# Management Of Invasive Fungal Infections In Immunosupressed Hosts

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# Outline

- Aspergillosis
- Candidiasis
- Emerging mycoses

# Challenges in the Management of IA

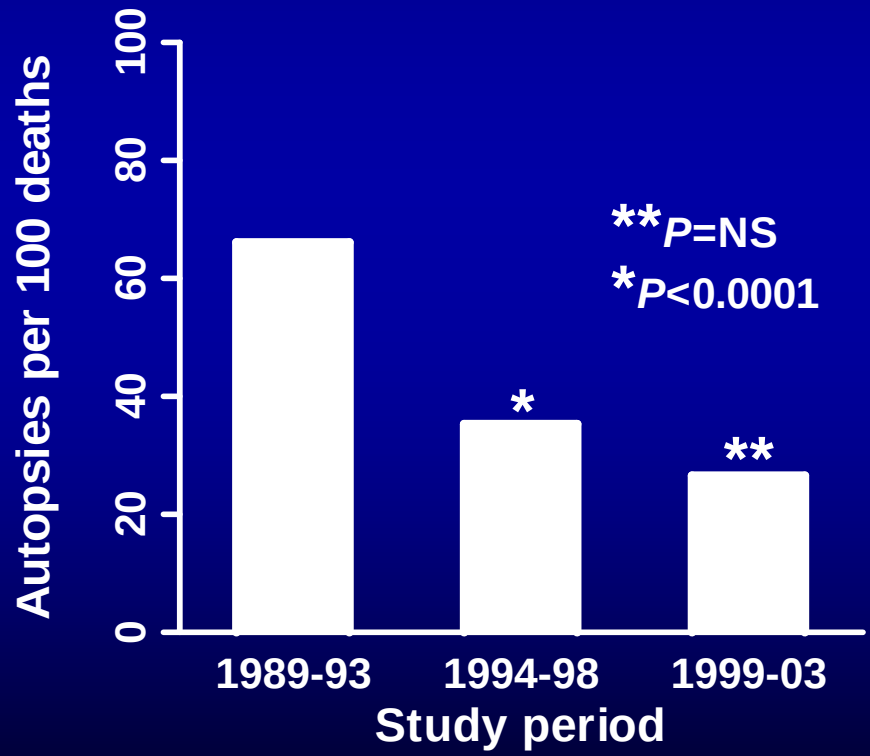
- Active underlying disease (e.g., leukemia, GVHD), pleiotropic immune defects following chemotherapy= poor host immunity
- Multiple co-morbidities, age=frequent drug toxicities
- Significant antifungal selection pressure=frequent resistance
- Diagnostic tests lack specificity and sensitivity=empiricism
- Heterogeneous population at risk
- Multiple interventions, either simultaneously or sequentially

# Difficulties Specific to Management of Invasive Pulmonary Aspergillosis

- Multiple pathogens are not uncommon
- Cultures have suboptimal sensitivity and specificity, timing and processing of BAL not standardized
- Surrogate markers: The vanishing “gold standard” (autopsy)
- Not all infiltrates in immunosuppressed patients with are due to IPA
- Dissemination is not uncommon

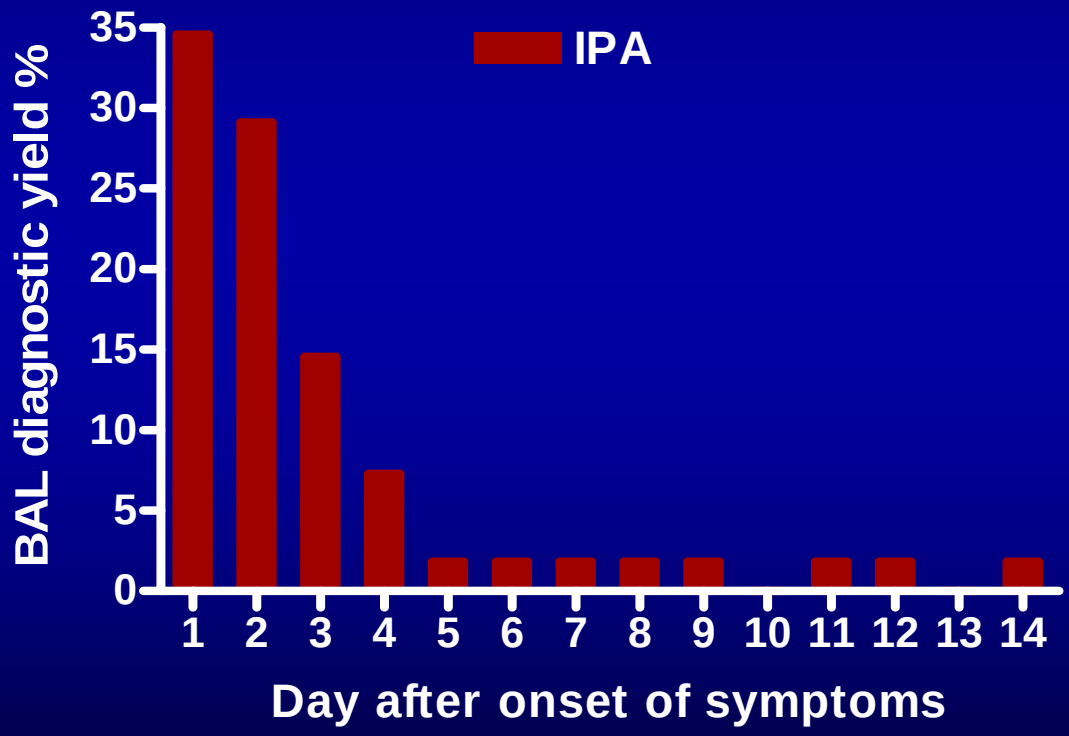
# We increasingly do not know the cause of death in patients with IA

Autopsy Rate (Autopsies/deaths) at MDAAC (1015 Autopsies, 1989-2003)




Chamilos G & Kontoyiannis DP. Hematologica 2006

# Influence of BAL Timing on Diagnosis of IPA Following HSCT



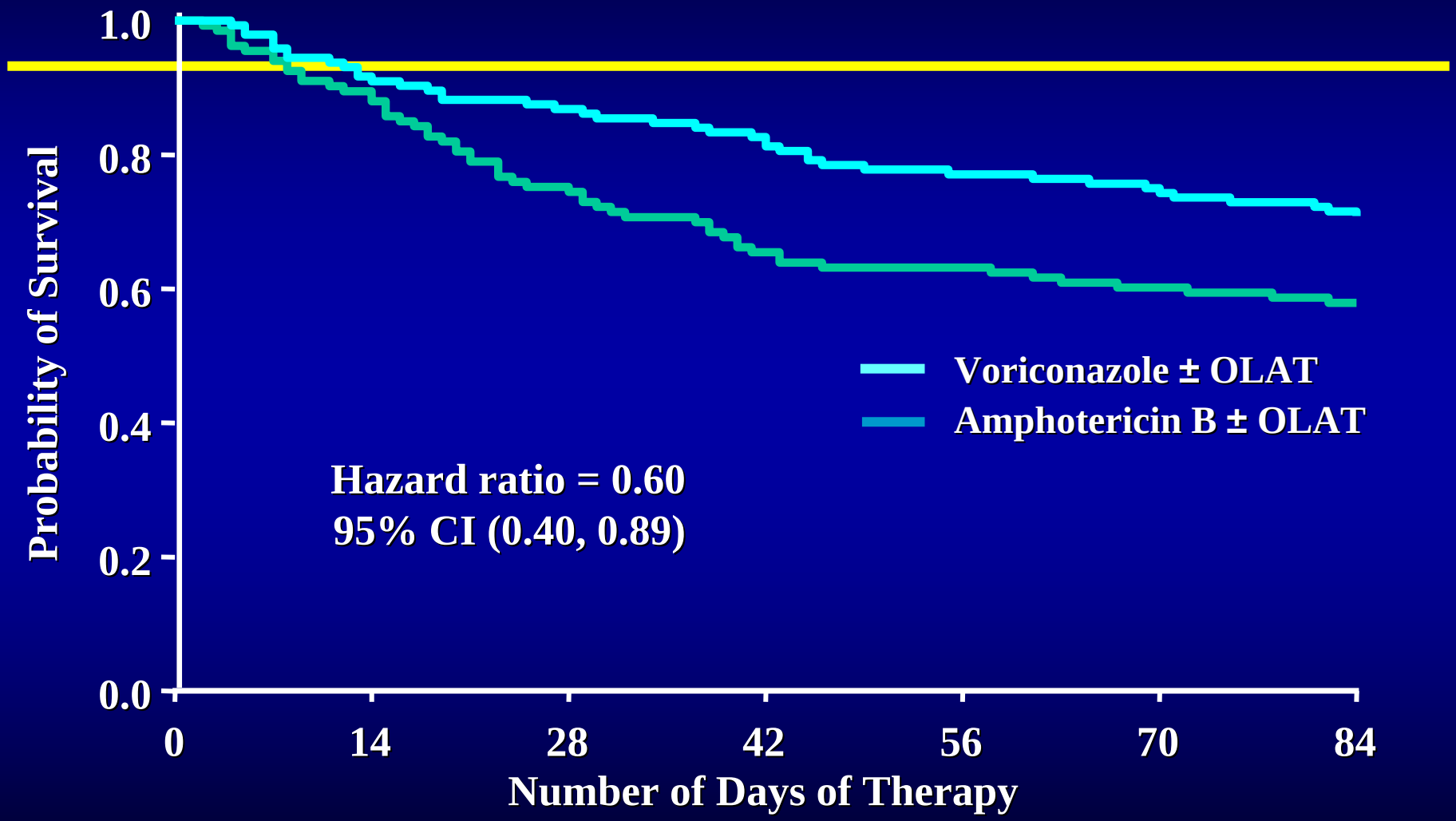

Shannon V & Kontoyiannis DP, unpublished

# Controversies in the Management of IA-1

- **How to deal with voriconazole failures, the preferred agent for IA?** **(Walsh TJ et al. IDSA guidelines. CID 2008)**
  - **Suboptimal VRC levels?**
  - **Resistant bugs?**
- **What is the role of posaconazole as primary or salvage therapy?**
- **What is the role of azole therapeutic drug monitoring?**
- **Is there a concern about cross-resistance and tolerance between triazoles for *Aspergillus*?**

# Global Comparative Aspergillosis Study

*Comparison of Mortality*

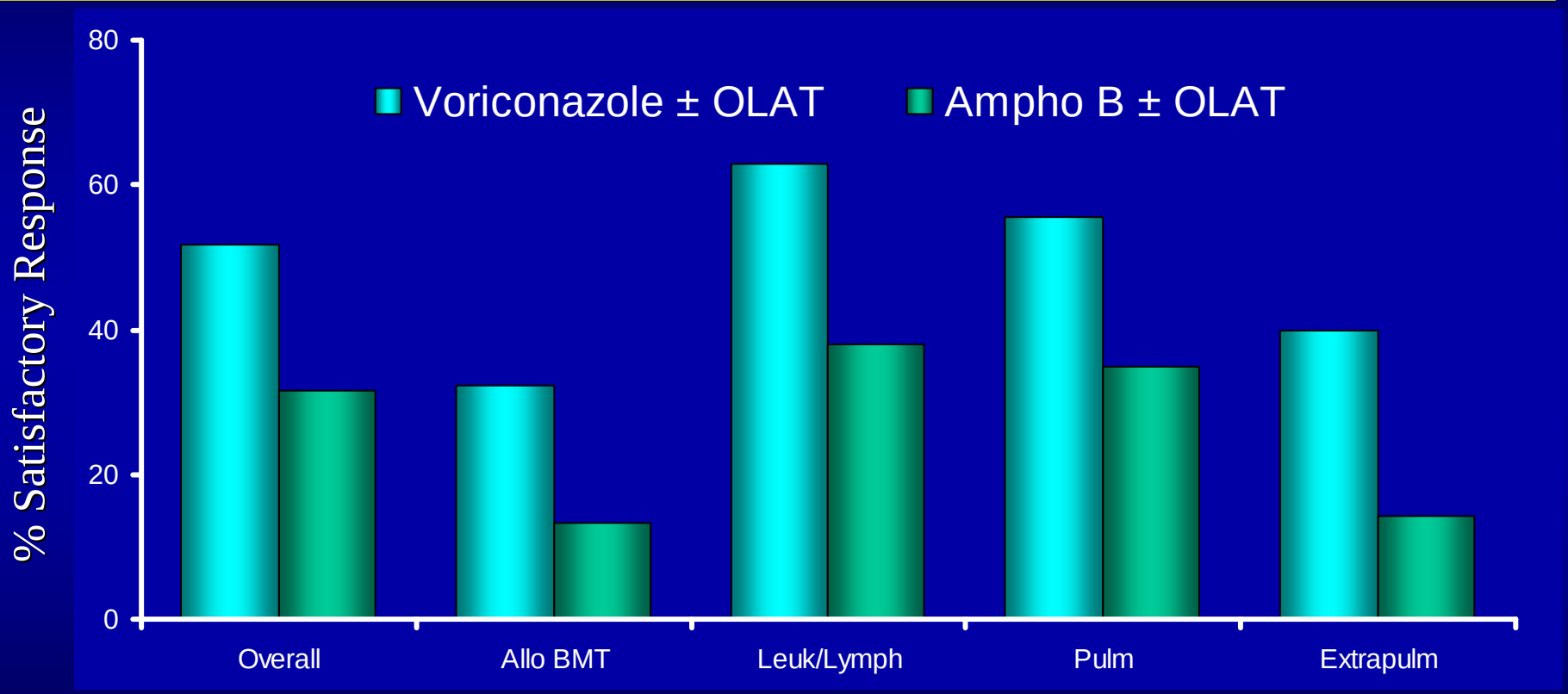



OLAT = other licensed antifungal therapy

Herbrecht et al. *N Engl J Med.* 2002;8:408-415

# Global Comparative Aspergillosis Study

## Responses at Week 12




OLAT = other licensed antifungal therapy.

