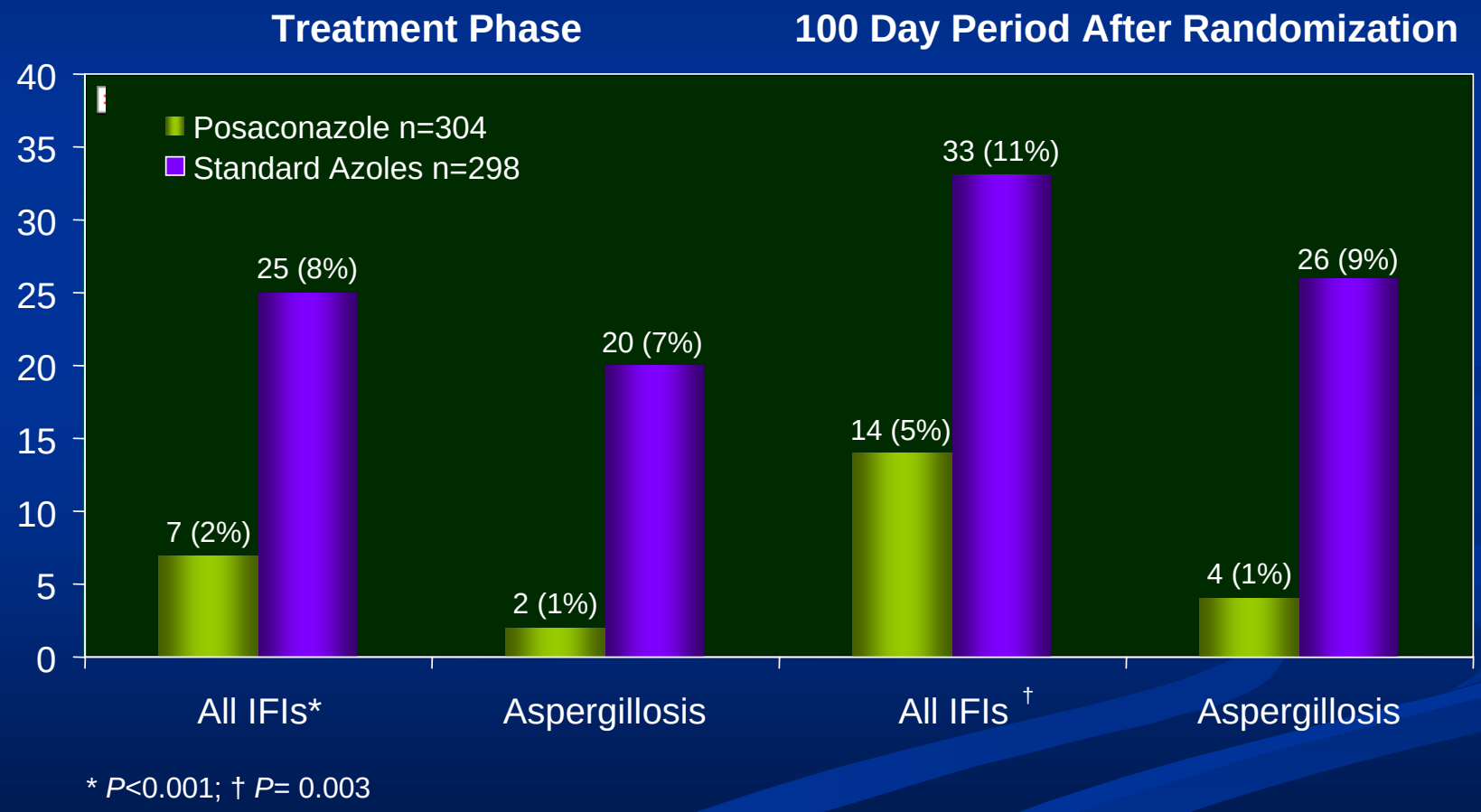
Micafungin vs. Fluconazole for Prophylaxis in HSCT



(van Burik JA et al. CID 2004;39:1407-1416)

