

# **When is Combination Antifungal Therapy Warranted in the ICU?**

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# Objectives

- 1. Review evidence that supports use of combination antifungal therapy.**
- 2. Discuss combinations that may be employed.**
- 3. Identify clinical situations and populations where combination antifungal therapy would be useful.**

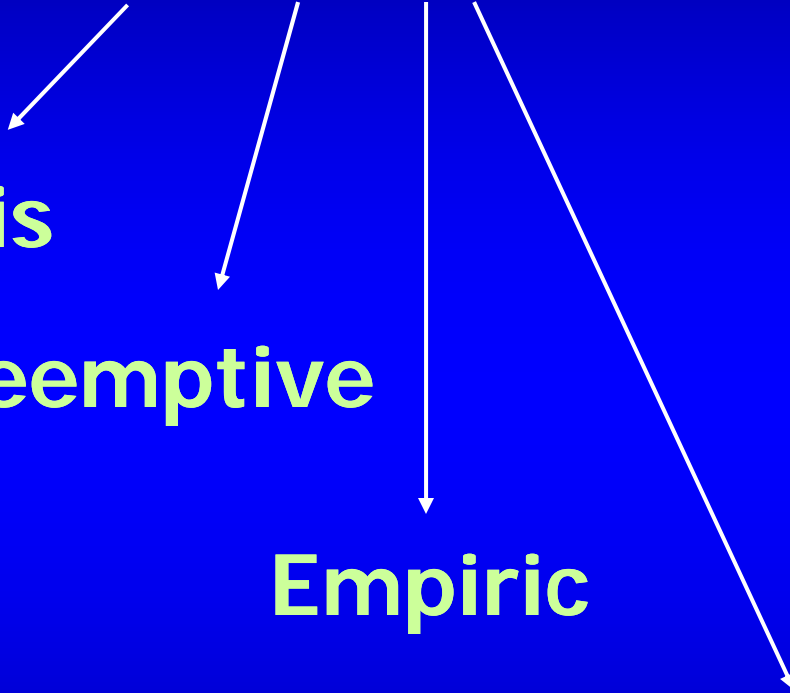
# Antifungal Therapy in Patients

Prophylaxis

Preemptive

Empiric

Documented



# Definition of Combination Antifungal Therapy

- Combination antifungal therapy = use of 2 or more antifungal agents (of different classes) together for treatment of invasive fungal infection.
- Why do it?
  - ◆ Theoretical reason:
    - synergistic (use less but enhanced efficacy & ↓ toxicity)
    - vs.
    - additive
    - vs.
    - antagonistic.
  - ◆ Decreased resistance
  - ◆ Pre-clinical evidence (animals) - not to be discussed.
  - ◆ Clinical evidence.
- What to use?
- When to use it?

