

NEW ANTI-INFECTIVE AGENTS IN 2003 : SPECTRUM AND INDICATIONS

20th Symposium (spring 2003)

Thursday May 22nd 2003

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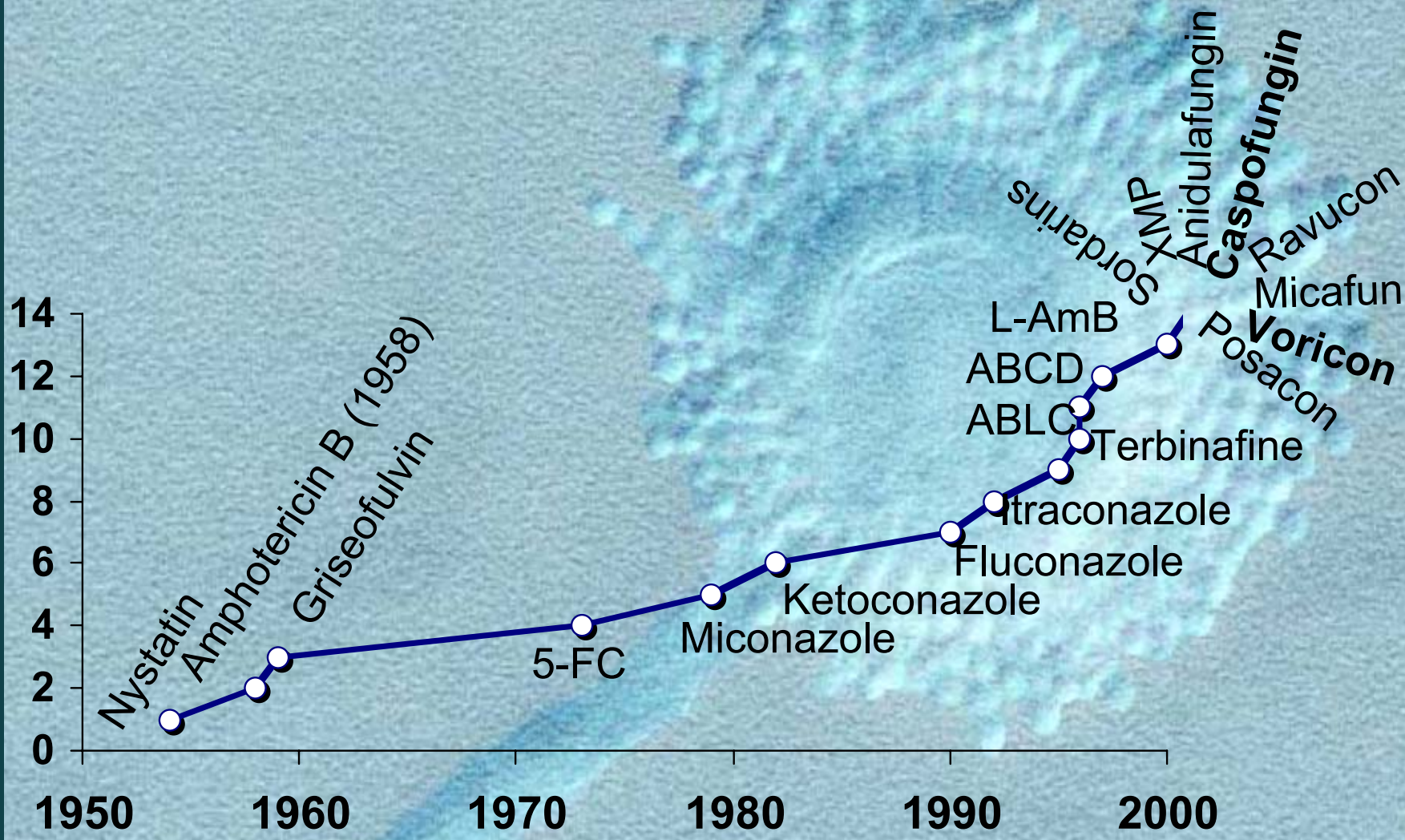


New antifungal drugs

Bart-Jan Kullberg, M.D.

NUCI Nijmegen University Center
for Infectious Diseases

Nijmegen • The Netherlands



Slide courtesy of John Rex

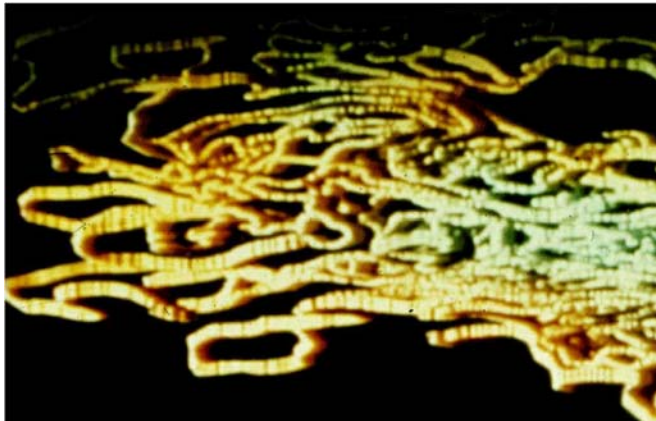
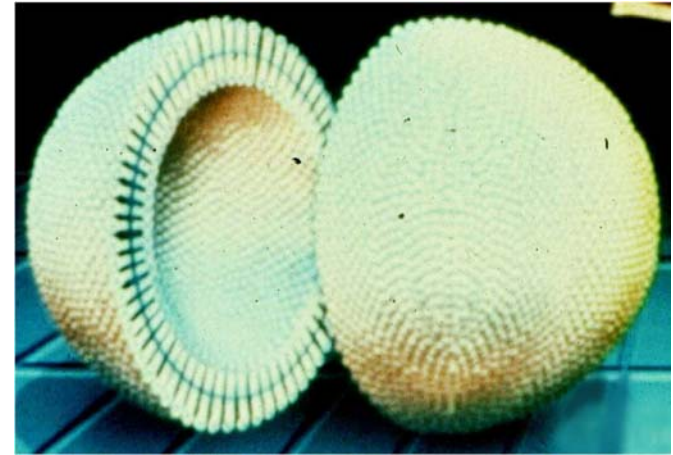
What's new?