Herbrecht et al. *N Engl J Med.* 2002;8:408-415

# Controversies in the Management of IA-2

- **What is the role of the echinocandins?**
- **What is the optimal dose of lipid formulations of AMB?**
  **Are they any PD reasons to choose a certain lipid formulations of AMB?**
- **What is the role of combination therapy (which drugs? when?)**
- **What is the impact of *Aspergillus* speciation (*eg A. terreus*) in the decision-making?**

# Controversies in the Management of IA-3

- What is the role of adjunctive surgery?
  - → Extent and timing

- **What is the role recovery from immunosupression in outcome?**
  What is the role of immune adjunct therapy?

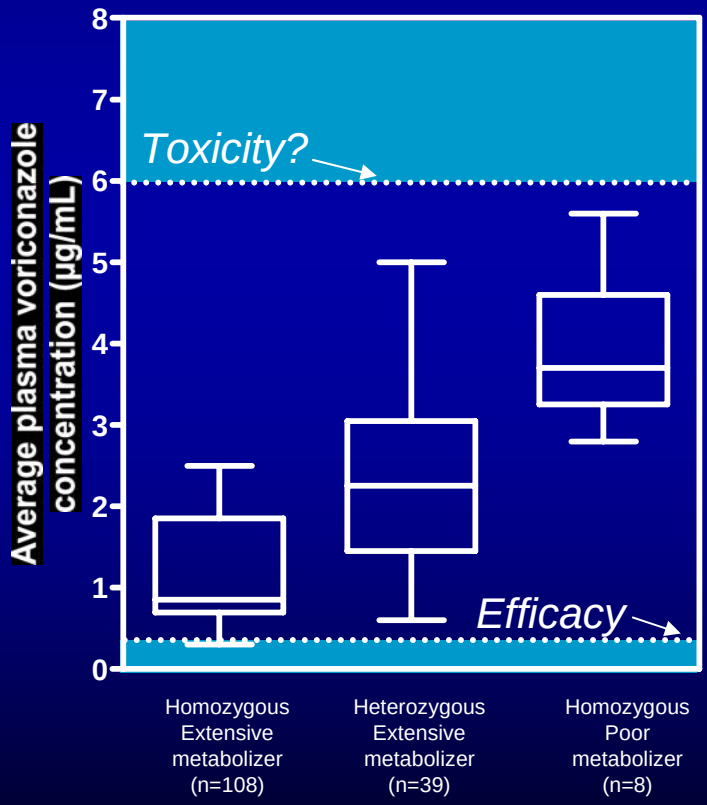
- **What is the role of local drug delivery?**

- **What is the best strategy for secondary prophylaxis?**

- **Do antifungals work differently based on the immunopathology of IA (steroids vs neutropenia?)**

# Voriconazole Exhibits Significant Inter-Patient Pharmacokinetic Variability

***Influence of CYP2C19 Genotype on Average Steady-State Plasma Voriconazole Concentrations***




**80% have sub-therapeutic levels with regular oral VRC dose (200mg BID)!**
**Bilaud et al. ISHAM 2006**

Vfend NDA Submission, www.fda.gov

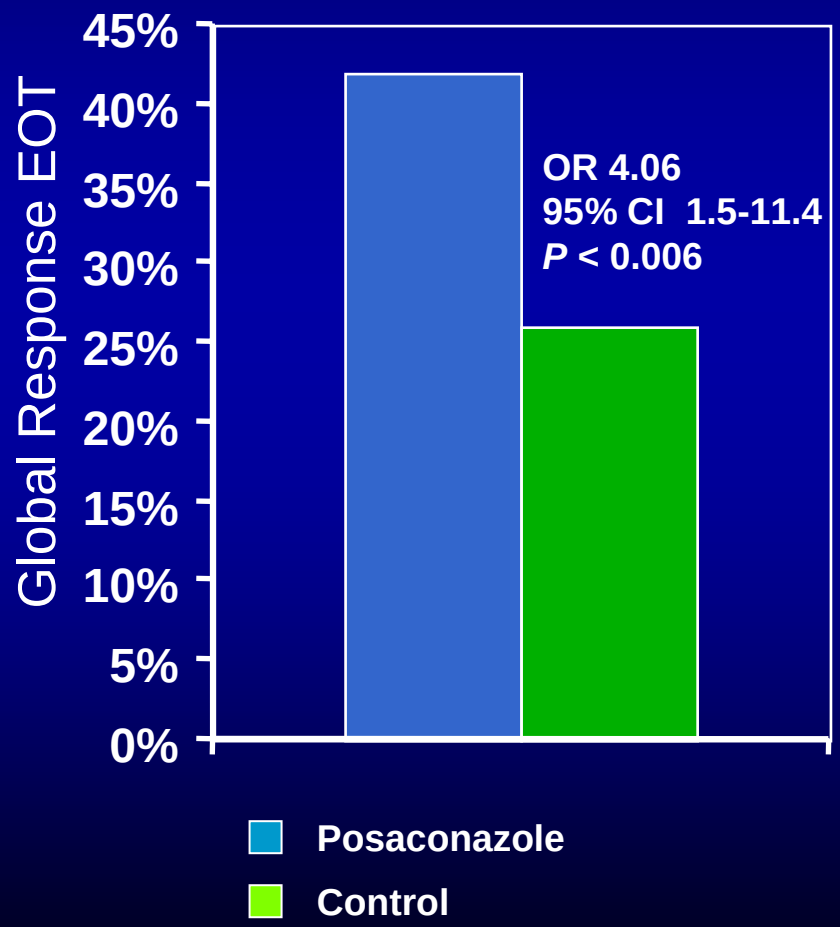
# Multi-triazole (ITC, VRC, POSA, RAVU)-resistant *Aspergillus*

- Netherlands survey: 0/114 pts (170 *A. fumigatus* isolates) from 1945-1998 vs 10/81 pts (13 isolates) from 2002-2006 ($p<0.001$)
- No clonality, but unique mechanism of resistant (L98H in Cyp51a) in 12/13 isolates
- Some isolates came from pts no previously exposed to azoles (? Role of OTC and agricultural use of azoles-Kontoyiannis & Lewis. Lancet 2001)

**Verweij et al. NEJM 2007**

# Posaconazole for the Treatment of IA in Patients Refractory to or Intolerant of Conventional Therapy (mostly AMB-Based)

- Treatment groups:
  - Posaconazole (107)
    - Heme malig. 74%
    - HSCT 51%
  - Controls (86)
    - Heme malig. 81%
    - HSCT 44%




Walsh TJ et al. CID. 2006

# Caspofungin in IA

| **Monotherapy** | Favorable Response % | Nº Pat |
|---|---|---|
| Candoni et al. Eur J Haematol 2005* | 56% | 32 |
| Walsh et Al. NEJM 2004* | 52% | 12 |
| Betts et al. Cancer 2006* | 42% | 12 |
| Maertens et al. CID 2004 | 56%** | 66 |
| Kartsonis et al. J of Infection 2005 | 44% | 45 |
| Betts et al. Cancer 2006 | 38% | 29 |

*First line ** >7 days of therapy

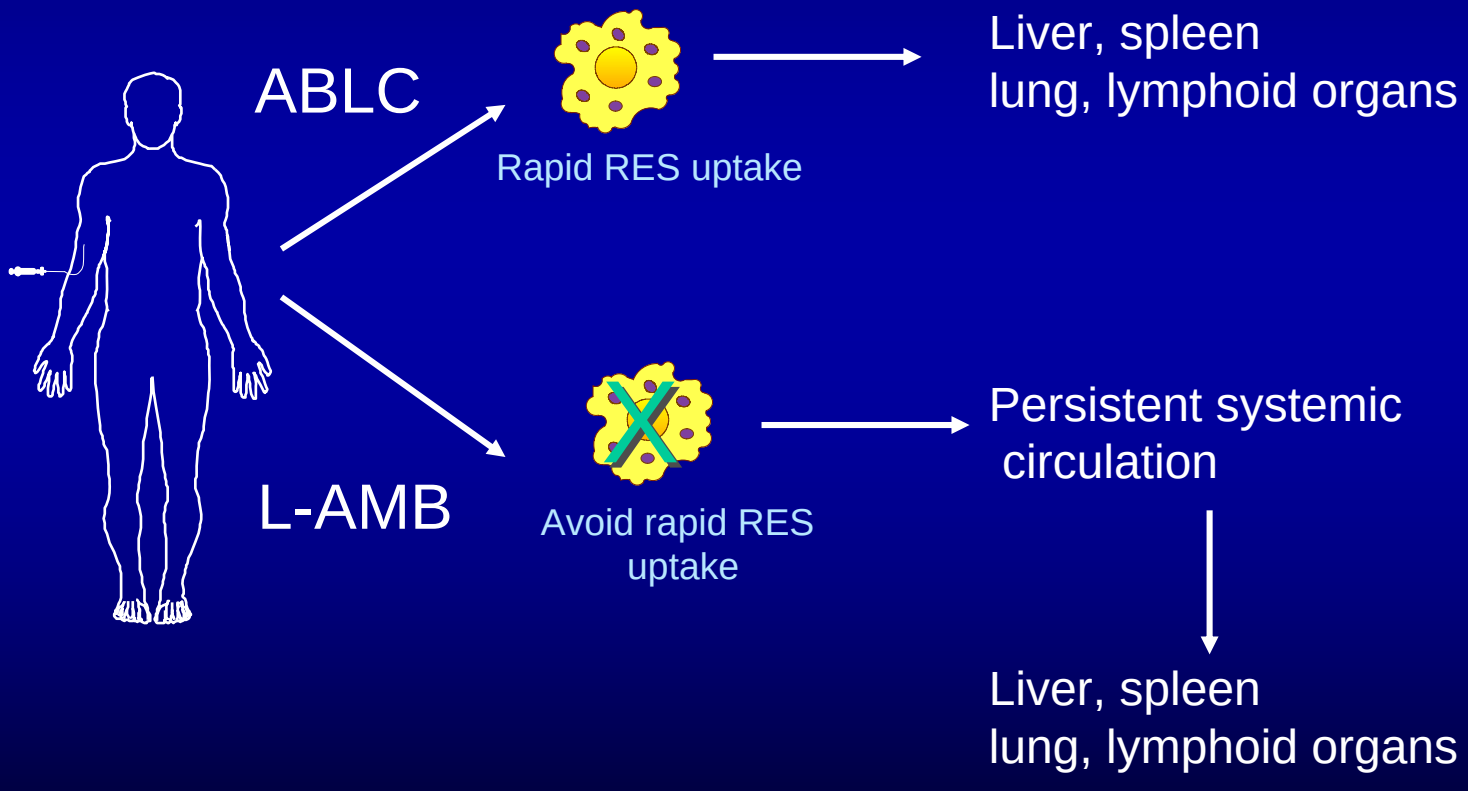
# Caspofungin as First Line Therapy For IFIs in Patients with Hematologic Malignancy

- Study design : Open-label, single institution study (2004-2006)
  - Patients:
    - N =28, mean age = 46 yrs (18-66 yrs)
    - Hematologic malignancy (13 AML, 5 ALL, 2 MM, 8 lymphoma)
    - Severe neutropenia in all, 22/28 possible IFIs, Lung infection in 27/28
    - HSCT 36 % ( 6 allogeneic + 4 autologous)
  - Caspofungin: 50 mg/day (70 mg/day loading)
- Results:
  - Response rate: 86% (24/28 ) w/ concomitant neutrophil recovery, 2 IFIs relapsed
  - No breakthrough Infection
  - Mean duration of CAS treatment : 18 d (6-21 d)
  - No dose modification (including 6 pts receiving CsA)
  - Safety
    - Well tolerated, no discontinuation due to AE

