Filamentous fungal infections and the role of amphotericin B

David W. Denning
Director, National Aspergillosis Centre
University Hospital of South Manchester
The University of Manchester

AGENDA

- Increasing fungal infections
- Histoplasmosis
- Visceral leishmanisis
- Cryptococcal meningitis
- Zygomycosis
- Candidaemia and invasive candidiasis
- Invasive aspergillosis
- Resistance

Histoplasmosis

Randomised trial of AmB and AmBisome in acute disseminated histoplasmosis in AIDS

2:1 randomisation

0.7 mg/Kg amphotericin B deoxycholate vs.

3mg/Kg AmBisome

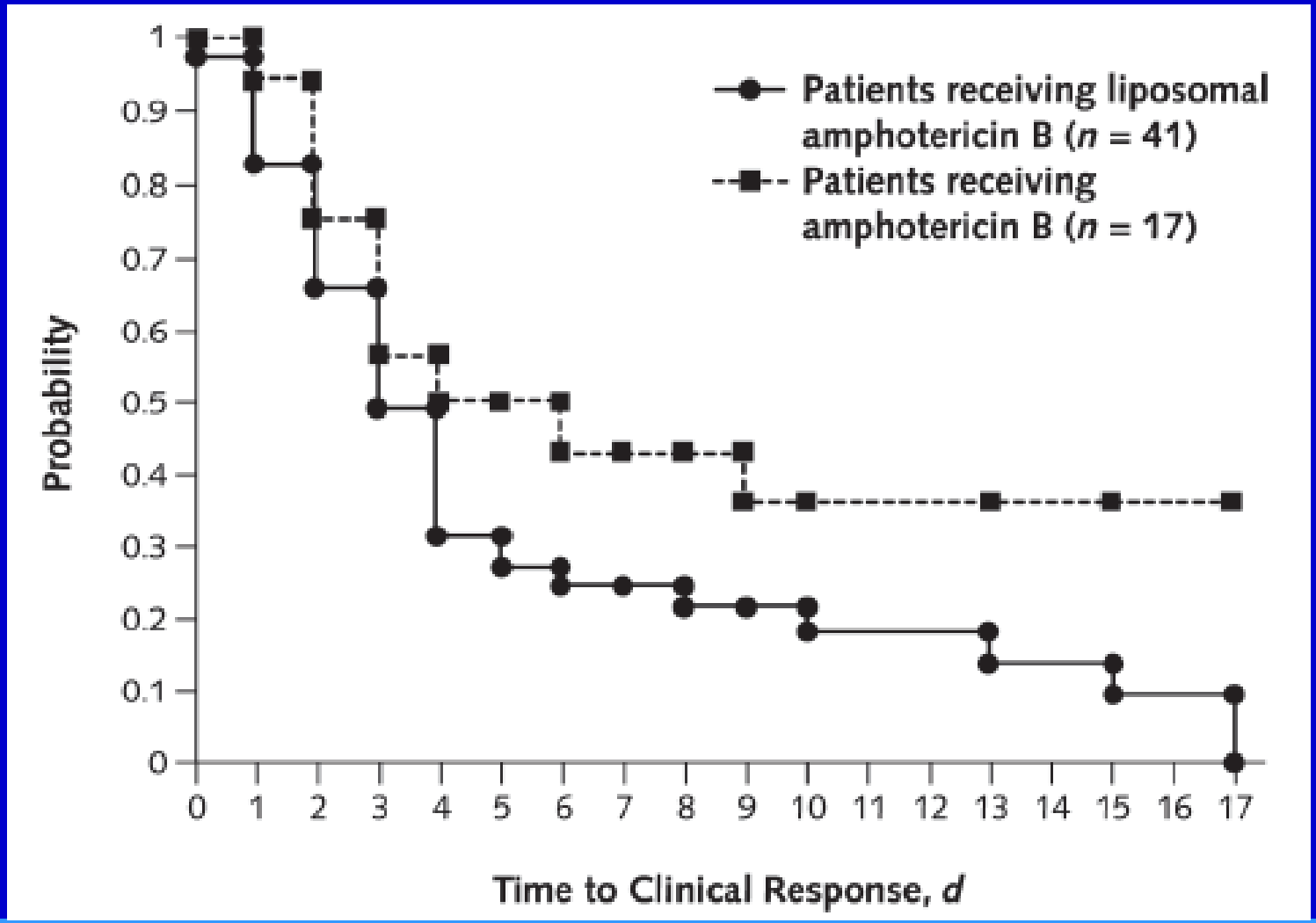
14 days Rx, then itraconazole orally

81 patients enrolled - responses

AmB	14/22 (64%, CI 42-83%)
AmBisome	45/51 (89%, CI 77-96%) p=0.014

Johnson et al, Ann Intern Med 2002;137:105

Randomised trial of AmB and AmBisome in acute disseminated histoplasmosis in AIDS



Johnson et al, Ann Intern Med 2002;137:105

Visceral leishmaniasis (kala-azar)

Visceral leishmanisis

Pentavalent antimony-based drugs:
Response rates 36-69%, + cardiac toxicity in 8-17%

AmBisome response rates (5 days treatment) 100%

cure rate @ 0.75mg/Kg = 89%
cure rate @ 1.5mg/Kg = 93%
cure rate @ 3mg/Kg = 97%

Sundar et al, Am J Trop Med Hyg 2002;66:143

Cryptococcal meningitis

Cryptococcal meningitis

Induction therapy (≥ 2 weeks)

- Amphotericin B 0.7mg/Kg and flucytosine

OR

- AmBisome 3mg/Kg and flucytosine
- Voriconazole

Maintenance therapy

- Fluconazole ≥400mg/d
- Voriconazole
- Itraconazole

Randomised study of cryptococcal meningitis comparing amphotericin B and AmBisome in AIDS

Amphotericin B deoxycholate 0.7mg/Kg vs
AmBisome 4mg/Kg
21 days treatment followed by fluconazole 400mg/d

	Clinical resp	Cultures negative (14d)
AmpB	11/13 (86%)	1/9 (11%)
AmBisome	12/15 (80%)	10/15 (67%)
	p = 1.0	p= 0.01

Leenders et al, AIDS 1997;11:1463

Randomised study of cryptococcal meningitis comparing amphotericin B and AmBisome in AIDS

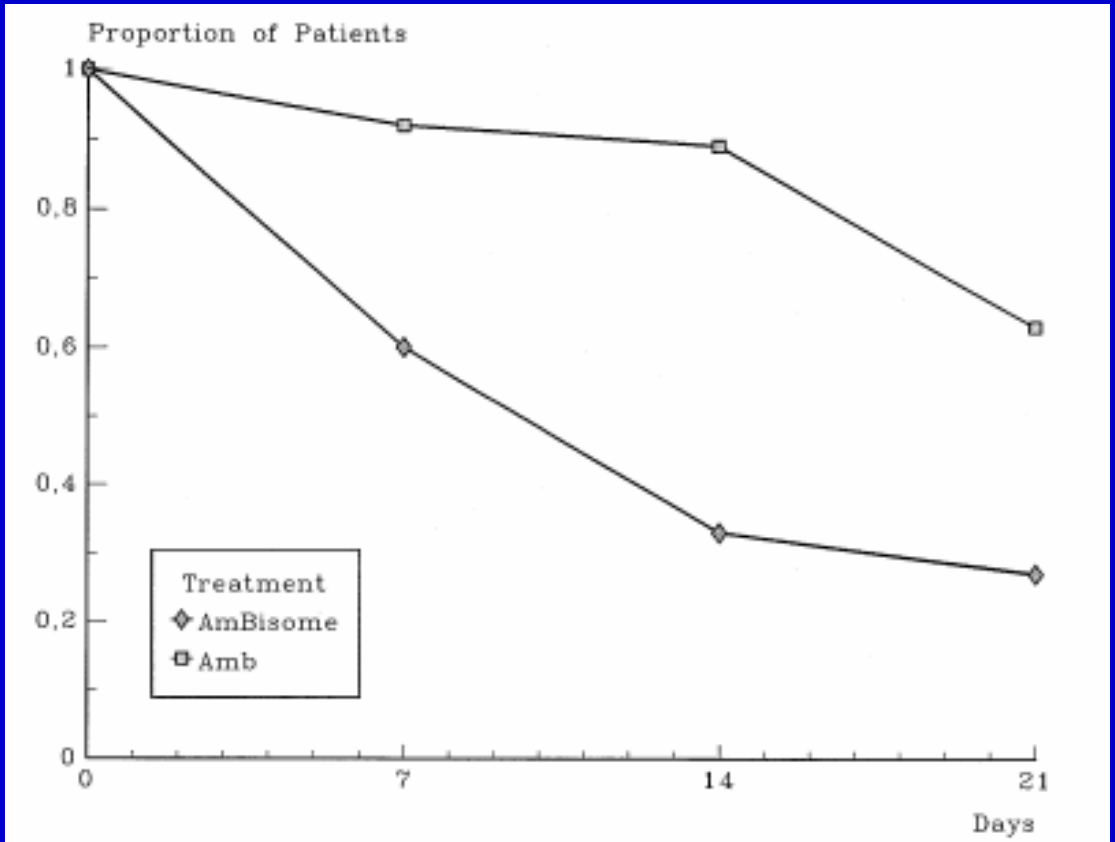
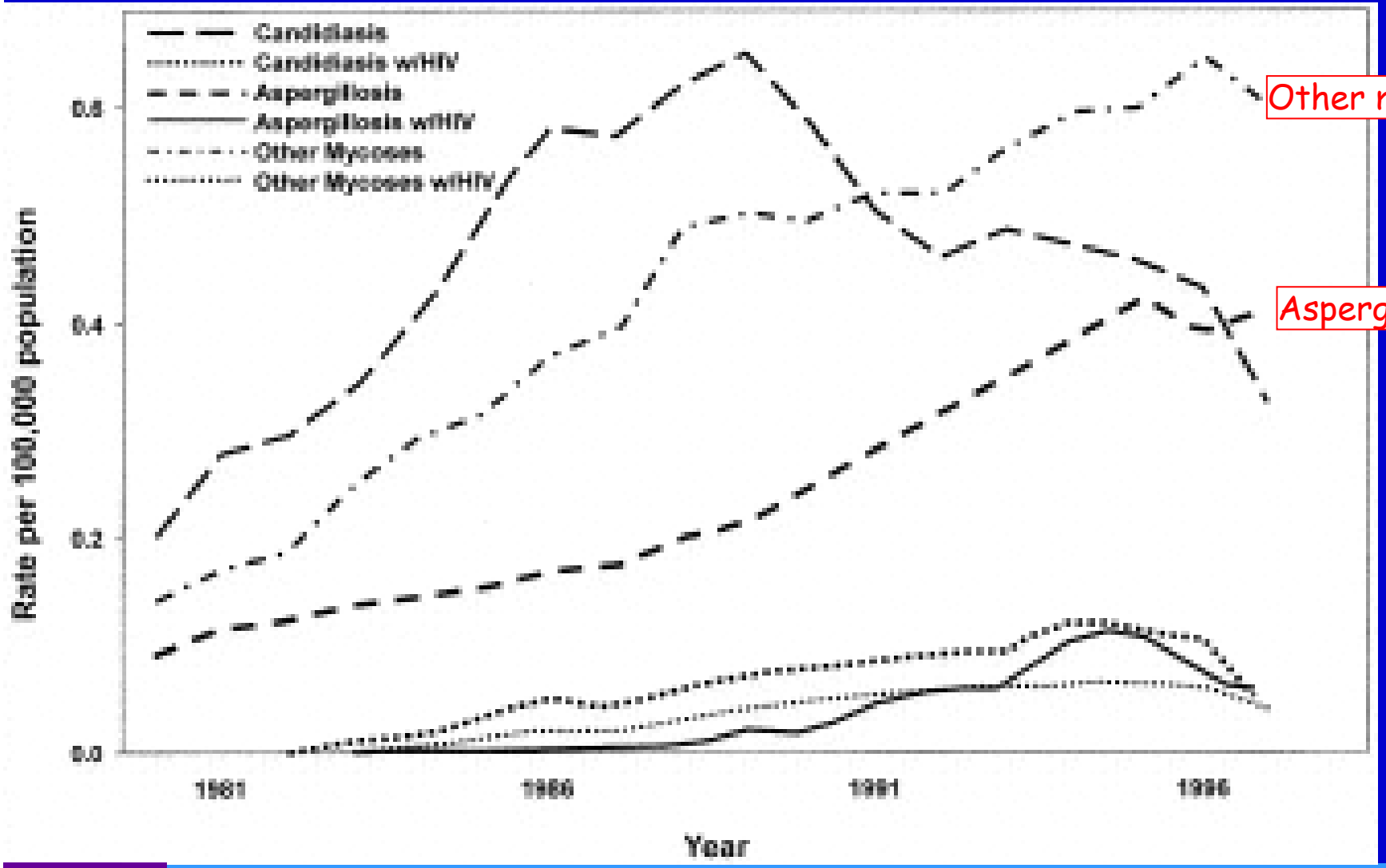


