Antifungal Therapies in 2003: where do we go? (focusing invasive aspergillosis)

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Roadmap for This Talk

Therapeutic strategies

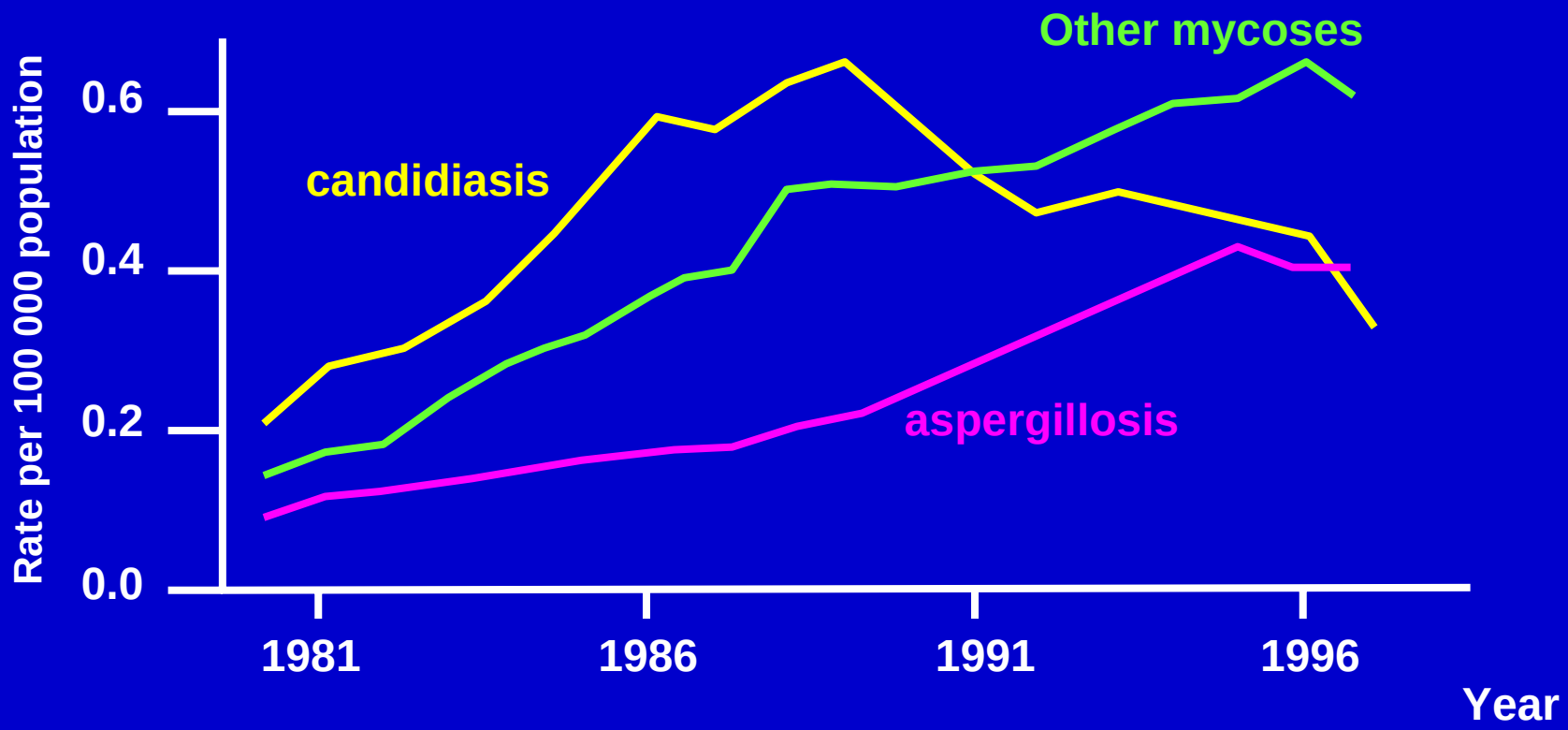
- What we have, what we need
- Introduction to new diagnostics – invasive aspergillosis as example (5 slides!)

New agents: Two are licensed

- Voriconazole
- Caspofungin

Combination therapy: hype or hope?

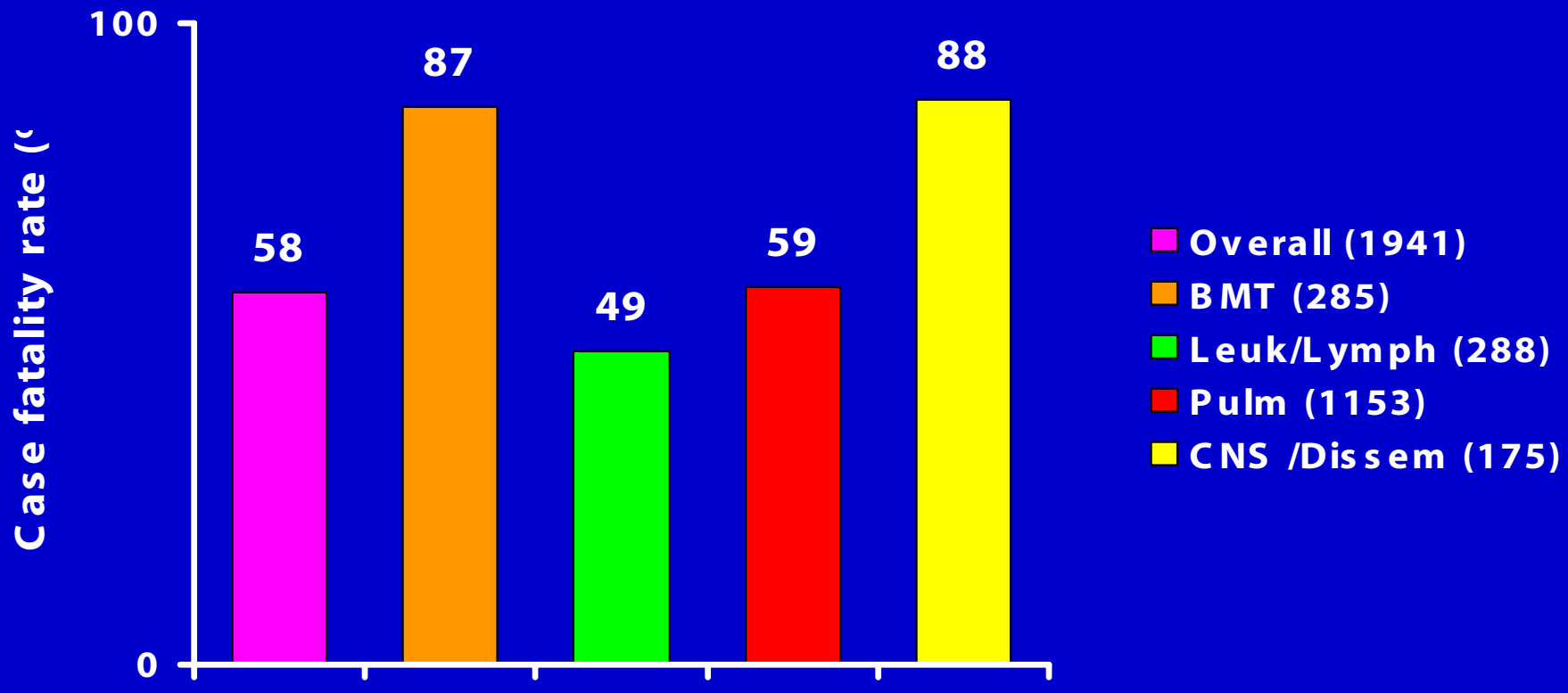
Mortality in the US, 1980-1997, due to candidiasis, aspergillosis, and other mycoses in persons not infected with HIV



