

# TREATMENT OF INVASIVE PULMONARY FUNGAL INFECTIONS

**Dr SACHIN KUMAR**  
**DM SEMINAR**

# PRESENTATION OVERVIEW

- Introduction
- Antifungal prophylaxis
- Empirical antifungal therapy
- Preemptive antifungal therapy
- Therapy of proven invasive mycoses/targeted

# Introduction : What's official about invasive mycosis?

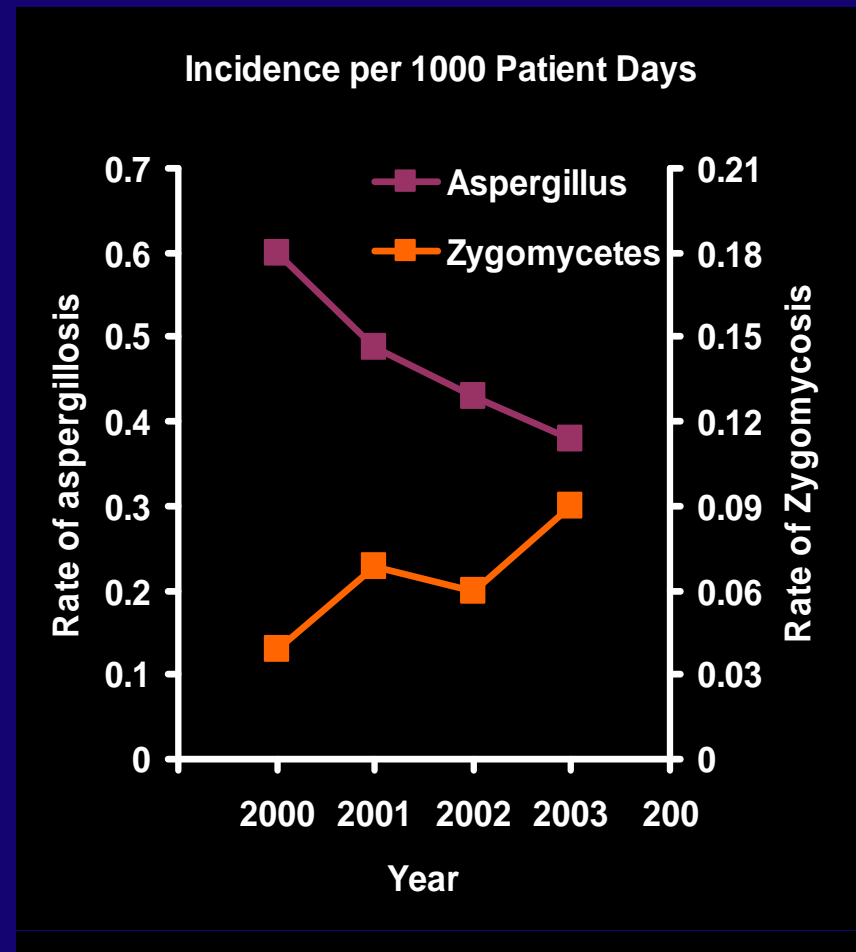
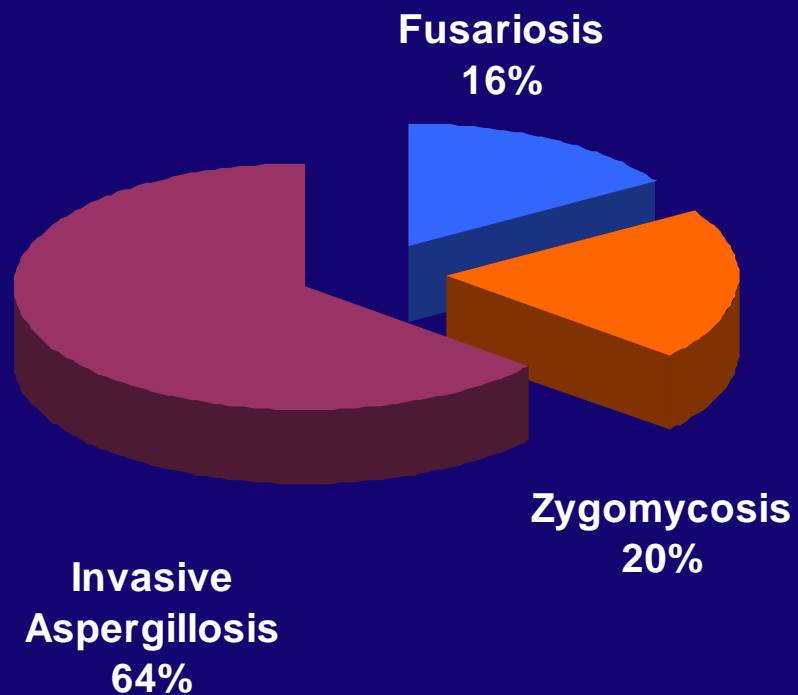
- Increasing incidence in hospitalized/ICU pts:
  1. Profound ↓ immunity with modern high intensity CT
  2. ↑ solid organ & BMT
  3. HIV/AIDS
  4. ↑ aggressive supportive care in high-risk populations
  5. ↑ population of pts with DM & on immunosuppressants incl steroids
- Difficult to Dx reliably & timely:
  1. Conventional μ-biologic approaches insensitive, non-specific and time-consuming
  2. Clinical S/S of invasive fungal infection often absent till advanced stage (absence of SIR)

# Invasive fungal infection.....

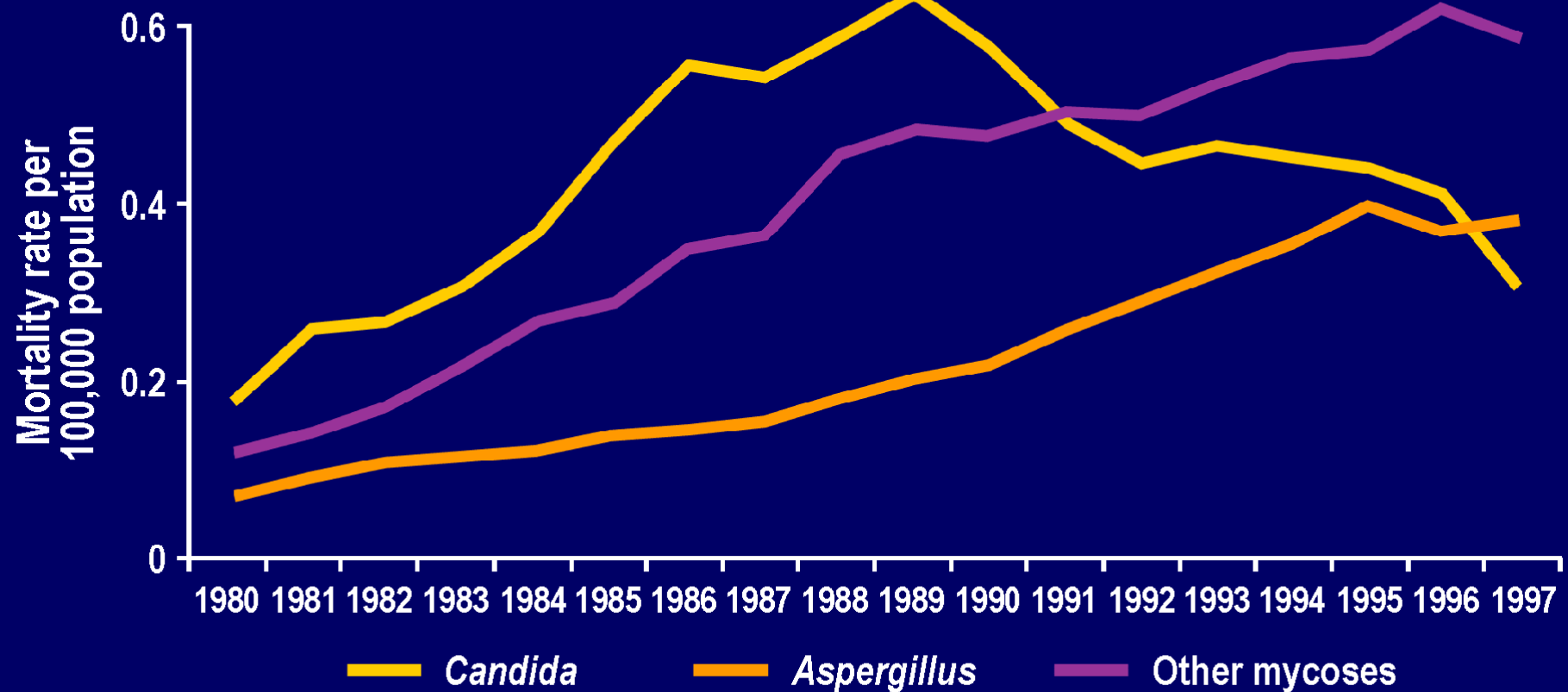
..an increasing challenge

- Relevance to intensive care
- Mortality higher than in bacterial infections
- ‘When to start treatment?’
- Balancing risk to benefit ratio of antifungal prophylaxis/ pre-emptive therapy
- Treatment options

