Treatment of invasive aspergillosis

David W. Denning
University Hospital of South Manchester
The University of Manchester

Treatment


Itraconazole
100mg Capsules
15 capsules
SANDOZ
Sporanox
10 mg/ml
Oral Solution
VFEND
200 mg film-coated tablets
Voriconazole
Pfizer
VFEND
50 mg film-coated tablets
Voriconazole
Noxafil
40 mg/ml
105 ml

Invasive aspergillosis

Table 2. Summary of recommendations for the treatment of aspergillosis.

Condition	Therapy[a]	
	Primary	Alternative[b]
Invasive pulmonary aspergillosis	Voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h)	L-AMB (3–5 mg/kg/day IV), ABLC (5 mg/kg/day IV), caspofungin (70 mg day 1 IV and 50 mg/day IV thereafter), micafungin (IV 100–150 mg/day; dose not established[c]), posaconazole (200 mg QID initially, then 400 mg BID PO after stabilization of disease[d]), itraconazole (dosage depends upon formulation)[e]

IDSA guidelines. Walsh et al. Clin Infect Dis 2008;46:327

Invasive aspergillosis

There are few randomized trials on the treatment of invasive aspergillosis. The largest randomized controlled trial demonstrates that voriconazole is superior to deoxycholate amphotericin B (D-AMB) as primary treatment for invasive aspergillosis. Voriconazole is recommended for the primary treatment of invasive aspergillosis in most patients (A-I). Although invasive

Why most and not all?

IDSA guidelines. Walsh et al. Clin Infect Dis 2008;46:327

August 1994 The American Journal of Medicine® Volume 97 135

NIAID Mycoses Study Group Multicenter Trial of Oral Itraconazole Therapy for Invasive Aspergillosis

David W. Denning, MBBS, *San Jose, California*, Jeanette Y. Lee, PhD, *Birmingham, Alabama*, John S. Hostetler, MD, *San Jose California*, Peter Pappas, MD, *Birmingham, Alabama*

Open study of 600 mg/day for 4 d, then 400 mg/d. Treatment extended for >97 weeks, median 46

	12 weeks		End of Treatment	
Complete	5%	31%	26%	39%
Partial	26%		13%	
Stable	34%		4%	
Failure	32%		56% (30% other causes)	
Deaths	--		31%	

Denning, Am J Med 1994;97:135

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)