McNeil et al., Clin Infec Dis 2001:33

Invasive aspergillosis mortality: Review of literature after 1995

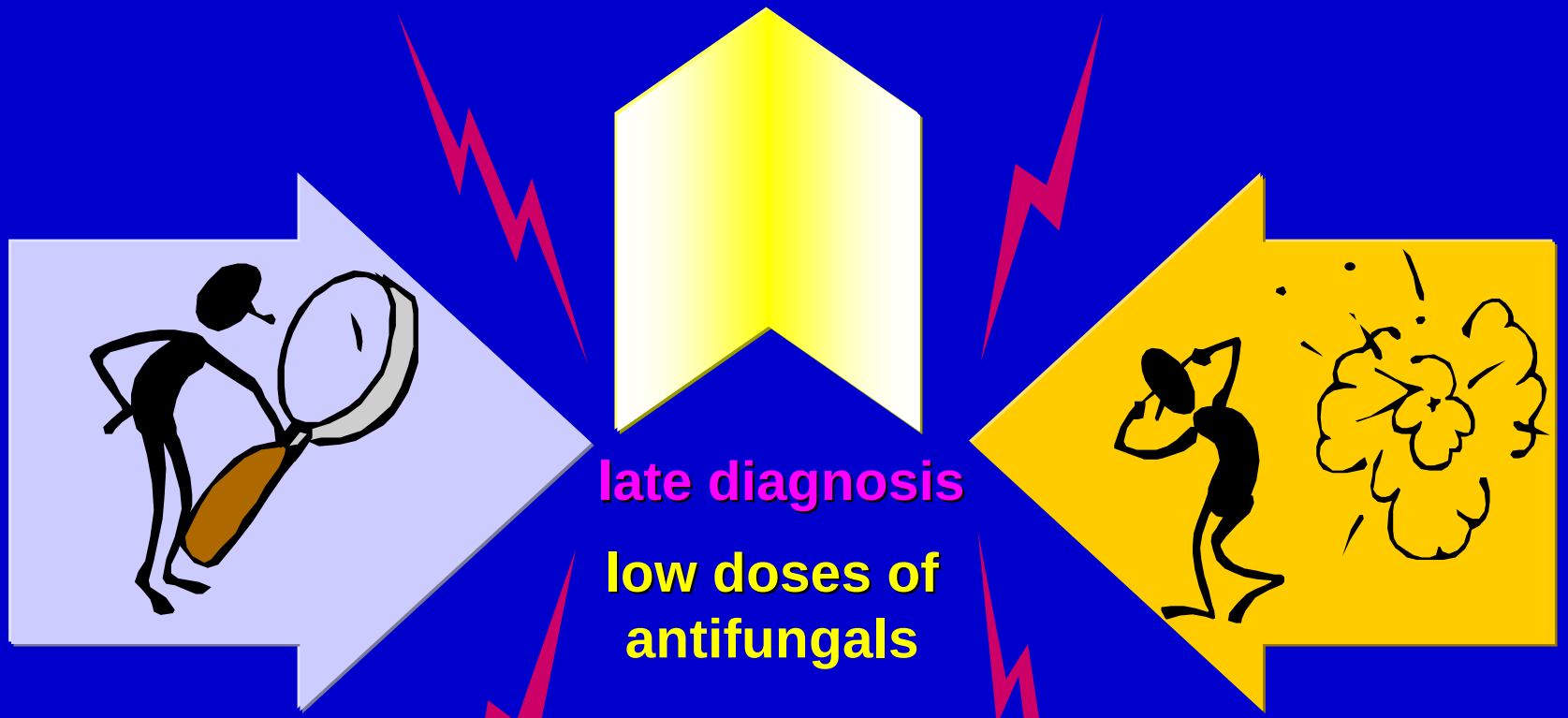
1941 patients from 50 studies



Lin et al., Clin Infect Dis 2001; 32: 358

Poor Treatment Results

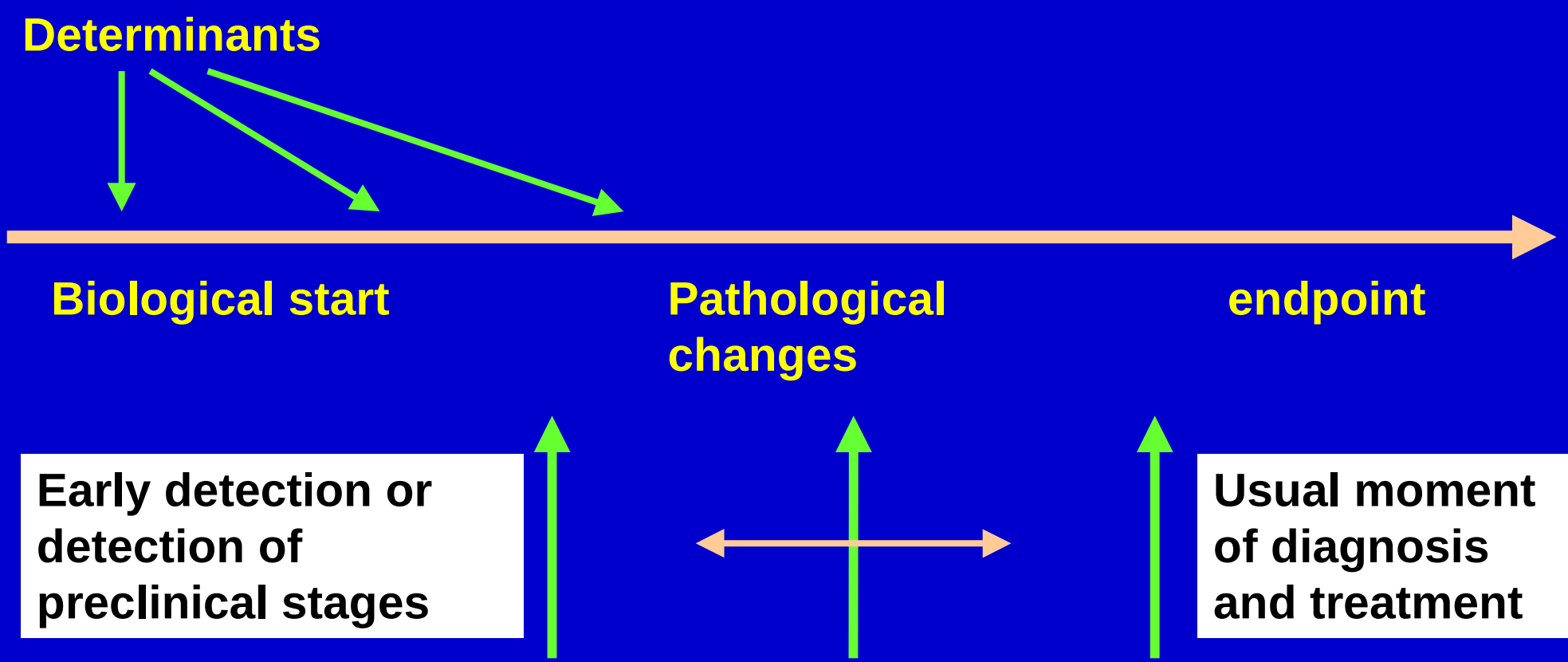
Slide stolen from Dr. Ben de Pauw



limited diagnostic options

relatively toxic/ expensive therapy

Diagnosis of IFI



Can we prevent (or reduce the complications of) IFI by early interventions?

Antifungal prophylaxis

Based on the *patient risk factors* in the absence of infection

Empirical antifungal therapy

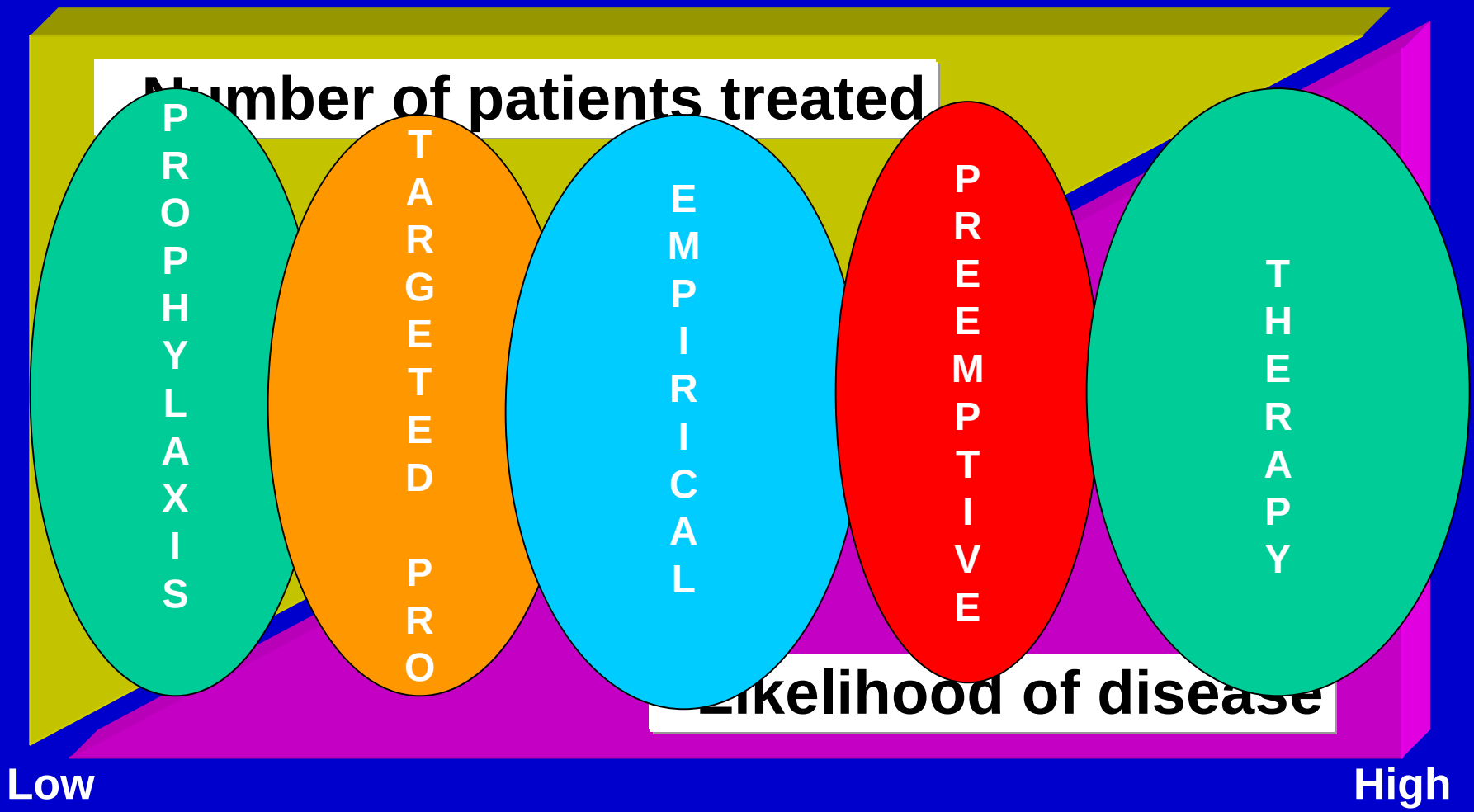
Patients with risk factors and *signs of infection* of unclear aetiology and the possibility of fungal origin

Pre-emptive antifungal therapy

Patients with risk factors + *additional evidence* for the presence of a fungal pathogen in a way *predisposing for infection* (e.g. additional diagnostic means/colonization

Early therapy

Number of patients vs. likelihood of disease



Fluconazole Prophylaxis

Fluconazole prophylaxis in Hematology/HSCT is safe and effective and has been endorsed by consensus guidelines

Goodman 1992; Slavin 1995; Marr 2000

Fluconazole prophylaxis reduces the risk of fungal infection in ICU

Pelz 2001; Garbino 2002

Fluconazole prophylaxis prevents superficial and invasive infections in liver transplant recipients

Winston 1999

Fluconazole prophylaxis is effective in preventing invasive fungal infection in preterm infants

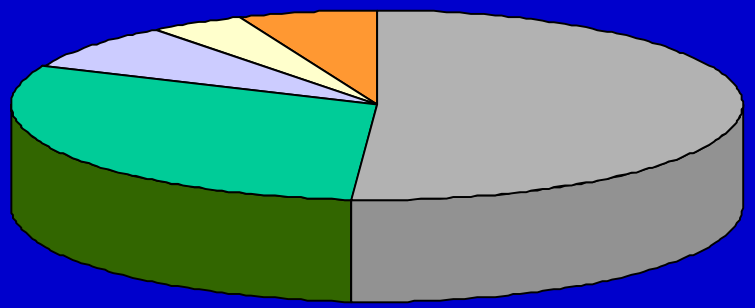
Kaufman 2001

Although Flu prophylaxis is associated with fewer deaths from fungal infection, it does not improve overall survival

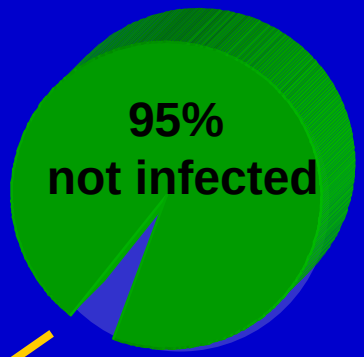
CANDIDA isolates and Candidemia in BMT after introduction of fluconazole prophylaxis

585 assessable patients

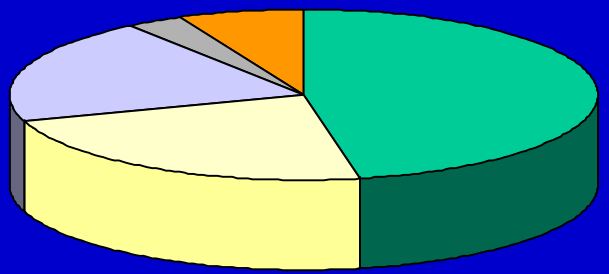
Oral colonization with *Candida*



fluco



34 (5%) candidemia



	Resistance fluconazole
albicans	7%
glabrata	99%
krusei	100%
parapsilosis	
others	

Marr et al., J Infect Dis 2000:309

What are the major fungal pathogens in high-risk patients?

Most common

- **Candida spp.**
- **Aspergillus spp.**

Less common

- **Yeasts**
  - **Trichosporon spp.**
  - **Cryptococcus neoformans**
- **Filamentous fungi**
  - **Fusarium spp.**
  - **Zygomycetes**
  - **Scedosporium/Pseudallescheria**
  - **Dematiaceous moulds**

Itraconazole versus Fluconazole

Winston et al. Ann Intern Med 2003; 138: 705

Marr et al. Blood 2003 (Oct)

- Open-label studies in myeloablative allogeneic HSCT
- **Itraconazole provides better protection against mould infections**
- Imbalances in patient characteristics
  - more unrelated donor Tx, more acute and chronic GvHD in fluconazole arm
- Itraconazole was associated with hepatotoxicity and more discontinuations (36 %) due to toxicity or GI intolerance

Not all hematology patients have the same risk: Targeted approaches?