Bonini A, et al. *ASH* 2006

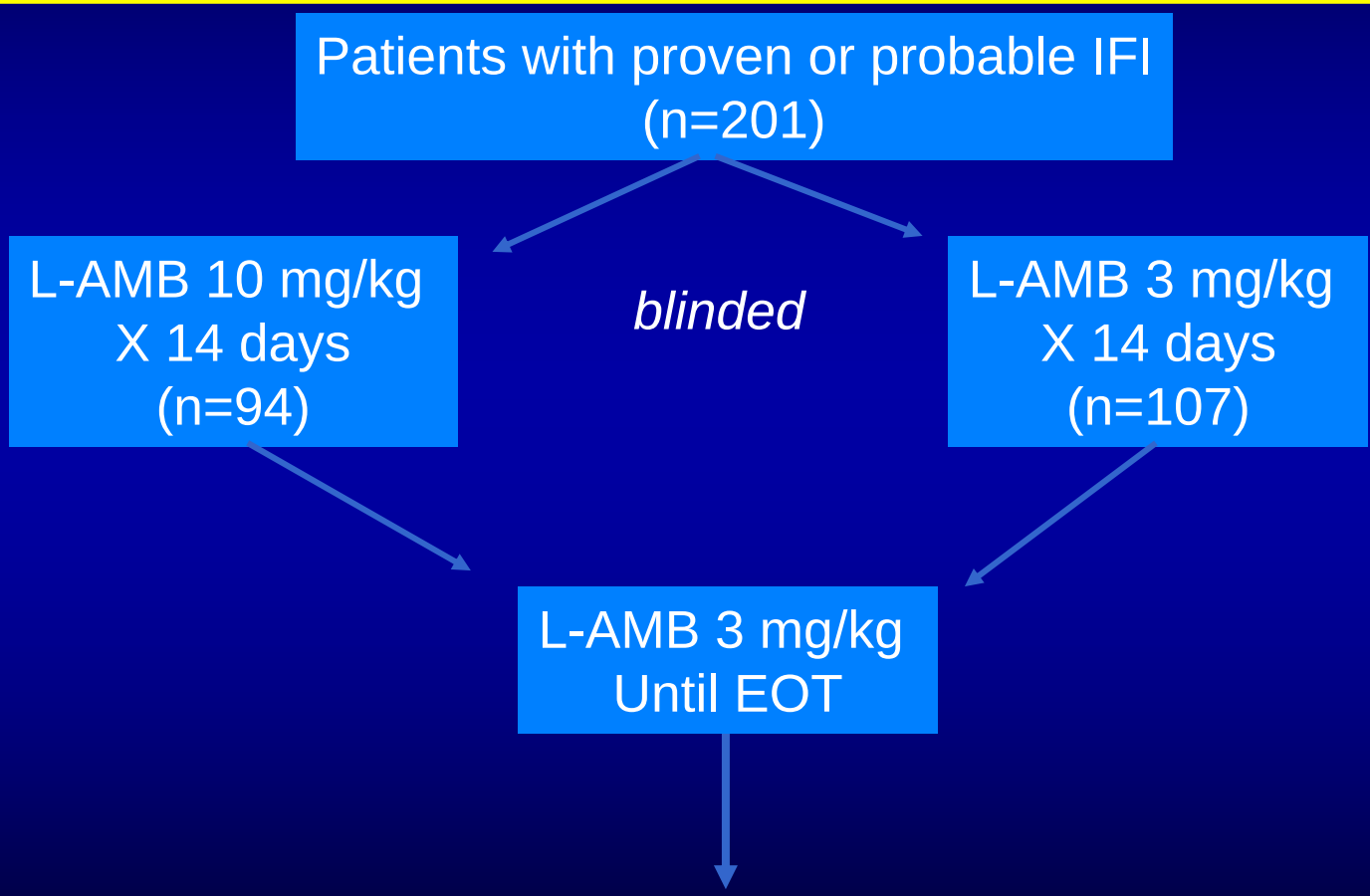
# ABLC vs. Liposomal Amphotericin B

## Pharmacokinetic differences



# A Randomized, Prospective Trial of a High-Loading Regimen vs. Standard Dosing

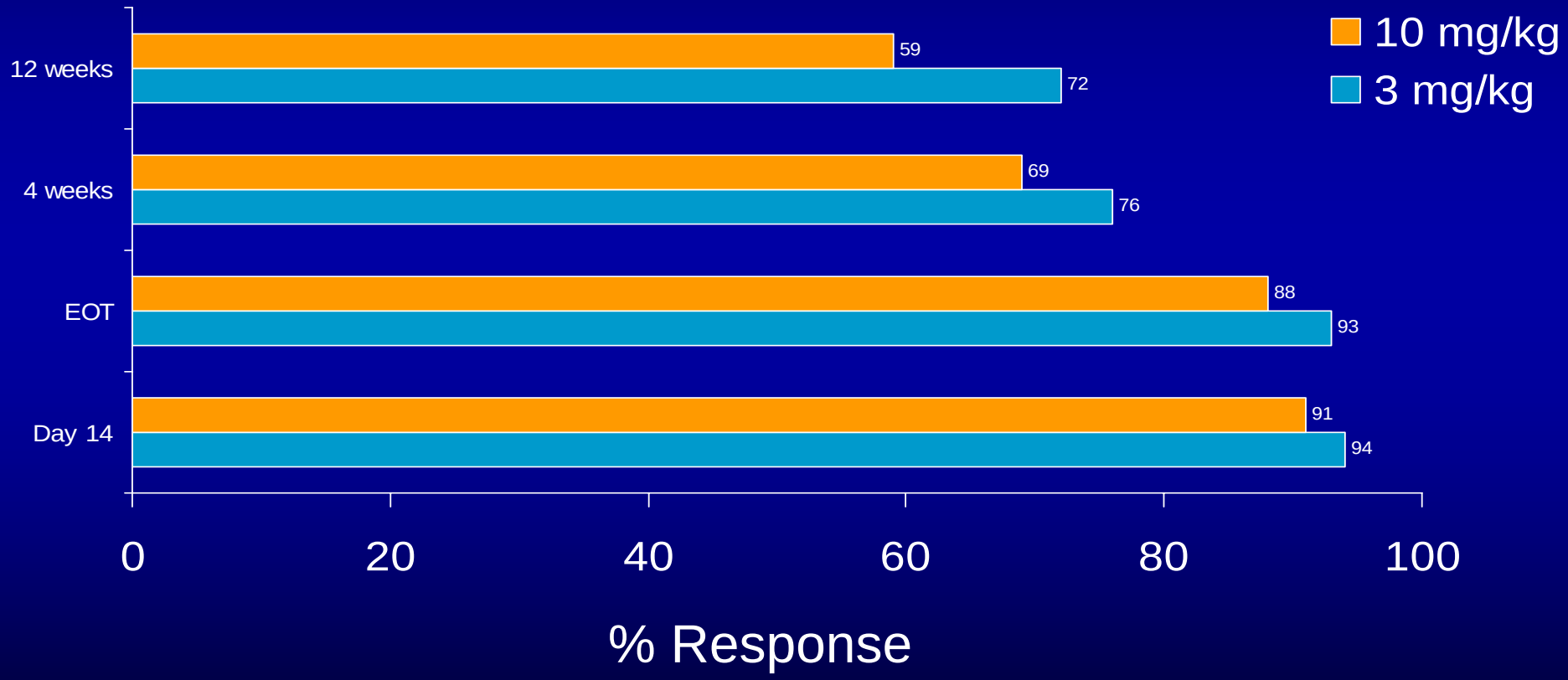
## Ambiload Trial




Cornely et al ASH 2005

# Survival

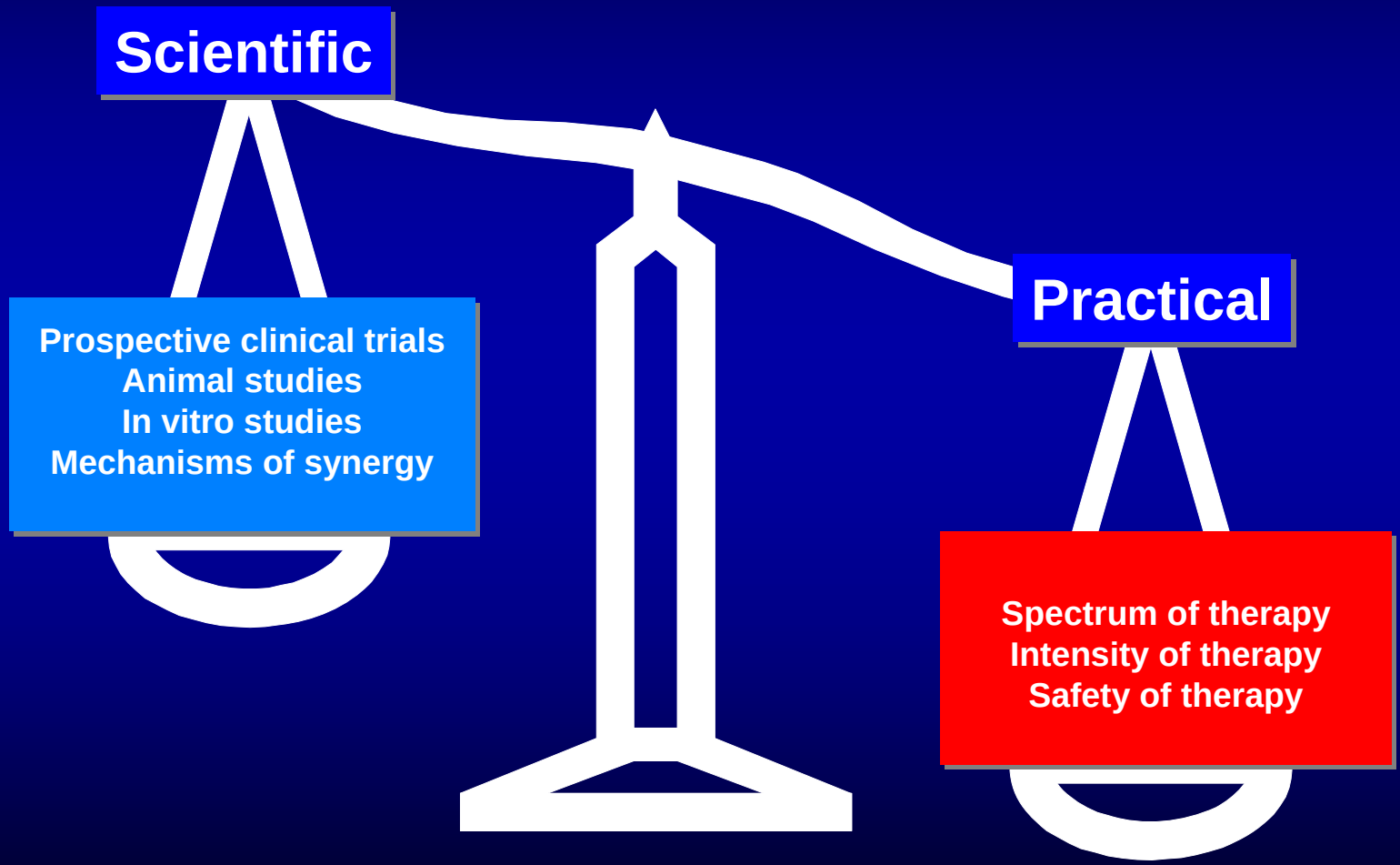
## Ambiload Trial




***No differences were statistically significant***

Cornely et al ASH 2005

# Pragmatism vs. Science and Decisions to Use Combination Therapy

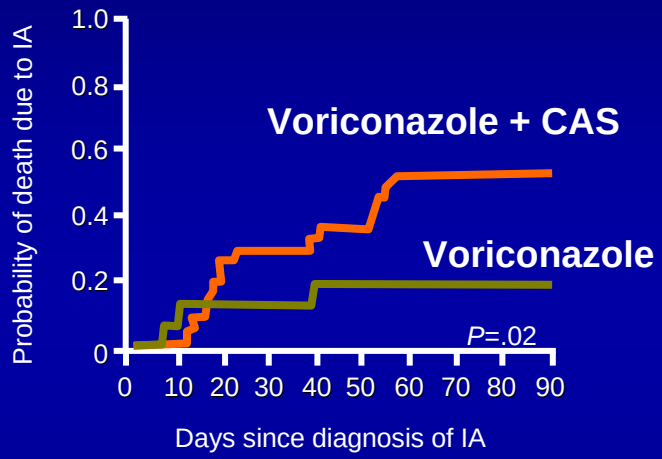



Lewis REL & Kontoyiannis DP. Br J Hematology 2005

# Combination therapy for invasive aspergillosis

## Accumulating evidence for benefit?

Marr KA. *Clin Infect Dis.* 2004;39:797.

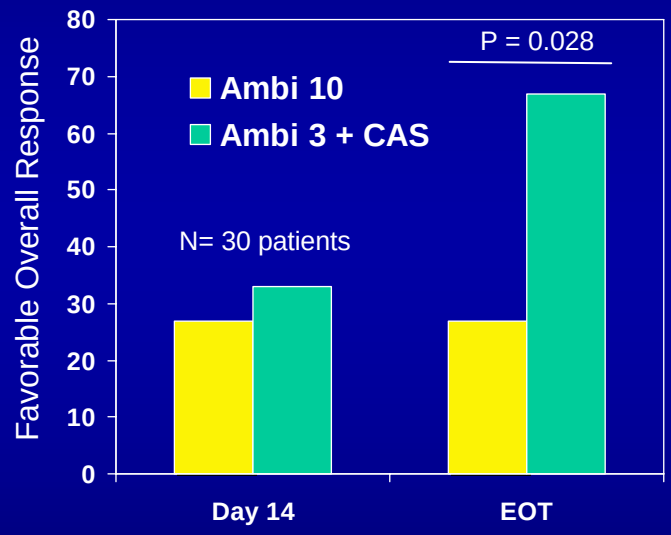



Singh et al. *Transplantation* 2006;81:320-6.

| Variable | Odds ratio | 95% C.I. | P-value |
|---|---|---|---|
| Treatment with VRC + CAS | 0.419 | 0.139-1.263 | 0.12 |
| Renal failure | 2.803 | 0.946-8.304 | 0.062 |
| CMV infection | 4.340 | 1.443-13.057 | 0.009 |

When controlled for renal failure and CMV infection, patients in the study group were 2.4 times less likely to die within 90 days compared to the control group (O.R.=0.419, 95% CI, 0.14-1.3). The difference however, was not statistically significant (p = 0.12).