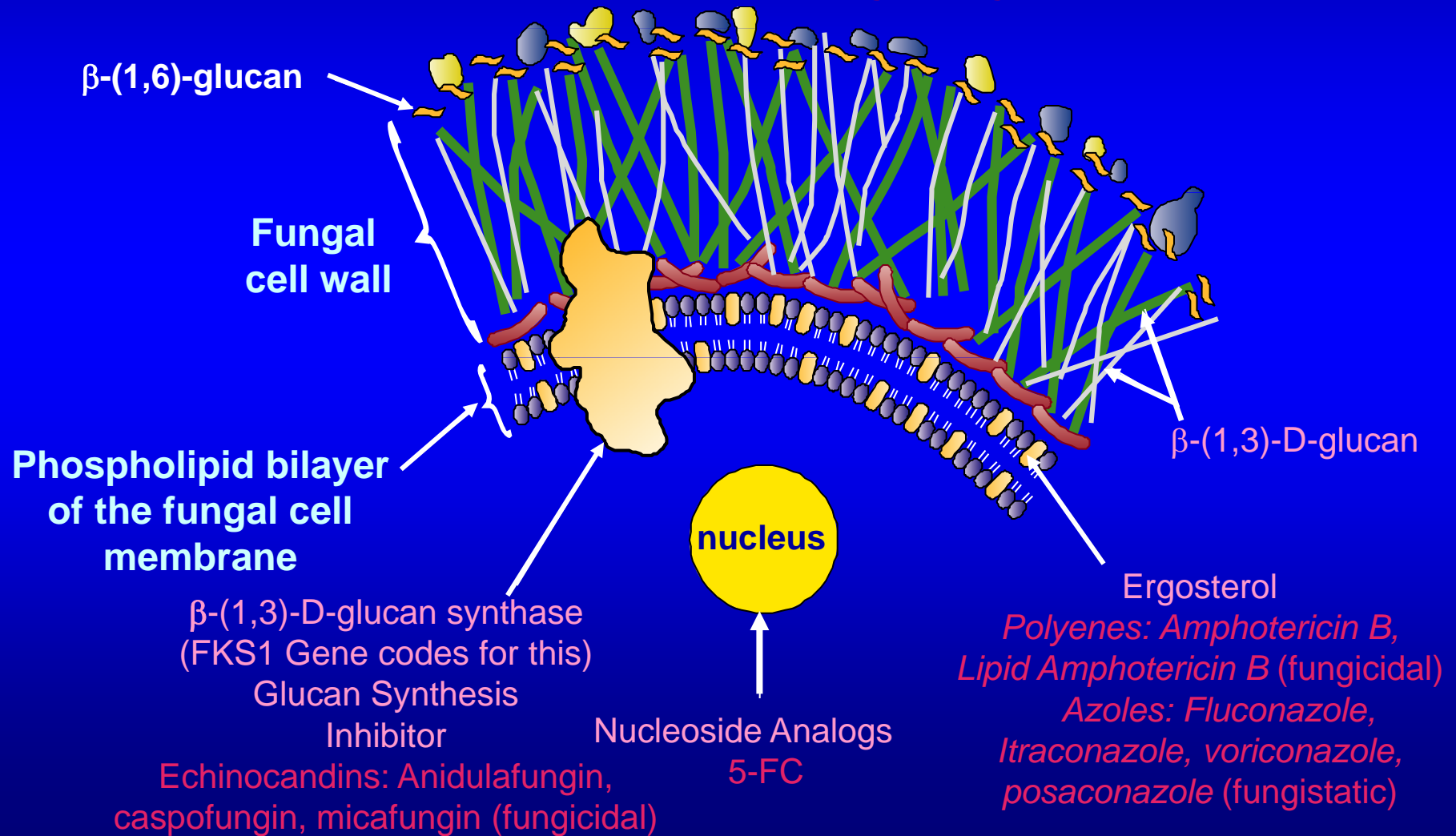
# When to use it?

- Candidemia/invasive candidiasis.
- Invasive aspergillosis.
- Invasive zygomycosis.