Fig. 1. Kaplan–Meier estimates of the proportion of patients who had positive cerebrospinal fluid cultures during the first 3 weeks of treatment, according to treatment group.

Leenders et al, AIDS 1997;11:1463

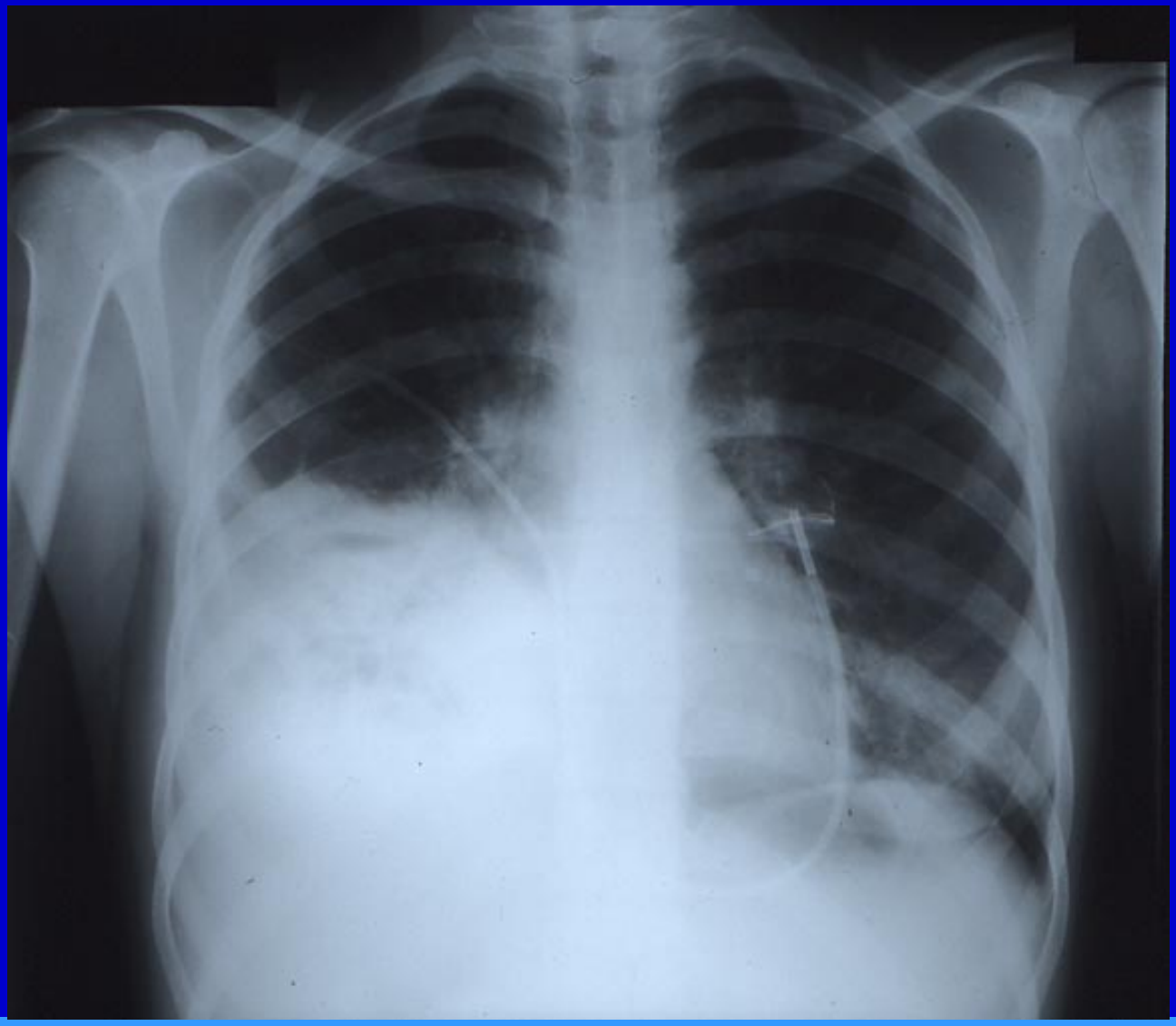
Zygomycosis [mucormycosis]

Changing incidence of fatal invasive mycoses in non-HIV patients in USA



McNeil *et al*, Clin Infect Dis 2001;33:641

1st induction AML – pulmonary mucormycosis – culture negative



Frequency of mucormycosis in leukaemia

391 pts with leukaemia (225 with AML) and a filamentous fungal infection

80% neutropenia for >14 days, and 71% neutropenic at time of diagnosis

85% pulmonary infection

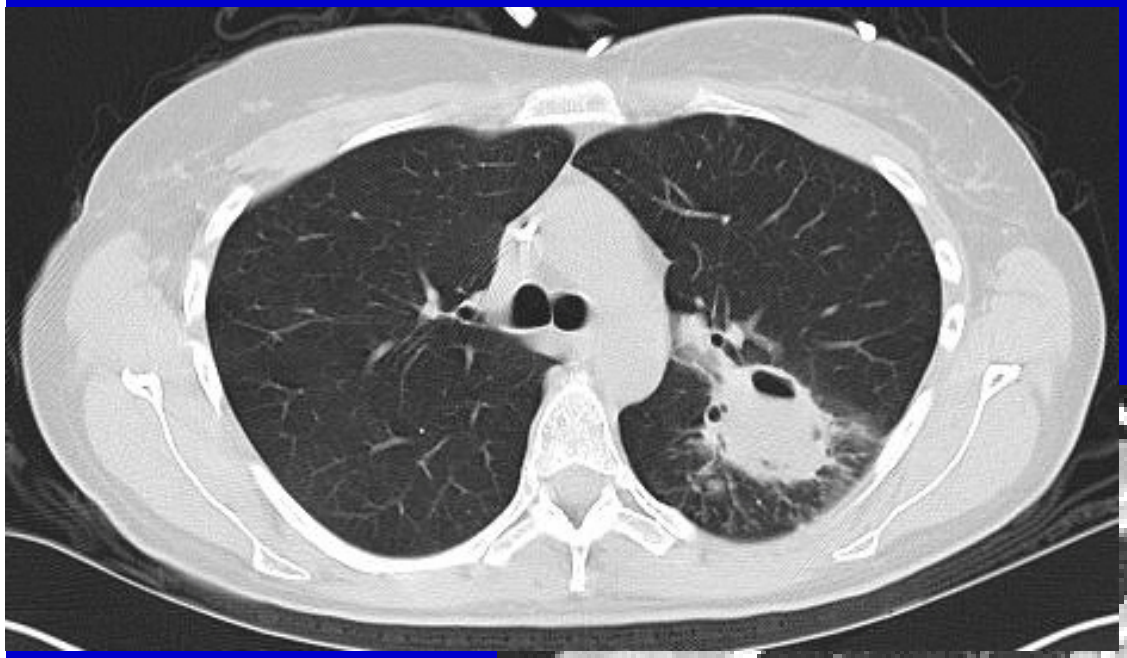
Antemortem diagnosis in 79%

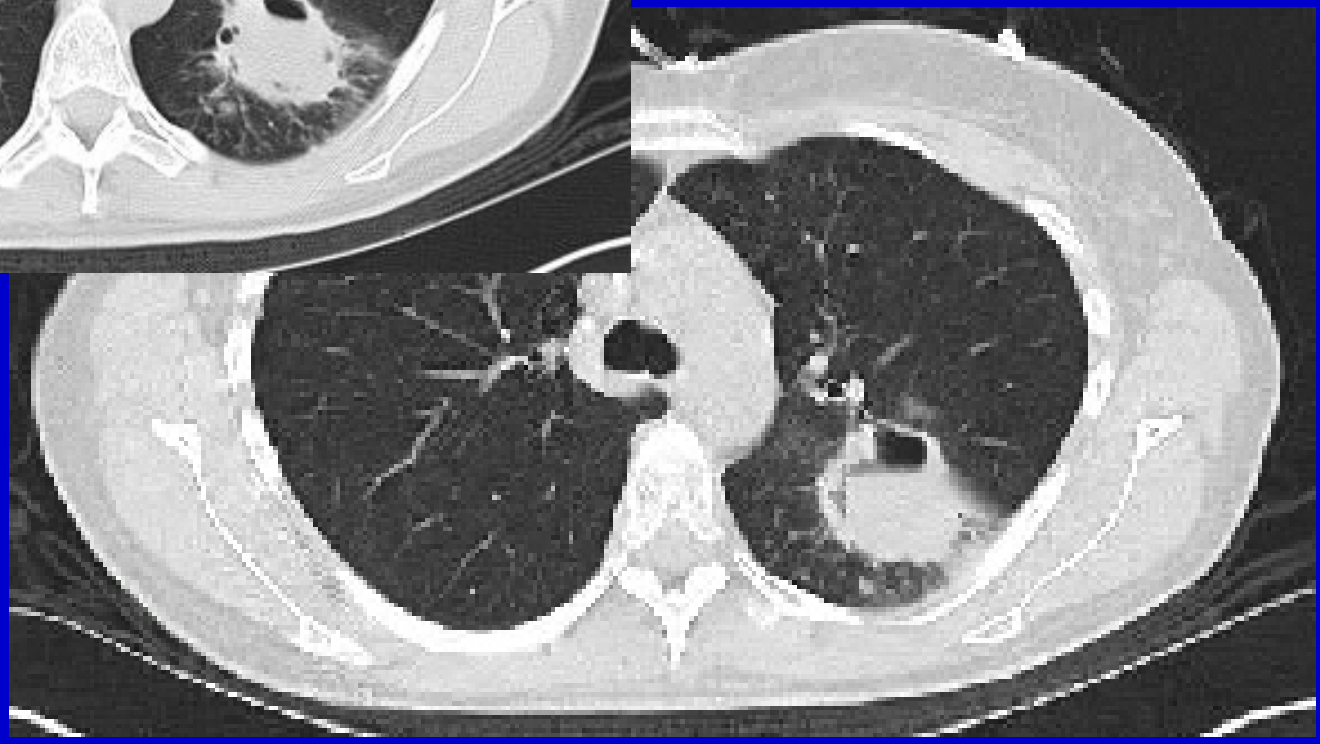
- Aspergillus 296 (76%)
- Mucorales 45 (11.5%)
- Fusarium 6
- Other 4
- Unidentified in 40