- **Lipid-associated amphotericin B**
- **Echinocandins**
- **Azoles**
- **Is amphotericin B dead?**

Lipid-associated amphotericin B

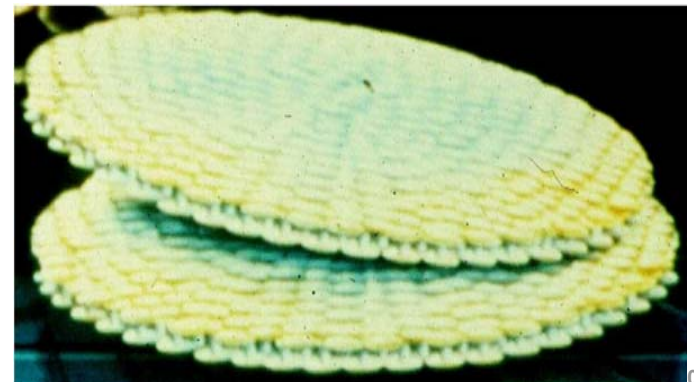
Lipid-associated antifungal compounds

- liposomal amphotericin B
- AmBisome®
- Vestar -> NeXstar -> Gilead -> Fujisawa



- amphotericin B lipid complex
- ABLC / Abelcet®
- Wyeth-Lederle -> Liposome Company -> Elan

- amphotericin B colloidal dispersion
- ABCD / Amphocil® / Amphotec®
- Zeneca / LTI-> Sequus -> Alza



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Amphotericin B versus AmBisome

Proven/probable mycoses in cancer patients

	L-AmB (5mg/kg)	c-AmB	<i>P</i>
n	32	34	
Complete response	44%	18%	.03
Failures	34%	44%	.09
Mortality	22%	38%	.19
Renal toxicity	22%	6%	.001

Leenders, Br J Haemat 98

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Lipid-associated antifungal compounds

- **Limited number of comparative trials for proven infection**
- **Some indications of a dose-effect relationship (4-8 mg > 1-3 mg)**
- **Liposomal amphotericin B tolerated up to 15 mg/kg**
- **Trend towards superiority compared to conventional AmB**
- **Clear safety advantage**
- **No trials – No approved indication for other than salvage therapy!**

Not all lipid-associated amphotericin Bs are equal

	ABLC 5 mg/kg n=78	AmBisome 3 mg/kg n=85	5 mg/kg n=81
• Success	33%	40%	42%
• Mortality	14%	6%	2%
- to fungal infection	4%	1%	0%
• Nephrotoxicity	42%		14%
• Infusion related	=	—	—

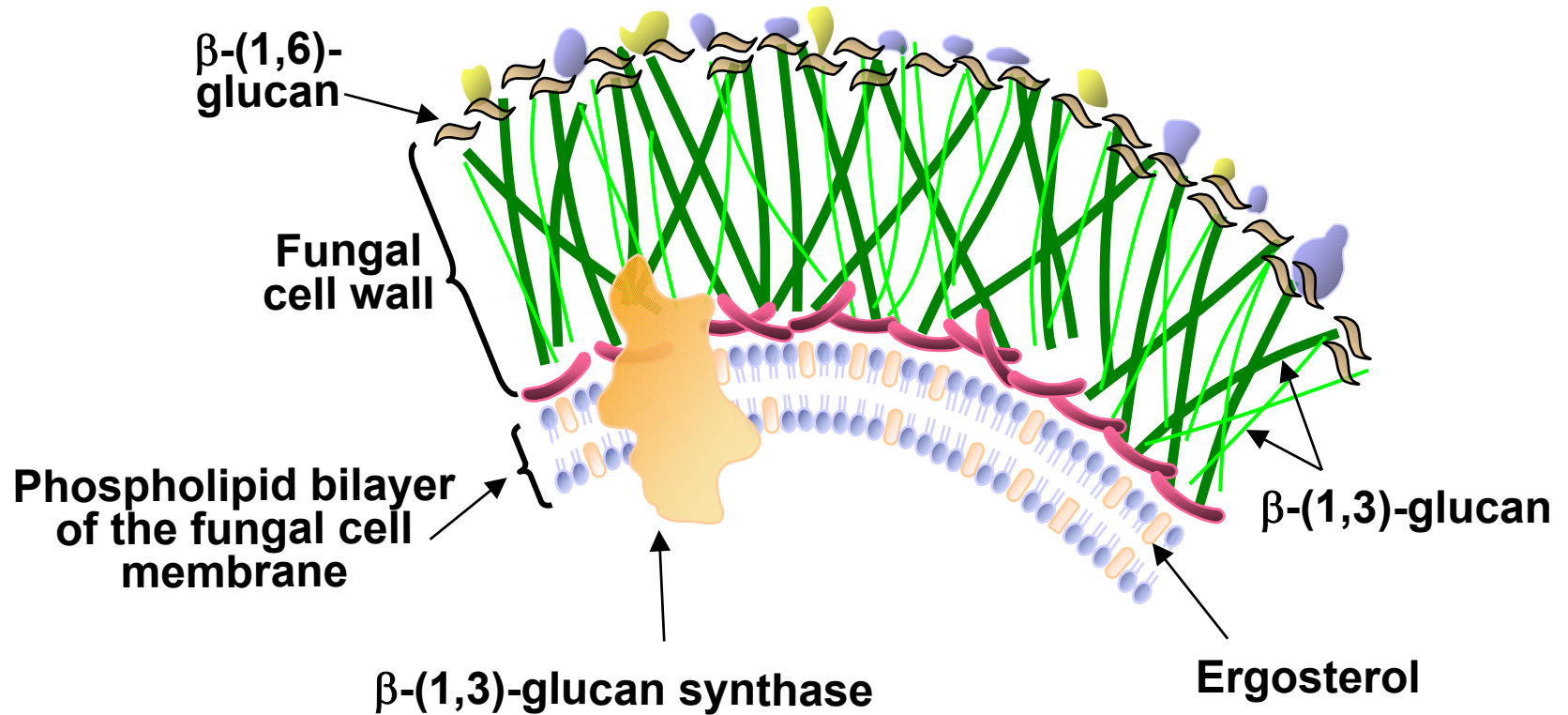
Wingard CID 2001

Lipid-associated antifungal compounds

- **We're in the data-free zone**
- **AmBisome appears to have less nephrotoxicity and fewer infusion-related side effects than conventional AmB**
- **The others? May not be equal**
- **Please, no more studies,
A missed opportunity!**

It's time to move on!

