Application of PK/PD concepts and the role of TDM in the management of patients with fungal disease

The role of combination therapy as of May 2011

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Conflict of interest disclosure

- Speaker board
  - Astellas
  - BMS
  - Gilead
  - MSD
  - Novartis
  - Pfizer
- Research grant for my institution
  - Abbott
  - BMS
  - Gilead
  - Pfizer
- International Principal Investigator
  - MSD
- Local Principal Investigator
  - Abbott
  - BMS
  - MSD
  - Pfizer
- No other conflict to disclose

In vivo pharmacodynamic characteristics of major antifungals

Drug class	Time course of activity		Pharmacodynamic parameter	
	Killing	PAFE	Type	Magnitude*
Triazole	Static	Long	AUC_{free}/MIC	20 - 25
Polyene	Cidal	Long	Peak/MIC	4 (10)
Flucytosine	Static	Short	T > MIC	25 %
Echinocandin	Cidal/Static	Long	Peak/MIC	3 (10)
Sordarin	NA	NA	AUC/MIC	NA

* to achieve 50% of maximal effect
( ) maximal efficacy

Andes D, AAC, 2003, modified

AMPHOTERICIN B

PK-PD correlation: C_{max}/MIC = 4 (10)

Concentration-dependent effects and prolonged PAFE suggest:

- Is important to achieve to achieve high peak concentrations
- Large daily doses given relatively rapidly should exert optimal efficacy (prolonged infusion is in contrast with PK/PD optimization)
- Dose escalation might be more effective than standard doses

Groll AH et al., Pharmacotherapy, 2001; Mukherjee PK et AL., Clin Microbiol Rev, 2005

Walsh TJ, Goodman JL, Pappas P,
Bekersky I, Buell DN, Roden M,
Barrett J, Anaissie EJ.

Safety, tolerance, and pharmacokinetics of high-dose liposomal amphotericin B (AmBisome) in patients infected with Aspergillus species and other filamentous fungi: maximum tolerated dose study (7.5-15mg/kg/day)

Antimicrob Agents Chemother 2001 Dec; 45 (12): 3487-96

AmBisome®

Maximum Tolerated Dosage (MTD) study

- MTD was not reached with doses up to 15 mg/kg/day
- Drug was well tolerated at all 4 dosing regimens
- No dose-related differences observed for
  - Nephrotoxicity*
  - Infusion-related reactions
  - Drug discontinuations because of adverse events
  - Hepatotoxicity
  - Anaemia
- Severe hypokalaemia observed at 12.5- and 15-mg/kg/day dose levels (9 of 26 [35%] patients)
- Nonlinear pharmacokinetics over dose range of 7.5 to 15 mg/kg/day
- Cmax and AUC reached maximal values at a dose of 10 mg/kg/day

* Serum creatinine ≥ 2.0 × baseline.

Walsh TJ, et al. *Antimicrob Agents Chemother.* 2001;45:3487-3496.

Liposomal Amphotericin B as Initial Therapy for Invasive Mold Infection: A Randomized Trial Comparing a High–Loading Dose Regimen with Standard Dosing (AmBiLoad Trial)

Oliver A. Cornely, Johan Maertens, Mark Bresnik, Ramin Ebrahimi, Andrew J. Ullmann, Emilio Bouza, Claus Peter Heussel, Olivier Lortholary, Christina Rieger, Angelika Boehme, Mickael Aoun, Heinz-August Horst, Anne Thiebaut, Markus Ruhnke, Dietmar Reichert, Nicola Vianelli, Stefan W. Krause, Eduardo Olavarria, and Raoul Herbrecht, for the AmBiLoad Trial Study Group[a]

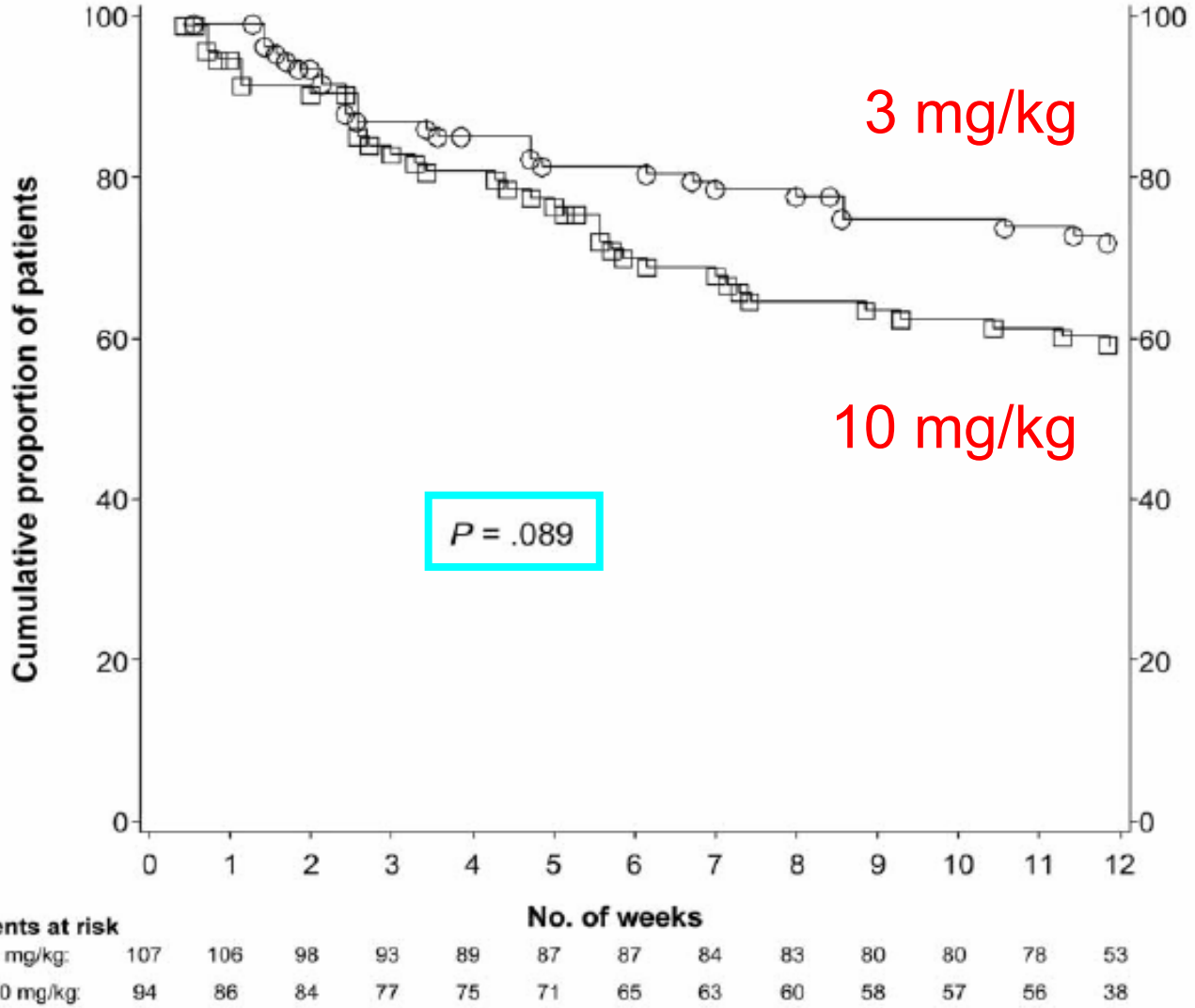
Clinical Infectious Diseases 2007; 44:1289–97

Favourable overall response

Pt group or characteristic	Patients (%) with favourable response, by AmphoB dosage		Difference, % (95% CI)
	3 mg/kg/day	10 mg/kg/day	
All pts	50	46	4 (-10, 18)
All pts with aspergillosis	50	46	4 (-10, 18)
Pts with microbio. confirmed aspergillosis	39	42	-3 (-26, 18)
Pts with diagnosed aspergillosis (halo sign)	56	48	8 (-10, 26)
Allogeneic stem cell transplant			
Yes	47	50	-3 (-36, 30)
No	50	45	5 (-10, 20)
Haematologic malignancy			
Controlled	53	45	-1 (-26, 24)
Uncontrolled	48	44	4 (-14, 21)
Neutropenia at BL			
Yes	43	42	1 (-15, 17)
No	67	57	10 (-18, 37)
Pulmonary infection	51	48	3 (-11, 18)
Extrapulmonary infection	33	30	3 (-39, 45)

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

Survival with AmphoB



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

AmBiLoad Trial: Laboratory Abnormalities

N (%)	AmBi-3mg N=115	AmBi-10mg N=111	P-value
Nephrotoxicity[1]	16/111 (14)	31/100 (31)	<0.01
Hypokalaemia			
K^+ <3.0 (grade 3)	18/113 (16)	32/106 (30)	0.015
K^+ <2.5 (grade 4)	3/113 (3)	4/106 (4)	NS
LFT abnormalities[2]	18 (16)	16 (14)	NS

1. Serum creatinine > 2x baseline
2. Treatment emergent grade 3 or 4 values of ALT, AST, alkaline phosphatase, or bilirubin

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

12 Week Survival: Adjusting Treatment Effect by Predictive Factors

AmBi-3 (72%) vs AmBi-10 (59%)	P-value*
• Unadjusted	0.053
• Adjusted for	
● Allo-SCT	0.078
● Uncontrolled malignancy	0.078
● Allo-SCT + Uncontrolled malignancy	0.12