Overall mortality in 3 months 74%, 51% attributable

Pagano et al, Hemtaologia 2001;86:862

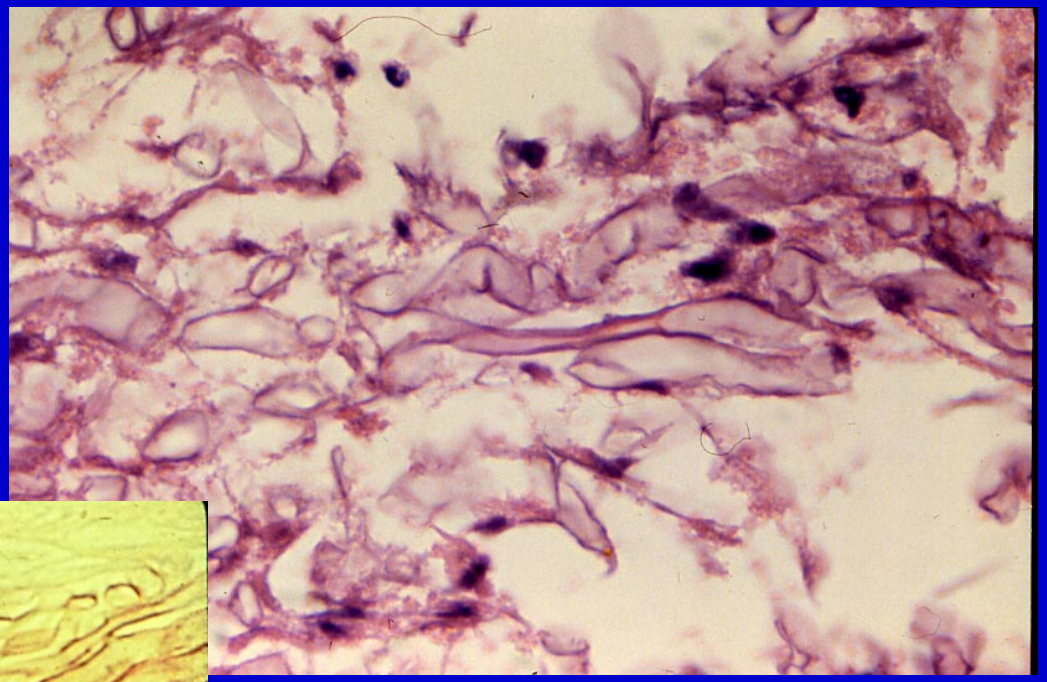
Pulmonary mucormycosis

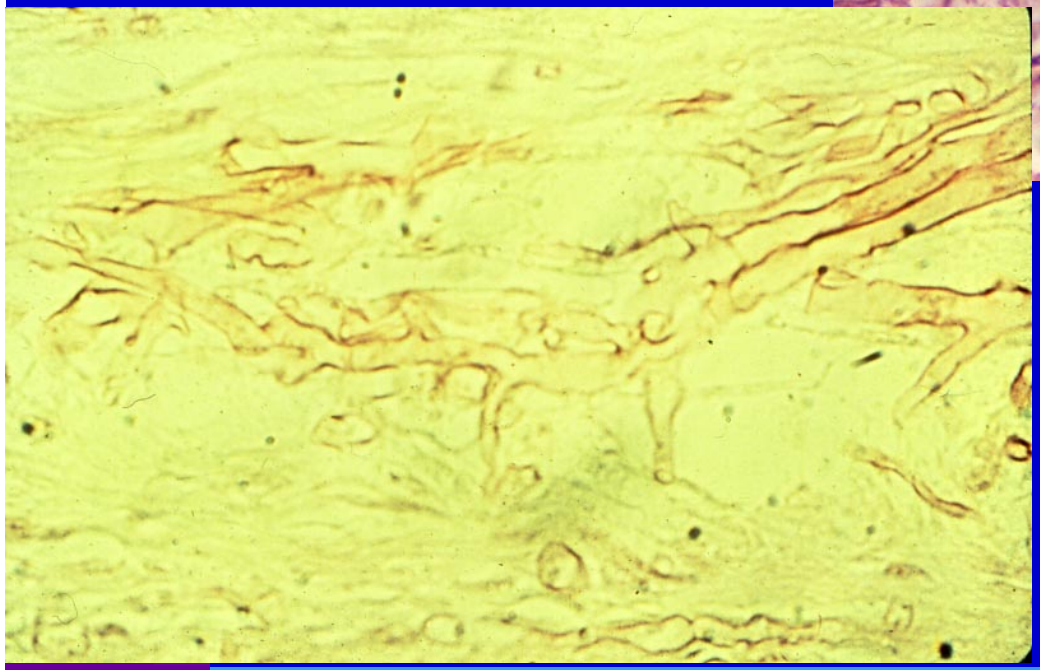




ALL induction
Breakthrough infection on voriconazole prophylaxis

Microscopy of mucormycosis





Common species of Mucorales causing disease

Rhizopus oryzae
Rhizopus microsporus
Absidia corymbifera

} >80-90% of human cases

Apophysomyces elegans
Cunninghamella bertholetiae
Rhizomucor pusillus
Saksenaea vasiformis

Treatment

- Amphotericin B
- Posaconazole
- Surgery
- ?hyperbaric oxygen

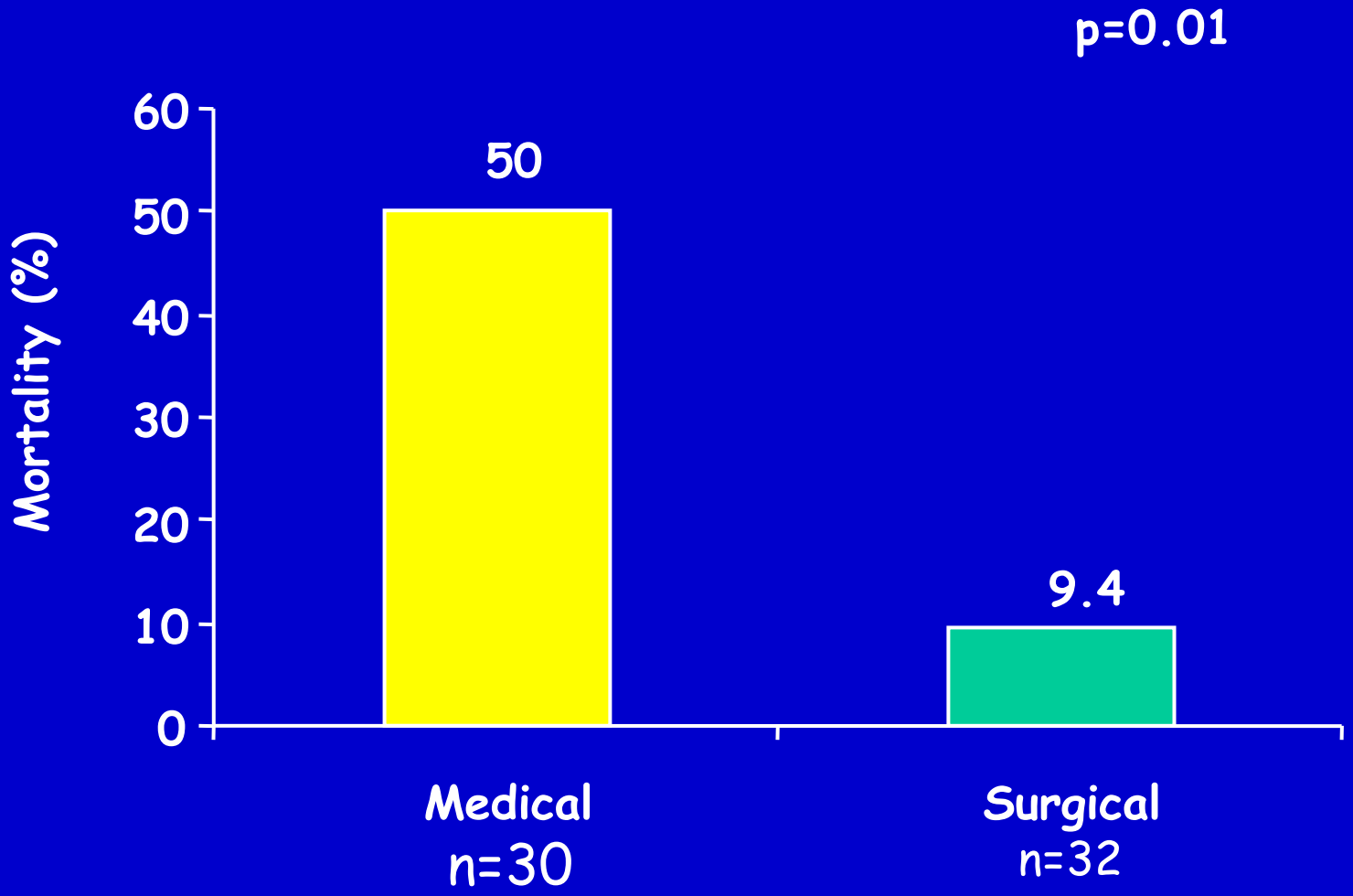
AmBisome treatment of mucormycosis

Study	Patients	Treatment	Number	Response	Survival
First-line treatment	Haematological malignancies	LAmB 3 mg/kg/day	12	58%	20% (month 3)
		AmBD 1 mg/kg/day	39	23%	
First-line treatment	Haematological malignancies	LAmB 3–5 mg/kg/day	2	50%	37%
		AmBD 1 mg/kg/day	6	33%	
First- or second-line treatment	Diverse underlying diseases	LAmB	116		69%
		AmBD	532		61%

AmBD, amphotericin B colloidal dispersion; LAmB, liposomal amphotericin B

Lanternier & Lortholary. Clin Microbiol Infect 2008;14(Suppl 4):71

Importance of surgery for pulmonary mucormycosis



Tedder et al, Ann Thorac Surg 1994;57:1044

Candidaemia and invasive candidiasis

Randomised study of fluconazole alone compared with fluconazole and amphotericin B

219 patients received either

1) Flu 800 mg/d + placebo

or 2) Flu 800 mg/d + AmB deoxycholate 0.7mg/Kg/d

	Success (%)	Persistent pos B/C (%)
Flu only	56	17
Flu + AmB	69*	6#

* P = 0.08
# p = 0.02

Rex J et al, Clin Infect Dis 2003;36:1221

Caspofungin v. amphotericin B for invasive candidiasis in adults – study design

Caspofungin 70mg then 50 IV daily

versus

Amphotericin B 0.6- 0.7mg/kg

All CVCs changed

239 patients enrolled with sterile site positive for *Candida* spp, and signs of infection; osteomyelitis, endocarditis and meningitis excluded.