# Changing Spectrum of Invasive Molds

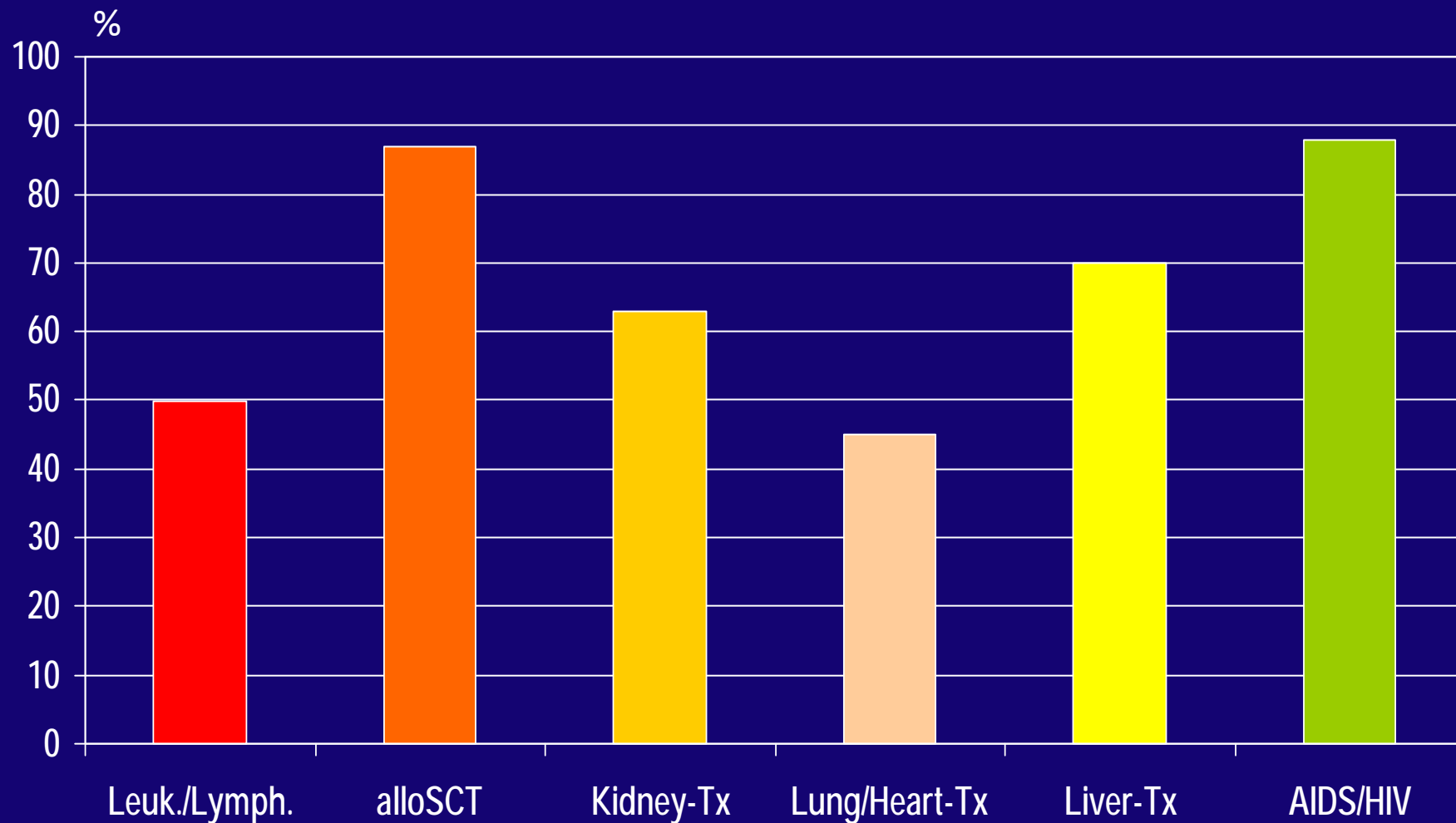


# Mortality Due to Invasive Mycoses



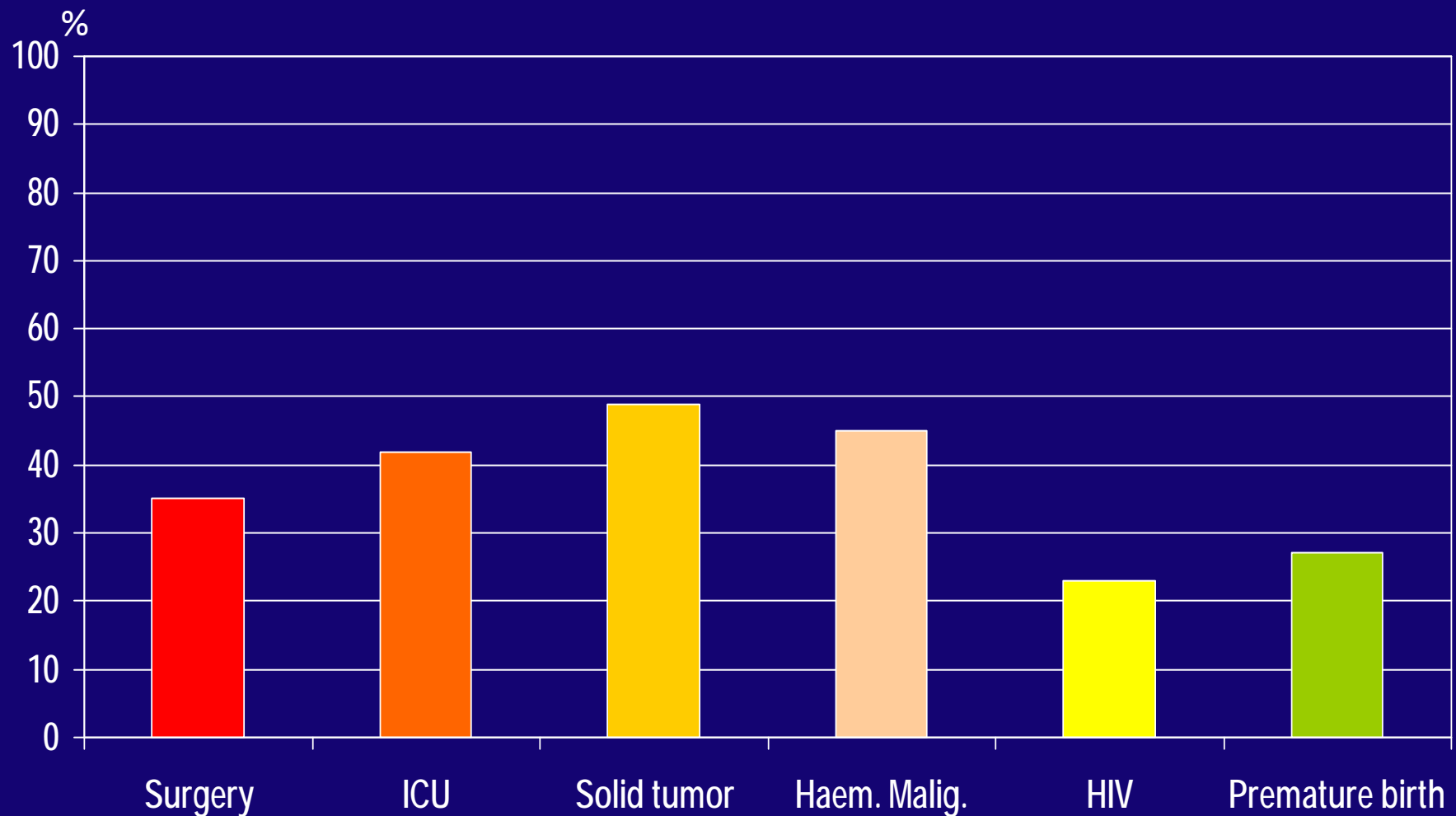
Adapted from McNeil MM et al. *Clin Infect Dis*. 2001;33:641-647.

# Mortality from invasive *Aspergillus* infections



*Lin et al., CID 2001; 32: 358*

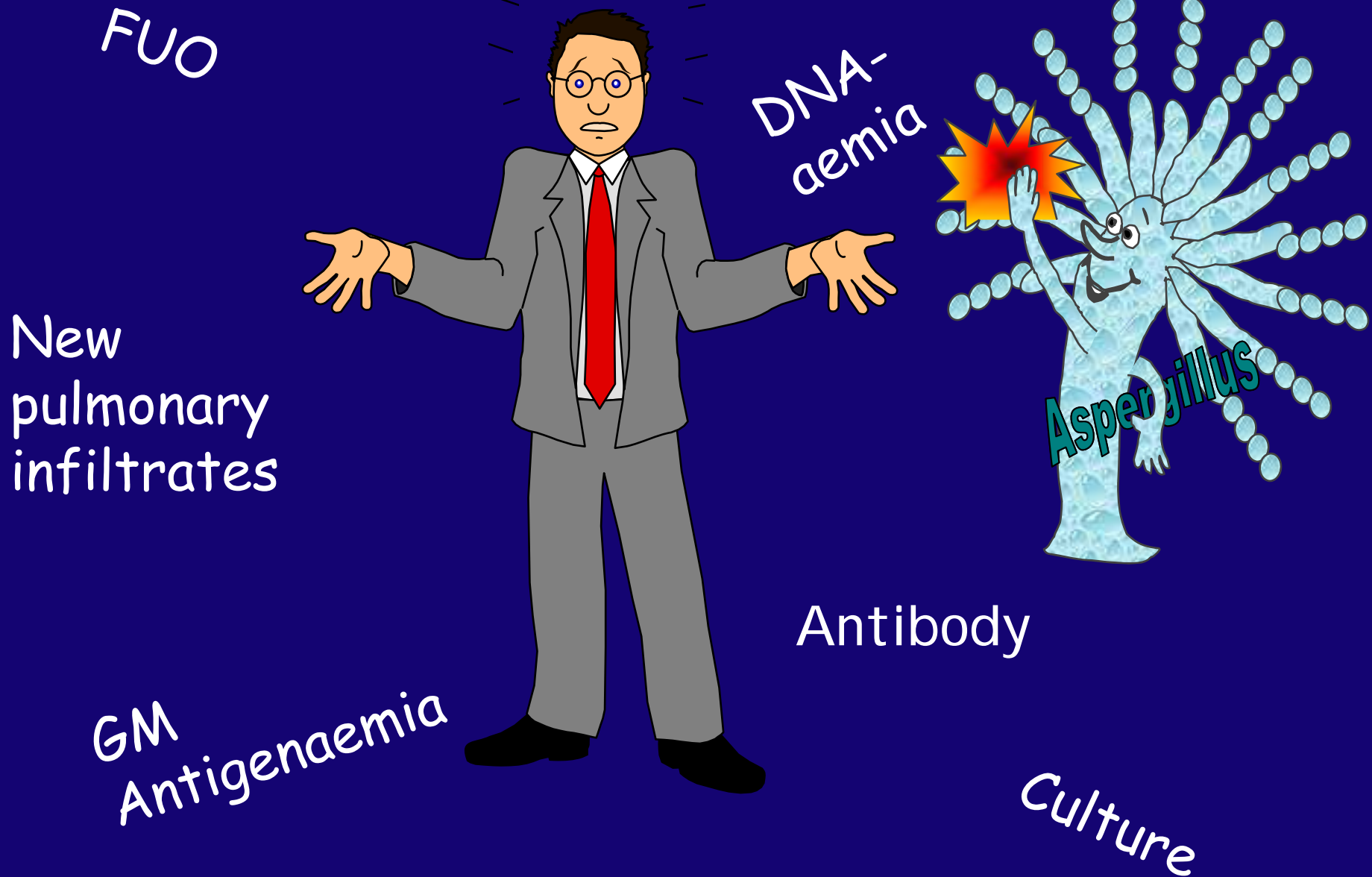
# Mortality from invasive *Candida* infections