**What combinations to  
use?**

# Classification of Antifungal Agents and their Sites of Action

## Mechanism of Action: Pathogen Targets



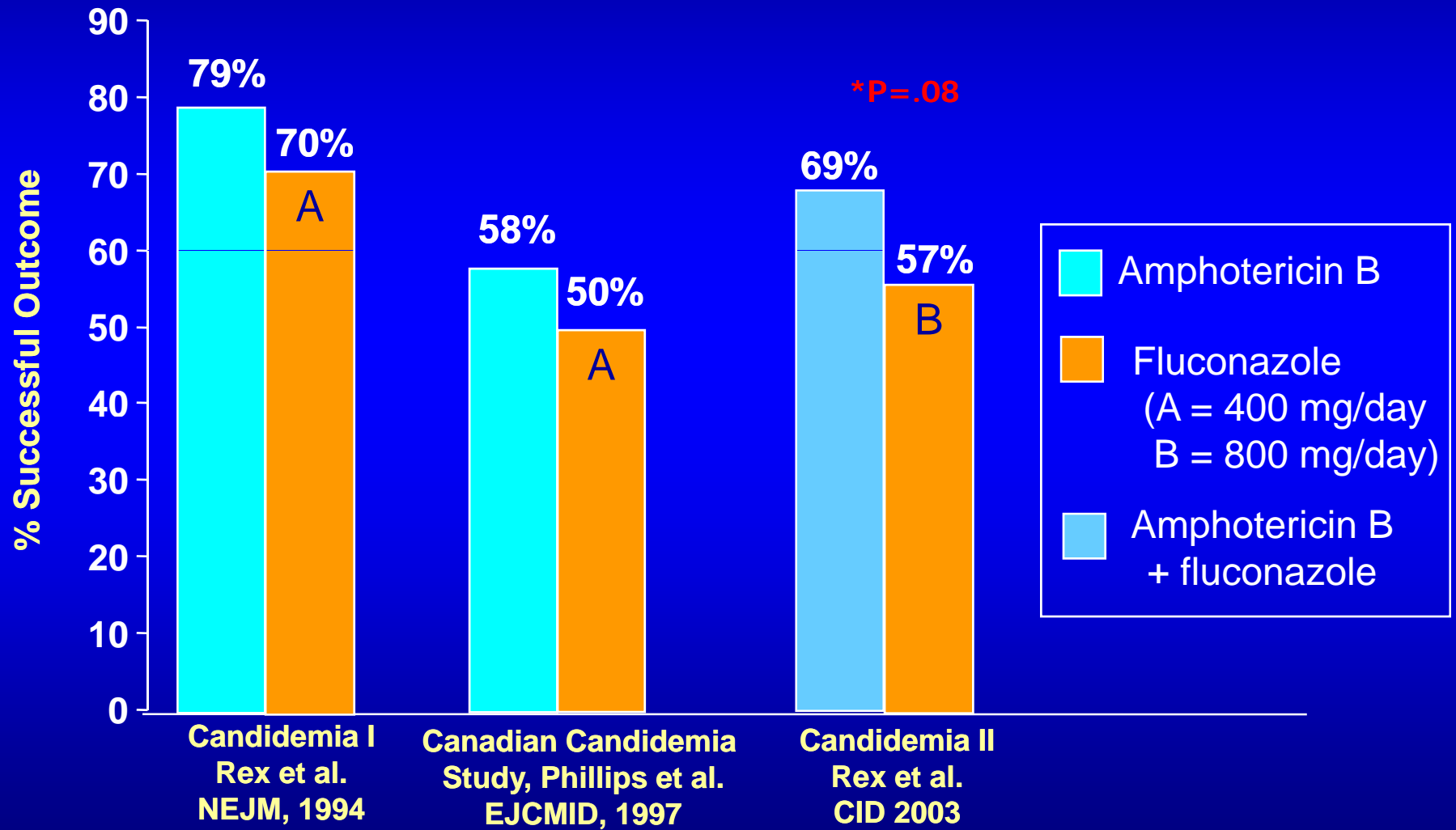
**What is the clinical  
evidence?**

# **Candidemia/ Invasive Candidiasis**

**Primary therapy?**

**Secondary or refractory therapy?**

# Efficacy Results for Candidemia in Nonneutropenic Patients



# Fluconazole + AmB vs. Fluconazole for Candidemia in Non-neutropenic Patients

- **RCT:**
  - ◆ Comparing fluconazole 800 mg/da to AmB 0.7 mg/kg/da + fluconazole 800 mg/da with AmB discontinued after 5-6 days for candidemia
- **Outcome:**
  - ◆ Primary outcome = time to failure
- **Patients:**
  - ◆ APACHE II score of fluconazole 16.8 +/-0.6 vs. 15.0 +/-0.7 for AmB + fluconazole: odds of failure increased with higher APACHE II score (OR 1.04, 95% CI 1.03-1.14, p=.001)

(Rex JH et al. CID 2003;36:1221-1228)