*P-value for treatment effect (3 mg/kg vs 10 mg/kg) on survival at 12 weeks

Survival driven by underlying risk factors, not treatment dose received

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

Ambisome in aspergillosis

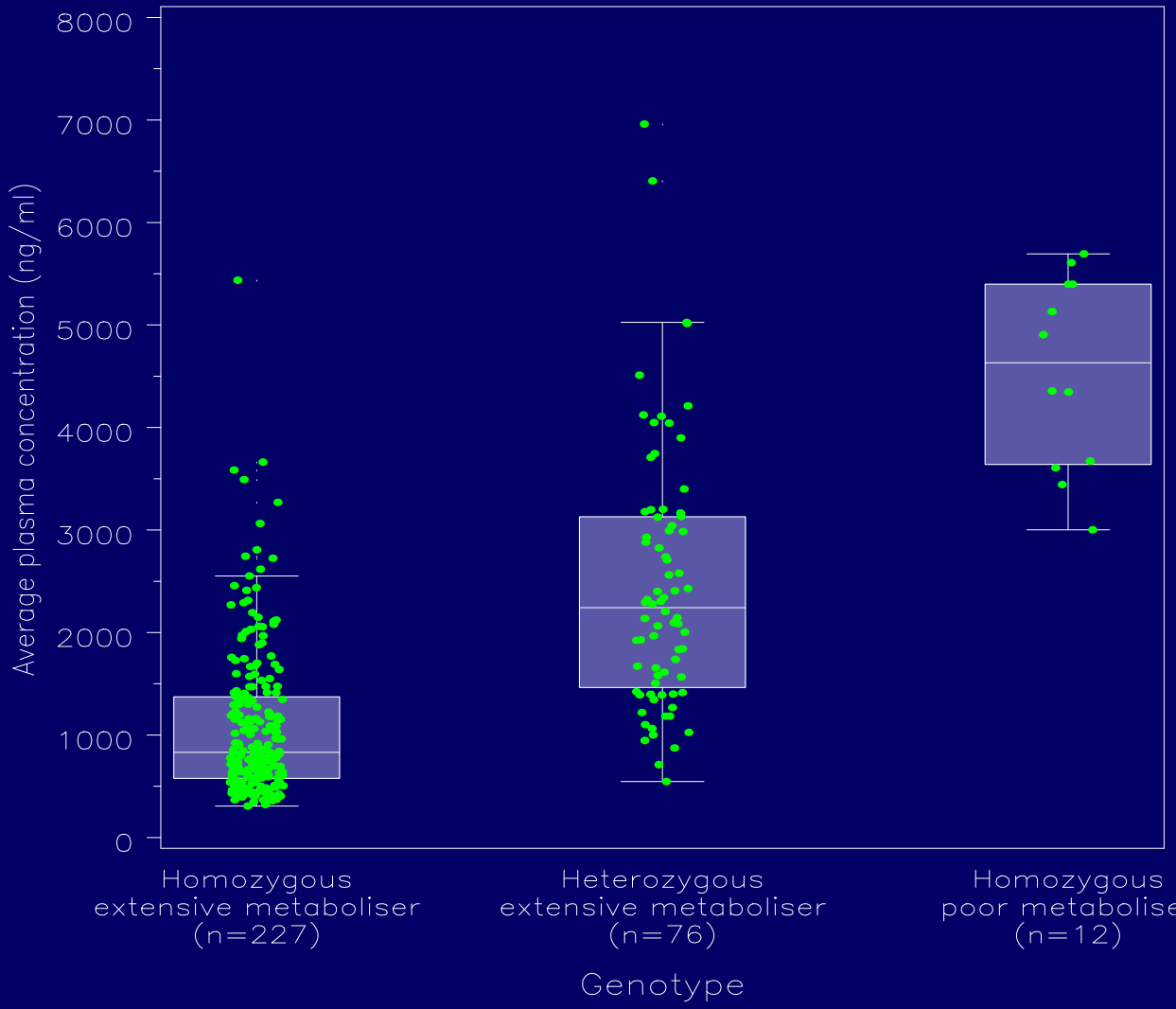
- **Ambisome is effective in invasive aspergillosis**
- **No benefit to increase the dose to 10 mg/kg probably because of excess toxicity**

Cornely et al., CID 2007, 44: 1289

New approaches in the use of lipid AmB

- Aerosol in prophylaxis
- High dose every 7-15 days for prophylaxis
  - Low concentrations in blood
  - High concentrations in tissues

Pharmacokinetics of Voriconazole
Influence of CYP2C19 genotype



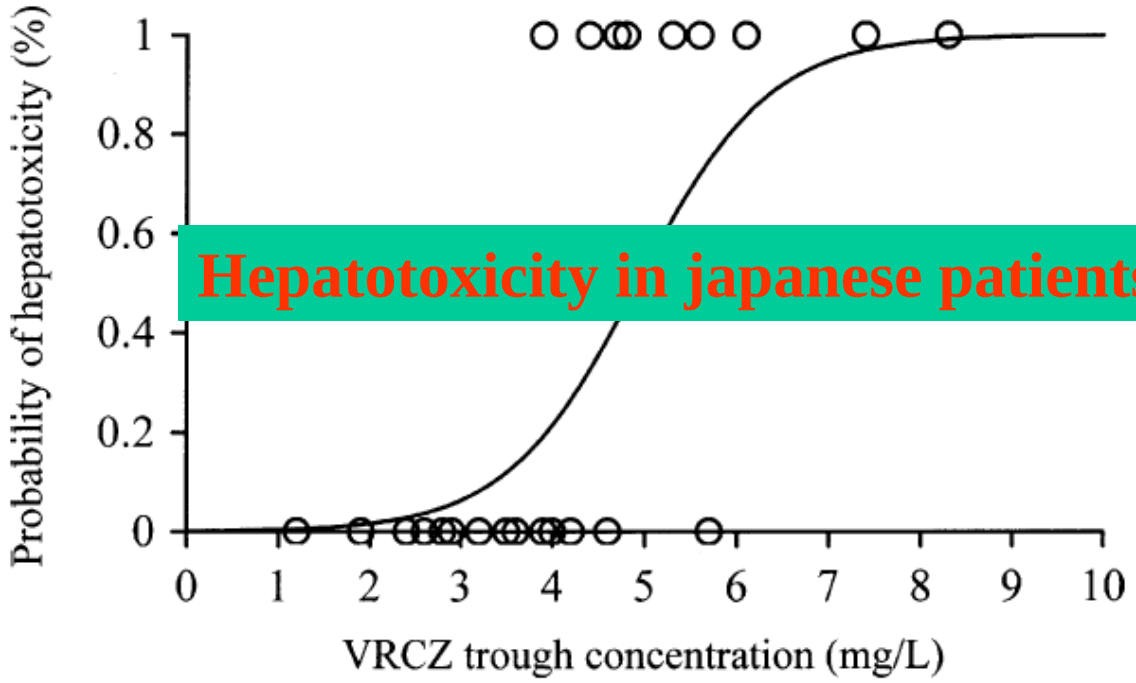
FDA - Briefing document for Voriconazole - Pfizer, October 2001
courtesy of Dr. N. Wood, Pfizer Central Research

Voriconazolo & TDM

International Journal of Antimicrobial Agents 34 (2009) 91–94

Correlation between voriconazole trough plasma concentration and hepatotoxicity in patients with different CYP2C19 genotypes

Kazuaki Matsumoto[a], Kazuro Ikawa[b], Kazuko Abematsu[a], Naoko Fukunaga[a], Kentaro Nishida[a], Tomohide Fukamizu[a], Yoshihiro Shimodozono[a], Norifumi Morikawa[b], Yasuo Takeda[a,*], Katsushi Yamada[a]



Hepatotoxicity in japanese patients: 34.5%

Fig. 1. Voriconazole (VRCZ) trough concentration and logistic regression model for hepatotoxicity (absence, $n = 19$; presence, $n = 10$).

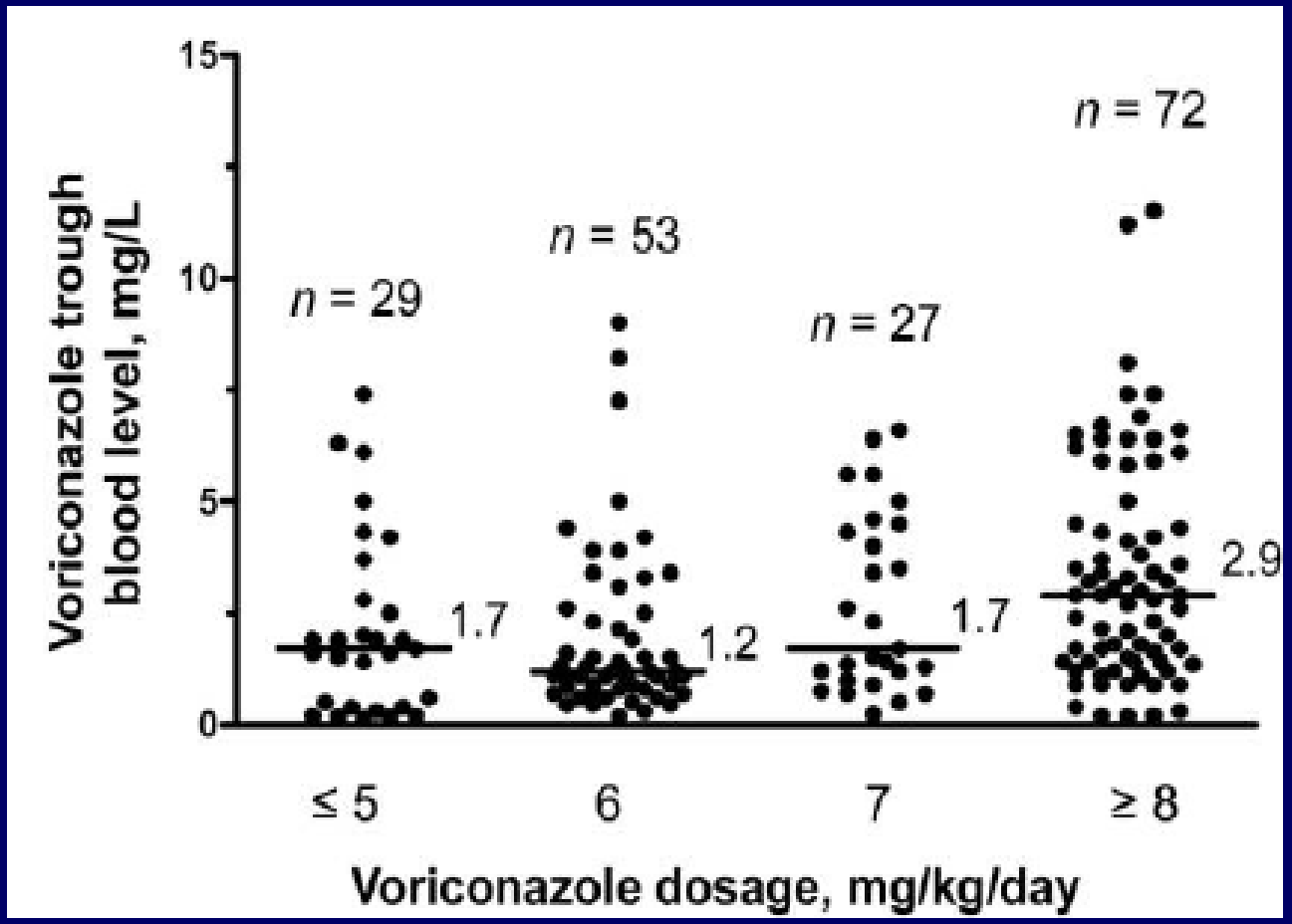
Cytochrome P450 interactions for the azoles

Drug	CYP3A4		CYP2C8/9		CYP2C19	
	Inhibitor	Substrate	Inhibitor	Substrate	Inhibitor	Substrate
Posaconazole[1]	√					
Fluconazole[2,3]	√		√			
Itraconazole[2-4]	√	√	√			
Ketoconazole[2,3,5]	√	√	√			
Voriconazole[3,6,7]	√	√	√	√	√	√

The results from in vitro and in vivo cytochrome P450 interactions do not necessarily predict clinical drug interactions

1. Wexler D et al. *Eur J Pharm Sci*. 2004;21:645-653.
2. Cupp MJ et al. *Am Fam Phys.* 1998;57:107-116.
3. Drug interactions. *Med Letter*. 2003;45(W1158B):46-48.
4. Sporanox IV [summary of product characteristics]. Bucks, UK; Janssen-Cilag Ltd; 2005.
5. Nizoral tablets [summary of product characteristics]. Bucks, UK; Janssen-Cilag Ltd; 2001.
6. Hyland R et al. *Drug Metab Dispos.* 2003;31:540-547.
7. VFEND [summary of product characteristics]. Kent, UK; Pfizer Ltd; 2005.