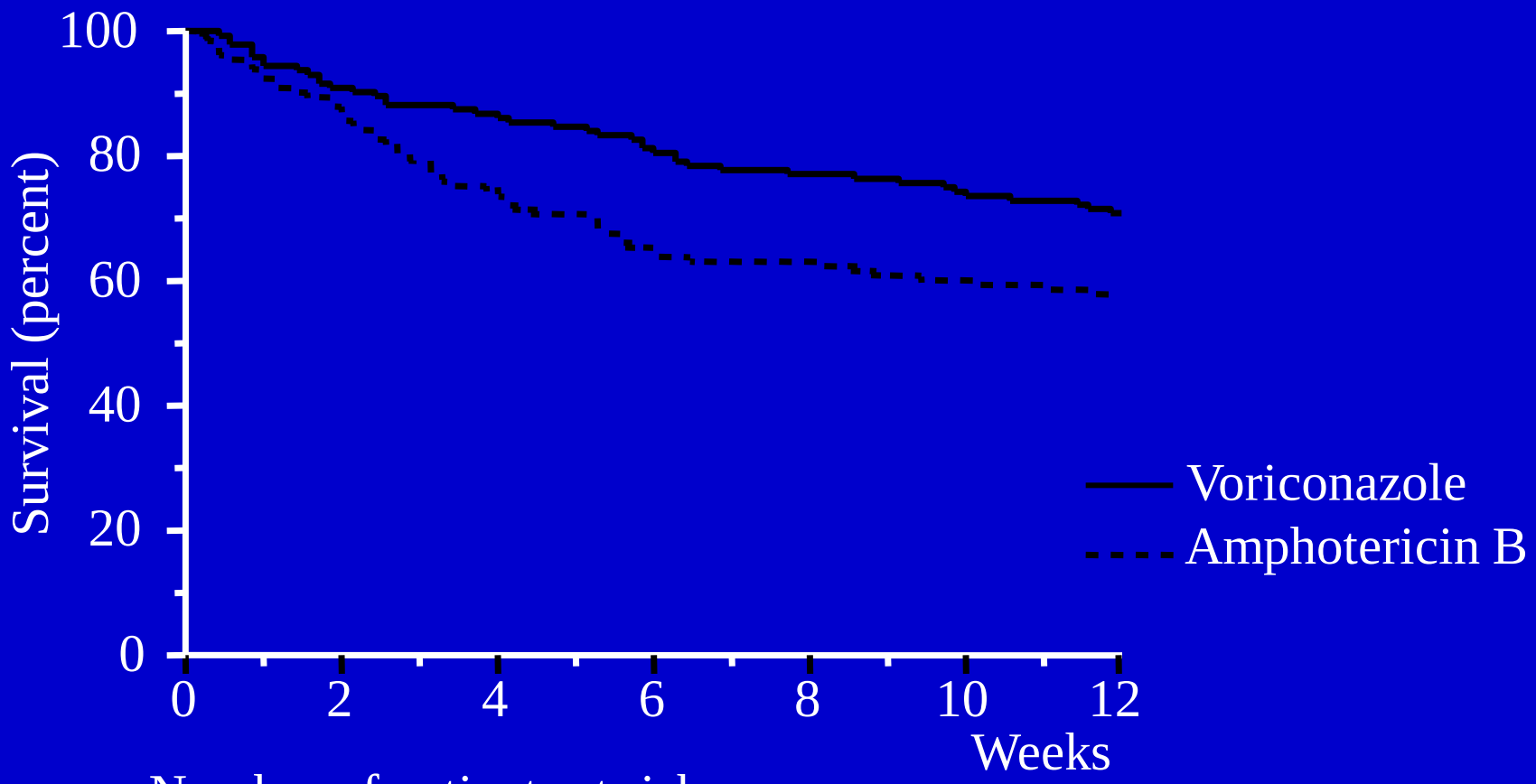
or 2) AmB 1.0 mg/kg/d for 12wks (or OLAT)