Antifungal Prophylaxis: Neutropenia

Primary Endpoint: Prevention of IFI

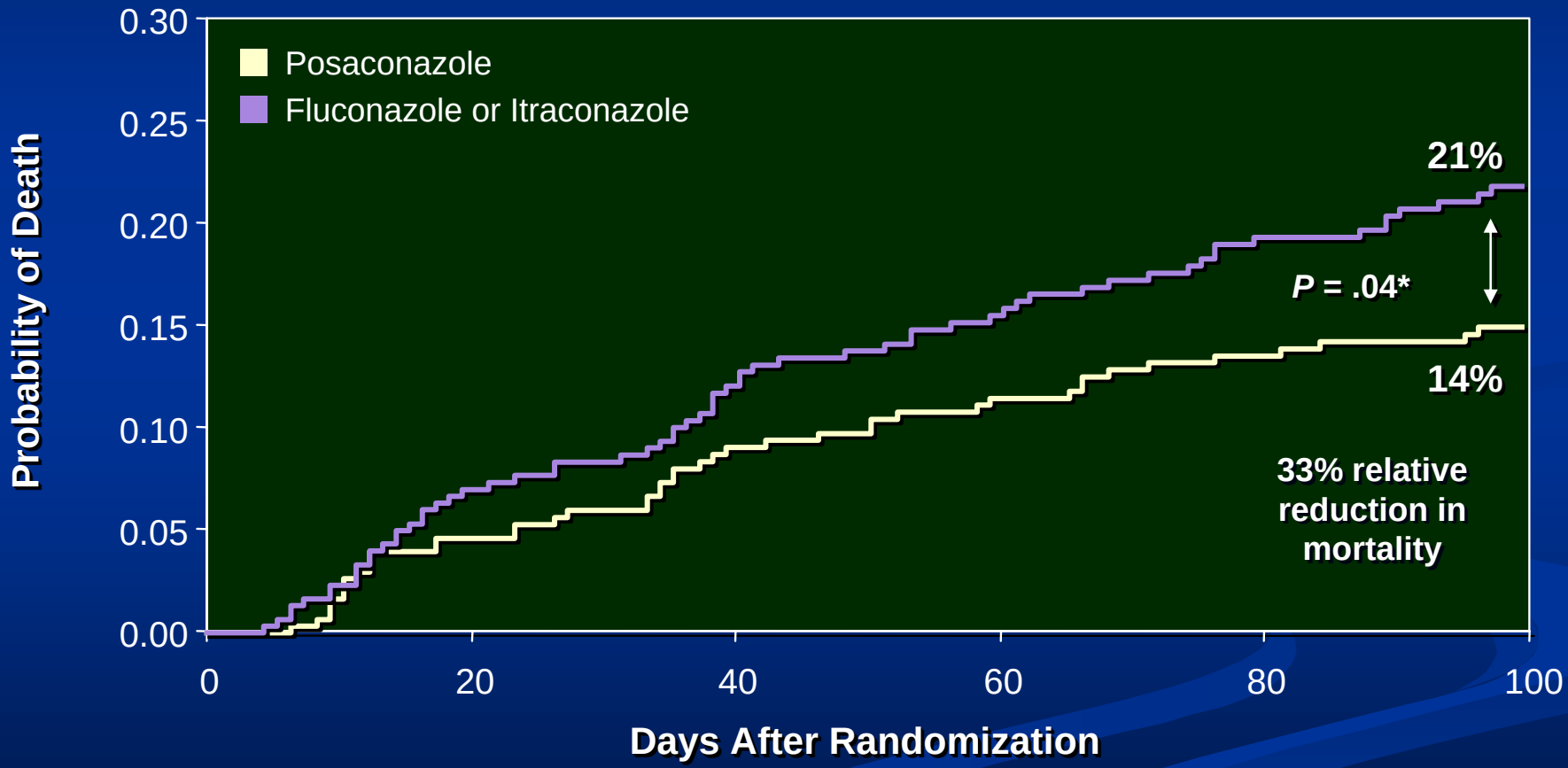


* *P*<0.001; † *P*= 0.003

(Cornely OA et al. *N Engl J Med* 2007;356:348-59)

Antifungal Prophylaxis: Neutropenia

Death From Any Cause (Decreased Mortality)



*Estimated using log-rank statistics.
Censoring time is the minimum of the last contact date and day 100.

