



# New Antifungals

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# New (and Newer) Antifungals for Invasive Mycoses

## Liposomal polyenes

- ABLC, ABCD, amphotericin B (AmBisome)
- Liposomal nystatin
- Inhaled amphotericin B

## Others

- Icofungipen (PLD-118)
- Sordarins
- hsp90 MAb (Mycograb)
- INH-A21 (Veronate)

## Azoles

- Itraconazole (IV)
- Voriconazole
- Posaconazole
- Ravuconazole
- Albaconazole
- BAL 8557/4815

## Echinocandins

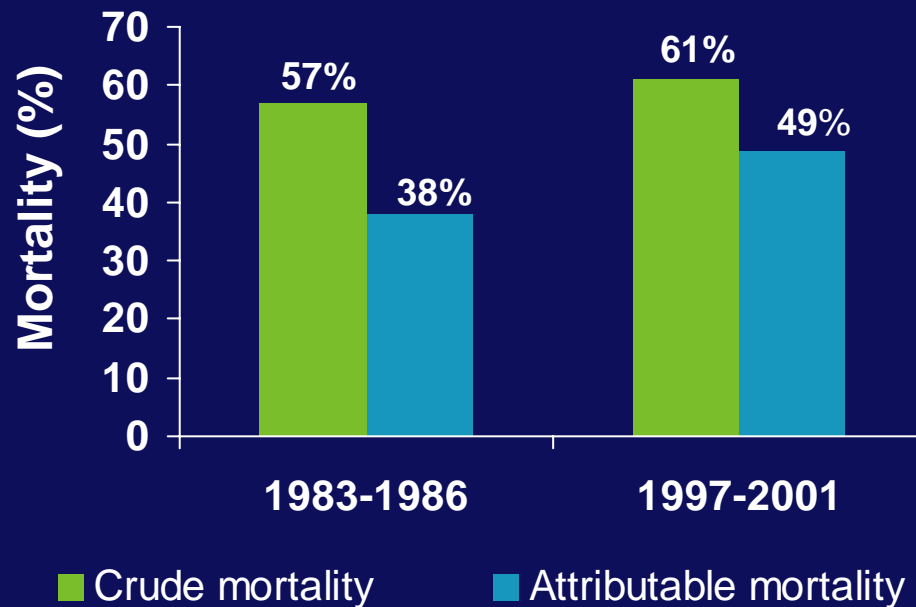
- Caspofungin
- Micafungin
- Anidulafungin
- Aminocandin

Blue text = earlier stage of development.

ABLC = amphotericin B lipid complex; ABCD = amphotericin B colloidal dispersion.

# Clinical Impact of Candidemia

## Crude and Attributable Mortality in Nosocomial Candidemia



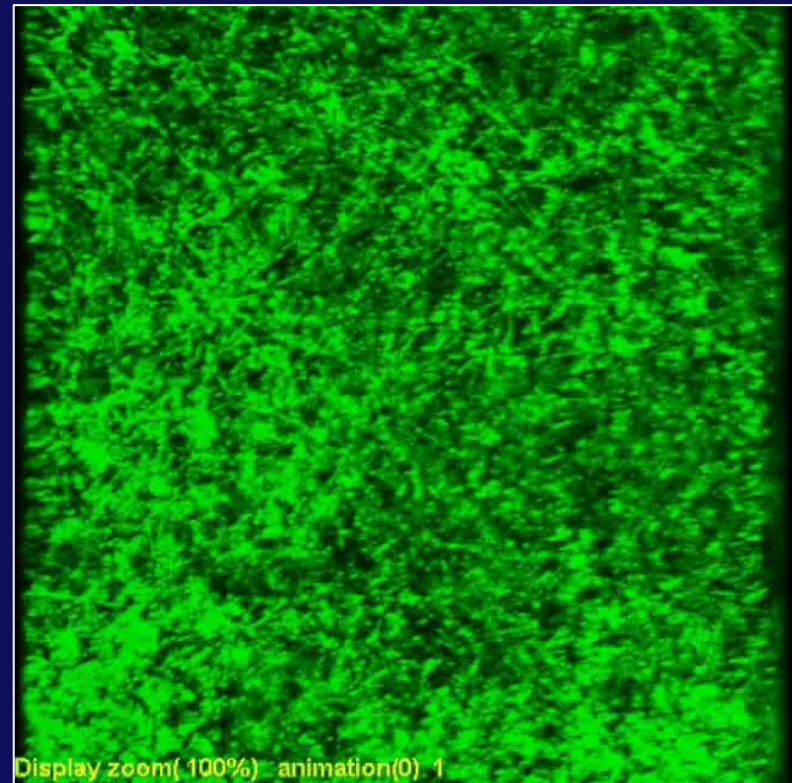
- Crude mortality rates in recent series: 30% – 61%
  - More than predicted by *Candida* alone
- Role of *Candida* in ICU sepsis (Martin, 2003)
  - 1979-2000: 207% increase
- Greatest increase for any organism
- Fungal sepsis associated with inadequate therapy (Garnacho-Montero 2003)
- Increased mortality with inadequate initial therapy (Ibrahim 2000)

Wey SB, et al. *Arch Intern Med.* 1988;148:2642-2645; Gudlaugsson O, et al. *Clin Infect Dis.* 2003;37:1172-1177; Martin GS, et al. *N Engl J Med.* 2003;348:1546-1554; Ibrahim EH, et al. *Chest.* 2000;118;146-155; Garnacho-Montero J, et al. *Crit Care Med.* 2003;31:2742-2751.

# Clinical Relevance of Biofilms

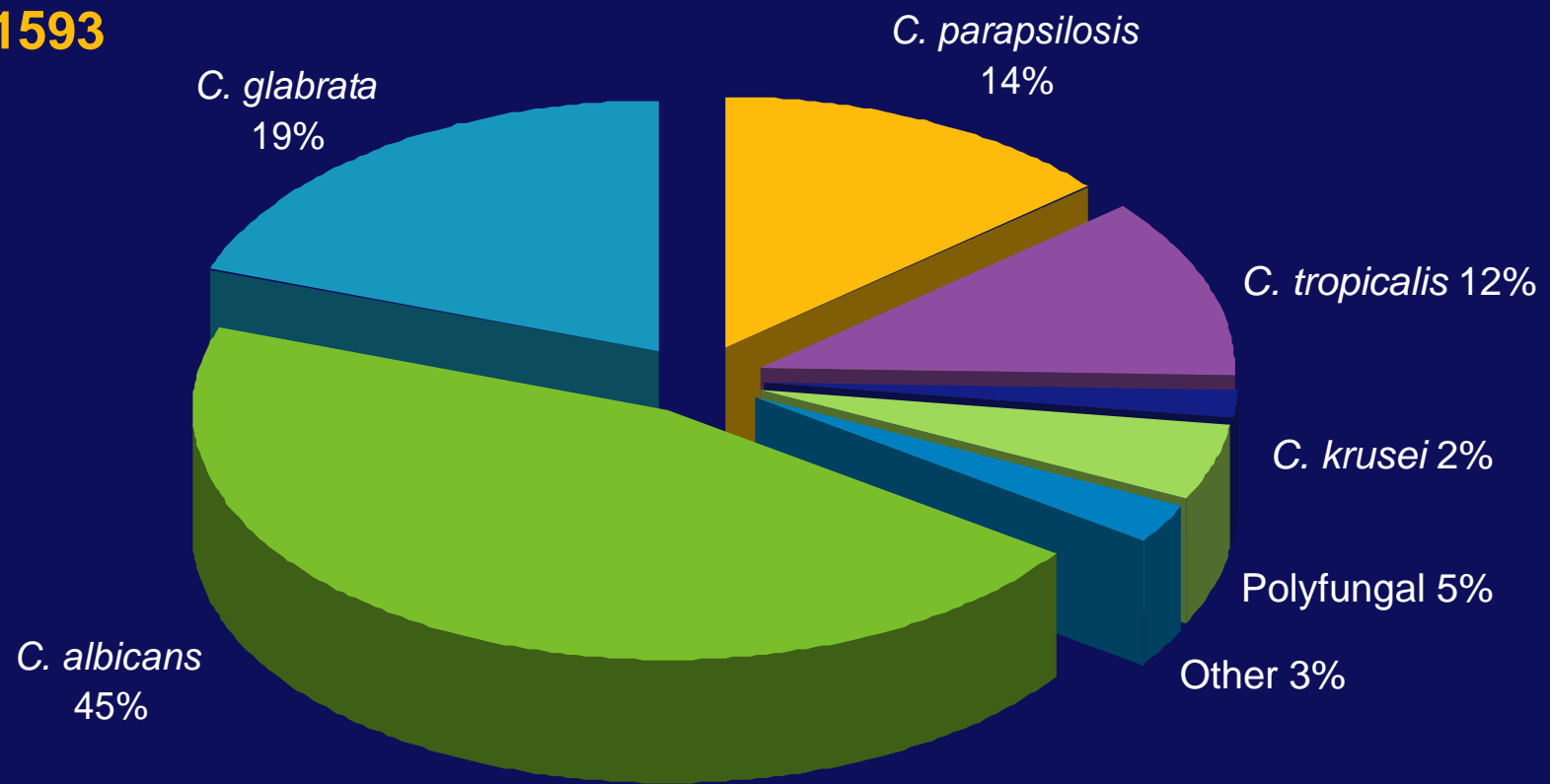
- *Candida* spp. adhere to inert and biological surfaces – associated with virulence
  - Catheter-related infections
  - Biomaterial surfaces (implants, dentures, prostheses)
  - Biofilm-associated infections (endocarditis, oropharyngeal candidiasis)
- High level of antifungal resistance
  - Fluconazole and polyene resistance
  - Echinocandin susceptibility

