# New Directions in Invasive Fungal Disease: Therapeutic Considerations

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# Disclosure Statement for Coleman Rotstein MD

## Financial Conflicts of Interest

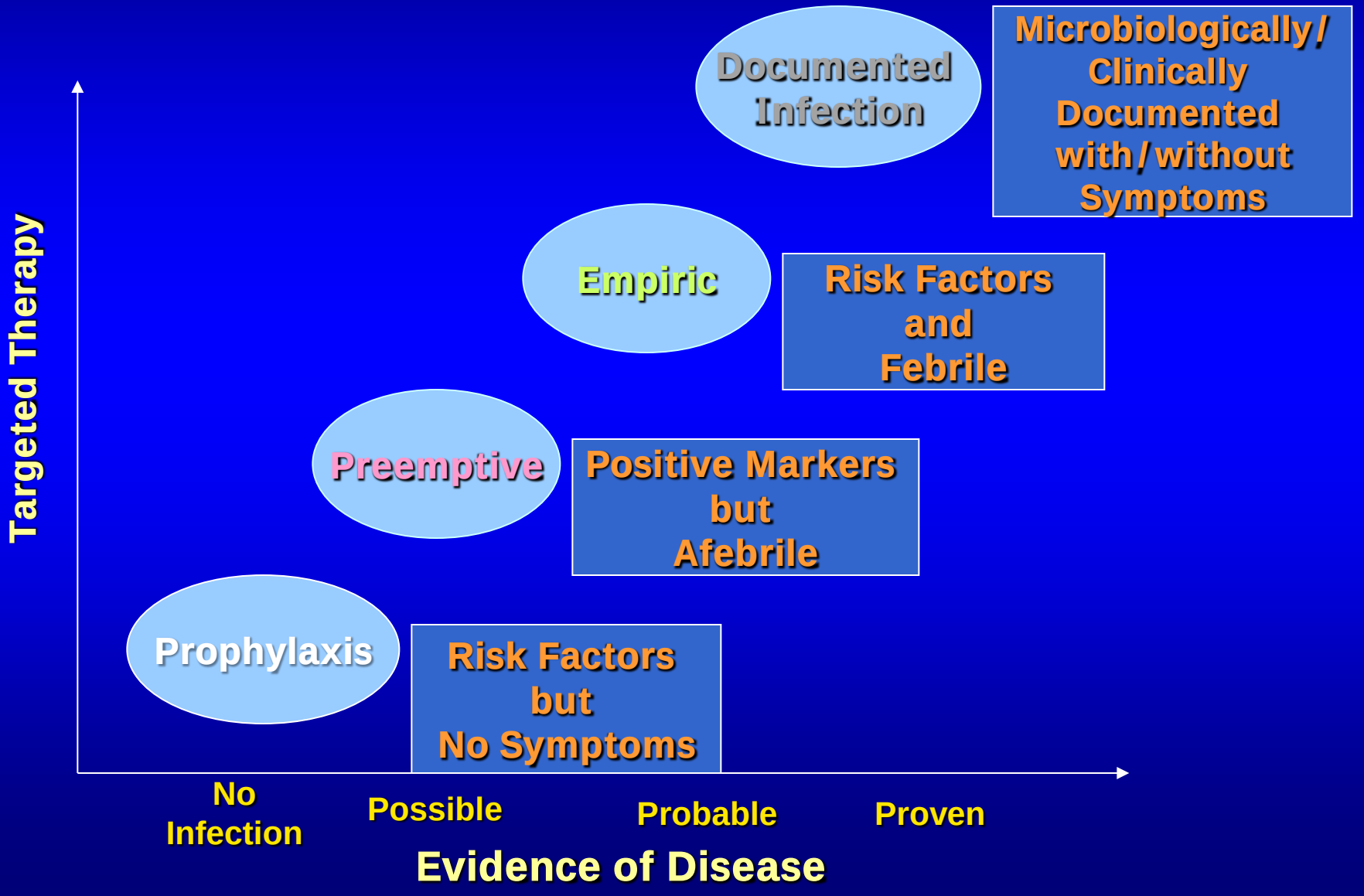
- **Grant / Research Support:**
  - **Astellas, Chimerix, Merck, Pfizer**
- **Consultant (Honoraria paid):**
  - **Astellas, Merck, Pfizer**
- **Speakers Bureau (honoraria paid):**
  - **Astellas, Merck, Pfizer, Sunovion**

# Objectives

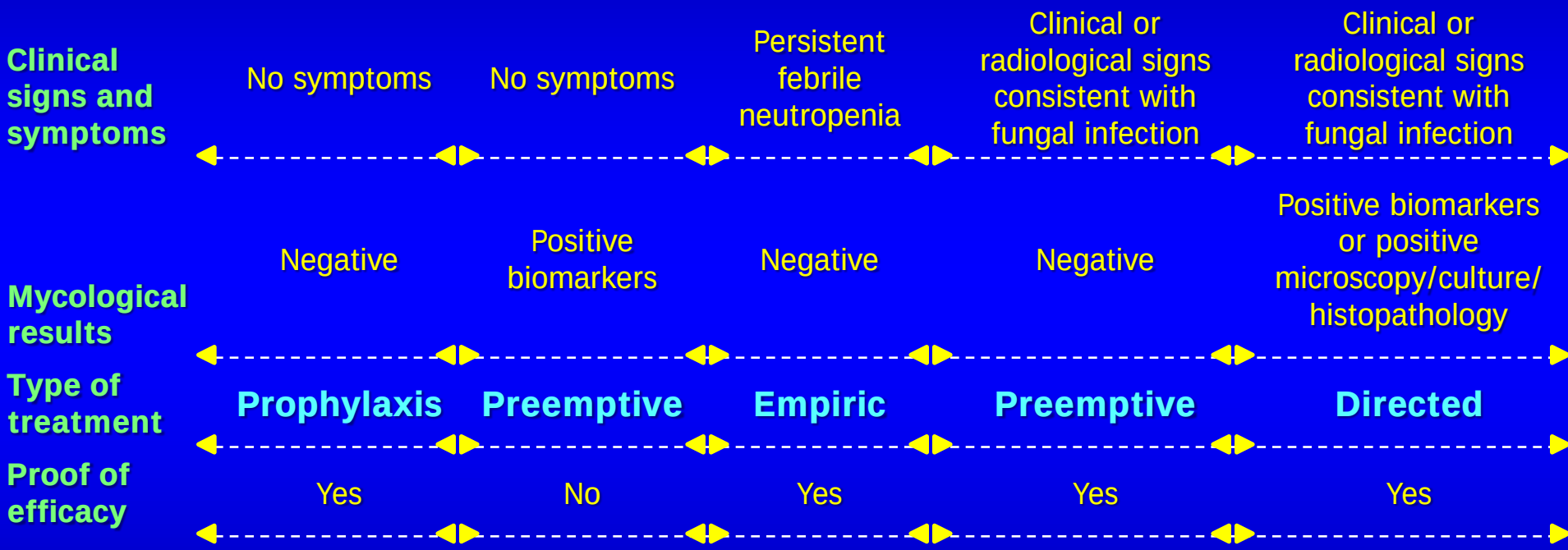
- Review therapeutic strategies for invasive fungal infections (IFIs) in hematological malignancies.
- Discuss the benefits of empiric vs. preemptive therapy.
- Describe therapeutic options for *Candida*, *Aspergillus* and *Mucorales* IFIs.