(Cornely OA, et al. *N Engl J Med* 2007;356:348-359)

Pre-Emptive Therapy

- Serological surrogate markers of IFI (beta glucan for Candida and beta galactomannan for Aspergillus) not universally available.
- Pre-emptive therapy can't be used effectively without these markers.

Treatment of Invasive Aspergillosis

Antifungal Therapy for Invasive Aspergillosis – IDSA Guidelines

- **IA involving lung, sinus, tracheobronchial tree and CNS:**
  - **Primary therapy – Voriconazole 6 mg/kg q12h X 1 d then 4 mg/kg q12h IV → 200 mg bid po [A-I]**
  - **Alternative – L-AmB 3-5 mg/kg/d (A-I), caspofungin 70 mg → 50 mg /d IV, Micafungin 100-150 mg/d IV, Posaconazole 200 mg qid po initially then 400 mg bid po after stabilization or Itraconazole (dose depends on formulation) [All B-II].**
- **Empiric and preemptive antifungal therapy:**
  - **L-AmB 3 mg/kg/d IV, Caspofungin 70 mg → 50 mg/d IV or Voriconazole 6 mg/kg q12h X 1 d then 3 mg/kg/d IV → Voriconazole 200 mg bid po.**

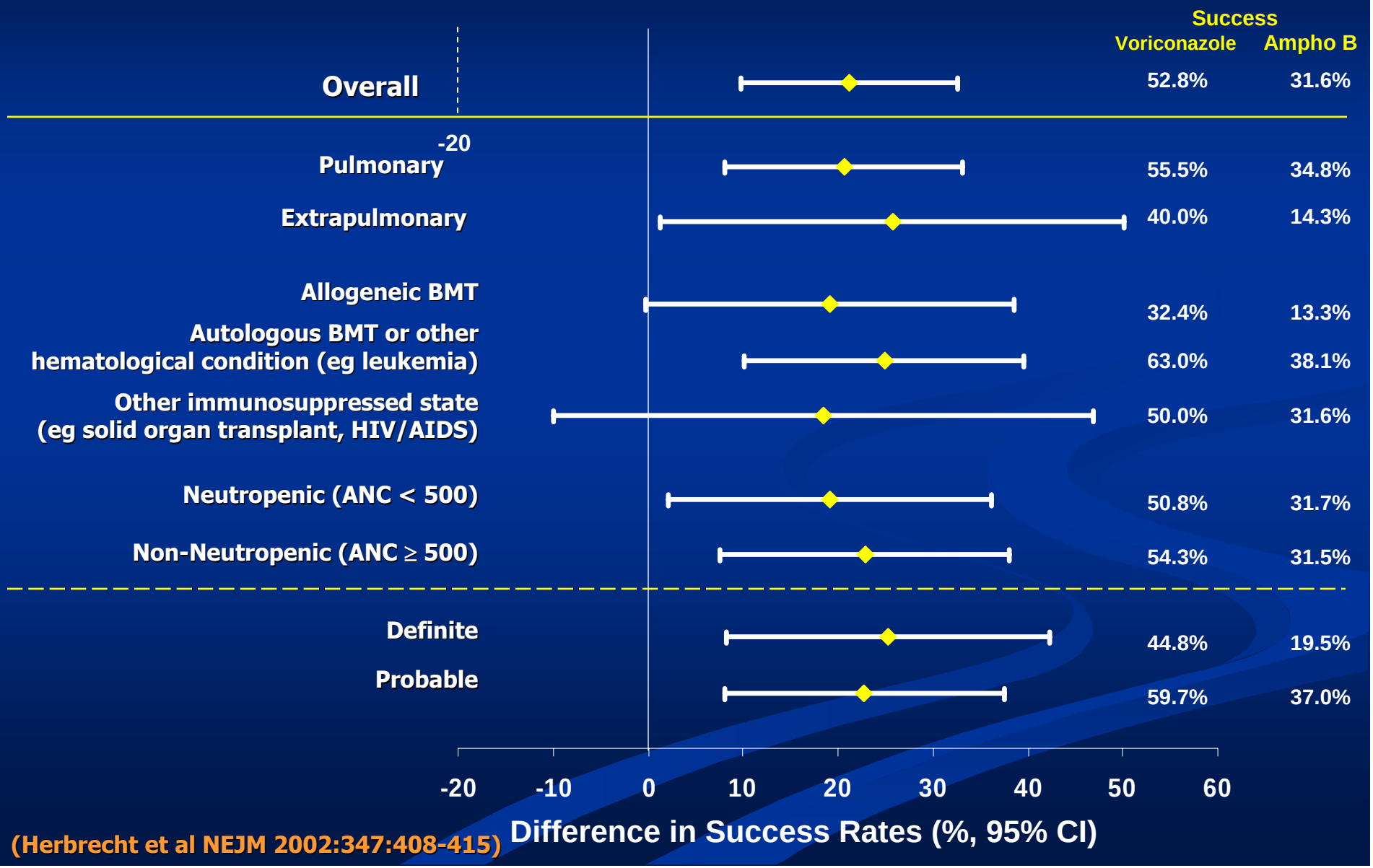
(Walsh TJ et al. Clin Infect Dis 2008;46:327-360)