# Fluconazole VS. AmB + Fluconazole

	F N = 104	AmB + F N = 112	P
Overall Success (2 <sup>o</sup> endpoint)	60/107 (56%)	77/112 (69%)	0.043
Death at 90 days	40%	41%	NS
Failure to clear bloodstream	17%	6%	0.02
Increased creatinine	3%	23%	<0.001

\*\*Combination of Flu + AmB – ?more effective but definitely more toxicity

(Rex et al. CID 2003;36:1221-1228)

# 2009 IDSA Guidelines for C/IC

Infectious Syndrome	2009 Guidelines
Stable patient (no prior azole therapy)	Fluconazole or Echinocandin (anidulafungin, caspofungin or micafungin)
2009 Moderately severe to severely ill patient +/- azole exposure	Echinocandin (anidulafungin, caspofungin or micafungin) [Amphotericin B or L-Amphotericin B only if other agents not available or intolerance]
<i>C. albicans</i> , <i>C. tropicalis</i> , <i>C. parapsilosis</i>	<i>C. parapsilosis</i> : Fluconazole Others: Echinocandin
<i>C. glabrata</i>	Echinocandin (Anidulafungin, Caspofungin or Micafungin) Continue fluconazole if used and improved

(Pappas PG et al. *Clin Infect Dis* 2009;48:503-535)

# 2009 IDSA Guidelines for C/IC

Infectious Syndrome	2009 Guidelines
<i>C. krusei</i>	Echinocandin (anidulafungin, caspofungin or micafungin)
<i>C. lusitaniae</i>	As above: Fluconazole or Echinocandin
Empiric therapy in non-neutropenic critically ill patient	Fluconazole or Echinocandin Echinocandin preferred for patient with prior azole exposure or moderately severe to severely ill patient

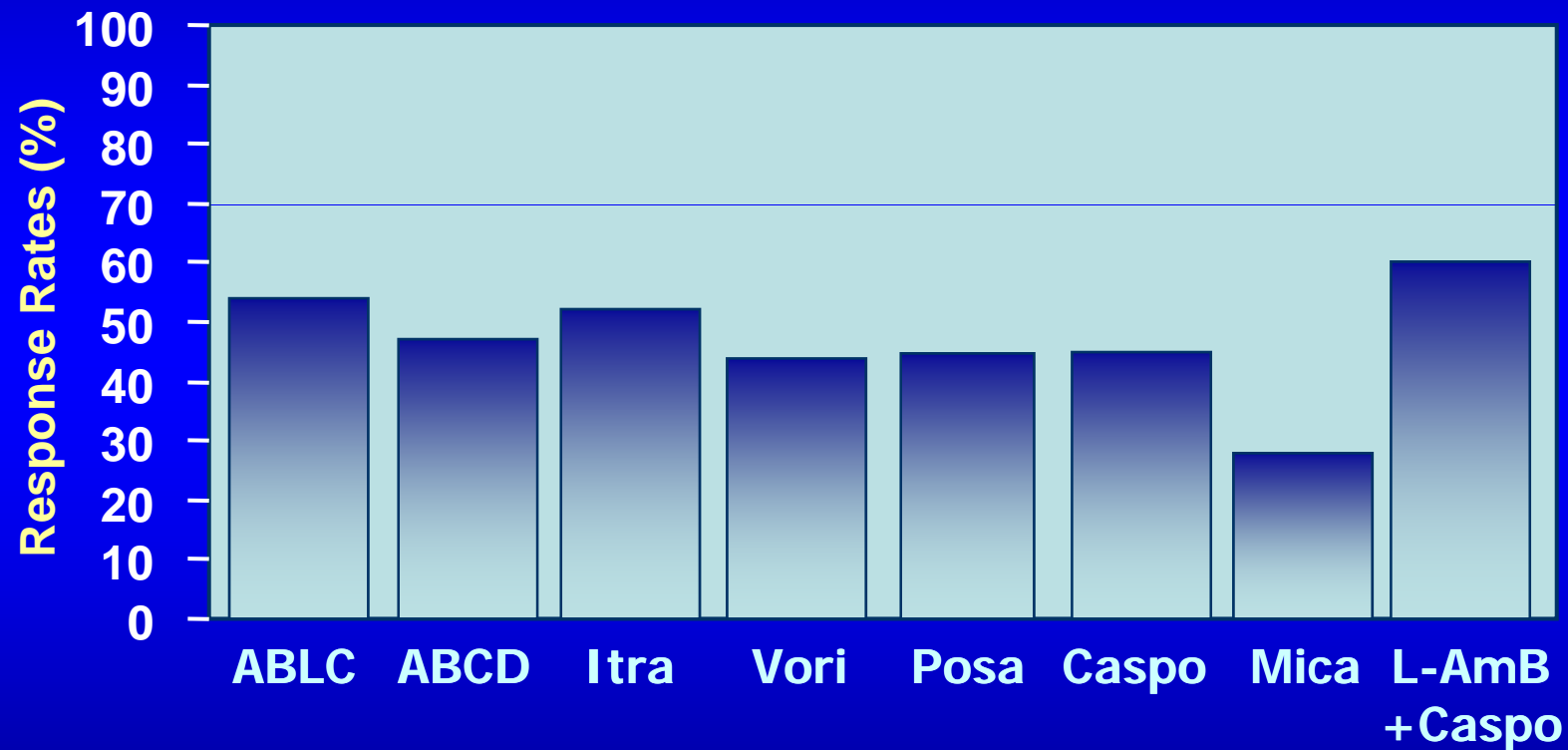
(Pappas PG et al. *Clin Infect Dis* 2009;48:503-535)