Caillot. et al. (Combistrat)
ISHAM 2006; Abstract 0-0017




Retrospective salvage data of LipoAMB+ CAS in IA: ? benefit (Alief et al. Cancer 2003, Kontoyiannis et al. Cancer 2003)

# CAS-based Combination Therapy for IA

**Overall Efficacy by Combination Treatment Regimen**

| | Caspofungin and amphotericin B formulation | Caspofungin and Triazoles |
|---|---|---|
| | N = 16 | N = 37 |
| | n/m* (%) | n/m (%) |
| | (95% CI) | (95% CI) |
| **End of combination therapy** | | |
| Success | 8/16 (50) | 21/37† (56.8) |
| | (24.7, 75.3) | (39.5, 72.9) |
| **Day 84 visit** | | |
| Success | 8/16 (50) | 17/35‡ (48.6) |
| | (24.7, 75.3) | (31.4, 66.0) |

Maertens J et al. Cancer. 2006;107(12):2888-97

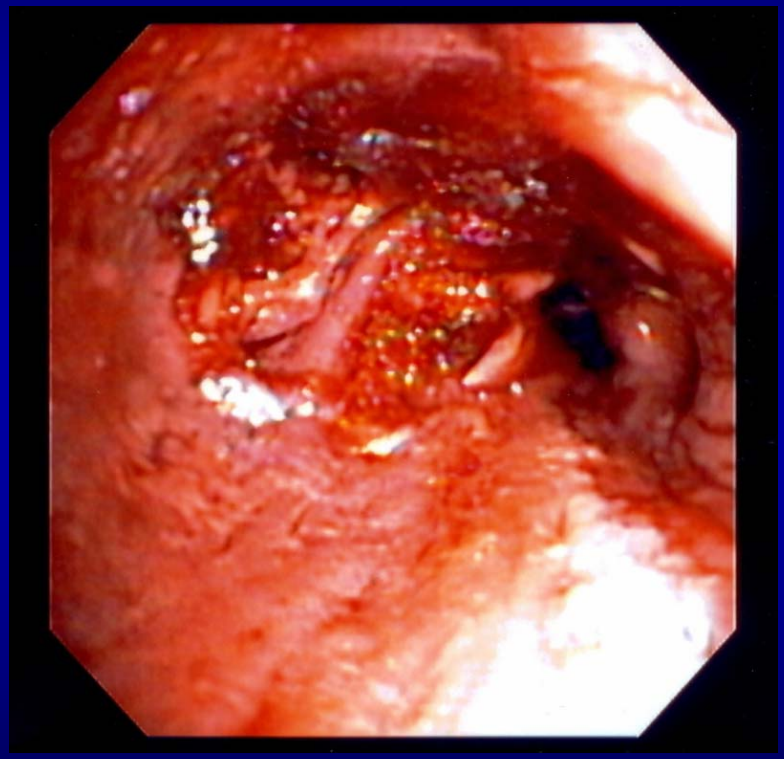
# Not All Combinations are Useful

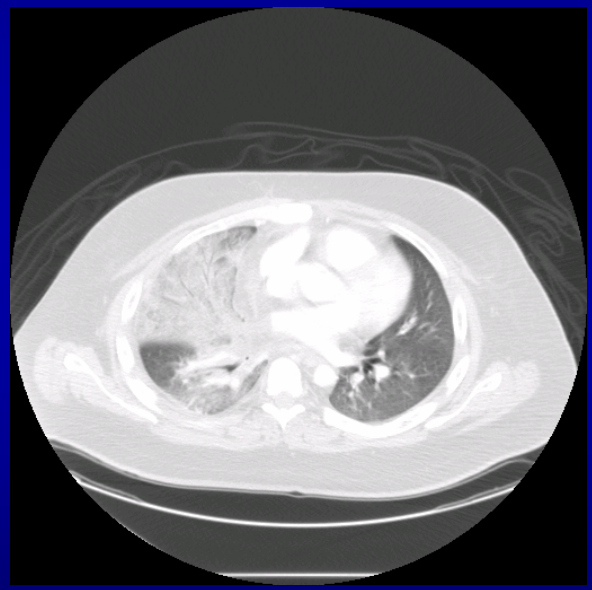
- Validated neutropenic rabbit model of IA
- Survival rates:
  - Control= 0%
  - L-AMB 1.5 mg/kg= 50%
  - Rav 5 mg/kg= 60%
  - Rav/L-AMB 1.5 mg/kg= 20%
  - Rav/ L-AMB 3 mg/kg= 17%
- Antagonism seen across all outcome markers (Meletiadis et al**. JID 2006**)
- Itraconazole+AMB: ? Antagonistic in IA (Kontoyiannis DP et al. Cancer 2005, Chandrasekar& Ito, CID 2005)

# The Role of Surgery in IA

- Has been associated with improved outcome in uncontrolled series
- Timing, approach varies, selected group of patients
- Usually in combination with antifungals, few patients treated with surgery alone
- Is delay from recovery puts patient at risk for relapse of malignancy?
- Is “pre-emptive” surgery important to prevent relapse of mycosis?
- Radical excision vs “debulking” of a dominant lesion?

# Emergent Surgery for Pulmonary Bleeding





**Active ALL, diabetes, neutropenia, pancytopenia, *Aspergillus flavus*+ *Rhizopus* spp**

# Lesions Suggestive of Aspergillosis (LISA)

- Lung sequestrum, “halo sign”, “air-crescent sign”, cavitation
- LISA have 90% positive predictive value for IPA (25/39)
- Resected LISA carry a relatively good prognosis

2 year-survival

- Resected LISA : 36%
- Unresected LISA, culture negative 20%
- No LISA, culture positive 5%

**Yeghen, et al: CID 2000;31:859-68**

# Role of Immune Enhancement

- Neutrophils, MC/macrophages are key effector immune cells against molds (Romani et al. Nat Rev Immun 2004)
- Abundant preclinical data (healthy volunteers, high infecting fungal inoculum, supra-physiologic doses of cytokines): ? relevance
  - Local ecology of bugs, plasticity of interactions between innate and adaptive immunity, cytokine circuitry in lung environment, chemokines
  - Immunopathogenesis is complex and dependent of underlying immune defect (steroids Vs neutropenia, Balloy et al. Inf & Immun 2004, Chamilos et al. Hematologia 2006)
  - Fungus-related immune dysfunction (Stanzani et al. Blood 2004)
- Timing, approach varies, selected group of patients
- Usually in combination with antifungals, no patients treated with immune enhancement alone
- Anecdotal evidence of beneficial adjunct use of GM-CSF or INF-gamma and or WBC transfusions in neutropenic and non-neutropenic patients with IMIs (Segal et al. CID 2006), appears safe (Safdar et al. Cancer 2006)

# Strategies for Secondary Prevention of Fungal Pneumonia

- Secondary antifungal prophylaxis (new triazoles)
- GM-CSF elicited WBC transfusions
- Surgery
- Role of non-culture based methods (e.g., GM) to prevent relapse?
- Adoptive Immunotherapy (Perrucio et al. Blood 2005, Shao C et al. Genes Immun 2005) ?

**Sipsas & Kontoyiannis. CID 2006**

# Local Antifungal Delivery For The Treatment Of IPA

- Aerosols, percutaneous catheter delivery
- Polyenes (AMB-d, lipid AMB)
- Case reports, concomitant systemic antifungals, different end points of efficacy and safety
- Drug distribution, stability, delivery devise, frequency: unclear

**Arthur R et al. Expert Opin Investig Drugs 2004**

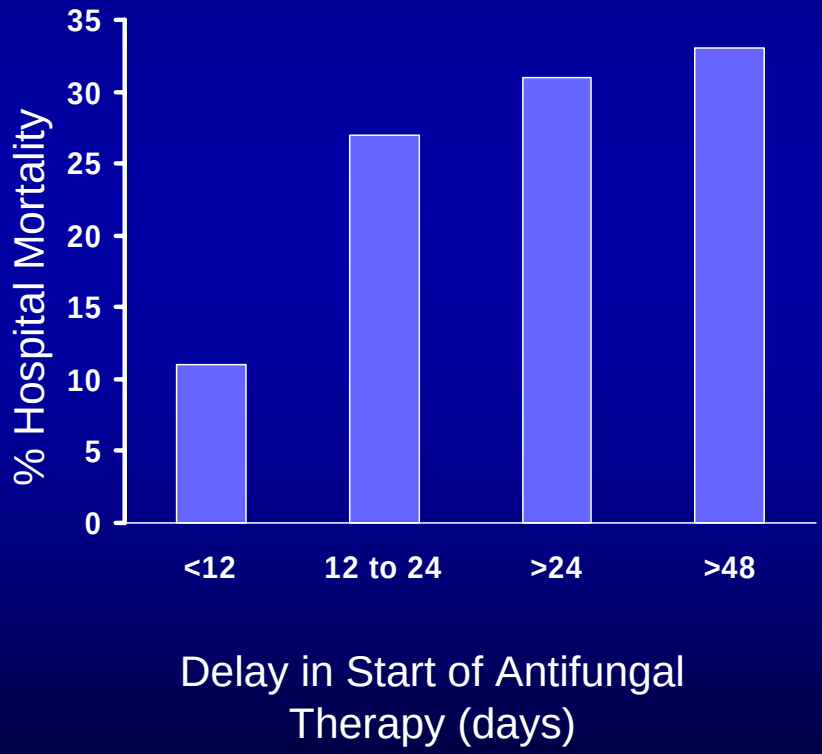
# Needs in Management of IA

- Improvements in diagnostics a) Culture yield, b) non-culture-based early diagnosis (-> pre-emptive combination therapy) and c) scorecards that differentiate early lung infection by different mycoses, d) Study of immunopathogenesis
- Understand the specific reasons why patients with fail antifungals
  - Resistance, PK/PD, toxicity, host issues
- New antifungal drug development
- Innovative combinations
  - Local+systemic antifungals
  - Antifungals and immunotherapy (? local, e.g, inhaled GM-CSF)
  - Antifungals +surgery

# Candidiasis

# Delaying the Empiric Treatment of *Candida* Bloodstream Infection

## A Risk Factor for Hospital Mortality



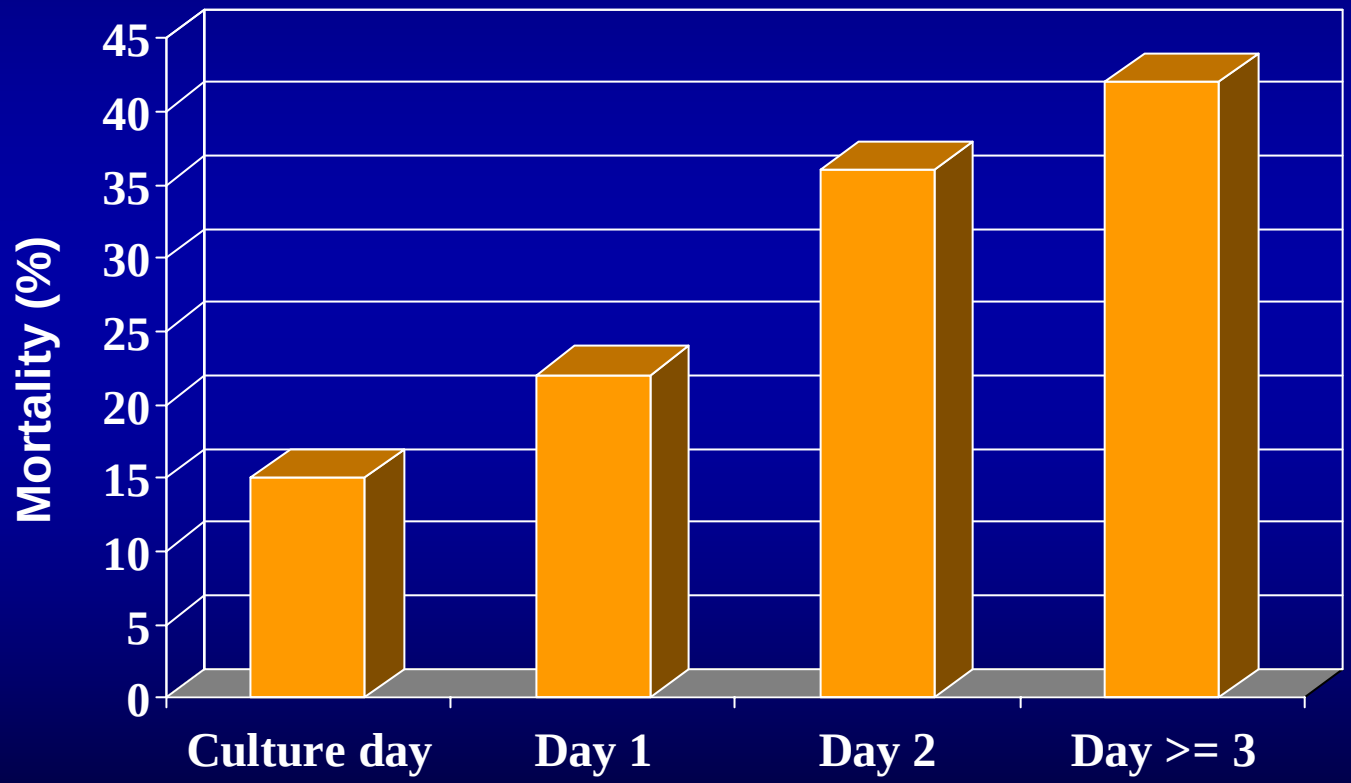

Multivariate analysis of independent risk factors for hospital mortality

| Variable | OR | 95% CI | *P* |
|---|---|---|---|
| APACHE II | 1.24 | (1.18-1.31) | <0.001 |
| Prior antibiotics | 4.05 | (2.14-7.65) | 0.028 |
| Delay in antifungal therapy | 2.09 | (1.53-2.84) | 0.018 |

Morrell et al. *Antimicrob Agent Chemother* 2005;49:3640.

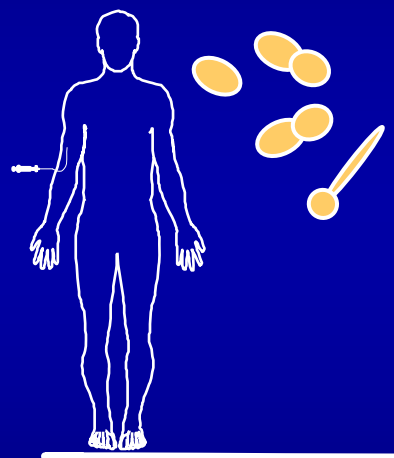
# Time to Initiation of Fluconazole Therapy Impacts Mortality in Patients with Candidemia

## A Multi-Institutional Study




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

# Difficulties in Establishing a Diagnosis for Candidemia



Antigen test or PCR?