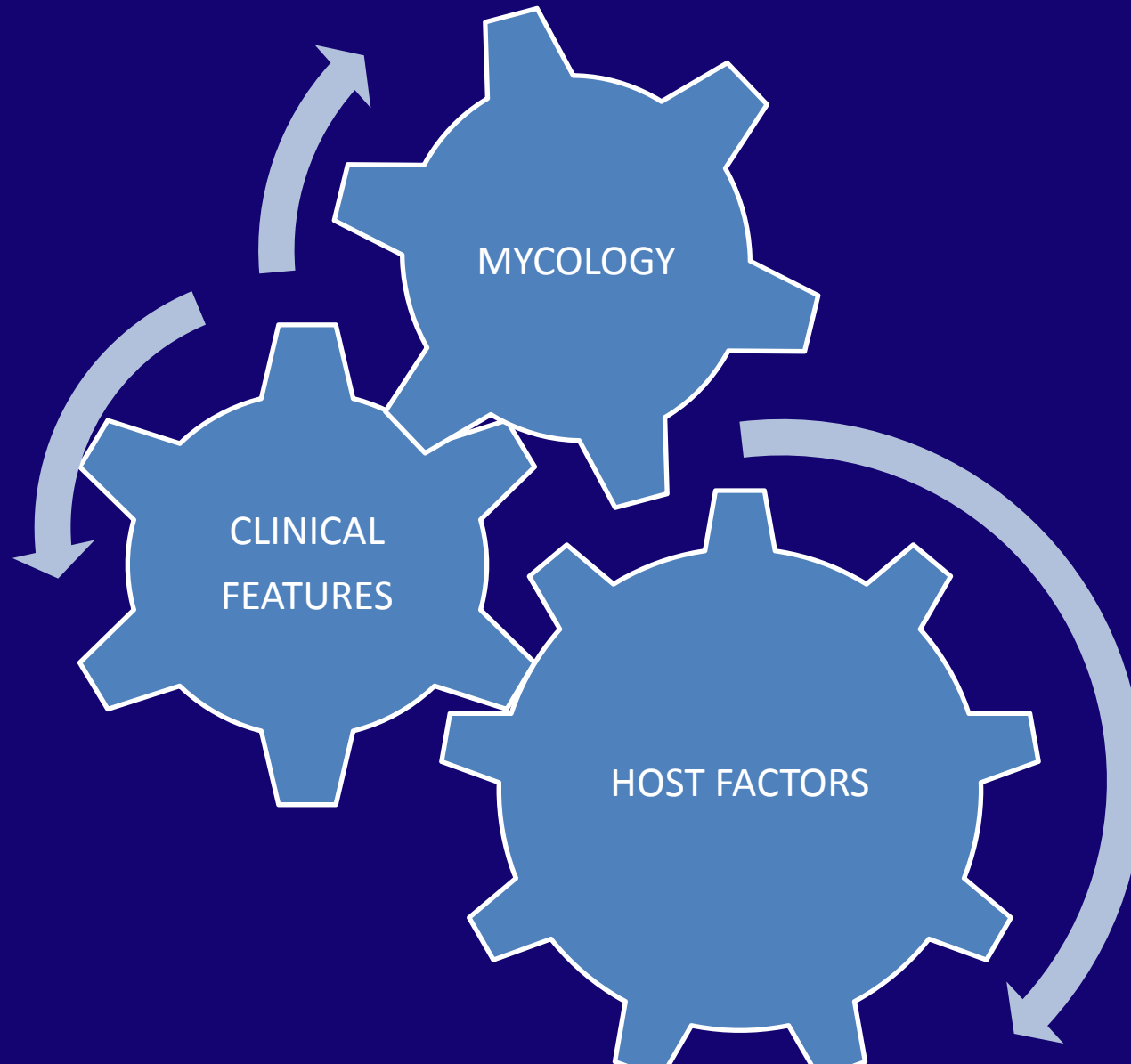
*Tortorano et al., EJCMI 2004; 23: 317*



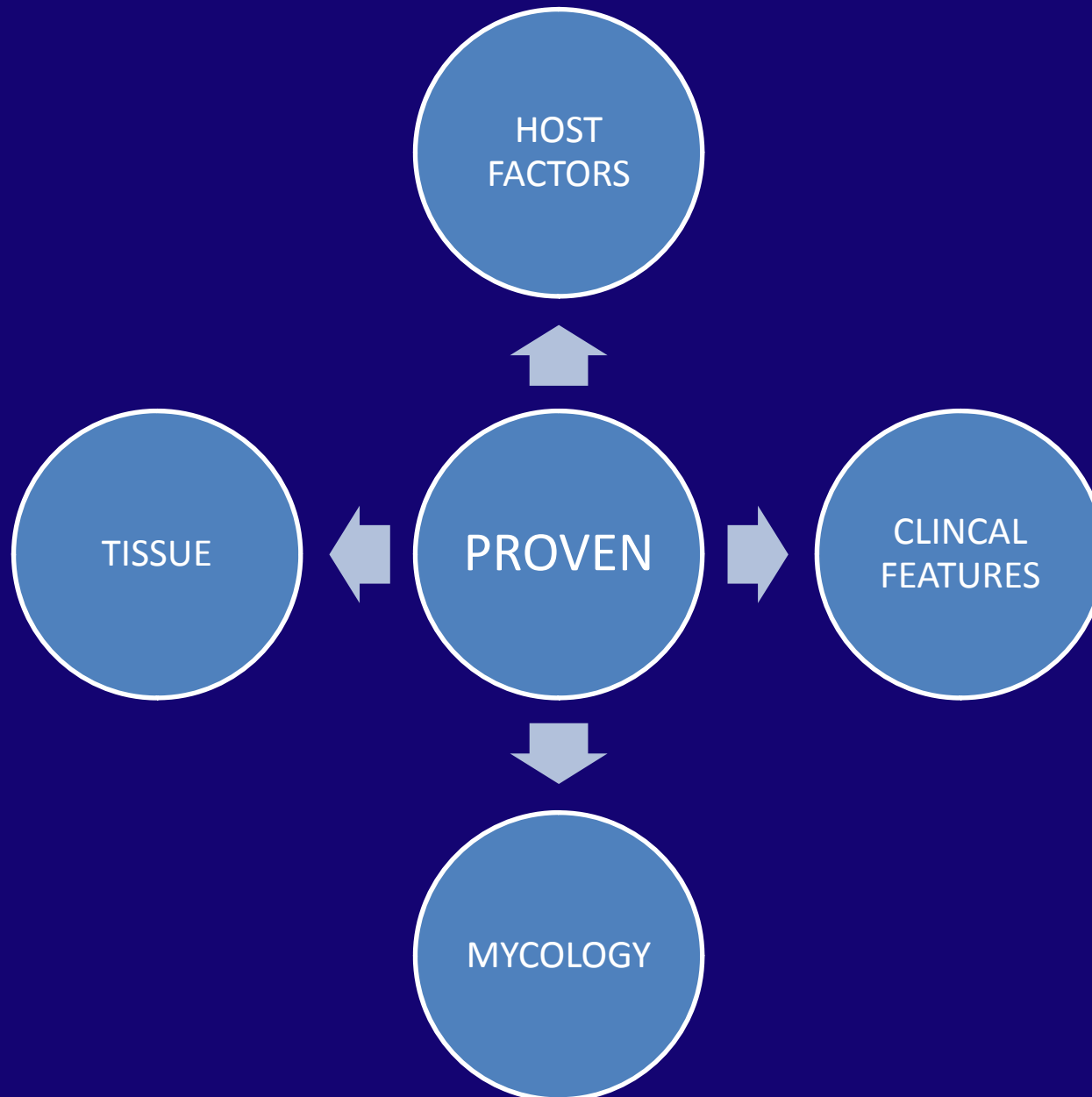
# When to treat and with what?