Efficacy (end of IV Rx) = favourable or unfavourable

Favourable = clinical resolution + culture negative (or presumptive)

Unfavourable = clinically or microbiologically unresponsive, early withdrawal of study drug (including toxicity)

Mora-Duarte et al, NEJM 2002;347:2020

Caspofungin v. amphotericin B for invasive candidiasis – patients enrolled

	Caspofungin 70/50 N=109	AmB 0.65mg/kg/d N=115
Candidaemia	90 (83%)	91(79%)
Peritoneal infection	8 (7%)	8 (7%)
Abscess	4 (4%)	9 (8%)
Neutropenia	14 (13%)	10 (9%)
Prior antifungal therapy*	61 (56%)	77 (67%)
C. albicans infection	36%	54%#

*< 1600mg fluconazole
< 2mg/kg AmB
< 10mg/kg Lipid AmB

P = 0.009

Mora-Duarte et al, NEJM 2002;347:2020

Caspofungin v. amphotericin B for invasive candidiasis – responses

	Caspofungin N=109	AmB N=115
Favourable response	80 (73%)	71 (62%)
Unfavourable response	29 (27%)	44 (38%)
Persistently positive cultures	9 (8%)	10 (9%)
New metastatic lesions	4 (4%)	5 (4%)
Persistent clinical findings	6 (6%)	5 (4%)
Toxicity requiring change in Rx	3 (3%)	19 (17%) #
Early withdrawal	7 (6%)	5 (4%)
Mortality	39 (34%)	30 (30%)
Relapse	7 (6%)	8 (7%)

P = 0.03

Mora-Duarte et al, NEJM 2002;347:2020

Micafungin v. AmBisome for invasive candidiasis in adults

Micafungin 100mg, fixed for 5d; 200mg/d, if failing

versus

AmBisome 3mg/Kg, fixed for 5d; 5mg/Kg if failing

55% patients in ICU

Mean Apache II score 15.7

42% steroids/anti-cancer/immunomodulatory drugs

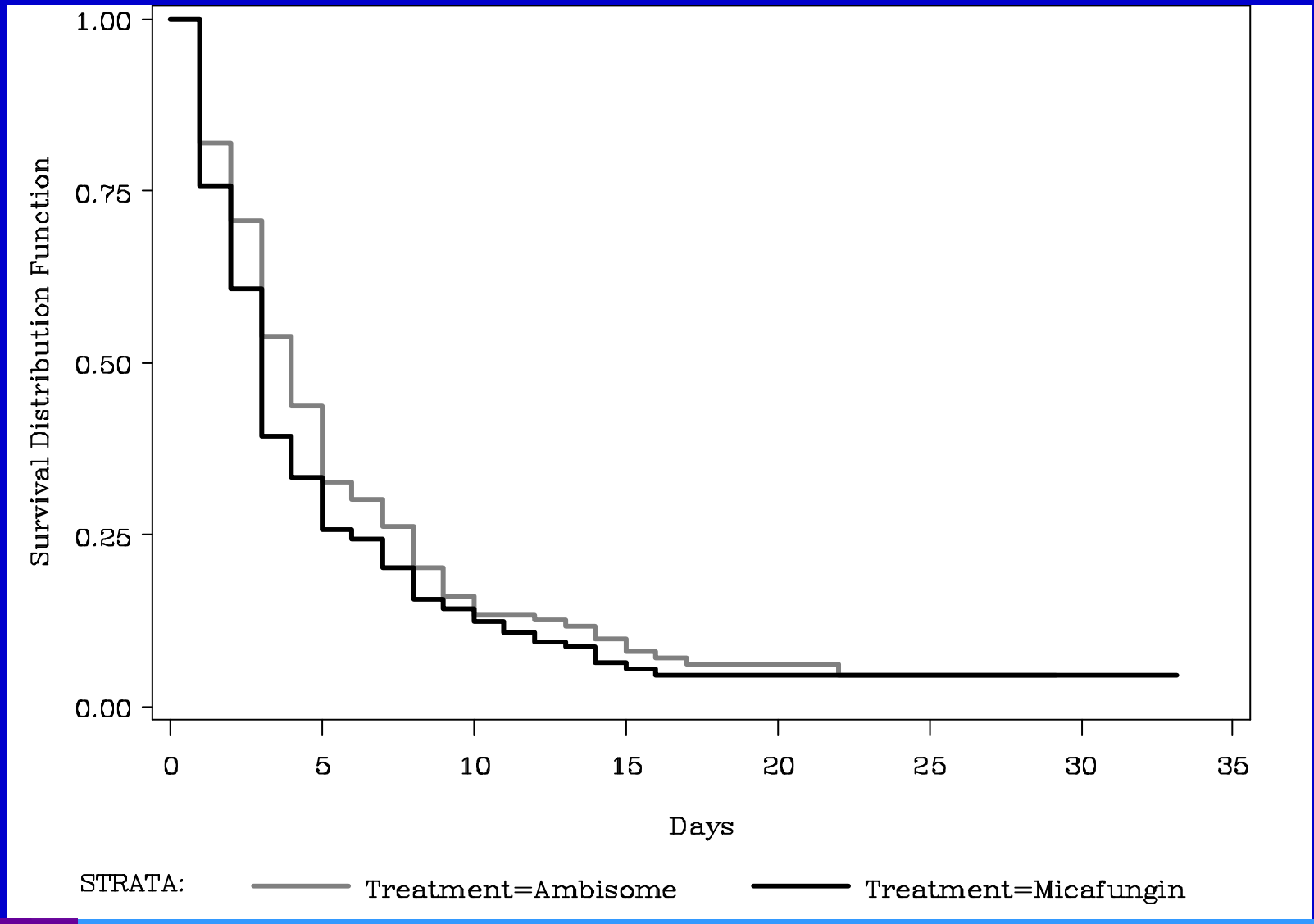
Kuse et al, Lancet 2007;369:1519

Micafungin versus Ambisome randomised study – MITT responses

	Micafungin		Ambisome		% Difference [97.5% CI]
	n	No. (%)	n	No. (%)	
Overall Treatment Success	247	183 (74)	247	172 (70)	4.5 [-3.5, 12.4]
Complete Response		159 (64)		150 (61)	
Partial Response		24 (10)		22 (9)	
Overall Treatment Success by Neutropenic Status					
Neutropenia baseline	32	18 (59)	25	14 (56)	4.9 [-3.0, 12.8] †
No neutropenia baseline	215	164 (76)	222	158 (71)	