Disease burden

**Crude Mortality 40%**

*Mortality doubles if antifungals are not started within 12 hrs of a positive blood culture**

**No disease** | **Cultures/Antigen** | **Signs and symptoms** | **Cultures/ histopathology** | **Sequelae**

**Prophylaxis** | **Preemptive** | **Empirical** | **Treatment** | **Morbidity/ Mortality**

* Morrell et al. *Antimicrob Agent Chemother* 2005;49:3640.

# (1→3) ß-D-Glucan as a Marker for Invasive Mycoses

- Cell wall component of yeast and filamentous fungi
- Amebocyte lysate assay
- Does detect:
  - *Aspergillus, Candida, Fusarium*, *Trichosporon*, *Saccharomyces,* and *Acremonium*
- Does not detect:
  - *Cryptococcus,* Zygomycetes

1. Yoshida M, et al. *J Med Vet Mycol*. 1997;35:371-374; 2. Obayashi T, et al. *Lancet*.1995;345:17-20; 3. Mori T, et al. EJCCCB. 1997;35:553-560.

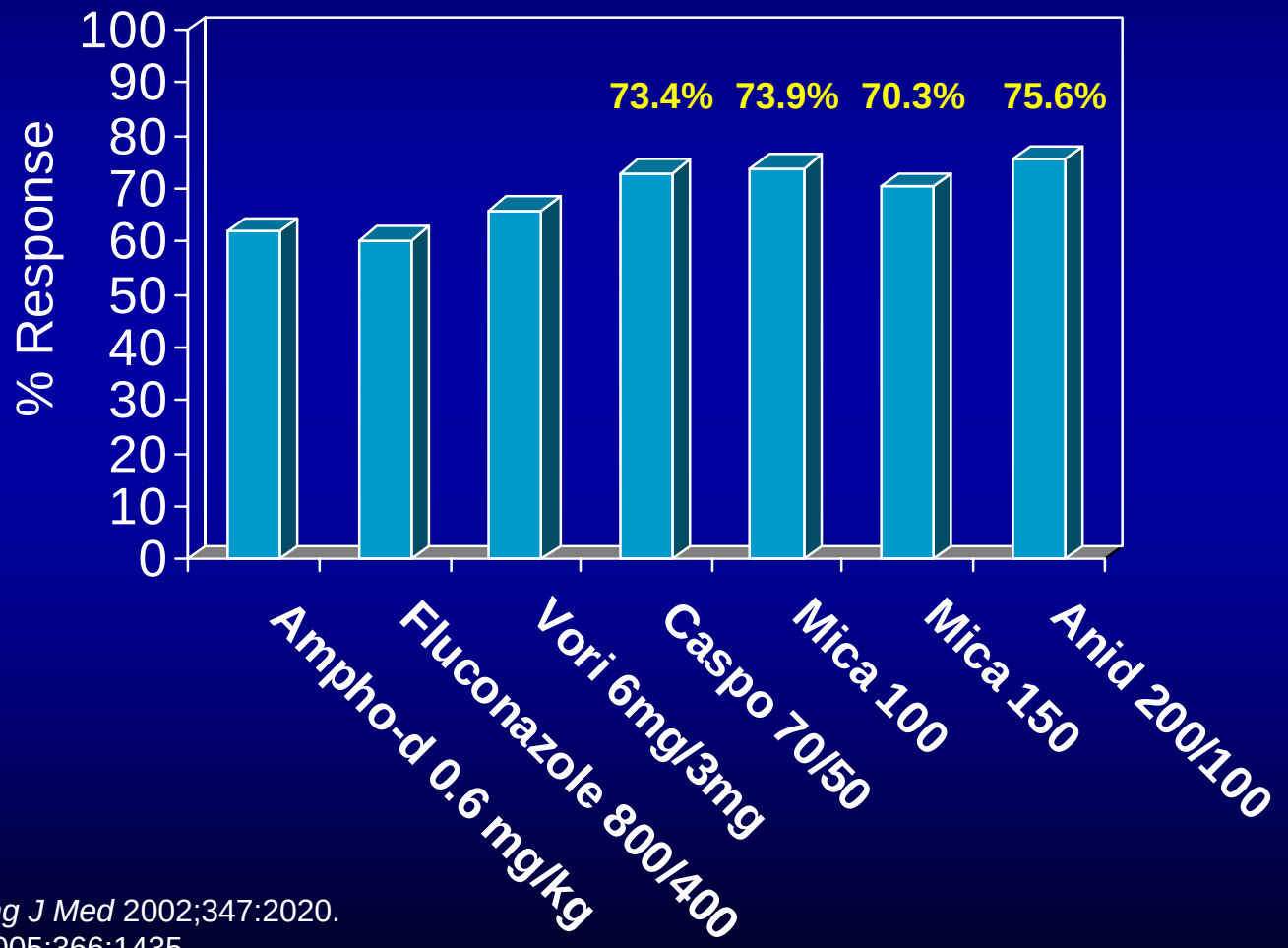
# Diagnostic Methods
# Rapid Culture/Identification

- Peptide nucleic acid fluorescence in situ hybridization assay (PNA FISH)
  - Utilizes fluorescent-labeled peptide nucleic acid probes targeting the specific rRNA sequences of *Candida albicans*
- Can reduce the median time required for the identification of *C. albicans* to 9.5 h (range, 3 to 17 h) vs. standard culture median time of 44 h (range, 36 to 92 h) ($P < 0.001$)
  - *Non C. albicans* by culture was even longer (61 h; range, 36 to 124 h).

Wilson DA, et al. *J Clin Microbiol.* 2005;43:2909-2912.

# Echinocandins: The preferred Drugs in The Treatment of Invasive Candidiasis

## End of IV Therapy (ITT/MITT Analysis)





Mora-Duarte et al. *N Eng J Med* 2002;347:2020.
Kullberg et al. Lancet 2005;366:1435.
Reboli et al. ICAAC 2005; LB Abstract M-718.
Betts et al ICAAC 2006; LB Abstract M-1308a

# Candidemia-Initial Therapy

## AI-Recommendation

- Caspofungin 70 mg d#1, 50 mg/d
- Fluconazole 400-800 mg/day
- Amphotericin B 0.7 mg/kg/d
- Amphotericin B (5-6 days) + Fluconazole 800 mg/day

## C-III

Liposomal AMB 3 mg/kg/d
Amphotericin B + 5-FC

## *C. glabrata*

- Caspofungin 70d#1, 50mg/d (A-I)
- Amphotericin B 0.7mg/kg/d (B-III)
- Fluconazole 12mg/kg/d(C-III)

## *C. krusei*

- Caspofungin 70d#1, 50mg/d(A-I)
- Voriconazole 4 mg/kg q12h(B-III)
- Amphotericin B 1mg/kg/d(C-III)

IDSA Guidelines for Treatment of Candidiasis. *Clin Infect Dis* 2004;38:161-189.

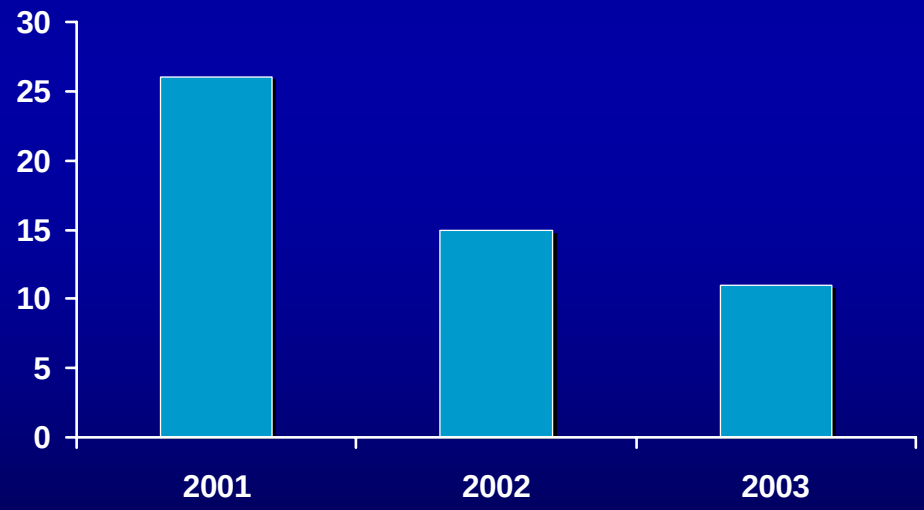
# Limitations of modern candidiasis trials

- No neutropenic patients
- Relatively stable, most with APACHEII<20
- Mostly CVC-related candidemias
- Low autopsy rate

# Caspofungin Use in a "Real-World" Setting

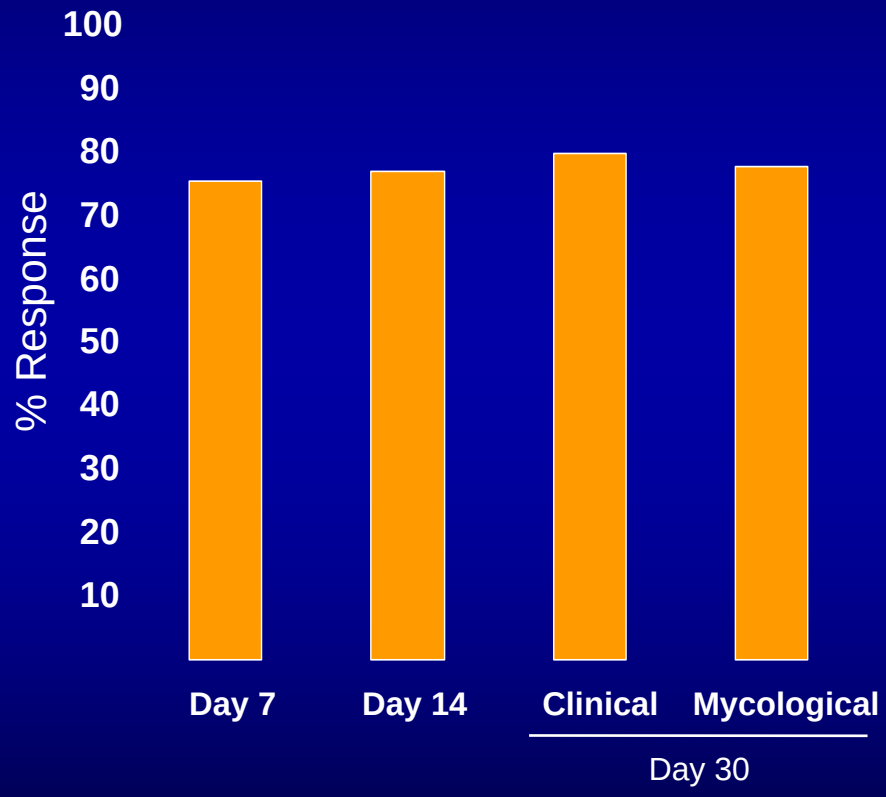
- **Clinical Cure rates 55/66 (83%)**
  - **23/26 (88%) intra-abdominal infections**
- **Attributable mortality to candidiasis (13%)**
- **Adverse events (rare)**

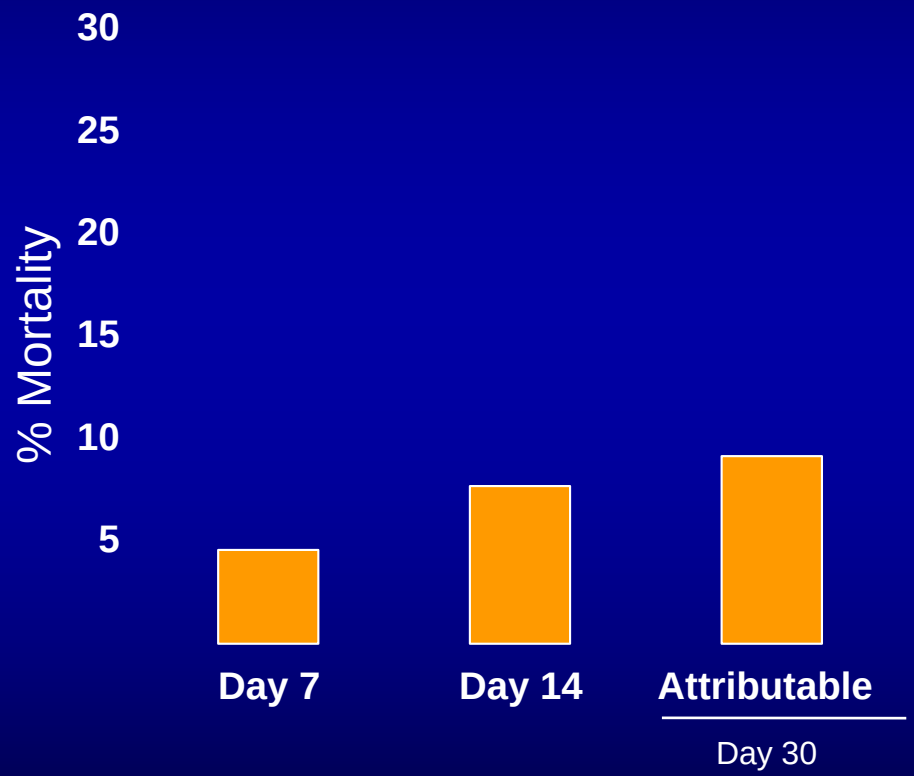
Invasive candidiasis failure rates




Zaas E et al. AJM 2006

# Caspofungin monotherapy treatment outcome at MDACC, 2001-2006 (n=64 patients)




Sipsas & Kontoyiannis. ECCMID 2007

# Caspofungin For Other Invasive *Candida* Infections

- Noncomparative study to evaluate caspofungin in less common cases of invasive candidiasis:
  - Osteomyelitis, meningitis, & endocarditis
  - Chronic disseminated candidiasis (CDC)
  - *Candida* intra-abdominal infections (peritonitis & abscesses)
- Diagnostic criteria: Clinical & microbiological evidence of infection
- Caspofungin dosing at 50 or 100 mg/day
  - Updosing of caspofungin (to 100 or 150 mg daily) allowed in patients not responding