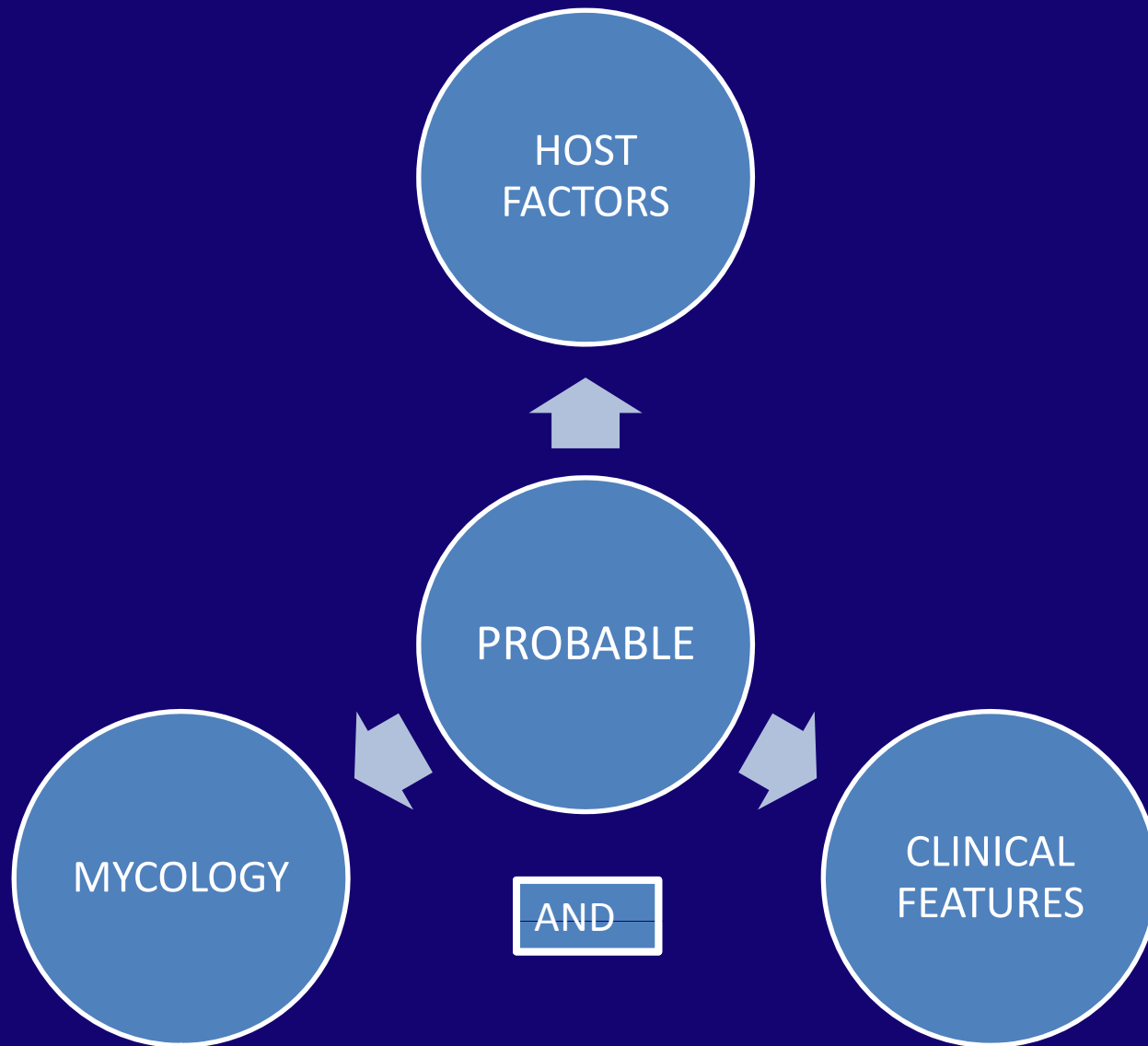
# Defining invasive fungal infection



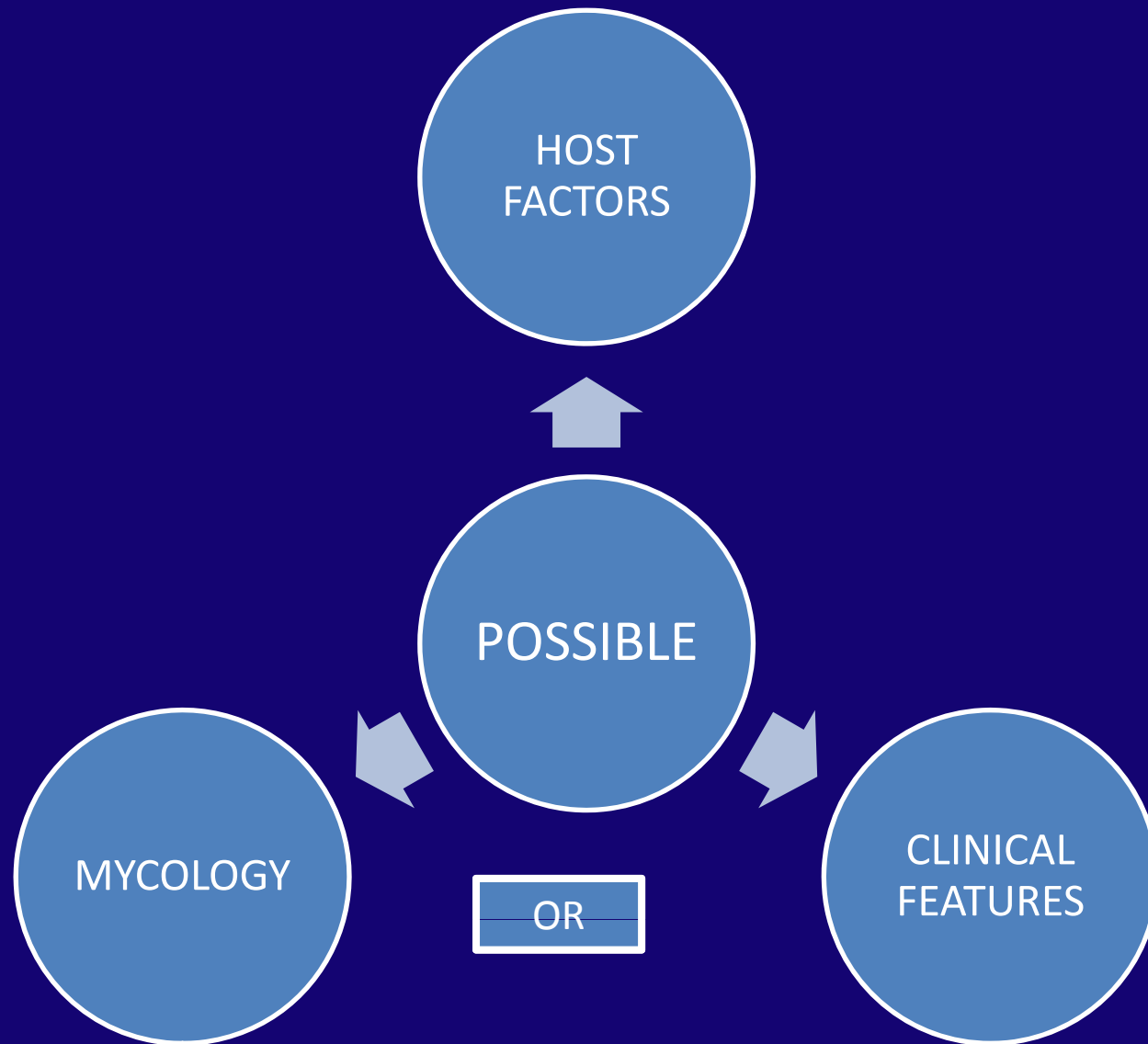
# Proven invasive fungal infection



# Probable invasive fungal infection



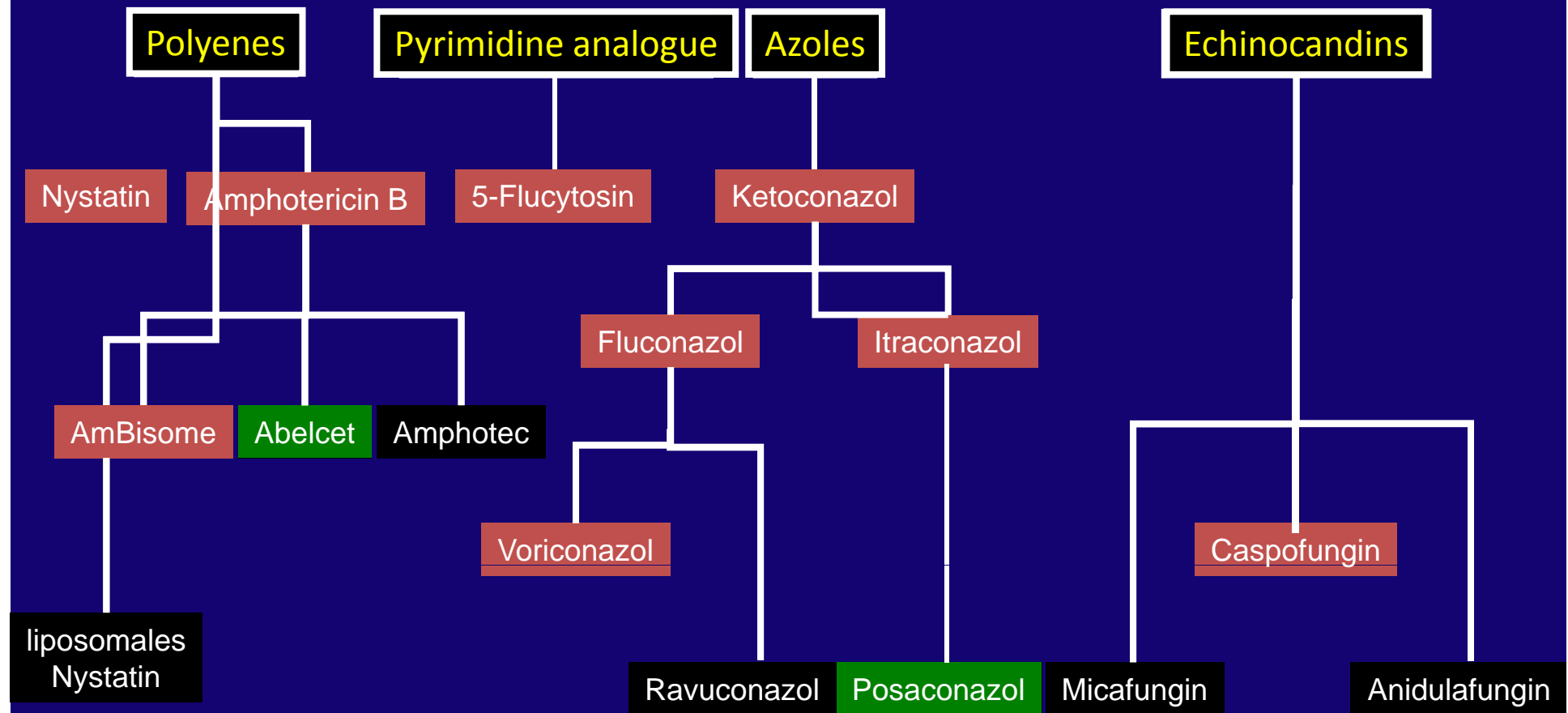
# Possible invasive fungal infection



# Antifungal strategies

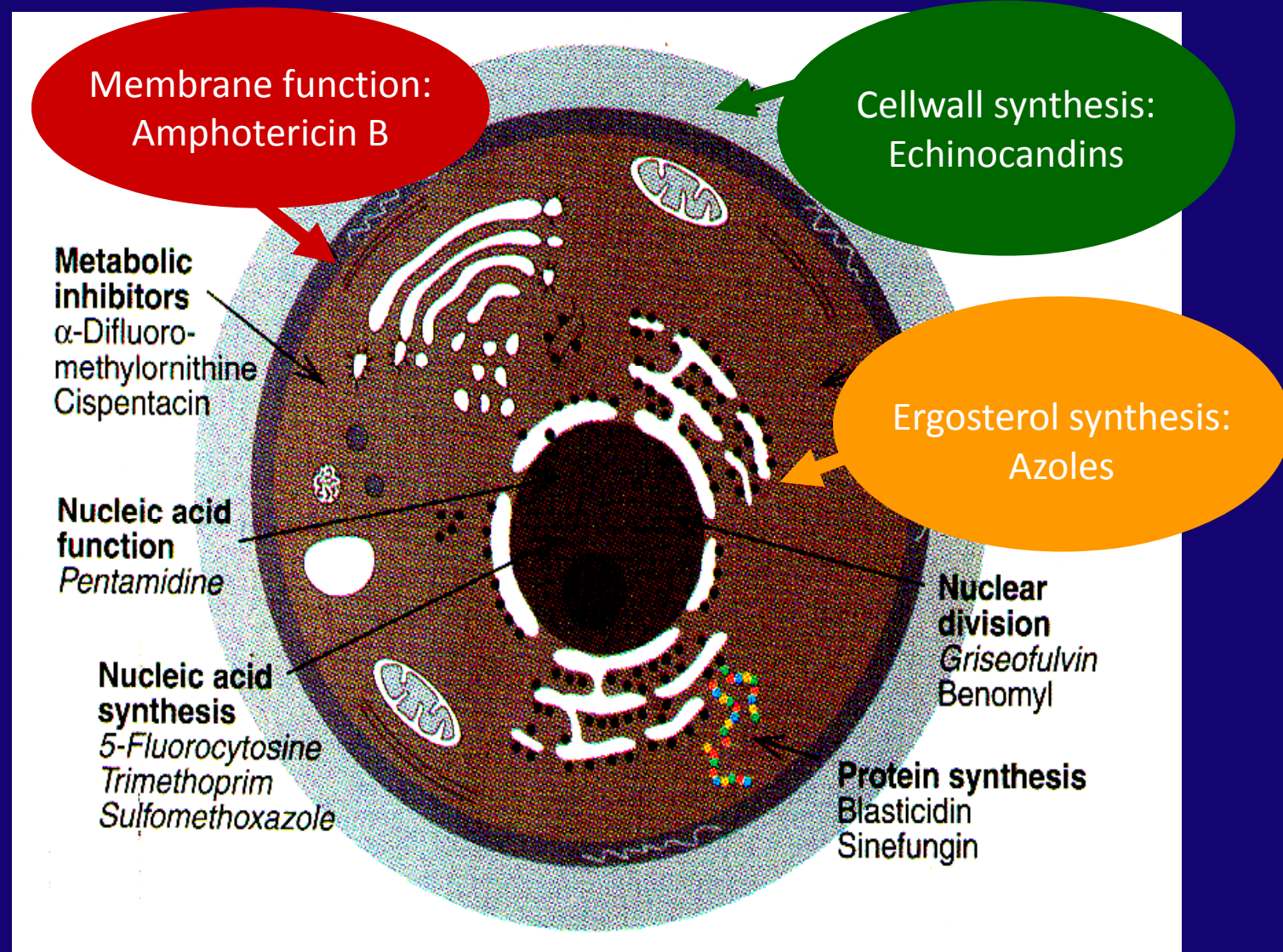
- **Prophylactic treatment:** preventive administration of antifungal to patients at risk of IFI without attributable signs and symptoms
- **Empiric treatment:** initiation of antifungal in patients at high risk of IFIs and established clinical signs and symptoms, but without microbiological documentation
- **Pre-emptive therapy:** decision of treatment based on early diagnostic test
- **Targeted therapy:** pathogen identification defined

# Development of antifungals



*mod. nach R. Lewis, ICAAC 2002*

# The (small) world of antifungals





# Antifungal Activity

(■ > 75% sensible, ■ ≤ 50%, ■ < 5%; mixed colours: differing results;  
modified after O'Brien et al., ASH Edu 2003)