# Therapeutic Strategies for IFIs

# Treatment Strategies



# Strategies for the Treatment of Invasive Fungal Infections in Cancer Patients

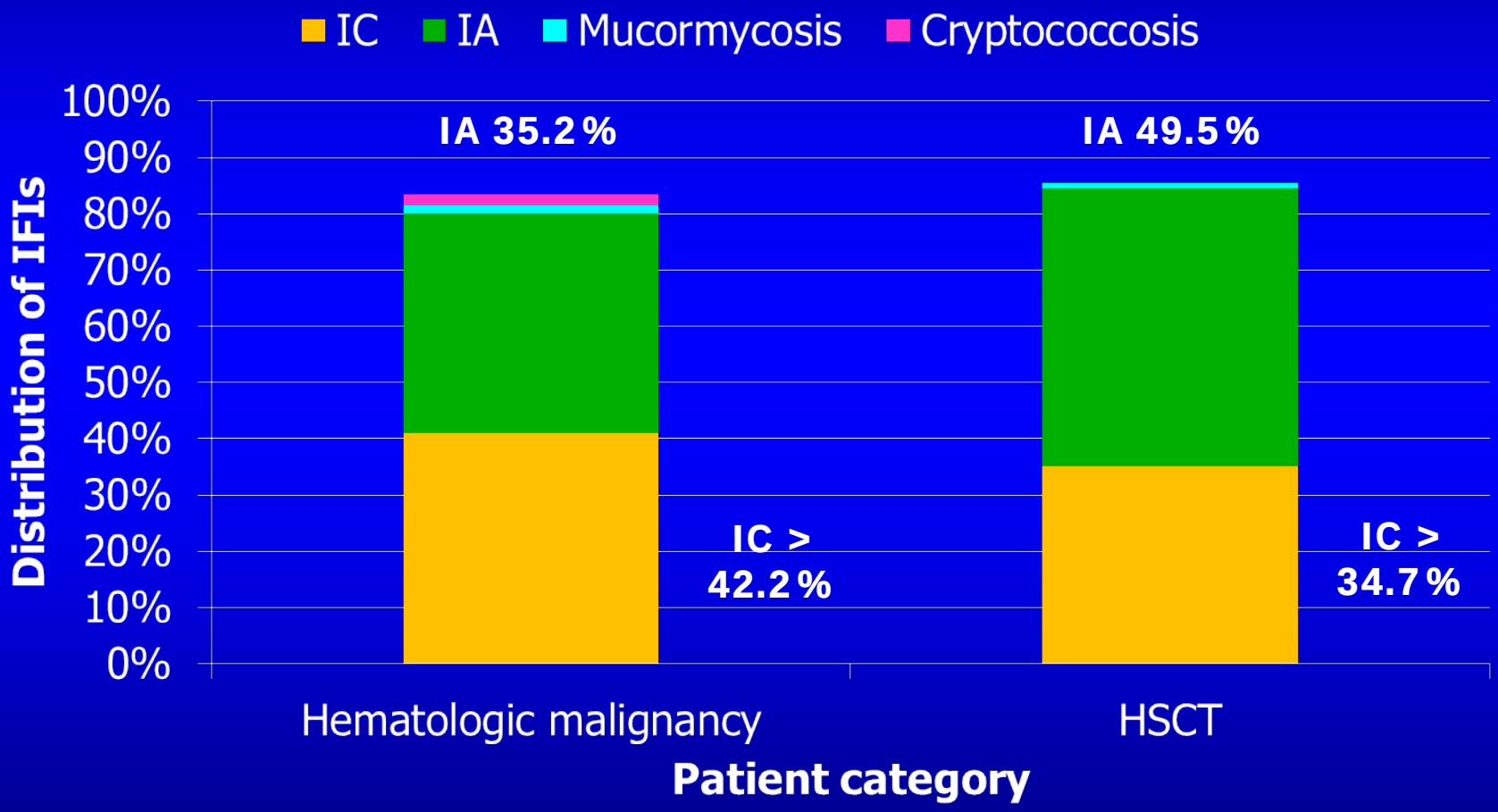



Herbrecht R, Berceanu A. CID 2008;46:886-889

# Burden of Illness of IFIs in Hematological Malignancies

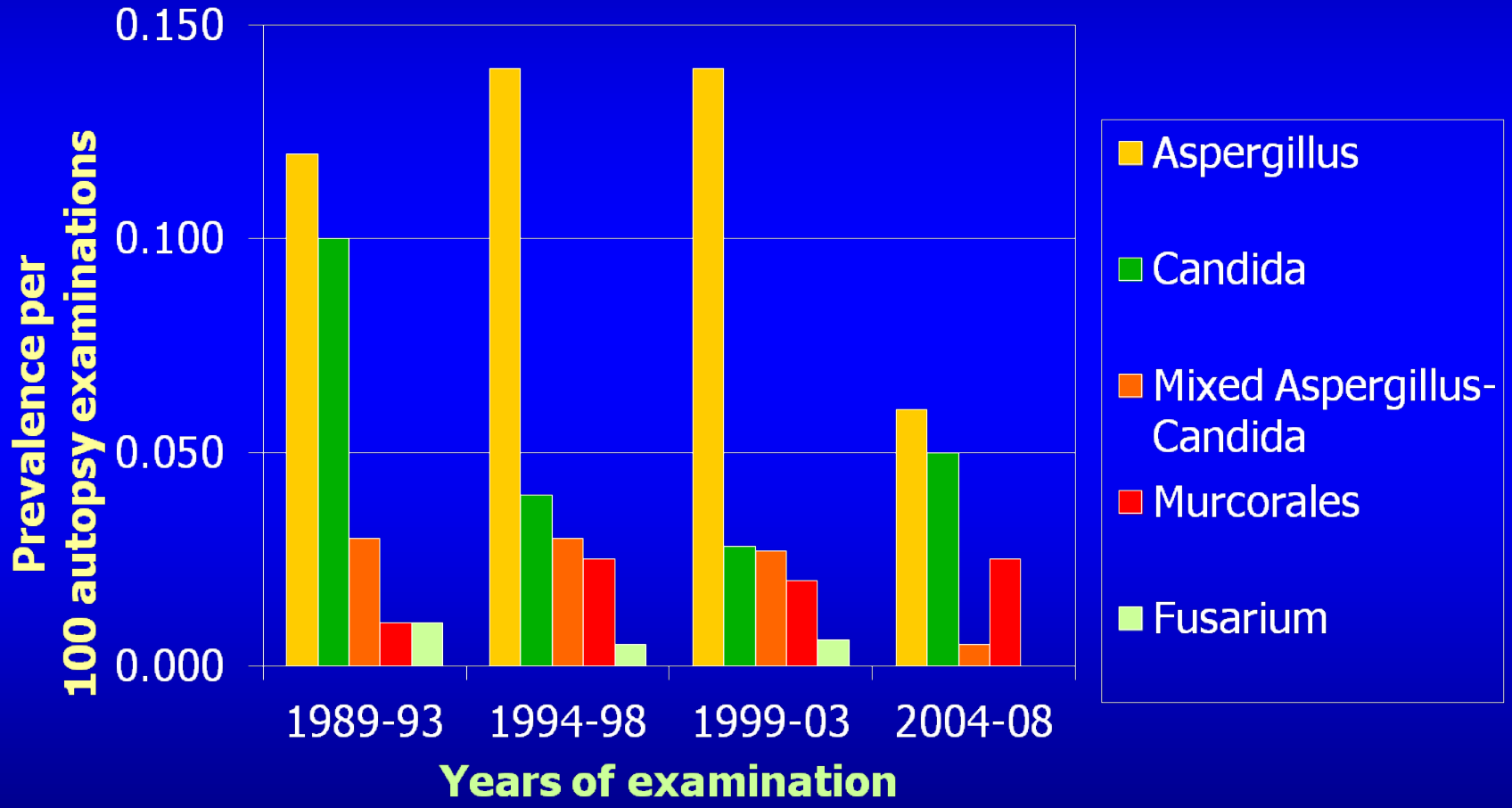
# PATH Alliance Registry: Invasive Fungal Infections 2004-2008

## [7526 IFIs in 6845 Patients (IA=13.3%)]




Azie N et al. Diagn Microbiol Infect Dis 2012;73:293-300

# Prevalence of the 5 Most Common IFIs in Patients with Hematological Malignancies – MD Anderson Autopsy Study




Lewis RE et al. Mycoses 2013;56:638-645

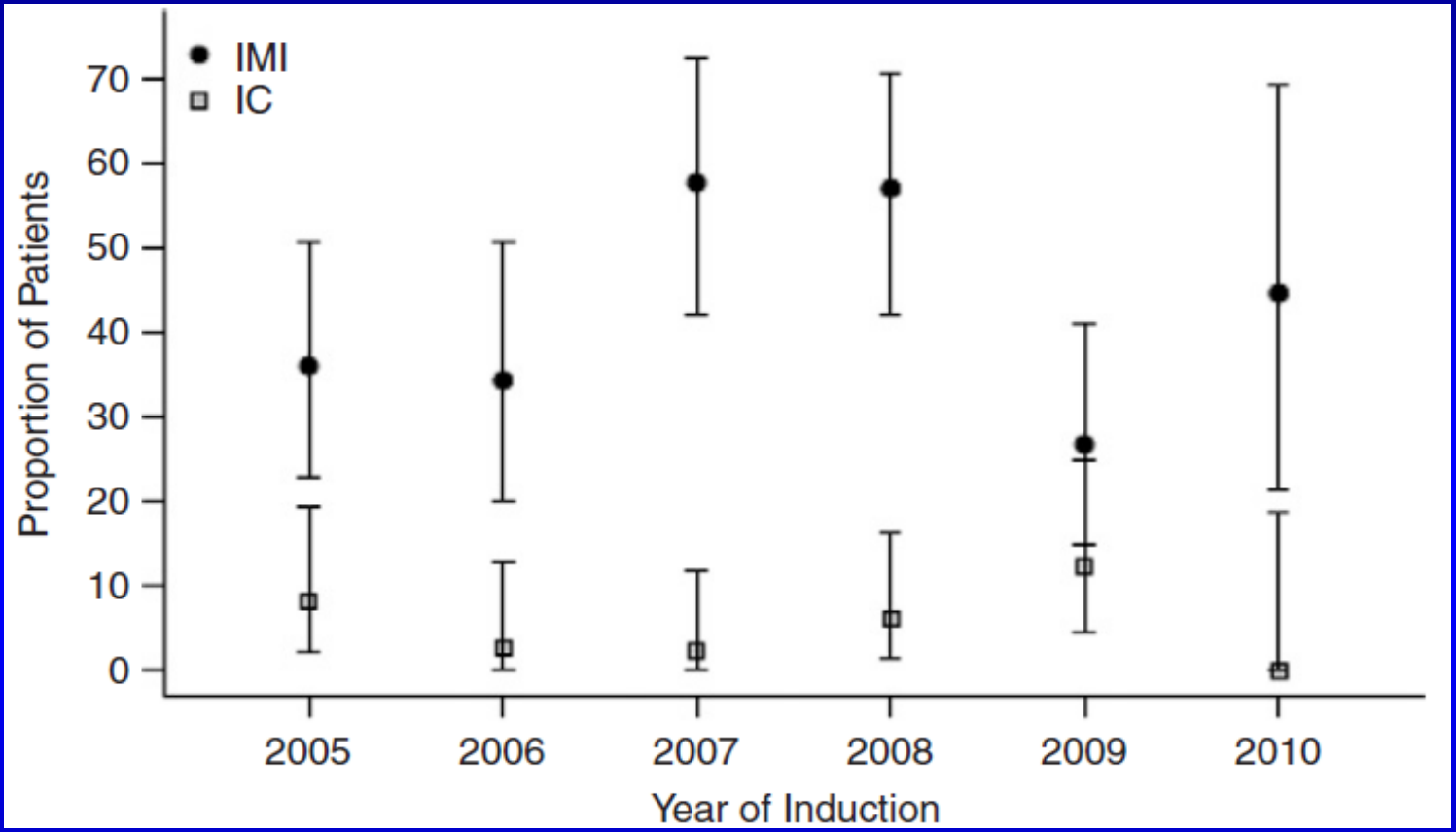
# IMI Trends in Patients with Haematological Malignancies – MD Anderson

| Characteristic | 1989-1993 n=79 (%) | 1994-1998 n=65 (%) | 1999-2003 n=62 (%) | 2004-2008 n=28 (%) | $X^2$ trend *P* value |
|---|---|---|---|---|---|
| **Aspergillosis** | | | | | |
| Culture negative | 54 (68) | 40 (62) | 30 (48) | 13 (46) | 0.01 |
| *A. fumigatus* | 4 (5) | 5 (8) | 8 (13) | 6 (21) | 0.01 |
| *A. terreus* | 4 (5) | 5 (8) | 7 (11) | 0 (0) | 0.99 |
| *A. flavus* | 8 (10) | 3 (5) | 5 (8) | 1 (4) | 0.35 |
| Other | 1 (1) | 0 (0) | 1 (2) | 1 (4) | 0.40 |
| **Fusarium** | 4 (5) | 2 (3) | 4 (6) | 1 (4) | 0.96 |
| **Mucorales** | 4 (5) | 10 (15) | 7 (11) | 6 (21) | 0.04 |

- Drop in autopsy rate – 0.63 autopsies/100 deaths 1989-93 vs. 0.06 in 2004-08 ($p<0.001$)
- *Aspergillus* dropped from 0.12-0.14 to 0.07/100 autopsies 2004-08 ($p=0.04$)
- *Mucorales* increased 0.06 to 0.2/100 autopsies 2004-2008 ($p=0.02$)