The Amazing Fungal Cell Wall



Graphic courtesy of Carole Sable, Merck Research Laboratories

Echinocandins

- **All are well underway**
 - ✓ **Poor oral bioavailability - always iv**
 - ✓ **Long half lives - once daily dosing**
 - ✓ **Generally, few side effects**

 - ✓ **Active against Aspergillus**
 - ✓ **Fungicidal for Candida**

 - ✓ **Not for Cryptococcus and zygomycetes**

In vitro Activity: *Candida*

- **MIC90 (Anidulafungin)**

- ✓ *C. albicans* 0.12

- ✓ *C. glabrata* 0.25

- ✓ *C. tropicalis* 0.25

- ✓ *C. krusei* 0.25

- ✓ *C. parapsilosis* 2 **Some ↑ is typical**

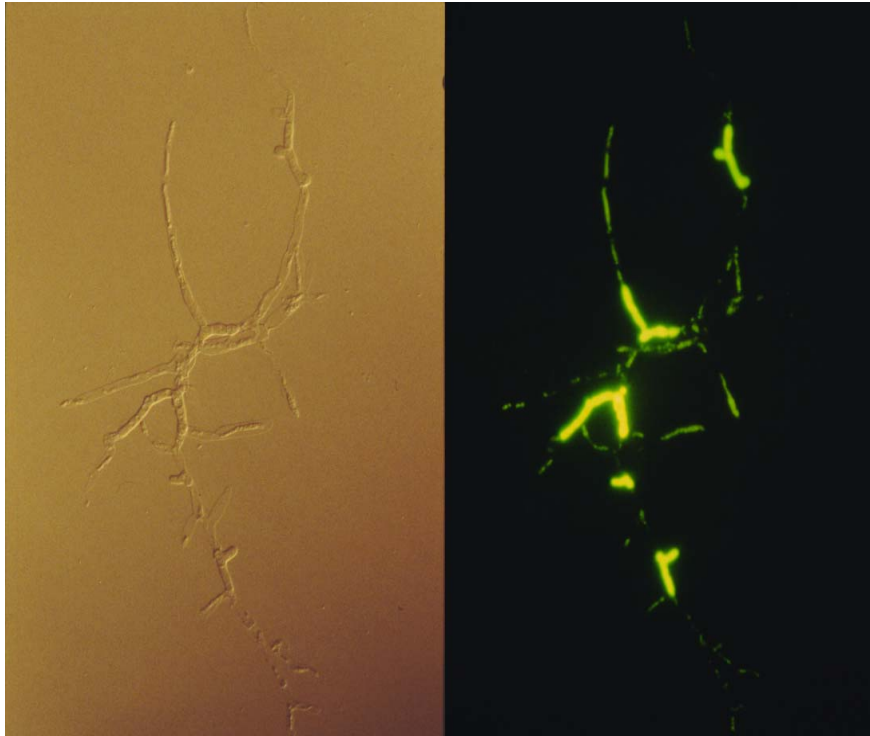
- **No cross resistance with azoles or amphotericin B**

- **Often cidal**

- ✓ **Precise result is media and isolate dependent**

Pfaller, AAC 41:763, '97; Ernst, DMID 33:75, '99; Klepser AAC 42:1387, '98

Killing *Aspergillus*



Visible Light

Stain only the
viable fungal
segments
Carboxyfluorescein
diacetate (CFDA)

- Candins are cidal for the growing tips and actively growing cells
- Static, non-growing interior cells are not killed
- Fragmentation due to death of interior cells may increase *apparent* CFU
- May increase antigenemia?

Bowman & Douglas, AAC Sep, 2002

Summary of Caspofungin Pharmacology

- **Half life of 9 -11h**
- **Largely metabolized, minimal renal clearance**
 - ✓ **Not via cytochrome P450**
- **Dose adjustments not routinely necessary**
- **Dose reduction recommended for patients with moderate hepatic insufficiency**
- **Few clinically significant drug-drug interactions**
 - ✓ **Use of cyclosporin A not yet recommended**

Caspofungin salvage therapy of aspergillosis

Favorable Response overall 41%

Site of Infection

Pulmonary

n
18/39

%

46

Disseminated

2/10

20

Other

2/5

40

Neutropenia

Neutropenic (ANC <500)

2/11

18

Non-neutropenic

20/43

46

Caspofungin invasive candidiasis trial

Overall Efficacy Results

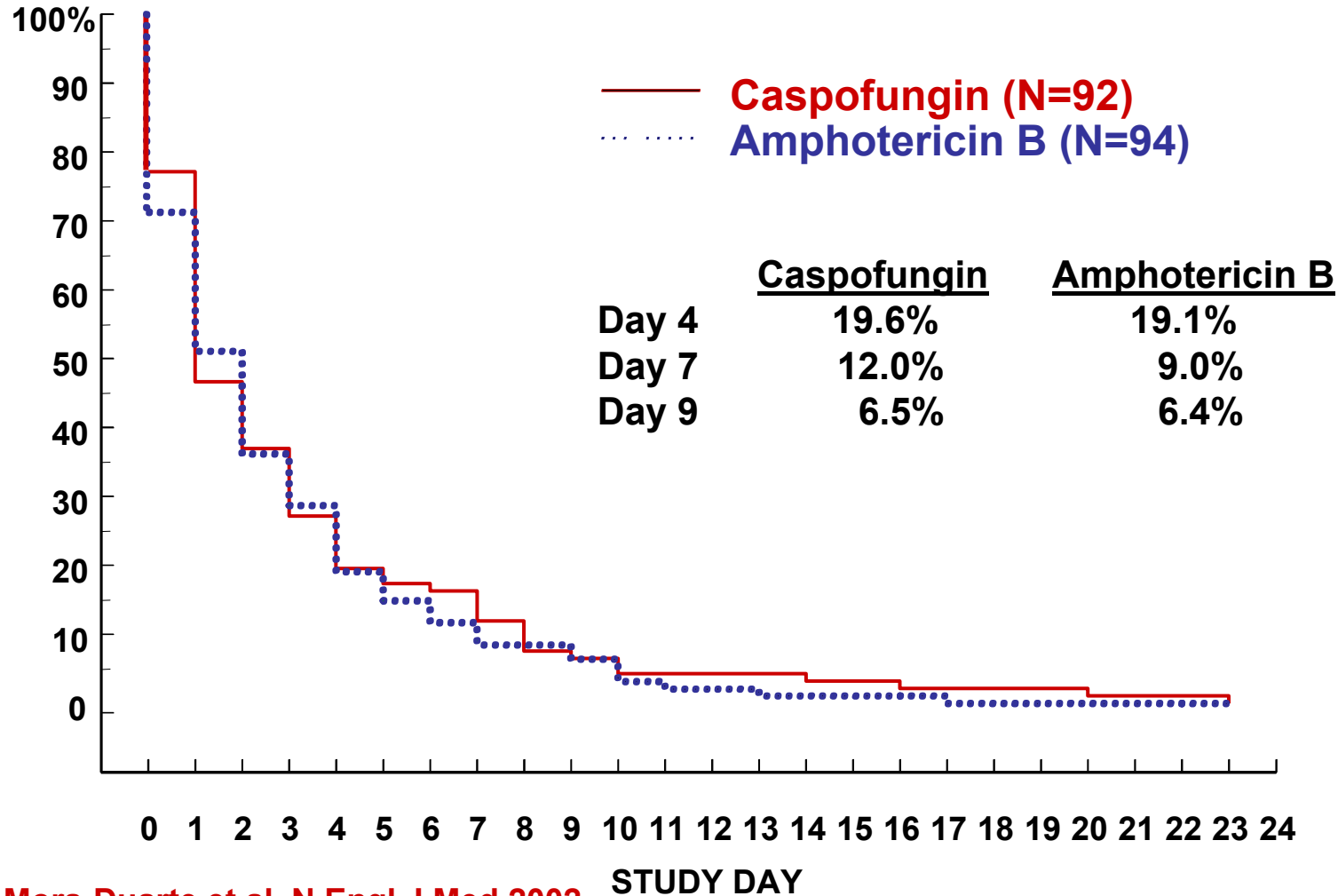
Randomized, double-blind, multicenter study
Caspofungin vs. Amphotericin B