Voriconazole: variability of blood concentrations



Pascual A et al. CID 2008; 46:201-211

Voriconazole trough blood levels and clinical response to antifungal therapy

Variable	Voriconazole trough blood level ≤1 mg/L (*n* = 13)	Voriconazole trough blood level >1 mg/L (*n* = 39)	*P*
Route of voriconazole administration			.05
Intravenous	4 (31)	24 (61)	
Oral	9 (69)	15 (39)	
Voriconazole dosage, median mg/kg/day (range)			
Overall	7 (2.5–9)	8 (2–11)	NS
Intravenous	7.5 (7–8)	8 (6–11)	NS
Oral	6 (2.5–9)	7 (2–11)	NS
Response to antifungal therapy			
Interval between start of voriconazle therapy and assessment, median days (range)	21 (10–120)	17.5 (10–180)	NS
Treatment success			
Overall	7 (54)[a]	34 (88)	.02
Complete response	5	27	
Partial response	2	7	
Lack of response	6 (46)	5 (12)	
Persistence	3 (23)	0 (0)	
Progression	3 (23)	4 (10)	
Breakthrough IFI	0 (0)	1 (2)	

Pascual A et al. CID 2008; 46:201-211

Voriconazole trough blood levels and safety of antifungal therapy

Variable	Vor trough blood level ≤5.5 mg/L (*n* = 36)	Vor trough blood level >5.5 mg/L (*n* = 16)	*P*
Vor route			.07
Intravenous	15 (42)	13 (81)	
Oral	21 (58)	3 (19)	
Vor dosage, median mg/kg/day (range)			
Overall	7 (2–11)	8 (6–11)	.13
Intravenous	7.5 (6–10)	8 (6–11)	NS
Oral	6 (2–11)	7 (6–8)	NS
Serious adverse event			
Encephalopathy			
Incidence	0	5 (31)	.002
Interval after start of Vor, days (range)	NA	9 (5–30)	
Cholestatic hepatopathy			
Incidence	3 (8)	3 (19)	NS
Interval after start of Vor, days (range)	50 (5–150	13 (6–20)	NS
Concomitant therapy			
Omeprazole	6 (17)	7 (44)	.04
Tacrolimus	0	1 (6)	NS

Pascual A et al. CID 2008; 46:201-211

Voriconazole TDM

Internal protocol for voriconazole testing, indications for TDM:

- day 4 after starting therapy;
- weekly during the first 42 days of therapy;
- anytime upon clinical indication, particularly inf treatment failures, toxicity or modified dosing.

Therapeutic range: 1–5.5 µg/ml (**Pasqual et al, CID 2008).**

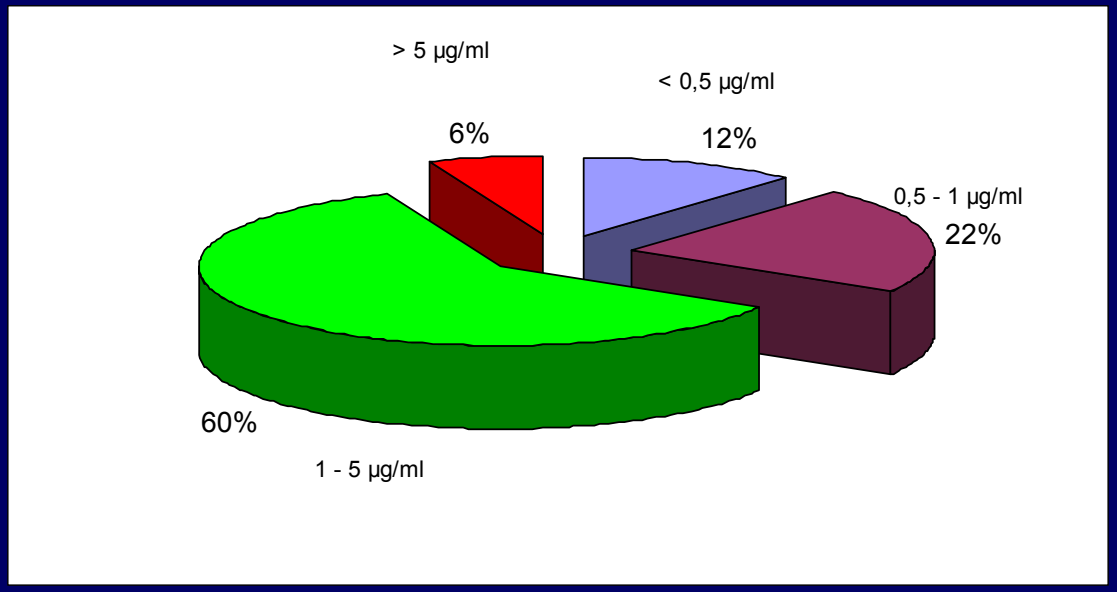
Voriconazole TDM in our center

From January 2010, 452 samples from 56 patients (both paediatric and adults) were tested for TDM

Medium number of samples per patient was 8 (range: 1-33)

Median voriconazole concentration was 1.7 µg/ml, ranging from 0.1 µg/ml to 11.2 µg/ml

Distribution of voriconazole levels:



53 samples - < 0.5 µg/ml

99 samples - 0.5-1 µg/ml

272 Samples -1-5

28 samples - > 5 µg/ml

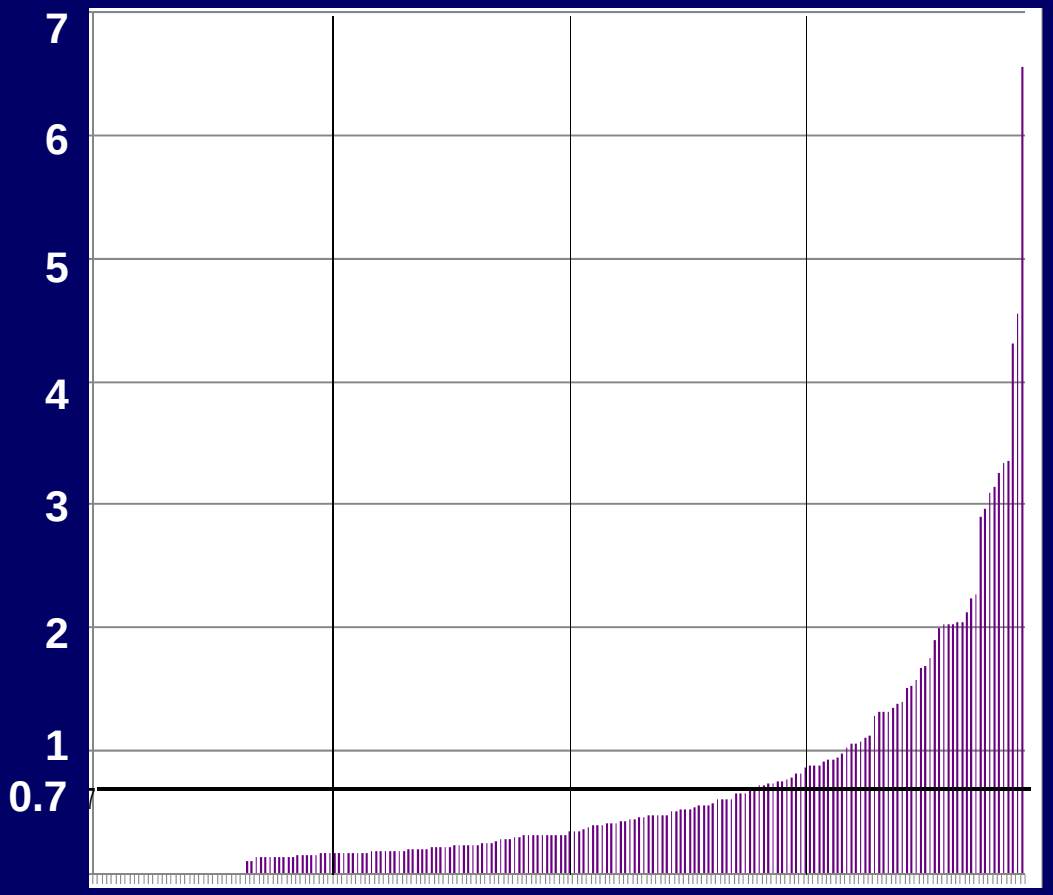
Quality controls

We participate in the International Interlaboratory Quality Control Program for Therapeutic Drug Monitoring of Voriconazole organised by the Dutch Association for Quality Assesment in Therapeutic Drug Monitoring and Clinical Tossicology (KKGT).

The objectives of the program are to define sources of error in bioanalytical methods, to contribute to the optimisation of the bioanalysis of antifungal drugs and to establish interconvertibility of results among laboratories and methods and comparison of interpretations and dosage recommendations.

Posaconazole Therapeutic Drug Monitoring: A Reference Laboratory's Experience

- POS serum drug levels have wide interpatient variability
- Posaconazole FDA briefing document recommends a serum level of >0.7 µg/mL
- Reference laboratory reported undetectable levels in 16.3% of samples; and 70.3% less than 0.7 µg/mL.