Lewis RE et al. Mycoses 2013;56:638-645

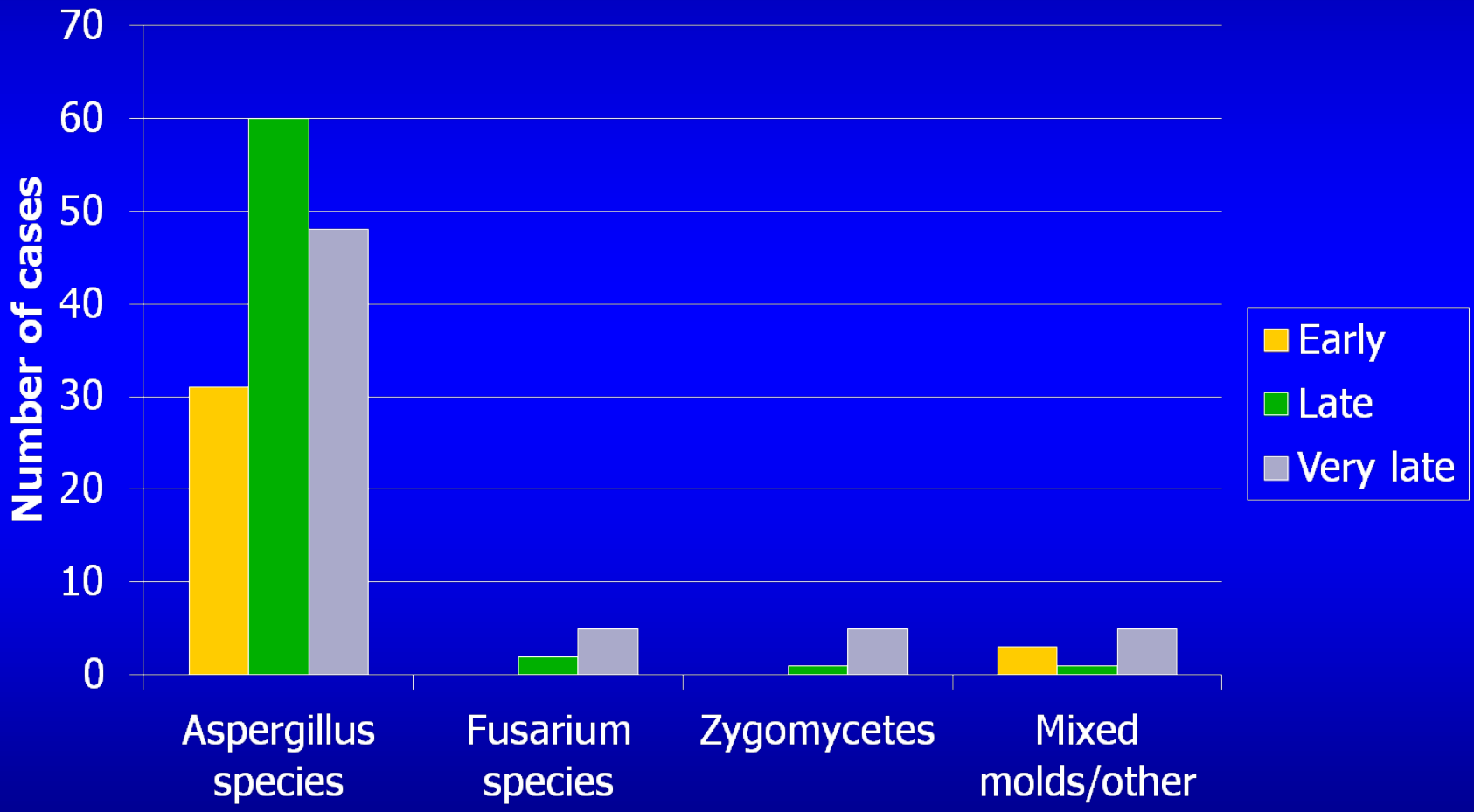
# Incidence of IFIs in AML Patients 1/1/05 – 6/30/10 - Johns Hopkins (N=254)




- N=254 AML patient undergoing induction chemo
- Rate of IFIs = 48.4%
- IC was 5.5%
- IMI was 42.5%
- 6 m mortality with IFI 23.7% (20.6% without IFI)

Neofytos D et al. Diagn Microbiol Infect Dis 2013;73:144-149

# Timing of Mold Infections in Allo-BMT (Seattle), 1998-2002

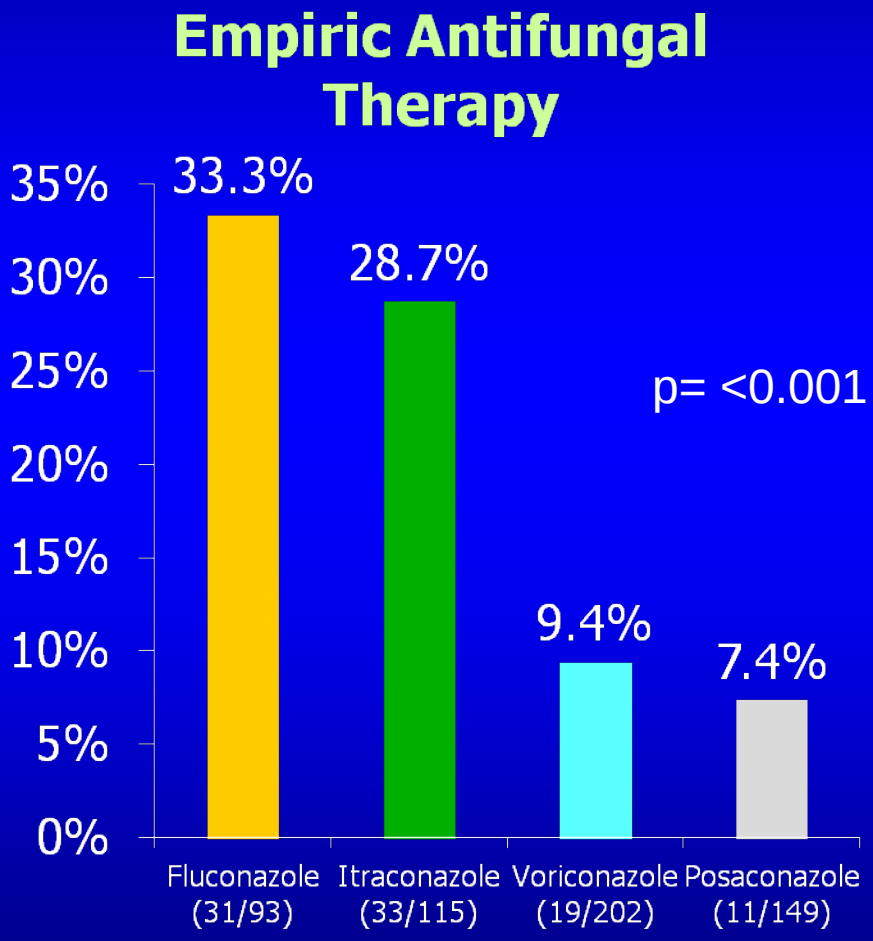


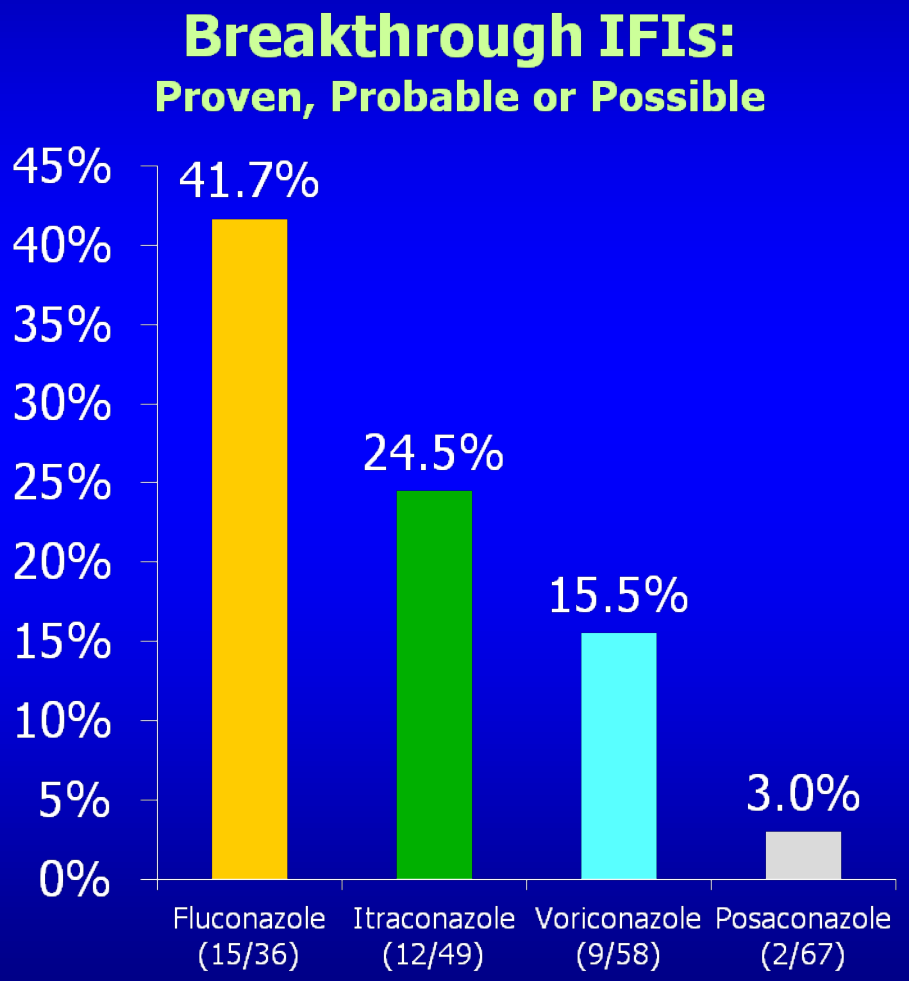

**early: 0-40 d; late: 41-100 d; very late >100 d*

Garcia-Vidal C et al. CID 2008;47:1041-1050

# Impact of Prophylaxis

# Prophylaxis in AML/MDS Over 12-Year Period, 1998-2010 (n=216)




Ananda-Rajah MR et al. Haematologica 2012;97:459-463

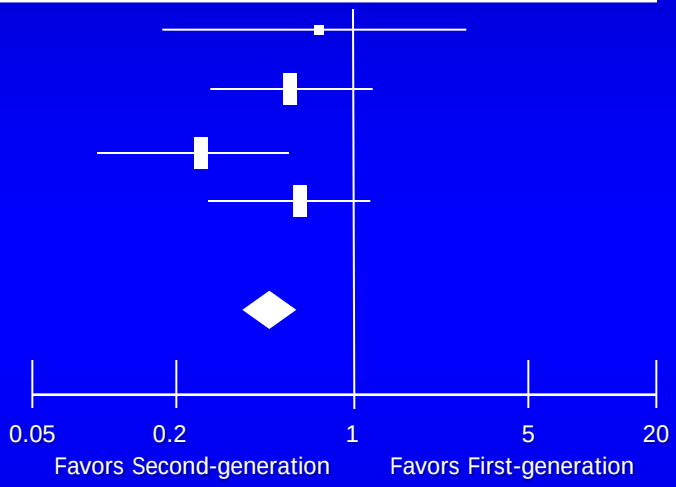
# Azole Prophylaxis 1st vs. 2nd Generation Azoles - Meta-analysis:

