Hôpital Erasme

ULB

Treatment of invasive aspergillosis

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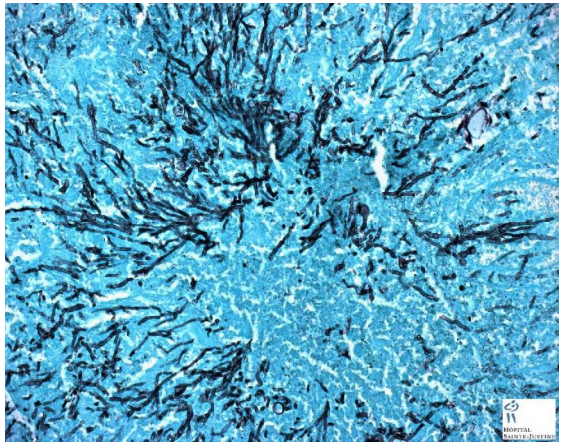
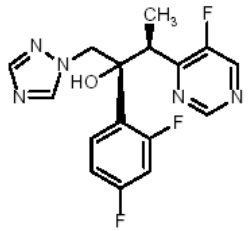
Infectious Diseases Clinic

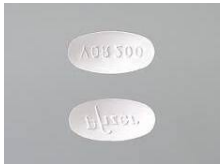
SBIMC
8 November 2012

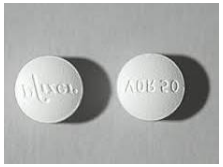


Triazoles

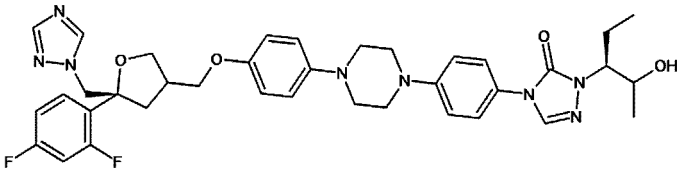


VFEND (voriconazole)



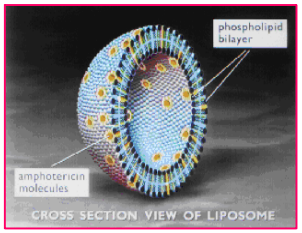


NOXAFIL posaconazole

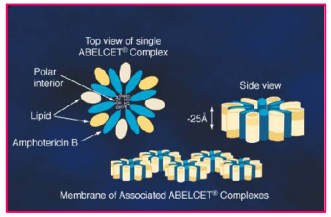


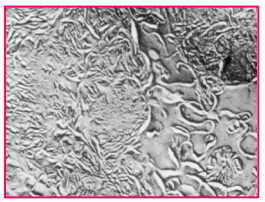
Polyens

Amphotericin B liposomiale (Ambisome®)



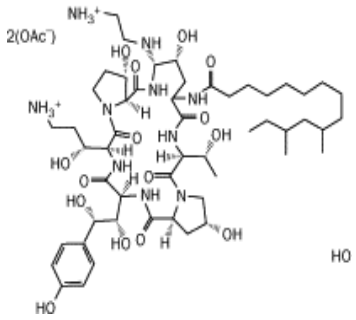
Amphotericin B lipid complex (Abelcet®)



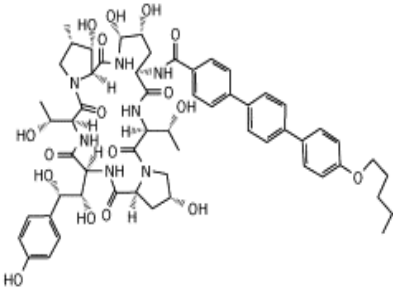


Echinocandins

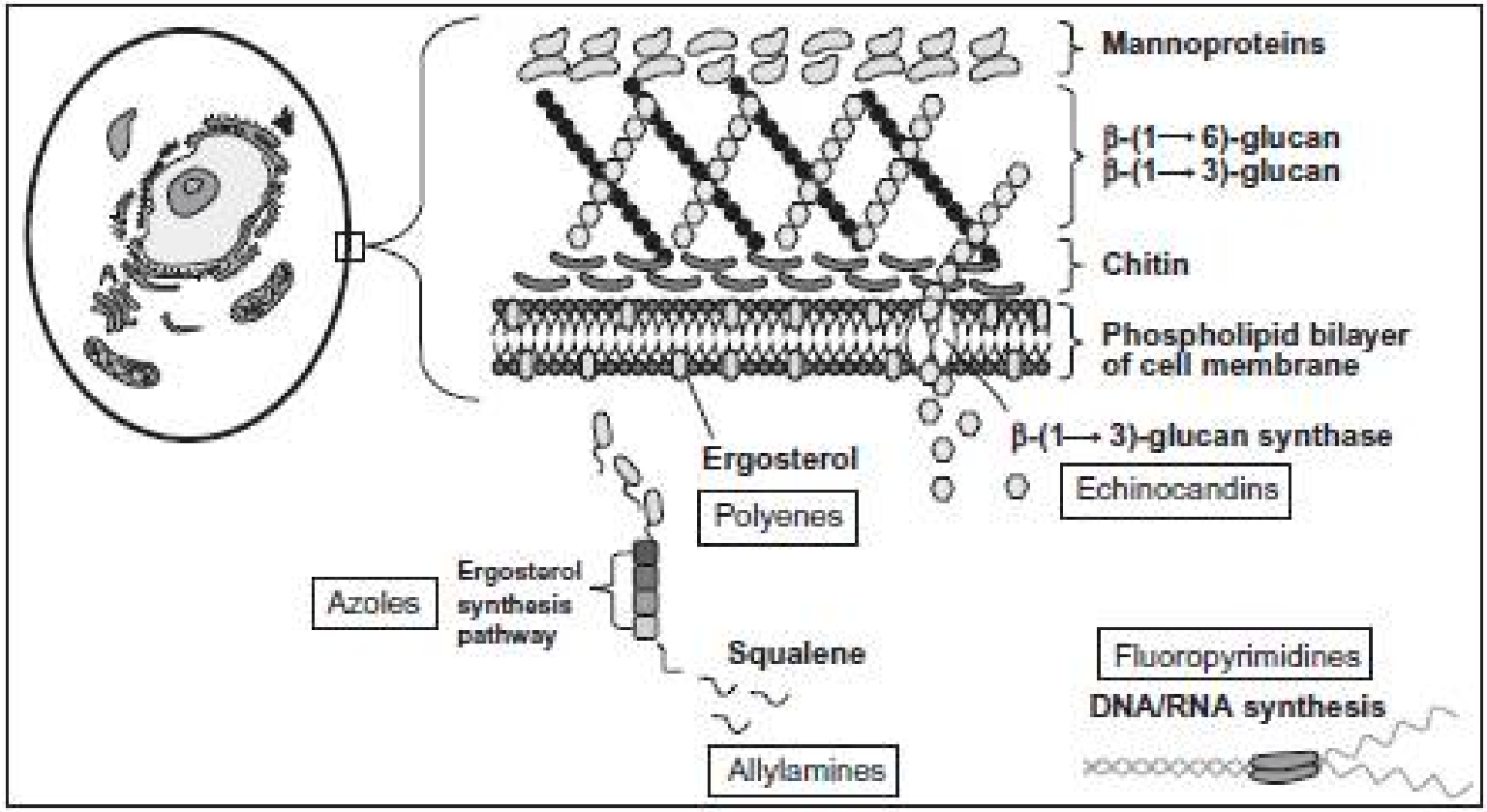
Caspofungin



Anidulafungin



Targets of systemic antifungal agents

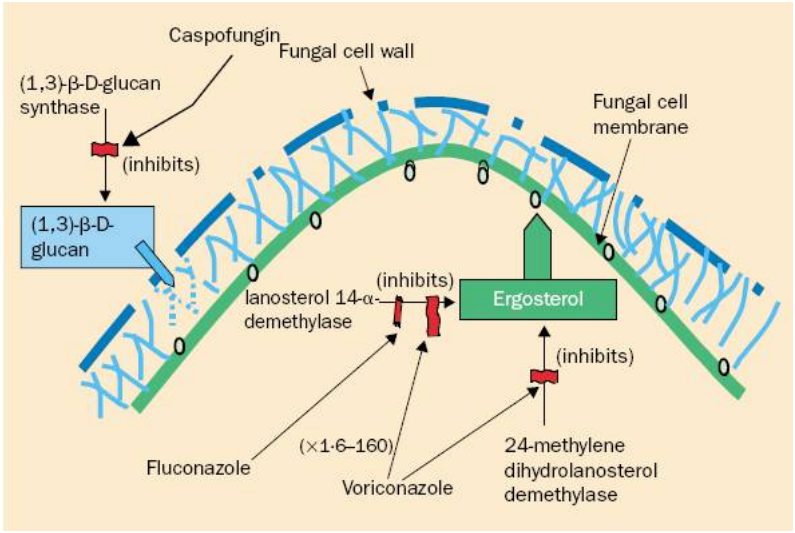


Dodds Clin Infect Dis 2006; 43: S28-39

Primary treatment
First line: voriconazole

Targets ergosterol synthesis by inhibiting the fungal cytochrome P450-dependent enzyme lanosterol 14-a-demethylase → altered cell membrane function and cell death or inhibition of cell growth and replication

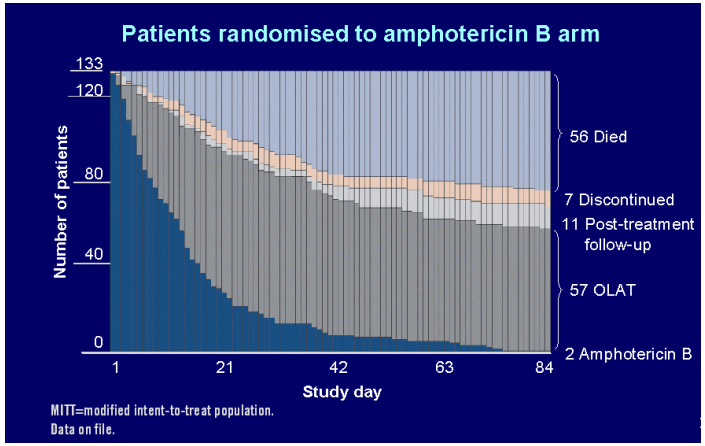
- First line treatment for invasive aspergillosis