High: >15%

Allo-BMT/PBSCT
- **Age >40**
- **Non-CML**
- **Graft failure**
- **Steroids**
- **GVHD (II-IV)**
- **Summer**
- **No LAF ?**

AML
- **Age >55**
- **Poor performance**
- **High dose Ara-C**
- **Fludarabine**

Moderate: 5-10/15%

Allo-BMT/PBSCT
- **Age 19-40**
- **Mismatch**
- **Matched unrelated**
- **Construction**
- **Fail**

AML

low: 1-5%

Allo-BMT/PBSCT
- **Age <19**
- **CML, chronic phase**

Auto-PBSCT (BMT)

Steroids (HD)

Chemotherapy (HD)

Transplant-specific risk factors for invasive aspergillosis in organ transplant recipients

Liver transplant

- Poor allograft function
- Renal failure, especially requiring dialysis
- Aspergillus colonization

Lung transplant

- Cytomegalovirus disease
- Allograft rejection, obliterative bronchiolitis

Kidney transplant

- Graft failure requiring reinstitution of hemodialysis
- Intense immunosuppressive therapy

TARGETED PROPHYLAXIS IN LIVER TRANSPLANT RECIPIENTS REQUIRING DIALYSIS

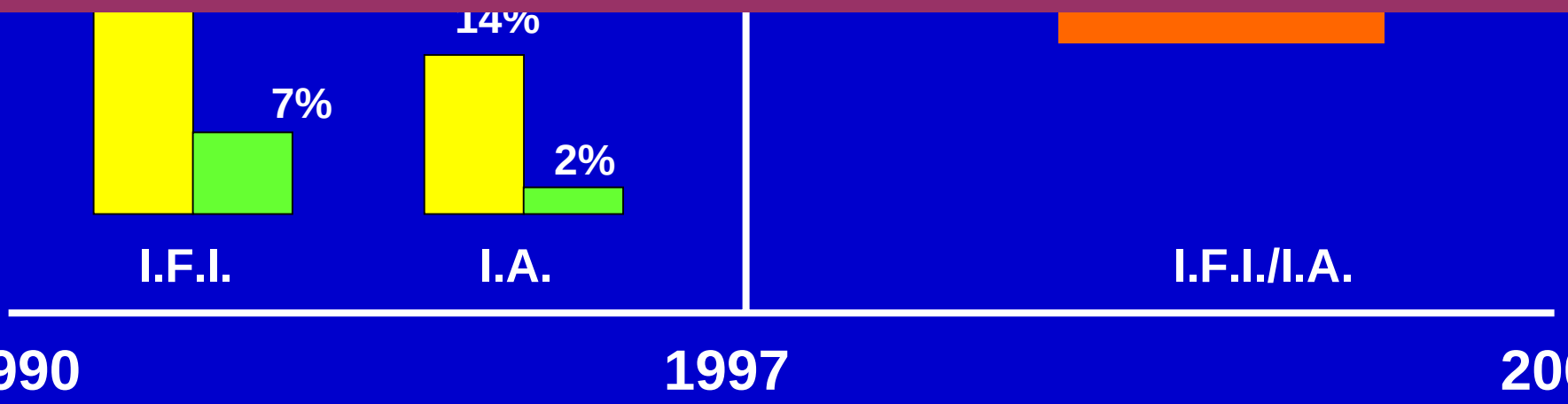
Singh et al. Transplantation 2001; 71: 910

N=148
Dialysis = 22 (15%)
No dialysis

P=0.017

N=38
Dialysis = 11 (29%)
ABLC / Ambisone

No reduction in mortality



Empirical antifungal therapy

The concept

- **In high risk IC patients with persisting or relapsing infectious symptoms, the probability of developing invasive fungal disease is high (> 10-15 %).**
- **The mortality of established fungal disease remains high (40-80 %).**
- **Diagnostic sensitivity and specificity is poor.**

Early empirical antifungal treatment is recommended

Empiric antifungal therapy

Challenging the concept

- All IC- or neutropenic patients are not the same: overtreatment.
- ‘Fever’ and ‘resolution of fever’ is a difficult criterion
- Toxicity of empirical treatment may be high.
- Local epidemiology and/or technology may change rapidly.
- Cost of empirical treatment may be high.

THE IDEAL STRATEGY

- USE ONLY
  - safe and effective antifungal drugs with spectrum adapted to local ecology and optimally adjusted dosage
- INCLUDE ONLY, BUT QUICKLY
  - patients with high probability of fungal disease, belonging to a well defined high risk category
- EXCLUDE CERTAINLY
  - patients with low risk profile or unlikely to have fungal disease
- RELY EXCLUSIVELY ON
  - optimal batteries of clinical, *radiological and laboratory* tests
- AVOID ALWAYS
  - indiscriminate primary prophylaxis
- ADOPT
  - early pre-emptive strategy (and secondary prophylaxis)

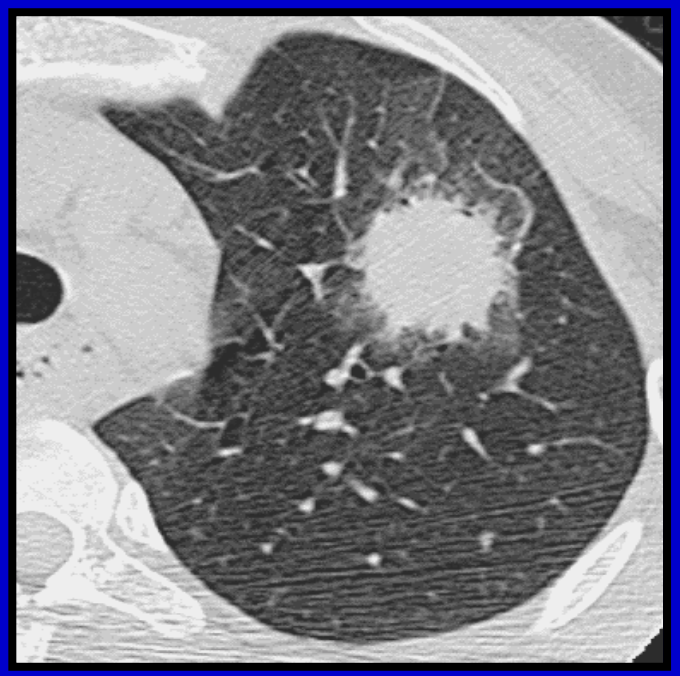
Diagnostic Tests and Techniques

- Histopathology
- Clinical Signs and Symptoms
- Standard radiography
- Culture
- Microscopy
- Antibody detection
- **High-Resolution CT scan/Ultrasound**
- **Antigen detection**
- **PCR**

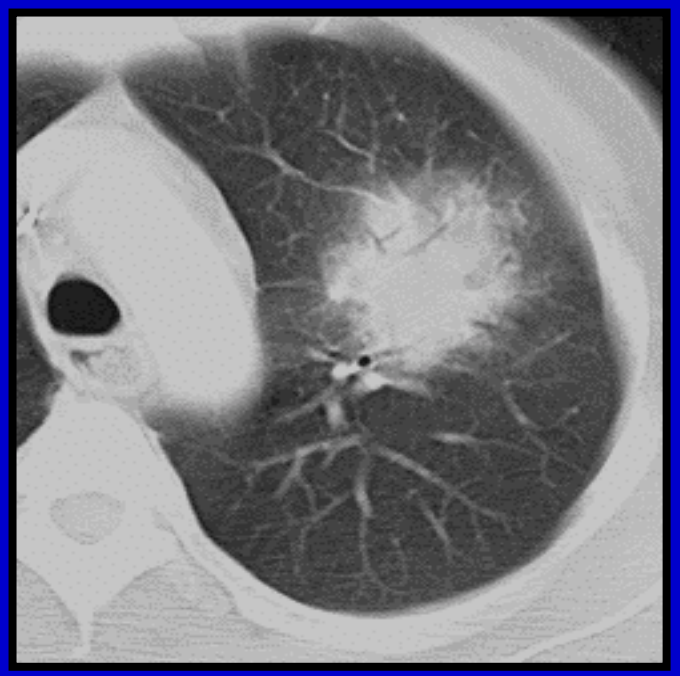
DEVELOPMENT OF PULMONARY CAT-IMAGE

Caillot et al. J Clin Oncol 2001; 19:253-9

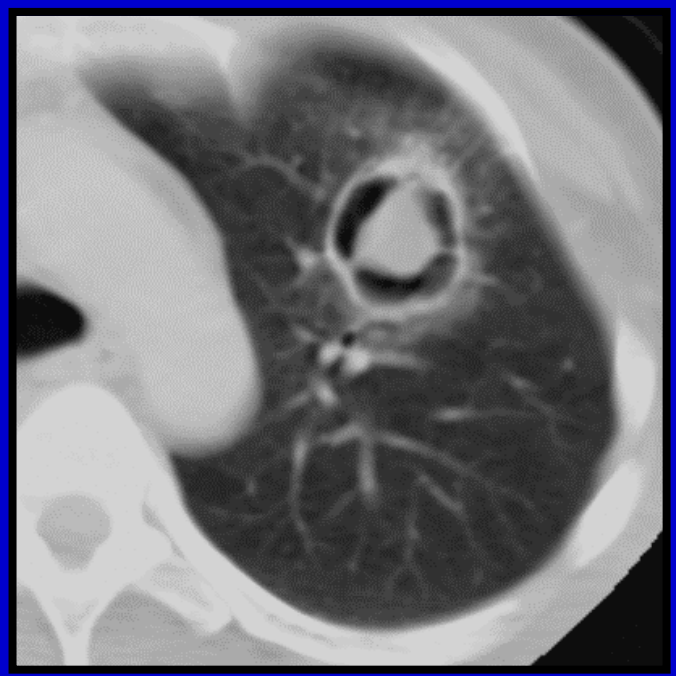
Neutropenia



Halo sign
D 0-5



Air-space consolidation
D 5-10



Air-crescent sign
D 10 -20

Reliability of the Halo Sign

Greene et al. 13th ECCMID Glasgow 2003; Abstr. O397

Nodules in IA	Nodule	Nodule with Halo
Neutropenia	97 %	82 %
Hematological dis., no neutropenia	96 %	49 %
Non-hematological disorder	82 %	24 %

Halo sign or air crescent sign was confirmed by the DRC in 64% of patients entered into the study with a diagnosis of IPA based on CT alone!

Can GM detection be used as a surrogate marker for early (preemptive) therapy ?

- Validation in non-hematology (non-neutropenic?) patients
- Accuracy in different age groups
- Promising results in other body fluids, including CSF and BAL need further confirmation
- Optimal threshold for positivity
- False-positive and false-negative results
- Role of anti-mould prophylaxis

No data on management strategies that incorporate GM / combined GM-CT

PCR (I)

Detection of a broad range of fungal pathogens (pan-fungal) and speciation in blood.

Early indicator of infection.

‘Real-time’ protocols allow quantitation of the amount circulating DNA (fungal load)

Variable performance partly due to non-standardization of the assays.

PCR (II)

In-house PCR assays

- Serum vs plasma vs whole-blood
- Different protocols for sample preparation
- Different fungal DNA segments

Commercialization → standardization assay

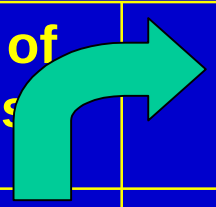
Automatisation → reproducibility and comparability

Molecular Approaches by PCR (blood)

Author	Patients/ controls	Number of samples	Sensitivity	Specificity
Einsele 97	172/35	601	100	98
Skladny 99	93/47	250	100	89
Williamson 00	37/-	175	100	79
Hebart 00	84/-	1193	100	65
Hebart 00	92/-	333	100	73
Lass-Flörl 01	121/-	619	75	96
Buchheidt 01	218/60	907	91.7	81.3