## Proven & Probable IFIs

| Study or subgroup | Second-generation Events | Second-generation Total | First-generation Events | First-generation Total | Weight | Odds ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Marks 2011 | 3 | 224 | 5 | 241 | 6.1% | 0.64 (0.15, 2.71) |
| Wingard 2010 | 14 | 305 | 24 | 295 | 29.7% | 0.54 (0.28, 1.07) |
| Cornely 2007 | 7 | 304 | 25 | 298 | 31.5% | 0.26 (0.11, 0.60) |
| Ullmann 2007 | 16 | 301 | 27 | 299 | 32.7% | 0.57 (0.30, 1.07) |
| Total (95% CI) | | 1134 | | 1133 | 100.0 % | 0.47 (0.32, 0.69) |
| Total events | 40 | | 81 | | | |

Heterogeneity: $Chi^2=2.59$, $df=3$ ($P=0.46$); $I^2=0\%$

Test for overall effect $Z=3.84$ ($P=0.0001$)



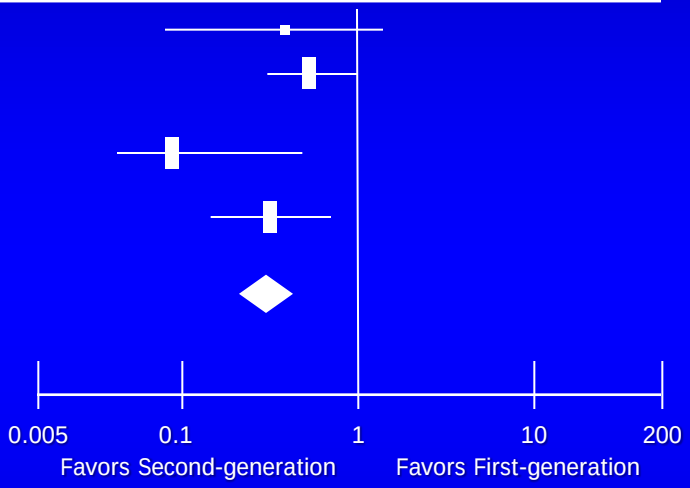

Ping B et al. Ann Hematol 2013;92:831-839

# 1st vs. 2Nd Generation Azoles: Meta-analysis: Cases of IA

| Study or subgroup | Second-generation Events | Second-generation Total | First-generation Events | First-generation Total | Weight | Odds ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Marks 2011 | 1 | 224 | 5 | 241 | 7.7% | 0.21 (0.02, 1.83) |
| Wingard 2010 | 9 | 305 | 17 | 295 | 27.0% | 0.50 (0.22, 1.13) |
| Cornely 2007 | 2 | 304 | 20 | 298 | 32.3% | 0.09 (0.02, 0.40) |
| Ullmann 2007 | 7 | 301 | 21 | 299 | 33.1% | 0.32 (0.13, 0.75) |
| Total (95% CI) | | 1134 | | 1133 | 100.0 % | 0.28 (0.17, 0.48) |
| Total events | 19 | | 63 | | | |

Heterogeneity: $Chi^2=4.18$, $df=3$ ($P=0.24$); $I^2=28\%$

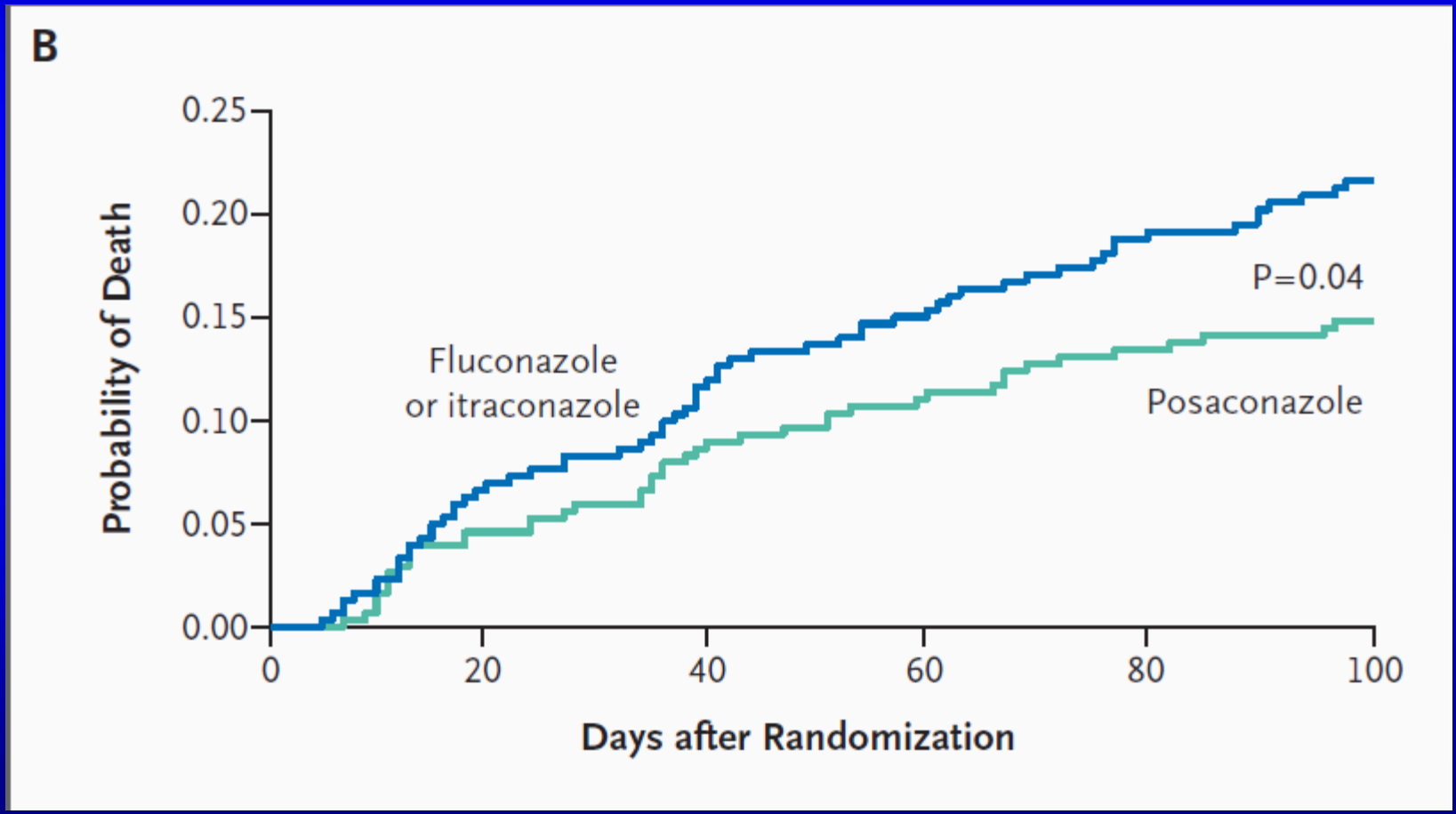
Test for overall effect $Z=4.73$ ($P<0.00001$)




Ping B et al. Ann Hematol 2013;92:831-839

# Antifungal Prophylaxis: Neutropenia in AML

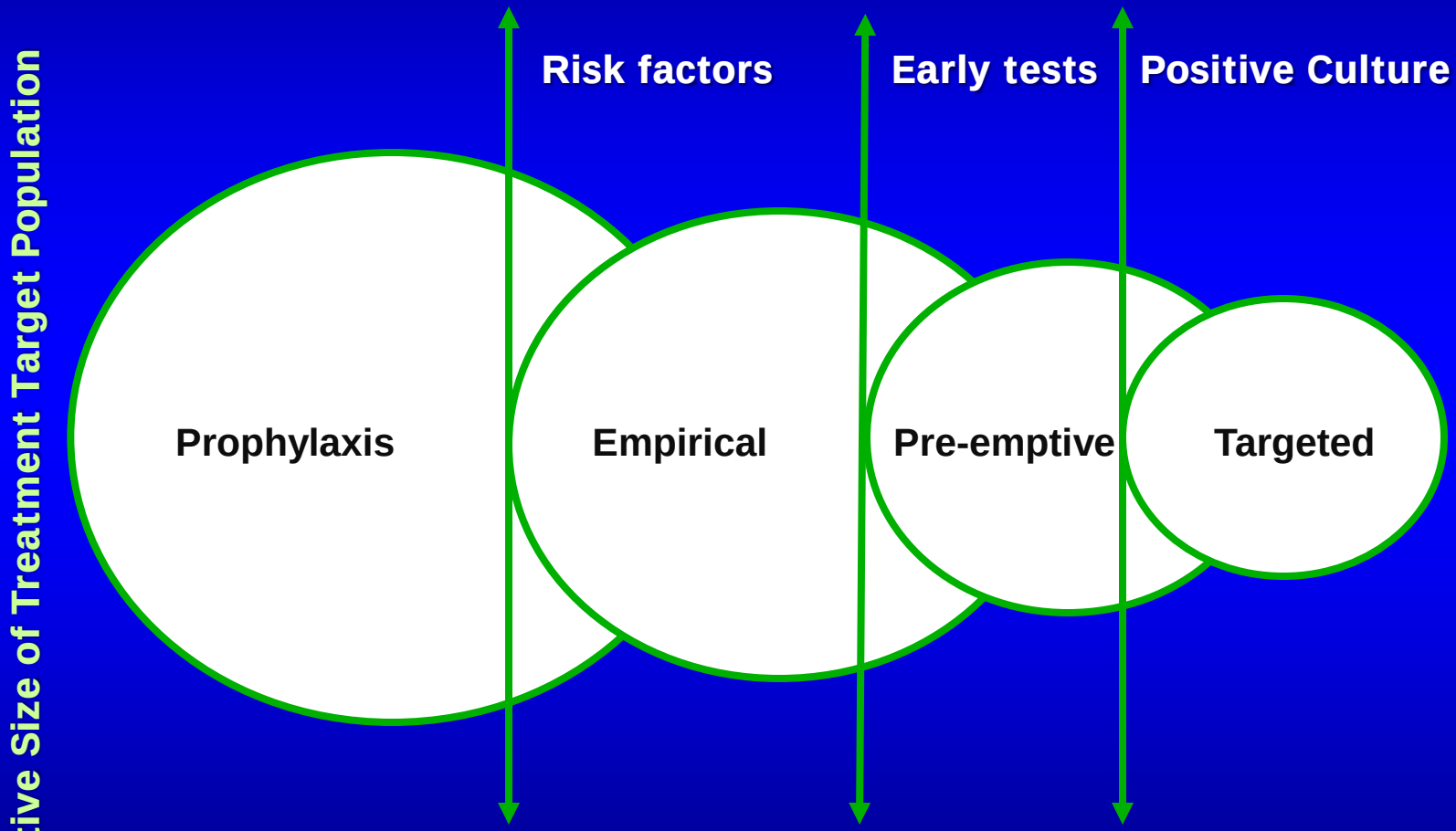
*Probability of Death: Fluconazole >Posaconazole*