## 3D view of a *Candida albicans* biofilm



# Nosocomial Candidemia: Epidemiology

**N = 1593**

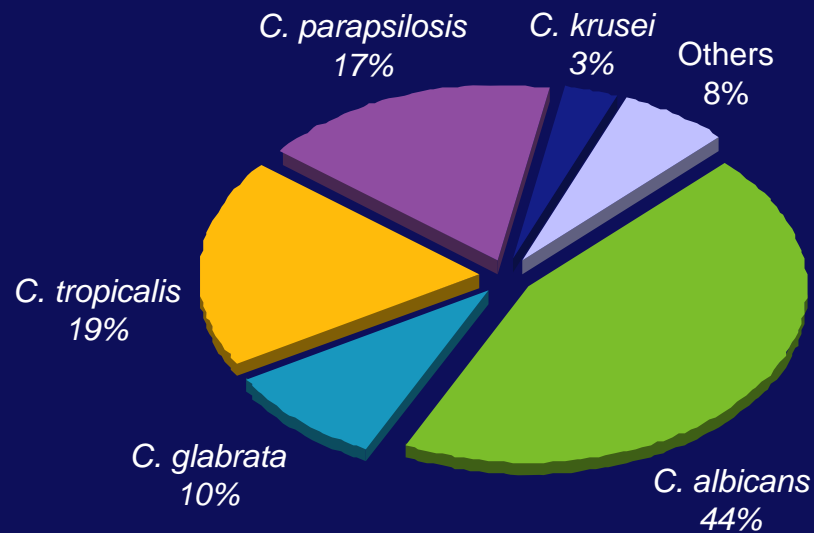


N = 1593.

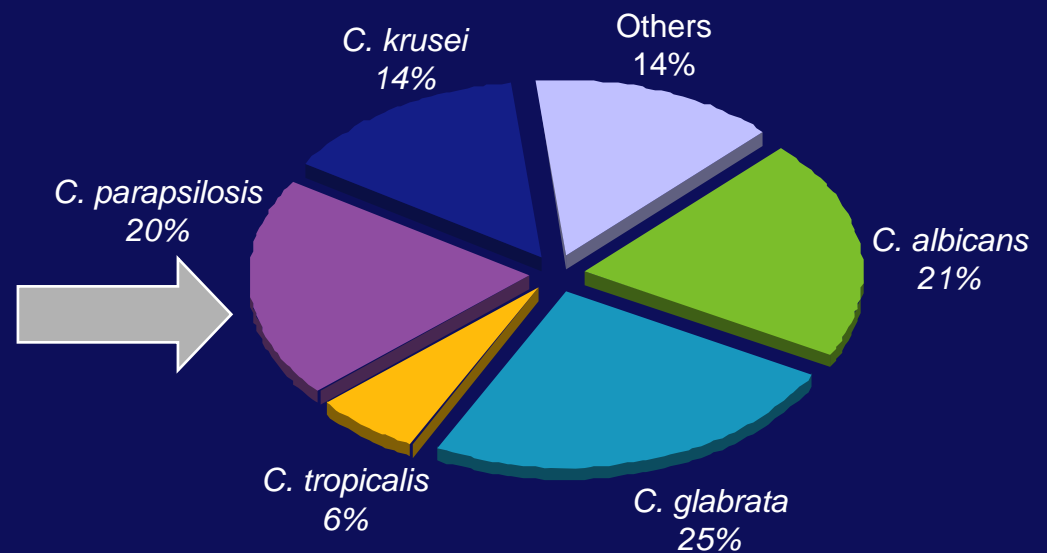
Pappas PG, et al. *Clin Infect Dis.* 2003;37:634-643.

# Epidemiology of Candidemia: Impact of Prior Antifungal Therapy

**Non-Breakthrough  
(n = 430)**



**Breakthrough  
(n = 49)**



**Mortality: 50% vs 76%**

## Typical In Vitro Susceptibility of *Candida* spp.

Species	Flu	Itra	AmB	Vori	Posa	Candins
<i>C. albicans</i>	S	S	S	S	S	S
<i>C. tropicalis</i>	S	S	S	S	S	S
<i>C. parapsilosis</i>	S	S	S	S	S	S / I
<i>C. dubliniensis</i>	S / S-DD	S	S / I	S / I	S / I	S
<i>C. glabrata</i>	S-DD / R	S-DD / R	S / I	S / I	S / I	S
<i>C. krusei</i>	R	S-DD / R	S	S	S	S
<i>C. lusitaniae</i>	S	S	S / R	S	S	S

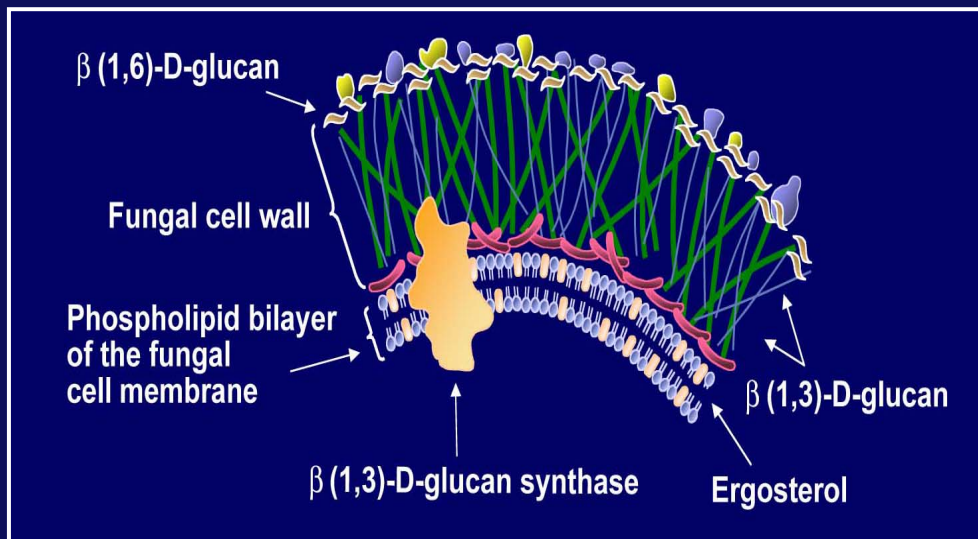
Flu = fluconazole; Itra = itraconazole; AmB = amphotericin B; Vori = voriconazole; Posa = posaconazole; S = susceptible; S-DD = susceptible–dose dependent; I = intermediate; R = resistant.