Antifungal Therapy for Invasive Aspergillosis – IDSA Guidelines

- **Prophylaxis against IA:**
  - **Primary therapy - Posaconazole 200 mg tid po**
  - **Alternative therapy – Micafungin 50 mg/d IV or Itraconazole 200 mg bid po**

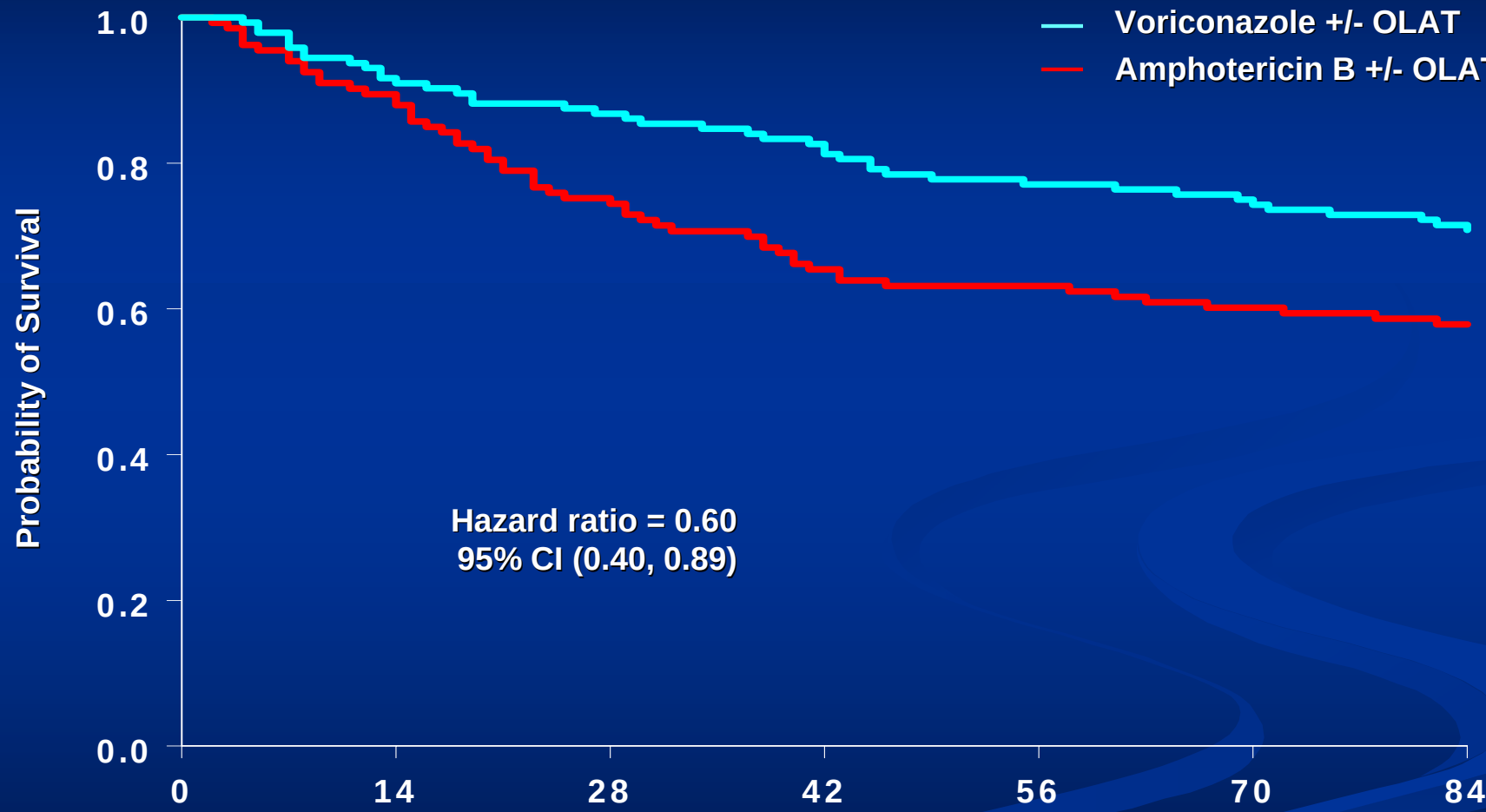
(Walsh TJ et al. Clin Infect Dis 2008;46:327-360)