	Caspofungin 70/50 mg n (%)	Amphotericin B 0.6-1.0 mg/kg n (%)	Estimated Difference Adjusted for Strata % (95.6% CI; P)
Success (MITT) n=224	80/109 (73%)	71/115 (62%)	12.7% (-0.7, 26.0; P=0.09)
Evaluable Patients n=185	71/88 (81%)	63/97 (65%)	15.4% (1.1, 29.7; P=0.04)
Crude Mortality	39 (34%)	38 (30%)	P=0.53

Mora-Duarte et al. N Engl J Med 2002

Caspofungin invasive candidiasis trial

Time to First Negative Blood Culture



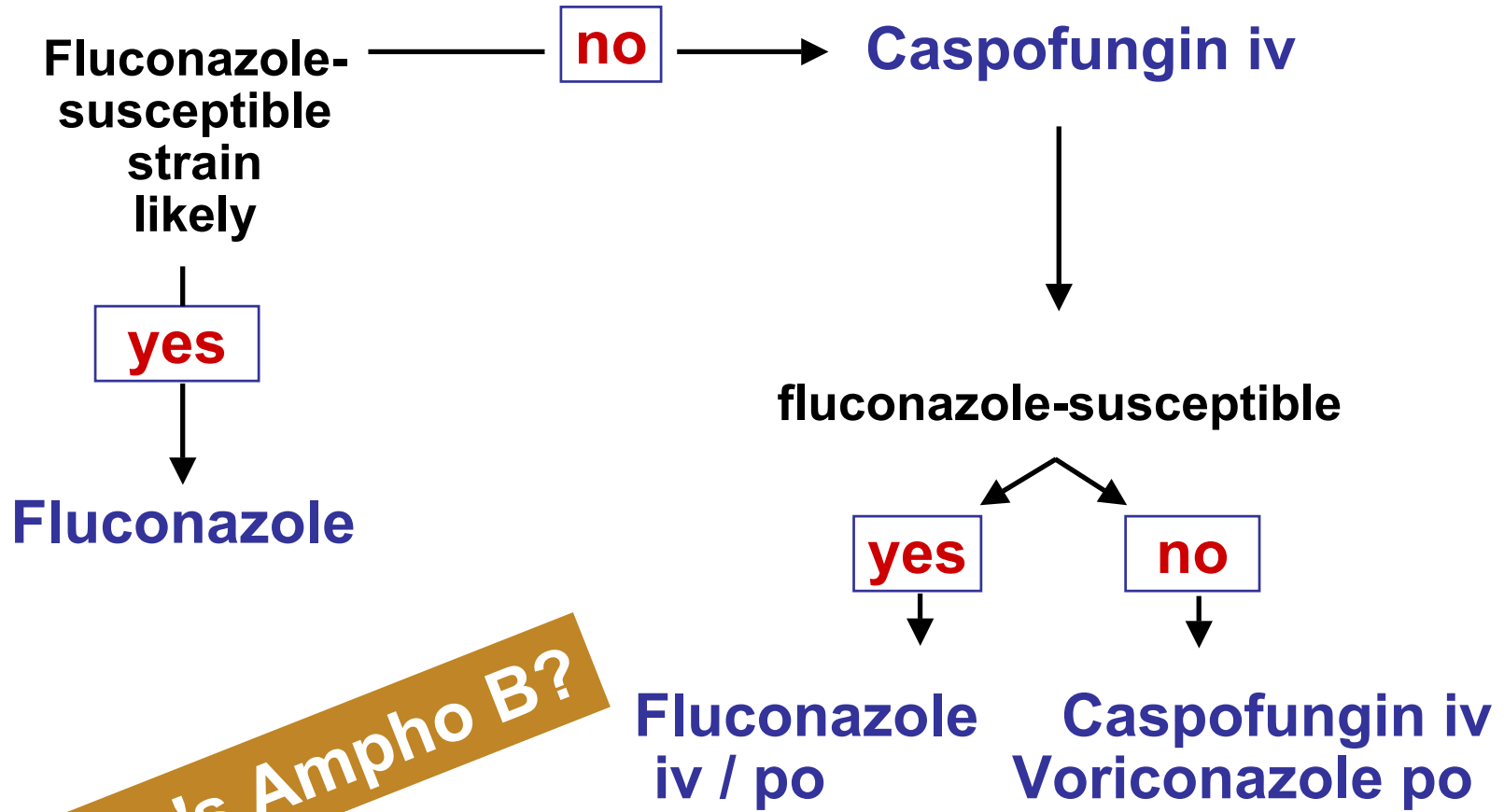
Mora-Duarte et al. N Engl J Med 2002

Echinocandin Safety Profile

Generally very well tolerated

- **Few serious adverse events or discontinuations due to drug-related adverse events**
- **Elevations in serum transaminases similar to fluconazole and amphotericin B**
- **Fever, rash, and eosinophilia occurred (rare)**

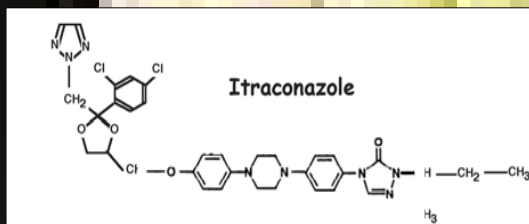
Management of candidemia: The future?