Pappas PG, et al. *Clin Infect Dis*. 2004;38:161-189; Bartizal K, et al. *Antimicrob Agents Chemother*. 1997;41:2326-2332; Patterson TF. *J Chemother*. 1999;11:504-512; Pfaller MA, et al. *Antimicrob Agents Chemother*. 2002;46:1723-1727; Pfaller MA, et al. *J Clin Microbiol*. 2002;40:852-856.

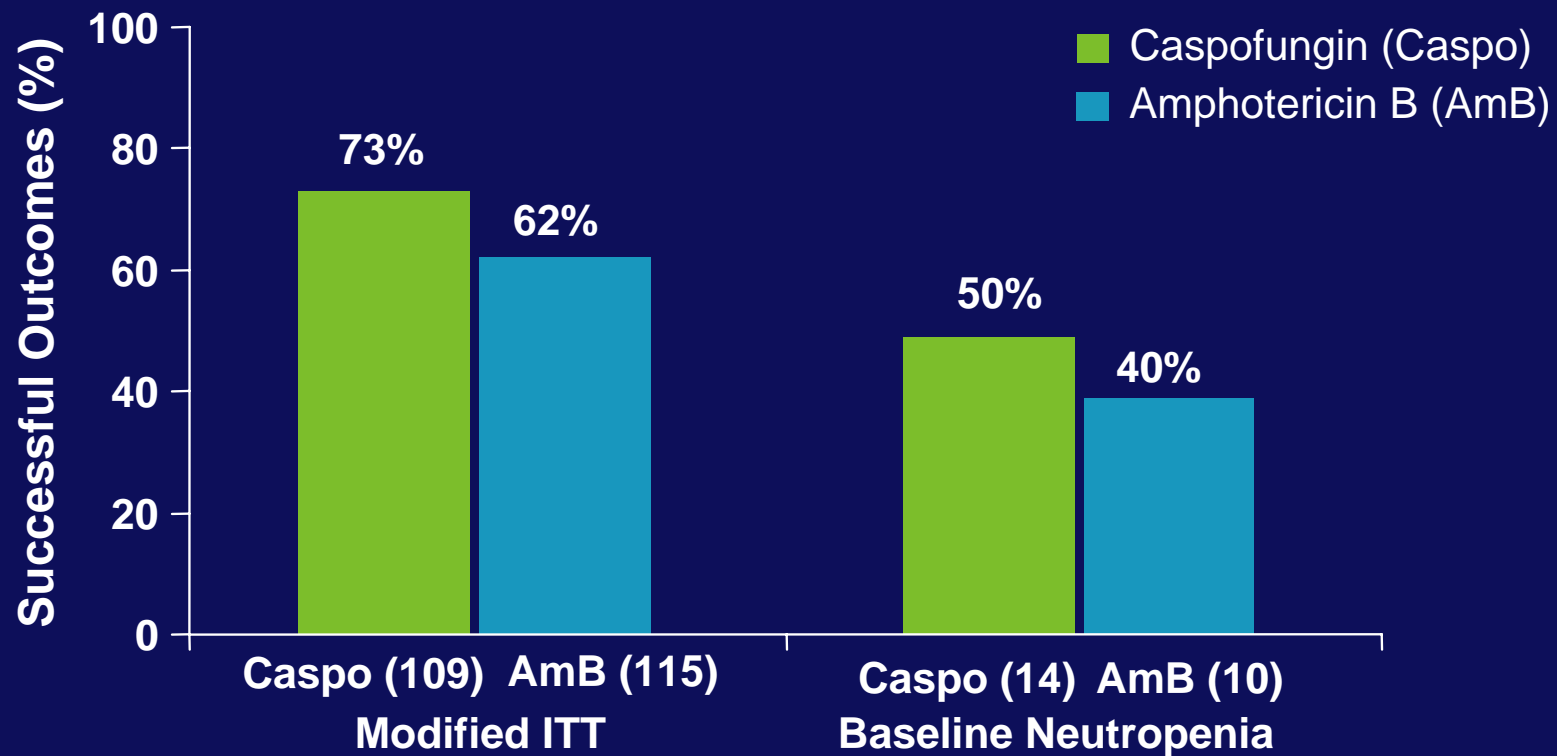
# Echinocandins

- Cyclic lipopeptide antifungals that inhibit  $\beta(1,3)$ -D-glucan synthase
  - Caspofungin
  - Micafungin
  - Anidulafungin

- Characteristics
  - Rapidly fungicidal for *Candida*
  - Intravenous administration
  - Minimal renal toxicity
- Activity
  - Yeasts (*C. albicans*; non-*albicans*)
  - Molds (*Aspergillus*; not Zygomycetes)
  - Others (endemic mycoses; not *Cryptococcus*)



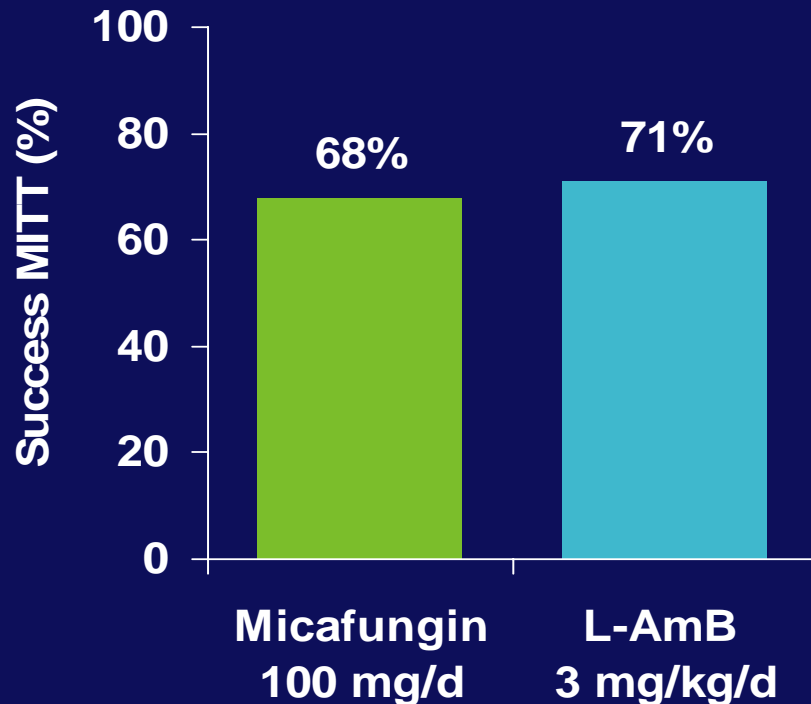
# Caspofungin vs Amphotericin B for Invasive Candidiasis



Successful outcome = symptom resolution and microbiologic clearance. Assessments at end of IV treatment.

Mora-Duarte J, et al. *N Engl J Med.* 2002;347:2020-2029.