Global Comparative Aspergillosis Study
Voriconazole vs. AmB Success at Week 12 (MITT)



(Herbrecht et al NEJM 2002:347:408-415)

Global Comparative Aspergillosis Voriconazole vs. AmB Time to Death (MITT)



At Risk (Censored)							
Vori	144 (0)	131 (0)	125 (0)	117 (0)	111 (0)	107 (0)	102 (0)
AMB	133 (0)	117 (0)	99 (0)	87 (0)	84 (0)	80 (0)	77 (0)

(Herbrecht et al NEJM 2002:347:408-415)

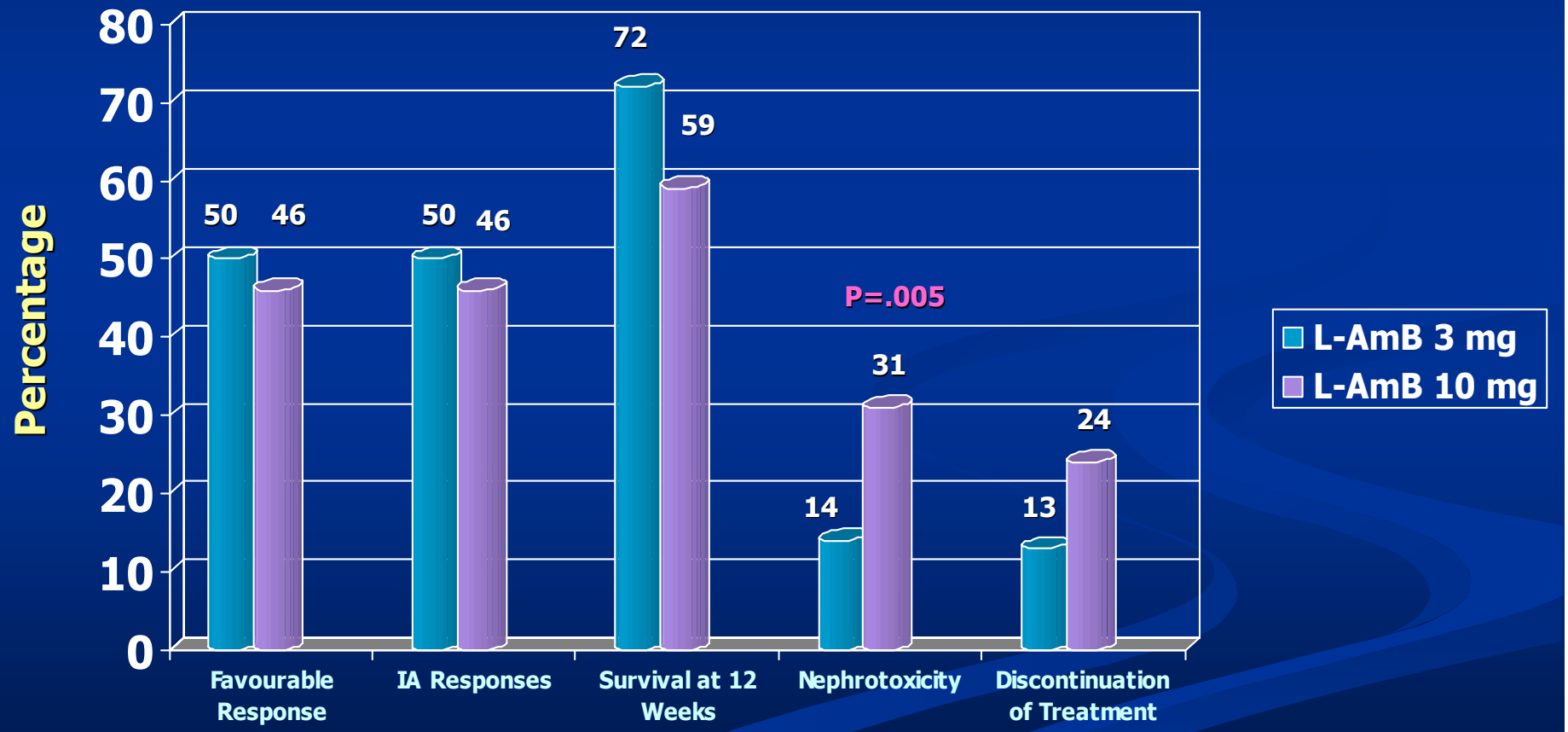
Invasive Mold Infection (IA, Zygomycosis): AmBiload Trial

- RCT: invasive mold infection in pt. with hematologic malignancy (93% of pt.).
- Performed in Europe & Australia:
  - L-AmB 3mg/kg/d IV

    vs.
  - L-AmB 10 mg/kg/d IV X 14 d Then 3 mg/kg/d IV
- Patient entry criteria:
  - Proven or probable IFI based on MSG/EORTC criteria host factor plus clinical [CT scan halo or air crescent signs] and if available microbiological findings within 4 days of enrollment.
- Analysis:
  - overall response (clinical, radiological and microbiological) in intent-to-treat population with proven or probable IFI & received ≥1 dose of drug.