Where's Ampho B?

Azoles

Itraconazole



Janssen
sporanox[®] 100 mg
(itraconazole) Capsules

1992



sporanox[®] 100 mg/10 mL
(itraconazole) Oral Solution

1997



2001

1978

Empiric Itraconazole versus amphotericin B

Randomized, open trial in persistently febrile (>72h) neutropenic (<500/mm³) patients, n=384

	itraconazole 200 mg	colloidal AmB 0.7-1.0 mg/kg	<i>P</i>
n	192	192	
Early withdrawal	7%	6%	ns
Survival	90%	87%	ns
Composite success rate	47%	38%	ns
New fungal infections	3%	3%	ns
Renal toxicity	5%	24%	<.001
Infusion-related rigor/chills	10%	40%	<.001

Boogaerts, Ann Intern Med 2001

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Empiric therapy for febrile neutropenia

- For those who think empiric therapy works... :
- Itraconazole iv **Boogaerts Ann Intern Med 2001**
- Voriconazole iv **Walsh N Engl J Med 2002**
- Caspofungin iv **pending**

Where's Ampho B?

Itraconazole iv for invasive aspergillosis

open study (n=31)

Itraconazole iv 400->200 mg for 2 weeks,
followed by oral 2x200 mg for 12 weeks

Hematologic malignancy 87%

Neutropenic 61%

Response after 2 wks (C/P) 32%

Response at end of study 48%

Stable disease 20%

Trough conc. >250, Day 2 91%

Caillot et al. Clin Infect Dis 2001

Itraconazole iv randomized candidemia study

Itraconazole iv 400->200 mg for 5-14 days,
followed by oral solution 2x200 mg, *versus*
Fluconazole 400 mg iv->oral

Investigator's assessment of outcome
Closed after 193/400 patients due to slow enrollment

	Itraconazole n (%)	Fluconazole n (%)	
Enrolled	96	97	
Completed 12wk	37	44	
Overall success	34/96 35%	44/97 41%	NS

Tuil et al., ISICEM Brussels, 2003

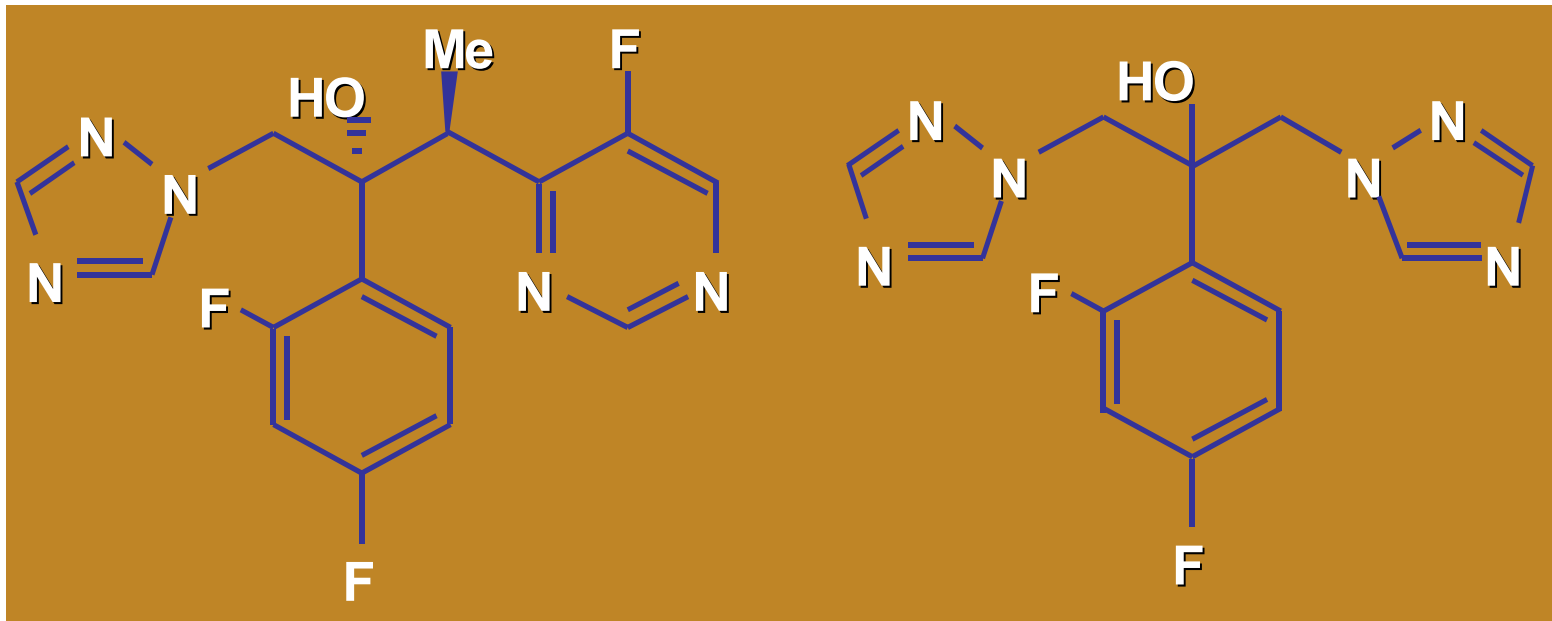
Now, the *new* New azoles

- **Voriconazole**
 - ✓ Vfend[®], Pfizer
 - ✓ iv + oral
- **Posaconazole**
 - ✓ Schering
 - ✓ oral solution
 - ✓ iv?
- **Ravuconazole**
 - ✓ Bristol-Myers Squibb
 - ✓ ?