# **Invasive Aspergillosis**

**Primary therapy?**

**Secondary or refractory therapy?**

# 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 of Caspofungin & L-AmB for IA

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- Memorial Sloan Kettering
  - ◆ 30 patients with leukemia and proven (n=6), probable (n=4) or possible (n=20) IA
  - ◆ Several patients with co-pathogens
  - ◆ Caspofungin added to L-AmB or AmB for “refractory” infection (median 12 days after Rx)
    - 18/30 patients (60%) favorable response
    - 6/18 patients (20%) complete resolution
    - 12/30 patients (40%) unfavorable response

(Aliff TB et al. Cancer 2003;97:1025-1032)

# Caspofungin in Combination with L-AmB for Primary or Salvage Therapy of IA in Hematologic Malignancies

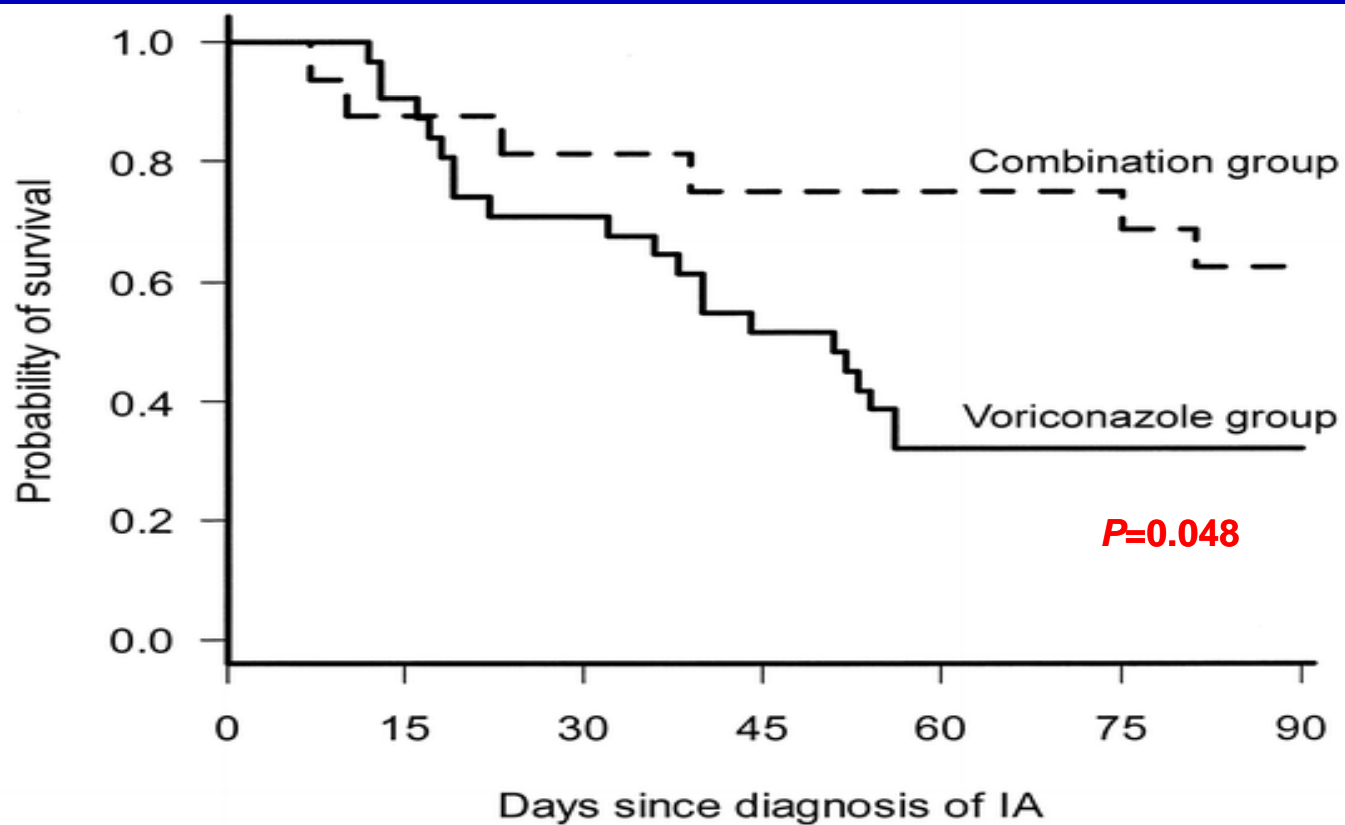
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- Retrospective review of 48 patients with IA: 23 documented (proven or probable) IA & 25 possible IA.
- 31 pt. received caspofungin + L-AmB as salvage therapy & 17 as primary therapy.
- Diagnosis: AML 19, CLL 5, CML 5, MDS 4, ALL 2 & HSCT 24.
- Response rates:
  - ◆ Documented IA 22%
  - ◆ Possible IA 60%
  - ◆ Primary therapy 53%
  - ◆ Salvage therapy 35%
- Combination therapy for <14 d ( $p=.001$ ) & documented IA ( $p=.003$ ) associated with failure in multivariate regression model.

(Kontoyiannis DP et al. Cancer 2003;98:292-299)