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

# Empiric vs. Preemptive Antifungal Therapeutic Strategies

# Strategies for Treatment of IFIs




Zaragosza R et al. Therapeutics and Clinical Risk Management 2008;4:1261-1280

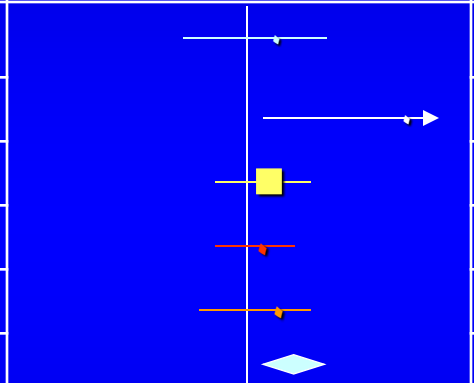
# Empiric Antifungal Therapy

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

**Comparison:** All Antifungals vs. Null Control – Including patients with suspected infection

**Outcome:** Defervescence

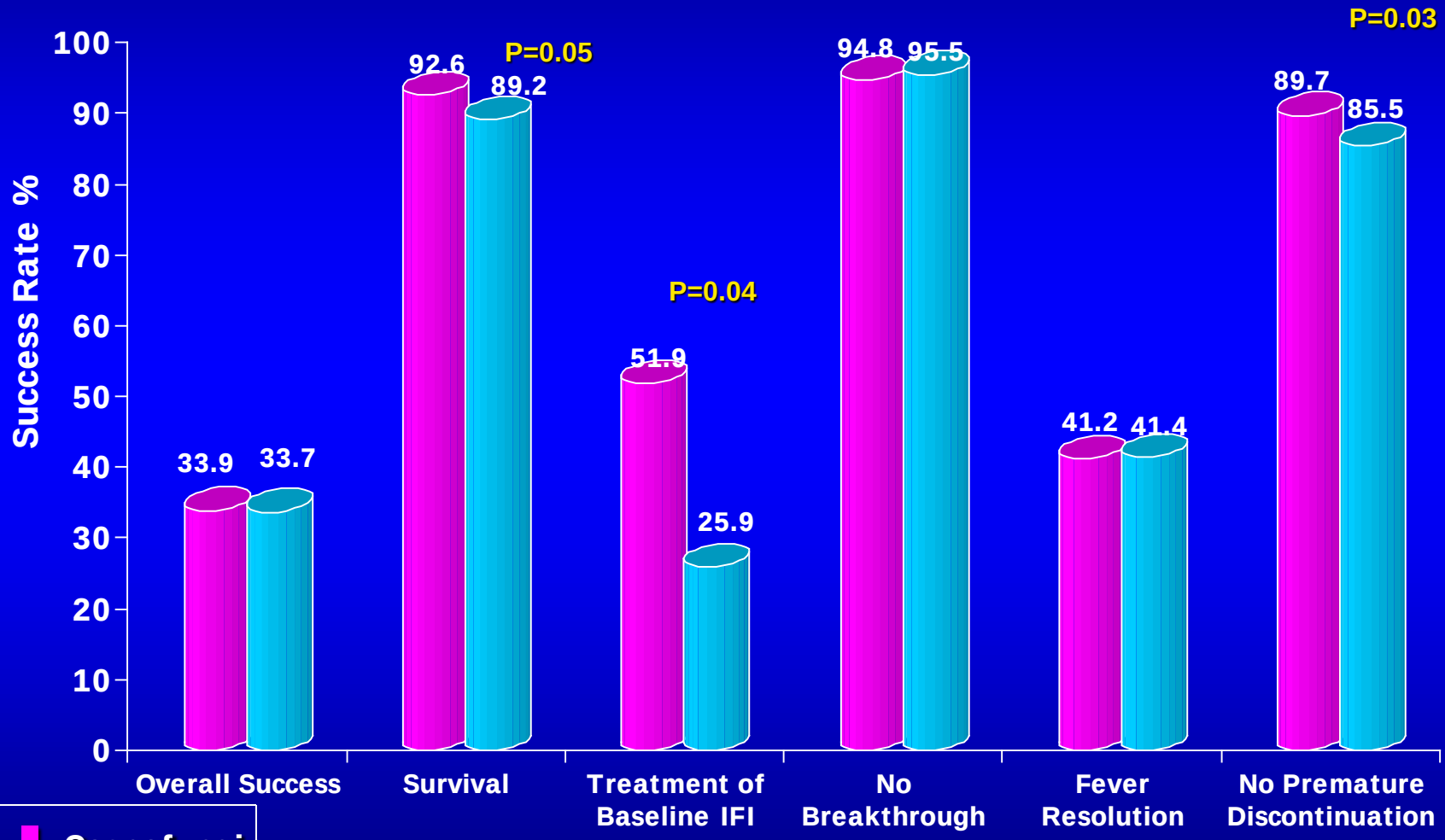
| Study or sub-category | Antifungals n/N | Null Control n/N | OR (random) 95% CI | Weight % | OR (random) 95% CI |
|---|---|---|---|---|---|
| Pizzo 1982 | 13/18 | 9/16 | | 10.95 | 2.02 (0.48, 8.43) |
| Lazarus 1984 | 7/8 | 0/6 | | 2.12 | 65.00 (2.24, 1887.35) |
| EORTC 1989 | 47/68 | 34/64 | | 34.95 | 1.97 (0.97, 4.02) |
| Goldstone 1994 | 41/64 | 32/60 | | 34.35 | 1.56 (0.76, 3.20) |
| Fukuda 1994 | 27/37 | 16/25 | | 17.63 | 1.52 (0.51, 4.53) |
| Total | 195 | 171 | | 100.00 | 1.88 (1.14, 3.08) |



Total (95% CI)
Total events: 135 (Antifungals), 91 (Null Control)
Test for heterogeneity: $Chi^2 = 4.72$, df=4 (P=0.32), $I^2 = 15.3\%$
Test for overall effect: Z=2.50 (P=0.01)

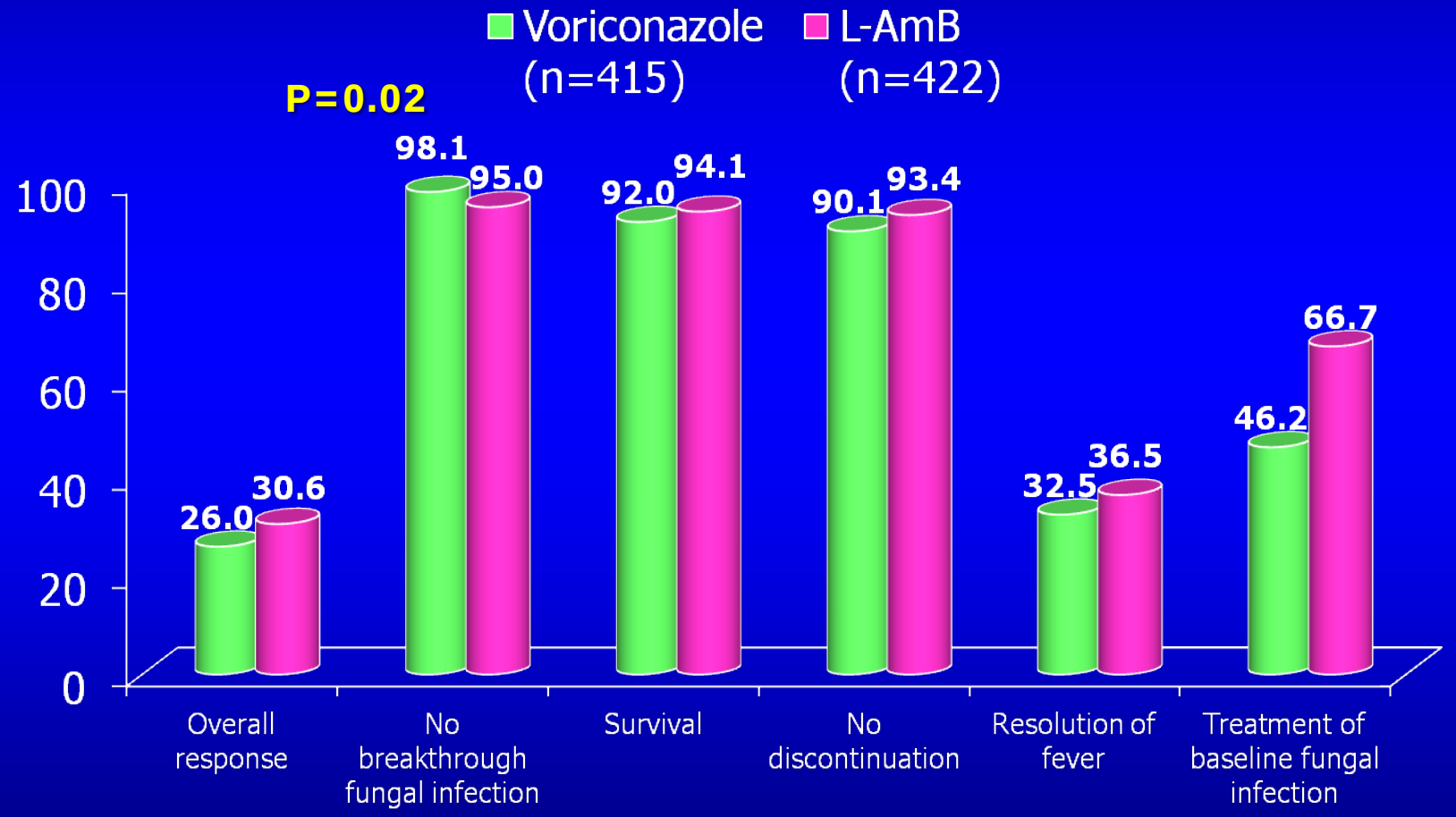
0.01 0.1 1 10 100
Favours control Favours treatment