IDSA guidelines. Clin Infect Dis 2008; 46, 327-60

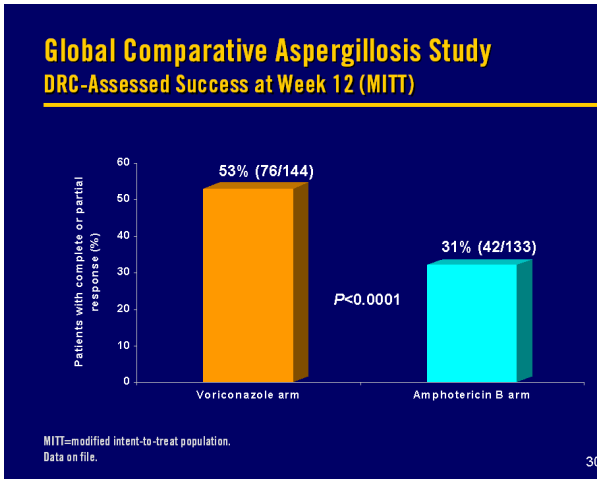
Voriconazole vs Amphotericin B

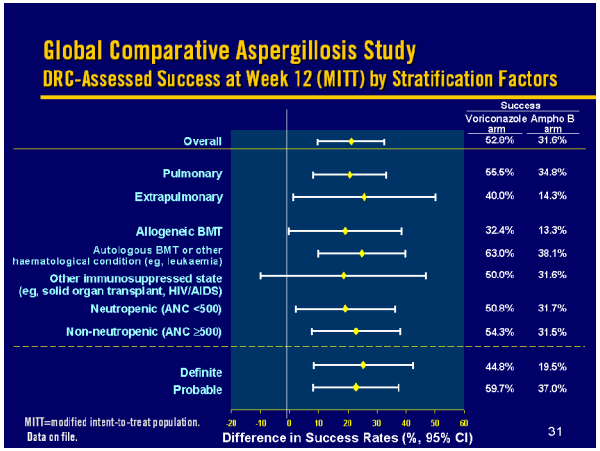
- Randomized controlled trial of primary treatment for invasive aspergillosis
- Shift from AmB to OLAT (other licenced antifungal therapy)

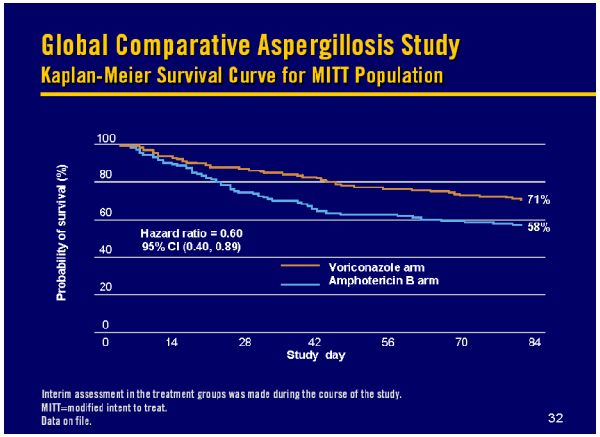


- 277 evaluable patients
- **Voriconazole is superior to deoxycholate amphotericin B**

Herbrecht et al. NEJM, 2002, 347, 408







Voriconazole

Efficacy of voriconazole also demonstrated in

- pediatric and adult patients
- with IA refractory or intolerant to conventional antifungal therapy

Denning Clin Infect Dis 2002; 34, 563-71;
Perfect Clin Infect Dis 2003; 36, 1122-31;
Walsh Pediat Infect Dis J 2002; 21: 240-8

Second line or salvage therapy

Lipid formulations of amphotericin B

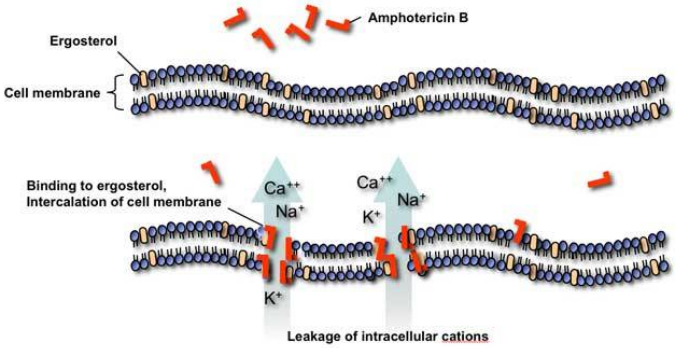
Caspofungine

Posaconazole

(itraconazole)

Amphotericin B

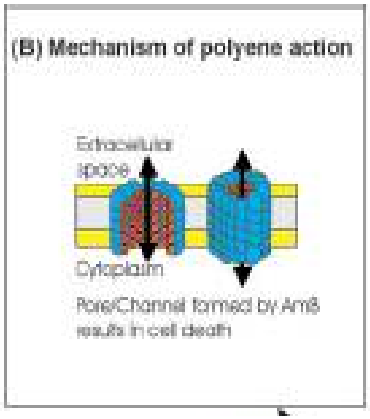
- Act by binding to ergosterol (the principal sterol in the cell membrane of most medically important fungi) leading to the formation of ion chanels and fungal cell death.



- Ampho B deoxycholate: not available anymore
- ABLC (Abelcet ®), L-AMB (Ambisome ®)

- Both preferentially distribute to reticulo-endothelial system tissues and functionnaly spare the kidney

- NB: most *Aspergillus terreus* are resistant in vitro and in vivo to AMB (also *A. lentulus, nidulans, ustus, versicolor*)



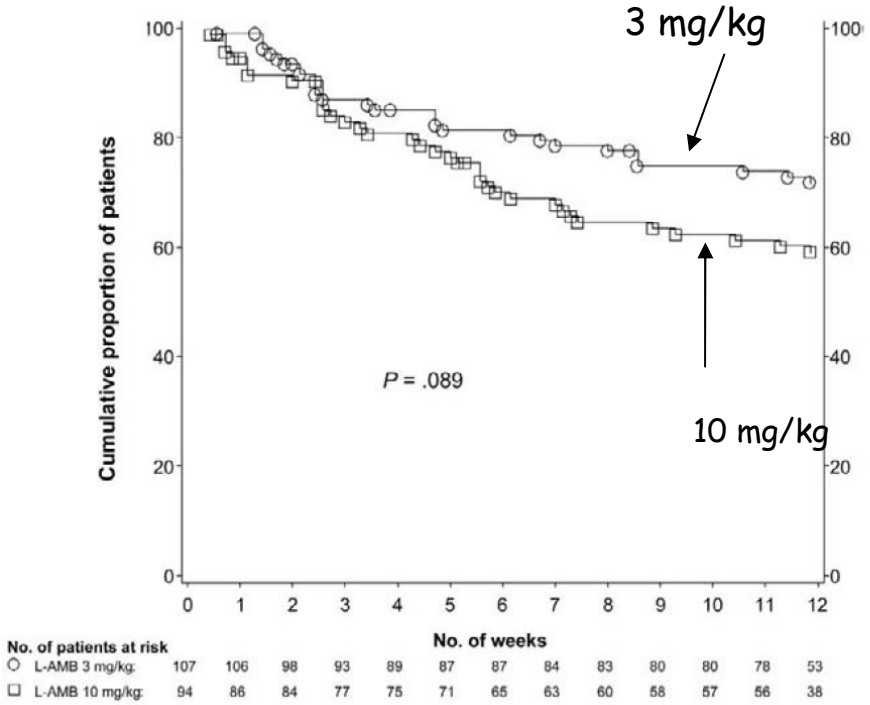
Lipid formulations of AmB

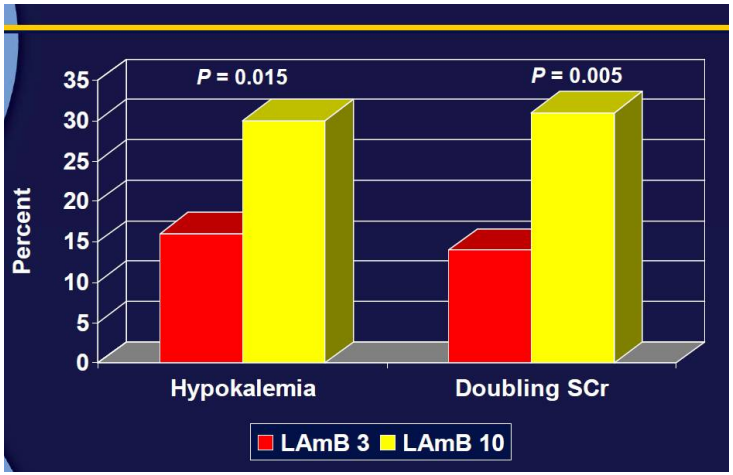
- Response rate +/- 40%
- Second line for patients who are intolerant of or refractory to voriconazole or patients with hepatotoxicity or other contraindications to voriconazole
- Which dose?
- Higher dosages required for equivalent efficacy:
  - ABLC (Abelcet®): 5 mg/kg,
  - L-AMB (Ambisome®): 3-5mg/kg

AmbiLoad study

No advantage to higher doses but higher toxicity

Rate of survival



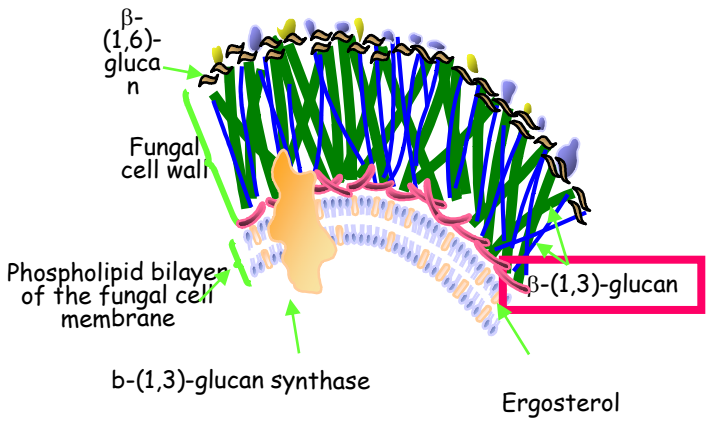


Hematological malignancies: 93% of patients
neutropenic at baseline: 73% of patients

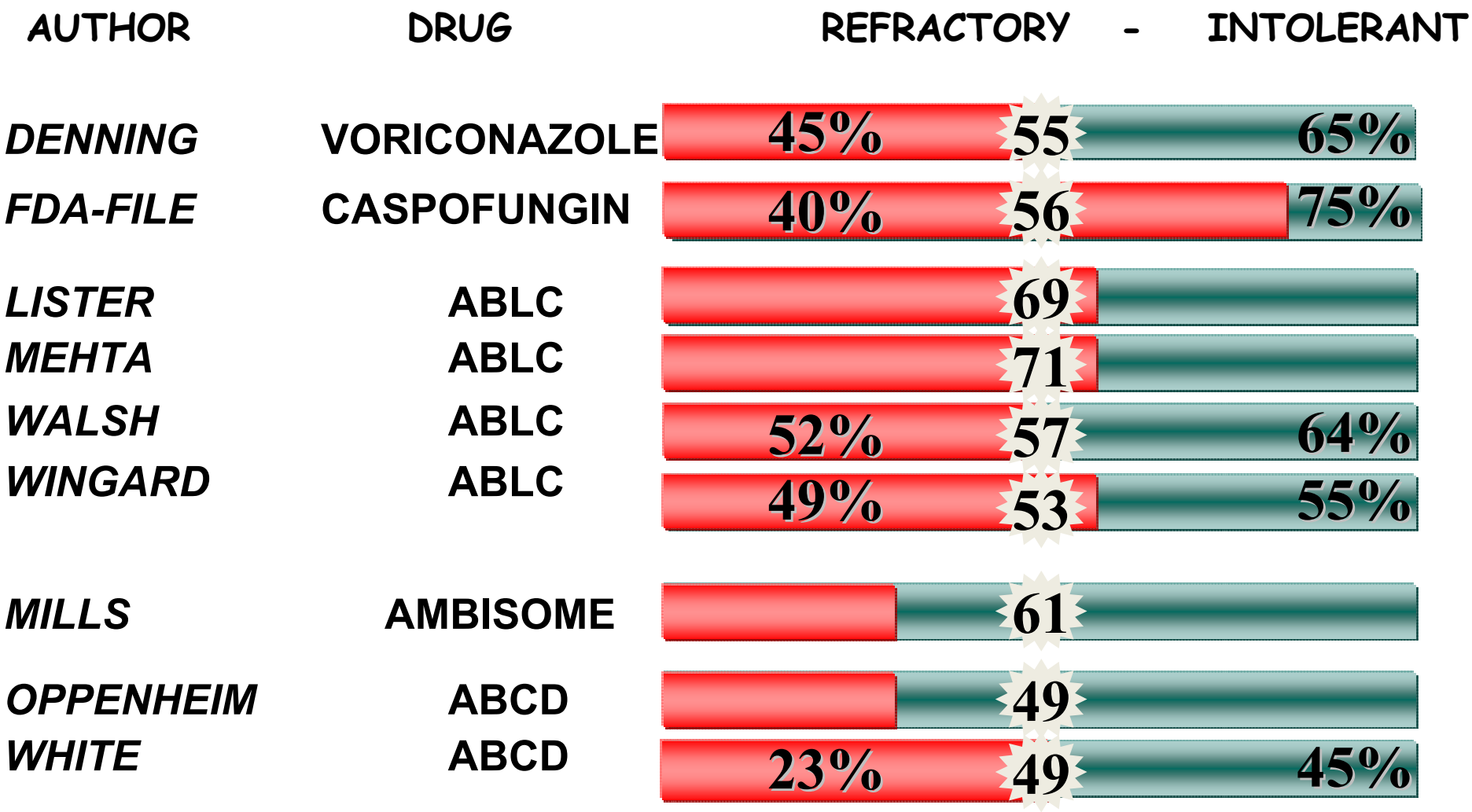
Cornely Clin Infect Dis 2007; 44; 1289-97