Cornely O et al, *ICAAC* 2006

# Caspofungin For Other Invasive *Candida* Infections (cont.)

- Total of 40+ sites in 13 countries
  - Enrollment at 17 sites in 10 countries, including US (4), Central or Latin America (6), Europe (5), & Australia (2)
- Target enrollment ~50 patients
- Enrollment August 2004 to February 2006
  - Since June 2005, enrollment limited to certain types of infections (i.e., endocarditis, meningitis, osteomyelitis, septic arthritis, endophthalmitis)
  - Final data available on all 48 patients

Cornely O et al, *ICAAC* 2006

# Efficacy Results

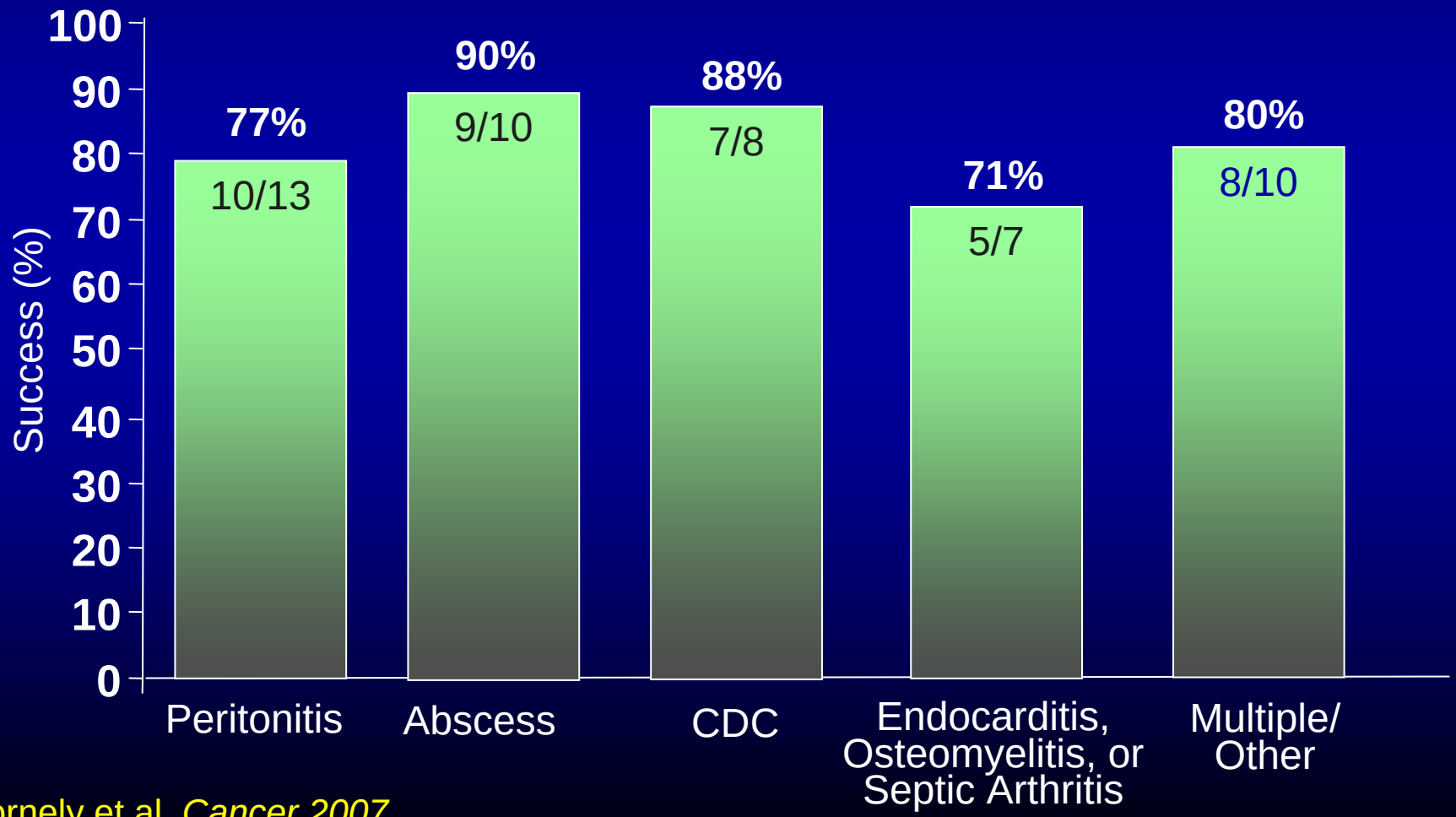
| Endpoint | n/m | (%) |
|---|---|---|
| Success at the End of Caspofungin Therapy (MITT) | 39/48 | (81) |
| Relapse out to 12 weeks posttherapy in patients with a favorable response | 2/39 | (5) |
| Mortality (to 12 weeks posttherapy) | 11/48 | (23) |

MITT defined as any patient with a confirmed diagnosis of invasive candidiasis who received at least 1 dose of caspofungin

Cornely O et al, *ICAAC* 2006

# Efficacy by Site of *Candida* Infection

Success at the End of Caspofungin Therapy




Cornely et al, *Cancer 2007*

# Controversies about treatment of candidiasis

- Antifungal activity in biofilm-associated *Candida*
- Catheter management
- Activity in neutropenic and critically ill patients
- Is there any role of in vitro echinocandin MICs?
- What is the potential of echinocandin resistance in *Candida*?
- Value of short term echinocandin therapy followed by azoles
- Are they any meaningful differences among the echinocandins?

# Echinocandins are fungicidal versus *Candida* species and exhibit activity against biofilm-embedded organisms

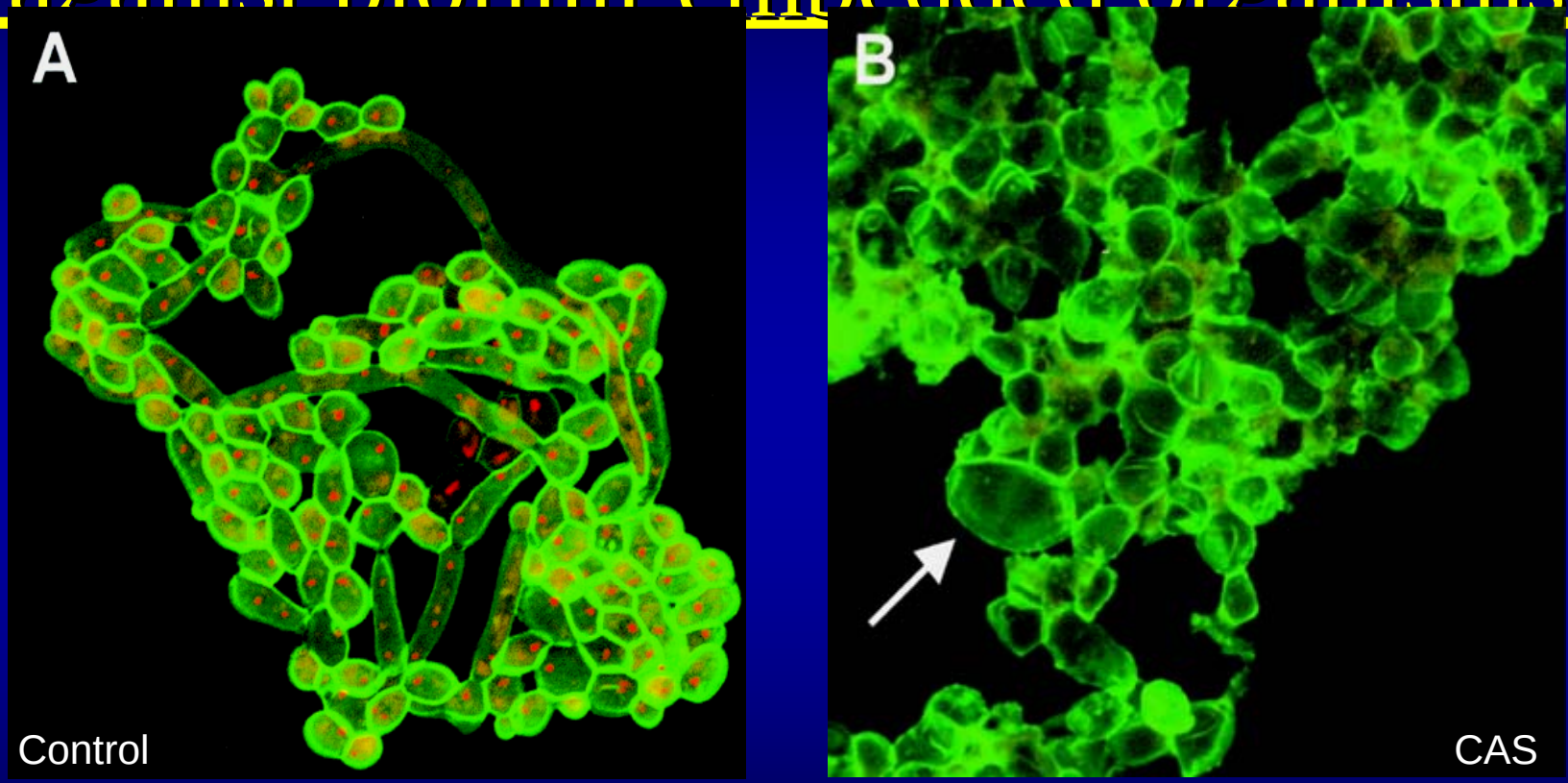
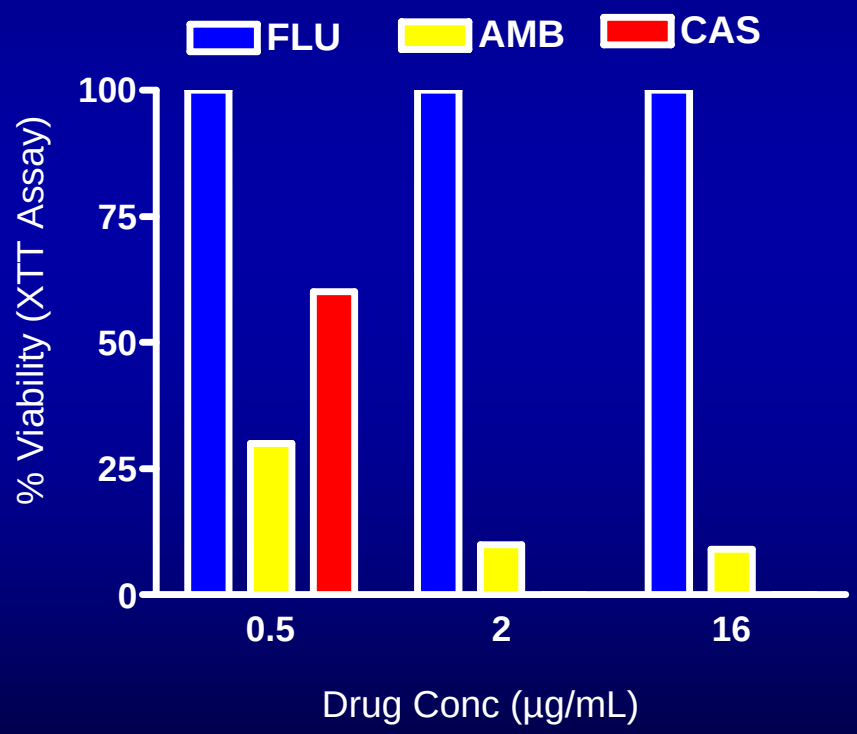



**FIG. 3. CSLM of planktonic *C. albicans* cells treated with antifungal agents. Images utilize CAAF and FUN-1 staining, a 63x oil immersion objective, and 2x magnification. Green CAAF staining highlights blastospore cell walls.**

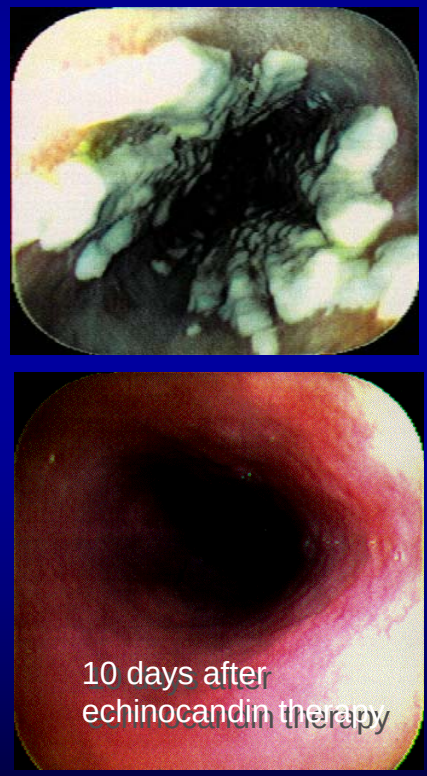
**Kuhn et al. *Antimicrob Agent Chemother.* 2002;46:1773-80**

# Echinocandin Activity vs. Biofilm-Embedded *Candida*

Antifungal Killing vs. Biofilm-Embedded *Candida* spp.