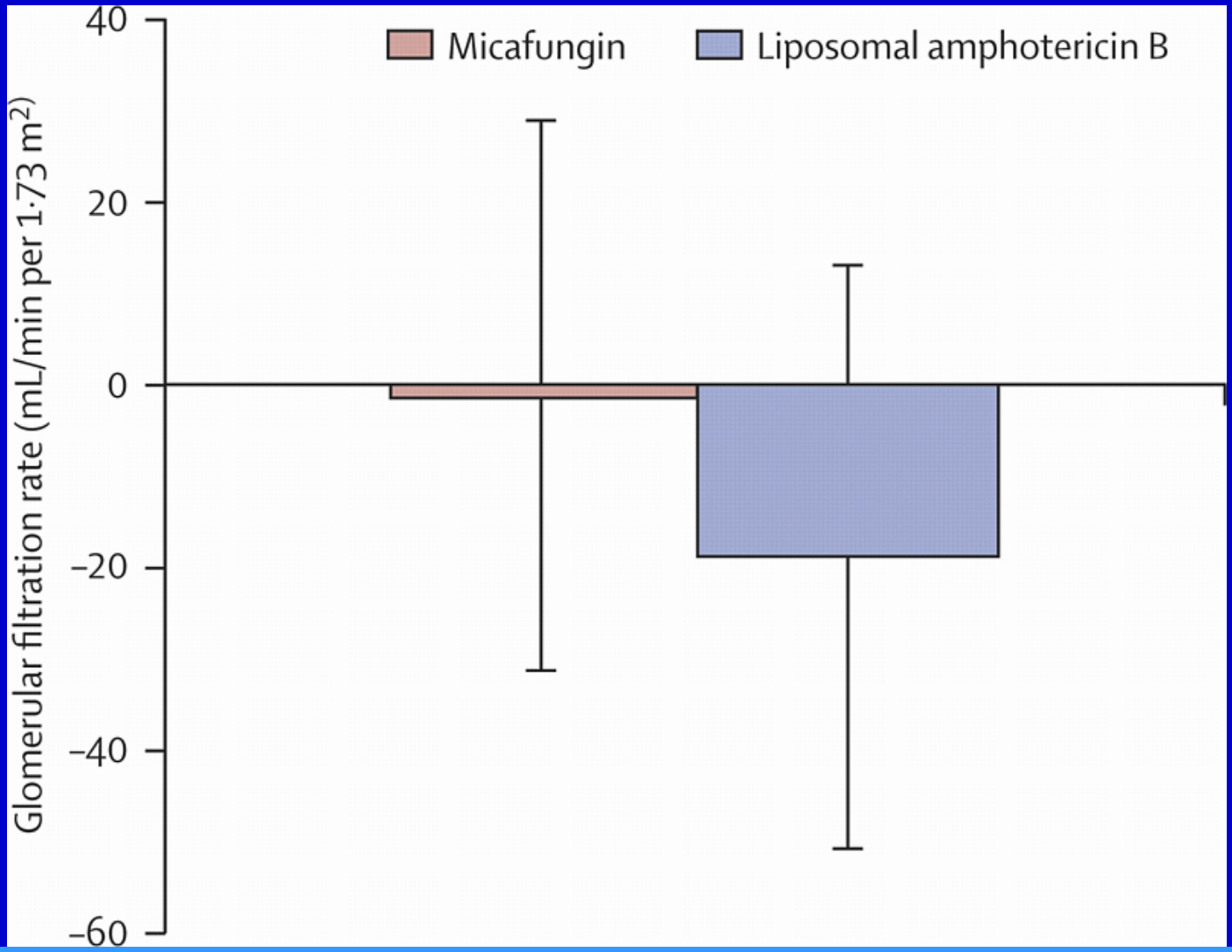
Kuse et al, Lancet 2007;369:1519

Micafungin versus Ambisome randomised study



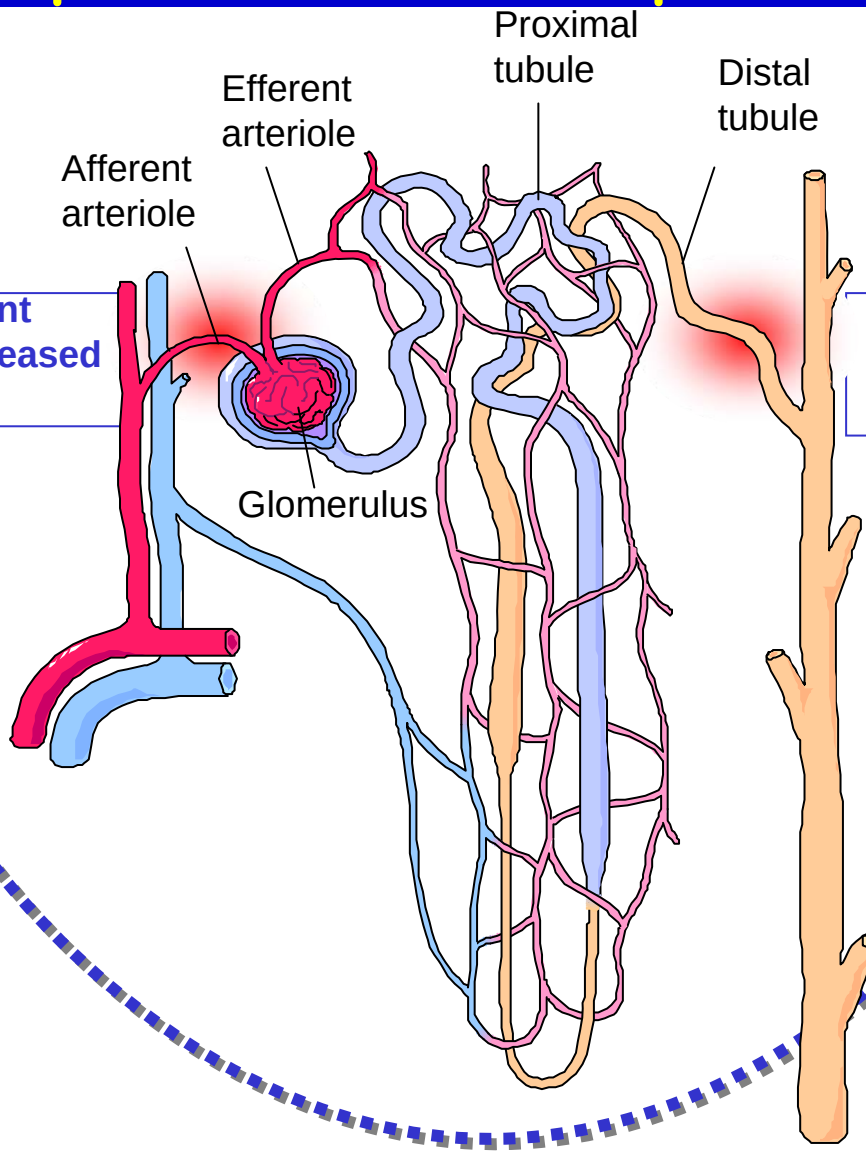
Kuse et al, Lancet 2007;369:1519

Micafungin versus Ambisome randomised study



Kuse et al, Lancet 2007;369:1519

Amphotericin B nephrotoxicity

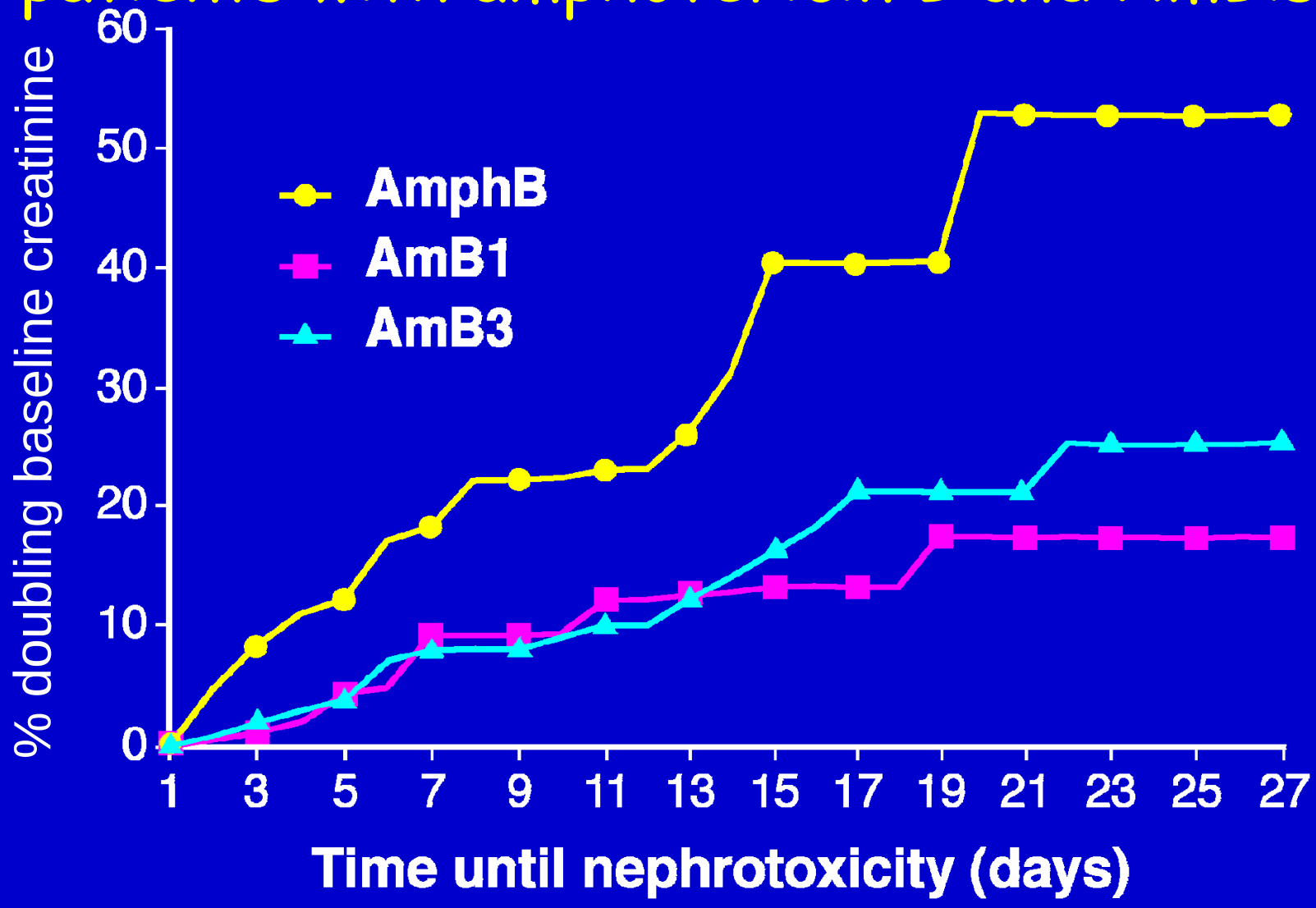


Constriction of the afferent arterioles leading to decreased glomerular filtration

Direct damage of distal tubular membranes leading to wasting of Na^+, K^+, and Mg^{++}

Tubular-glomerular feedback: Further constriction of arterioles

Comparative nephrotoxicity in leukaemic patients with amphotericin B and AmBisome



MANCHESTER 1824

Prentice HG, Br J Haematol 1997;98:711

AmBisome versus Abelcet (ABLC) in empirical therapy of febrile neutropenia

	AmBisome (5mg/kg)	Abelcet (5mg/kg)
Chills/rigors (%)	23.5	79.5
Fever (%)	19.8	57.7
Nephrotoxicity (%)	14.8	42.3

Wingard et al, Clin Infect Dis 2003;31:1155

Invasive candidiasis and candidemia treatment

1. Caspofungin/Micafungin/Anidulafungin
2. AmBisome 3mg/Kg
3. Fluconazole ≥400mg/d
4. Voriconazole if resistant species

Invasive aspergillosis

Randomised study of invasive aspergillosis with Amphocil versus amphotericin B

174 pts received either

1) Amphocil 6 mg/d for >2wks after symptoms gone

or 2) AmB 1.0 – 1.5 mg/kg/d >2wks after symptoms gone

70/174 (40%) in high risk (HSCT, liver Tx, AIDS, brain)

ITT analysis

	Success (%)	Tox (%)	Renal tox (%)	Died (due to IA)(%)
Amphocil	13	83	23	59 (22)
AmB	15	83	41	67 (20)

Bowden et al Clin Infect Dis 2002;35:359

Randomised study of invasive aspergillosis with 2 doses of AmBisome

339 pts randomised to receive either

1) L-AmB 3 mg/d for 2+wks (169 randomised; 107 in MITT)

or 2) L-AmB 10 mg/d for 2+wks (162 randomised; 94 in MITT)

44/201 (22%) high risk (HSCT, AIDS)

MITT analysis

	CR + PR	Stop Rx	Renal tox	Died
L-AmB 3	50%	20%	14%	28%
L-AmB 10	46%	32%	31%	41%

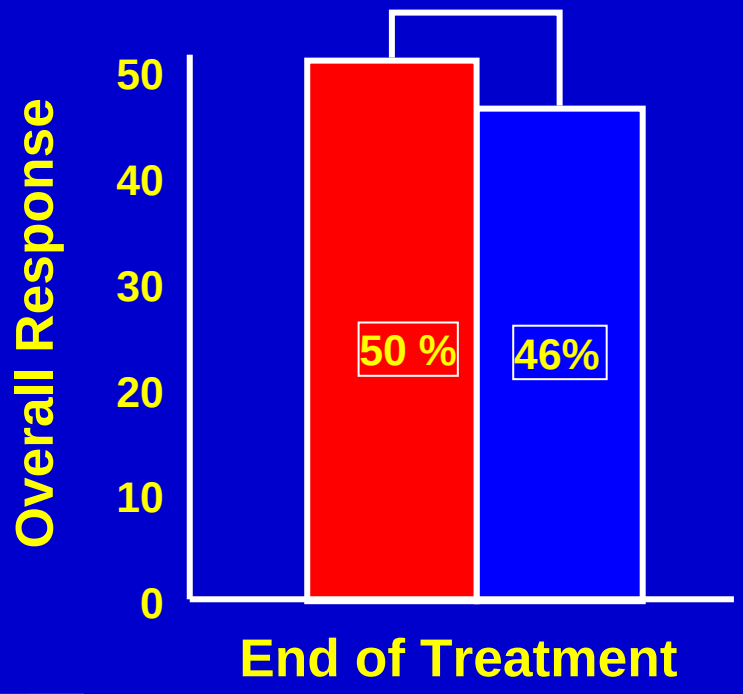
Cornely et al, Clin Infect Dis 2007;44:1289

AmBiload trial results

Response

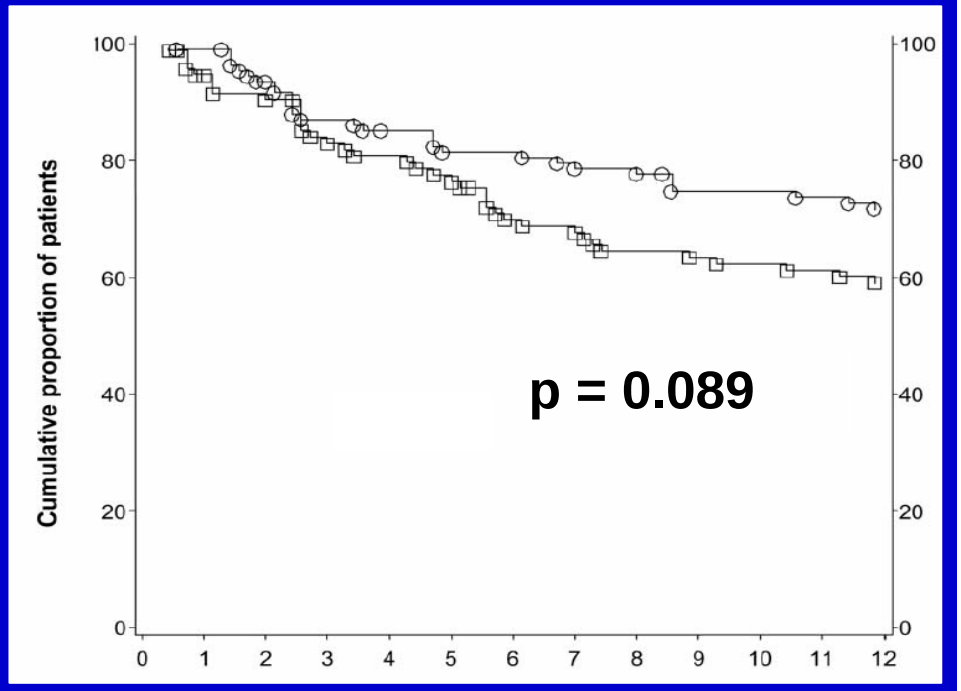
- LAmB 3 mg/kg (n = 107)
- LAmB 10 mg/kg (n = 94)