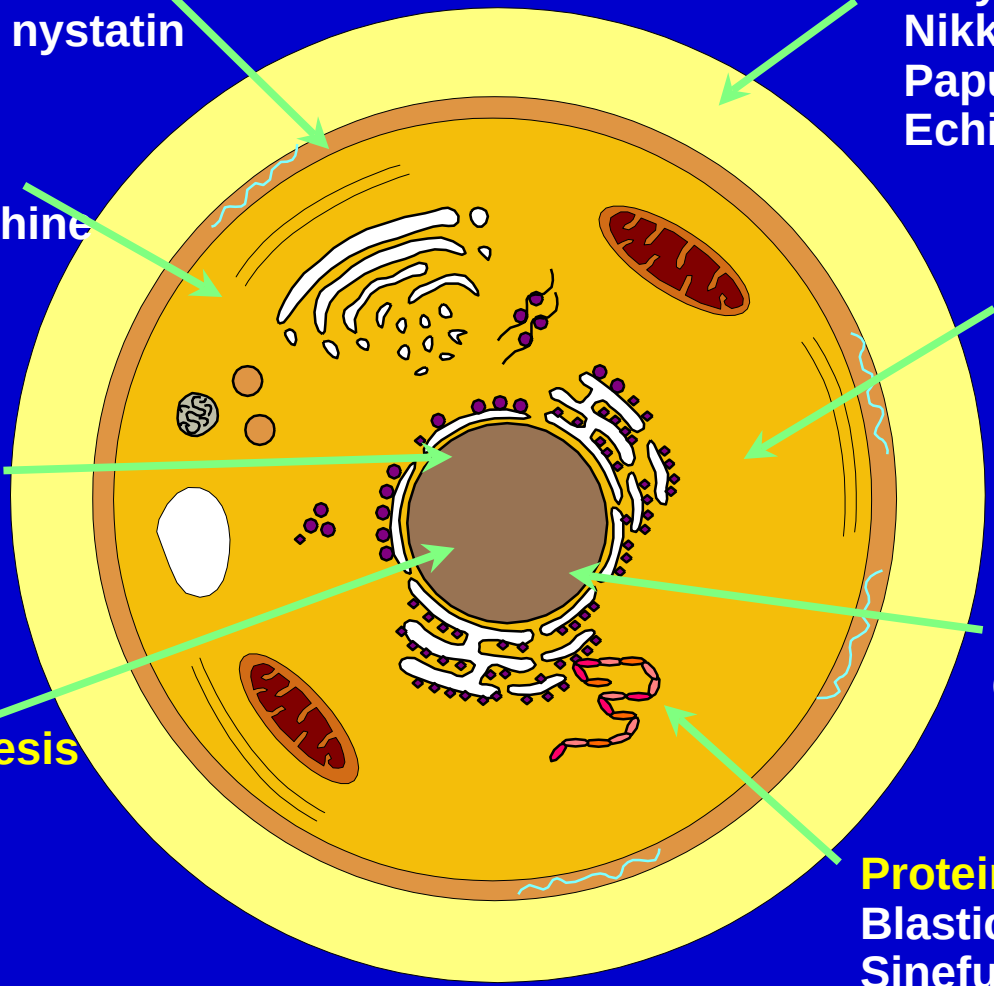
Molecular Approaches by PCR (blood)

Author	Patients/ controls	Number of samples	PPV	NPV
Einsele 97	172/35			
Skladny 99	93/47			
Williamson 00	37/-	175	80/100	100
Hebart 00	84/-	1193	15.2/27.8	100
Hebart 00	92/-	333	36.8	100
Lass-Flörl 01	121/-	619	42	98
Buchheidt 01	218/60	907	49.3	98



Colonization & Contamination

The antifungal agents



Membrane function
polyenes:
amphotericin B, nystatin

Cell wall synthesis
Polyoxins
Nikkomycins
Papulacandins
Echinocandins

Metabolic inhibitors
a-difluoromethylornithine
Cispentacin

Ergosterol synthesis
Azoles
Allylamines/
thiocarbamates
Morpholines

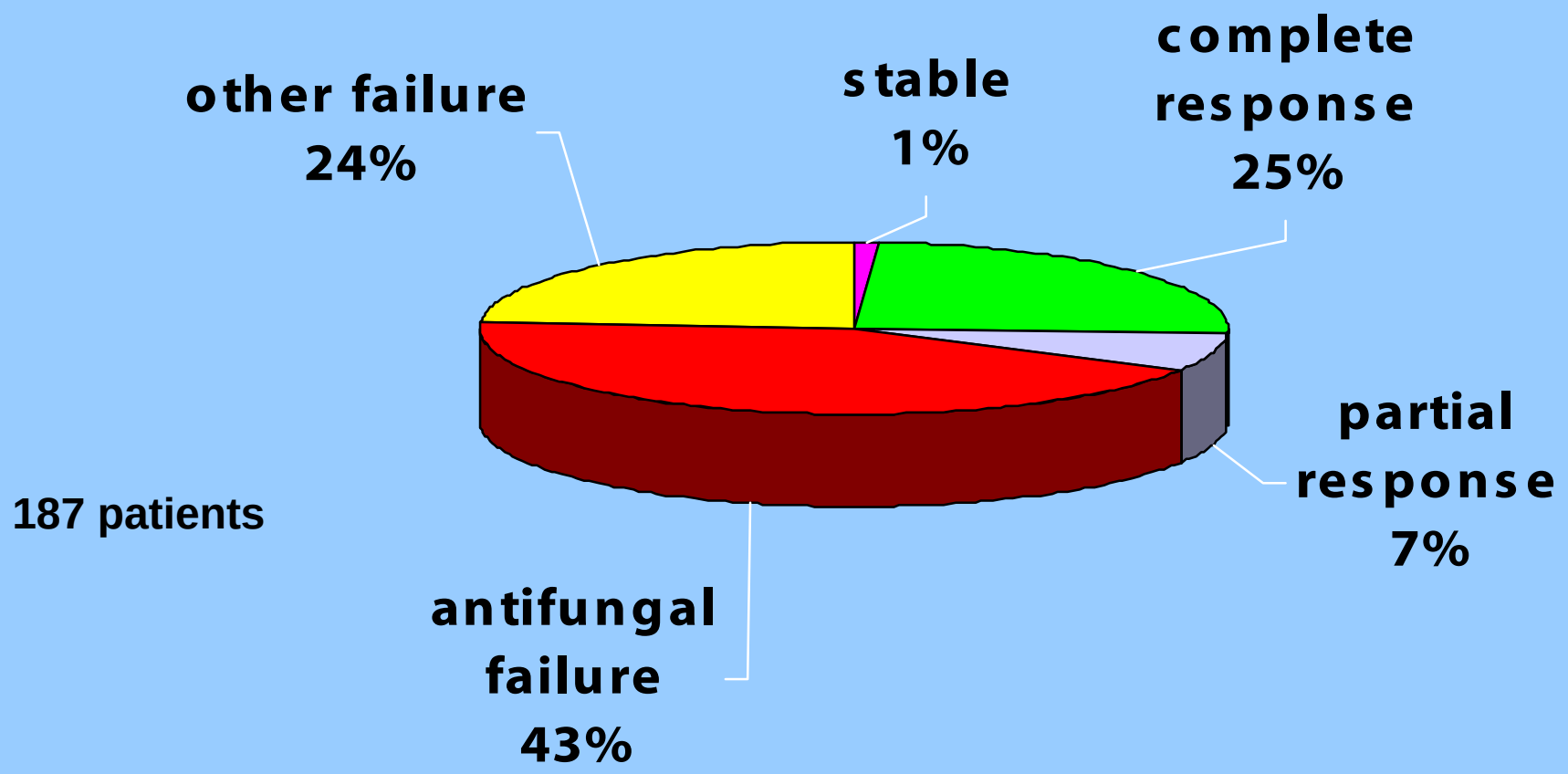
Nucleic acid function
Pentamidine

Nuclear division
Griseofulvin
Benomyl

Nucleic acid synthesis
5-fluorocytosine
Trimethoprim
Sulfomethoxazole

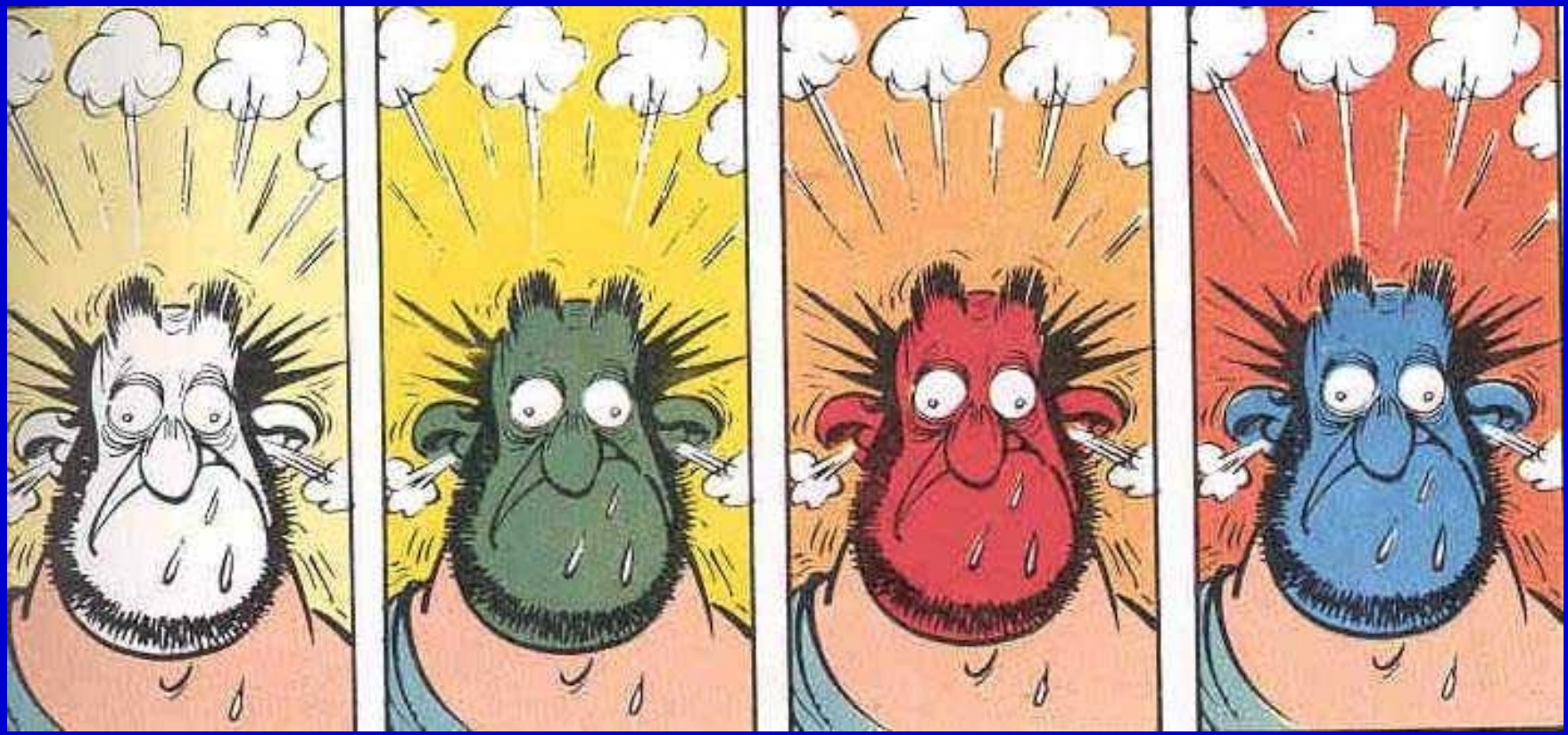
Protein synthesis
Blasticidin
Sinefungin

Amphotericin B in invasive aspergillosis: End of therapy responses



Patterson et al, Medicine 2000; 79; 250

Ampho B effect



Courtesy of Dr. Ben de Pauw

Clinical significance of nephrotoxicity

Wingard et al. CID 1999; 29: 1402

239 pts receiving AmB; mean duration 20 d

Cr > 2.5 mg/dL	29 %
dialysis	14 %
mortality	60 %

Risk of dialysis

allo BMT	6.34
auto BMT	5.06
Cr > 2.5	42.02

Increased mortality

dialysis	3.05
AmB duration	1.03/d
nephrotoxic agents	1.96

Commercially available ampho B drugs

Generic name	Trade name	Manufacturer	FDA
Amphotericin B deoxycholate	Fungizone	Bristol-Myers Squibb	1958
Amphotericin B lipid complex (ABLC)	Abelcet	The Liposome Company	1995
Amphotericin B colloidal dispersion (ABCD)	Amphocil Amphotec	Sequus	1996
Liposomal amphotericin B (L-AmB)	Ambisome	Gilead	1997