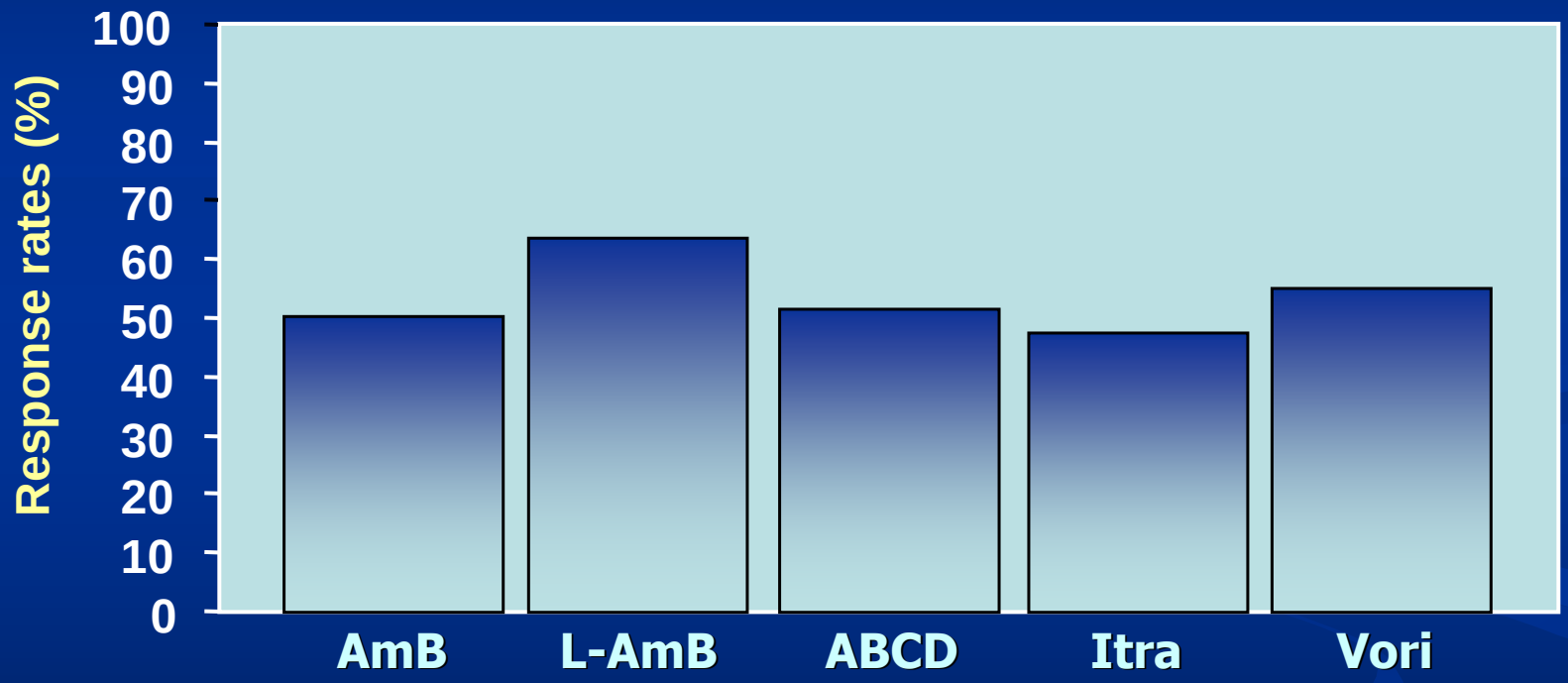
(Cornely OA et al. CID 2007;44:1289-1297)

Invasive Mold Infection (IA, Zygomycosis): AmBiload Trial (cont'd)