Alert!
Zygomycetes
Rare moulds

Voriconazole

Small difference - a big impact



Voriconazole

Fluconazole

Voriconazole *in vitro* activity

- **Fungicidal for moulds** including:
 - ✓ *Aspergillus* spp
 - ✓ *Scedosporium* spp
 - ✓ *Fusarium* spp
- Potent *in vitro* activity (fungistatic) for *Candida* spp, including *C. krusei* and less susceptible isolates
- Poor activity against Zygomycetes

Voriconazole

Pharmacokinetics

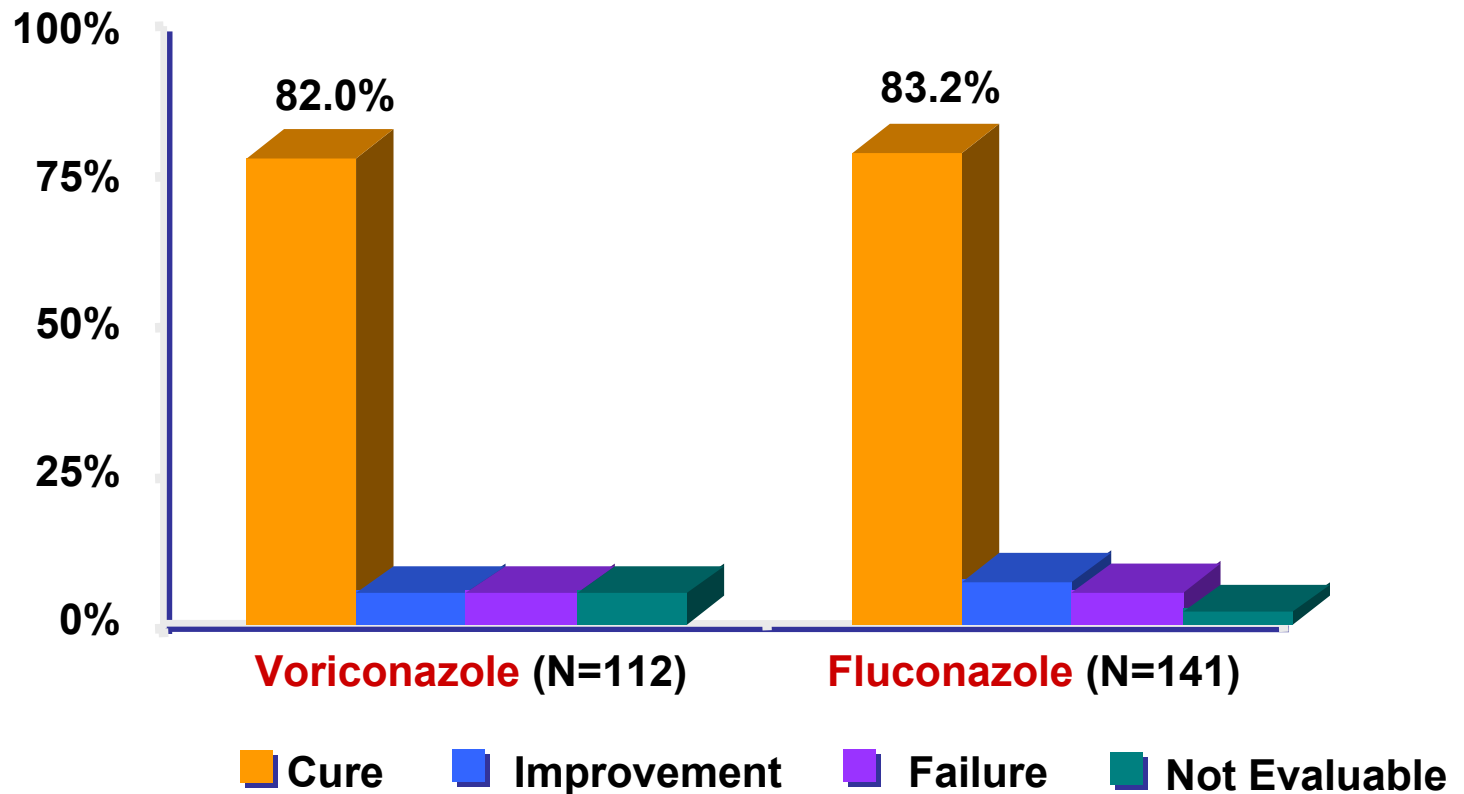
- Rapid oral absorption
- Oral bioavailability 96%
- Terminal phase T_{1/2} about 6–9 h
- Q12h dosing appropriate
- Loading dose on day 1 -> steady state in 24h
- Standard dosing:
 - ✓ Loading dose 6 mg/kg q12h iv
 - ✓ Maintenance 4 mg/kg q12h iv
 - ✓ Oral 200 mg q12h

Metabolism and Interactions

- **Clearance mostly hepatic**
- **Metabolized by cytochrome P-450**
- **Interaction with ciclosporin**
- **Contraindicated with voriconazole:**
 - ✓ **Astemizole**
 - ✓ **Barbiturates (Long Acting)**
 - ✓ **Carbamazepine**
 - ✓ **Cisapride**
 - ✓ **Quinidine**
 - ✓ **Rifampicin**
 - ✓ **Sirolimus**
 - ✓ **Terfenadine**

Esophageal Candidiasis

A proof of principle



Ally et al, Clin Infect Dis 2001

Voriconazole in refractory *Candida* infections

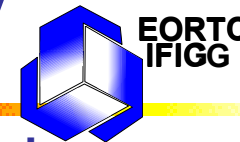
Refractory Candidiasis Population	Overall Success n/N (%)	Success in Fluconazole-Resistant (MIC \geq 64mg/L) Subgroup n/N (%)*
All Refractory Candidiasis	55/106 52%	14/19 74%
Systemic Candidiasis	24/55 44%	5/6 83%
Esophageal Candidiasis	31/51 61%	9/13 69%

Ostrosky & Kullberg, 40th IDSA, 2002

Indication & reimbursement (B)
for refractory and fluconazole-resistant
candidiasis (including *C. krusei*)