# Micafungin vs Liposomal Amphotericin (L-AmB) in Candidemia

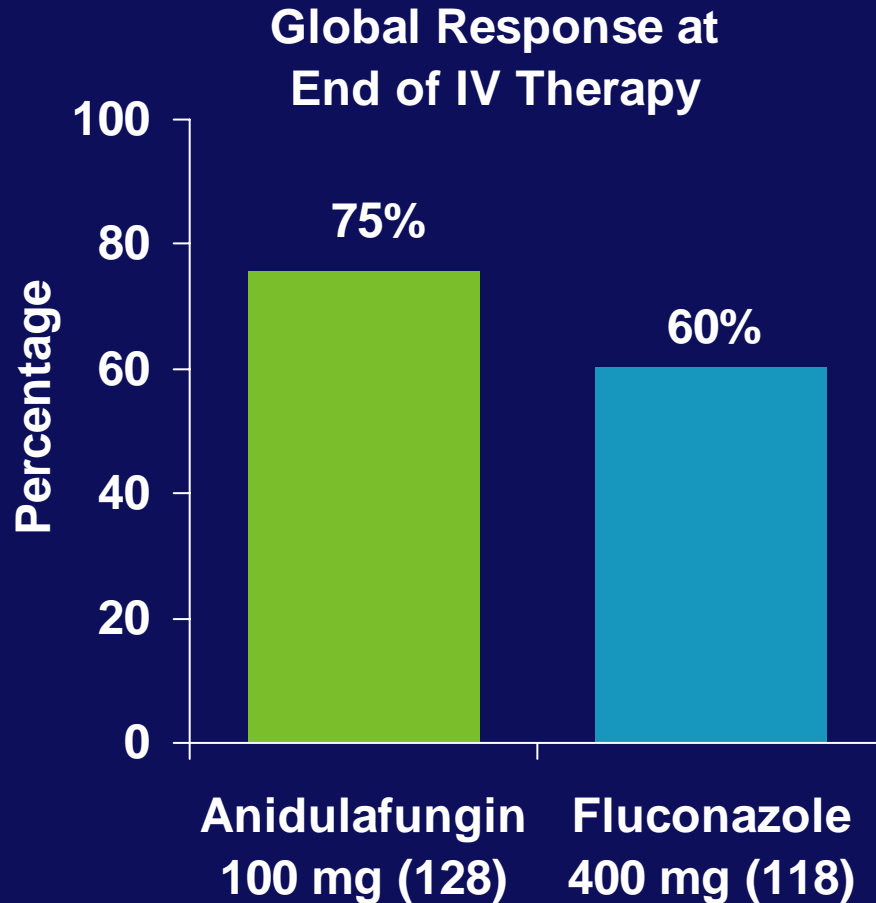


- Micafungin 100 mg/kg/d (n = 264) vs L-AmB 3 mg/kg/d (n = 267)
- Per-protocol success
  - Micafungin: 181/202 (89.6%)
  - L-AmB: 170/190 (89.5%)
- More infusion-related toxicity and renal abnormalities in L-AmB
- Optimal dose of micafungin not established

MITT = modified intent-to-treat [analysis].

Ruhnke M, et al. Presented at: 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); December 16-19, 2005; Washington, DC. Abstract M-722.

# Anidulafungin vs Fluconazole for Invasive Candidiasis and Candidemia

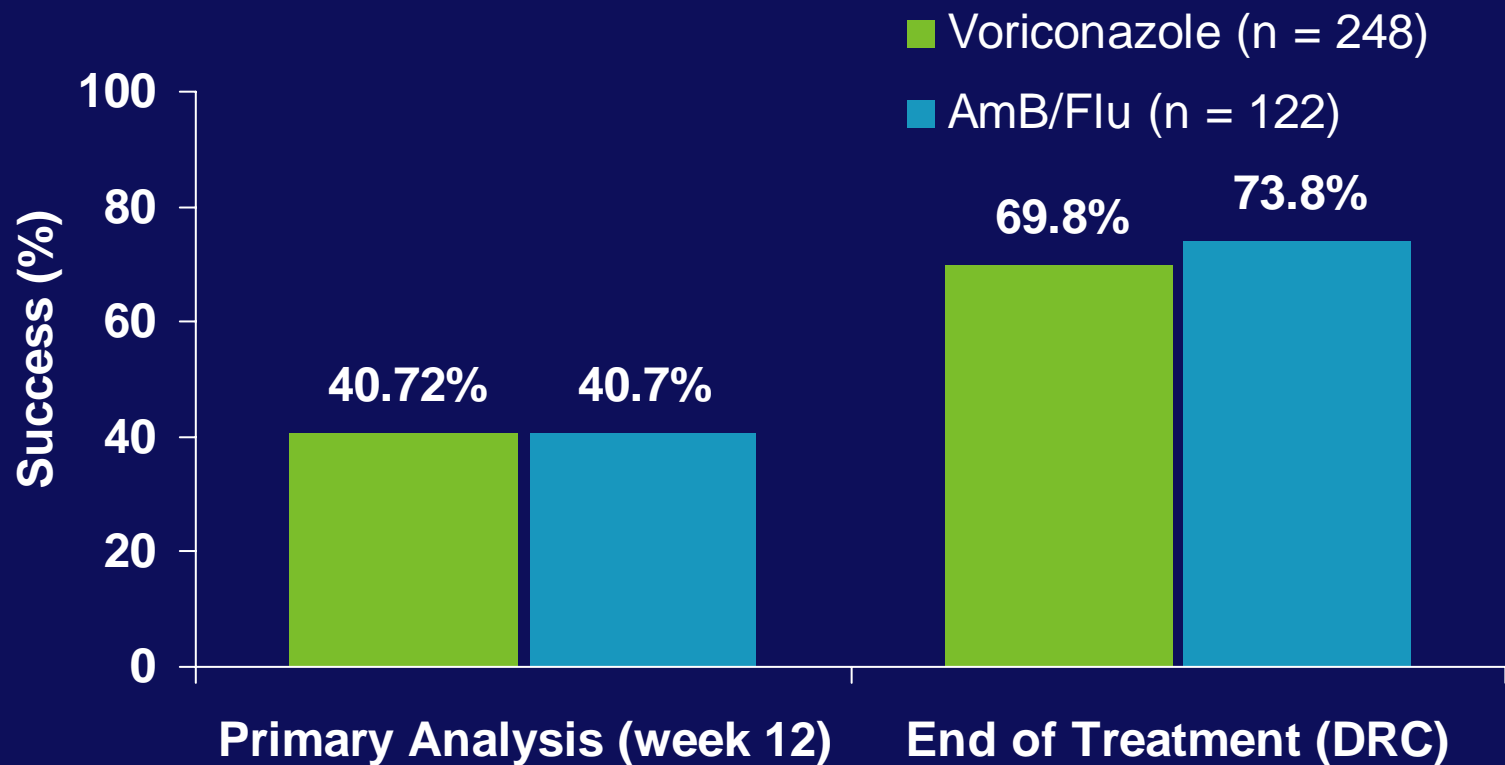


- **Primary end point: end of IV therapy**
  - Superiority of anidulafungin vs fluconazole
  - Difference: 15.4% (95% CI [3.85, 26.99])
- **Secondary end points favor anidulafungin**
  - Better 6-week global response
    - 55.9% vs 44.1%
  - Improved survival
- **Similar tolerability**

CI = confidence interval.

Reboli A, et al. Presented at: 45th ICAAC; December 16-19, 2005; Washington, DC. Abstract M-718.