Lipid formulation of ampho B

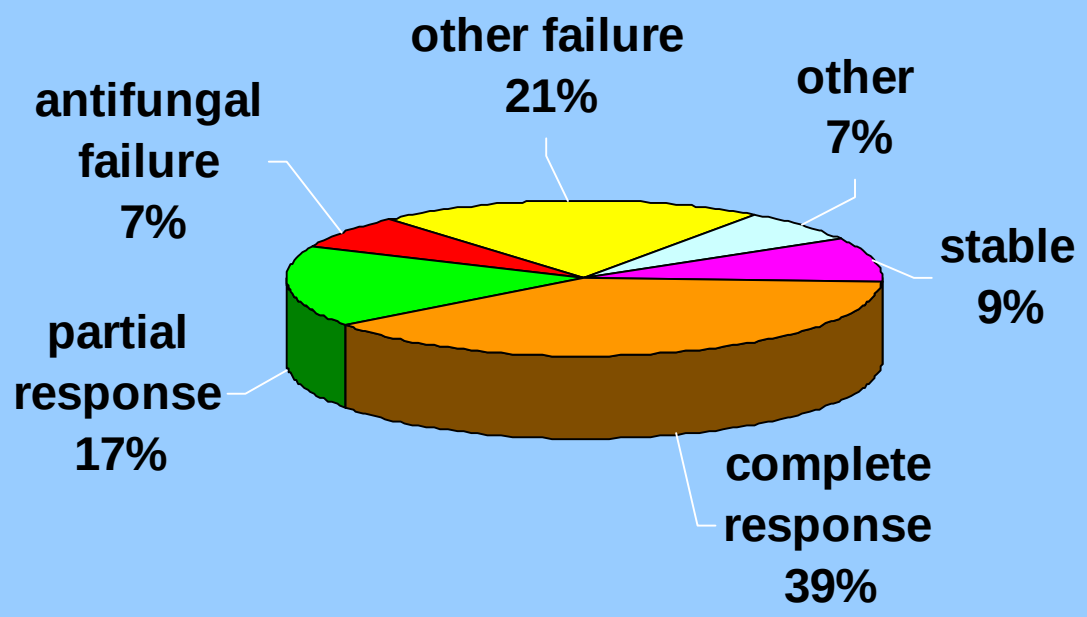
Tissue penetration	Abelcet lung > Ambisome
Efficacy in proven IF	Ampho B = Abelcet = Amphocil = Ambisome
Toxicity	
• infusion-related	Amphocil > AmphoB = Abelcet > Ambisome
• renal	AmphoB > Amphocil
	AmphoB > Abelcet > = Ambisome
• liver	AmphoB = Amphocil = Ambisome > = Abelcet
• discontinuation	Amphocil = Ampho B > Abelcet > = Ambisome
Acquisition cost	Ambisome > Amphocil > Abelcet > AmphoB
	dose dependent
Cost effectiveness	no prospective data
Outpatient infusion	Ambisome > Abelcet > Amphocil > AmphoB

Response rates, overall survival rates, and toxicities associated with lipid formulations of amphotericin B as first-line therapy for invasive fungal infections, relative to conventional amphotericin B therapy, according to published randomized trials.

			Rate relative to conventional AmB			
					Toxicity	
Reference	Pathogen(s)	Agent	Clinical response	Survival	infusional	renal
Leenders et al	Mixed	L-Amph	Same	Same	Lower	Lower
Leenders et al	Cryptococcus species	L-Amph	Same	Same	Lower	Lower
Anaissie et al	Candida species	ABLC	Same	Same	Same	Lower
Bowden et al	Aspergillus species	ABCD	Same	Same	Greater	Lower
Hamill et al	Cryptococcus species	L-Amph	Same	Same	Lower	Lower
Johnson et al	Histoplasma capsulatum	L-Amph	Greater	Greater	Lower	Lower

Wingard et al, CID, 2002

Itraconazole: End of therapy responses



- 595 patient survey
- 58 itraconazole capsules
  - Highly selected patients
  - Few highly patients immunosuppressed
- Clinical responses:
  - CR/PR: 33/58 (56%)

Patterson et al, Medicine 2000; 79; 250

The New Azoles & The Candins

The New Broad-Spectrum Azoles

Voriconazole. Now licensed

- **Oral and IV forms**

Posaconazole. Phase III

- **Oral only, at least at present**

Ravuconazole. Phase II. Limited public data

- **Oral for sure, IV is hopeful**

Others for which we don't have time

- **Albaconazole (UR-9825), CS-758, etc.**

What makes the new azoles special?

1. A promise of better *Candida* activity
   - All work for *C. albicans, tropicalis, parapsilosis*
   - *C. glabrata* (MIC90, 48h)
     - Flu: 32, Vori: 1, Posa: 2, Ravu: 2
   - *C. krusei* (MIC90, 48h)
     - Flu: > 64, Vori: 1, Posa: 0.5, Ravu: 0.5
     - Neutropenic guinea pig model
       - Vori reduced kidney CFU/g better than AmB or Flu

Ostrosky IDSA #642, '01; Pfaller AAC 46:1723, '02; Ghannoum J Chemother 11:34, '99

What makes the new azoles special?

2. Potent anti-*Aspergillus* activity
   - *A. fumigatus* (MIC90 at M38-P's MIC-2)
     - Itra: 2, Vori: 0.5, Posa: 0.25, Ravu: 1
   - *A. flavus*
     - Itra: 0.5, Vori: 1, Posa: 0.5, Ravu: 1
   - These newer azoles often appear fungicidal
     - Vori: Sterilized valves in *A. fumigatus* endocarditis model
     - Posa: Also sterilizes tissue in some models
     - Ravu: Less data. At least equal to Itra & AmB

Pfaller AAC 46:1032, '02; Martin AAC 41:13, '97; Graybill JAC 42:539, '98; Petraitiene AAC 45:857; Kirkpatrick JAC 49:353, '02

What makes the new azoles special?

3. **Other fungi … More active, but they differ!**

Fusarium (Vori & Posa. Limited data on Ravu)

Vori: ~50% salvage rate. Licensed for this

Posa: Sterilized organs in an animal model

Scedosporium (Vori, Posa, Ravu)

Vori: ~50% salvage rate. Licensed for this.

Posa, Ravu: Not a lot of clinical data as yet

Encouraging in vitro data (both) & case reports (Posa)

Zygomycetes (Posa)

Active in vitro and in vivo. Quite encouraging. See ASH 2003.

Lozano-Chiu AAC 43:589, ’99; Carrillo AAC 45:2151, ’01; Mellinghoff CID 34:1648, ’02; Sun AAC 46:2310, ’02

What remains problematic?
Drug Interactions and Pharmacokinetics (PK)

- Interference with critical concomitant medications:
  - Dosing adjustments, discontinuations, or avoidance to prevent toxicity (e.g., CsA)
  - Difficulty in predicting CsA and tacrolimus blood concentrations
- CYP450 drug-drug interactions can result in:
  - Antifungal failure: if induction of metabolism occurs
  - Potentiation of effect of concomitant therapies $\rightarrow$ toxicity
- Unpredictable PK:
  - Potential for toxicity as plasma concentrations rise more than expected with increasing doses of antifungal

Adverse Events

Hepatic

- **Overall rate of 13%. ~ 2-fold more than Flu**

Visual

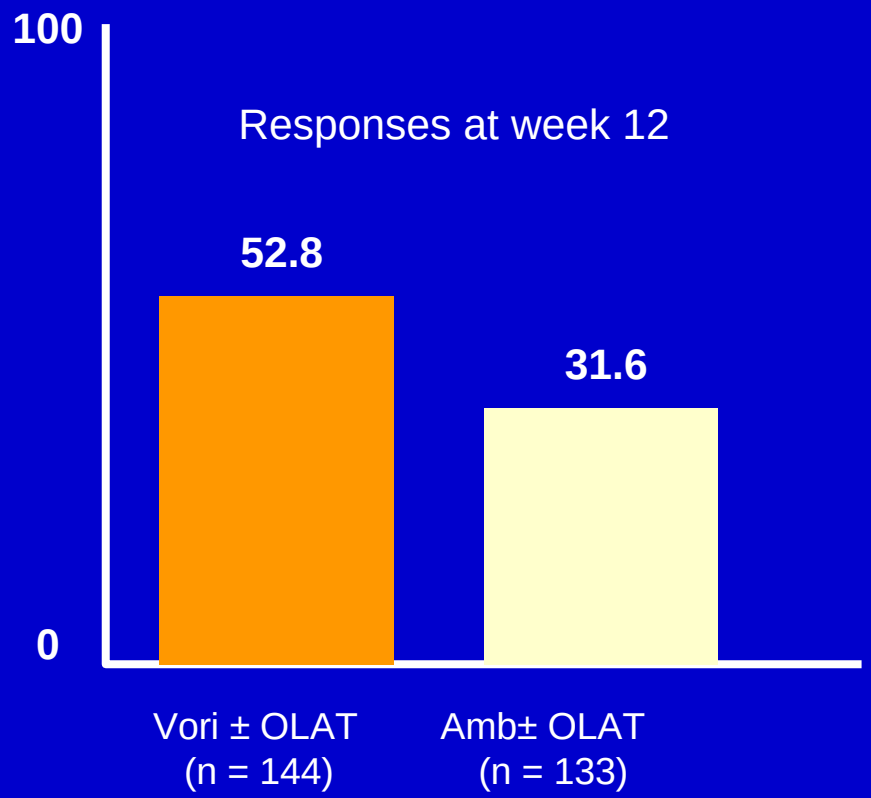
- **Noted by ~30%. A sense of altered light perception, blurring, or photophobia**
- **EXHAUSTIVELY studied. No apparent consequences.**

Miscellaneous

- **Photosensitivity (~1%)? Avoid strong sunlight.**
- **Renal function and IV form**

Sabo Ann Pharmacother 34:1032, ’00; Voriconazole package insert, May 2002; Voriconazole FDA Advisory Cmte, ‘01