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

Survival after primary Rx with amphotericin B or voriconazole



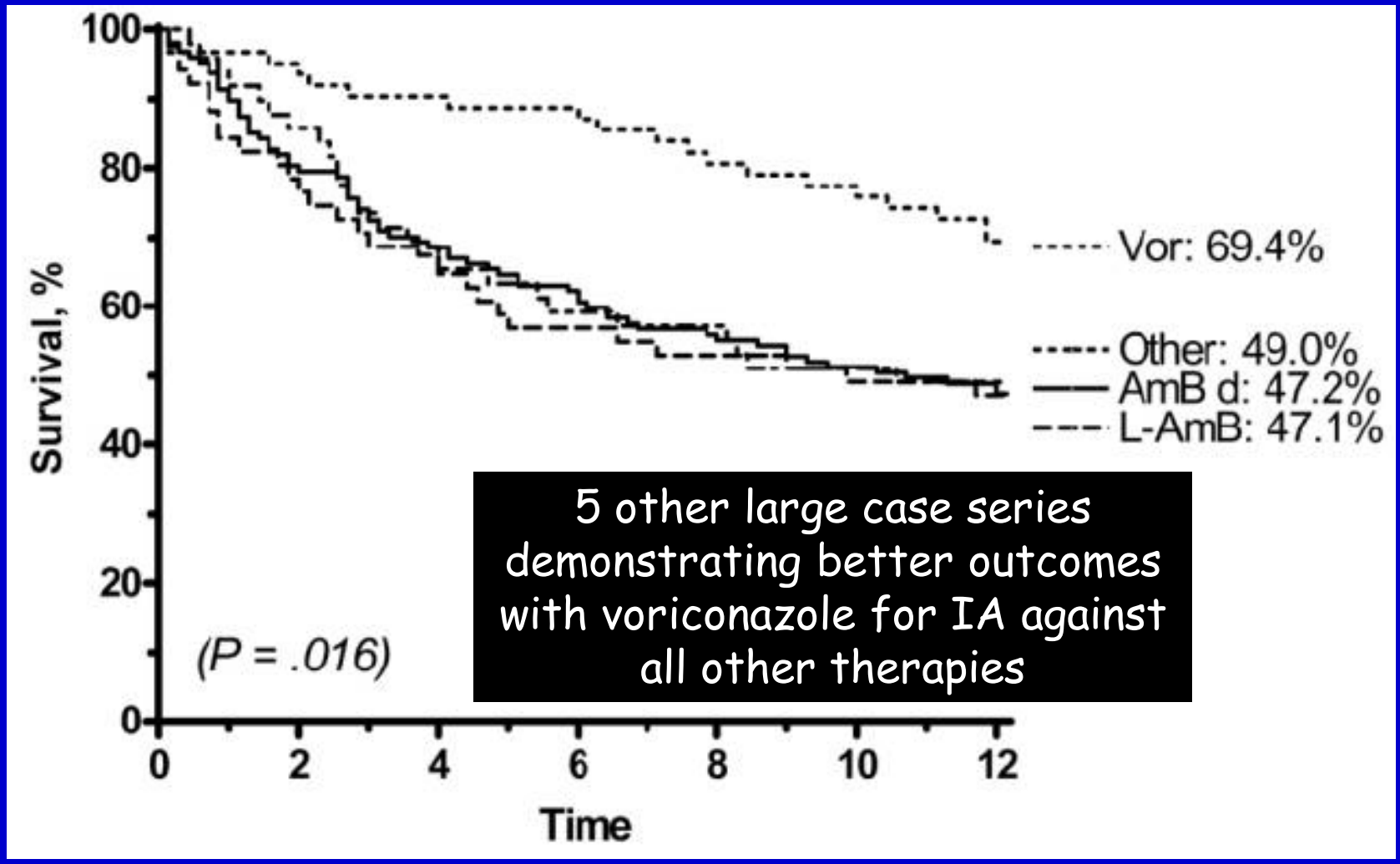
Number of patients at risk

144	131	125	117	111	107	102	Voriconazole
133	117	99	87	84	80	77	Amphotericin B

Overall logrank test p=0.015

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