Caspofungine (Cancidas®)

- Act by noncompetitive inhibition of the synthesis of 1,3-β-glucan, a polysaccharide in the cell wall of many pathogenic fungi
- Dose-proportional plasma pharmacokinetic
- Indicated in patients with invasive aspergillosis that is refractory to or intolerant of other approved therapies (Maertens Clin Infect Dis 2004; 39, 1563-71)
- Response rate +/- 40%
- Higher response (50%) in pulmonary aspergillosis than in disseminated aspergillosis (23%)
- Few adverse events (discontinuation of the drug in only 2.7% of 1951 patients) and few drug-drug interactions



Caspofungine for the treatment of invasive aspergillosis



An EORTC Phase II study of caspofungin as first-line therapy of invasive aspergillosis in haematological patients

C. Viscoli[1]*, R. Herbrecht[2], H. Akan[3], L. Baila[4], A. Sonet[5], A. Gallamini[6], A. Giagounidis[7], O. Marchetti[8], R. Martino[9], L. Meert[4], M. Paesmans[10], L. Ameye[10], M. Shivaprakash[11], A. J. Ullmann[12] and J. Maertens[13] on behalf of the Infectious Disease Group of the EORTC†

- Low response rate: favourable response (complete and partial) 33% (95% CI 21-46)

- The role of the severity of the underlying disease was quite evident in this study.

J Antimicrob Chemother. 2009 Dec;64(6):1274-81

First-line treatment of invasive aspergillosis

Table 3. First-line Treatment of Invasive Aspergillosis: Prospective Controlled Trials.

Study	N=	Design	Treatment	MDST (range)	Response (CR+PR)	Survival week 12
Herbrecht	277	op, rd	AmB Desoxycholate 1-1.5 mg/kg	10 (1-84)	31.6%	57.9%
2002 NEJM			Vori 2x6mg/kg d1 and 2x4 mg/kg d2+ i.v.*	77 (2-84)	52.8%	70.8%
Cornely	201	db, rd	LAmB 3mg/kg (d1-14) } op 3mg/kg d 15+	14 (1-60)	50%	72%
2007 CID			LAmB 10 mg/kg (d1-14) } op 3mg/kg d 15+	15 (1-57)	46%	59%
Herbrecht 2010 BMT **	24	op, sa	Caspofungin 70mg d1/50 mg d2+	24	33%	50%
Viscoli 2009JAC #	61	op, sa	Caspofungin 70mg d1/50 mg d 2+	15 (3-84)	33%	53%

Abbreviations: op = open, rd = randomized, db = double blind, sa = single arm, MDST = Median duration of study drug treatment in days, * a switch to oral voriconazole was allowed after day 7, **allogeneic cohort of patients, # hematological malignancies and autologous transplantation

Posaconazole

- Structural analog of itraconazole
- Large hydrophobic compound
- MIC90 of fungal pathogens: 0.5 mg/L
- Oral drug available
- Approved in Europe for salvage therapy of patients with IA who are refractory to AMB or itraconazole
- Global response at the end of treatment 42% for posaconazole

Treatment of Invasive Aspergillosis with Posaconazole in Patients Who Are Refractory to or Intolerant of Conventional Therapy: An Externally Controlled Trial

Thomas J. Walsh,[1] Issam Raad,[3] Thomas F. Patterson,[4] Pranatharthi Chandrasekar,[5] Gerald R. Donowitz,[6] Richard Graybill,[4] Reginald E. Greene,[7] Ray Hachem,[3] Susan Hadley,[8] Raoul Herbrecht,[16] Amelia Langston,[9] Arnold Louie,[10a] Patricia Ribaud,[17,a] Brahm H. Segal,[11] David A. Stevens,[12] Jo-Anne H. van Burik,[13] Charles S. White,[2] Gavin Corcoran,[14,a] Jagadish Gogate,[14,a] Gopal Krishna,[14] Lisa Pedicone,[14] Catherine Hardalo,[14] and John R. Perfect[15]

CID 2007:44 (1 January) • Walsh et al.

IDSA recommendations

- Early initiation of antifungal therapy
- Voriconazole:
  - First line therapy
  - IV formulation for seriously ill patients
- Insufficient clinical data to support combination therapy as routine primary treatment of IA
- Reversal of immunosuppression (reduction in the dosage of corticosteroids) or recovery from neutropenia

- Surgical resection of Aspergillus-infected tissue in patients with lesions
  - that are contiguous with the great vessels or pericardium,
  - causing hemoptysis from a single focus, and
  - lesions causing erosion into the pleural space or ribs

In case of renal or liver dysfunction

- Creatinine clearance < 50ml/min:
  - Vorico: accumulation of cyclodextrine (IV) → use oral vorico.
  - Same dose of caspofungine
  - Lipid AmB: nephrotoxicity

- Liver failure (cirrhosis)
  - Child-Pugh A et B; 50% of the dose of vori and caspo (hepatic metabolism)
  - Child-Pugh C:
    - no data.
    - Same dose of caspo? (Spriet J. Antimicrob. Chemother. (2009) 63 (4): 767-770)
  - Lipid AmB: no dose reduction. ! Renal toxicity!

Salvage therapy in case of failure of voriconazole

- Change of class using an AMB formulation or an echinocandin (also in case of breakthrough IA in the context of azole prophylaxis)

- Combination therapy with drugs from different classses other than those in the initial regimen may be considered

- Most of the prospective studies of second-line therapy have been conducted by replacing the compound against which the infection is progressing

  Wether both drugs should be administered simultaneously has selfom been prospectively studied

Combination therapy

- Echinocandin combined with either an azole or ampho B formulation
- Distinct mechanisms of action offer the possibility of synergistic activity
- Possibility of antagonism? Particularly when these drugs are given sequentially (drugs blocking ergosterol synthesis given before the polyenes)

- 8 comparative studies (one RCT and seven cohorts)
  - Pilot RCT (Combistral trial): liposomal AmB (3mg/kg) + caspofungine vs liposomal AmB 10mg/kg (total of 30 patients) (Caillot Cancer 2007; 110: 2740)
  - Different antifungal combinations

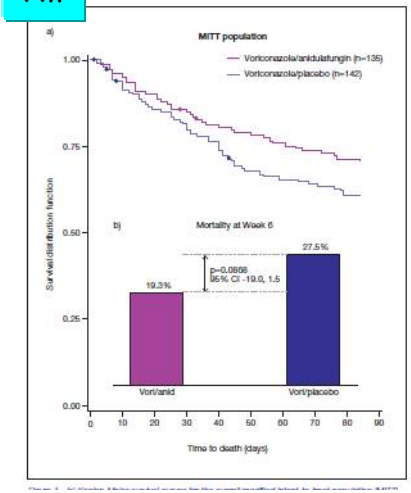
VORI + Anidula vs VORI Primary treatment of IA

ECCMID 2012

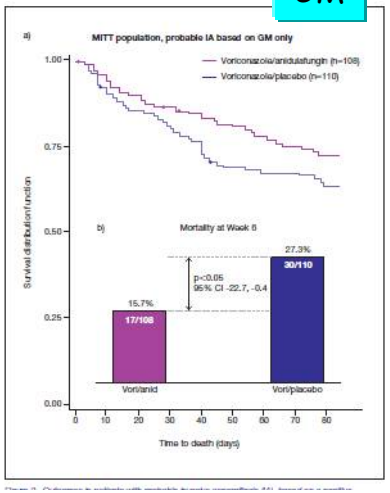
- Prospective, randomised, double-blind clinical trial
- Allo-HSCT recipients and patients with haematological malignancies
- Proven or probable IA
- Combination therapy was administered for 2–4 weeks; after 2 weeks, voriconazole monotherapy, to complete at least 6 weeks of antifungal treatment
- Combination therapy → trend towards improved overall survival in patients with proven or probable IA diagnosed after allo-HSCT or treatment of haematological malignancies.
- In the subset of patients with antigen-diagnosed disease: the combination increased the rate of overall 6-week survival (statistically significant).

Survival

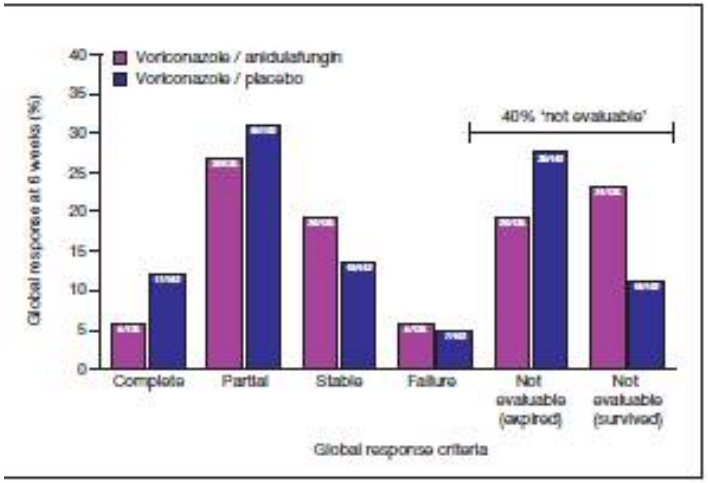
All



GM



Global response at 6 weeks



Marr et al. ECCMID 2012

Duration of antifungal therapy

- Not well defined
- Minimum of 6-12 weeks
- In immunosuppressed patients, therapy should be continued troughout the period of immunosuppression and until lesions have resolved
- CT scan at regular intervals
  - Frequency ? Should be individualized
  - The volume of pulmonary infiltrates may increase for the first 7-10 days of therapy, especially in the context of granulocyte recovery (Caillot J Clin Oncol 2001, 19: 253-9)
- GM-driven therapy: to be evaluated in non hematological patients

TDM of antifungal drugs?