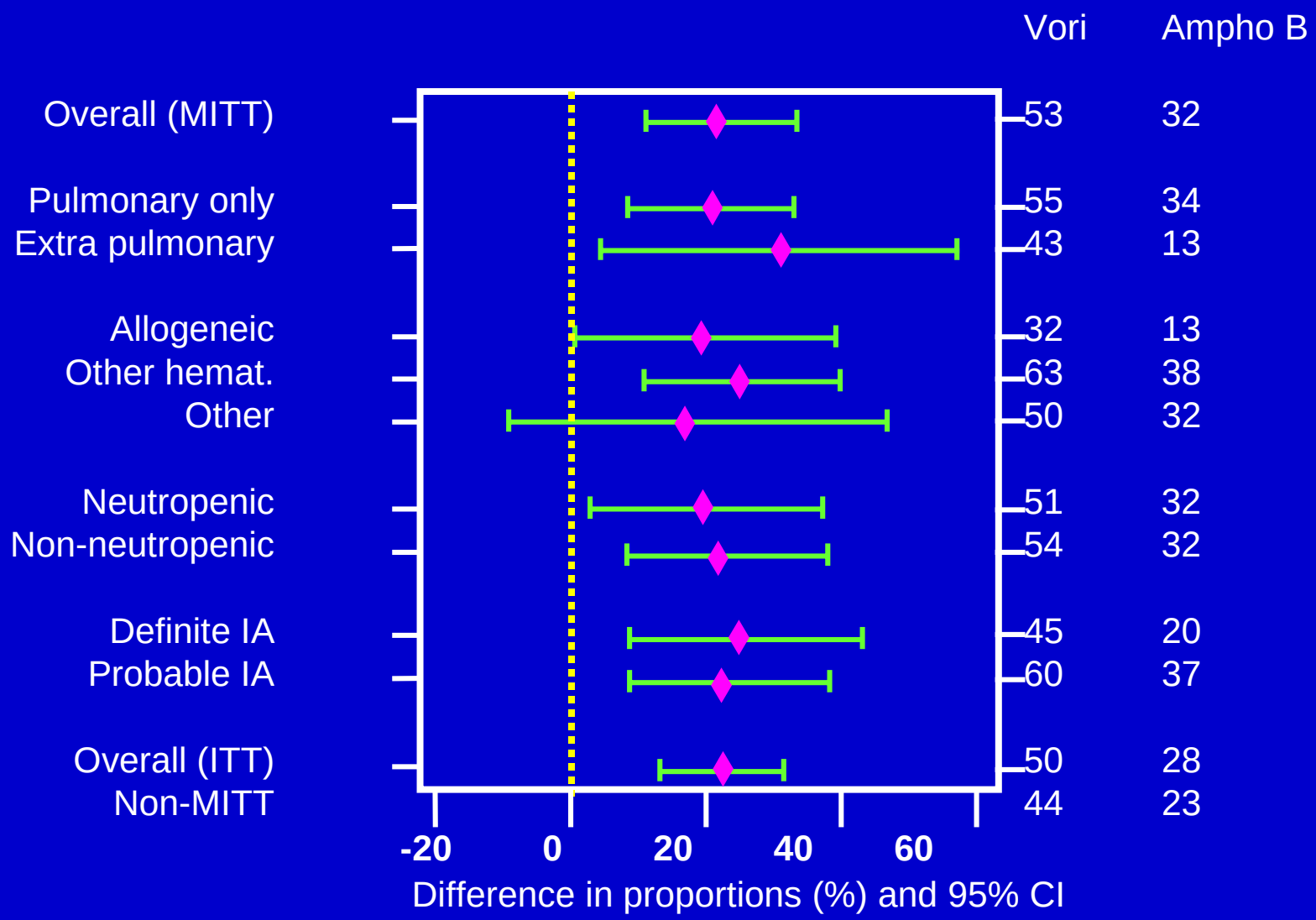
Global comparative aspergillosis study



- Satisfactory (CR/PR) responses at week 12
  - Difference: 21.2% (95% CI[9.9, 32.6])
- Responses at end of initial randomized therapy
  - Vori ± OLAT: 53.5%
  - AmB ± OLAT: 21.8%
  - Median duration of IRT:
    - ✓ Vori: 77 days
    - ✓ AmB: 11 days
- Discontinuations due to AE/lab abnormality
  - Vori 20% / Amb 56%

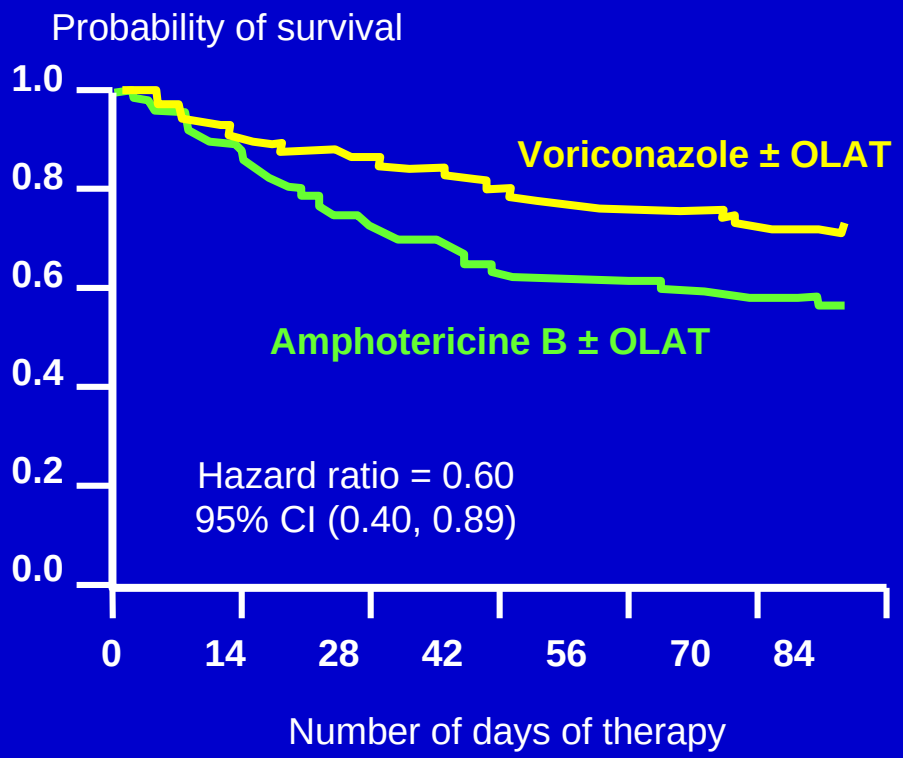
Herbrecht et al, NEJM 2002; 347

Week 12 successful response rate (%)



Herbrecht et al, NEJM 2002; 347

Global comparative aspergillosis study: Survival

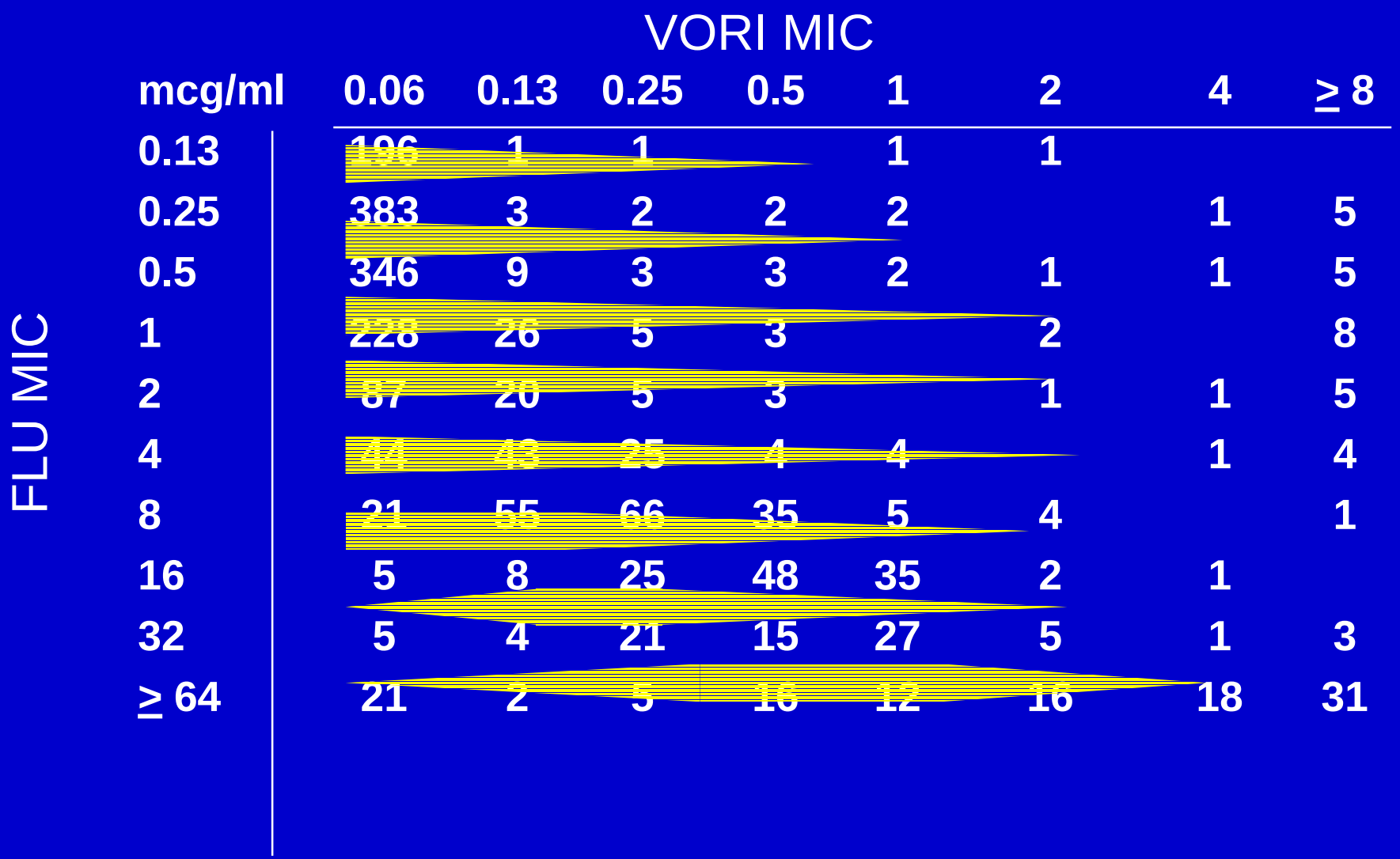


- Survival at week 12
  - Vori ± OLAT: 70.8%
  - AmB ± OLAT: 57.9%
- Discontinuations due to AE/lab abnormality
  - Vori 20% / Amb 56%

Herbrecht et al, NEJM 2002; 347

48h NCCLS M27 MIC, 2000 bloodstream isolates

Vori MIC follows Flu MIC



Vori for Refractory Candidiasis

A series of patients have been collected from several different studies

- Salvage therapy protocol
- Compassionate use protocol

106 enrolled

- Candidemia: 21, 48% overall response
- Other invasive: 34, 41% overall response
- EC: 51, 61% overall response

Ostrosky, 40th IDSA Abstract 352, 2002.

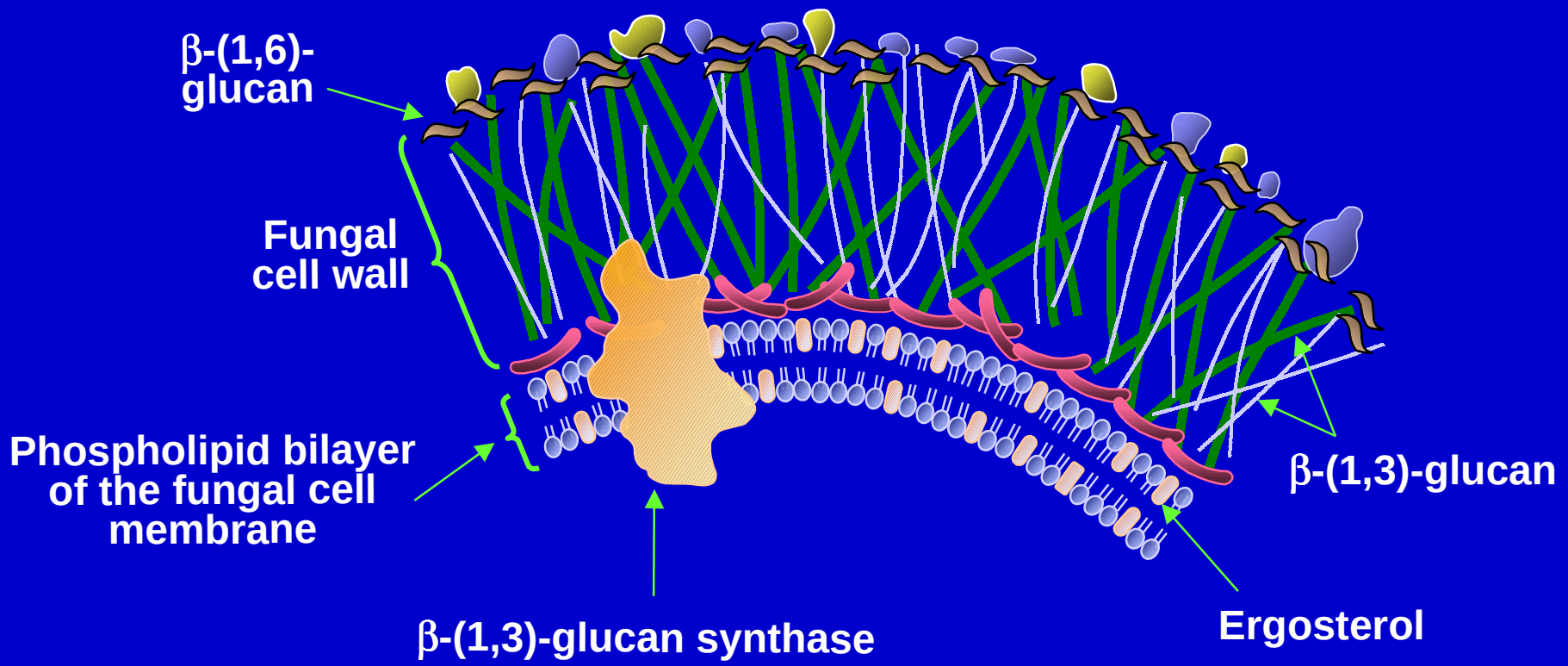
Voriconazole summary

- **Usage**
  - **Lots of drug interactions, significant subject-to-subject PK variability, follow liver enzymes**
- **Microbiology**
  - ***Aspergillus***
    - **Impressive results in a well-done trial**
  - ***Candida***
    - **Need more data**
  - ***Fusarium & Scedosporium***
    - **Response rates at least equal historical data**

The ‘Unmet’ Need

- Fungicidal activity against the most common pathogens, incl. azole-resistant *Candida* species and all *Aspergillus* species.
- No potential for cross-resistance
- Safety profile allowing continued therapy (esp. renal and hepatic)
- No cytochrome P450 drug-drug interactions
- Simple and predictable pharmacokinetics
- Cost-effective

CASPOFUNGIN – ANIDULAFUNGIN - MICAFUNGIN



Spectrum of Activity

Spectrum of activity includes *Candida albicans*, non-*albicans Candida* spp., and *Aspergillus* spp.