P = NS



Survival

- L-AmB 3 mg/kg
- L-AmB 10 mg/kg



MANCHESTER 1824

Cornely et al, Clin Infect Dis 2007;44:1289

Randomised study of invasive aspergillosis with voriconazole versus amphotericin B

391 pts received either

1) Voriconazole 4 mg/d BID (after loading) for 12wks (or OLAT)

or 2) AmB 1.0 mg/kg/d for 12wks (or OLAT)

mITT analysis

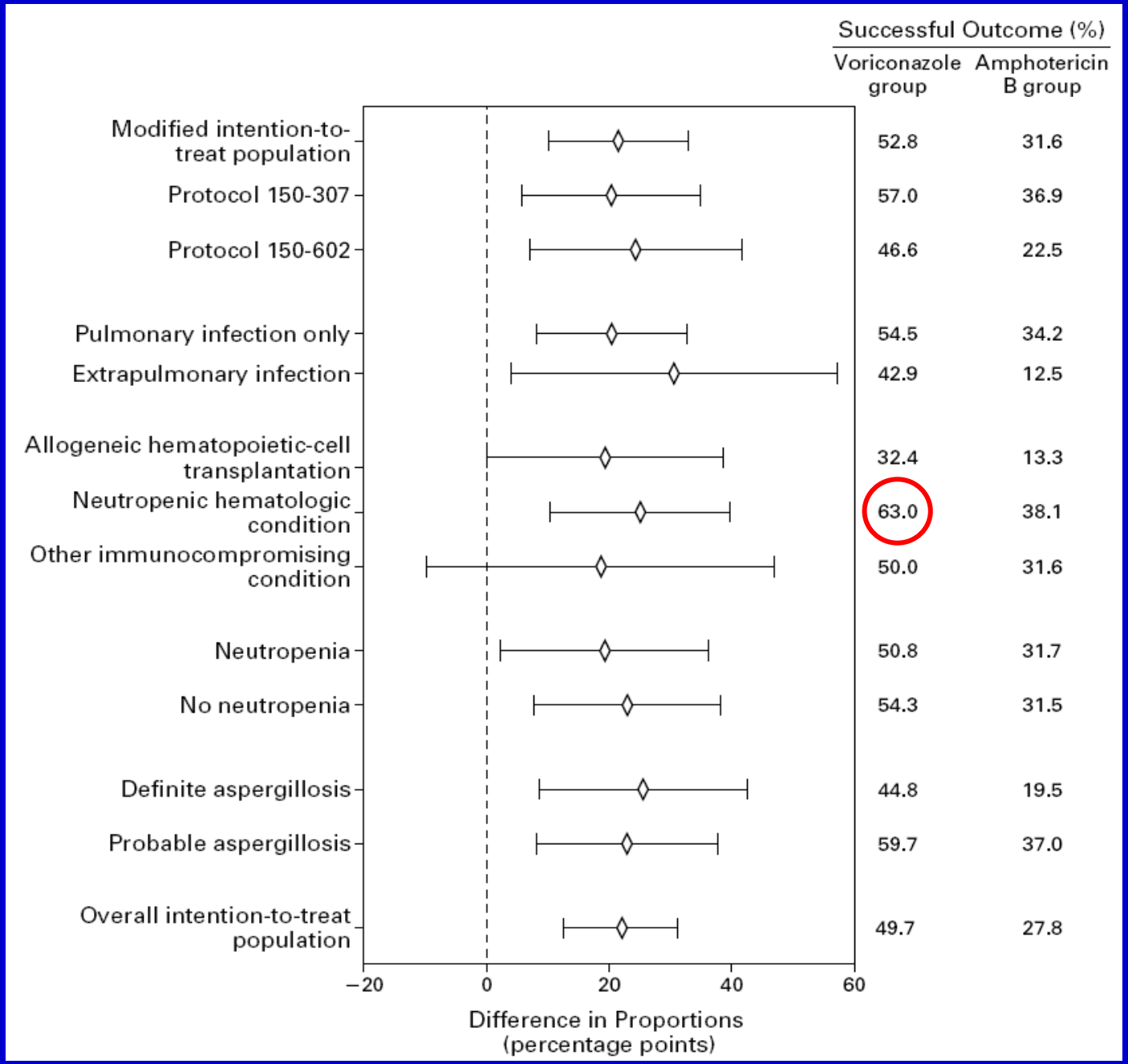
	Success (%)		Severe AEs (%)	Renal tox (%)	Died (all) (%)	
Vori	53	21%	13	1	29	13%
AmB	32		24	10	42	

Herbrecht, Denning et al, NEJM 2002;347:408

Variable	Modified intent-to-treat subgroup						
	Herbrecht et al. [7]			Cornely et al. [1]			
	Voriconazole group, % of patients	AmB group, % of patients	Total no. of patients	3 mg/kg of L-AmB group, % of patients	10 mg/kg of L-AmB group, % of patients	Total no. of patients	P[a]
Underlying disease							.002
Hematological malignancy	52.1	58.6	153	93	93	186	
Autologous HSCT	4.2	4.5	12	1	4	5	
Allogeneic HSCT	25.7	22.6	67	16	19	35	
Solid organ transplant	6.2	3.8	14	1	0	1	
HIV/AIDS	4.2	5.3	13	2	2	4	
Other	7.6	5.3	18	5	2	7	
Diagnostic modalities							<.001[b]
Microbiologically confirmed	68.1	63.2	182	38	38	77	
Antigen testing only	0	0	0	25	19	45	
Culture and histologic and microscopic examinations	68.1	63.1	182	13	17	30	
Halo sign only	31.9	36.8	95	58	60	118	
Certainty of diagnosis							<.001
Proven IA	46.5	30.8	108	7	11	18	
Probable IA	53.5	69.2	169	93	89	183	
Outcome of IA only							
Success at 12 weeks	52.8	31.6	118	NA	NA		
Success at end of therapy	53.5	21.8	106	50	46		
Favorable response							<.001
Complete response	20.8	16.5	52	1[c]	2[c]	3	
Partial response	31.9	15.0	66	49[c]	41[c]	93	
Unfavorable response							.004
Stable	5.6	6.0	18	7[c]	5[c]	13	
Treatment failure	38.2	58.6	133	34[c]	38[c]	72	
Indeterminate	3.5	3.8	10	9[c]	11[c]	20	
Survival at 12 weeks	70.8	57.9	179	72	59	132	.81

Variable	Modified intent-to-treat subgroup						
	Herbrecht et al. [7]			Cornely et al. [1]			
	Voriconazole group, % of patients	AmB group, % of patients	Total no. of patients	3 mg/kg of L-AmB group, % of patients	10 mg/kg of L-AmB group, % of patients	Total no. of patients	P[a]
Outcome of IA only							
Success at 12 weeks	52.8	31.6	118	NA	NA		
Success at end of therapy	53.5	21.8	106	50	46		
Favorable response							<.001
Complete response	20.8	16.5	52	1[c]	2[c]	3	
Partial response	31.9	15.0	66	49[c]	41[c]	93	
Unfavorable response							.004
Stable	5.6	6.0	18	7[c]	5[c]	13	
Treatment failure	38.2	58.6	133	34[c]	38[c]	72	
Indeterminate	3.5	3.8	10	9[c]	11[c]	20	
Survival at 12 weeks	70.8	57.9	179	72	59	132	.81
Success in various subgroups							
At 12 weeks in Europe[d]	57.0	36.9	170	50	46	201	
At 12 weeks in the United States[e]	46.6	22.5	107	…	…		
In the context of hematological malignancy	63.0	38.1	83	53	54	103	
In the context of allogeneic HSCT	32.4	13.3	16	47	50	17	
In patients with neutropenia at baseline	50.8	31.7	52	43	42	63	
In patients with pulmonary IA	54.5	34.2	107	51	48	90	
In patients with extrapulmonary IA	42.9	12.5	11	33	30	6	