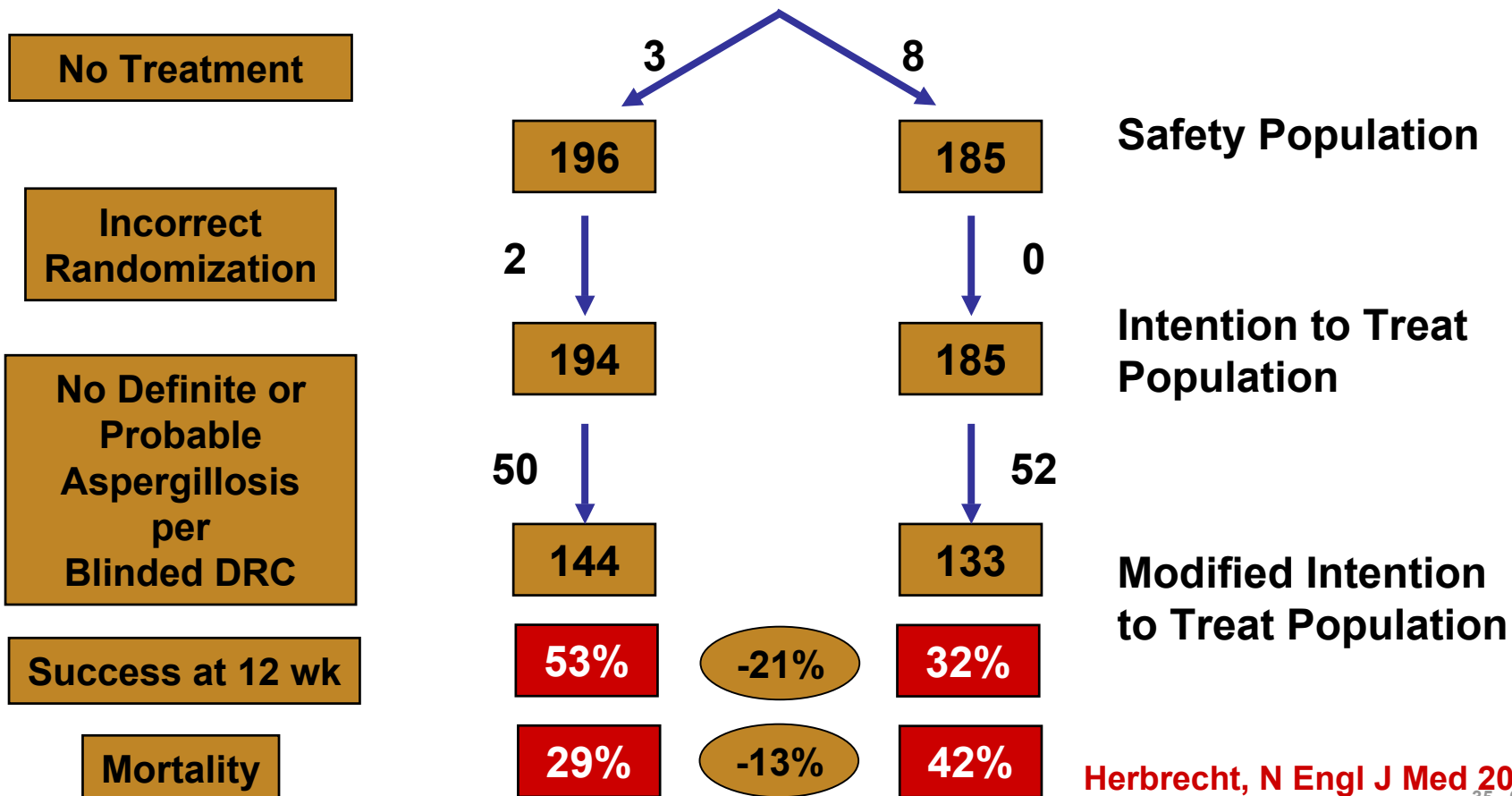
Global Comparative Aspergillosis Study

EORTC (253) + US study group (139)



Comparing 2 strategies for proven/probable invasive aspergillosis:
Voriconazole versus AmB followed by other licenced antifungal therapy