Erreger	AmB	Fluco	Itra	Vori	Caspo	Flucyt.
<i>C. albicans</i>	■	■	■	■	■	■
<i>C. parapsilosis</i>	■	■	■	■	■	■
<i>C. tropicalis</i>	■	■	■	■	■	■
<i>C. glabrata</i>	■	■	■	■	■	■
<i>C. krusei</i>	■	■	■	■	■	■
<i>A. fumigatus</i>	■	■	■	■	■	■
<i>A. flavus</i>	■	■	■	■	■	■
<i>A. terreus</i>	■	■	■	■	■	■
<i>Zygomycetes</i>	■	■	■	■	■	■
<i>Fusarium</i> spp.	■	■	■	■	■	■

# Antifungal prophylaxis

- Prophylaxis useful in high-risk groups (eg, HCT recipients or patients with prolonged neutropenia) in which benefits of treating outweigh risks
- IFI rate at which prophylaxis becomes justified is usually 10%

Fluconazole: 200-400mg/day

Low dose Ampho B: 0.1-0.25 mg/kg/day

Ampho B solution, spray, inhalation

Ambisome: 1mg/kg/day, 3 X weekly

Full dose Ambisome in patients with previous aspergillosis

IN GOD  
WE TRUST  
FROM ALL OTHERS  
WE NEED HARD DATA

*Journal of Antimicrobial Chemotherapy* (2006) **57**, 628–638

doi:10.1093/jac/dki491

Advance Access publication 3 February 2006

JAC

## Antifungal agents for preventing fungal infections in non-neutropenic critically ill and surgical patients: systematic review and meta-analysis of randomized clinical trials

E. Geoffrey Playford<sup>1,2\*</sup>, Angela C. Webster<sup>3,4</sup>, Tania C. Sorrell<sup>2,5</sup> and Jonathan C. Craig<sup>3,4</sup>

**Conclusions:** Prophylaxis with fluconazole or ketoconazole in critically ill patients reduces invasive fungal infections by one-half and total mortality by one-quarter. Although no significant increase in azole-resistant *Candida* species associated with prophylaxis was demonstrated, trials were not powered to exclude such an effect. In patients at increased risk of invasive fungal infections, antifungal prophylaxis with fluconazole should be considered.

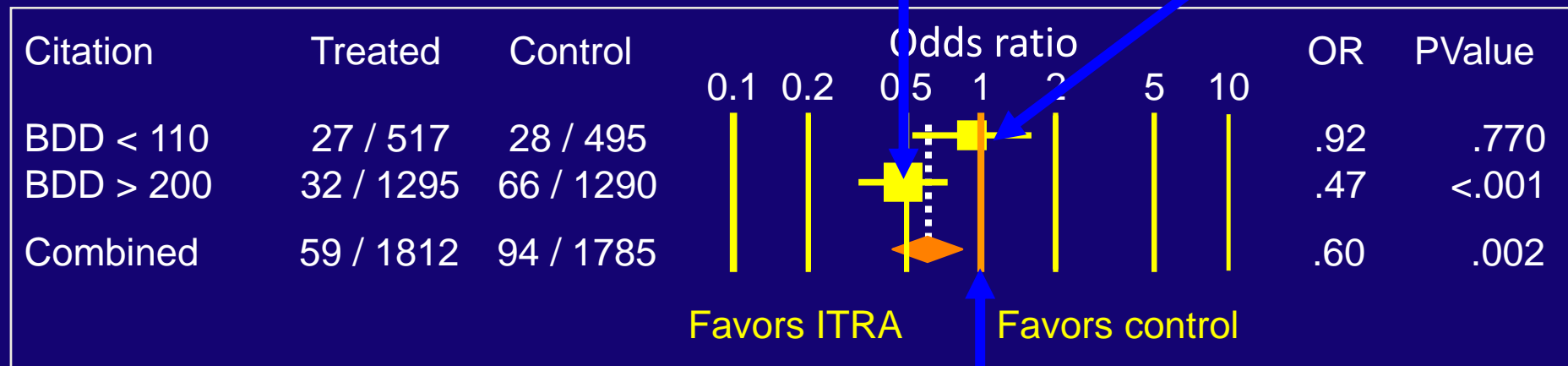
# Itraconazole prophylaxis for invasive fungal infections

Glasmacher et al., JCO 2003; 21: 4615

Odds ratio

95% Confidence Interval

BDD = bioavailable daily dose



Test for heterogeneity (13 trials),  $X^2=10.87$ ,  
P=0.54

n=3597; OR = Peto odds ratio

Reduction = Relative risk reduction

Overall:

- BDD < 110 mg/d

- BDD > 200 mg/d

40% reduction

8% reduction

53% reduction

p=0.049

# Posaconazole vs. "Standard" Azole

- Patients with AML or MDS and intensive chemotherapy
- Prophylaxis during all courses
- Posaconazole (600 mg/d) vs fluconazole (400 mg/d) or itraconazole (400 mg/d OS)

	Posaconazole	"Standard" Azole	P
N	304	298	
IFI during Tx	2%	8%	0.0009
IA during Tx	1%	7%	0.0001
IFI $\leq$ 100d	5%	11%	0.0031

IFI = invasive fungal infection, IA = invasive *Aspergillus* infection

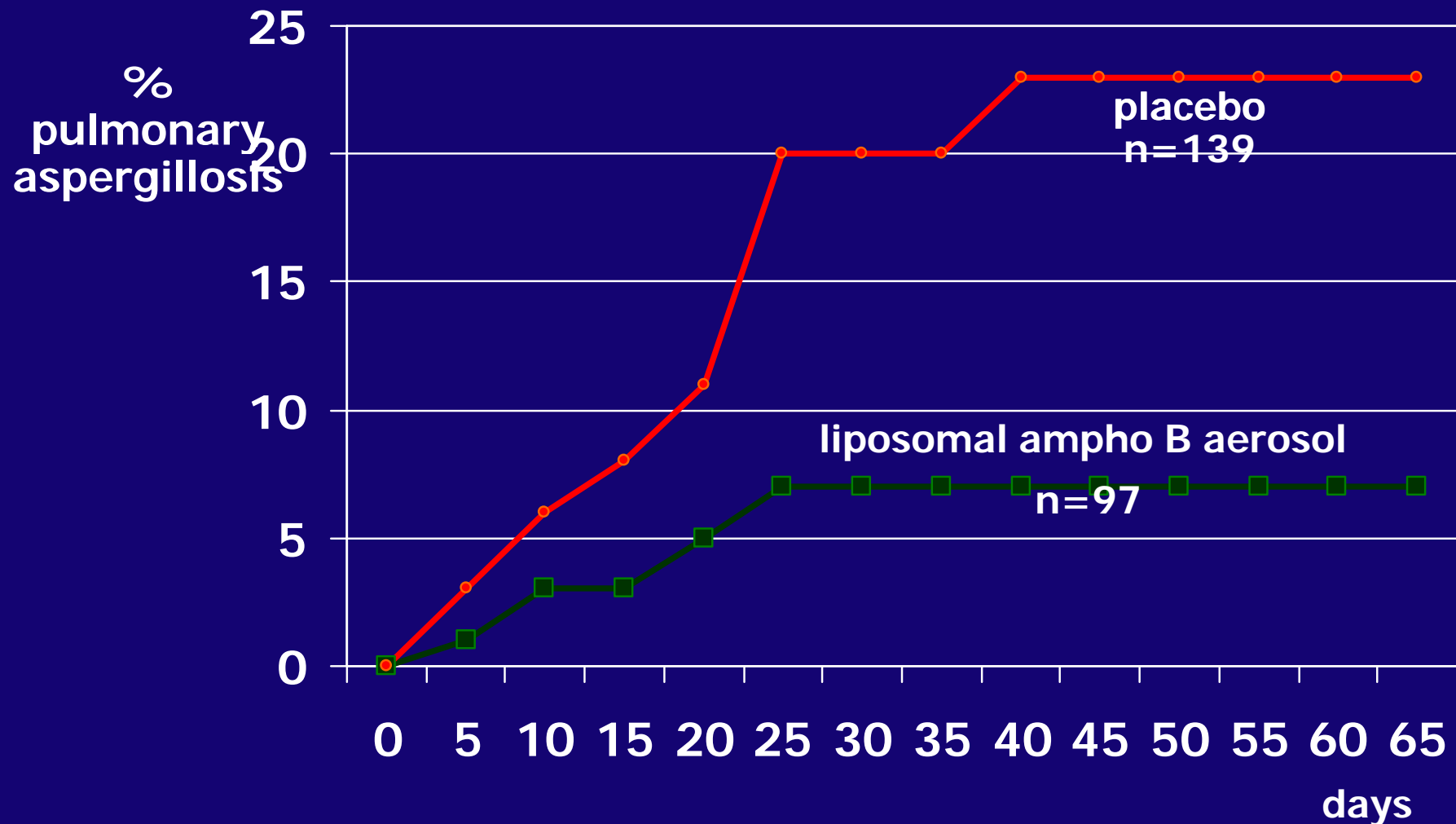
OR = odds ratio

N Engl J Med 2007;356:348–59.

# AEROSOLISED LIPOSOMAL AMPHO-B TO PREVENT INVASIVE ASPERGILLOSIS

*Rijnders et al. CID 2008; 46: 1401-1408*

2.5 ml 5 mg/kg LAMB solution 30 min per day 2days/week



## IDSA GUIDELINES

### Aspergillosis: 2008

*Key recommendation.* Antifungal prophylaxis with posaconazole can be recommended in HSCT recipients with GVHD who are at high risk for invasive aspergillosis and in patients with acute myelogenous leukemia or myelodysplastic syndrome who are at high risk for invasive aspergillosis (A-I). Itraconazole may be effective, but tolerability limits its use (B-I). Further investigation of antifungal prophylaxis is recommended in this population and other high-risk groups.

### Candidiasis: 2009

- For solid-organ transplant recipients, fluconazole (200–400 mg [3–6 mg/kg] daily) or liposomal AmB (L-AmB) (1–2 mg/kg daily for 7–14 days) is recommended as postoperative antifungal prophylaxis for liver (A-I), pancreas (B-II), and small bowel (B-III) transplant recipients at high risk of candidiasis.
- For patients hospitalized in the ICU, fluconazole (400 mg [6 mg/kg] daily) is recommended for high-risk patients in adult units that have a high incidence of invasive candidiasis (B-I).
- For patients with chemotherapy-induced neutropenia, fluconazole (400 mg [6 mg/kg] daily) (A-I), posaconazole (200 mg 3 times daily) (A-I), or caspofungin (50 mg daily) (B-II) is recommended during induction chemotherapy for the duration of neutropenia. Oral itraconazole (200 mg twice daily) is an effective alternative (A-I), but it offers little advantage over other agents and is less well tolerated.
- For stem cell transplant recipients with neutropenia, fluconazole (400 mg [6 mg/kg] daily), posaconazole (200 mg 3 times daily), or micafungin (50 mg daily) is recommended during the period of risk of neutropenia (A-I).