# Global Comparative Candidemia Study: Success at Week 12 and End of Treatment



# Diagnosis and Management of Nosocomial Candidemia

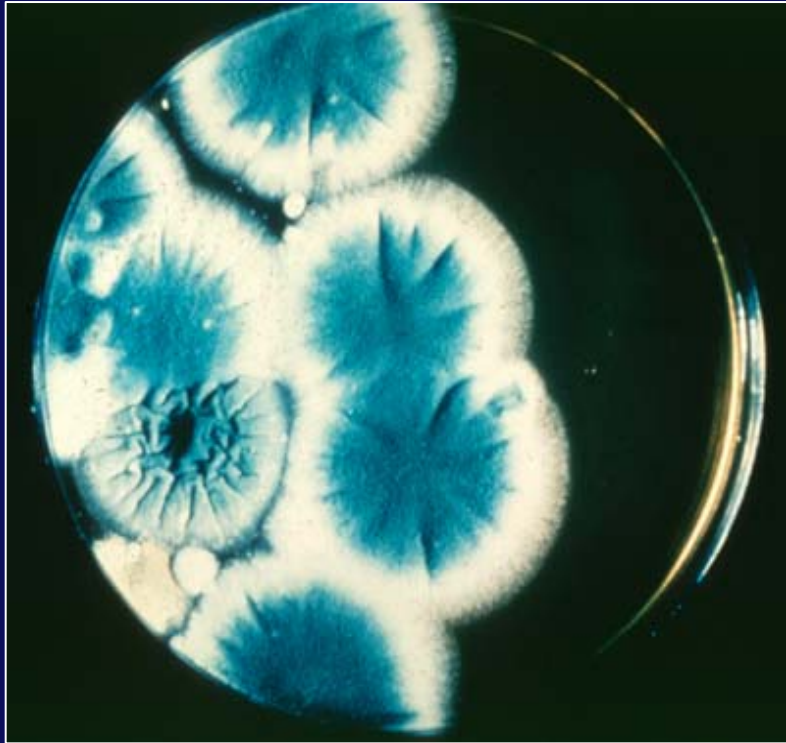
- Positive blood cultures = infection (Pappas, 2004)
  - Blood cultures
    - Better detection with newer methods (BACTEC 9240; BacT/ALERT) (Horvath, 2004)
  - Other sterile (non-urinary) sites
- Importance of colonization
  - Role of yeasts other than *C. albicans* (especially *C. glabrata*) (Redding, 2004)
  - Oropharynx, urine, respiratory tract
- Approach to therapy
  - Evaluation of risk factors
    - Central catheter; comorbid illness; critically ill
  - Consideration for empiric therapy (Pelz, 2001)

# IDSA 2004: Guidelines for Therapy of Candidemia

- Not neutropenic, no prior azoles, germ-tube–positive (*C. albicans*)
  - Fluconazole at 400-800 mg/d
  - AmB (0.5-0.6 mg/kg/d): inc. toxicity
  - Caspofungin 70 mg load; 50 mg/d (other echinocandins?)
- Non-*albicans* yeasts; neutropenic
  - Amphotericin B 0.7 mg/kg/d; Flu at 800/mg/d; Caspo 50 mg/d
  - Sequential AmB (other IV?) → PO Flu (Vori?) therapy
    - Susceptible organism and clinical response
  - Consider susceptibility testing
  - New agents: voriconazole, anidulafungin; investigational: posaconazole, micafungin

Pappas PG, et al. *Clin Infect Dis*. 2004;38:161-189; Mora-Duarte J, et al. *N Engl J Med*. 2002;347:2020-2029; Kullberg BJ, et al. *Lancet*. 2005;366:1435-1442; Reboli A, et al. *ICAAC 2005* (abstract M-718); Ruhnke M, et al. Presented at: 45th ICAAC; December 16-19, 2005; Washington, DC. Abstract M-718; Ruhnke M, et al. Presented at: 45th ICAAC; December 16-19, 2005; Washington, DC. Abstract M-722c.

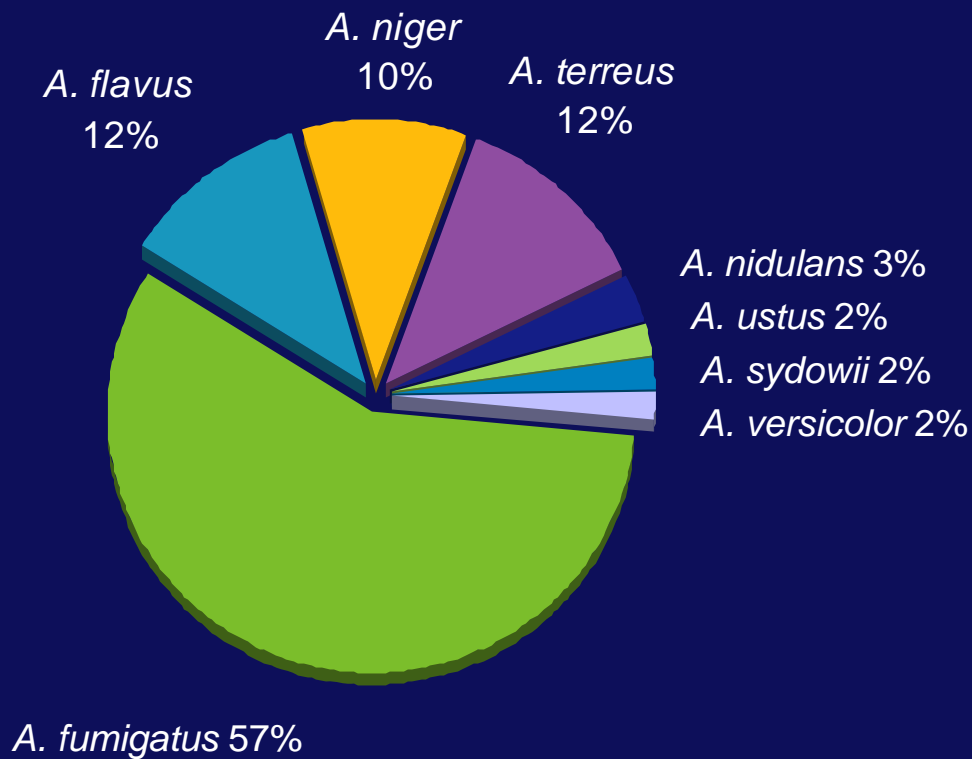
# Invasive Aspergillosis



Have We Made  
Progress??

# Aspergillus spp. Isolates Submitted to San Antonio Fungus Testing Laboratory

918 Isolates; Jan. 2001-July 2004



- AmB MFC >16 µg/mL
  - *A. fumigatus* 24%

AmB MIC ≥2 µg/mL

- *A. terreus* 90%
- *A. flavus* 51%
- *A. ustus* 50%



MFC = minimum fungicidal concentration; MIC = minimum inhibitory concentration.

Sutton D, et al. Presented at: Advances Against Aspergillosis; September 9-11, 2004; San Francisco, Calif. Abstract 16.

# Acute Renal Failure and Amphotericin B: Hidden Costs of Toxicity

- Mortality and costs of acute renal failure
  - 707 adult patients receiving AmB
- Clinical impact
  - Acute renal failure: 212 (30%)
  - Higher mortality with acute renal failure: 54% vs 16% (OR: 6.6)
- Economic impact
  - Mean increase in length of stay: 8.2 days
  - Mean increase in hospital cost: \$29,823