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




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

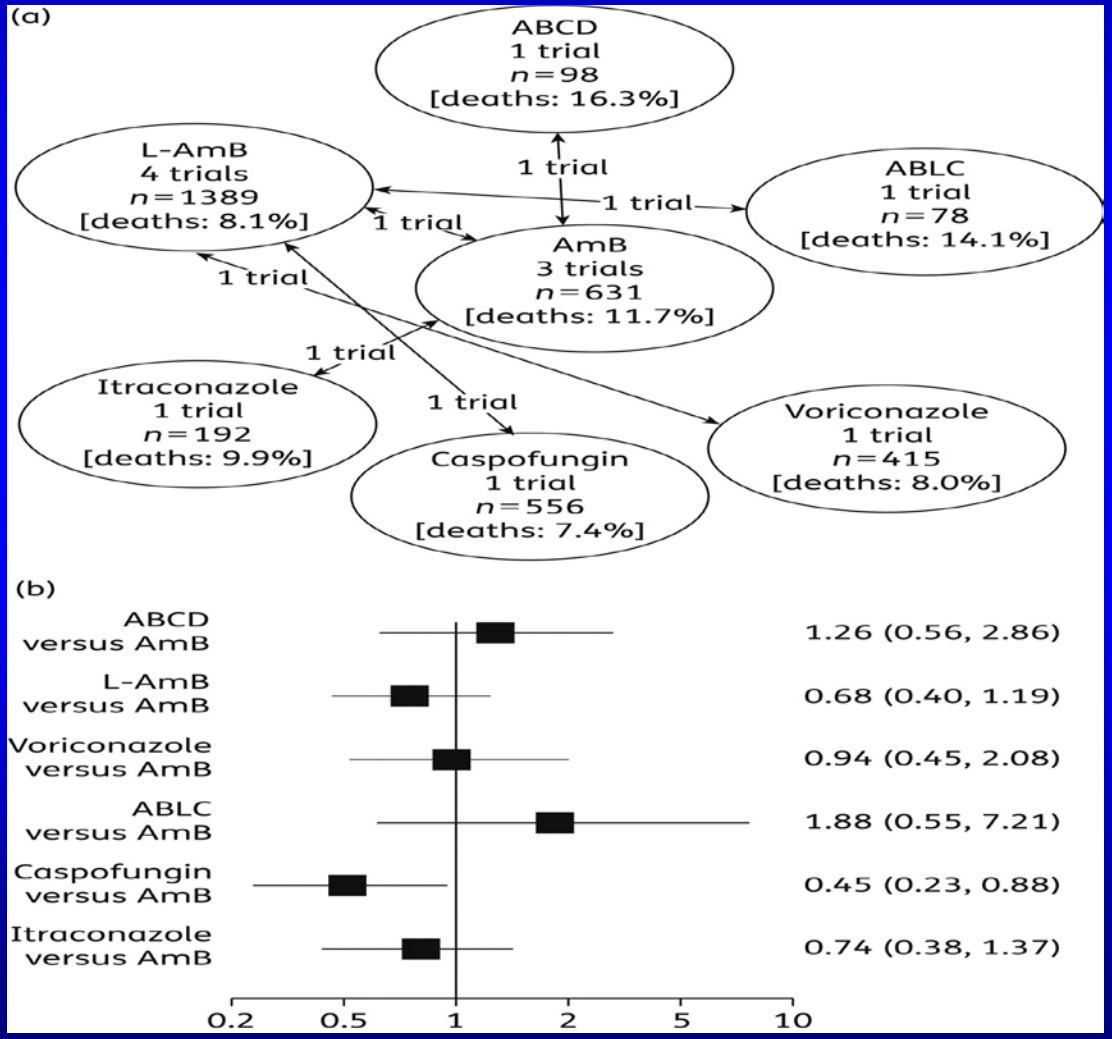
# Voriconazole vs. L-AmB for Empiric Antifungal Therapy in FNE




Walsh TJ et al. New Engl J Med 2002;346(4):225-234

# Survival in Empiric Antifungal Therapy

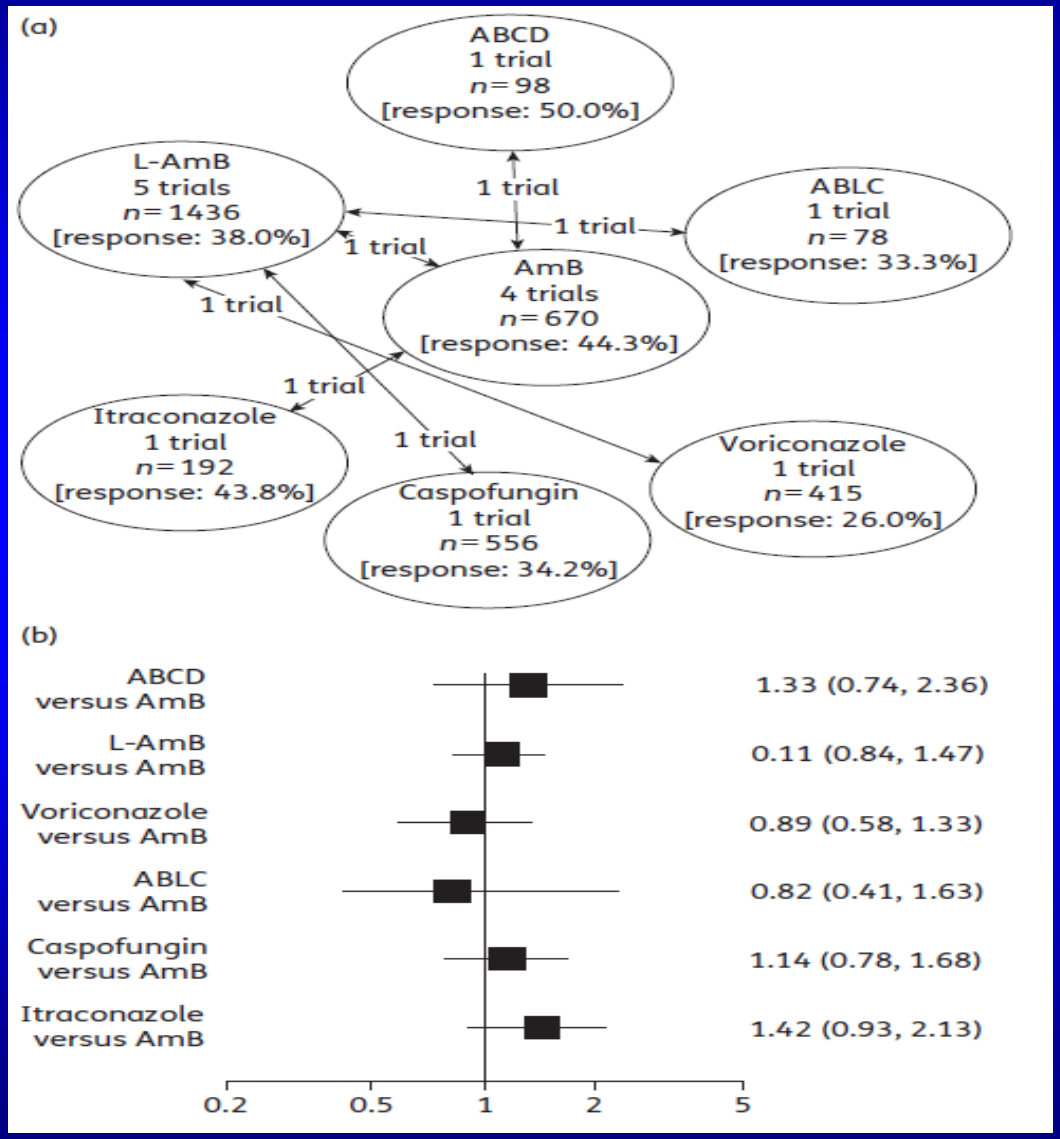
- Odds ratio >1 indicates benefit to AmB for survival
- Caspofungin superior survival vs. AmB




Freemantle N et al. J Antimicrob. Chemother 2011;66:i25-i35

# Empiric Therapy Response

- Odds ratio <1 indicates benefit to AmB for response
- No clear benefit of any regimen vs. AmB




Freemantle N et al. J. Antimicrob. Chemother. 2011;66:i25-i35

# Preemptive Antifungal Therapy

# Empiric vs. Preemptive Antifungal Therapy in Neutropenic Fever

- Empiric therapy employs fever as threshold to initiate AF therapy – fever non-specific
- Open label randomized non-inferiority trial
- Patients: hematological malignancy or autologous-HSCT with neutrophils $<0.5X10^9/L$ for $\geq 10$ days
- Compared:
  - Empiric therapy (AF therapy initiated for persistent fever @ 4 days or recurrent fever days 4 to 14)

  vs.
  - Preemptive therapy (AF therapy started at any time after 4 days of fever with imaging of pneumonia, sinusitis, shock or other clinically documented site of infection or galactomannan assay $\geq 1.5$ with accompanying CXR or CT scan)

Cordonnier C et al. CID 2009;48:1042-1051

# Empiric vs. Pre-emptive Antifungal Therapy in Neutropenic Fever

- AF therapy:
  - AmB 1 mg/kg/d IV for pt with CrCl 40-59 ml/min if no concomitant nephrotoxins or ≥60 ml/min if concomitant nephrotoxic drugs

  or

  - L-AmB 3 mg/kg/d IV if CrCl 20-39 ml/min or 40-59 ml/mi if concomitant nephrotoxic drugs
- End point: survival 14 days after recovery from neutropenia
- More IFIs in pt receiving induction chemo vs. consolidation or a-BMT 15 (16.4%) vs. 2 (3.9%), p<.01

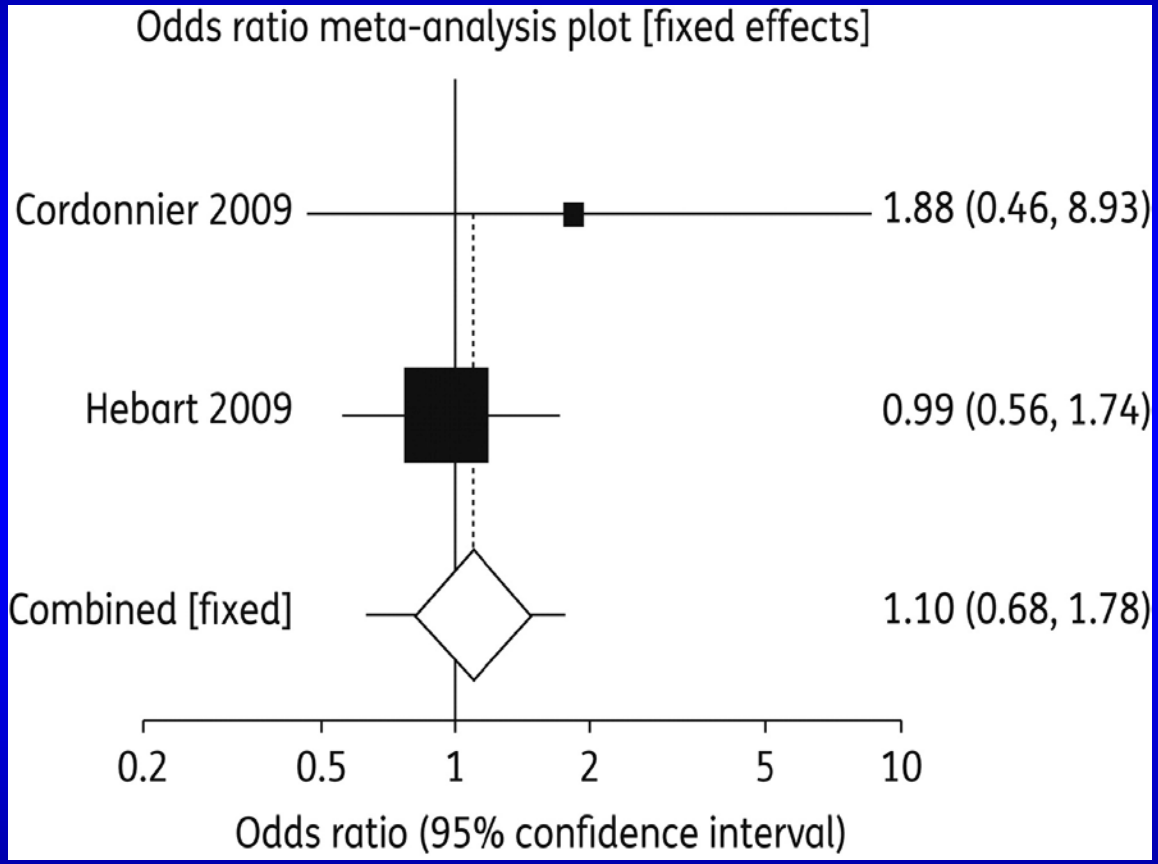
Cordonnier C et al. CID 2009;48:1042-1051