# Why do we need empirical antifungal therapy?

- Treatment administered when microbiological documentation, species identification or susceptibility data still not available
- For at-risk (eg, neutropenic) patients with persistent fever despite broad-spectrum antibacterial therapy
- Insufficient diagnostics
  - Culture-based methods
    - Helpful only with *Candida*, but even then 10% false negative
    - Almost never diagnostic for invasive *Aspergillus* infections
  - Non-culture based methods (GM,1-3 b glucan, PCR)
    - Still high false negative rate
- Many invasive fungal infections are diagnosed too late or only at autopsy
- Late treatment greatly reduces success rates

## When to start Antifungal therapy ?

- Retrospective cohort study of 230 patients from 4 medical centers
- 162 patients (70%) with nonsurgical hospital admission
- *C. albicans* most commonly isolated (56% of patients)
- 192 patients with no previous fluconazole treatment
- Mortality rates based on time of initiation of fluconazole  
( $P = .0009$  for trend)

Day 0	Day 1	Day 2	Day $\geq 3$
14/92 patients (15%)	9/38 patients (24%)	12/33 patients (37%)	12/29 patients (41%)

# Whom to start empirical therapy ?

- Ostrosky-Zeichner prediction rule( 10% rule –NPV: 97 %)
  - systemic abx treatment (days 1–3)
  - indwelling central venous catheter (days 1–3)and at least two of following :
  - TPN (days 1–3)
  - Any dialysis (days 1–3)
  - Major surgery, pancreatitis, use of steroids or use of other immunosuppressive agents (days –7–0)
- Candida score
  - Parenteral nutrition (+0.908)
  - Prior surgery (+0.997)
  - Multifocal *Candida* colonization (+1.112)
  - And severe sepsis (+2.038).
- Patients with “*Candida* score” of 2.5 would benefit from early antifungal treatment (sensitivity 81%, specificity 74%)

*Eur J Clin Microbiol Infect Dis*2007, 26:271–6

*Crit Care Med*2006,34:730–7

# Development of empirical antimycotic therapy

- Period I (1982-1988)
  - Conventional amphotericin B vs. no therapy / placebo
  - Pizzo et al. 1982, EORTC 1988
  - Significant reduction of breakthrough infections if both studies combined
- Period II (1993-1998)
  - Conventional amphotericin B vs. fluconazole or liposomal AmB
  - Defervescence as main outcome, mostly no statistically signif. differences
  - Only one study (Prentice 1997) with a significant difference
- Period III (1998-2001)
  - Introduction of the composite outcome score (Walsh et al., COS)
  - Conventional AmB vs. liposomal AmB, fluconazole, itraconazole, ABCD
  - No significant differences
- Period IV (2000-today)
  - Liposomal AmB vs. ABLC, voriconazole, caspofungin

# Overview of Trials for Empirical Antifungal therapy

	Walsh et al., NEJM 1999		Walsh et al., NEJM 2002		Walsh et al., NEJM 2004	
Comparator s	LipoAmB	ConvAmB	LipoAmB	Vori- conazole	LipoAmB	Caspo- fungin
N	344	343	415	422	556	539
Design	Double blind		Unblinded		Double blind	
Intervention	3 mg/kg/d	0.6 mg/kg/d	3 mg/kg/d	12→6 mg/kg/d	3 mg/kg/d	70 →50 mg/d

# Empirical anti fungal: IDSA

*Key recommendation.* Empirical antifungal therapy with AMB, an LFAB, itraconazole, voriconazole, or caspofungin is recommended for high-risk patients with prolonged neutropenia who remain persistently febrile despite broad-spectrum antibiotic therapy (A-I). Empirical antifungal therapy is not recommended for patients who are anticipated to have short durations of neutropenia (duration of neutropenia, <10 days), unless other findings indicate the presence of an invasive fungal infection (B-III).

## Treatment of Aspergillosis

Clinical Infectious Diseases 2008;46:327–60

## Treatment Guidelines for Candidiasis

Clinical Infectious Diseases 2009;48:503–35

- LFAmB (3–5 mg/kg daily), caspofungin (loading dose of 70 mg, then 50 mg daily) (A-I), or voriconazole (6 mg/kg administered intravenously twice daily for 2 doses, then 3 mg/kg twice daily) are recommended (B-I).
- Fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) and itraconazole (200 mg [3mg/kg] twice daily) are alternative agents (B-I).

# Prophylactic, Preemptive or Empiric Use of Anti-fungals

- PROS

- High Mortality
- Difficulty in Diagnosis
- Undetected Infection
- Reduced systemic mycoses and improved mortality with prophylaxis

- CONS

- Toxicity
- Expense
- Diagnosis not certain
  - Too much treatment without infection
  - Too little treatment with infection

# Galactomannan

Table 1

Monitoring for invasive aspergillosis in hematologic patients using the Platelia *Aspergillus* enzyme immunoassay

Sensitivity (%)	Specificity (%)	Reference
96 (N = 29) <sup>a</sup>	99 (N = 74)	Maertens (2004) <sup>11</sup>
92 (N = 38)	98 (N = 196)	Maertens (2007) <sup>12</sup>
88 (N = 24)	74 (N = 43)	Marr (2004) <sup>13</sup>
79 (N = 407)	86 (N = 3060)	Pfeiffer (2006) <sup>9,a</sup>

Table 2

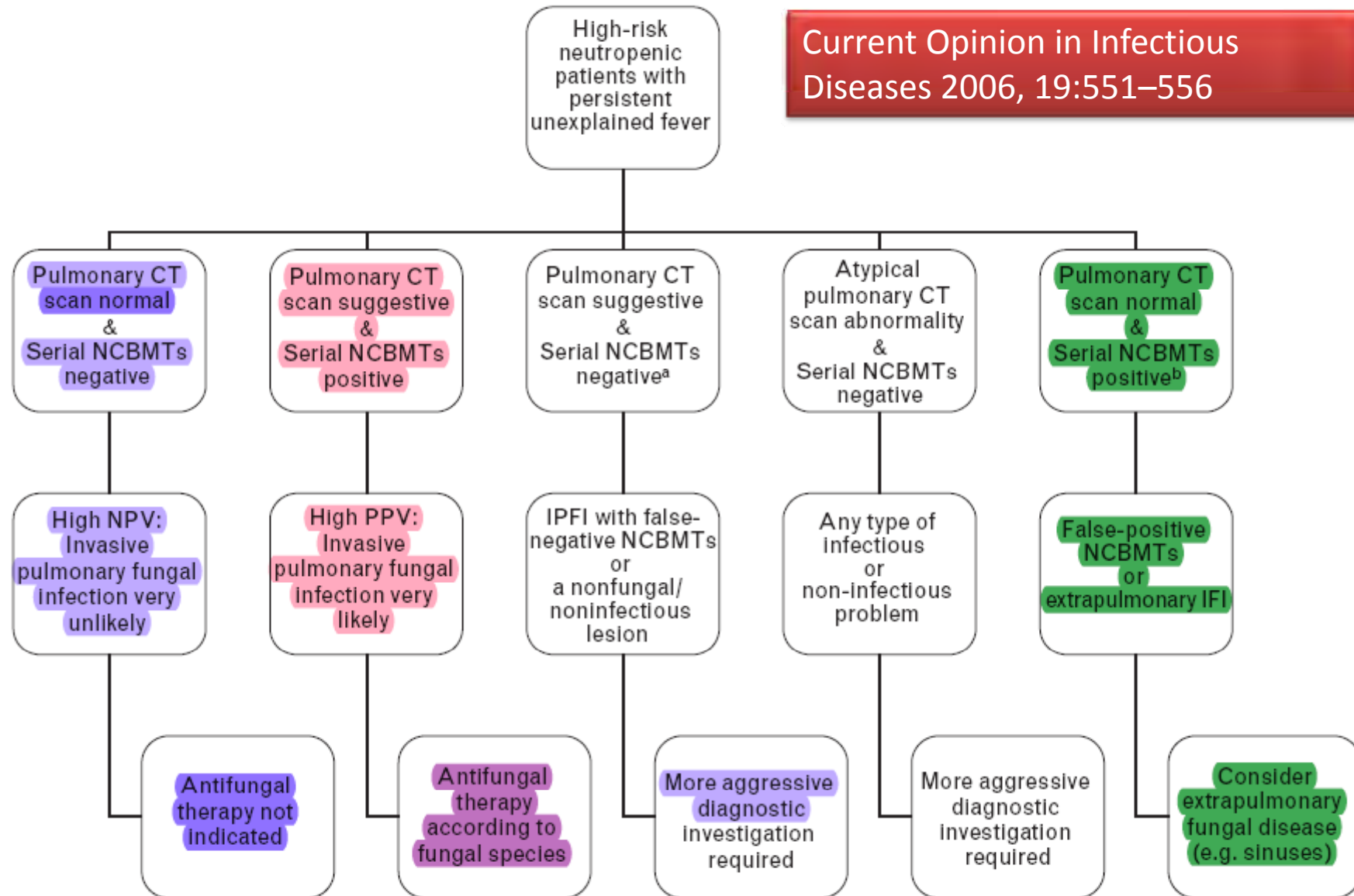
Detection of galactomannan in bronchoalveolar lavage using the Platelia *Aspergillus* enzyme immunoassay

Group	Sensitivity (%)	Specificity (%)	Reference
Hematologic patients (CO 1.0)	100 (N = 17)	100 (N = 18)	Becker (2003) <sup>31</sup>
Hematopoietic stem cell transplantation (CO 0.5)	76 (N = 49)	94 (N = 50)	Musher(2004) <sup>32</sup>
Lung transplantation (CO 0.5)	67 (N = 6)	91 (N = 110)	Husain (2007) <sup>33</sup>
Solid organ transplantation (CO 0.5)	100 (N = 5)	84 (N = 76)	Clancy (2007) <sup>34</sup>
Nonimmunosuppressed (CO 0.5)	100 (N = 6)	78 (N = 67)	Nguyen (2007) <sup>36</sup>
Immunosuppressed ICU patients (CO 0.5)	88 (N = 26)	87 (N = 46)	Meerseman (2008) <sup>8</sup>

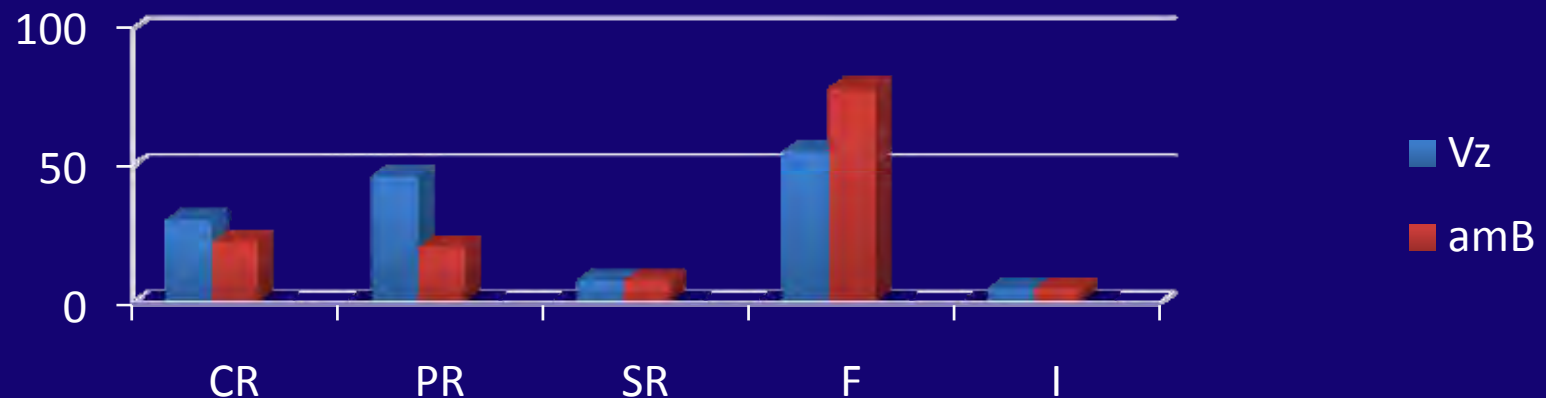


# PRE EMPTIVE PROTOCOL

Current Opinion in Infectious Diseases 2006, 19:551–556



## VORICONAZOLE Vs AMPHO B



- Mostly immunocompromised patients amphotericin B (n=133), voriconazole (n=144)
- In ITT population, successful outcome at week 12 observed in 49.7% of voriconazole group and 27.8% of amphotericin B group
- At week 12, survival rate was 70.8 percent in patients treated with voriconazole, as compared with 57.9 percent in amphotericin B group (hazard ratio, 0.59)
- Significantly fewer adverse events in voriconazole group