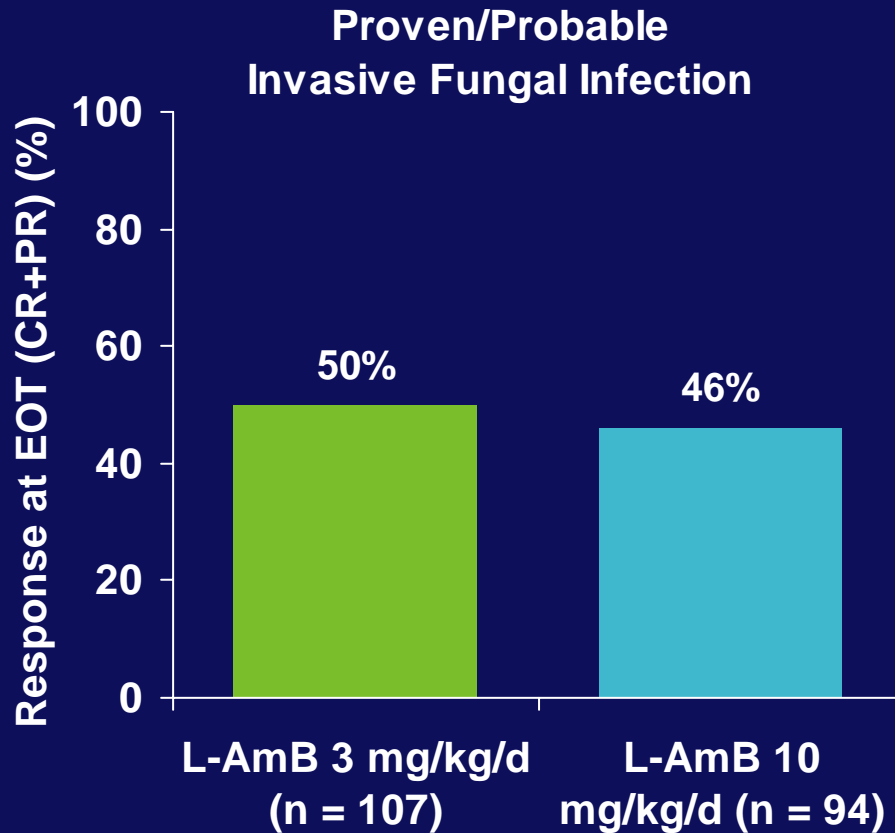
OR = odds ratio.

Bates DW, et al. *Clin Infect Dis*. 2001;32:686-693.

# Lipid Preparations of Amphotericin B: Rationale for Use

- Lipid formulations of AmB
  - Reduced toxicities of AmB deoxycholate
  - Improved therapeutic index:  $\geq 5$  mg/kg/d well tolerated
    - Salvage therapy (limited efficacy  $\approx 40\%$  responded)
    - Empiric therapy (reduced efficacy vs molds at lower doses)
  - Expense limits use
- Selection of lipid formulation
  - No experimental or clinical evidence to definitively guide selection of one agent over another
  - Toxicity: ABCD (Amphotec) > ABLC (Abelcet) > amphotericin B (AmBisome)
- Use targeted to high-risk patients
  - Refractory infection
  - Renal dysfunction and risk for nephrotoxicity

# Efficacy of L-AmB in Invasive Mycoses: AmBisome Load Trial



- 14-day loading dose of L-AmB 3 or 10 mg/kg/d followed by L-AmB 3 mg/kg/d

	L-AmB 3	L-AmB 10
IPA	96%	97%
CT Halo	58	60
Allo-SCT	16	19
Neutropenia	71	76
Survival	72	59
Toxicity	20	32

CR+PR = complete response + partial response.

Cornely OA, et al. Presented at: American Society of Hematology (ASH) 47th Annual Meeting; December 12, 2005; Atlanta, Ga. Poster 3222.

# In Vitro and Clinical Activity of Echinocandins Against *Aspergillus*

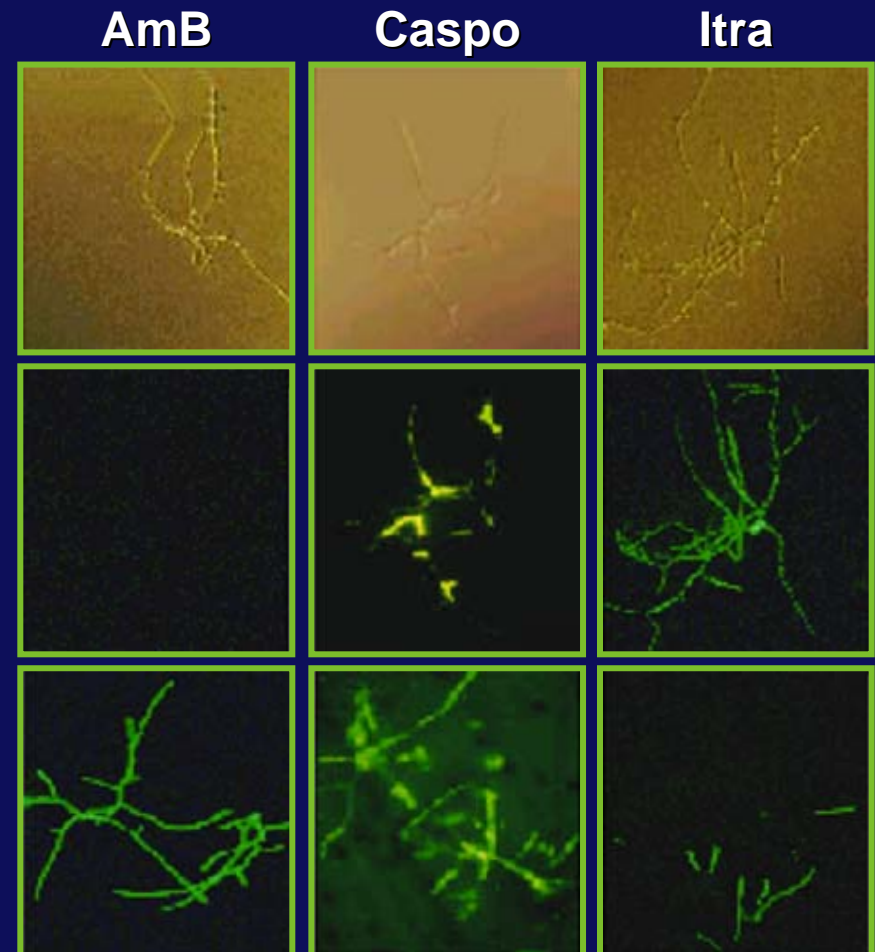
## In vitro activity

- Not classically fungicidal or fungistatic
- Activity against other *Aspergillus* spp. (*A. terreus*)
- Animal models demonstrated prolonged survival

## Clinical efficacy

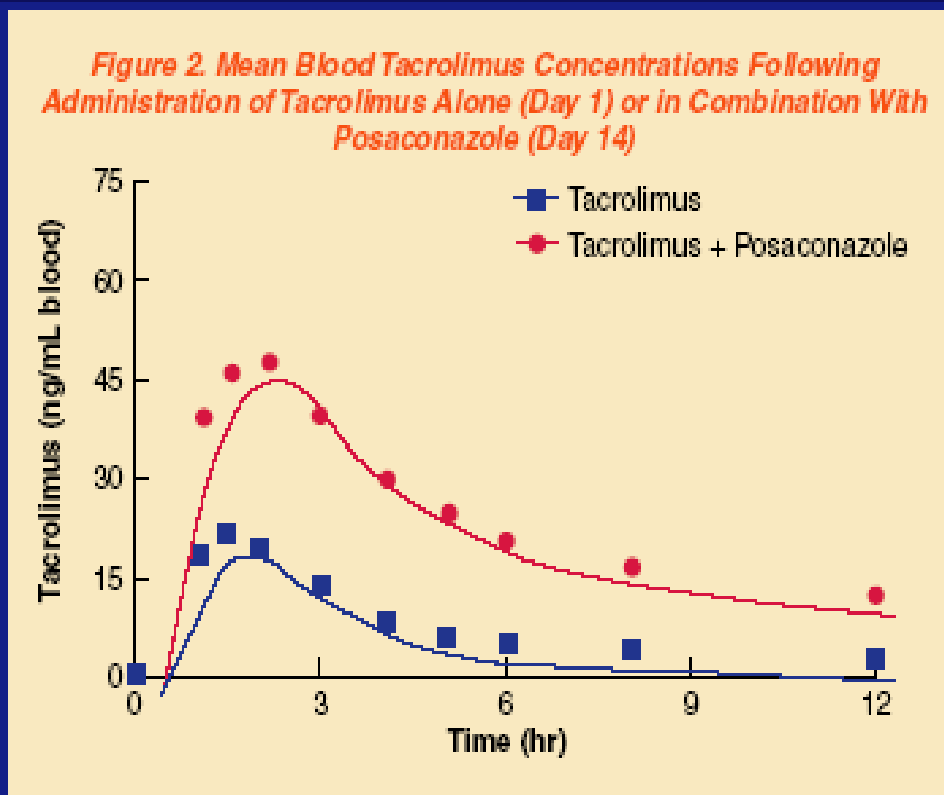
- Salvage therapy; ~40% efficacy with progressive infection
- Excellent tolerability
- Role in combination therapy