# Empiric vs. Pre-emptive Antifungal Therapy in Neutropenic Fever

| Parameter | Empiric N=150 | Pre-emptive N= 143 | P value |
|---|---|---|---|
| Treated with AF therapy | 92/150 (61.3%) | 56/143 (39.2%) | <.001 |
| Duration of fever before AF therapy median days | 7 | 13 | <.01 |
| Duration of AF therapy mean days | 7.0 +/-8.5 | 4.5 +/-7.3 | <.01 |
| Proven & probable IFIs | 2.7% (4/150) | 9.1% (13/143) | <.02 |
| Cost of AF therapy € | 2252 +/-4050 | 1478 +/-3329 | <.001 |
| LOS mean days | 30.3 +/-10.5 | 30.3 +/-10.2 | NS |
| Aspergillus infections | 4 | 8 | NS (.108) |
| Survival | 97.3% | 95.1% | NS |

Cordonnier C et al. CID 2009;48:1042-1051

# Pre-emptive vs. Empiric for Invasive Mold Disease




- Odds ratio <1 indicates benefit of preemptive therapy for survival

Freemantle N et al. J Antimicrob. Chemother 2011;66:i25-i35

# Treatment of IC & IA

# Canadian C/IC Guidelines

| Therapeutic strategy | Antifungal therapeutic options | |
|---|---|---|
| | Preferred | Second line |
| **Empiric therapy:** | | |
| Neutropenic | IV LFAmB 3 mg/kg/day (A-I); or caspofungin 70 mg on day 1, then IV 50 mg daily (A-I); or IV AmB-d 0.6 mg/kg/day to 1.0 mg/kg/day (B-II in the absence of risk factors for nephrotoxicity) | Fluconazole 800 mg or IV/oral 400 mg/day (for less severely ill patients [B-II]); or voriconazole 6 mg/kg every 12 h for 24 h, then IV doses of 4 mg/kg every 12 h or oral doses of 200 mg twice daily (if risk of mould infection present) (B-I) |

Bow EJ et al. CJIDMM 2010;21:e122-e150

# Canadian C/IC Guidelines

| Therapeutic strategy | Antifungal therapeutic options | |
|---|---|---|
| | Preferred | Second line |
| Neutropenic therapy for microbiologically or histologically documented C/IC | IV AmB-d 0.6 mg/kg/day to 1.0 mg/kg/day (A-I); or IV LFAmB 3 mg/kg/day (A-I); or IV ECH (IV anidulafungin 200 mg → 100 mg daily [B-III]; or IV caspofungin 70 mg → 50 mg daily [A-I]; or IV micafungin 100 mg daily [B-III] | Fluconazole 800 mg or IV/oral 400 mg/day daily (for less severely ill patients [A-III]); or IV voriconazole 6 mg/kg every 12 h for 24 h then 4 mg/kg every 12 h or oral doses of 200 mg twice daily (if risk of mould infection is present) (B-I) |

Bow EJ et al. CJIDMM 2010;21:e122-e150

# New Formulations

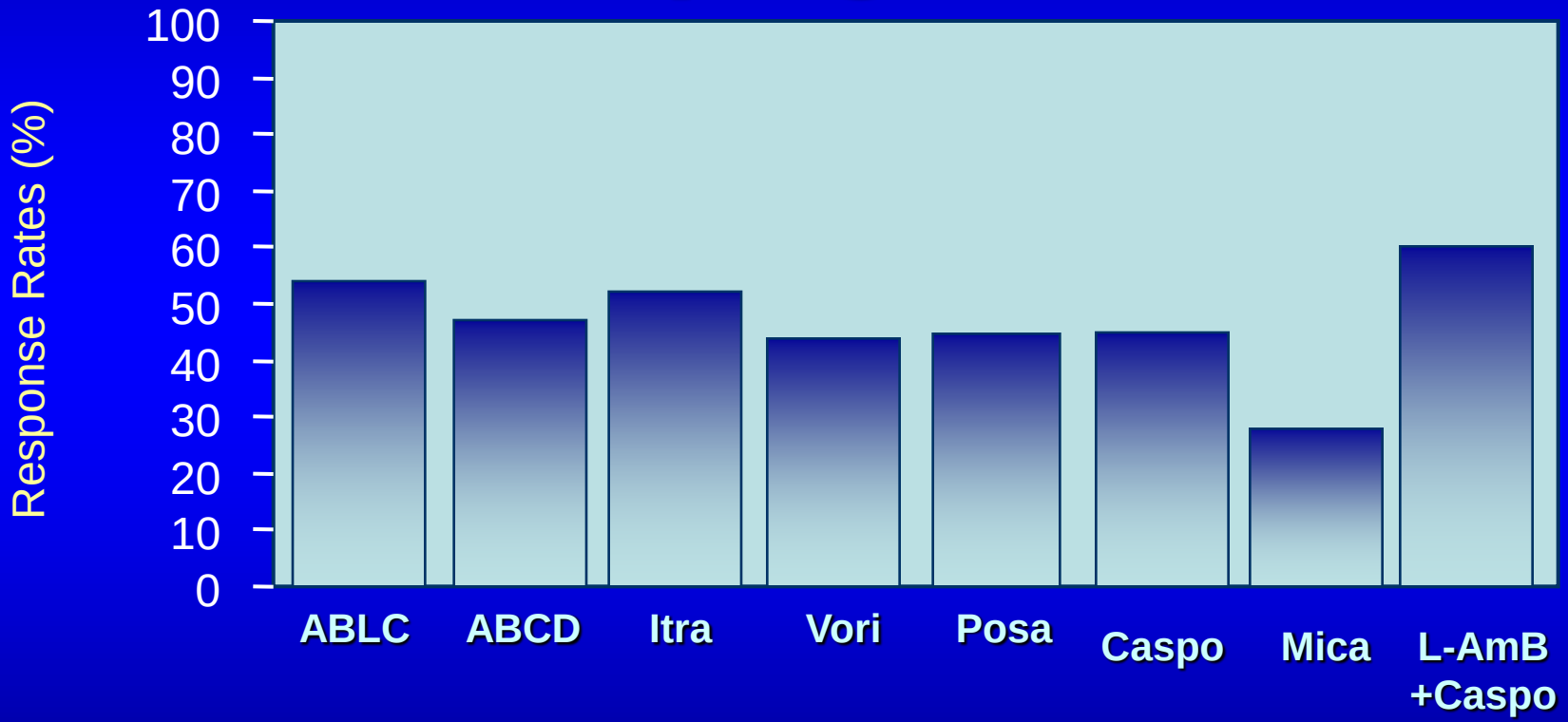
- Posaconazole po tablets – prophylaxis or treatment 300 mg daily (3 x 100 mg)
- Administered fasting or irrespective of food
- Posaconazole IV formulation 300 mg q day

# Antifungal Therapy for IA – 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

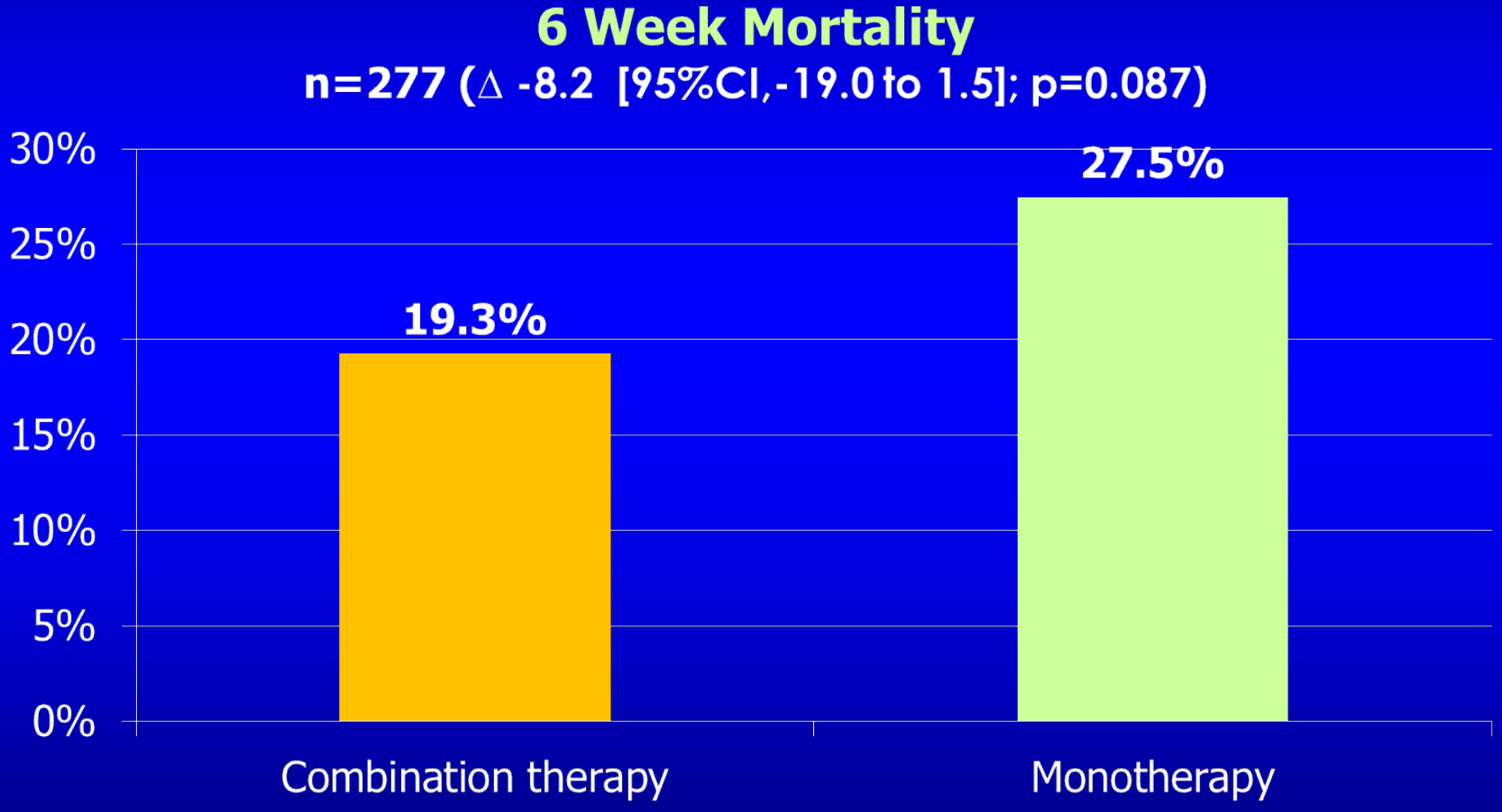
# Clinical Success in the Treatment of Refractory Aspergillosis