Thompson GR, et al. *Antimicrob Agents Chemother* 2009;.

Courtesy
Tom Patterson

Posaconazolo & TDM

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2009, p. 5224–5229 Vol. 53, No. 12
0066-4804/09/$12.00 doi:10.1128/AAC.00939-09
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Therapeutic Drug Monitoring of Posaconazole: a Monocentric Study with 54 Adults[▽]

David Lebeaux,[1,2] Fanny Lanternier,[1,2*] Caroline Elie,[1,3] Felipe Suarez,[1,4] Agnès Buzyn,[1,4] Jean-Paul Viard,[1,2] Marie-Elisabeth Bougnoux,[1,5] Marc Lecuit,[1,2,6] Vincent Jullien,[1,7] and Olivier Lortholary[1,2,8]

- Retrospective, 54 patients
- 36 prophylaxis (200mgx3), 18 treatment (400mgx2)
- A low POSA plasma concentration was defined as < 500 ng/ml.
- 44% (16/36) in the prophylaxis group and 22% (4/18) in the treatment group had low levels
- Low levels were more frequent in case of diarrhaea (71% vs 27%)
- 2 breakthough IFI, both with low levels

Posaconazole in healthy volunteers

- Absorption improved
  - –With fat meal
  - –With any meal or nutritional supplement
  - –Coke-like drink
  - –By subdividing doses (4x)
  - –Avoiding proton pump inhibitors
- Absorption seems to worsen if drug administered through naso-gastric tube

Table 8. Posaconazole plasma concentration versus global response in patients with invasive aspergillosis (MITT subset).

Quartile	No. of subjects[a]	Plasma C_{max} Mean ng/mL	Plasma C_{max} CV, %	Plasma C_{avg} Mean ng/mL	Plasma C_{avg} CV, %	No. (%) of responders
1	17	142	51	134	45	4 (24)
2	17	467	27	411	21	9 (53)
3	17	852	15	719	12	9 (53)
4	16	1480	16	1250	28	12 (75)

Walsh et al, CID 2007

Exposure–Response of Posaconazole Used for Prophylaxis Against Invasive Fungal Infections: Evaluating the Need to Adjust Doses Based on Drug Concentrations in Plasma

SH Jang[1], PM Colangelo[1] and JVS Gobburu[1]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 88 NUMBER 1 | JULY 2010

Table 1 Posaconazole steady-state average plasma concentrations (C_{avg}) vs. clinical failure rate following administration of POS 200 mg t.i.d. in hematopoietic stem cell transplant recipients also receiving immunosuppressive therapy for graft-vs.-host disease (study 1) and in patients undergoing chemotherapy for acute leukemia or myelodysplastic syndromes (study 2)

	Study 1 ($N = 252$)[a]		Study 2 ($N = 215$)[a]	
Quartile	Posaconazole C_{avg} (ng/ml)[b]	Clinical failure rate	Posaconazole C_{avg} (ng/ml)[b]	Clinical failure rate
1st Q	21.5–557 (289)	44% (28/63[c])	89.65–322 (206)	55% (29/53)
2nd Q	557–915 (736)	21% (13/63)	322–490 (406)	37% (20/54)
3rd Q	915–1,563 (1,239)	18% (11/63)	490–733.5 (612)	46% (25/54)
4th Q	1,563–3,650 (2,607)	18% (11/63)	733.5–2,200 (1,467)	28% (15/54)

Antifungal Therapeutic Drug Monitoring: Established and Emerging Indications[▽]

David Andes,[1]* Andres Pascual,[2] and Oscar Marchetti[2]

AAC 2009

TABLE 3. Evidence for and against monitoring of blood levels during azole therapy

Evidence for monitoring of blood levels during azole therapy	Evidence against monitoring of blood levels during azole therapy
Large and unpredictable variability of blood levels	Real-time measurements not routinely available
Multiple factors influencing drug absorption, distribution, and elimination, including age, genetic background, compliance and gastrointestinal function, comedication, and liver and/or renal dysfunction	Target blood levels not established; lacking data from prospective controlled studies systematically exploring efficacy and toxicity associated with drug over- or underdosing
Emergence of fungal pathogens with decreased susceptibility requiring optimal adjustment of drug exposure	Drug blood concn might not reflect exposure and efficacy in infected tissues
Multiple clinical reports of failure associated with drug underdosing and toxicity associated with drug overdosing	

TABLE 4. Tentative recommendations for monitoring of blood levels during antifungal therapy

Drug	Indication	Time of first measurement after start of therapy (days)	Target blood concn[a] (μg/ml) for:	
			Efficacy	Safety
Flucytosine	Routine during first wk of therapy, renal insufficiency, lacking response to therapy	3–5	Peak of >20	Peak of <50
Itraconazole	Routine during first wk of therapy, lacking response, gastrointestinal dysfunction, comedication	4–7	For prophylaxis, trough of >0.5; for therapy, trough of >1 to 2	NA
Voriconazole	Lacking response; gastrointestinal dysfunction; comedication; children; intravenous-to-oral switch; severe hepatopathy; unexplained neurological symptoms/signs	4–7	For prophylaxis, trough of >0.5; for therapy, trough of >1 to 2	Trough of <6
Posaconazole	Lacking response; gastrointestinal dysfunction, therapy with proton pump inhibitors; comedication	4–7	For prophylaxis, trough of >0.5; for therapy, trough of >0.5 to 1.5	NA

[a] Total or bound and unbound drug concentrations. NA, not applicable.

Recommendations for antifungal drug monitoring

Antifungal agent	Drug monitoring recommended	Indication for drug monitoring	Timing of sample	Target range (mg/l)
Amphotericin B and lipid-based preparations	No	–	–	–
Echinocandins	No	–	–	–
5-FC	Routine	To monitor for toxicity	2h post dose	< 100
Fluconazole	(No)	Consider if renal insufficiency, suspected non-compliance or malabsorption	After 5-10 days of therapy	Unknown
Itraconazole	Targeted	To ensure adequate absorption, therapeutic concentration	Trough after steady state reached (4-5 days)	> 0.5
Voriconazole	Targeted	To detect therapeutic and toxic concentrations	Peak and Trough after steady state reached (1-2 days)	2-6
Posaconazole	(No)?	Consider if suspected malabsorption	Trough after steady state reached (5-6 days)	Unknown Peak >1.48mg/l*

*data based on treatment of *Aspergillus*

Worth LJ et al., Internal Medicine Journal, 2008, Goodwin ML & Drew RH, J Antimicrob Chemother, 2008

Application of PK/PD concepts and the role of TDM in the management of patients with fungal disease

The role of combination therapy as of May 2011

WHAT WE CAN EXPECT FROM COMBINATION ANTIFUNGAL THERAPY

- **Possible benefit**
  - Improved clinical efficacy
  - Reduced dosages
- **Possible disadvantage**
  - Risk of antagonism
  - Increased toxicity
  - Increased cost

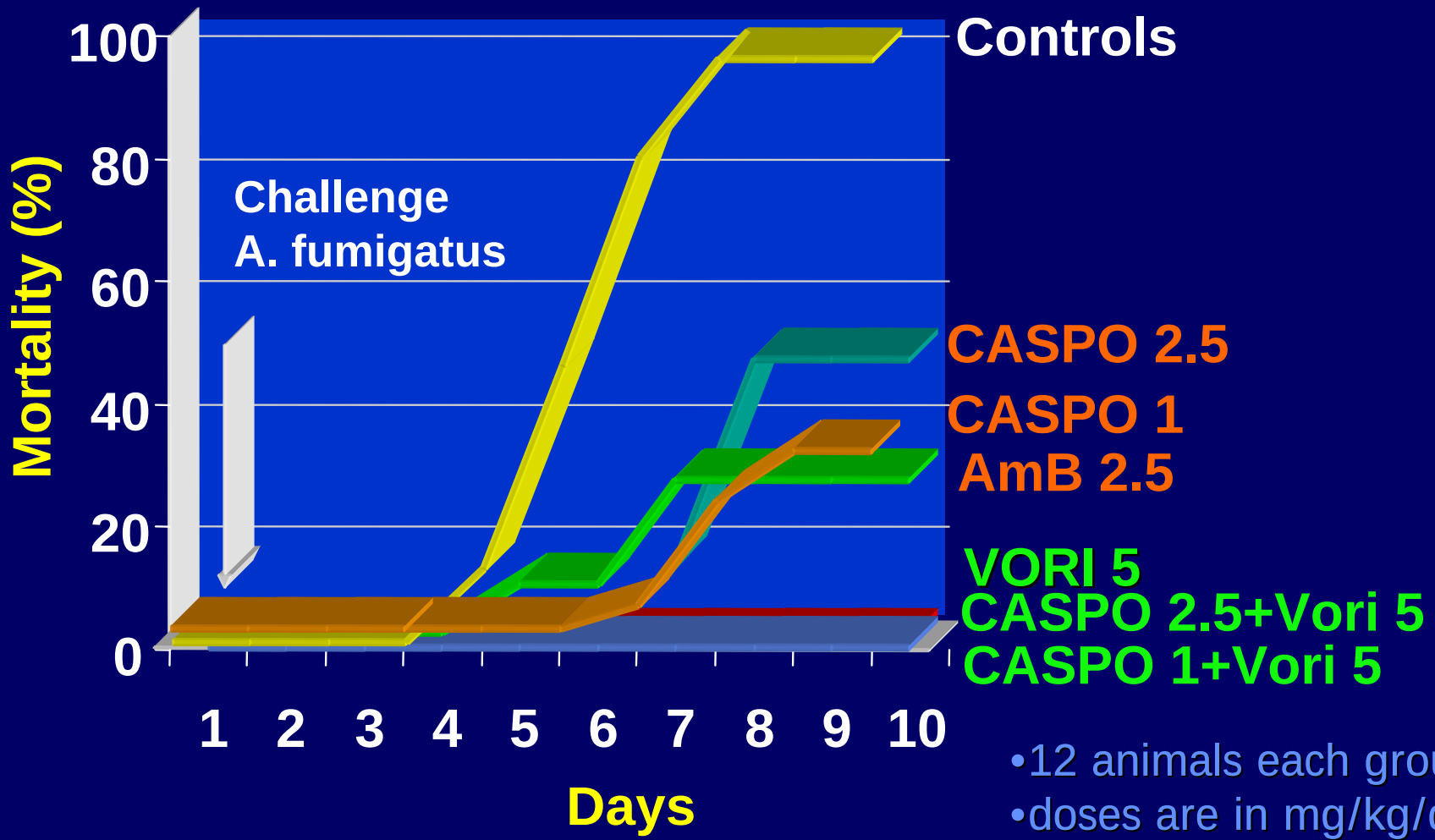
A methodological algorythm for showing that combination therapy is more effective than monotherapy