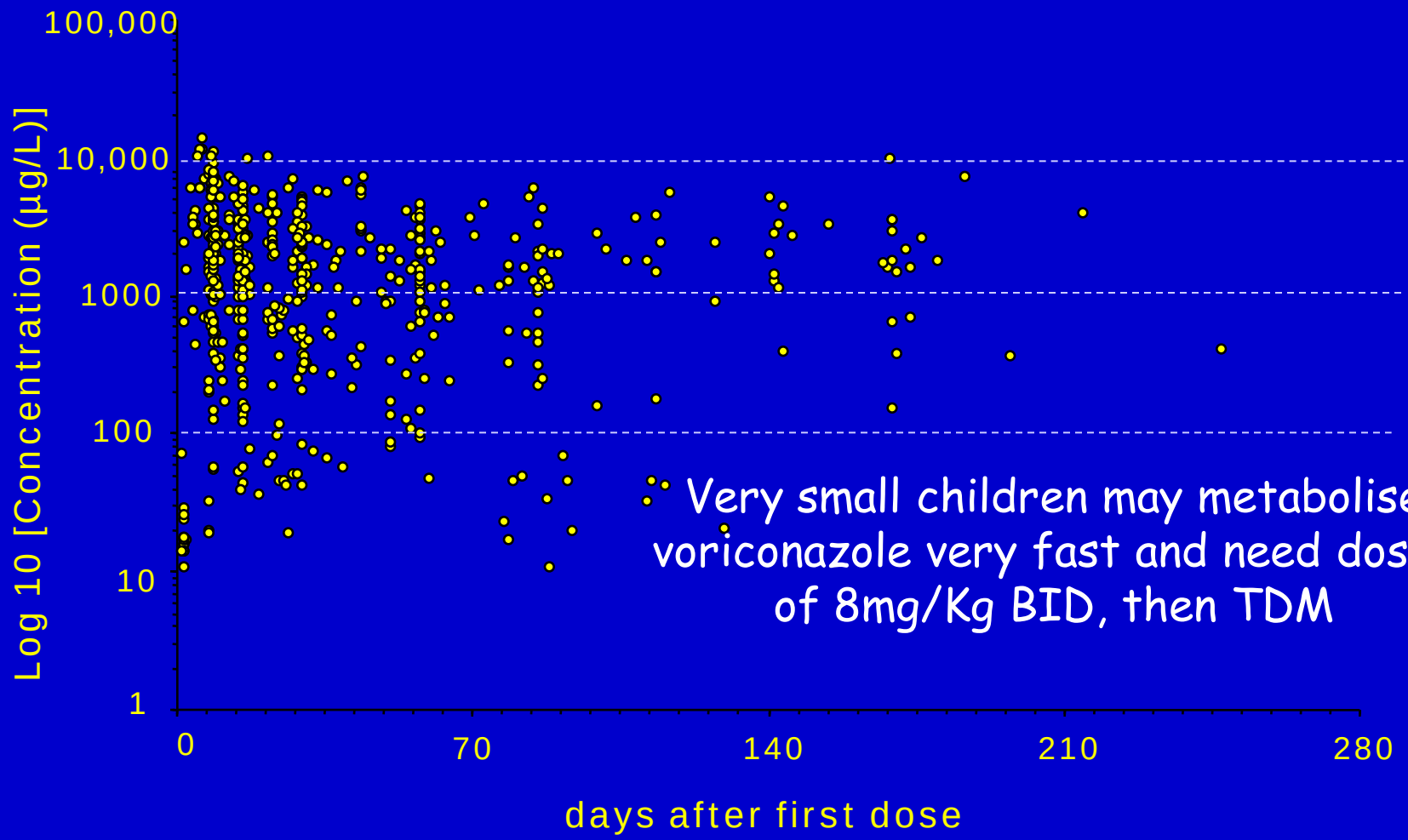
Impact of voriconazole in real life - France



5 other large case series demonstrating better outcomes with voriconazole for IA against all other therapies

Nivoix et al, Clin Infect Dis 2008;47:1176

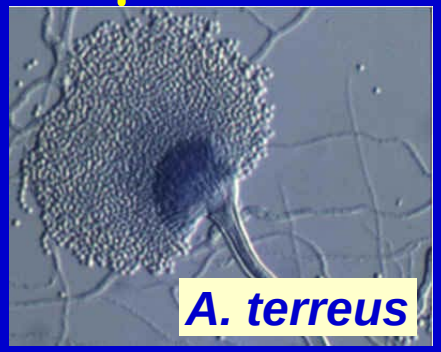
Random voriconazole concentrations in adults receiving 3mg/Kg BID