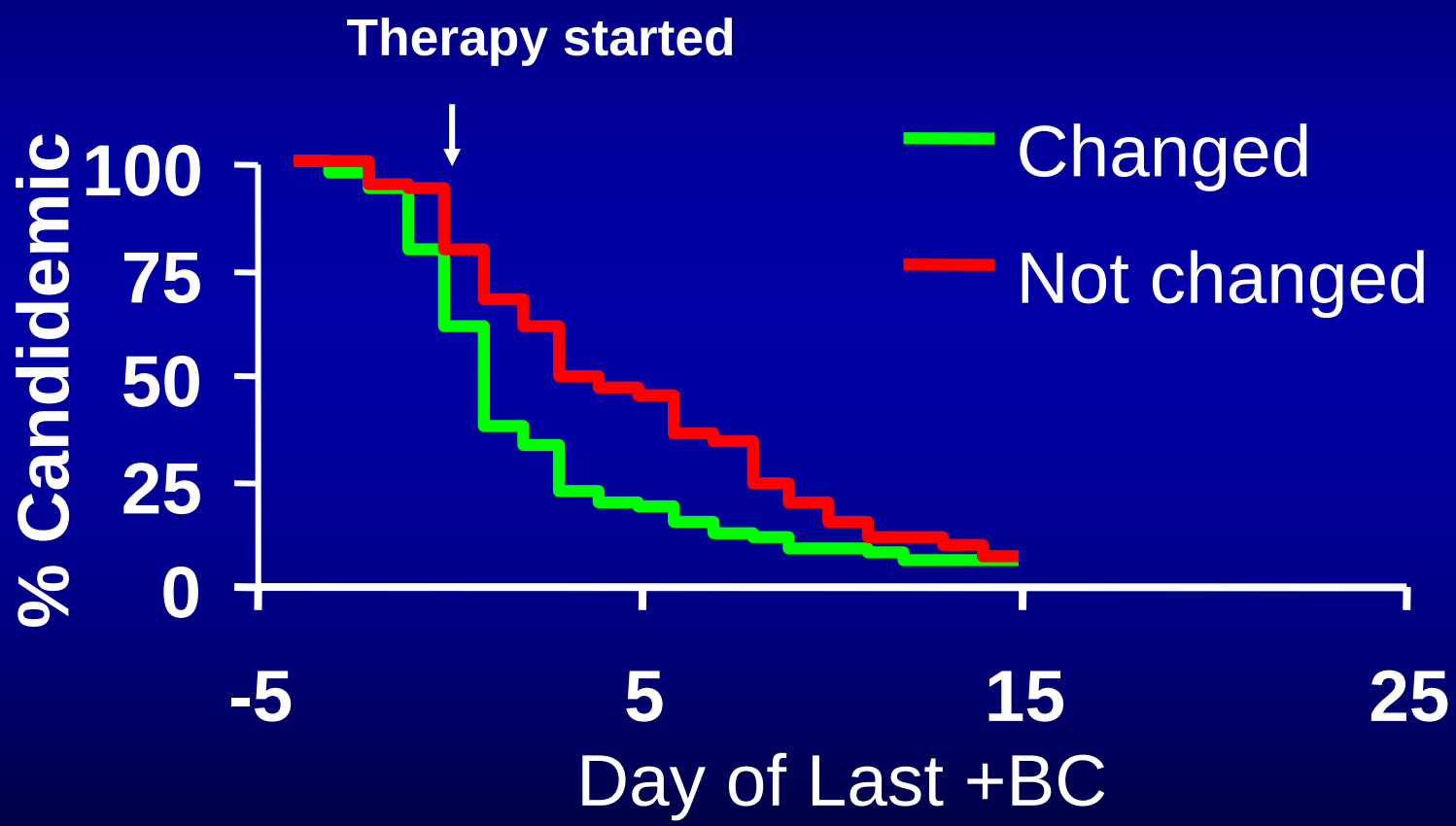



Echinocandin response in azole-refractory esophagitis



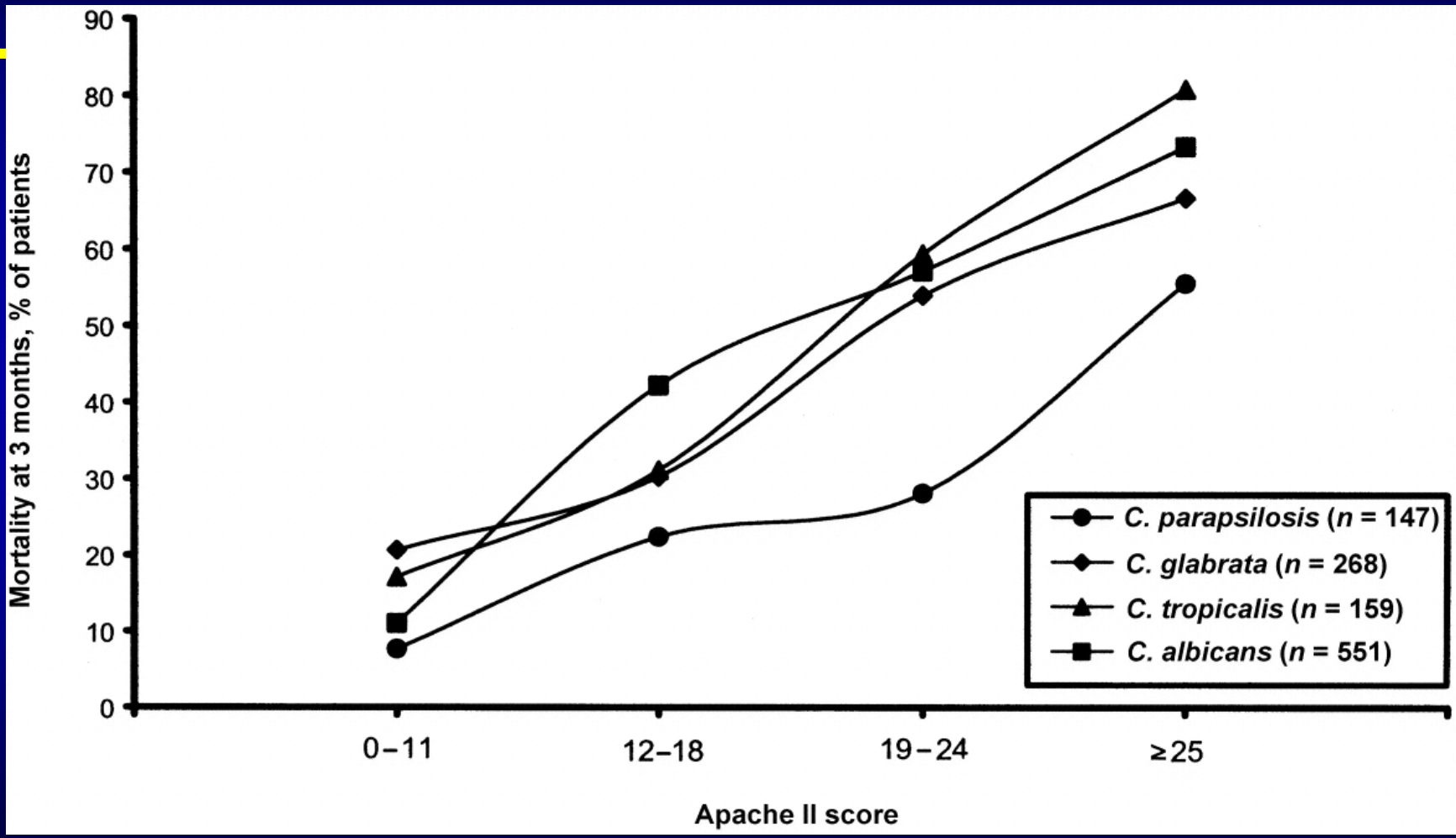

Ramage et al. *Antimicrob Agent Chemother* 2002;46:3634

# Removal of Infected Catheters




Rex et al *Clin Infect Dis 1995:*21;994-6.

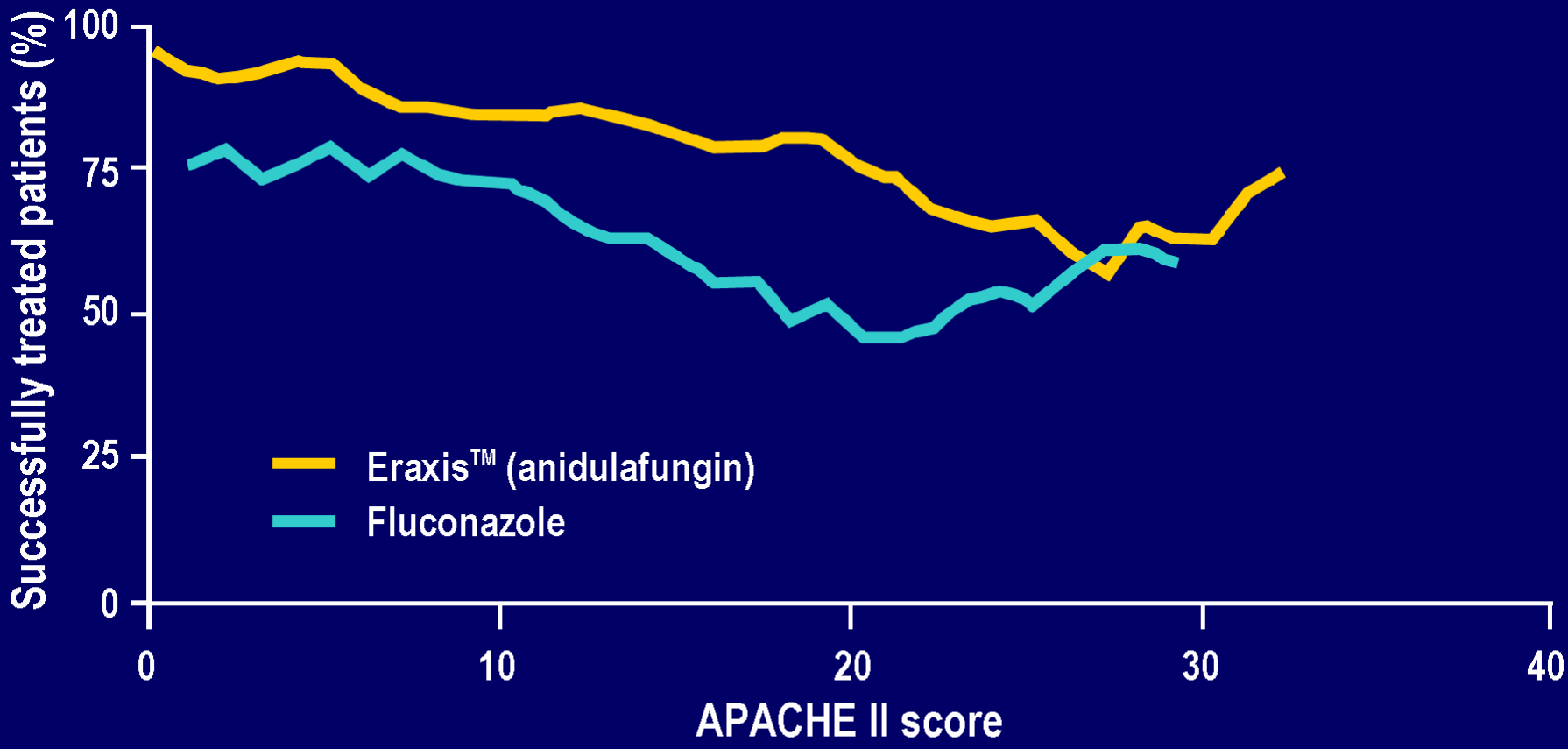
# Mortality 3 months after the initial positive blood culture among adults with candidemia, according to *Candida* species and APACHE II score




Pappas et al. *Clin Infect Dis.* 2003;37:634-643

## Candidemia Study

# Success at End of IV Therapy by APACHE II Score (MITT Population)




Data on file. Pfizer Inc.

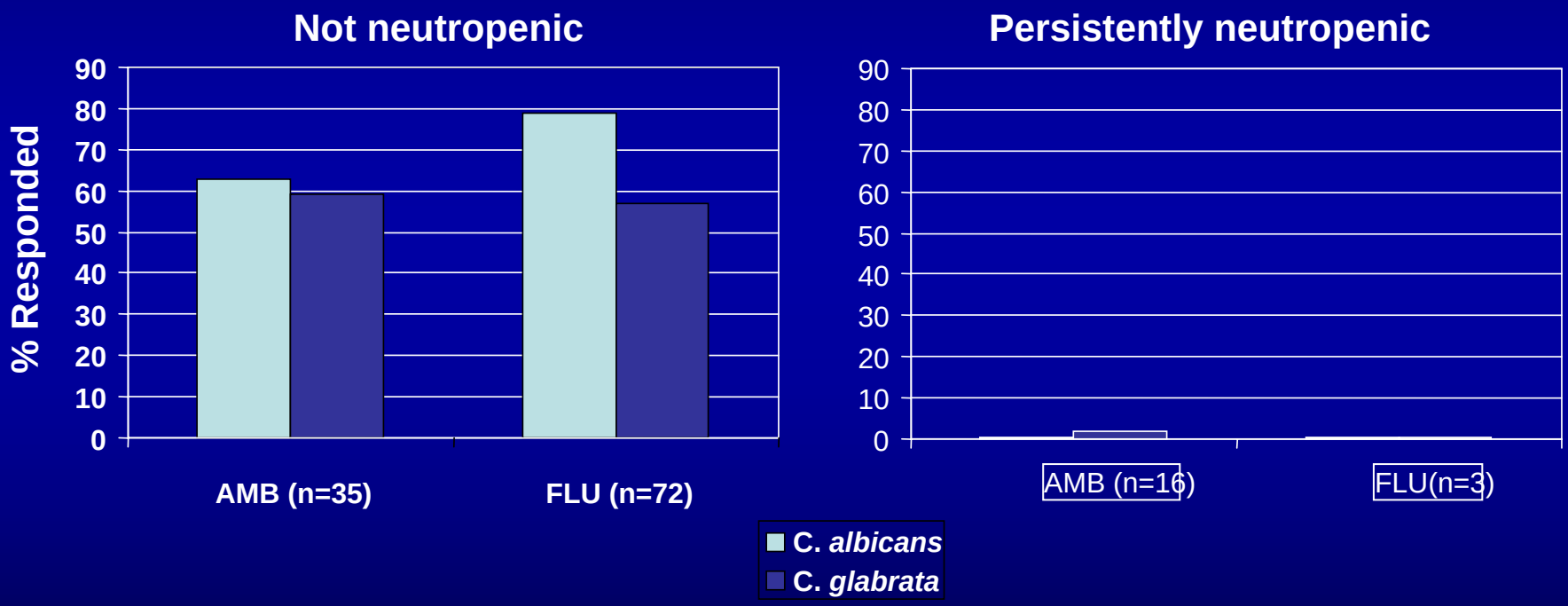
# Does CAS Work in Neutropenic Patients?