- In vitro studies
- Animal models
- Clinical trials

Animal models

GUINEA PIG MODEL OF DISSEMINATED INVASIVE ASPERGILLOSIS

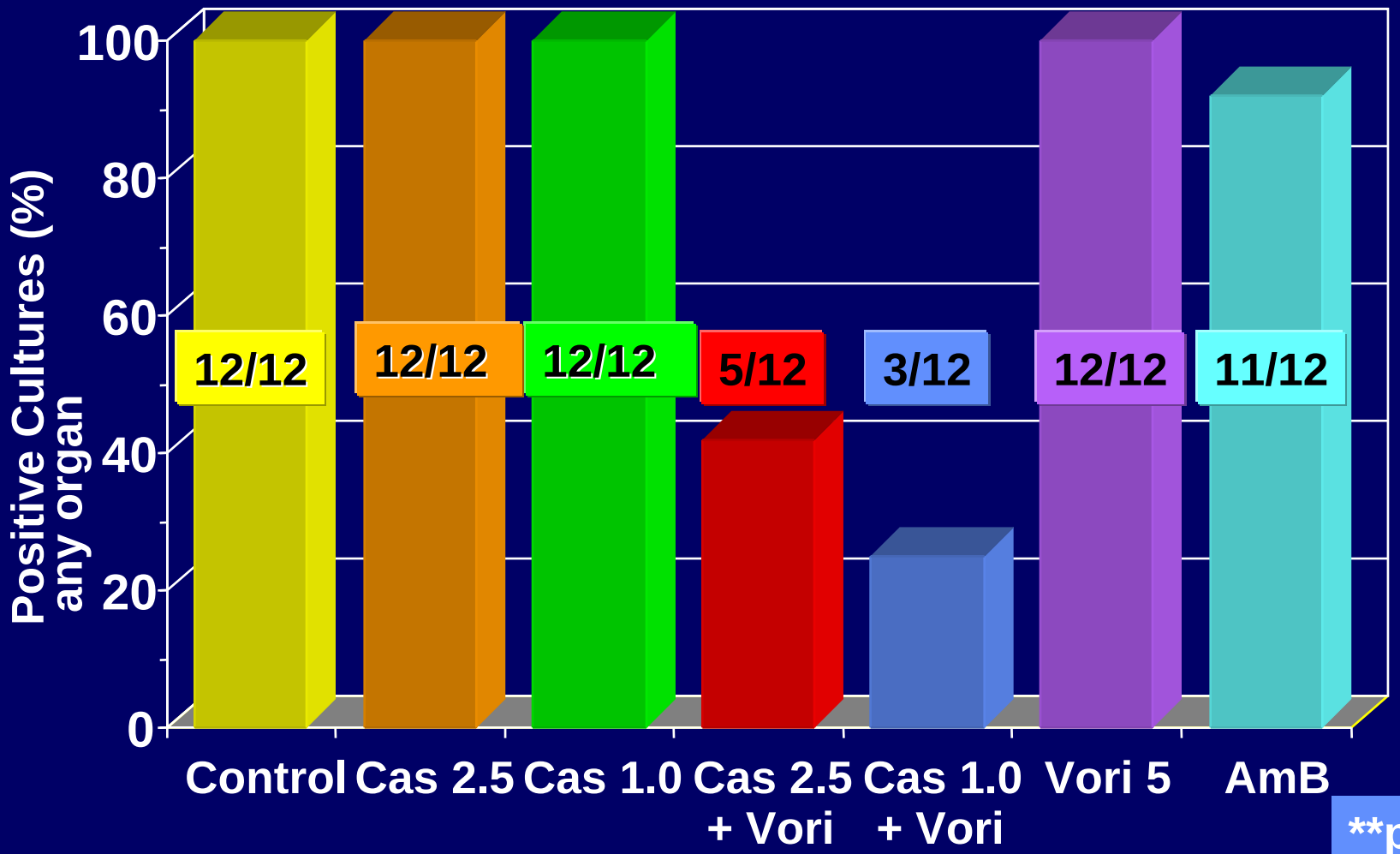
Kirkpatrick et al. Antimicrob Ag Chemother 2002



- 12 animals each group
- doses are in mg/kg/day

GUINEA PIG MODEL ORGAN CULTURES OF DISSEMINATED INVASIVE ASPERGILLOSIS

Kirkpatrick et al. Antimicrob Ag Chemother 2002

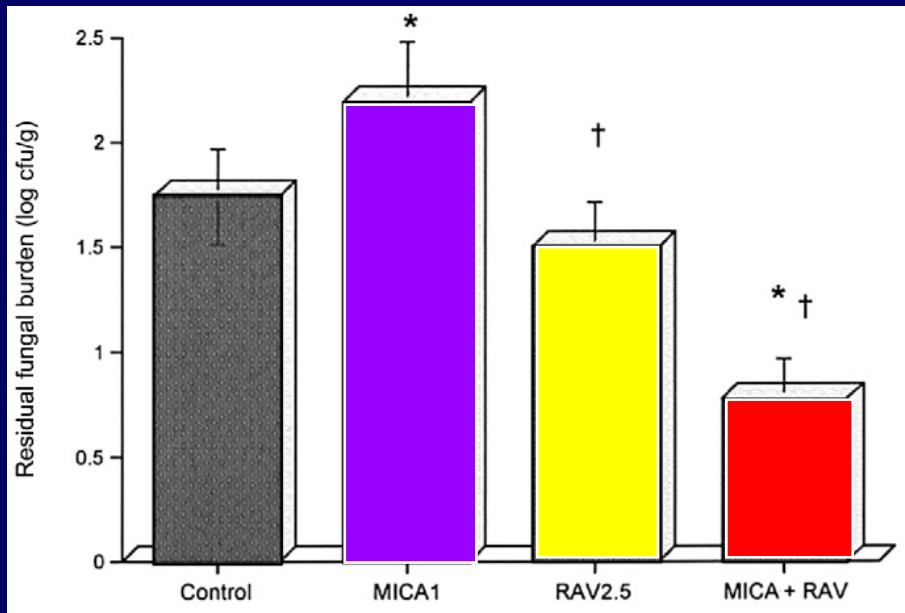


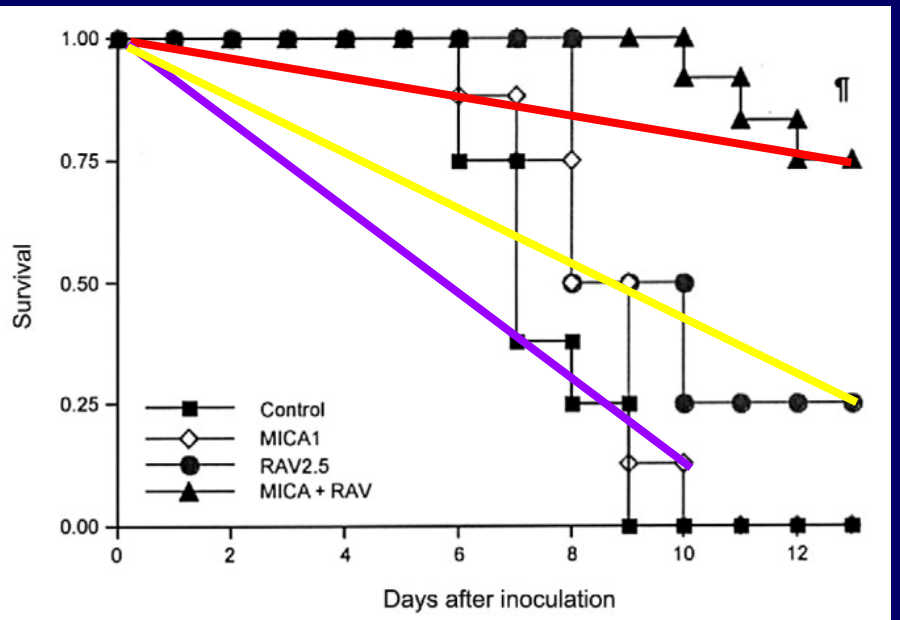
**p<.0025

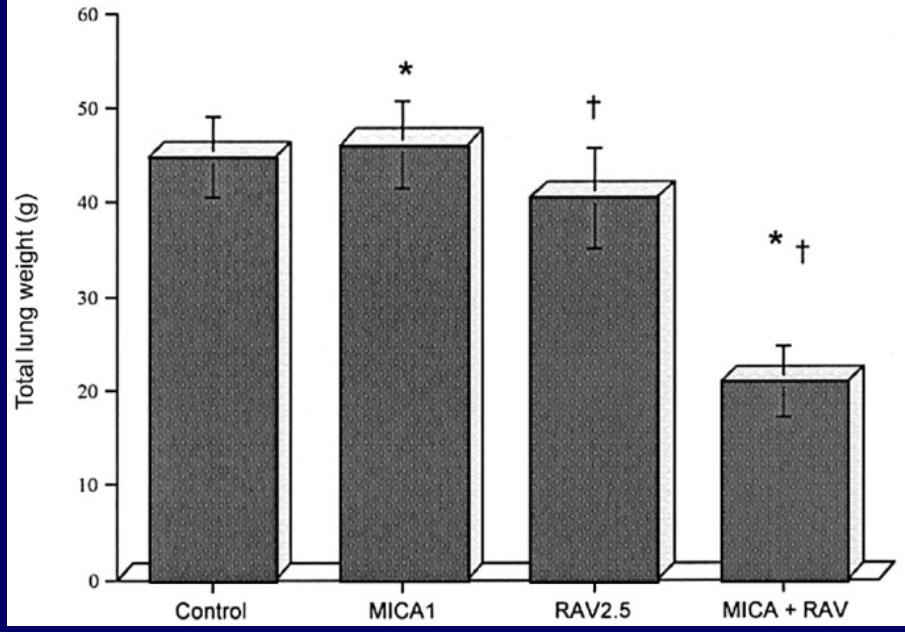
Combination Therapy in Treatment of Experimental Pulmonary Aspergillosis: Synergistic Interaction between an Antifungal Triazole and an echinocandin