- 3 general criteria for TDM
  - Variable pharmacokinetics
  - Narrow therapeutic window
  - Established relationship between plasma drug concentration and either efficacy or toxicity

Antifungal triazoles

Serum concentrations variability

Inter and intra-patient variability in serum concentrations (adults and children)

- Impaired absorption
- *CYP2C19* genetic polymorphism →Nonlinear pharmacokinetics
- Potential drug-drug interactions

Large inter-personnal variability

- TDM to avoid subtherapeutic levels in HSTC recipents
- 43 allogenic hematopoietic SCT: prophylaxis with VORI

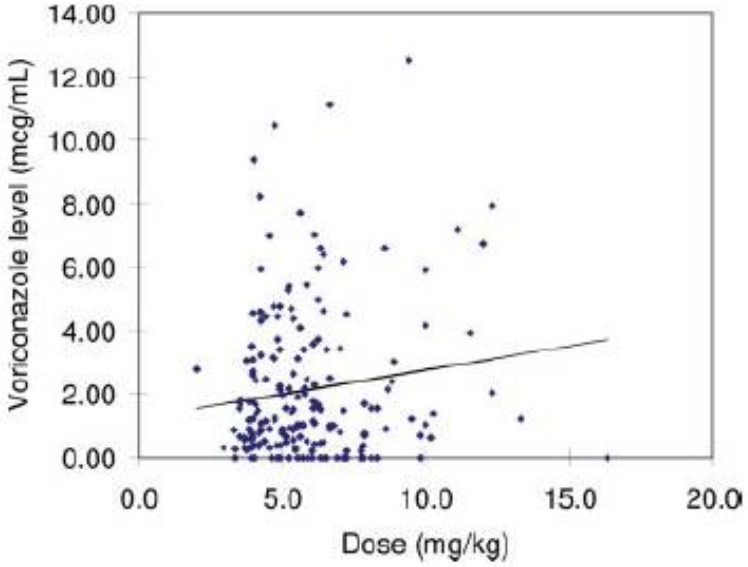


FIGURE 1. Correlation between voriconazole dose and drug level ($r = 0.14$; $P = .051$).

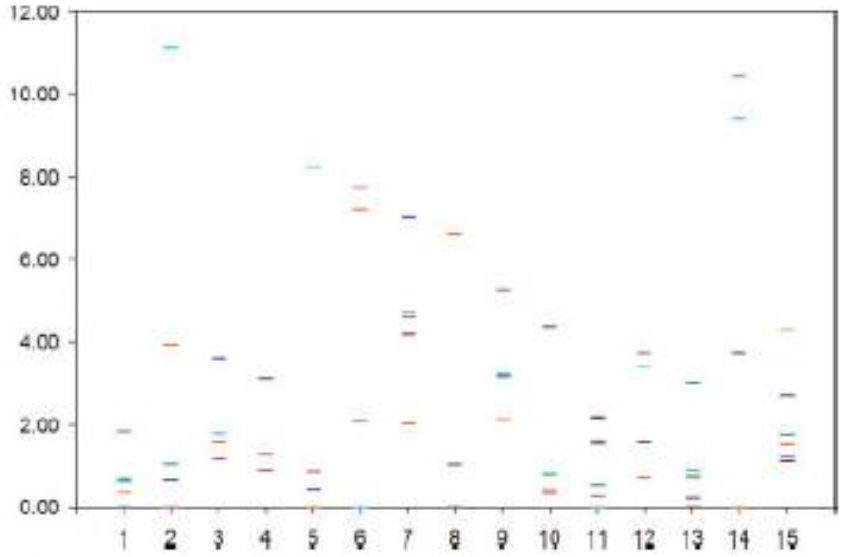


FIGURE 2. Voriconazole levels in 15 patients in whom ≥4 values were available illustrating variability.

Trifilio Blood 2006; 108, 806a

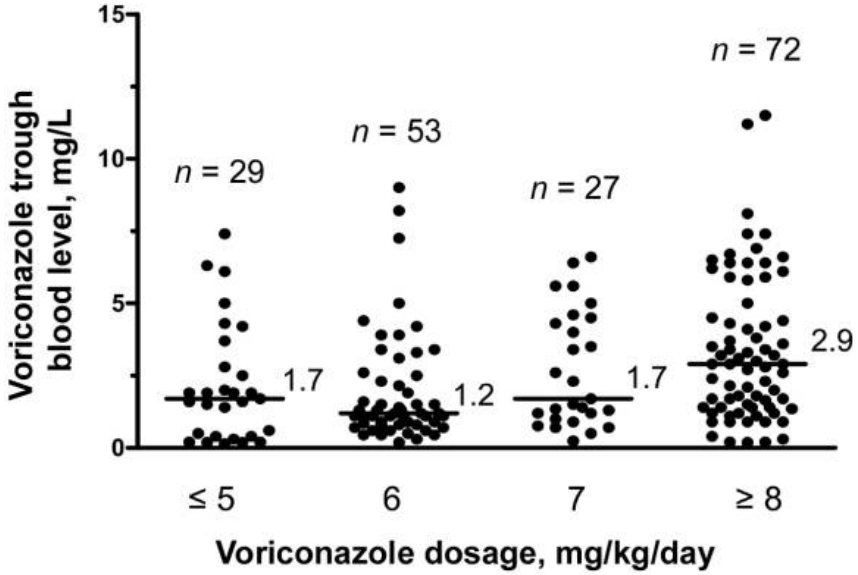
Bone Marrow Transplantation (2007) 40, 451–456

Voriconazole Therapeutic Drug Monitoring in Patients with Invasive Mycoses Improves Efficacy and Safety Outcomes

Andres Pascual,[1] Thierry Calandra,[1] Saskia Bolay,[1] Thierry Buclin,[2] Jacques Bille,[3] and Oscar Marchetti[1]

[1]Infectious Diseases Service, [2]Division of Clinical Pharmacology, and [3]Institute of Microbiology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland

- 52 patients treated with VORI (31 for IA)
- Loading dose: 12mg/kg/d; maintenance: 6.5 mg/kg/d (5-8)
- Trough levels (after a median of 5 days)
- A higher proportion of patients with levels ≤ 1 mcg/ml received oral VORI



Pascual CID 2008; 46, 201-211

1. Impaired absorption

- Volunteers:
  - Bioavailability 96%
  - Effect of food: delays absorption, decreases bioavailability → Empty stomach
  - Patients with enteral nutrition: discontinued during 1/3 of timeperiod
- Decreased bioavailability in severely ill patients as compared to volunteers
  - LTX: 46% during the early postoperative period
  - CF patients: lower by 87% as compared to non CF patients

Han AAC 2010; 54: 4424-4431

Voriconazole pharmacokinetic variability in cystic fibrosis lung transplant patients

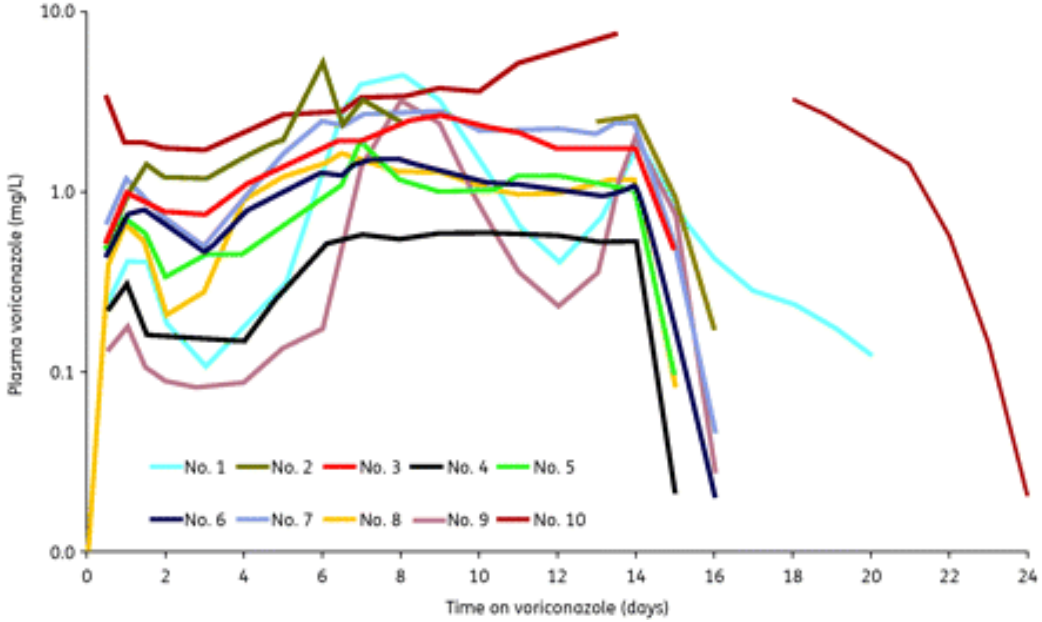
- Very low serum concentrations
  - Increased clearance (young age and enzymatic induction by high doses corticosteroids)
  - Decreased absorption

- Importance of TDM

- The risk of long under-dosed periods could justify, on a PK basis, the need for combination with an exclusive parenteral antifungal while waiting for azole relevant drug level.

M. Berge, R. Guillemain, V. Boussaud, M.-H. Pham, P. Chevalier, A. Batisse, C. Amrein, E. Dannaoui, M.-A. Loriot, A. Lillo-Le Louet, E.M. Billaud. Voriconazole pharmacokinetic variability in cystic fibrosis lung transplant patients.
Transpl Infect Dis 2009: **11**: 211–219.

Role of impaired absorption?



IV voriconazole in allogenic HSCT recipents

Loading dose 6mg/kg bid day 1, then 4mg/kg bid

Considerable inter- and intrasubject variation

Single trough concentration may not be representative of a patient's average level

Bruggemann J Antimicrob Chemother 2010; 65, 107-13

IV voriconazole in ICU patients

Table 3
Steady-state pharmacokinetic parameters of voriconazole, estimated from the concentration–time data by
in critically ill patients (N= 18) with either normal renal function or moderate renal impairment.