**Control  
Cells**



# Newer Azoles: Posaconazole

- Broad spectrum (Zygomycetes)
- Oral (no IV) linear to 800 mg
- Posaconazole absorption increased by food
  - Saturable absorption
- Posaconazole metabolized minimally by glucuronidation
- Posaconazole inhibits CYP3A4
  - Potential interaction with many other drugs, such as tacrolimus
  - Increase in catabolism by rifampin – stimulates glucuronidase – posaconazole levels reduced dramatically



# Posaconazole Salvage Therapy for Invasive Aspergillosis

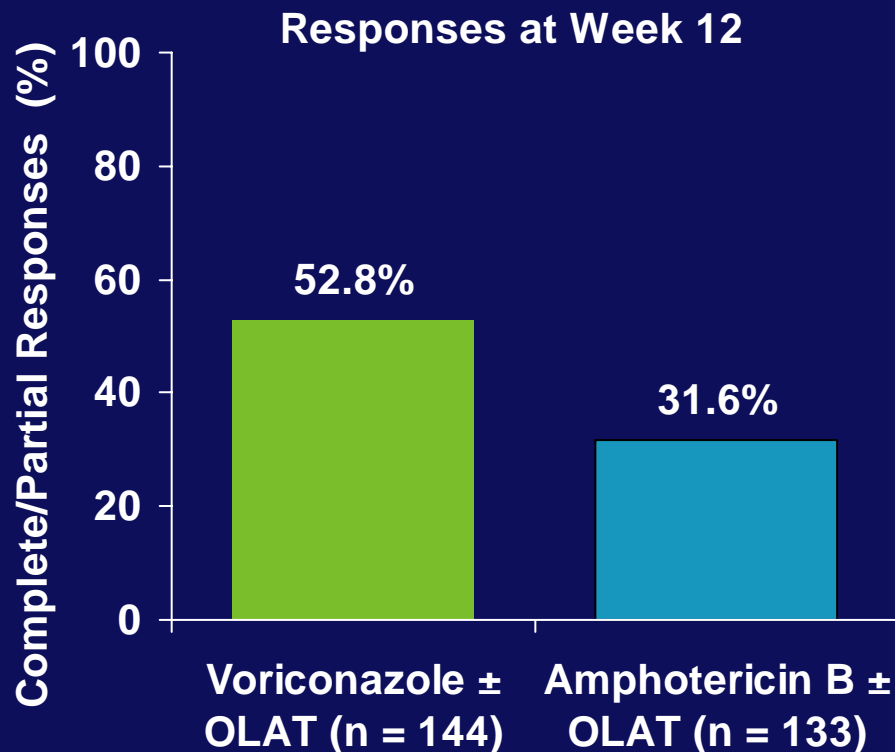
- Open salvage therapy; historical controls refractory or intolerant of standard therapy
- Posaconazole: oral solution (200 mg qid × 2 wk/400 mg bid)

<i>Aspergillus</i> species	Posaconazole (n)	Historical Controls (n)
All <i>Aspergillus</i>	42% (107)	26% (86)
<i>A. fumigatus</i>	41% (29)	35% (34)
<i>A. flavus</i>	53% (19)	19% (16)
<i>A. terreus</i>	29% (14)	18% (11)

# Newer Azoles: Voriconazole

- Broad spectrum (non-*albicans* yeasts: *C. glabrata*, *C. krusei*; *Aspergillus*; molds – including *Fusarium*, *Scedosporium*, NOT zygomycetes)
- Oral (good bioavailability); IV (cyclodextrin)
- Twice-daily administration/loading dose: non-linear
- Safety satisfactory:
  - Visual effects ~30%; hepatic 10%; rash 5%, nausea 2%
- Metabolized by hepatic cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4
  - Relatively large potential for drug interactions
  - CYP2C19 exhibits genetic polymorphism
  - Dosage adjustments for patients with hepatic insufficiency

# Voriconazole in Invasive Aspergillosis: Global Comparative Study



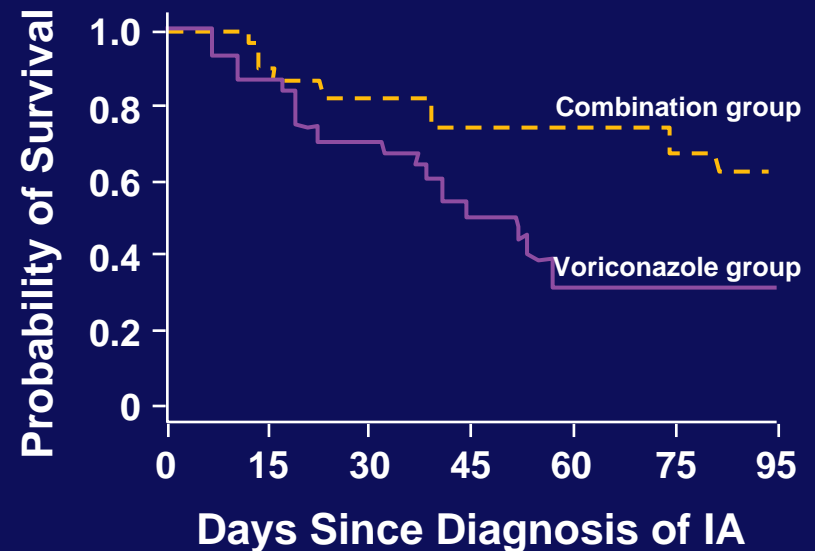
- Satisfactory (complete/partial responses [CR/PR]) responses at week 12
  - Difference: 21.2%
- Improved survival with voriconazole
- Importance of early therapy
- Limited role for rescue therapy
- Lower success in high-risk patients
  - Disseminated infection
  - Allogeneic bone marrow transplantation
    - Voriconazole: 32.4%
    - Amphotericin B: 13.3%

Note: OLAT = other licensed antifungal therapy.

Herbrecht R, et al. *N Eng J Med*. 2002;347:408-415; Patterson TF, et al. *Clin Infect Dis*. 2005;41:1448-1452.

# Combination Therapy in Invasive Aspergillosis (IA)

- In vitro
  - Most interactions show synergy/additive effects (Perea, 2002)
  - Poor in vivo/in vitro correlation (Johnson, 2004)
- Experimental infections
  - Candin + AmB (Kohno, 2000)
  - Candin + azole (Kirkpatrick, 2002; Petraitiene, 2002)
    - Improved sterilization of tissues
    - Reduced tissue burden
- Limited clinical data
  - Anecdotal reports (Kontoyiannis, 2002; Aliff, 2003)
  - Improved survival: vori + caspo (Marr, 2004)