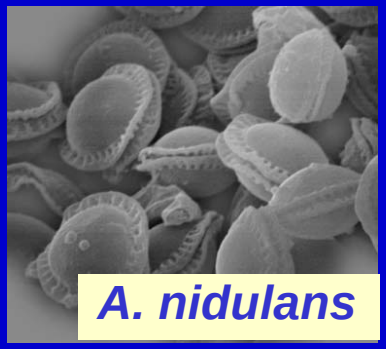


Data from Denning et al, Clin Infect Dis 2002;34:563

Intrinsic and acquired resistance among the *Aspergilli*

Amphotericin B resistance/insensitivity





Azole resistance

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

Micafungin for invasive aspergillosis

Table 3 Efficacy at end of therapy

	Primary (%)		Refractory/toxicity failure[a] (%)		Total (%) ($N = 225$)
	Micafungin in combination ($n = 17$)	Micafungin alone ($n = 12$)	Micafungin in combination ($n = 174$)	Micafungin alone ($n = 22$)	
Complete response	2 (11.8)	0	13 (7.5)	3 (13.6)	18 (8.0)
Partial response	3 (17.6)	6 (50.0)	47 (27.0)	6 (27.3)	62 (27.6)
Favorable response	*5 (29.4)*	*6 (50.0)*	*60 (34.5)*	*9 (40.9)*	*80 (35.6)*
Stabilization	3 (17.6)	2 (16.7)	17 (9.8)	3 (13.6)	25 (11.1)
Progression	9 (52.9)	4 (33.3)	97 (55.7)	10 (45.5)	120 (53.3)
Not successful	*12 (70.6)*	*6 (50)*	*114 (65.5)*	*13(59.1)*	*145 (64.4)*

[a] Four patients who had failed previous therapy due to toxicities are included in the micafungin-alone group.

Denning et al, J Infect 2006;53:337.

Open study of invasive aspergillosis with caspofungin as primary therapy

61 pts with chemotherapy or auto HSCT received
Caspofungin 70 then 50mg IV daily

	MITT population (N=61)	
Response	*n*	% (95% CI)
Complete	1	2 (0–9)
Partial	19	31 (20–44)
Stable disease	9	15 (7–26)
Disease progression	31	51 (38–64)
Not evaluable[a]	1	2 (0–9)

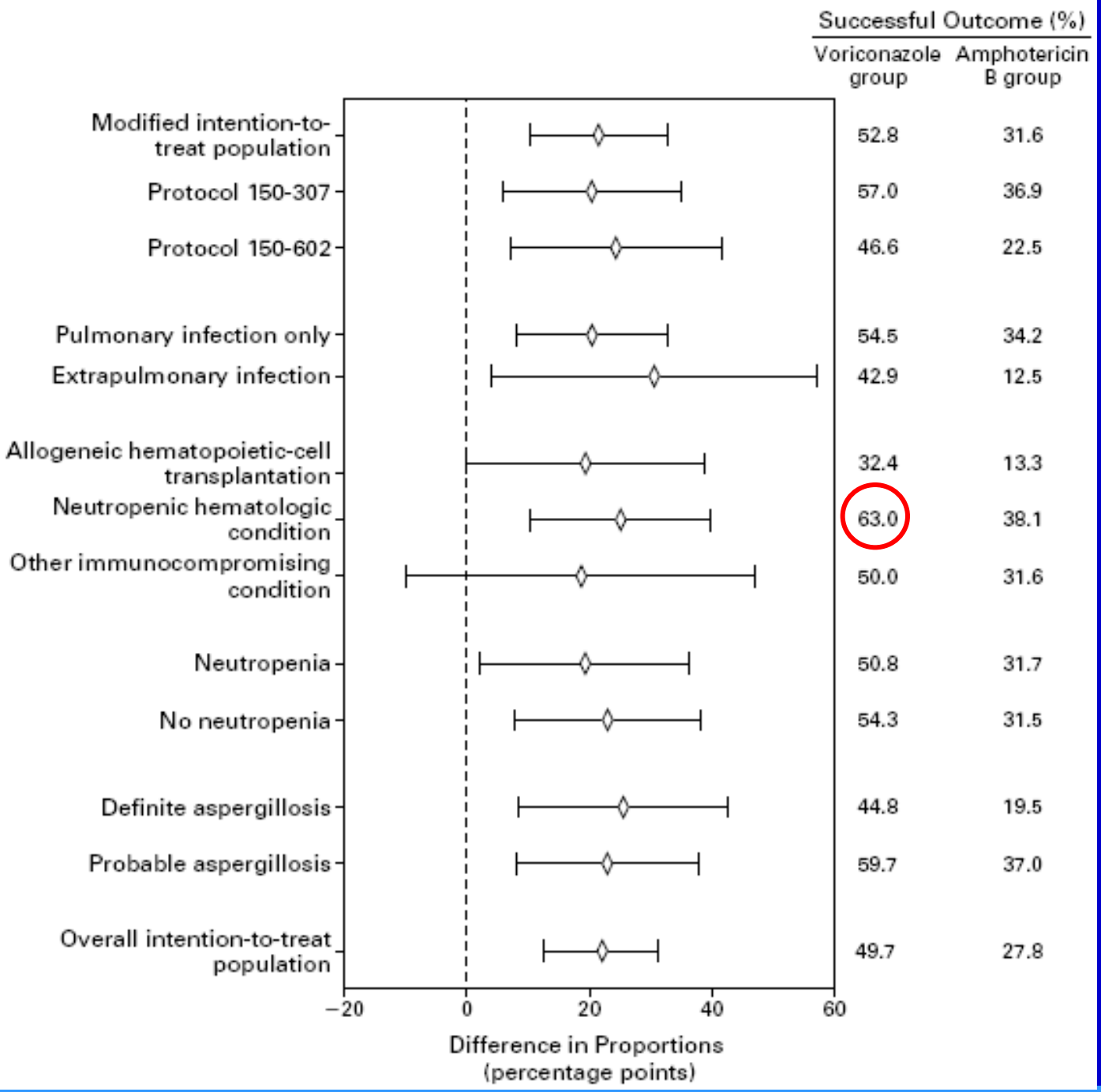
[a]Patient refused treatment.