Patient No.	Dose (mg/12 h)	C_{ave} (S.D.) (mg/L)	C_{min} 0 h (mg/L)	C_{min} 12 h (mg/L)	C_{max} (mg/L)
			steady state D 3-5		
1	240	0.78 (0.88)	0.17	0.15	2.7
2	200	2.94 (1.10)	1.99	1.82	5.3
3[a]	320	4.55 (1.10)	3.12	4.04	7.0
4	250	7.73 (1.51)	5.62	5.95	10.4
5	400	4.26 (2.56)	2.33	2.66	9.7
6[a]	245	0.50 (0.65)	N/A	N/A	1.9
7[a]	200	1.51 (1.95)	0.08	0.18	5.5
8[a]	200	6.03 (2.00)	4.01	3.6	8.9
9	320	1.78 (1.30)	0.55	0.72	4.7
10	240	0.23 (0.24)	N/A	N/A	0.7
11	200	0.60 (0.25)	0.32	0.40	1.1
12[a]	300	4.33 (2.42)	2.09	2.10	9.6
13	280	5.71 (1.98)	3.61	3.90	9.6
14	240	1.09 (1.23)	0.33	0.27	3.8
15[a]	240	4.69 (3.71)	0.78	0.8	11.4
16	400	1.05 (1.29)	N/A	0.33	4.1
17	320	1.22 (1.89)	N/A	0.44	5.9
18	300	1.49 (0.74)	0.79	0.69	2.7

Myrianthefs Int J Antim Agents 2010

2. Genotyping variation

- Genetic polymorphism in CYP2C19
  - Normal = homozygous extensive metabolizers
  - Heterozygous extensive metabolizers
  - Poor metabolizers:
    - 20% of non-Indian Asians
    - 5% of Caucasians or African-Americans

    → Up to 4 times higher serum Voriconazole concentrations

- Caucasians: about 75% are homozygous extensive metabolizers and have lower voriconazole concentrations

- Autoinduction of voriconazole metabolism at higher doses is possible → voriconazole trough levels seem to decrease over time without apparent explanation (Mulanovich J Infect 2007; 55, 129)

- Accounts for 30% of the intersubject variability in voriconazole PK

3. Drug-drug interactions

Voriconazole is both a substrate and an inhibitor of CYP isoenzymes

•Voriconazole is a **substrate of CYP enzymes** → concomitant drugs can affect voriconazole serum concentrations

- **CYP inducers:** rifampin, rifabutin, phenytoin, barbiturates, efavirenz, protease inhibitors, ritonavir → low serum concentrations
- **CYP inhibitors:** omeprazole, oral contraceptive → high serum concentrations

•Voriconazole is **an inhibitor of CYP enzymes**

→ can affect serum concentrations of other drugs

Table 4 Summary of voriconazole-mediated drug–drug interactions

Type of interaction, drug	Recommendation
Decreases voriconazole levels	
Carbamazepine	Contraindicated
Long-acting barbiturates	Contraindicated
Rifampin	Contraindicated
Ritonavir	Avoid unless benefit outweighs risk
Levels increased by voriconazole	
Astemizole	Contraindicated
Cisapride	Contraindicated
Cyclosporine	Reduce cyclosporine dosage by half and monitor cyclosporine levels
Ergot alkaloids	Contraindicated
Omeprazole	Reduce dosage by half
Quinidine	Contraindicated
Sirolimus	Contraindicated Reduce sirolimus dose by 90% and monitor sirolimus levels
Tacrolimus	Reduce tacrolimus dosage by two-thirds and monitor tacrolimus levels
Terfenadine	Contraindicated
Warfarin	Monitor prothrombin time and international normalized ratio
Decreases voriconazole levels and increases other drug levels	
Rifabutin	Contraindicated
Phenytoin	Double voriconazole dosage and monitor for increased phenytoin levels
Efavirenz	Double voriconazole dosage and reduce efavirenz dose by half
Levels likely increased by voriconazole: sulfonylureas, statins, vinca alkaloids, calcium channel blockers, benzodiazepines	Monitor effect of drug and consider decreasing dosage when voriconazole is started

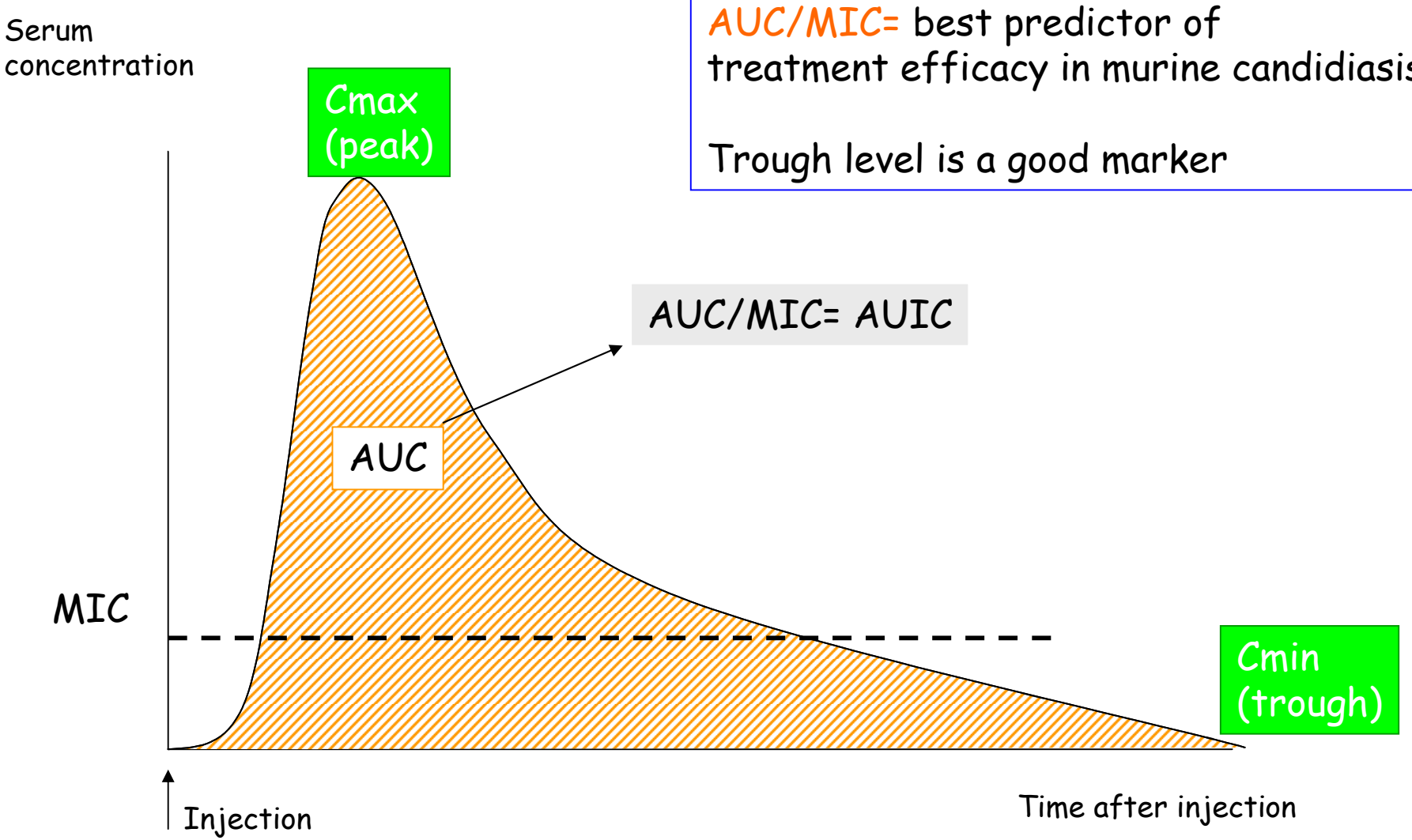
Exposure-efficacy relationship

- Numerous reports on a possible link between serum voriconazole concentrations and its efficacy

Voriconazole: PK parameters

AUC/MIC= best predictor of treatment efficacy in murine candidiasis

Trough level is a good marker



Voriconazole prophylaxis in HSTC recipients

- 43 allogenic hematopoietic SCT: prophylaxis with VORI
  - 6 breakthrough IFIs if trough C° <2mg/L
  - 0 if >2mg/L p= 0.061

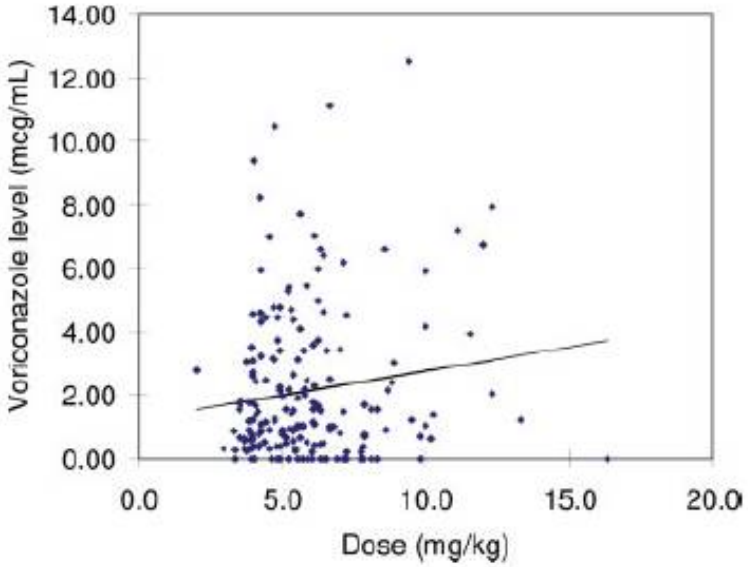


FIGURE 1. Correlation between voriconazole dose and drug level ($r = 0.14$; $P = .051$).

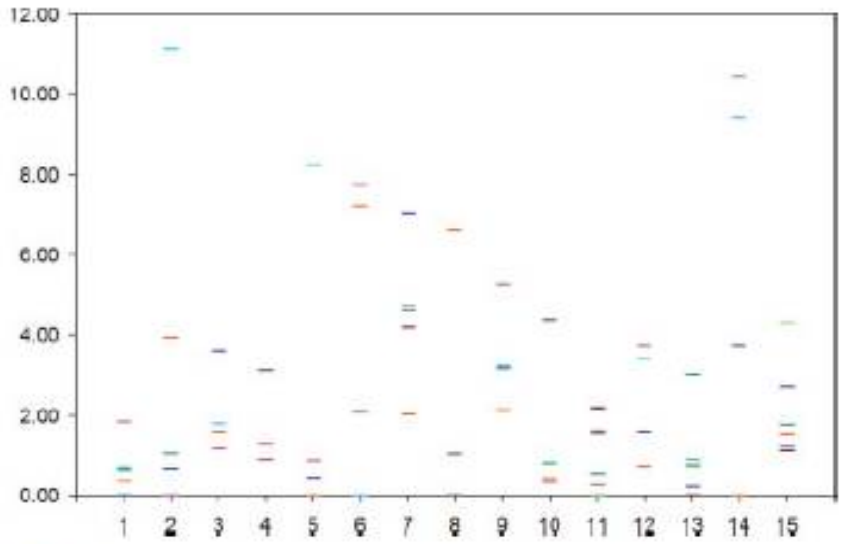


FIGURE 2. Voriconazole levels in 15 patients in whom ≥4 values were available illustrating variability.

Trifilio Blood 2006; 108, 806a

Bone Marrow Transplantation (2007) 40, 451–456

Response to antifungal therapy

Table 2. 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*
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)	

NOTE. Data are no. (%) of patients, unless otherwise indicated. NS, not significant.