Voriconazole 392 **Amphotericin B**
Enrolled

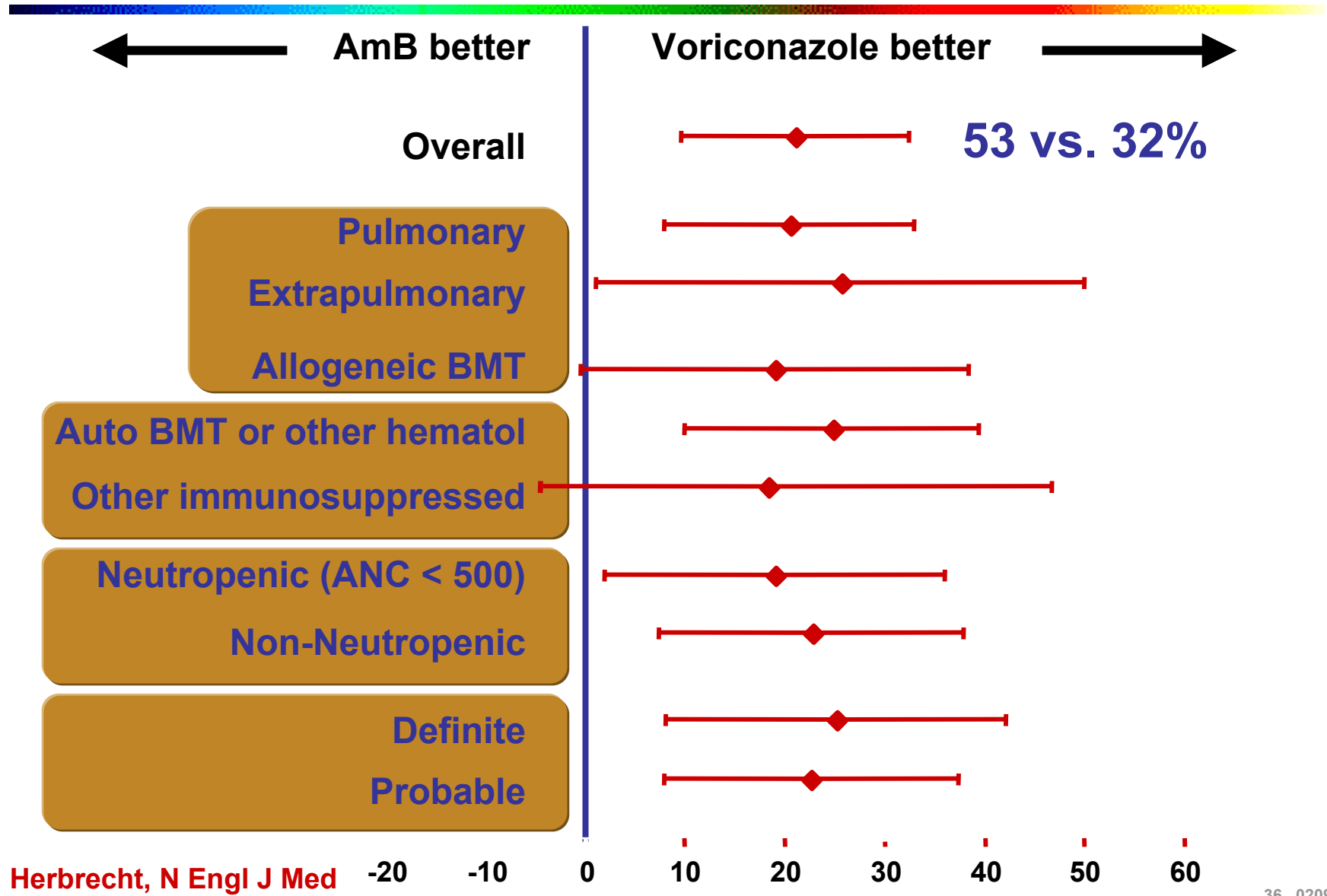


Herbrecht, N Engl J Med 2002

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Voriconazole is superior to Amphotericin B

DRC-Assessed Success at Week 12 (MITT)



Global Comparative Aspergillosis Study

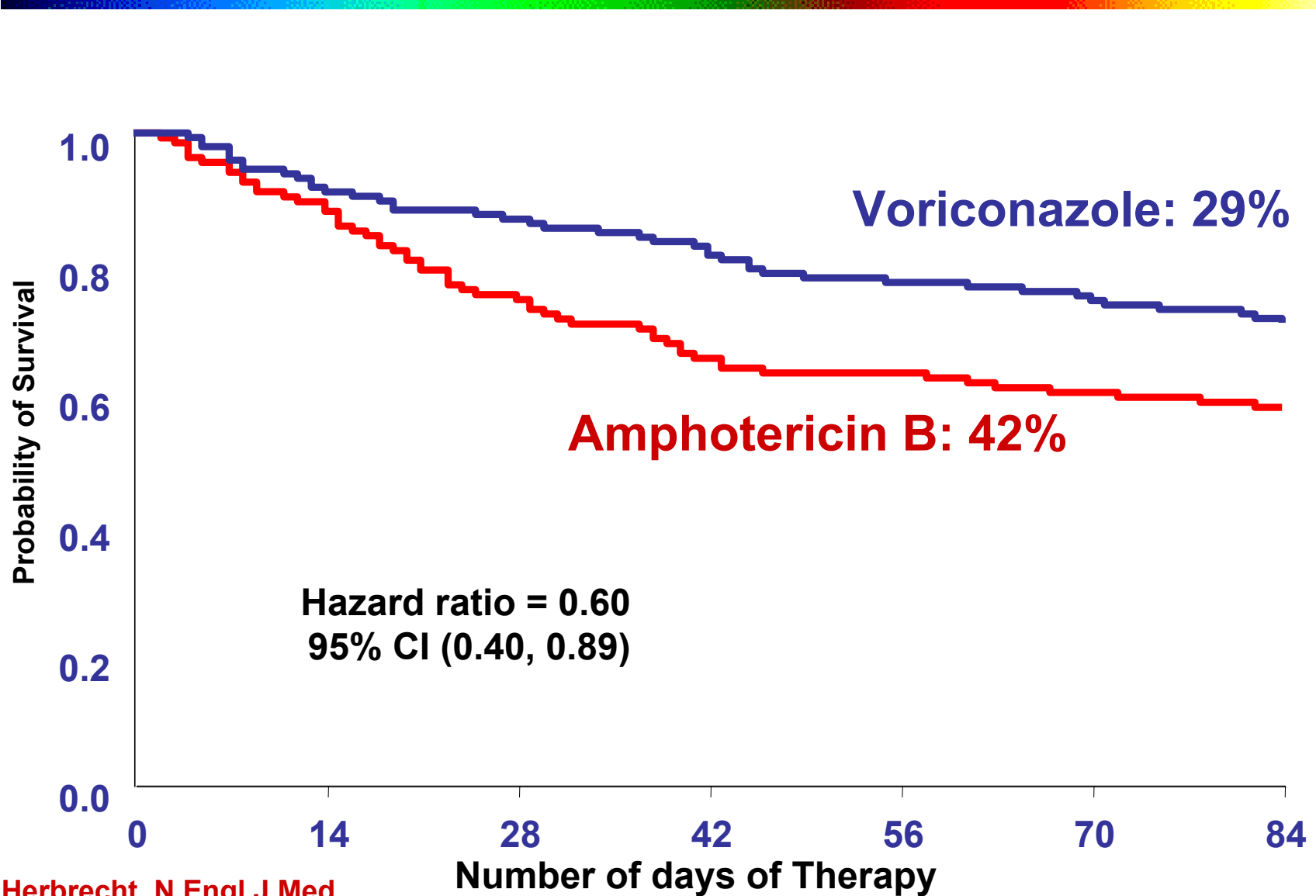
Outcome in subgroups

	Voriconazole	Amphotericin B
	N = 144	N = 133
	n (%)	n (%)
• Total (CR+PR)	76 (53%)	42 (32%)
• Definite aspergillosis	45%	20%
• Probable	60%	37%
• Pulmonary	55%	34%
• Extrapulmonary	43%	13%
• Neutropenic	51%	32%
• Allogeneic BMT	32%	13%

Herbrecht, N Engl J Med 2002

Global Comparative Aspergillosis Study

Time to Death



Herbrecht, N Engl J Med

Safety and Tolerability: Visual Events

- Occurs in ~30% of subjects (iv and oral)
30 -30- 30 rule
- Median time to onset ~30 min
- Median time to resolution ~30 min
 - ✓ Majority resolved within 60 min
- Altered visual perception, blurred vision, color vision change, photophobia
- Dissipates with continued administration

Treatment of invasive aspergillosis

- **Voriconazole** is the drug of choice
- Itraconazole iv may also be effective - no data
- Caspofungin for salvage therapy
- Any of these for empiric therapy

Where's Ampho B?



New antifungal drugs

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