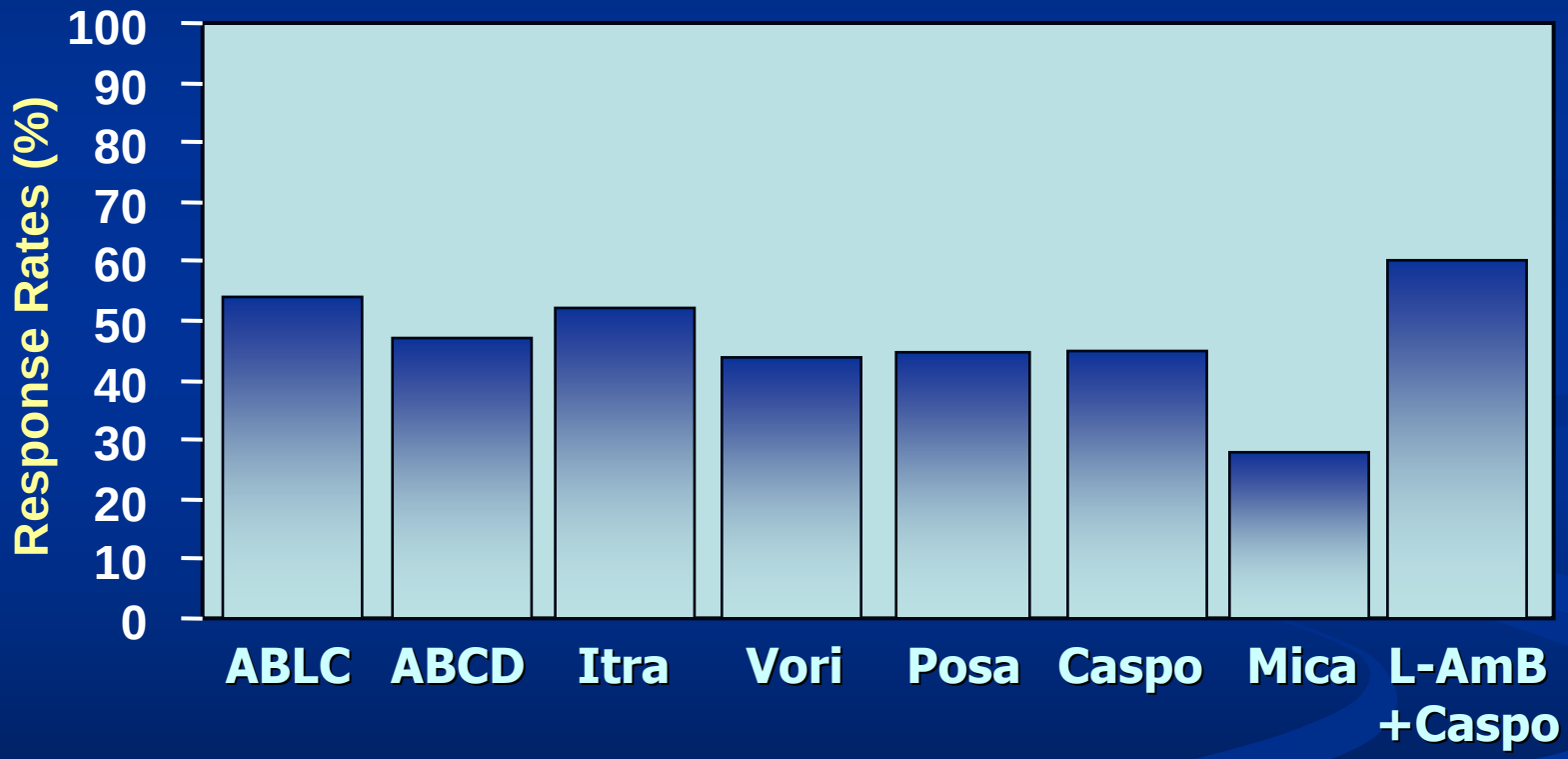
(Cornely OA et al. CID 2007;44:1289-1297)

Clinical Success in the Primary Treatment of Invasive Aspergillosis



1. Bowden. *CID* 2002:35;359
2. Lenders. *Br J Haematol* 1998:103;205
3. Bowden. *CID* 2002:35;359
4. Caillot. *CID* 2001:33;e83
5. Herbrecht. *NEJM* 2002:347;408

Clinical Success in the Treatment of Refractory Aspergillosis



1. Kuback. *FOFI* 2002
2. White. *CID* 1997:24;633
3. Caillot. *Acta Hematol* 2003:109;111
4. Perfect. *CID* 2003:36;1122
5. Walsh. *CID* 2007;44:2-12
6. Maartens. *CID* 2004:39;1563
7. Ratanatharathorn. *ASH* 2002
8. Aliff. *Cancer* 2003:97;1025

Summary

- Treatment of candidemia/invasive candidiasis (C/IC) is changing.
- Echinocandins are very useful agents in both neutropenic and nonneutropenic pt. for treatment of C/IC.
- Treatment of IA involves voriconazole as primary therapy; L-AmB considered an alternative.
- Combination therapy for IA cannot be advocated as first line but may be a consideration in refractory cases.
- Posaconazole & Micafungin effective prophylaxis in HSCT recipients particularly when there is risk for IA.