} 33% response rate

Neutropenia at enrolment (not assessable in one case)		
no	5/9 (56)	0.14
yes	15/51 (29)	

Survival by day 84 = 33/61 (54%)

Viscoli et al, JAC 2009;64:1274



Herbrecht at al, New Engl J Med 2002:347:408-15

Voriconazole versus amphotericin B [Spectrum/activity]

Favours voriconazole

Much more active for IA (~20% better)

Active against *A. terreus*

Active against *A. nidulans*

More active *A. flavus*

Active against *S. apiospermum*

Favours Amp B

Mucorales possible

Azole resistant *A. fumigatus*

Voriconazole versus echinocandin [Spectrum/activity]

Favours voriconazole

Much more active for IA (~20% better)

Active against *A. terreus*

Active against *A. nidulans*

More active *A. flavus*

Active against *S. apiospermum*

Favours micafungin/caspofungin

Azole resistant *A. fumigatus*

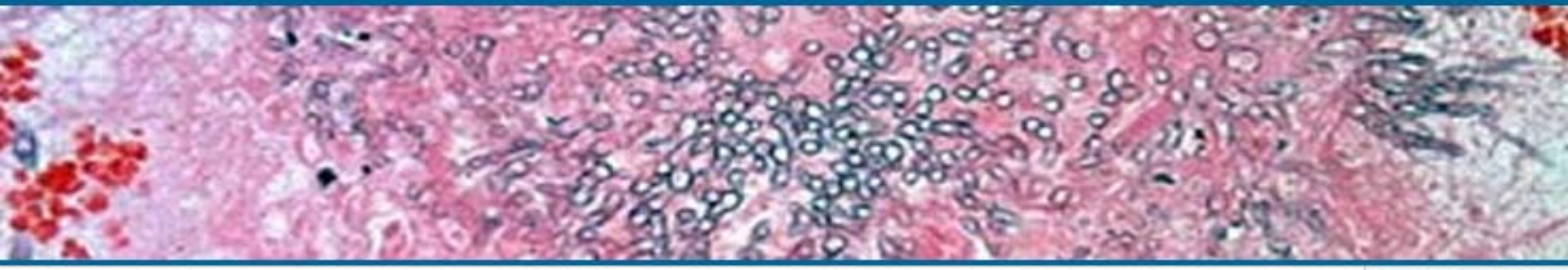
Cytochrome P450 interactions

	Fluc	Itra	Posa	Vori
Inhibitor				
2C19	+			+++
2C9	++	+		++
3A4	++	+++	+++	++
Substrate				
2C19				+++
2C9				+
3A4		+++		+

Dodds Ashley & Alexander. Drugs Today 2006;41:393.