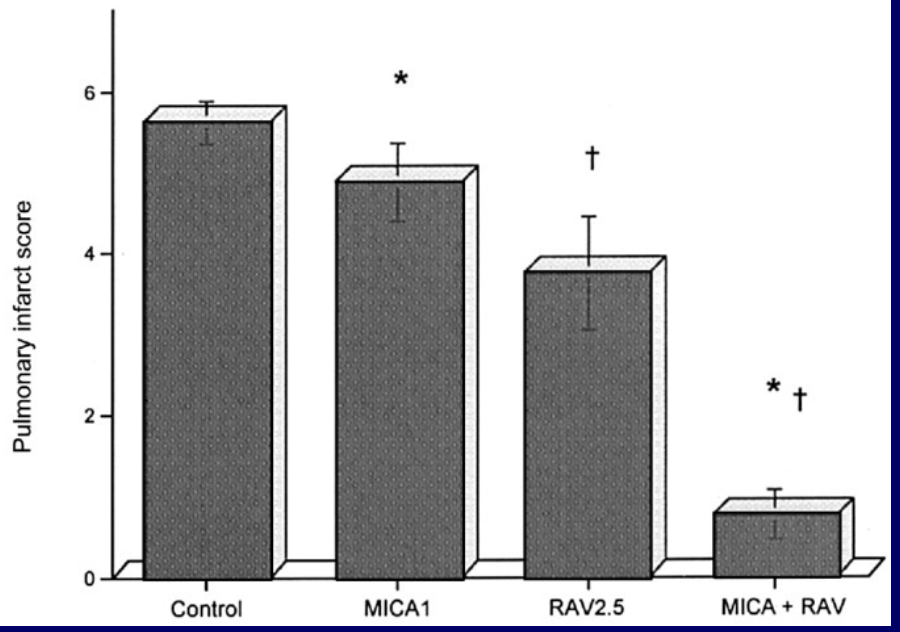
Vidmantas Petraitis, Ruta Petraitiene, Alia A. Sarafandi, Amy M. Kelaher, Caron A. Lyman, Heather E. Casler, Tin Sein, Andreas H. Groll, John Bacher, Nilo A. Avila, and Thomas J. Walsh

J. Infectious Disease 15 June 2003


Residual fungal burden (log cfu/g)
2.5
2
1.5
1
0.5
0
*
†
* †
Control
MICA1
RAV2.5
MICA + RAV


Survival
1.00
0.75
0.50
0.25
0.00
¶
Control
MICA1
RAV2.5
MICA + RAV
0
2
4
6
8
10
12
Days after inoculation


Total lung weight (g)
60
50
40
30
20
10
0
*
†
* †
Control
MICA1
RAV2.5
MICA + RAV


Pulmonary infarct score
6
4
2
0
*
†
* †
Control
MICA1
RAV2.5
MICA + RAV

PROBLEMS IN EVALUATING DATA FROM ANIMAL MODELS

- Methods for simulating the human disease
- Dosages (often chosen arbitrarily)
- Blood or tissue levels sometimes from those obtained in humans, with consequent different exposure

Antifungal Combination Therapy

Clinical Potential

John W. Baddley[1,2] and *Peter G. Pappas*[1]

Drugs 2005

Table III. Selected antifungal drug interactions for *Aspergillus* spp.[a]

Combination	*In vitro*	*In vivo*
Amphotericin B + flucytosine[54,86,103-105,112,113]	S, Add, I	S, Add, I
Amphotericin B + itraconazole[46,86,103,104,106]	Ant	Ant
Amphotericin B + fluconazole[103,104,106,115]	I, Ant	I
Amphotericin B + terbinafine[33,34]	Add, I	I
Amphotericin B + echinocandin[107-109,119-121]	S, Add, I	S, Add, I
Amphotericin B + rifampicin[34,86,104,112]	S, I	Add
ExS triazole + echinocandin[110,111,116-118]	S, Add	S, Add
Amphotericin B + ExS triazole[22]	I	ND
Itraconazole + nikkomycin Z[39]	S	ND

Clinical studies and guidelines

Cryptococcosis

Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America

John R. Perfect,[1] William E. Dismukes,[2] Francoise Dromer,[11] David L. Goldman,[3] John R. Graybill,[4] Richard J. Hamill,[5] Thomas S. Harrison,[14] Robert A. Larsen,[6,7] Olivier Lortholary,[11,12] Minh-Hong Nguyen,[8] Peter G. Pappas,[2] William G. Powderly,[13] Nina Singh,[10] Jack D. Sobel,[10] and Tania C. Sorrell[15]

Clinical Infectious Diseases 2010; 50:291–322

Table 2. Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Human Immunodeficiency Virus–Infected Individuals

Regimen	Duration	Evidence
Induction therapy		
AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)[a]	2 weeks	A-I
Liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, with renal function concerns) plus flucytosine (100 mg/kg per day)[a]	2 weeks	B-II
AmBd (0.7–1.0 mg/kg per day) or liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, for flucytosine-intolerant patients)	4–6 weeks	B-II
Alternatives for induction therapy[b]		
AmBd plus fluconazole	…	B-I
Fluconazole plus flucytosine	…	B-II
Fluconazole	…	B-II
Itraconazole	…	C-II
Consolidation therapy: fluconazole (400 mg per day)	8 weeks	A-I
Maintenance therapy: fluconazole (200 mg per day)[a]	⩾1 year[c]	A-I
Alternatives for maintenance therapy[b]		
Itraconazole (400 mg per day)[d]	⩾1 year[c]	C-I
AmBd (1 mg/kg per week)[d]	⩾1 year[c]	C-I

Table 3. Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Transplant Recipients

Regimen	Duration	Evidence
Induction therapy:[a] liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day) plus flucytosine (100 mg/kg per day)	2 weeks	B-III
Alternatives for induction therapy		
Liposomal AmB (6 mg/kg per day) or ABLC (5 mg/kg per day)	4–6 weeks	B-III
AmBd (0.7 mg/kg per day)[b]	4–6 weeks	B-III
Consolidation therapy: fluconazole (400–800 mg per day)	8 weeks	B-III
Maintenance therapy: fluconazole (200–400 mg per day)	6 months to 1 year	B-III

Invasive candidiasis

A Randomized and Blinded Multicenter Trial of High-Dose Fluconazole plus Placebo versus Fluconazole plus Amphotericin B as Therapy for Candidemia and Its Consequences in Nonneutropenic Subjects

John H. Rex, Peter G. Pappas, Adolf W. Karchmer, Jack Sobel, John E. Edwards, Susan Hadley, Corstiaan Brass, Jose A. Vazquez, Stanley W. Chapman, Harold W. Horowitz, Marcus Zervos, David McKinsey, Jeannette Lee, Timothy Babinchak, Robert W. Bradsher, John D. Cleary, David M. Cohen, Larry Danziger, Mitchell Goldman, Jesse Goodman, Eileen Hilton, Newton E. Hyslop, Daniel H. Kett, Jon Lutz, Robert H. Rubin, W. Michael Scheld, Mindy Schuster, Bryan Simmons, David K. Stein, Ronald G. Washburn, Linda Mautner, Teng-Chiao Chu, Helene Panzer, Rebecca B. Rosenstein, and Jenia Booth, for the National Institute of Allergy and Infectious Diseases Mycoses Study Group[a]

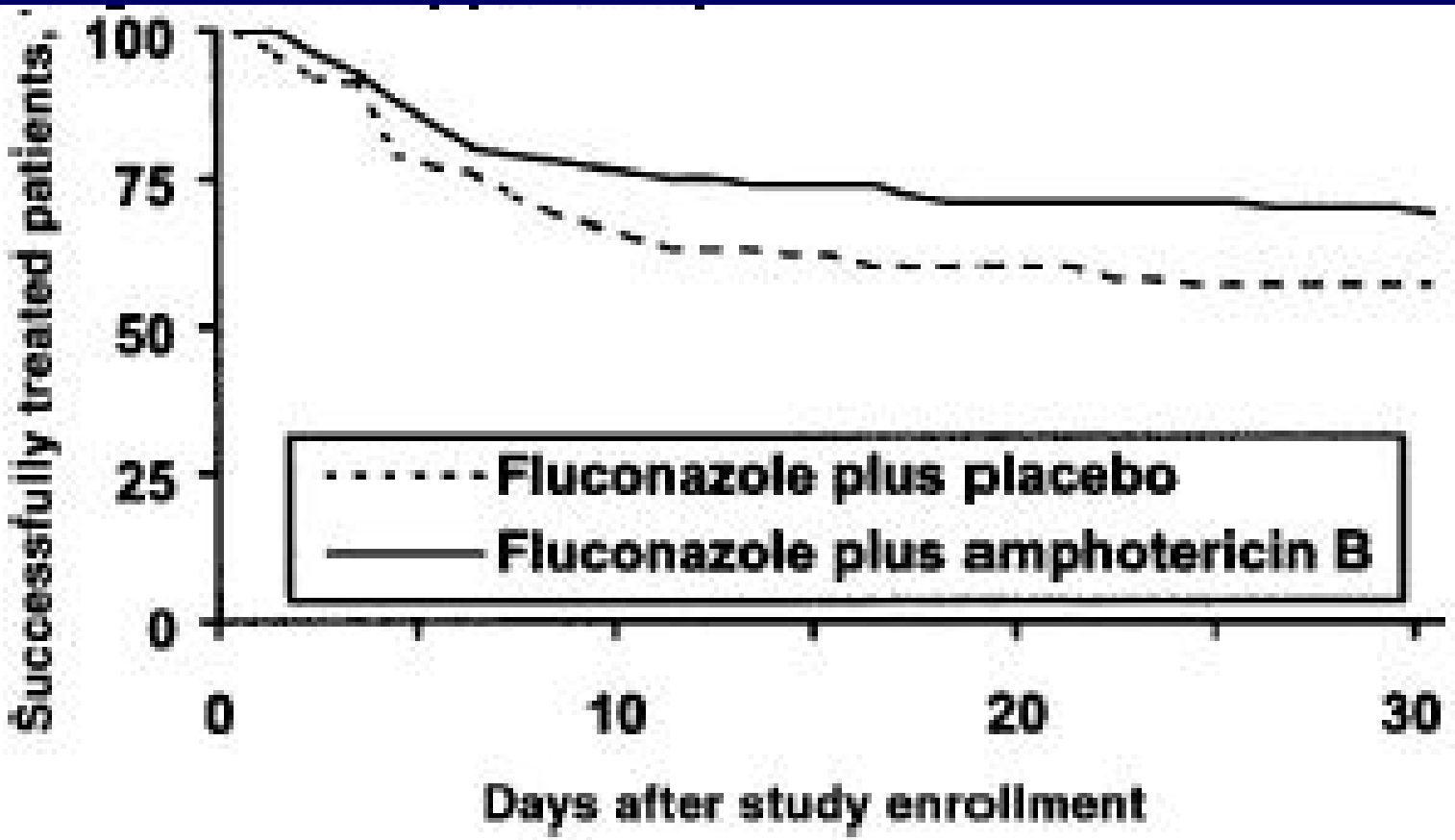


Figure 1. The proportion of subjects still successfully treated for the first 30 days of the study, by Kaplan-Meier analysis of time to failure. By the log-rank test, the 2 curves do not differ ($P = .08$). Success rates at 30 days were 57% for the fluconazole plus placebo group and 69% for the fluconazole plus amphotericin B group.