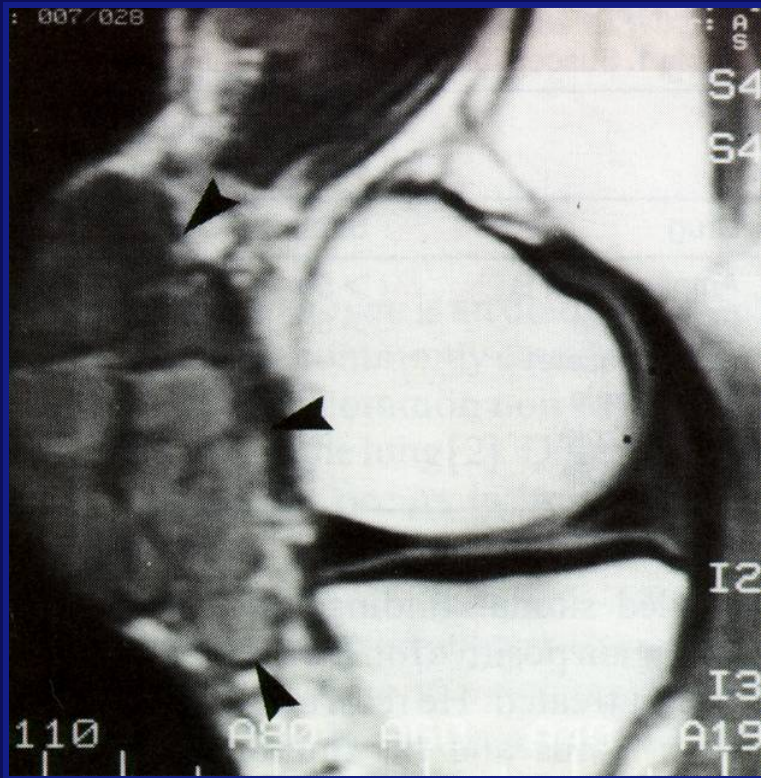
Perea S, et al. *AAC* 2002;46:3039-41; Johnson MD, et al. *AAC* 2004;48:693-715; Kohno S, et al. *ICAAC* 2000; Kirkpatrick WR, et al. *AAC* 2002;46:2564-8; Petraitiene R, et al. *AAC* 2002;46:12-23; Kontoyiannis DP, et al. *Cancer* 2003;98:292-9; Aliff TB, et al. *Cancer* 2003;97:1025-32.; Marr KA, et al. *Clin Infect Dis* 2004;39:797-802.



**Other Fungi:**

**Zygomycetes and  
Weird Moulds!**

# Emerging Fungal Infections: *Scedosporium* and *Fusarium*



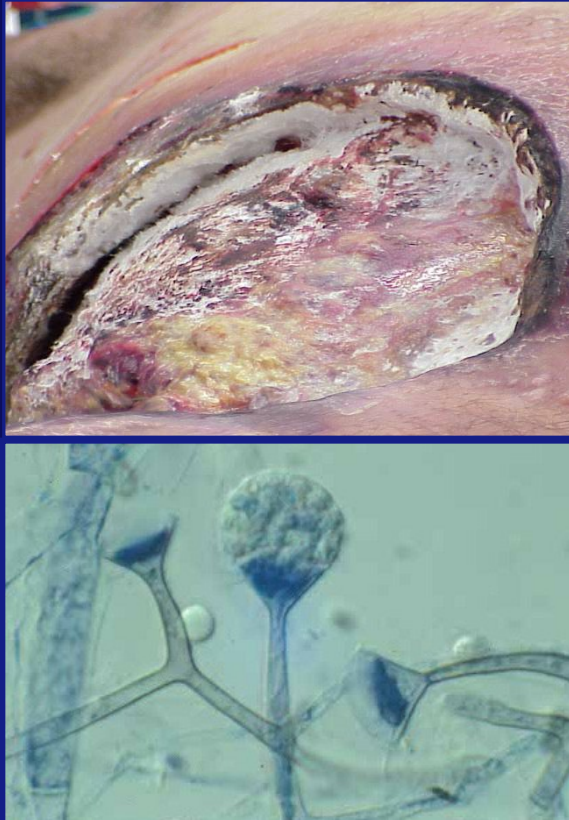
Pseudallescheriasis (*S. apiospermum*).  
MR scan of right knee, post-heart  
transplantation. Arrows indicate cystic  
lesions in the prepatellar bursa.

- In vitro/in vivo: voriconazole, posaconazole, ravuconazole
- Refractory to available agents: mortality 50% to >80%
- Efficacy in patients refractory or intolerant to standard therapy

Voriconazole	No. of pts	Response
<i>Fusarium</i>	11	45%
<i>Scedosporium</i>	10	30%
Posaconazole	No. of pts	Response
<i>Fusarium</i>	18	39%

Patterson TF, et al. *Mycoses*. 1990;33:297-302; Perfect JR, et al. *Clin Infect Dis*. 2003;36:1122-1131; Raad I, et al. Presented at: 44th ICAAC; October 30-November 2, 2004; Washington, DC. Abstract M-669.

# Emerging Resistant Mycoses: Zygomycetes



- Emergence of resistance during suppressive therapy (voriconazole)
  - Severely immunosuppressed (allo BMT)
  - Pulmonary/disseminated infections
- Other clinical presentations: trauma; burns
  - Tsunami victim: polymicrobial wound infection, including *Apophysomyces elegans*
  - May not grow in culture (homogenized tissue)
- Echinocandins and voriconazole: no activity
- In vivo activity: posaconazole
  - Clinical trials (Greenberg, 2006)
    - 71% response in 55 patients
- Primary therapy with high-dose lipid formulation of amphotericin B

*Saksenaea vasiformis*: traumatic wound infection; and *Apophysomyces elegans*: light microscopy (420 ×, cotton-blue stain)  
BMT = bone marrow transplant.

Greenberg RN, et al. *Antimicrob Agents Chemother.* 2006;50:126-133; Andersen D, et al. *Lancet.* 2005;365:876-878.

# Antifungal Prophylaxis Against Moulds

- Amphotericin B
  - Intravenous (dose-limiting toxicity, lower doses not effective)
  - Intranasal/aerosol (limited delivery, poor tolerability)
- Azoles
  - Fluconazole (lack of efficacy for molds)
  - Itraconazole (erratic bioavailability, toxicity)
- New agents–potential activity
  - Echinocandins (intravenous, daily cost, spectrum)
  - Newer azoles (bioavailability, spectrum of activity, potential for resistance, drug interactions)
  - Inhaled amphotericin (improved delivery, efficacy)

Centers for Disease Control and Prevention, et al. *MMWR Recomm Rep*. 2000;49(RR-10):1-25, CE1-7;  
Winston DJ, et al. *Transplantation*. 2002;74:688-695; Palmer SM, et al. *Transplantation*. 2001;72:545-8; van Burik J, et al.  
*Clin Infect Dis*. 2004;36:1407-1416; Ullman AJ, et al. Presented at: 45th ICAAC; December 16-19, 2005; Washington, DC.  
Abstract M-716.

# Posaconazole vs Fluconazole for Prophylaxis of Invasive Fungal Infections (IFI) in HSCT Patients With GvHD

Proven/Probable IFI (EORTC/MSG)	Posaconazole 200 mg tid n = 301	Fluconazole 400 mg qd n = 299
At any time	20 (7%) $P = 0.003$	42 (14%)
Study period (16 wk)		
Total	16 (5%) $P = 0.07$	27 (9%)
<i>Aspergillus</i>	7 (2%) $P = 0.004$	21 (7%)
Breakthrough (during therapy)		
Total	7 (2%) $P = 0.004$	22 (8%)
<i>Aspergillus</i>	3 (1%) $P = 0.001$	17 (6%)

EORTC = European Organization for Research Treatment of Cancer; GvHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplant; MSG = monosodium glutamate.

Ullmann AJ, et al. Presented at: 45th ICAAC; December 16-19, 2005; Washington, DC. Abstract M-716.

# New Antifungals 2006: Recent Advances and Ongoing Challenges!

- Epidemiological assessment of risk
  - Changing etiological agents, timing of infections
  - Importance of establishing diagnosis
- Poor outcomes in advanced infection
  - Severely immunosuppressed patients
  - Disseminated and central nervous system infection
- Efficacy of new antifungals
  - Importance (and cost-effectiveness) of initial antifungal choice
  - Clinical trial for assessing utility of combination therapy
  - Role for targeted therapy in high-risk patients
- Potential for prevention of invasive molds in high-risk patients

Thank you!



**Want to know more?**

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