Web www.aspergillus.org.uk

Patients | Scientific Information | Medical Information | Images | Educational Materials | Library



The Aspergillus Website

The **Aspergillus website** is a worldwide comprehensive resource providing a wide range of information about the **fungus Aspergillus** and the diseases - such as **Aspergillosis** that it can cause.This site is free to use and provides an encyclopaedia of Aspergillus for doctors, scientists, patients and their relatives. Some parts of the site for example the image bank require free registration.

13 years and counting
Over 2M pages read monthly in >125 countries
Supported by the Fungal Research Trust – 20 year anniversary in 2011

Aspergillosis is a group of diseases which can result from aspergillus infection and includes invasive aspergillosis, ABPA, CPA and aspergilloma. Some asthma patients with very severe asthma may also be sensitised to fungi like aspergillus (SAFS). There is a section devoted to the needs of patients, friends and family suffering from the effects of Aspergillosis.
The UK's fi
centre is supported by the Regional Mycology Lab which also provides both air sampling and mould identification services for domestic and working environments.

New section on drug interactions which you can search very quickly

Aspergillosis may affect patients whose immune system may be compromised - including those with **leukaemia, chemotherapy patients or those on steroids, transplant patients, cystic fibrosis, HIV or AIDS, chronic obstructive pulmonary disease (COPD), chronic granulomatous disease (CGD), severe asthma with fungal sensitivity (SAFS) and many others.**

Aspergillus does not solely affect humans; **birds and animals can also develop aspergillosis**, and some plant

search

Useful links

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Headlines

A new database
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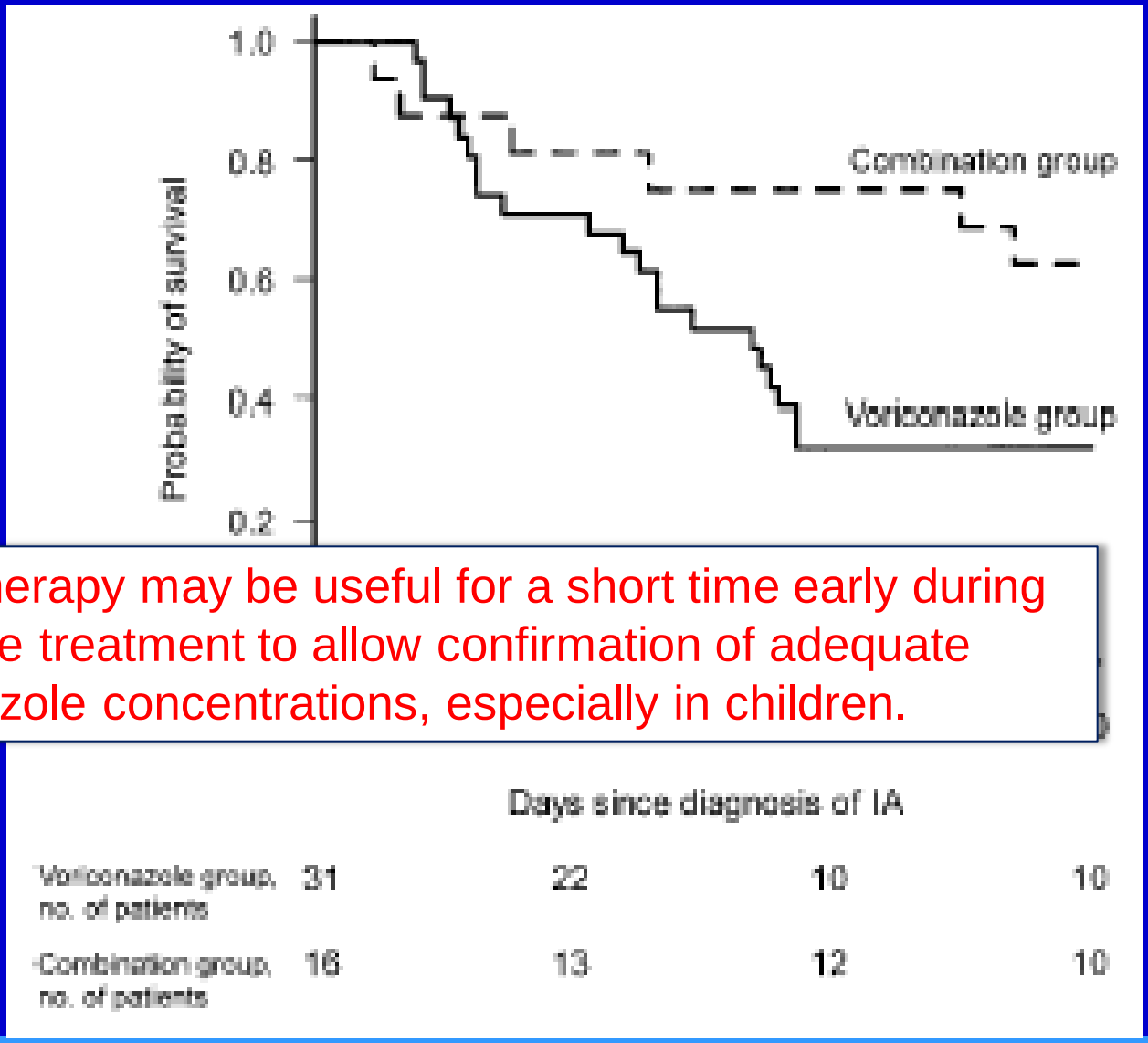
Combination therapy (voriconazole + caspofungin)