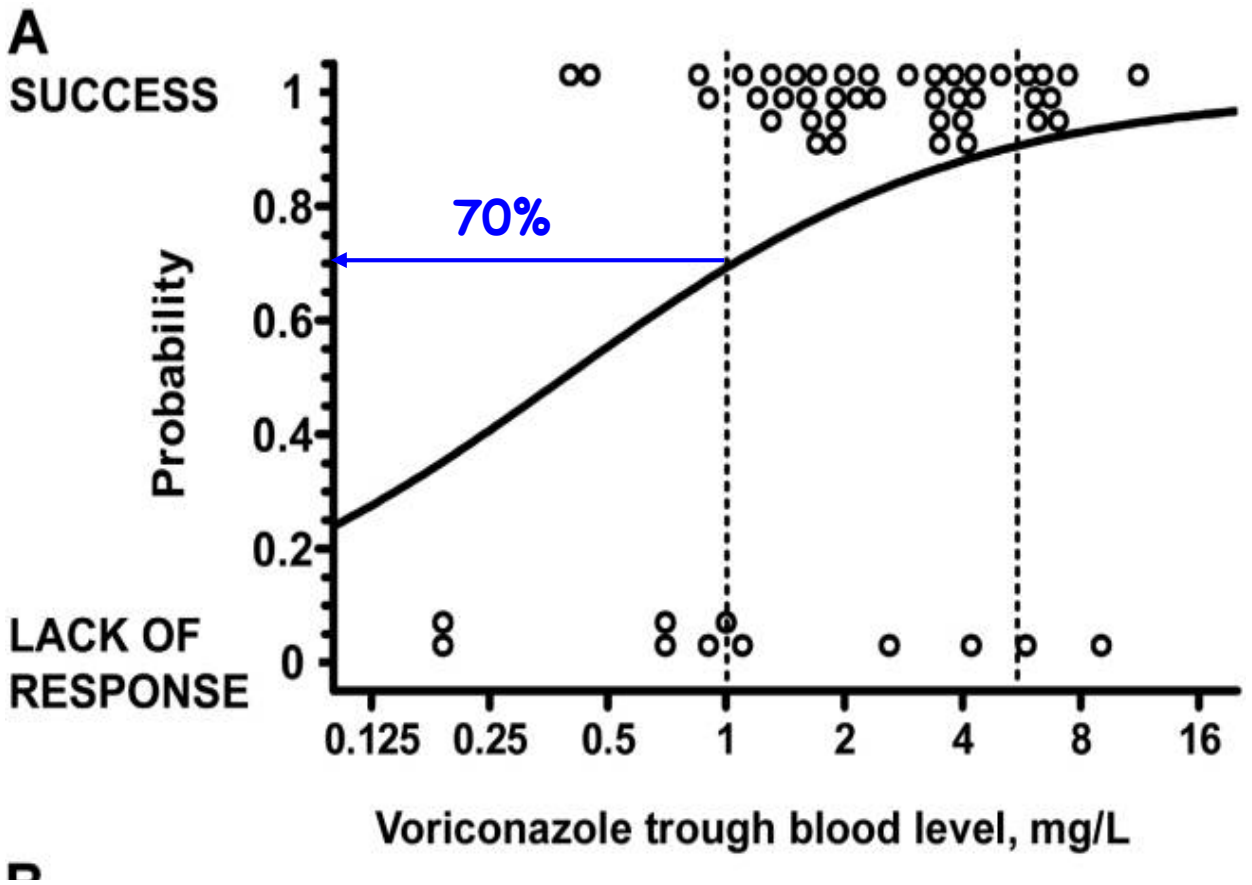
[a] In 1 patient, comedication with rifampin resulted in low voriconazole blood levels.

MIC_{90} 0.5-1mg/L for the majority of pathogenic fungi

- 6 patients with persistence or progression of IFI and VORI levels ≤1mg/L: il all 6, IFI responded after an increase in VORI doses
- 5 pts with VORI levels >1mg/L and lack of response to therapy:
  - Probable invasive candidiasis (1), probable IA (1), possible IFI (2), 1 breakthrough zydomycosis

Pascual CID 2008; 46, 201-211

Logistic regression model



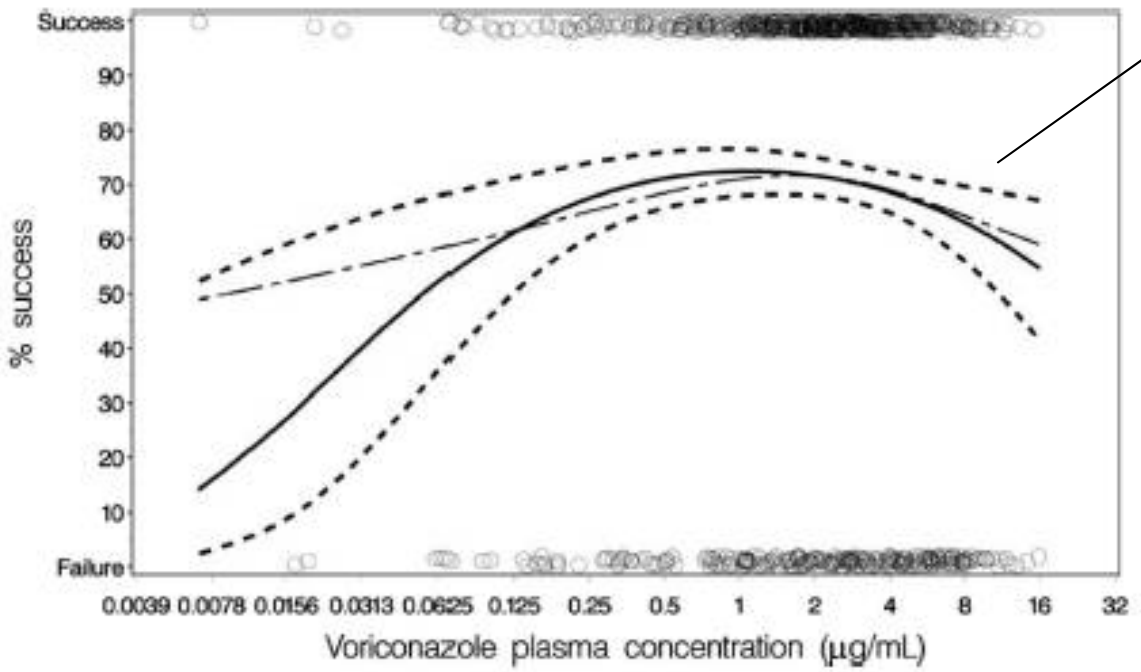
- 70% probability of response at a VORI trough level of 1mg/L

Correlation between voriconazole concentration and survival

- 25 patients (5 HSCT) treated for IFI
- Initial steady-state trough vori concentration was the best predictor for associated IFI-related mortality
  - All patients died when initial trough concentration was < 0.35 mg/L
  - Other factor strongly associated with IFI mortality: immunosuppression
  - A median voriconazole concentration > 2.2 mg/L was the best predictor of microbiological and clinical success

Miyakis Clin Microbiol Infect 2010; 16, 927-33

Relationship with clinical response



Drug toxicity?
Severity of the disease???

FIG. 1. Binomial data and quadratic logistic fit for investigator outcome versus the mean voriconazole plasma concentration for 825 patients. ○, Data points separated as clinical success or clinical failure; - — -, spline (moving average); ——, line of predicted fit; - - -, upper and lower 95% confidence intervals. The curvature was significant at $P < 0.003$.

Troke AAC 2011

Trough concentration/MIC

Trough 2-5

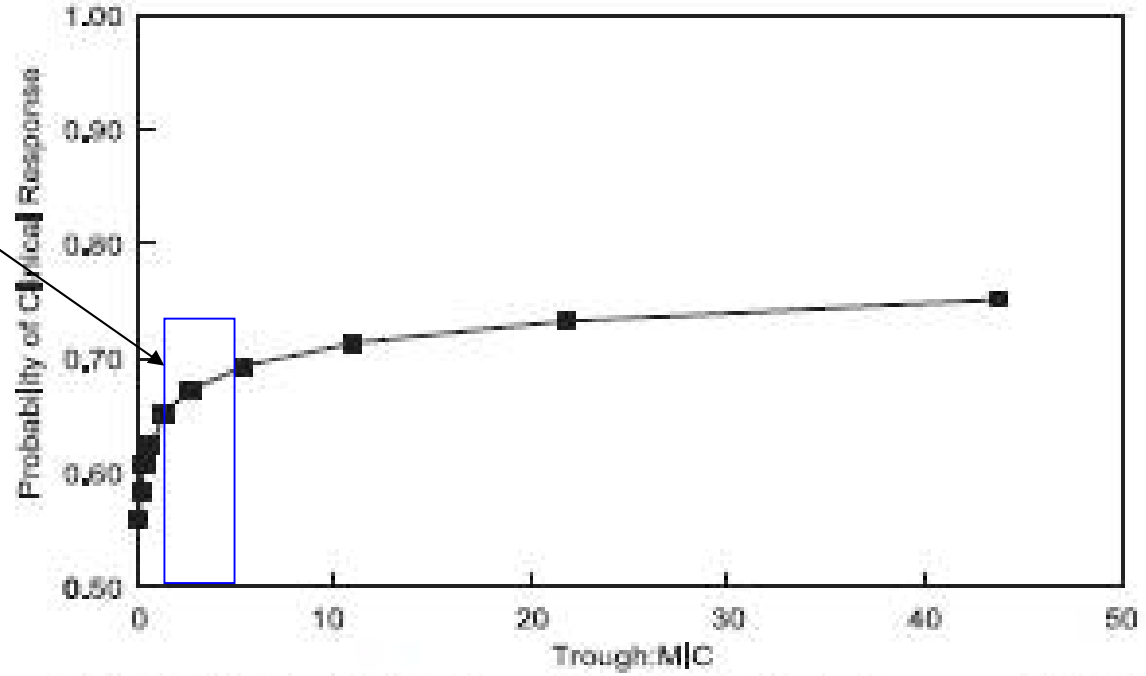


FIG. 3. Relationship between the estimated trough concentration/MIC ratio and the probability of clinical response.

Exposure-toxicity relationship

- Photopsia or disturbance of vision: the most frequent 30%
  - Concentration dependent
  - Transient and fully reversible → no TDM required

- Neurotoxicity and elevated liver enzyme levels

Table 2 Adverse effects of voriconazole

Organ system	Adverse effect
Special senses	Altered light perception Photophobia, blurred vision (<30%)
Cardiovascular system	QTc prolongation
Gastrointestinal disorders	Nausea, vomiting (<5%) Abdominal pain (<10%)
Endocrine system	Adrenal insufficiency (rare)
Liver and biliary system	Increased transaminases (<15%) Hepatitis (rare)
Central nervous system	Hallucinations, confusion (10%) Headache
Skin and appendages	Pruritis, rash (<10%) Photosensitivity (<2%)
Immunologic	Anaphylaxis reported
Maximum tolerated dose in clinical trials	800 mg/day (10 mg/kg/day)

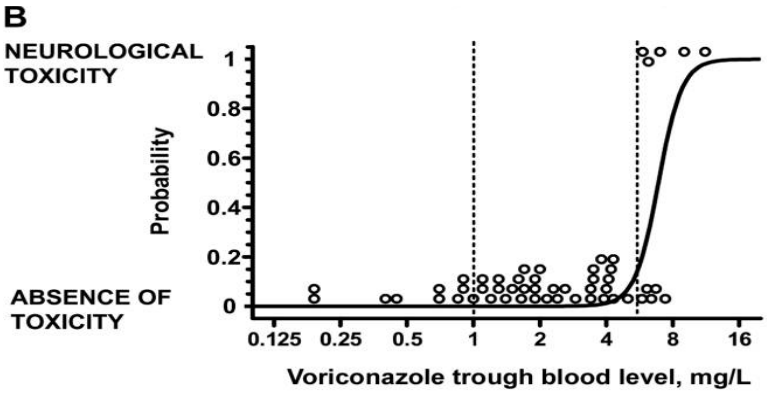
Safety of voriconazole therapy

Table 4. Voriconazole (Vor) 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)[a]	
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

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] The time interval elapsed between start of Vor therapy and documentation of Vor blood levels >5.5 mg/L in patients without encephalopathy was a median of 5 days (range, 2–7 days); $P = .04$, vs. time interval in patients with encephalopathy.