# IA Salvage Therapy

- Voriconazole vs. Voriconazole + Caspofungin



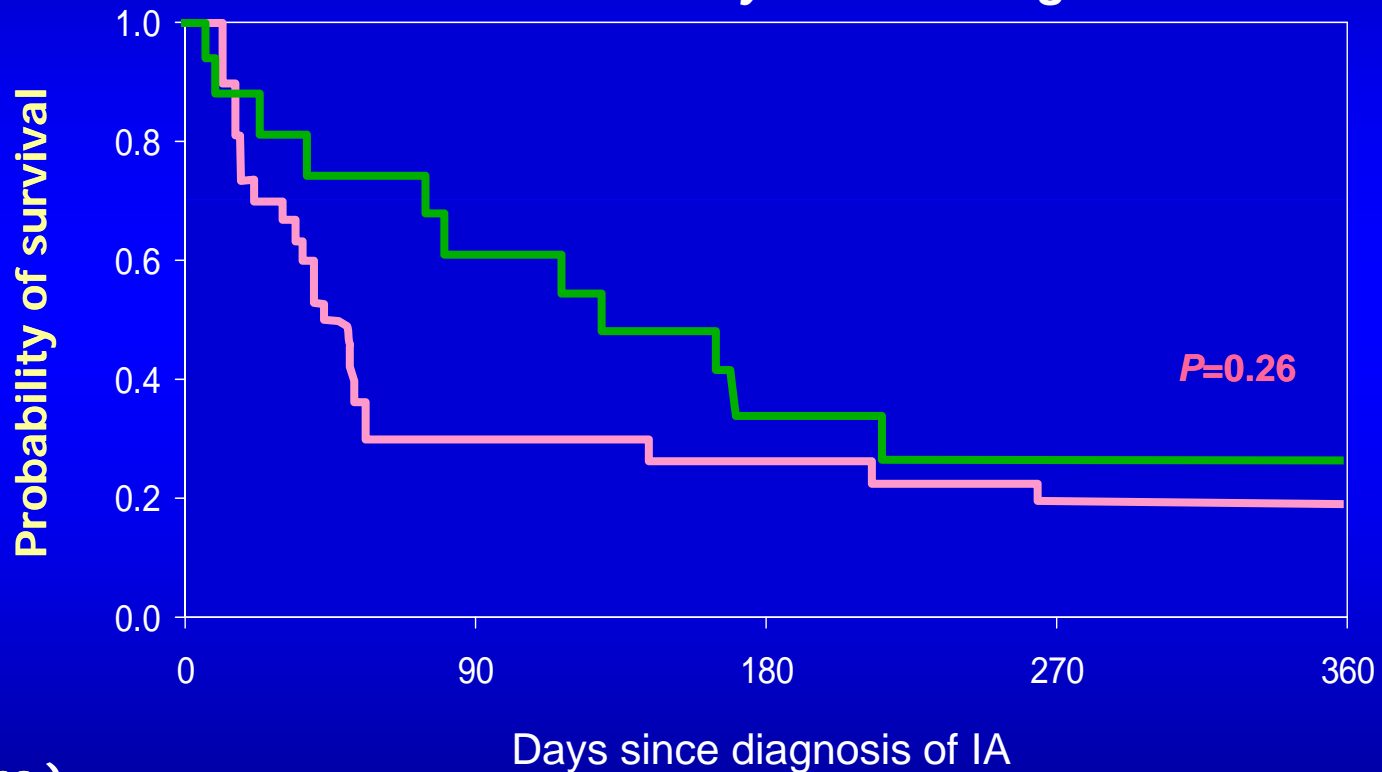
Voriconazole group, no. of patients	31	22	10	10
Combination group, no. of patients	16	13	12	10

(Marr KA et al. *Clin Infect Dis.* 2004;39:797-802)

# IA Salvage Therapy

- Voriconazole vs. Voriconazole + Caspofungin

Overall survival 1 year after diagnosis



Patients (no.)

■ Voriconazole	31	10	9	7	7
■ Combination	16	10	5	1	1

(Marr KA et al. *Clin Infect Dis.* 2004;39:797-802)

(Marr KA et al. *Clin Infect Dis.* 2005;40:1075-1076)

# Voriconazole & Caspofungin in SOT Recipients with IA

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- Prospective observational study of SOTs 2003 to 2005.
- Primary therapy with combination of vori + caspo for IA compared to historical control group 1999 to 2002.
- 40 cases received vori + caspo & 47 received a lipid formulation of AmB.
- Outcomes:
  - ◆ Survival at 90 d 67.5% for combination vs. 51% in controls; particularly those with renal failure & A. fumigatus infection.
  - ◆ CMV & renal failure predictive of mortality ( $p < .03$ ).