| | Caspofungin n/m (%) | L-AMB n/m (%) |
|---|---|---|
| Overall* | 14/27 (51.9) | 7/27 (25.9) |
| *Aspergillus* spp. | 5/12 (41.7) | 1/12 (8.3) |
| *Candida* spp. | 8/12 (66.7) | 5/12 (41.7) |
| Other | 1/3 (33.3) | 1/3 (33.3) |

* p = 0.043

Walsh et al. *N Eng J Med* 2004;351:1391-1402

# *C. glabrata* Fungemia in Patients With Cancer




**Bodey et al. *Am J Med* 2002;112:380-386.**

# Comparing the echinocandins

- **Are MIC differences clinically important?**

  MIC data (unstandardized, mixed results, differences not consistent with animal data)

  – Pharmacokinetics (Serum exposures MICA, CAS, > Anidul)

  – Clinical outcome (no correlation with outcomes in candidemia)

- **Is there a difference in the potential to select or treat echinocandin resistant *Candida* species? No**

- **Pharmacokinetic differences, drug interactions, and hepatic toxicity? Some, unclear clinical significance**

- **Important differences in pivotal clinical trials and indications? Probably not**

- **Formulary considerations: Complex, cost**

# Comparison of Micafungin and Caspofungin for Candidemia or Invasive Candidiasis

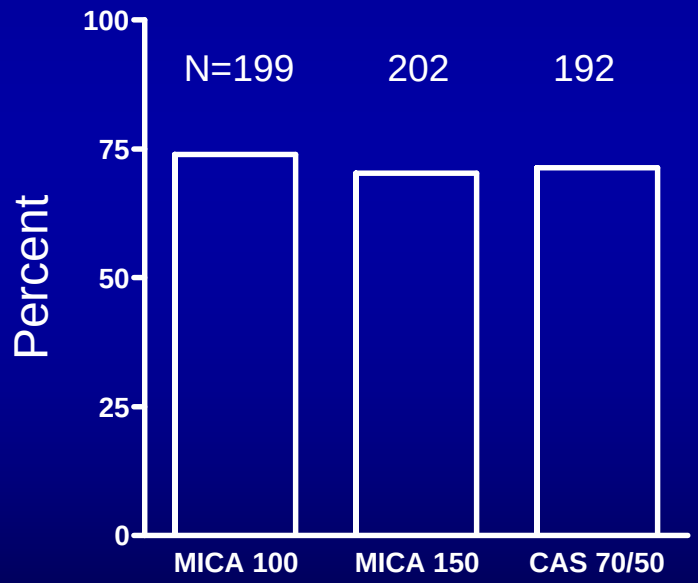
- Phase 3, 1:1:1 randomized double-blind non-inferiority study in adults:
  - Micafungin 150 mg/day
  - Micafungin 100 mg/day
  - Caspofungin 70/50 mg/day

- Primary endpoint:
  - Clinical and mycological response at end of IV therapy with a pre-specified $\Delta$ - 15%

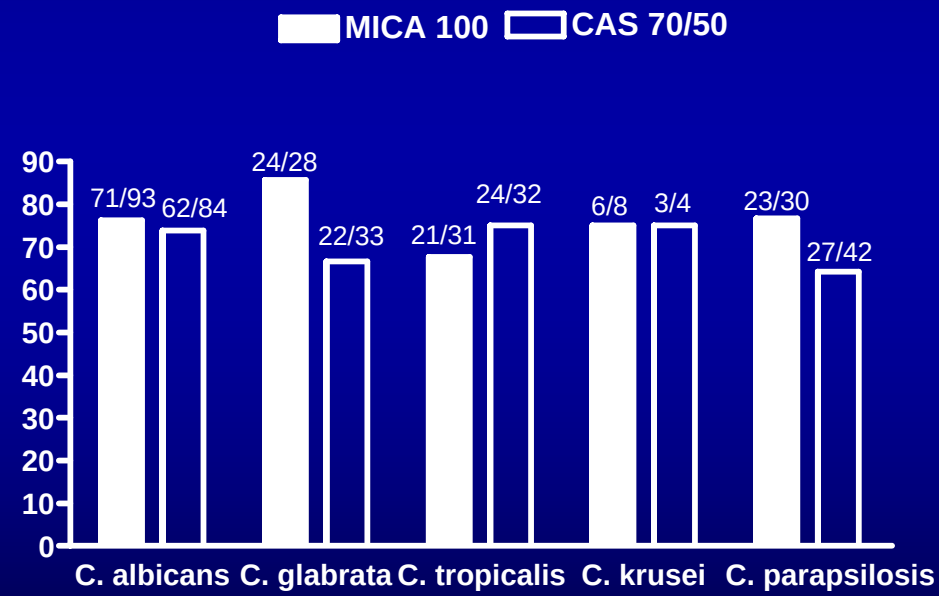
Betts et al. ICAAC 2006. Abstract M-1308a

# Comparison of Micafungin and Caspofungin for Candidemia or Invasive Candidiasis

## Overall Success




## Success by Baseline Pathogen




Betts et al. ICAAC 2006. Abstract M-1308a

# Invasive candidiasis

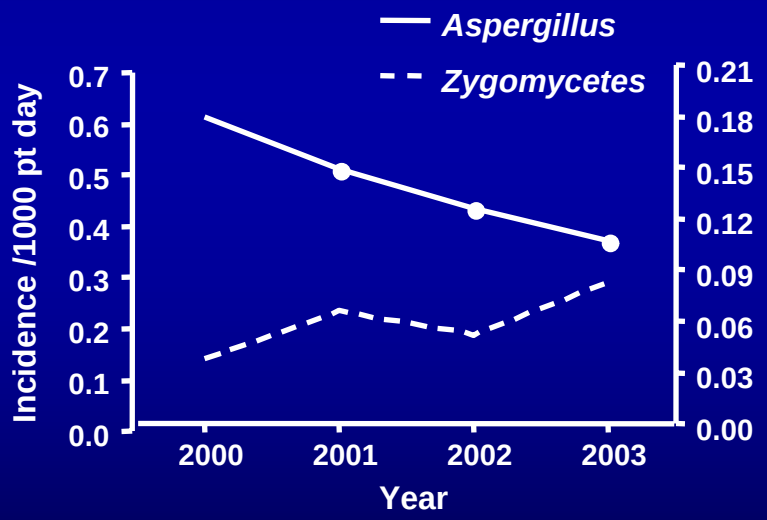
## Where we've been, where we're going….

- Successes
  - Improved prevention/treatment of serious *Candida* infections
  - Less toxic alternatives to AmB-based therapy
  - Resistance remains relatively uncommon overall

- Challenges: Further reductions in mortality!
  - Improved prevention strategies for high risk pts
  - Early initiation of therapy with the best drug, at an effective dose
  - Improved non-culture based diagnosis
  - Better laboratory support for management and detection of antifungal resistance

# Changing Epidemiology of Invasive Moulds Era of Voriconazole?

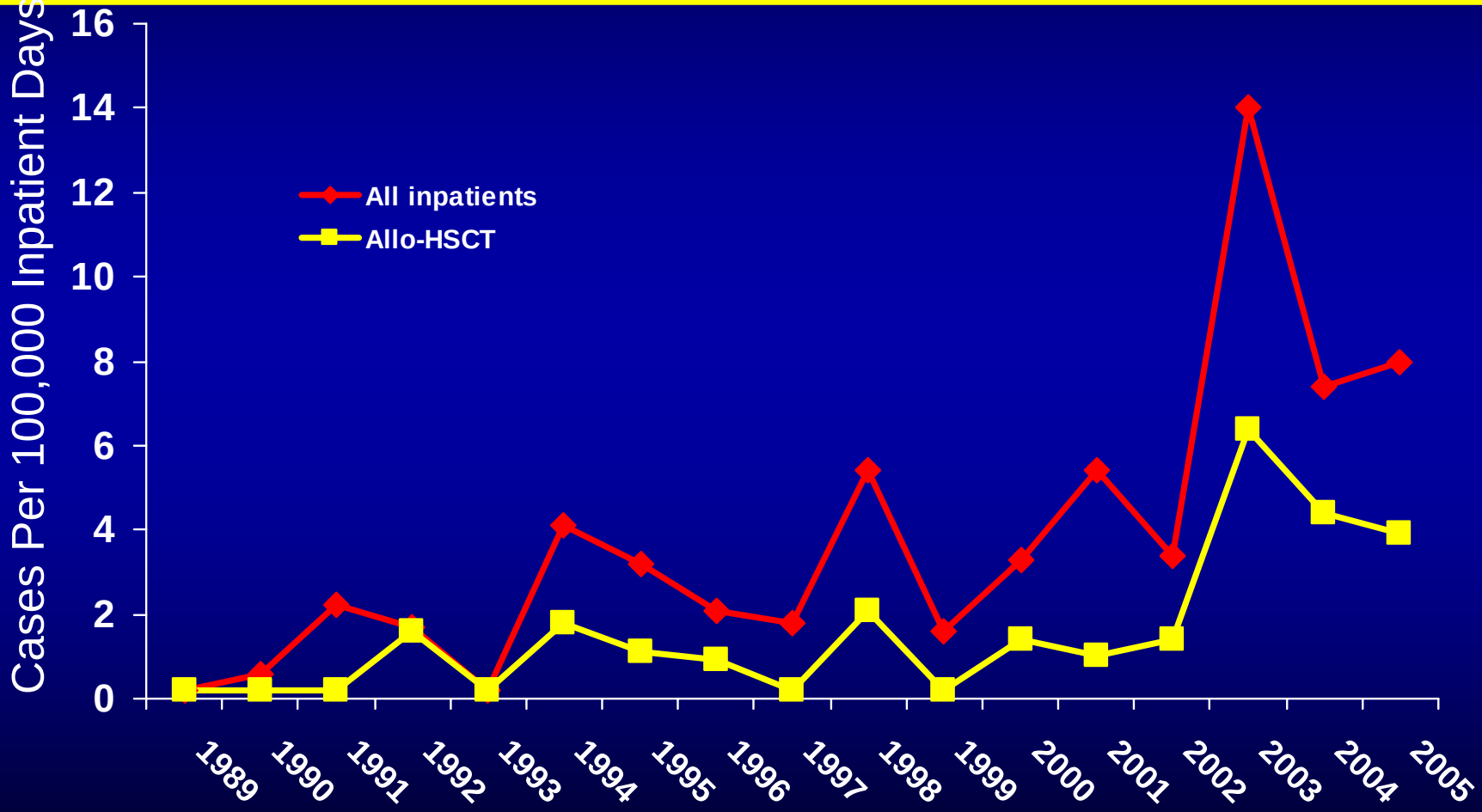
- In untreated patients, currently considered first-line therapy for invasive aspergillosis
- Has activity against many AMB-resistant species
  - *Aspergillus terreus*
  - *Aspergillus flavus*
  - *Fusarium* spp.
  - *Scedosporium apiospermum*




**Kontoyiannis et al. *J Infect Dis* 2005: 191:1350**

# Zygomycosis at MDACC (1989-2005)

## A review of 100 cases




Chamilos G, et al. ICAAC 2006 Abstract A-2156

# Case 1

**Persistent fever on day 4 of neutropenia in a patient with leukemia during remission induction chemotherapy on fluconazole prophylaxis**

**All are false but one:**

A. **Empiric antifungal therapy is not justified**
B. **Fluconazole is appropriate**
C. **Viruses are common cause of fever in that setting**
D. **Caspofungin, lipid AMB formulations, voriconazole are appropriate choices**

# Case 2

**Development of fever, positive cultures for yeasts in a febrile critically patient with in ICU while on fluconazole prophylaxis.**

**The most common yeasts in that setting is:**

**A.** ***C. glabrata***
**B.** ***C. parapsilosis***
**C.** ***C. albicans***
**D.** ***C. tropicalis***

# Case 3

**Development of fever, increased alkaline phosphatase, and multiple lucent lesions in liver and spleen on CT scan after engraftment post-HSCT is most likely due to:**

A. *Fusarium* spp
B. *Aspergillus fumigatus*
C. *Candida* spp
D. *Staphylococcus* spp
E. *Zygomycetes*

# Case 4

**In the late postengraftment period after HSCT a pulmonary cavitary nodule seen on chest CT would most likely be due to:**

A. *Candida tropicalis*
B. Invasive moulds, most likely *Aspergillus* spp
C. *Candida glabrata*
D. *Pseudomonas aeruginosa*
E. *Staphylococcus aureus*

# Case 5

**A non-neutropenic patient with AML developed postnasal drainage and left maxillary sinus pain 52 days after allogeneic BMT while receiving voriconazole prophylaxis (400 mg/day) since transplantation. The patient had been receiving high-dose methylprednisolone (total dose> 600 mg in the month prior) for GvHD**

**What is a major consideration here?**

**A) *Candida***
**B) *Fusarium***
**C) *Aspergillus***
**D) *Zygomycetes***

# Case 6

**A profoundly neutropenic patient with refractory AML develops sepsis, acute pneumonia and multiple necrotic skin lesions**

**What is a major consideration here?**

**A) *Candida***

**B) *Fusarium***

**C) *Aspergillus***

**D) *Zygomycetes***

***Thank you!***