VORICONAZOLE

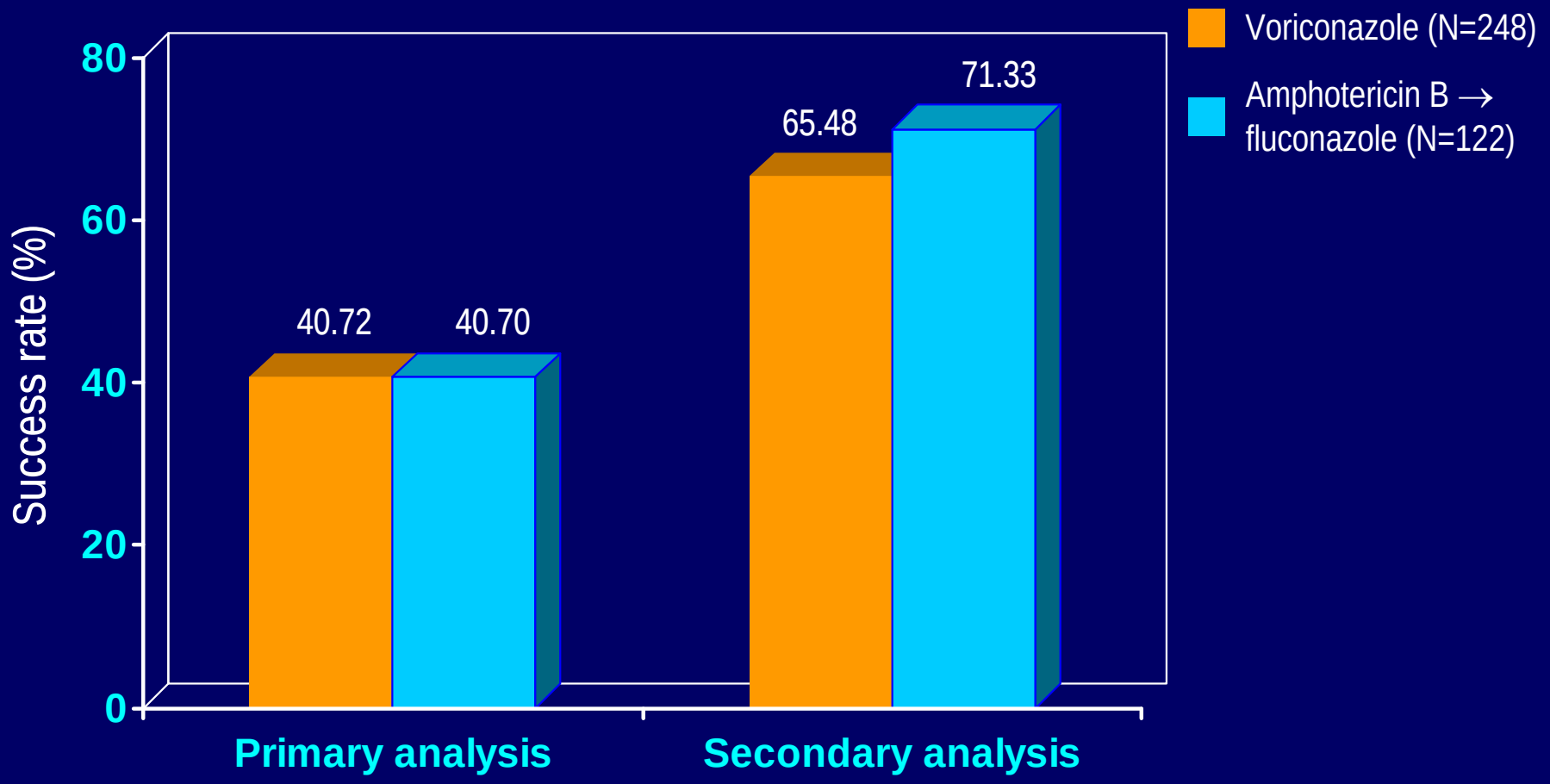
A Randomised, Open Label, Comparative, Multicenter Study of Voriconazole versus Conventional Amphotericin B Followed by Fluconazole in the Treatment of Candidemia in Non-neutropenic Subjects

Kullberg et al Lancet 2005

Treatment

- Voriconazole (IV for ≥ 3 days)
  - Loading 6 mg/kg IV q12h on day 1, followed by 3 mg/kg IV q12h
  - After 3 days, allowed switch to oral tablets at 200 mg q12h
- Amphotericin B → fluconazole
  - Amphotericin B IV at 0.7-1.0 mg/kg/day
  - After 3-7 days, allowed switch to IV or oral fluconazole at 400 mg qd
- Treatment for at least 14 days after resolution of candidemia, up to 8 weeks
- Follow-up 12 weeks

Primary and Secondary Analyses (MITT Population)



Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David Andes,[4] Daniel K. Benjamin, Jr.,[5] Thierry F. Calandra,[11] John E. Edwards, Jr.,[6] Scott G. Filler,[6] John F. Fisher,[7] Bart-Jan Kullberg,[12] Luis Ostrosky-Zeichner,[8] Annette C. Reboli,[9] John H. Rex,[13] Thomas J. Walsh,[10] and Jack D. Sobel[3]

Clin Infect Dis 2009

CNS candidiasis	LFAmB 3–5 mg/kg with or without 5-FC 25 mg/kg qid for several weeks, followed by fluconazole 400–800 mg (6–12 mg/kg) daily (B-III)	Fluconazole 400–800 mg (6–12 mg/kg) daily for patients unable to tolerate LFAmB	Treat until all signs and symptoms, CSF abnormalities, and radiologic abnormalities have resolved. Removal of intraventricular devices is recommended.
Candida endophthalmitis	AmB-d 0.7–1 mg/kg with 5-FC 25 mg/kg qid (A-III); or fluconazole 6–12 mg/kg daily (B-III); surgical intervention for patients with severe endophthalmitis or vitreitis (B-III)	LFAmB 3–5 mg/kg daily; voriconazole 6 mg/kg q12h for 2 doses, then 3–4 mg/kg q12h; or an echinocandin[a] (B-III)	Alternative therapy is recommended for patients intolerant of or experiencing failure of AmB and 5-FC therapy. Duration of therapy is at least 4–6 weeks as determined by repeated examinations to verify resolution. Diagnostic vitreal aspiration should be done if etiology unknown.
Candida infection of the cardiovascular system			
Endocarditis	LFAmB 3–5 mg/kg with or without 5-FC 25 mg/kg qid; or AmB-d 0.6–1 mg/kg daily with or without 5-FC 25 mg/kg qid; or an echinocandin[b] (B-III)	Step-down therapy to fluconazole 400–800 mg (6–12 mg/kg) daily for susceptible organism in stable patient with negative blood culture results (B-III)	Valve replacement is strongly recommended. For those who are unable to undergo surgical removal of the valve, chronic suppression with fluconazole 400–800 mg (6–12 mg/kg) daily is recommended. Lifelong suppressive therapy for prosthetic valve endocarditis if valve cannot be replaced is recommended.

Invasive aspergillosis

Combination Antifungal Therapy for Invasive Aspergillosis

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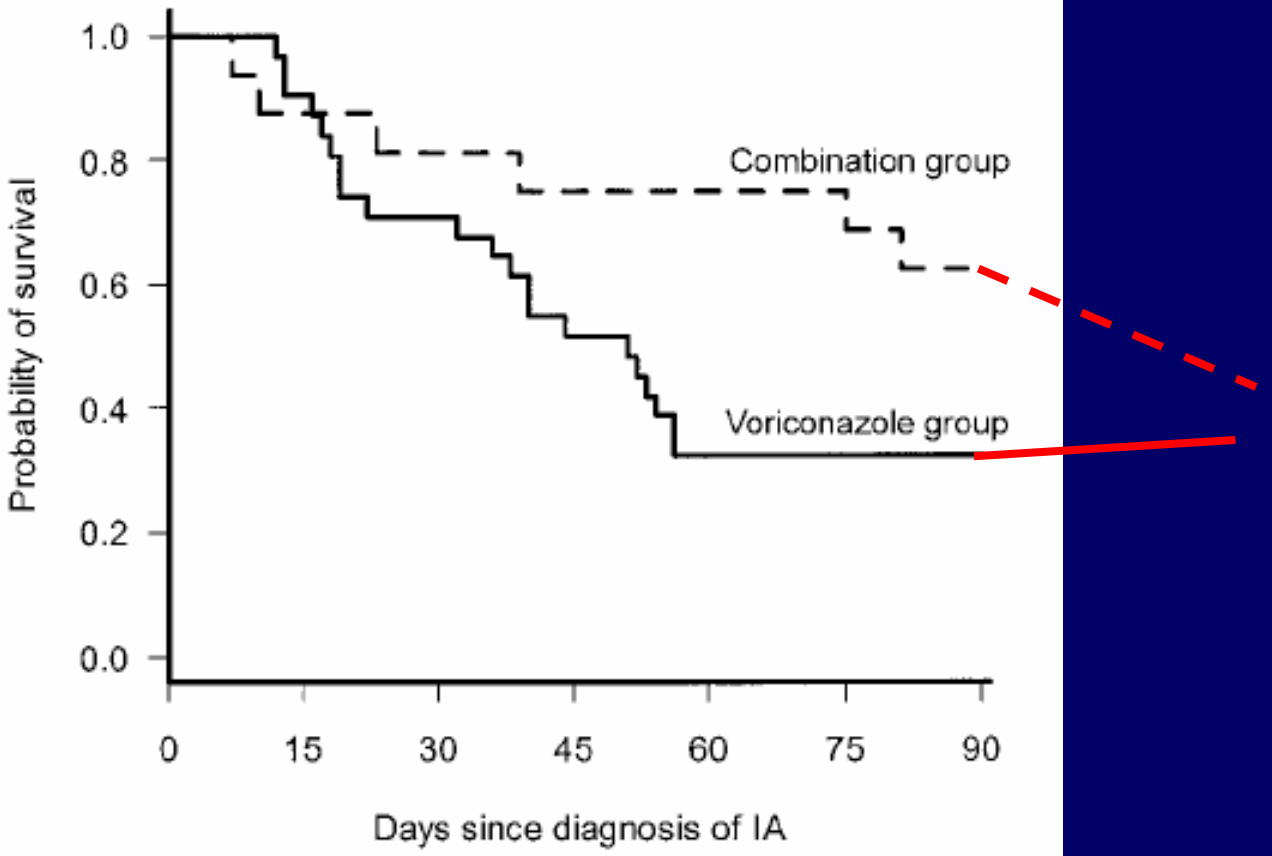
(See the editorial commentary by Viscoli on pages 803–5)