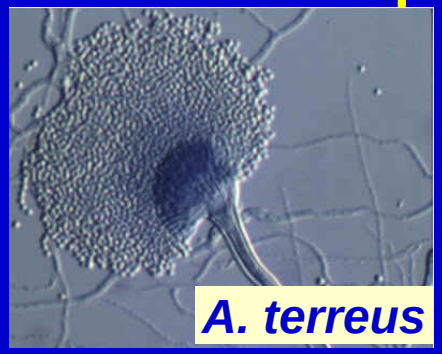
Denning, CID 2007;45:1106-8

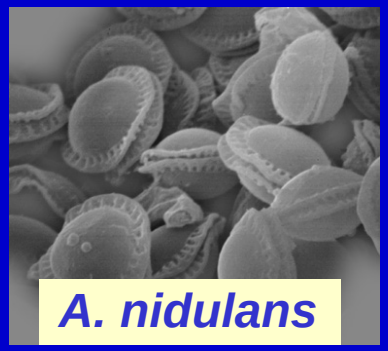


Herbrecht et al, NEJM 2002:347:408

Intrinsic and acquired resistance among the *Aspergilli*

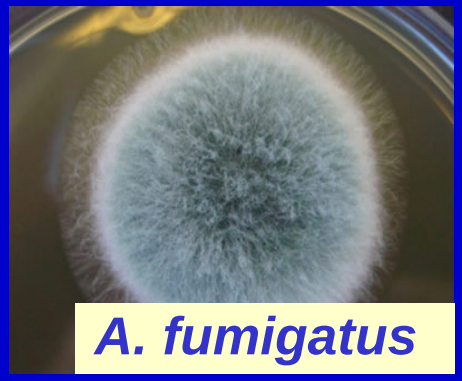
Amphotericin B resistance


A. terreus


A. nidulans


A. flavus

Azole resistance


A. fumigatus

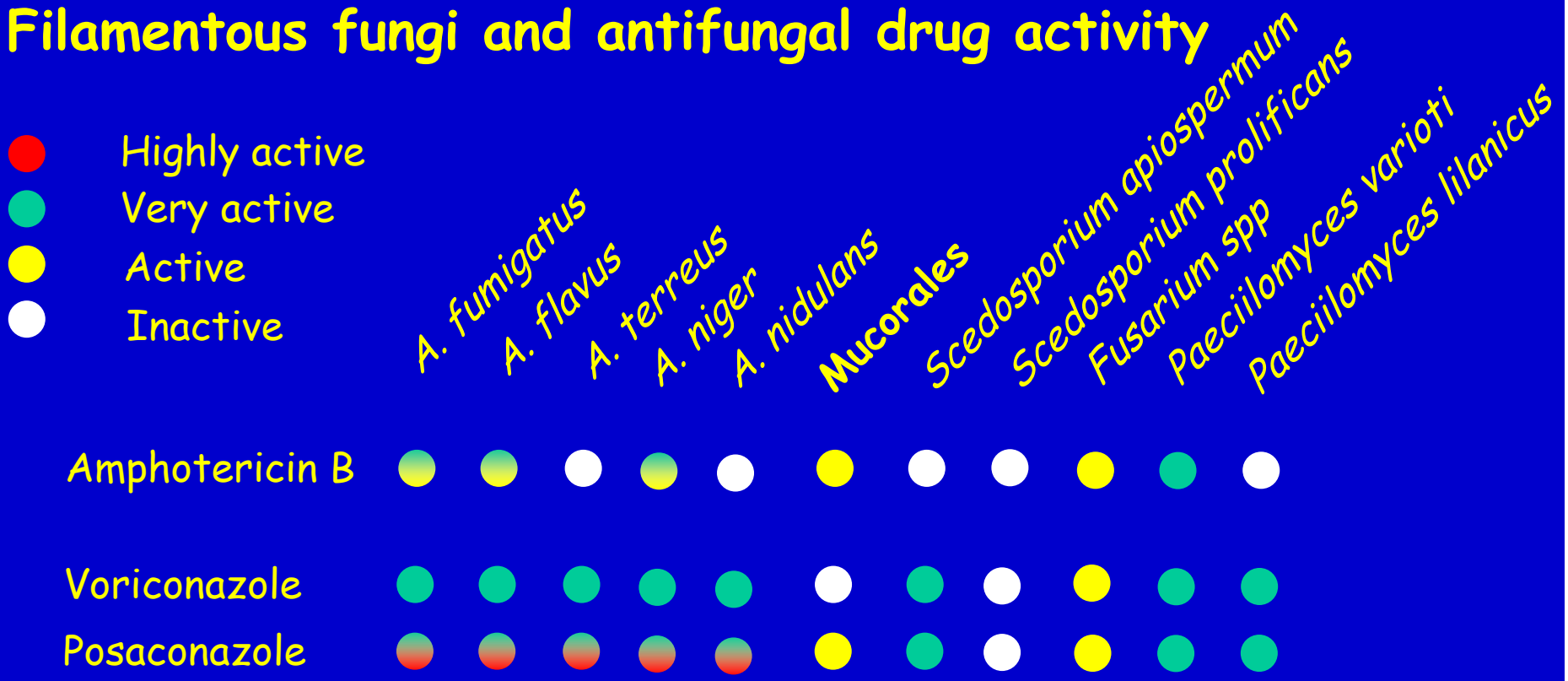

A. niger

Antifungal susceptibility of *Aspergillus nidulans*

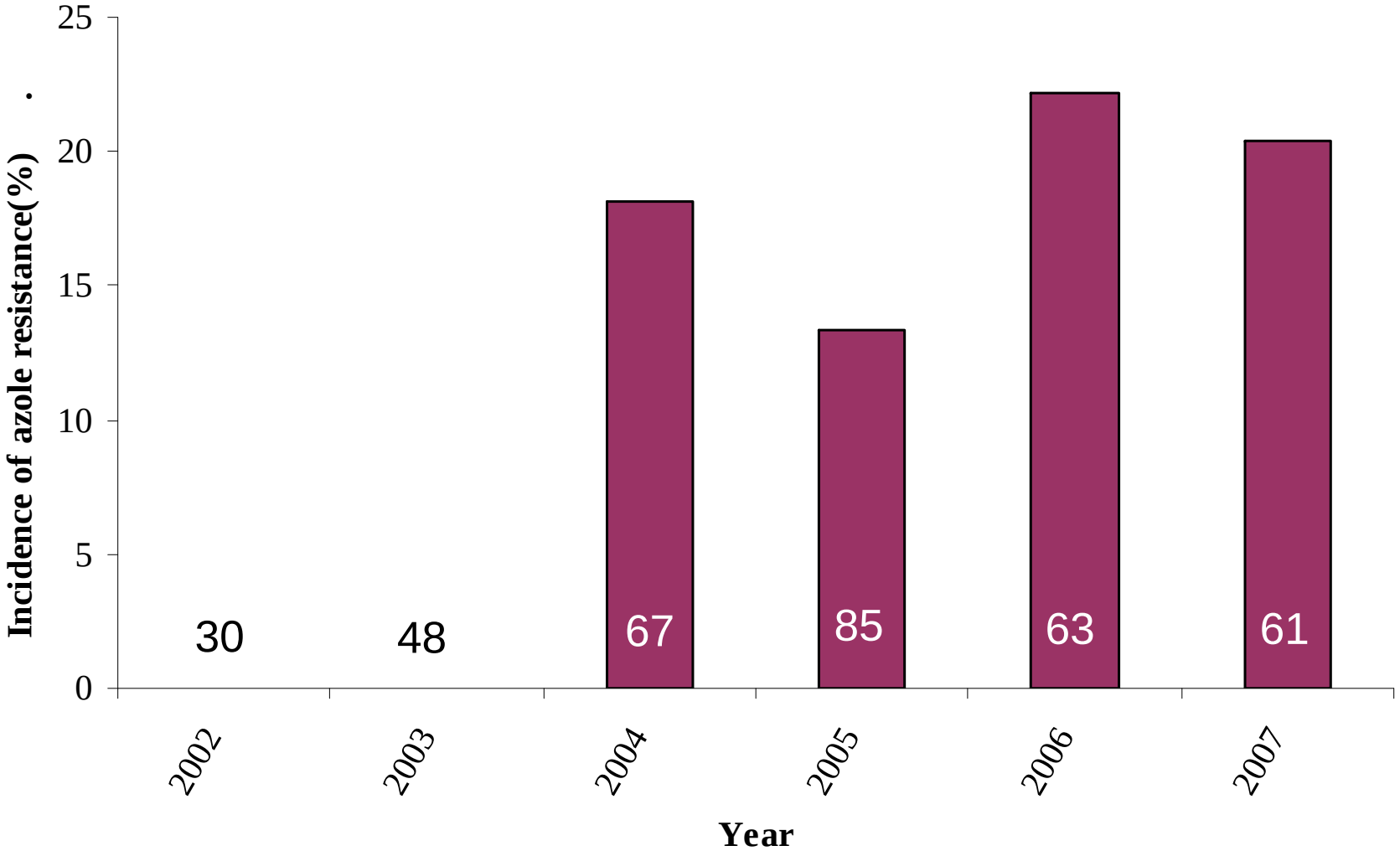
	MIC90	ranges (µg/mL)
Amphotericin B	4	1–8 (52.3% ≥4)
micafungin	0.062	0.062- 0.125
itraconazole	2	0.25–4
voriconazole	2	0.062–2
posaconazole	1	0.25–1

Peláez et al, ECCMID 2009; P1297

Filamentous fungi and antifungal drug activity



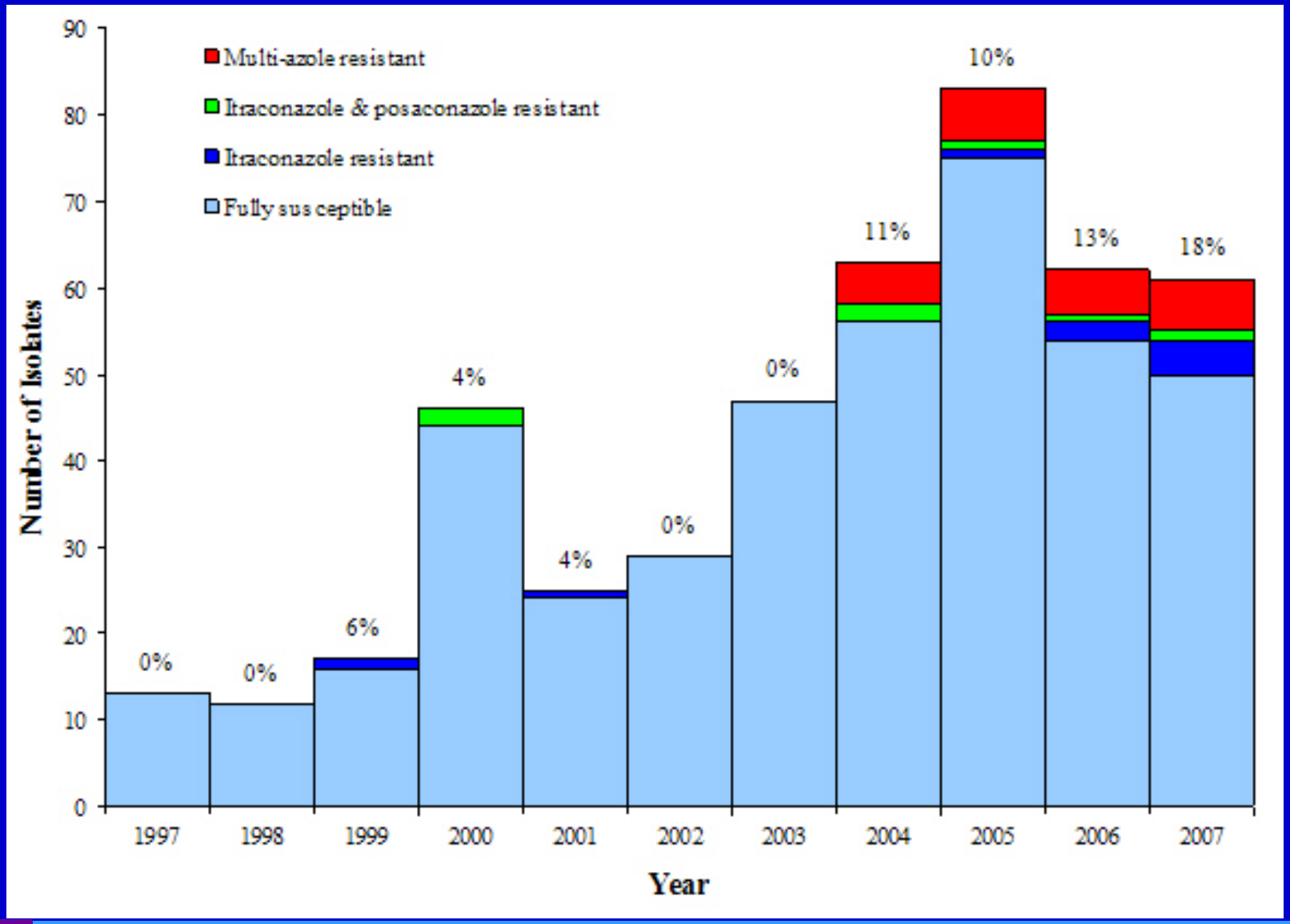
Azole resistance in *Aspergillus fumigatus* - Manchester