Vori trough level (mg/L)	Estimated probabilitu of neurotoxicity
5.5	15%
8	90%

Only weak correlation between VORI exposure and severity of hepatotoxicity

Pascual CID 2008; 46, 201-211

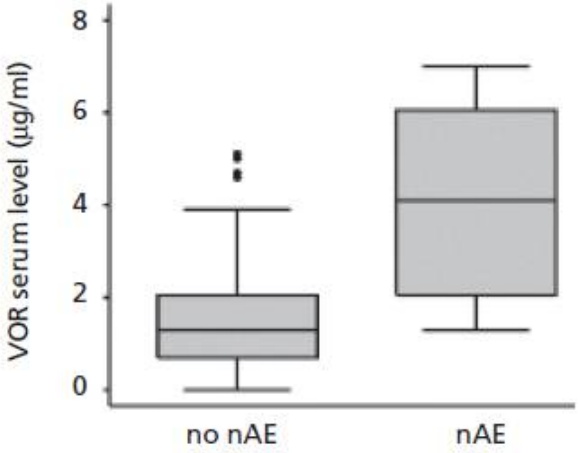
Neurological adverse events to voriconazole: evidence for therapeutic drug monitoring

Alexander Imhof[a], Dominik J. Schaer[a], Urs Schwarz[b], Urs Schanz[a] SWISS MED WKLY 2006;136:739–742 · www.smw.ch

- Analysis of 28 treatment courses
- 6 pts presented with neurological adverse event (hallucination, encephalopathy, visual disturbance)

Figure 1

Box-plot of trough voriconazole levels in patiens with and without neurological adverse events (nAE). Thick bar, median level; box, interquartile range (IQR); whiskers, minimum and maximum levels after exclusion of outliers; dots, outliers (values that are more than the third quartile plus 1.5 × IQR).



Effect of TDM on safety and efficacy

- Randomized, assessor-blinded, controlled, single center trial (110 patients)
- TDM (target range 1.0-5.5 mg/L) versus fixed standard dosage
- No difference in the incidence of adverse events (90% of the adverse events developed within 10 days after starting therapy)
- Discontinuation of VORI due to adverse events: 4 (TDM) vs 17% (no TDM) p: 0.02
- Complete or partial response: 81% (TDM) vs 57% (no TDM →both toxic and subtherapeutic levels) p= 0.04

- Korean patients →poor metabolizers: 13% (prolonged half-life) → TDM may be more useful in non Asian patients

Park Clin Infect Dis 2012; 55: 1080-7

TDM (Australian study)

- Multicenter retrospective study
- 201 patients-783 VORI trough concentrations

- < 1.7 mg/L → greater incidence of treatment failure 26% vs 7%
- > 5 mg/L: more neurologic adverse events (32% vs 1.2%)

- Low concentrations: increasing patient weight, oral administration, coadministration of phenytoin or rifampin
- High concentrations: increasing patient age, coadministration of proton pump inhibitor
- Coadministration of glucocorticosteroids sigificantly reduces VORI concentrations

Dolton AAC 2012; 56: 4793-9

Recommendations for TDM

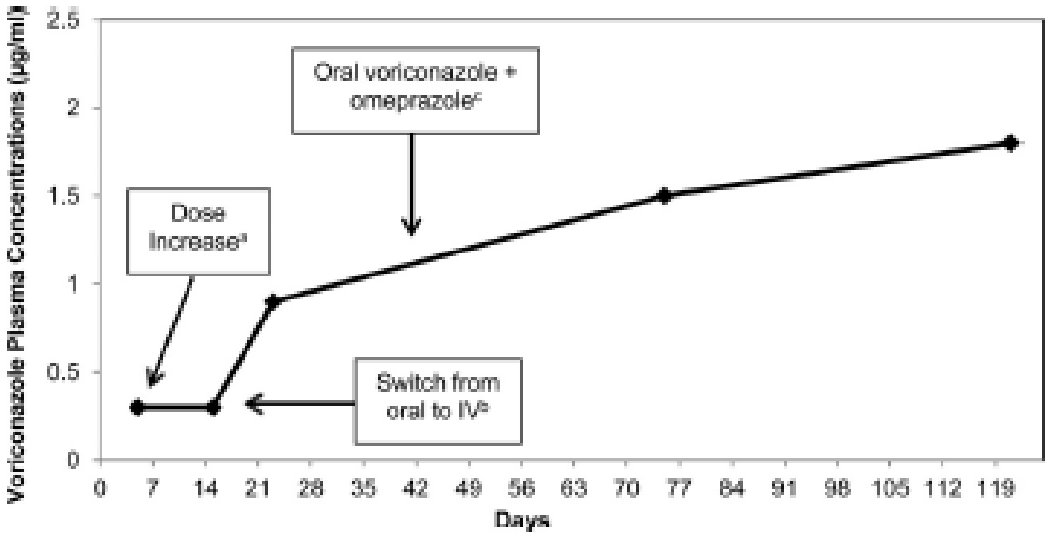
- Efficacy: wide range for voriconazole trough concentrations required for efficacy: 0.35-2.2 mg/L → at least 1-2 mg/L

- Toxicity: increased risk of neurotoxicity (and perhaps hepatotoxicity) when trough concentrations > 5-6mg/L

Optimal serum concentrations:
Between 1 and 5,5 mg/L
(2-4)

Persistently low serum concentration

Try OMEPRAZOLE !!



Boyd Antimicrob Agents Chemother 2012; 56: 6001-2

Critically ill patients

- Initial trough drug level within 48h after a loading dose
- Repeated drug level at the steady state

- In acute severe infection, combination therapy with an other drug untill therapeutic vori serum concentration are obtained

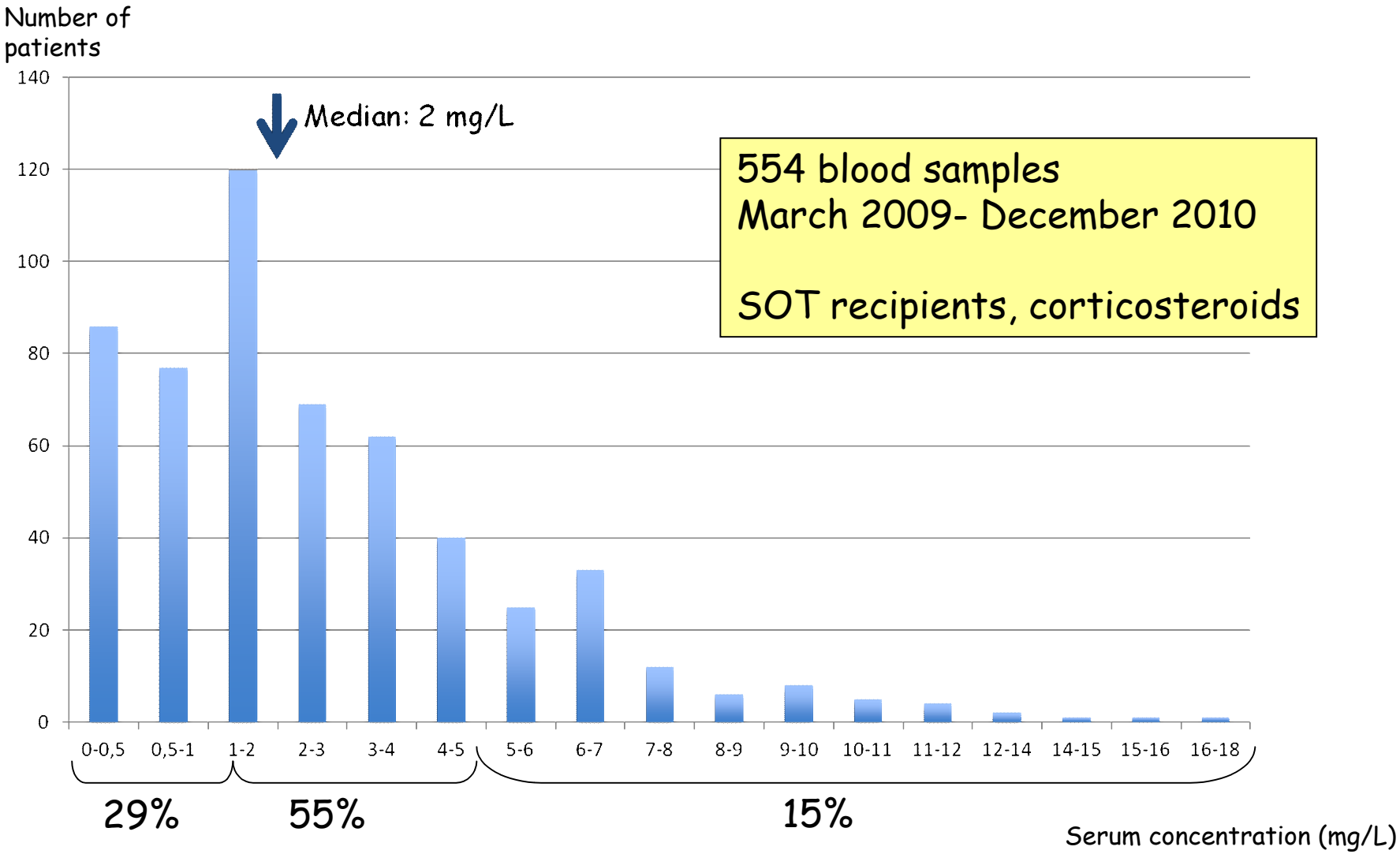
Obese adults

- 8 healthy volunteers (BMI 46 kg/m2):

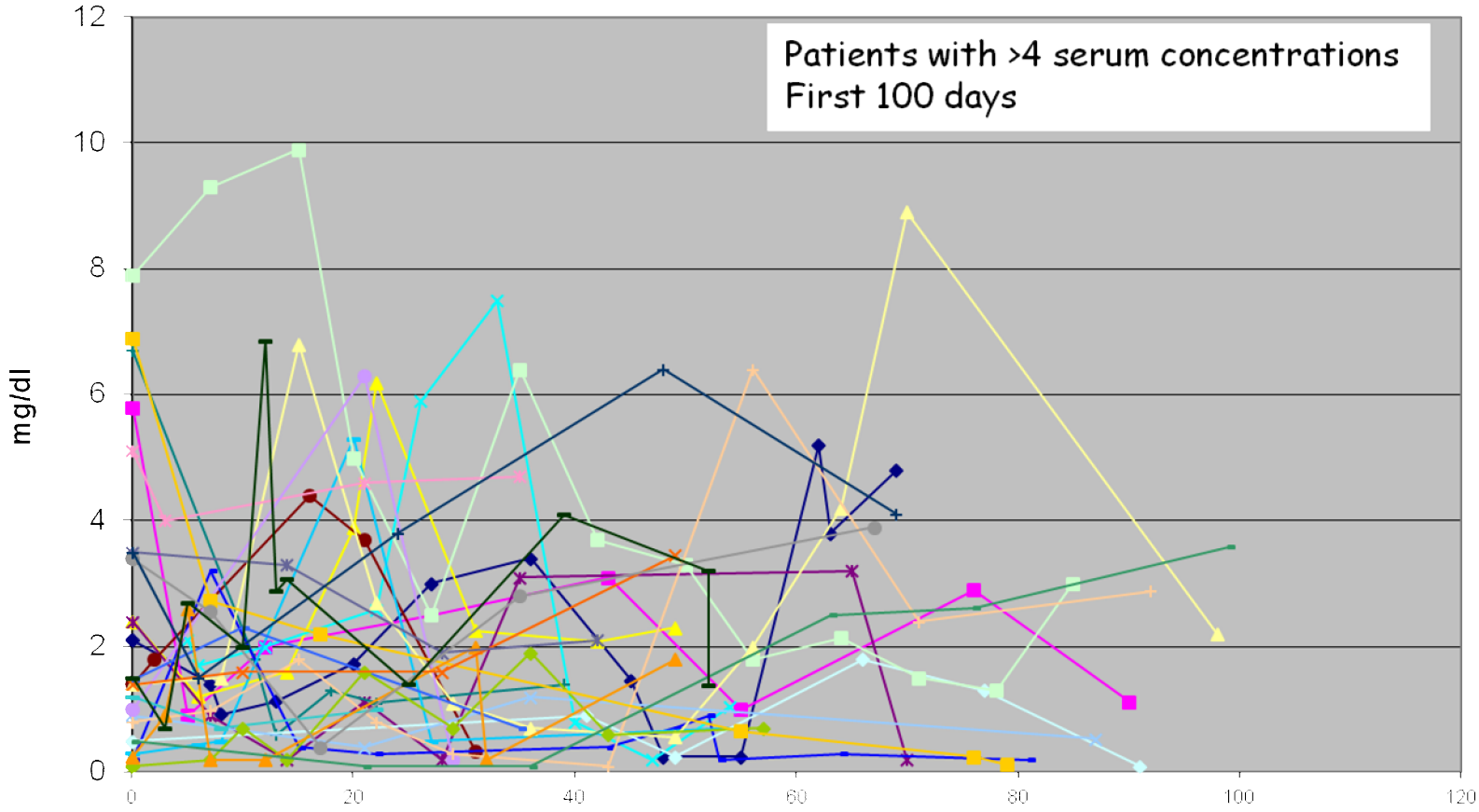
- Positive correlation between lean body weight (stronger than TBW)