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

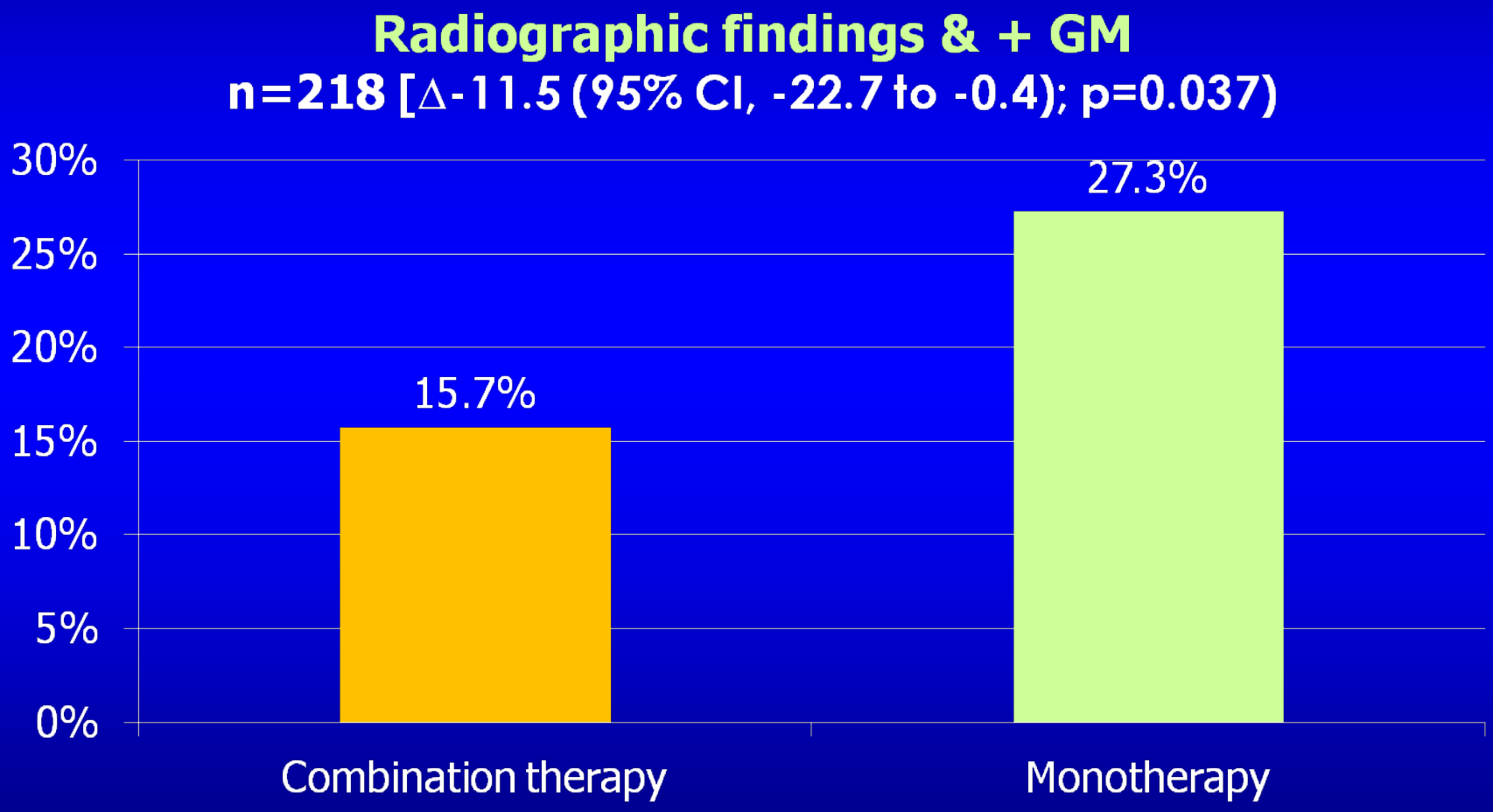
# Combination Therapy for IA

# Voriconazole & Anidulafungin Combination vs. Voriconazole Therapy for Treatment of IA (Hematologic Malignancy & HSCT)




Marr KA et al. Ann Intern Med 2015;162:81-89

# Voriconazole & Anidulafungin Combination vs. Voriconazole Therapy for Treatment of IA (Hematologic Malignancy & HSCT)




Marr KA et al. Ann Intern Med 2015;162:81-89

# Therapeutic Drug Monitoring (TDM) For Voriconazole

- RCT of voriconazole levels adjusted via TDM to target level (1.0-5.5 mg/L) vs. fixed standard dose (6 mg/kg BID → 4 mg/kg BID); most of pt. hematologic disease.
- Lower adverse events with TDM group 45 vs. 17% (p=.02).
- Complete or partial response in TDM group 81% vs. 57% in standard dose group (p=.04).

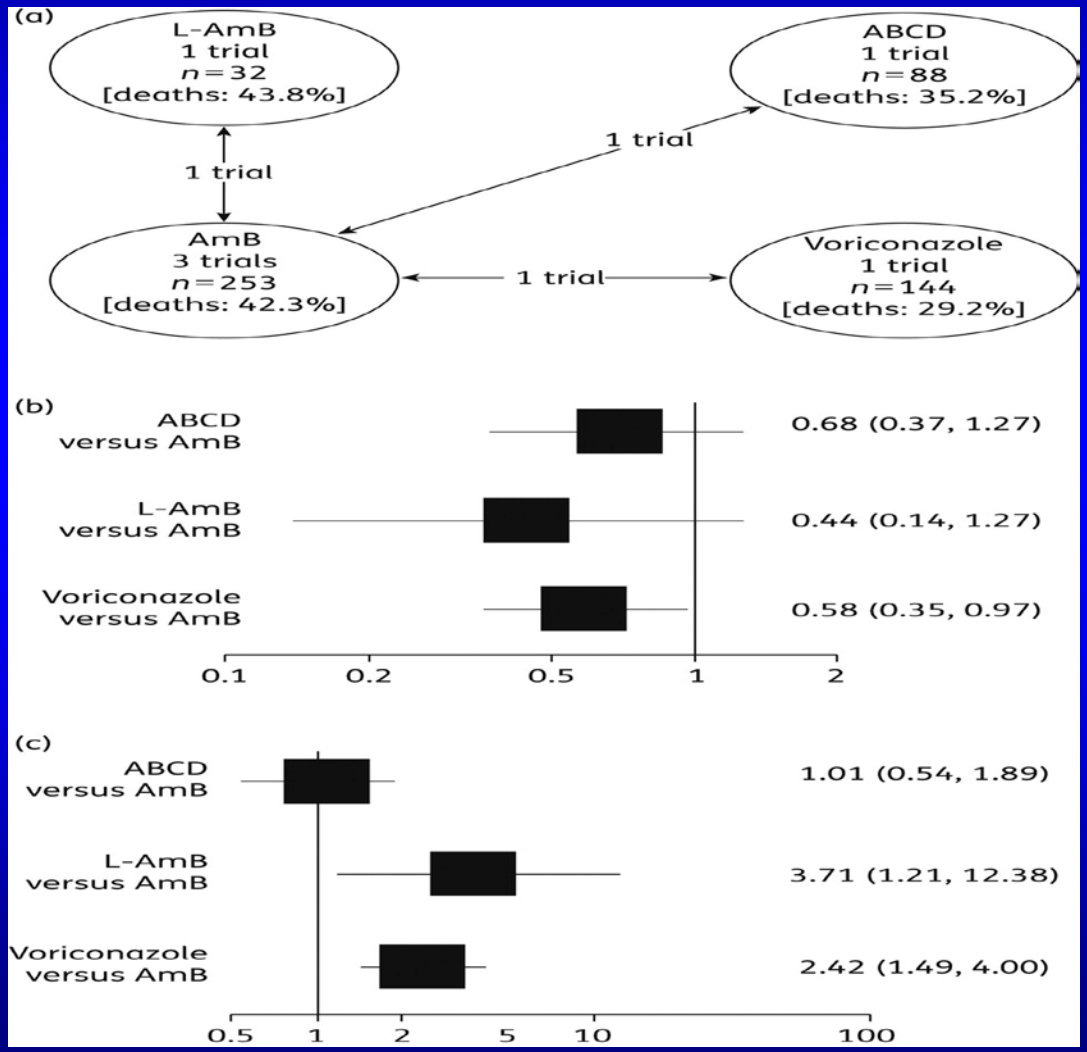
Kim WB et al. CID 2012;55:1080-1087

- Canadian TDM Guidance: For efficacy: voriconazole prophylaxis level >0.5 mg/L; treatment level 1.5 to 5.5 mg/L; toxicity associated with >5.5 mg/L.
- TDM for posaconazole not usually required (only when using PPIs): prophylaxis level >0.7 mg/L & therapy 1.0-1.5mg/L.

Laverdiere M et al. CJIDMM 2014;25:327-343

# Treatment of Documented Infection

- (b) Odds ratio >1 indicates survival benefit to AmB.
- (c) Odds ratio <1 indicates response benefit for AmB.




Survival

Response

Freemantle N et al. J. Antimicrob. Chemother. 2011;66:i25-i35

# Treatment of Mucormycosis in Adult Patients (ESCMID)

| Population | Intention | Intervention | SoR | QoE |
|---|---|---|---|---|
| **First-line therapy** | | | | |
| 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<br>A | IIu<br>IIu |
| | To cure and to increase survival rates | L-AmB ≥5 mg/kg | | |
| CNS | To cure | L-AmB 10 mg/kg, initial 28 days | A | II |
| Any | To cure | Posconazole 4 x 200 mg/day or 2 x 400 mg/day | B | IIu |
| **Salvage therapy** | | | | |
| Any | To cure | Posaconazole + L-AmB | C | III |

Cornely OA et al. Clin Microbiol Infect 2014;20(S3):5-26

# Summary

- Various therapeutic strategies can be used for the prevention and treatment of IFIs in patients with hematological malignancies.
- Empiric antifungal therapy is more widely used than preemptive therapy and may produce better survival; the preemptive strategy permits more directed therapy.
- New formulations of antifungal therapy and the use of combination therapy may be useful for certain types of IFIs.