- fungicidal for *Candida* spp.
- 'fungistatic' against *Aspergillus* spp.
  - MIC and in vitro/vivo data
  - Efficacy proven in animal models

No cross-resistance to *Candida* spp. with intrinsic or acquired resistance to fluconazole, amphotericin B, or flucytosine

No activity against *Cryptococcus neoformans*

Activity against other fungi less well defined

Pharmacokinetics and Metabolism

- Poor oral bioavailability
- Loading dose followed by maintenance
- PK differences
  - Long plasma half life : anidula > mica > caspo
  - Volume of distribution: anidula > mica > caspo
  - Unbound fraction: anidula > caspo > mica
- Metabolism and elimination
  - Not a substrate for nor an inhibitor of the cytochrome P-450 enzyme system
  - Metabolized by the liver (ex. anidula) + spontaneous chemical degradation
  - No urinary excretion

Safety and Interactions

Excellent safety and tolerability profile
No dosage adjustments required for adults due to:

- **Age**
- **Gender**
- **Weight**
- **Ethnicity**

- **Concomitant medications** — **Inducers of drug clearance; CyA**
- **Hepatic insufficiency** — **Severe hepatic insufficiency**
- **Renal insufficiency**
- **Disease status**

ECHINOCANDINS
Clinical Development Programs

	Caspo	*Anidula*	*Mica*
Prophylaxis	**+**	**-**	**RCT** **Mica vs. Fluco in HSCT**
Empiric	**RCT** **Caspo vs. Ambisome**	**-**	**-**

ECHINOCANDINS
Clinical Development Programs

	Caspo	*Anidula*	*Mica*
Candida esophagitis	**RCT Caspo vs. fluco**	**RCT Anidula vs. fluco**	**+**
Invasive Candidiasis	**RCT Caspo vs. ampho B**	**+**	**+**
Invasive Aspergillosis	**Open phase II (sal)**	**-**	**Open phase II (prim & sal)**
Combination Therapy	**-**	**-**	**Open phase II (prima & sal)**

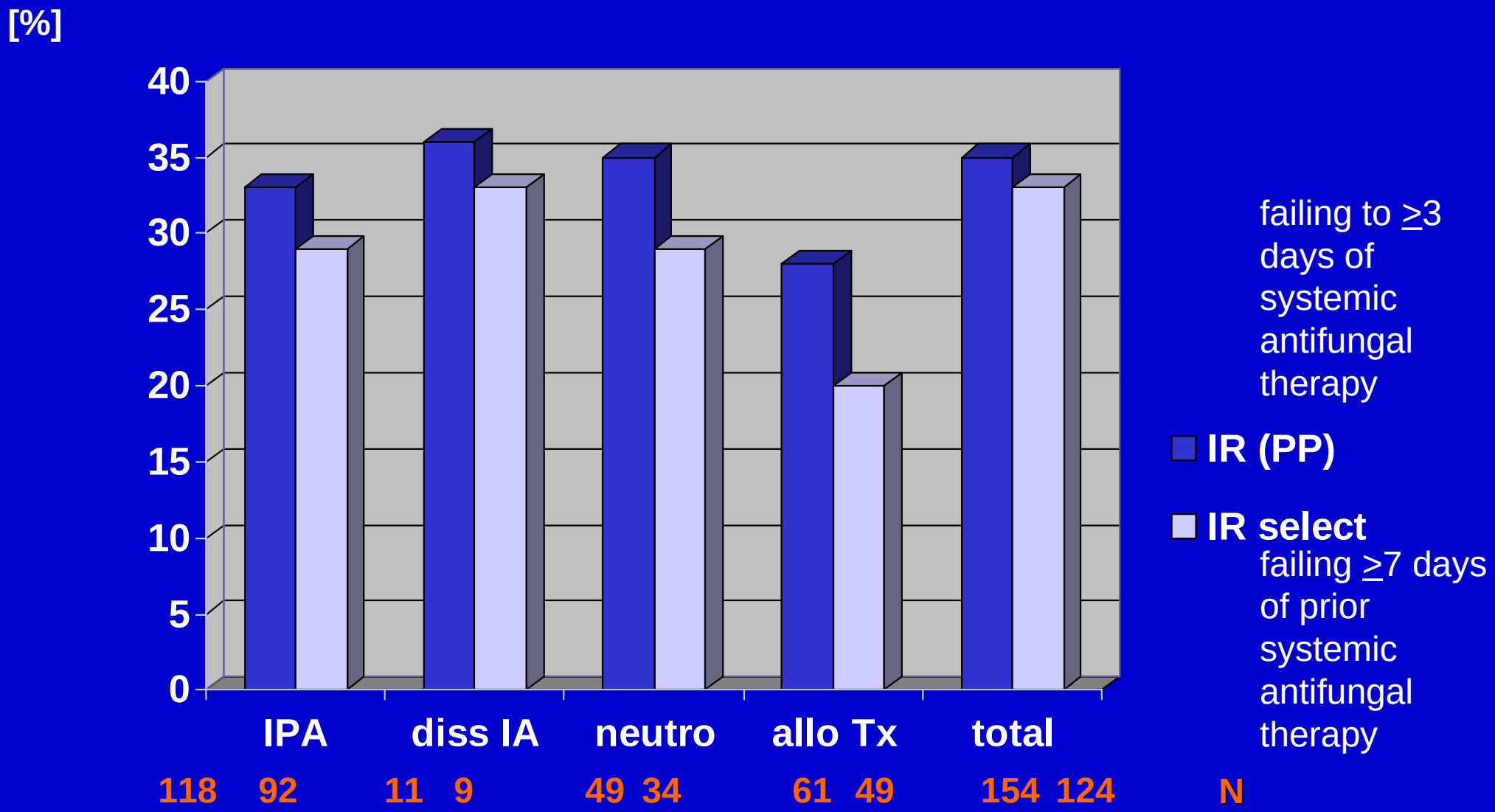
Efficacy outcome at the end of caspofungin therapy

Analysis	Favorable outcome on caspofungin		
	n/m	%	95% CI
Primary (MITT)	**37/83**	**44.6**	**(33.7, 55.9)**
Complete response	4	5	
Partial response	33	40	
Secondary (EP)	**37/66**	**56.1**	**(43.3, 68.3)**
Complete response	4	6	
Partial response	33	50	

Maertens, et al. ICAAC 2002 (M-868)