Retrospective
AmB failures
Most HSCT
30/47 proven IA

Multivariate analysis
P=0.008 for combination and survival



Combination therapy may be useful for a short time early during voriconazole treatment to allow confirmation of adequate voriconazole concentrations, especially in children.

Marr et al, Clin Infect Dis 2004:39:797

Arguments for not using voriconazole?

1. Amphotericin B is a broader spectrum agent – No
2. AmBisome is equivalent to voriconazole in IA – No
3. Patient was on itraconazole prophylaxis – No
4. The patient has cerebral aspergillosis – No (beware interactions, especially phenytoin)
5. The patient might have azole resistant *Aspergillus* – maybe
6. Major drug interactions – yes sometimes
7. Renal failure – only if IV therapy needed for any duration
8. My patient is a young child and I am worried about blood levels – yes use 9mg/Kg BD (200mg BD orally) and consider combination therapy with an echinocandin and measure levels

Choice of antifungal for invasive aspergillosis

Priority sequence

- Voriconazole (unless drug interaction)
- Micafungin/caspofungin (if not neutropenic)

OR

- AmBisome 3mg/Kg (if not 'nephro-critical')

3. Posaconazole (oral only, if no drug interactions)
4. Itraconazole

When not to use voriconazole as primary therapy?

Absolute contraindications

- Drug interactions (ie rifampicin, carbamazepine, phenytoin etc)
- Voriconazole used as prophylaxis (but not itraconazole or posaconazole)
- Resistance to voriconazole (esp zygomycosis, *A. lentulus* or azole resistance in *A. fumigatus*)

Relative contraindications

- Renal failure (IV only)
- Young children (need higher dose ?+ other agent)
- Severe hepatic dysfunction
- Interacting drugs (ie sirolimus)

Conclusions

- Voriconazole is the treatment of choice for invasive aspergillosis
- For those with toxicity, significant drug interactions or azole resistance, an echinocandin or lipid AmB is appropriate
- Current treatments are partially successful but more oral therapies are needed
- Isolates of *Aspergillus* should be susceptibility tested, if treatment given