*N Engl J Med 2002;347:408-15.*

# Voriconazole versus liposomal amphotericin B in febrile neutropenia

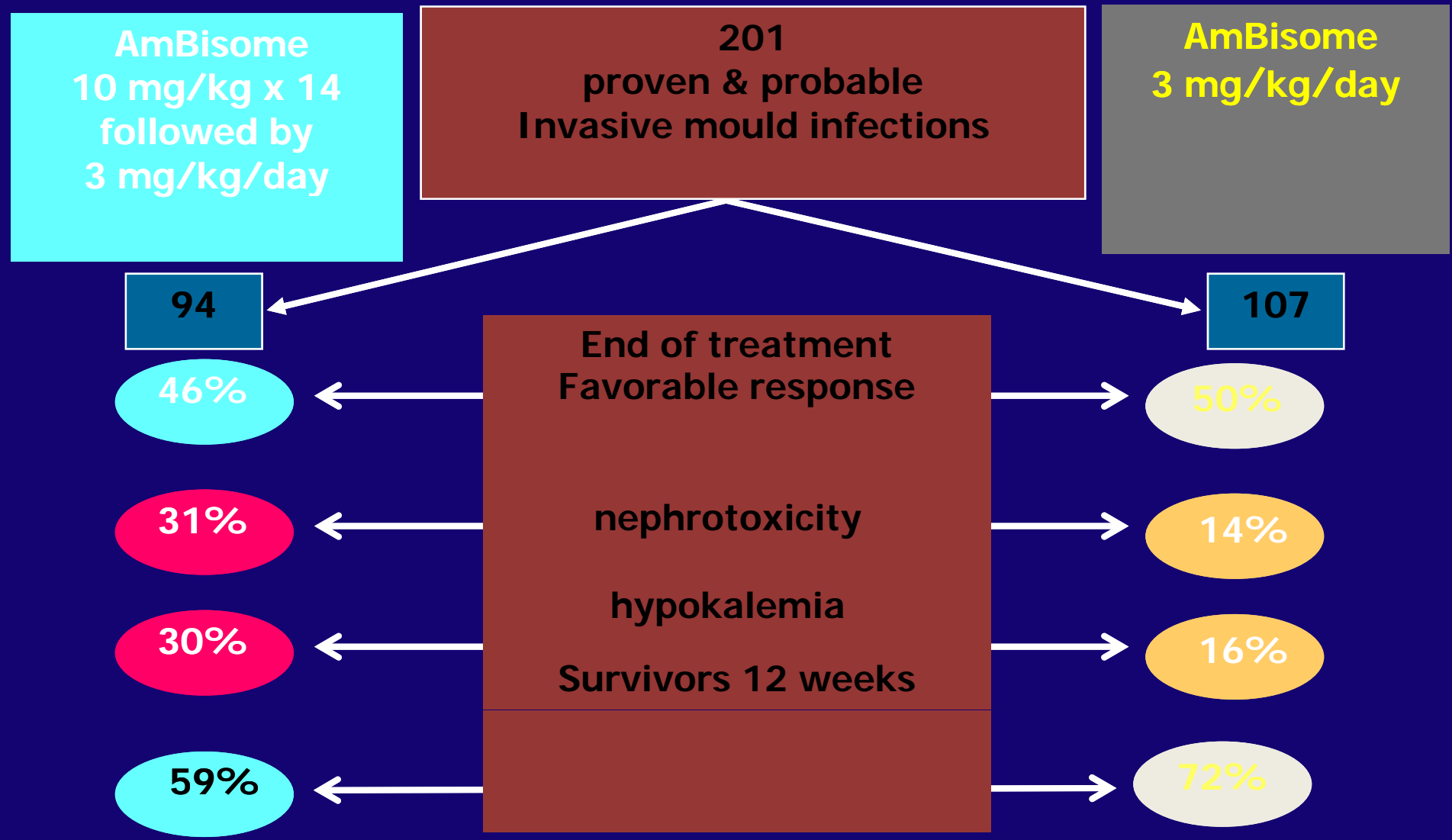
RESPONSE INDICATOR	VORICONAZOLE (N= 415)	LIPOSOMAL AMPHOTERICIN B (N= 422)
Overall response — no. (%)	108 (26.0)	129 (30.6)
No breakthrough fungal infections within 7 days of end of therapy — no. (%)	407 (98.1)	401 (95.0)
Survival 7 days after end of therapy — no. (%)*	382 (92.0)	397 (94.1)
No discontinuation due to toxicity or lack of efficacy before recovery from neutropenia — no. (%)	374 (90.1)	394 (93.4)
Resolution of fever during neutropenia — no. (%)	135 (32.5)	154 (36.5)
Complete or partial response of patients with base-line fungal infections by end of treatment — no./total no. (%)	6/13 (46.2)	4/6 (66.7)

- No significant difference in efficacy.
- Voriconazole was superior in
  - reducing documented breakthrough fungal infections (8% vs.21%)
  - infusion-related toxicity
  - nephrotoxicity

The low molecular weight of voriconazole may permit penetration into the endobronchial-lining fluid and other mucosal surfaces

# HIGH VERSUS STANDARD DOSE AMBISOME FOR INVASIVE MOULD INFECTIONS

*Cornely et al. Clin Infect Dis 2007; 44:1289-1297*

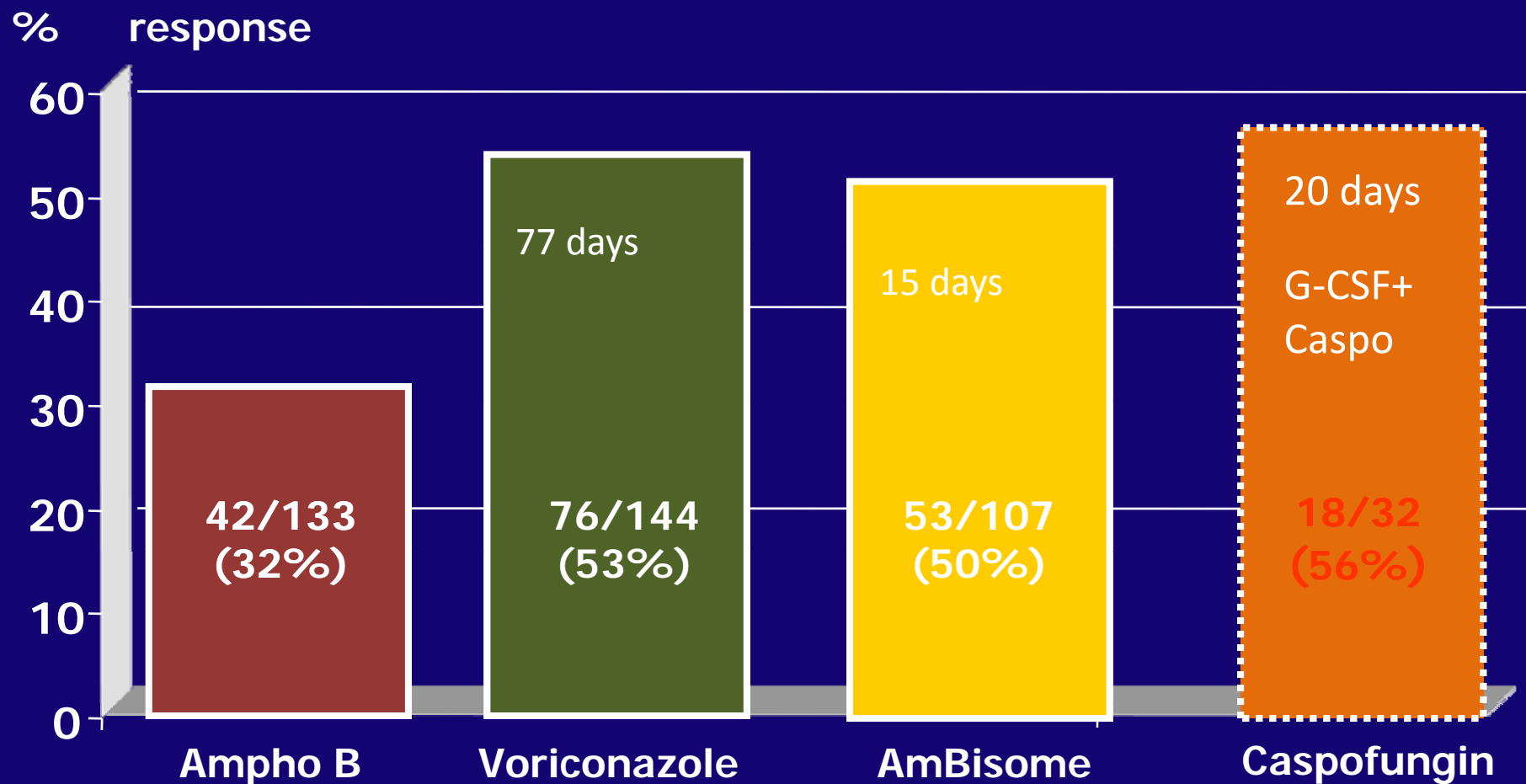


# RESULTS FIRST LINE TREATMENT OF INVASIVE ASPERGILLOSIS

*Herbrecht et al N Engl J Med 2002; 347:408-415*

*Cornely et al. Clin Infect Dis 2007; 44: 1289-97*

*Candoni et al. Eur J Haematol 2005; 75:227-233*



## REVIEW ARTICLE

# When Primary Antifungal Therapy Fails

**Marcio Nucci<sup>1</sup> and John R. Perfect<sup>2</sup>**

<sup>1</sup>University Hospital, Universidade Federal do Rio de Janeiro, Brazil; and <sup>2</sup>Department of Medicine, Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina

---

(See the editorial commentary by Wingard on pages 1434–5)

## EDITORIAL COMMENTARY

# Learning from Our Failures: The Antifungal Treatment Conundrum

**John R. Wingard**

University of Florida College of Medicine, Gainesville

---

(See the article by Nucci and Perfect on pages 1426–33)