(Singh N et al. Transplantation 2006;81:320-326)

# L-AmB in Combination with Caspofungin for Primary IA Therapy in Patients with Hematologic Malignancies

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- Prospective randomized pilot study comparing L-AmB 10mg/kg/d IV to combination of caspo + L-AmB 3 mg/kg/d IV.
- 30 pt. – 15 in each arm.
- Response rates:
  - ◆ Favourable response at week 12 - combination group 67% (10/15) vs. 27% (4/15) in monotherapy group (p=.028).
  - ◆ Survival 100% in L-AmB + caspo vs. 80% in monotherapy group with L-AmB.
- Increased creatinine in 23% of high dose L-AmB vs. 7% in combination group.

(Caillot D et al. Cancer 2007;110:2740-2746)

# Micafungin in Combination with Other Antifungal Therapy for IA

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- Micafungin administered alone or in combination with other licensed antifungal therapy for IA in: HSCT 98, Allogeneic transplant 88, Autologous transplant 10, HIV 6, SOT 13 & others 17.
- For primary combination therapy for IA:
  - ◆ Favourable Response – 5/17 (29.4%)
- For refractory/toxicity failure:
  - ◆ Favourable Response – 60/174 (34.5%)

(Denning DW et al. J Infect 2006;53:337-349)

# Micafungin Alone or in Combination with Other Antifungal Therapy for IA in HSCT

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- 98 HSCT recipients with IA (83 refractory to therapy)
- 8 received micafungin alone; 90 received combination therapy
- 43% had GVHD
- 27% neutropenic ( $< 500$  neutrophils/mm<sup>3</sup>)
- mean duration 51 +/- 60 d
- mean dose of micafungin 105 mg/day +/- 60 mg/day
- **Response:**
  - ◆ overall response 26% (25/98)
  - ◆ 2/9 (22%) with de novo therapy
  - ◆ 21/87 (24%) in refractory pt.
  - ◆ **22/90 (24%) with combination therapy:** L-AmB (63), AmB (10), L-AmB + itra (8), AmB + itra (2), plus OLAT (7)

(Kontoyiannis DP et al. Trans Infect Dis 2009;11:89-93)

# Antifungal Therapy for Invasive Aspergillosis – IDSA Guidelines

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- 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)

# Invasive Zygomycosis

# Therapy of Zygomycosis with Polyene-Caspofungin Combination

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- Study identified 41 cases of ROCM: 21 ROM & 20 ROCM (diabetes 83%, cancer 34%, corticosteroid use 46%, neutropenia 12% & transplantation 10%).
- Pt. treated with ABLC, lower response rate than those treated with AmB & L-AmB (37% vs. 72%).
- ABLC + caspofungin response rate 100% (4/4) vs. 20% (3/15) of ABLC alone.
- MRI more sensitive than CT.

(Reed C et al. CID 2008;47:364-371)

# Combination Therapy for Mucormycosis

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- Micafungin or anidulafungin plus L-AmB synergistic in murine model of DKA with disseminated mucormycosis.
- Deferoxamine iron chelation therapy enhances risk of mucormycosis by delivery of iron to Mucorales.
- Deferasirox (oral iron chelator) is fungicidal for Mucor-RCT of deferasirox + L-AmB is underway (DEFEAT Mucor study).
- Posaconazole monotherapy or combination therapy with L-AmB in murine model of mucormycosis did not improve survival.
- AmB dose of 1mg/kg/d or L-AmB 5-7.5 mg/kg/d IV currently recommended.
- Posaconazole with or without a polyene may be used as salvage therapy.

(Spellberg B et al. CID 2009;48:1743-1751)

# Summary of Combination Antifungal Therapy in ICU

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- **Why use it?**
- **For C/IC** – combination therapy doesn't offer significant advantage for primary therapy based on combinations used in past.
- **For IA** – combination therapy (caspo + L-AmB) improved survival as **primary therapy** in possible infection - ?secondary therapy.
- For invasive zygomycosis – insufficient data.
- More randomized studies required assessing other combinations – now RCT for primary therapy comparing voriconazole IV/po alone to voriconazole IV + anidulafungin IV → voriconazole po in both arms after 2 or 4 weeks .
- **What to use?**
- **When to use it?** Probably as primary therapy for most benefit.