MANCHESTER 1824

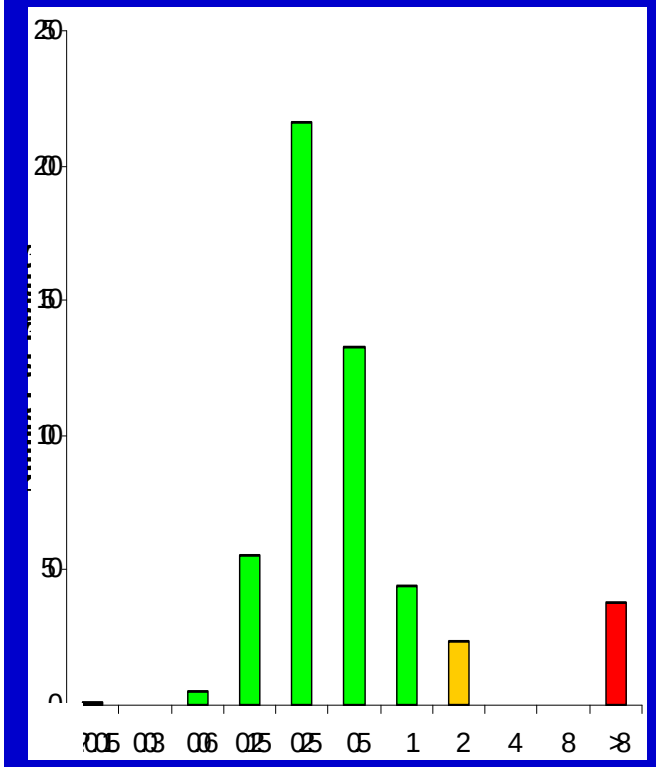
Howard et al, Emerg Infect Dis 2009 In press

Frequency of itraconazole resistance in *A. fumigatus*

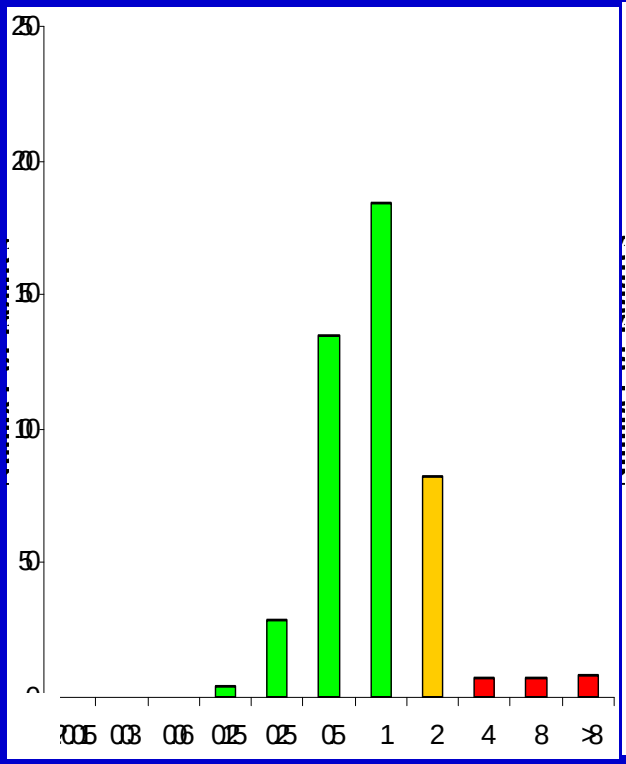


Howard et al, Emerg Infect Dis In press

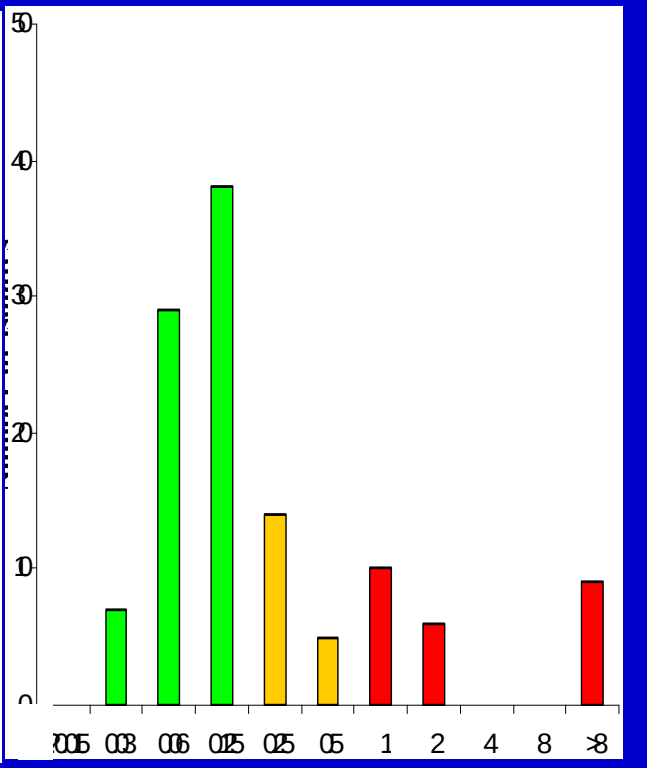
Manchester azole MIC distributions



Itraconazole MIC (mg/L)



Voriconazole MIC (mg/L)



Posaconazole MIC (mg/L)

modified EUCAST method - 0.5 x 10^5 not 1-2.5 x 10^5 cfu/mL

Clinical features of patients with azole resistant *A. fumigatus*

17 patients, 15 from UK, different cities

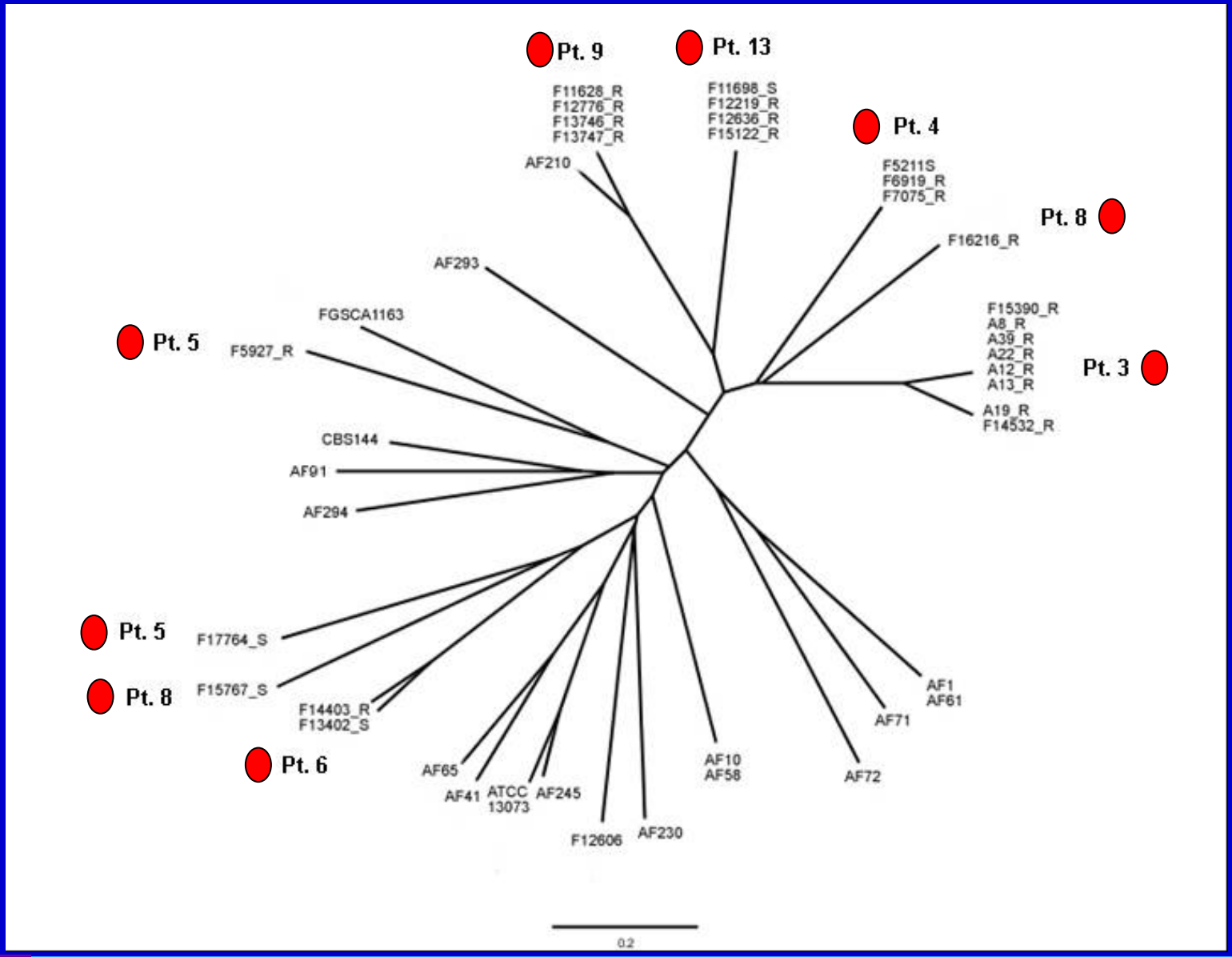
9 had CCPA, all with aspergilloma
3 had sputum isolate, with no treatment data
2 had ABPA
2 had IA
1 had *Aspergillus* bronchitis

13 of 14 patients had prior azole exposure

8 failed therapy and 5 failed to improve
(12 itraconazole, 1 voriconazole)

Howard et al, Emerg Infect Dis In press

Typing of itraconazole resistance in *A. fumigatus*



Howard et al, Emerg Infect Dis In press

Multiple mutations contributing to resistance

Cyp51A codon	Number of patients	Number of isolates	Amino acid substitutions	MIC (mg/L)[a]		
				itra	vori	posa
F46	3	4[b]	Y	>8	2-4	0.125-0.5
G54	4	5	E, R, V	>8	0.125-1	1->8
L98+TR	2	2	H	>8	8	1-2
G138	1	10	C	>8	8->8	2->8
H147	1	1[c]	Y	>8	>8	0.5
M172						.125-0.5
P216						1
M220						0.5->8
N248						0.25
D255						0.25
E427	4	5[b]	G, K	>8	2-4	0.125-0.5
Y431	1	1	C	>8	4	1
G434	1	1	C	>8	4	1
G448	2	2	S	>8	>8	0.5-1
no Cyp51A substitutions	2	3	N/A	>8	2-8	0.25-1

Of 34 itraconazole resistant isolates studied, 58% and 66% were cross-resistant to voriconazole and posaconazole respectively

Howard et al, Emerg Infect Dis In press; Al-Barraq et al, unpublished;

Azole resistance in *Aspergillus*

- Azole resistance is relatively common, especially among pre-treated patients
- Itraconazole resistance does not predict voriconazole or posaconazole resistance
- Rarely voriconazole resistance may occur without itraconazole or posaconazole resistance
- Multiple mechanisms of resistance can be found
- ? High loads of fungi (ie fungal balls) and low concentrations of azole may precipitate emergence of resistance

Conclusions

AmBisome is the treatment of choice for:

- Disseminated histoplasmosis
- Visceral leishmaniasis
- Zygomycosis (mucormycosis)
- Azole resistant aspergillosis (probably)

AmBisome is second-line treatment for:

- Cryptococcal meningitis (with flucytosine) if deoxycholate amphotericin B problematic
- Invasive candidiasis if an echinocandin not possible or failing
- Invasive aspergillosis if voriconazole not possible or failing, especially in neutropenia

AmBisome is one option for:

- Empirical therapy of febrile neutropenia
- Antifungal prophylaxis in solid organ transplant recipients

AmBisome is the least toxic amphotericin B preparation


The Aspergillus Website
Patient Information
Educational Materials
Medical Information
Scientific Information
www.aspergillus.org.uk
Image Bank
Register Here
What is Aspergillus?
The Fungal Research Trust

4th ADVANCES AGAINST ASPERGILLOSIS

February 3-6, 2010

Rome, Italy

Sheraton Roma

www.AAA2010.org

University of California San Diego–School of Medicine