# RECOMMENDATIONS FOR ASPERGILLOSIS 2008 - IDSA

I

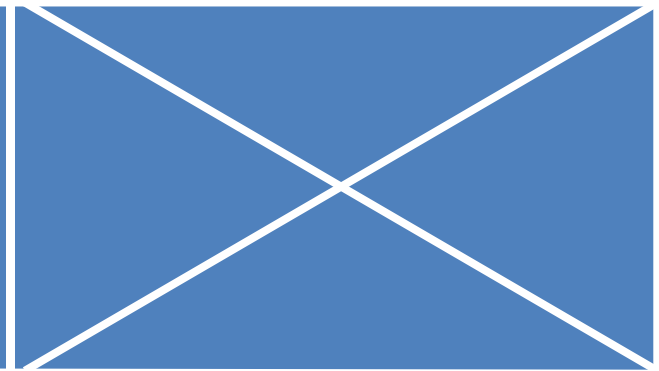
II

III

**A**

- Voriconazole for first line
- LAMB 3mg/kg /day for first line

- Lipid ampho B's in compromised kidneys
- Caspofungin rescue



**B**

- Liposomal ampho B for first line
- Posaconazole as prophylaxis

- Other ampho B's, itra for primary treatment
- Pre-emptive works
- Early intervention is important

- Ampho B followed by itraconazole
- Surgery in selected cases

**C**



- Posaconazole (oral) for rescue

- Biological response modifiers
- Combination therapy

# IDSA Treatment Guidelines for Candidemia

## Nonneutropenic Patients

- Fluconazole 400-800 mg/day iv or po
- Caspofungin 70 mg loading dose followed by 50 mg iv daily
- micafungin: 100 mg daily
- Anidulafungin: loading dose of 200 mg, then 100 mg daily

## Neutropenic Patients

- Caspofungin 70 mg loading dose followed by 50 mg iv daily
- micafungin: 100 mg daily
- Anidulafungin: loading dose of 200 mg, then 100 mg daily
- Liposomal amphotericin B 3.0-6.0 mg/kg/day

*Clin Infect Dis* 2009;38:161-189

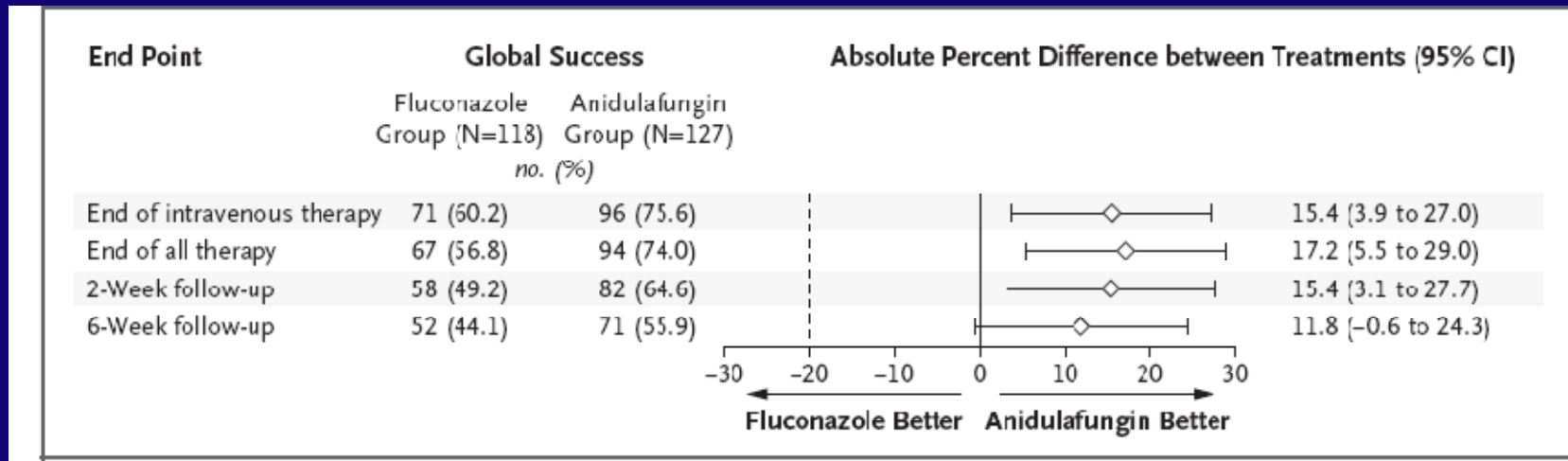


# Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis

	Micafungin		Liposomal amphotericin B		Difference in proportion (95% CI)
	Number of patients	Number treated successfully (%)	Number of patients	Number treated successfully (%)	
Overall	247	183 (74.1%)	247	172 (69.6%)	4.5% (-3.5 to 12.4)
Complete response*		159 (64.4%)		150 (60.7%)	
Partial response*		24 (9.7%)		22 (8.9%)	
Neutropenic status at baseline					4.9% (-3.0 to 12.8)†
<500 cells per $\mu$ L	32	19 (59.4%)	25	14 (56.0%)	
$\geq$ 500 cells per $\mu$ L	215	164 (76.3%)	222	158 (71.2%)	

- Micafungin was as effective as liposomal amphotericin B
- Efficacy was independent of the *Candida* spp and primary site of infection, as well as neutropenic status, APACHE II score
- Fewer adverse events with micafungin

# Anidulafungin versus Fluconazole for Invasive Candidiasis



- Patients were randomly assigned to receive either intravenous anidulafungin (200 mg on day 1 and then 100 mg daily) or intravenous fluconazole (800 mg on day 1 and then 400 mg daily)
- Anidulafungin was found to be non-inferior to fluconazole
- Adverse events were significantly less in anidulafungin group as compared to fluconazole group (1.5% vs 7.5%,  $p=0.02$ )

## Clinical Roles of newer echinocandins- F.D.A.approved indications -

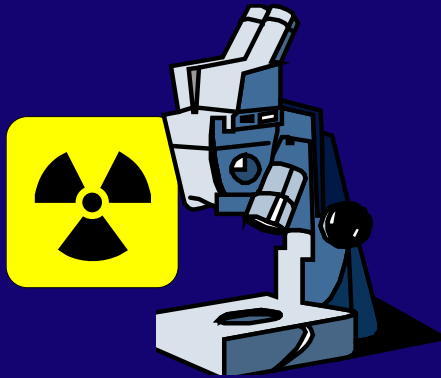
### Micafungin

- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation
- Treatment of esophageal candidiasis

### Anidulafungin

- Candidemia
- Intra-abdominal abscess and peritonitis due to *Candida* infection
- Esophageal candidiasis

# Future Antifungal Strategies

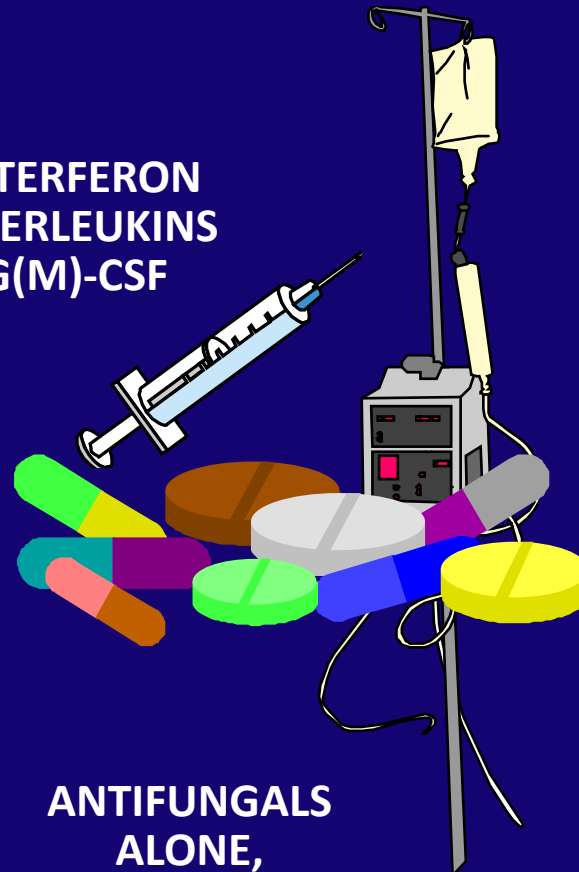


DIAGNOSTICS

HYGIENE  
ISOLATION

ELIMINATION OF  
RISK FACTORS

INTERFERON  
INTERLEUKINS  
G(M)-CSF



ANTIFUNGALS  
ALONE,  
IN COMBINATION, OR  
INTERMITTENT DOSES



SURGERY

*CID 2008: 46: 1889-1901*

# Combination Antifungal Therapy for Mold Infections: Much Ado about Nothing?

**Jose A. Vazquez**

Division of Infectious Diseases, Henry Ford Hospital, Wayne State University School of Medicine, Detroit, Michigan

In general, mortality rates associated with systemic fungal infections have not improved much in more than a decade, although the number of antifungal agents available for the treatment of serious fungal infections has increased in the past few years. A possible approach to decreasing mortality rates associated with fungal infections may be to treat patients with combinations of different classes of antifungals. Recently, in vitro and animal studies evaluating different combinations of antifungal agents have demonstrated important synergistic and/or additive activity against many genera of fungi. However, prudence is required, because some antifungal combinations have demonstrated antagonistic activity. Well-controlled clinical trials are still necessary to define the most efficacious antifungal combination. In addition, these clinical trials should evaluate the adverse event profile of the combination regimens, as well as their pharmacoeconomic impact.

IDSA GUIDELINES

In the absence of a well-controlled, prospective clinical trial, routine administration of combination therapy for primary therapy is not routinely recommended (B-II). The committee recognizes, however, that in the context of salvage therapy, an additional antifungal agent might be added to current therapy, or combination antifungal drugs from different classes other than those in the initial regimen may be used (B-II). In addition, management of breakthrough in-

# What about zygomycosis?

- Mucorales order
- Ubiquitous in environment
- Thick walled non-septate hyphae with right angle branching
- Rare & mimics other invasive mould infections
- Inherent resistance to antifungal agents
- Angioinvasive disease

# Zygomycosis & Mortality

- Multiple clinical forms
  - Cutaneous - 31 %
  - Pulmonary - 76 %
  - Gastrointestinal – 85 %
  - Rhinocerebral - 62 %
  - Sino-orbital - 24 %
  - Disseminated - 100 %
- Direct inoculation, inhalation, ingestion of spores

# Zygomycosis

- Treatment is multifaceted
  - Immune reconstitution
  - Aggressive surgical debridement
  - Ampho B
  - Prayer
- Posaconazole as oral alternative
- Despite this still highly fatal (mortality 50-80%)

## Zygomycosis

*Rhizopus spp*

*Absidia corymbifera*

*Mucor spp*

*Cunninghamella spp*

AmB lipid (5 mg/kg/d)<sup>a</sup>

D-AmB (1.0–1.5 mg/kg/d)

Posaconazole or combination

therapy (G-CSF or GM-CSF,  
deferasirox, hyperbaric oxygen  
therapy)



# CONCLUSIONS

- Invasive mycoses pose a major diagnostic and therapeutic challenge
- Advances in antifungal agents and diagnostic methods offer the potential for improved outcomes in patients with these infection
- Together with assessment of clinical signs, cultures and especially CT scanning, prudent to start aggressive antifungal therapy preemptively
- Development of cost-effective and technically simplified systems for early detection of common and emerging fungal pathogens is need of the hour