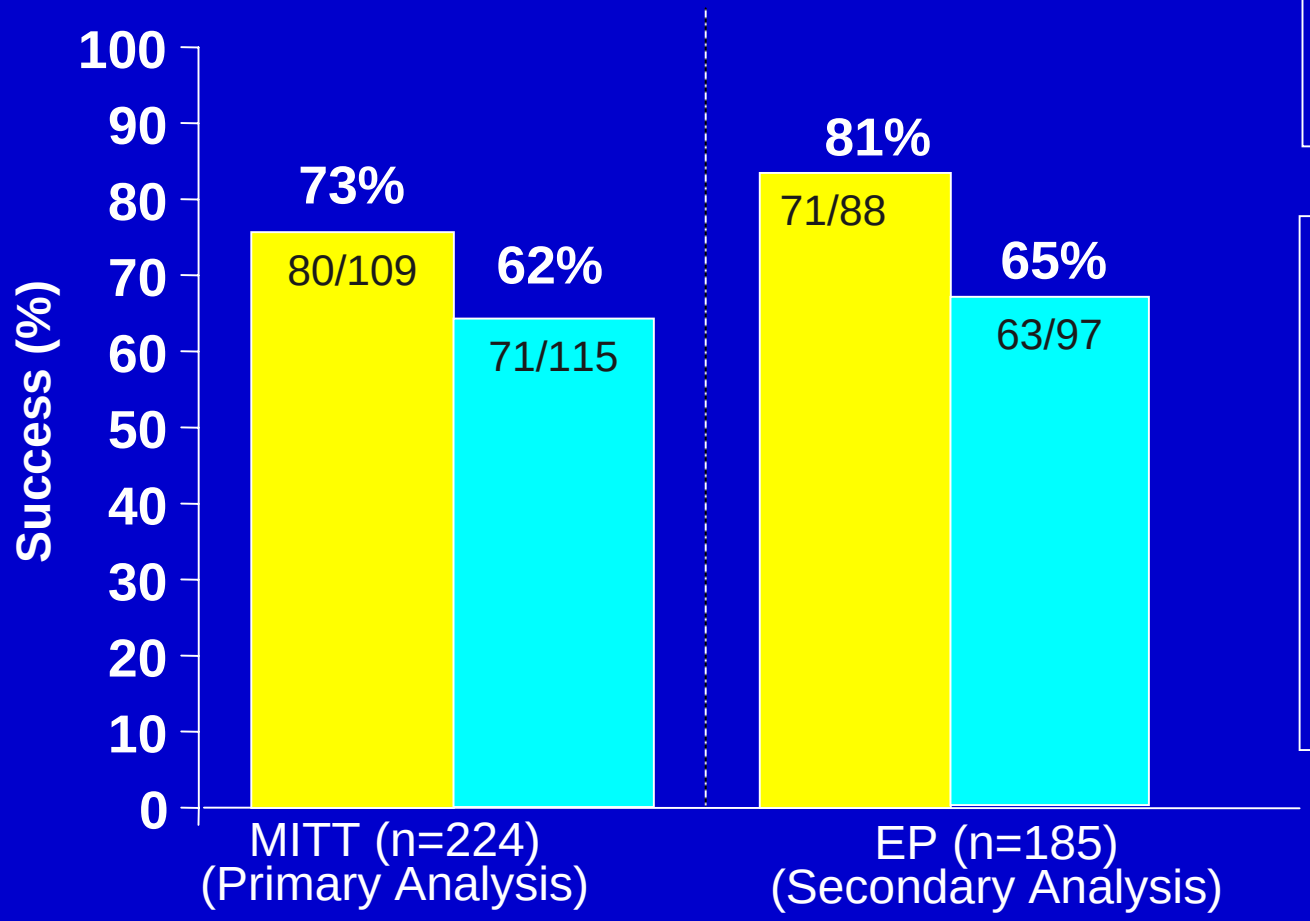
Efficacy Data-Refractory Disease

ECCMID 2003 Glasgow: Courtesy of Dr. A. Ullmann



Invasive Candida: Overall Efficacy Results

Overall Response at End of IV Therapy



Caspofungin

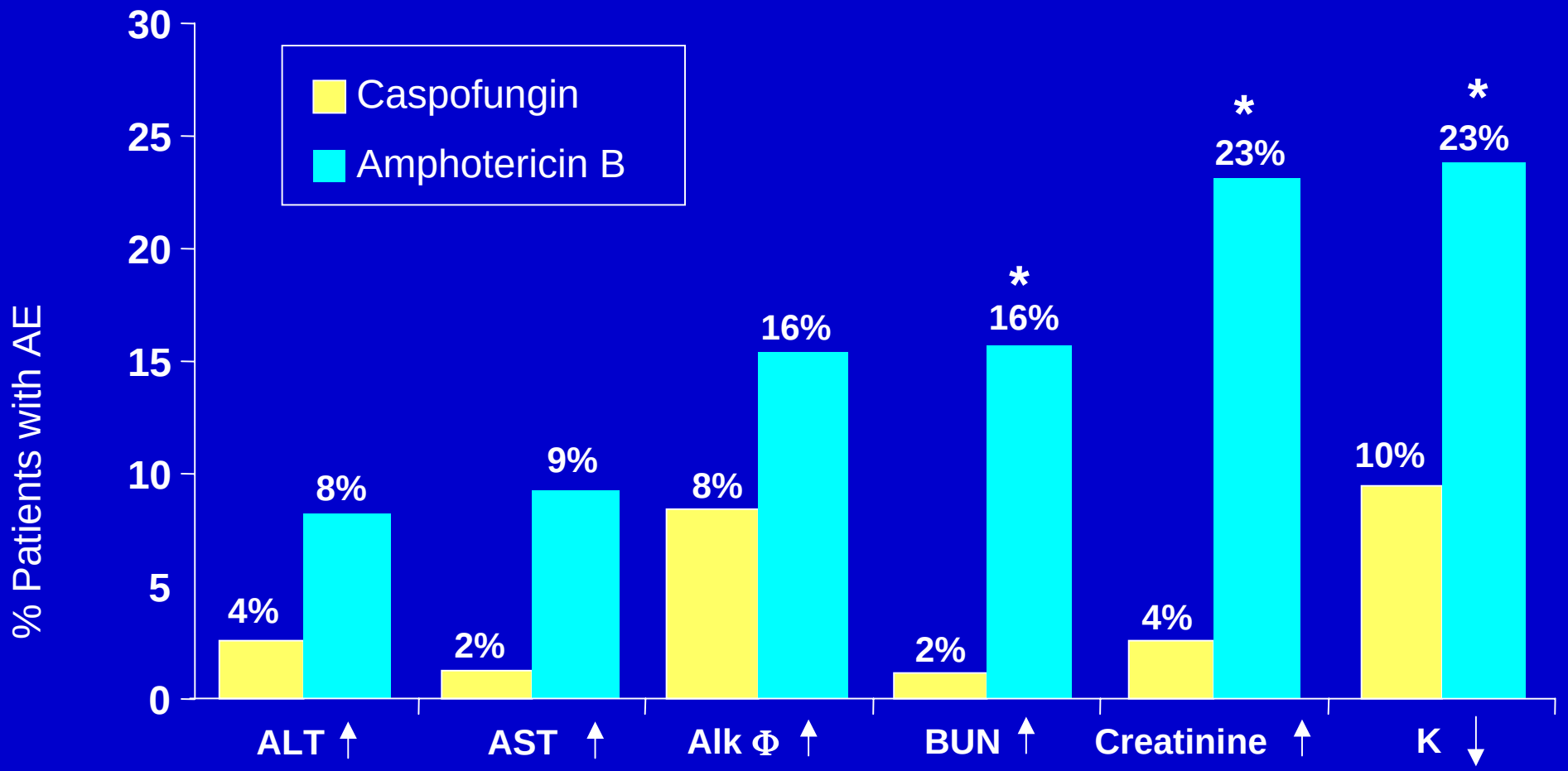
Amphotericin B

Estimated Difference

MITT: 12.7% (-0.7, 26.0)
p value 0.086

EP: 15.4% (1.1, 29.7)
p value 0.035

Drug-related Laboratory Adverse Experiences (Candida)



* P < 0.05

Echinocandins and biofilms

- ‘Antifungal susceptibility of Candida biofims: unique efficacy of Ampho B lipid formulations and echinocandins’

  Kuhn et al. AAC 2002; 46: 1773

- ‘In vitro activity of caspofungin against Candida abicans biofilms’

  Bachmann et al. AAC 2002; 46: 3591

- ‘In vitro pharmacodynamic properties of antifungal agenst against preformed candida albicans biofilms determined by time-kill studies’

  Ramage et al. AAC 2002; 46: 3634

Micafungin and Candidaemia

Ostrosky-Zeichner et al. 13th Focus on Fungal Infections

46 C. albicans	85%
30 C. glabrata	93 %
21 C parapsilosis	86 %
11 C. tropicalis	82 %
9 C. krusei	67 %
4 other	100 %

New infection	88 %
Refractory	76 %
26 neutropenic	73 %
Non-neutropenic	86 %
17 HSCT	82 %
101 adults	85 %
18 pediatric pts	72 %
7 neonates	86 %

Conclusions:
Things we know about candins

- Spectrum of activity:
  - Fungicidal against all Candida spp.
  - Inhibits growth of Aspergillus
  - No clinically meaningful activity against ‘emerging fungi’
    - Efficacy data from animal studies and clinical phase II and III trials
- Azole cross-resistance is unlikely:
  - Novel mechanism of action: act directly at fungal cell wall
- PK:
  - Long half-life, single daily dosing, minimal renal clearance
- Safety profile:
  - excellent safety profile
  - no CYP450 drug-drug interactions
  - Manageable interaction with inducers of drug clearance
  - No dose adjustments in renal (and mild hepatic) impairment

Conclusions:
Some things we need more info

- Activity
  - in primary treatment of invasive aspergillosis and in prolonged neutropenic patients
  - efficacy in CNS involvement (other body sites)
  - pediatric patients and neonates
  - Combo?
- Mechanism and development of resistance/selection
- PK:
  - MTD
  - Importance of PK differences
- Safety profile:
  - CyA and caspo
  - Dose adjustments in moderate/severe hepatic impairment

The Hot Topic
Echinocandins in Combination?

Distinct molecular targets ▪ possible synergy?

- Ergosterol synthesis
- Fungal cell wall membrane ergosterol
- Fungal cell wall (glucan synthesis)

Lowered dosing of potentially toxic drugs

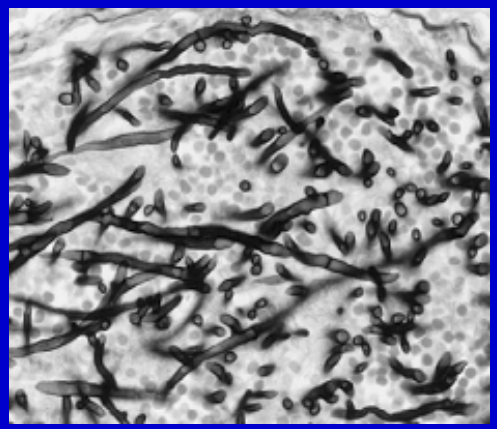
Reduced risk of antifungal resistance?

Increased fungistatic/fungicidal action may be useful in compromised hosts

Pulmonary aspergillosis (A. fumigatus)

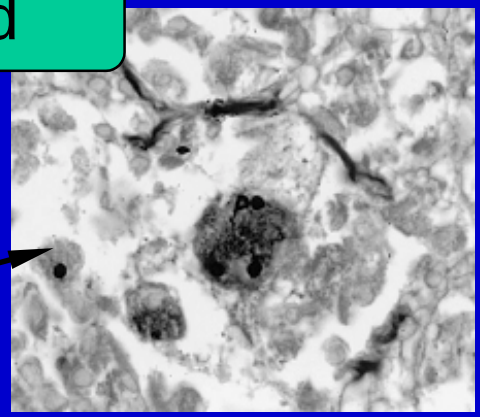
Persistently neutropenic rabbits

Petraitis, et al. AAC 42:2898, 1998

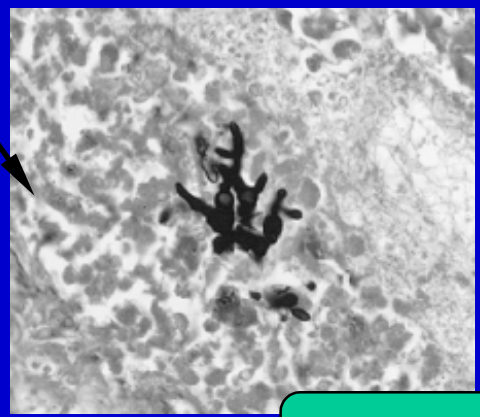


Control

Dead



AmB, 1 mg/kg/d
~1.5 log ↓ CFU/g



AFG, 10 mg/kg/d
No ↓ CFU/g

Not quite dead

Courtesy of Dr. John Rex

IN VITRO DATA	Type of interaction		
Combo	**Synergy**	**Add/Indiff**	**Antagonism**
Itra + Cas	+		
Itra + Mica	+	+	
Vori + Cas	+	+	
Vori + Mica		+	
Posa + Cas	+		
Amb + Cas	+	+	
Amb + Mica	+	+	
L-amb + Mica		+	

Steinbach, et al. Clin Infect Dis 2003; 37 (Suppl 3): S188-224

Caspofungin plus Voriconazole: animal model

Kirkpatrick WR et al.: AAC 2002, 46: 2564-68

- **Immunosuppressed transiently neutropenic guinea pig model of IA**
- **Mortality occurred in 12 of 12 untreated controls**
- **Mortality in 4/12 treated with 1 mg/Kg/day and 6/12 with 2.5 mg/Kg/day of caspofungin**
- **No mortality occurred with CAS plus VRC (or VRC alone)**
- **CAS plus VRC was the only regimen that significantly reduced the number of positive cultures**

Ravuconazole and micafungin significantly reduced mortality and residual fungal burden in persistently neutropenic rabbits

Petraitis et al. J Infect Dis 2003; 187: 1834-43

Human Data?

Retrospective studies !!!

- **Denver[1]**
  - **35 patients (28/7) with IA and different combinations**
  - **Combo 22 vs. mono 13**
  - **Mortality 68.2 % vs. 84.6 % (p = 0.43)**
- **MD Anderson[2]**
  - **48 patients (5/18/25) with IA receiving CAS + L-Amb**
  - **ORR 42 % (22 % proven/probable vs. 60 % possible)**
  - **53 % primary vs. 35% salvage**
- **MSKCC[3]**
  - **30 patients (6/4/20) with Amb-refractory IFI ▪ CAS + (L) Amb**
  - **60% had a favorable response**

[1]O'Connor, ICAAC 2003 M-997; [2] Kontoyiannis, Cancer 2003; 98: 292;
[3]Aliff, Cancer 2003; 97: 1025

Micafungin +/- ampho B +/- azole in refractory aspergillosis in BMT recipients

Ratanatharathorn et al, ASH 2002, # 2472

Patients subgroup	Response Rate (PR + CR by investigator)
All patients	33/85 (39%)
Adults	27/69 (39%)
Children	6/16 (38%)
Allogeneic transplants	30/75 (40%)
Autologous transplants	3/10 (30%)
Neutropenic patients	7/22 (32%)
GvHD	14/40 (35%)
Proven/probable	32/49%

28 % expert panel

Conclusion

- Epidemiology: growing importance of non-albicans Candida species and Aspergillus species.
- Strategies:
  - Therapy for proven infections is often delayed (too late!)
  - New diagnostic tools are available but not yet fully incorporated in decision making
  - Targeted prophylaxis and early empirical therapy remain the best options but may be gradually replaced by pre-emptive approaches
- Drugs:
  - New azoles: Aspergillus >> Candida ?
  - Candins: Candida > Aspergillus ?; empirical?
- Combo: only for use in clinical studies