Historical controlled study (retrospective review) comparing the outcomes (90 days survival) of patients with IA who failed initial therapy with AmB formulations and received either voriconazole Or voriconazole + caspofungin (CID 2004)



Voriconazole group, no. of patients	31	22	10	10
Combination group, no. of patients	16	13	12	10

Combination of Voriconazole and Caspofungin as Primary Therapy for Invasive Aspergillosis in Solid Organ Transplant Recipients: A Prospective, Multicenter, Observational Study

Nina Singh,[1,16] Ajit P. Limaye,[2] Graeme Forrest,[3] Nasia Safdar,[4] Patricia Muñoz,[5] Kenneth Pursell,[6] Sally Houston,[7] Fernando Rosso,[8] Jose G. Montoya,[8] Pamela Patton,[9] Ramon del Busto,[10] Jose M. Aguado,[11] Robert A. Fisher,[12] Goran B. Klintmalm,[13] Rachel Miller,[14] Marilyn M. Wagener,[1] Russell E. Lewis,[15] Dimitrios P. Kontoyiannis,[15] and Shahid Husain[1]

Background. The efficacy of the combination of voriconazole and caspofungin when used as primary therapy for invasive aspergillosis in organ transplant recipients has not been defined.

Methods. Transplant recipients who received voriconazole and caspofungin (n=40) as primary therapy for invasive aspergillosis (proven or probable) in a prospective multicenter study between 2003 and 2005 were compared to a control group comprising a cohort of consecutive transplant recipients between 1999 and 2002 who had received a lipid formulation of AmB as primary therapy (n=47). In vitro antifungal testing of *Aspergillus* isolates to combination therapy was correlated with clinical outcome.

Results. Survival at 90 days was 67.5% (27/40) in the cases, and 51% (24/47) in the control group (HR 0.58, 95% CI, 0.30–1.14, P=0.117). However, in transplant recipients with renal failure (adjusted HR 0.32, 95% CI: 0.12–0.85, P=0.022), and in those with *A. fumigatus* infection (adjusted HR 0.37, 95% CI: 0.16–0.84, P=0.019), combination therapy was independently associated with an improved 90-day survival in multivariate analysis. No correlation was found between in vitro antifungal interactions of the *Aspergillus* isolates to the combination of voriconazole and caspofungin and clinical outcome.

Conclusions. Combination of voriconazole and caspofungin might be considered preferable therapy for subsets of organ transplant recipients with invasive aspergillosis, such as those with renal failure or *A. fumigatus* infection.

Keywords: Aspergillus, Fungal infections, Transplants.

(*Transplantation* 2006;81: 320–326)

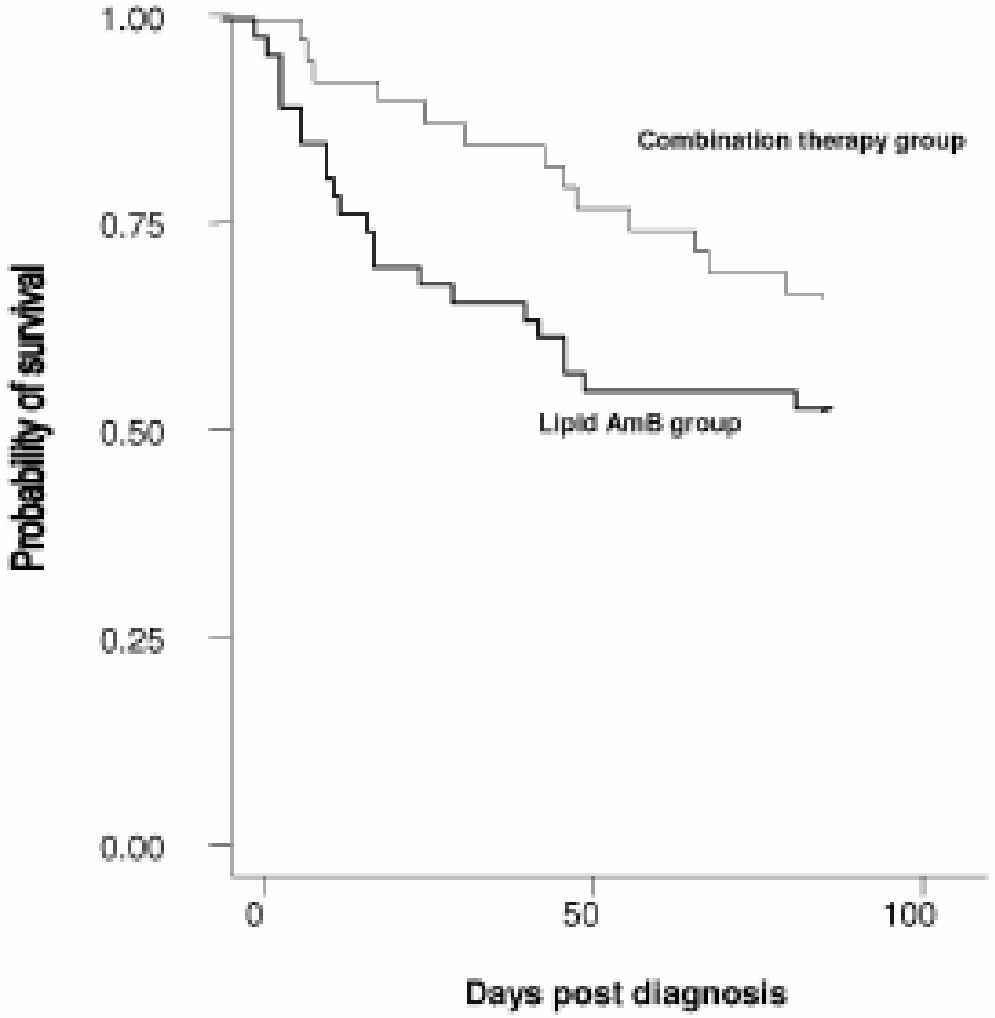


FIGURE 1. Kaplan-Meier survival analysis showing the probability of survival after the diagnosis of invasive aspergillosis in cases compared to controls ($P=0.13$, log rank test).

TABLE 2. Variables associated with mortality at 90 days in the study patients based on Cox proportional hazard analysis

Variable	Hazard ratio (95% CI)	*P* value
Univariate analysis		
Cytomegalovirus infection	2.48 (1.3–4.8)	0.01
Dialysis	2.0 (1.0–3.9)	0.04
Onset of infection >3 months posttransplant	1.5 (0.8–2.9)	0.19
Retransplantation	1.39 (0.58–3.3)	0.47
Multivariate analysis[a]		
Cytomegalovirus infection	2.09 (1.08–4.04)	0.028
Renal failure	2.11 (1.04–4.08)	0.026
Combination therapy	0.58 (0.30–1.14)	0.117

[a] The multivariate model was constructed from patient factors found to be associated with mortality at the 0.10 level in univariate analysis and removed in a stepwise fashion at the 0.15 level. Treatment was then added to the final model.

IN TRANSPLANT RECIPIENTS WITH RENAL FAILURE AND IN THOSE WITH A. FUMIGATUS INFECTION COMBO THERAPY WAS SIGNIFICATLY ASSOCIATED WITH IMPROVED SURVIVAL

Multicenter, Noncomparative Study of Caspofungin in Combination With Other Antifungals as Salvage Therapy in Adults With Invasive Aspergillosis

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Cancer 2006

Liposomal Amphotericin B in Combination With Caspofungin for Invasive Aspergillosis in Patients With Hematologic Malignancies

A Randomized Pilot Study (Combistrat Trial)

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Cancer 2007

Problems in evaluating combination therapy clinical studies

- Small sample sizes
- Historical control studies tend to underestimate results in control groups and to show larger treatment effects
- New diagnostic procedures have been introduced overtime, that might have lead to earlier diagnoses and consequent better therapeutic results

Viscoli C. Editorial CID 2004

First line therapy for IA

	ECIL III 09	IDSA 08	BSH 08
Voriconazole	A I (oral CIII)	A I (1° line)	Recommended
L-AMB	B I	A I (1° line for some pts)	Recommended
ABLC	B II	-	-
ABCD	D I	-	-
D-AMB	D I	-	Not recommended - A I
Caspofungin	C II	Alternative	Recommended
Micafungin		Alternative	-
Posaconazole		Alternative	-
Itraconazole	C III	Alternative	-
Combination	**D III**	**Not recommended – B II**	**Discouraged – A I**
Surgery (selected pts)	C III	B III	B III

Salvage therapy

	ECIL III 2009	IDSA 2008	BSH 2008
L-AMB	B III	A II	No recommendation The design of these trials is so heterogeneous that it is not possible to make a recommendation on the basis of their evidence.
ABLC	B III		
Posaconazole	B II	B II	
Vorico	B II		
Itraconazole	C III	B II	
Caspofungin	B II	B II	
Micafungin		B II	
Combination therapy	C II (Caspo + L-AMB or Caspo + Vori)	B II	

Possible role of calcineurin inhibitors in invasive aspergillosis (IA)

- Calcineurin has a role in the fungal cell wall homeostasis, fungal growth and virulence
- The use of calcineurin-inhibitors (cyclosporin) was associated with a decrease in the

The challenge is to develop a calcineurin-inhibitor not cross-reacting with human calcineurin

Singh, Clin Inf Dis 2003)

- These data have been confirmed in experimental models (Steinback, 2006)
- Calcineurin inhibition prevents the caspofungin-associated “paradoxical effect” (regrowth at high concentrations)