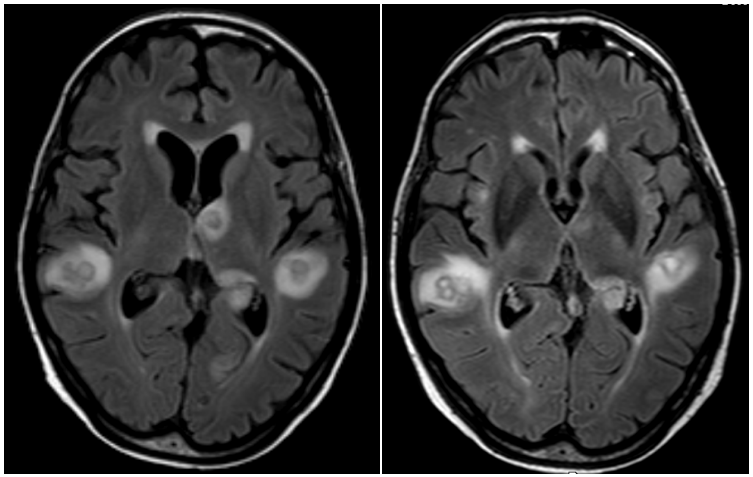
→ no adjustment of doses on the basis of body weight

TDM of voriconazole



Erasme hospital: first 100 days of treatment





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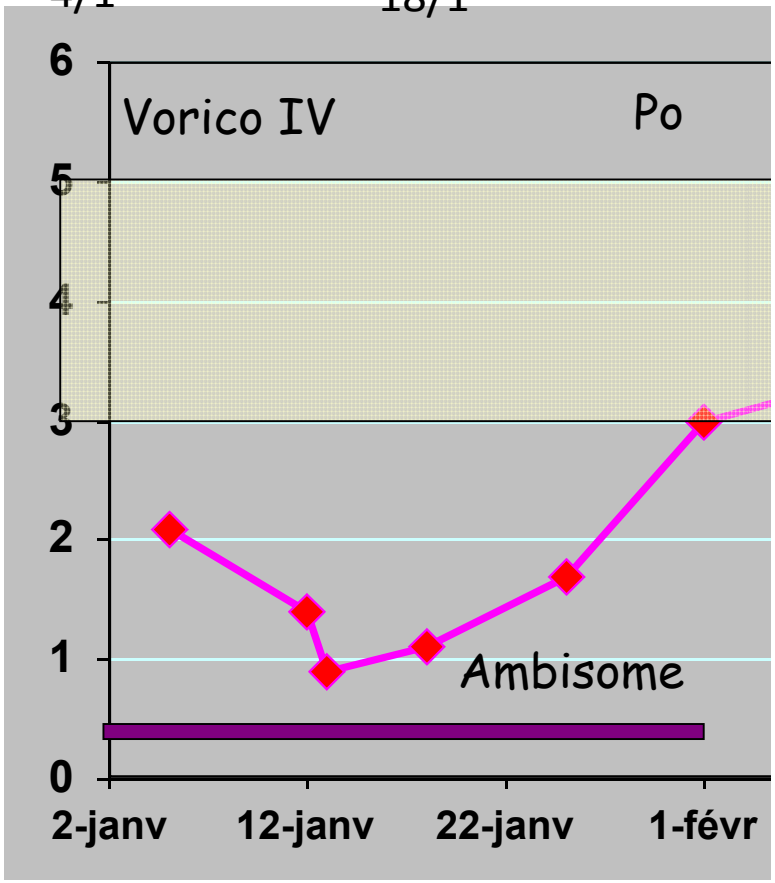

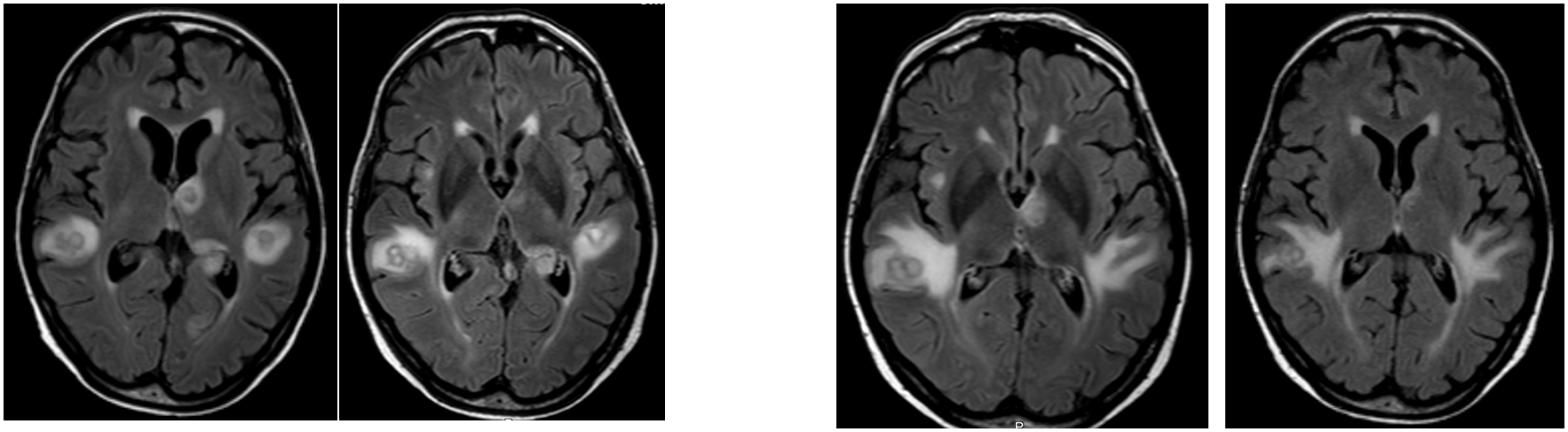
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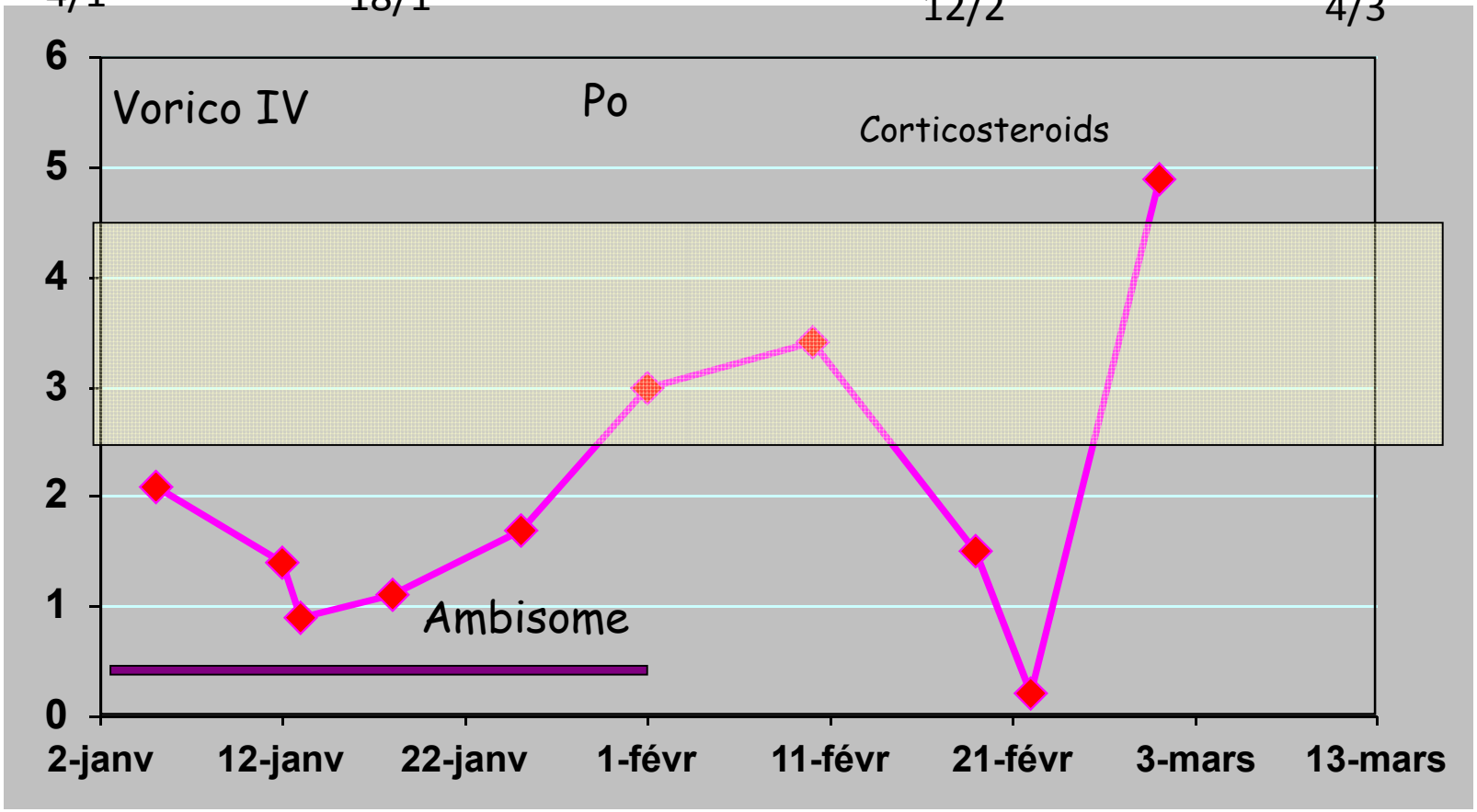
Vorico IV
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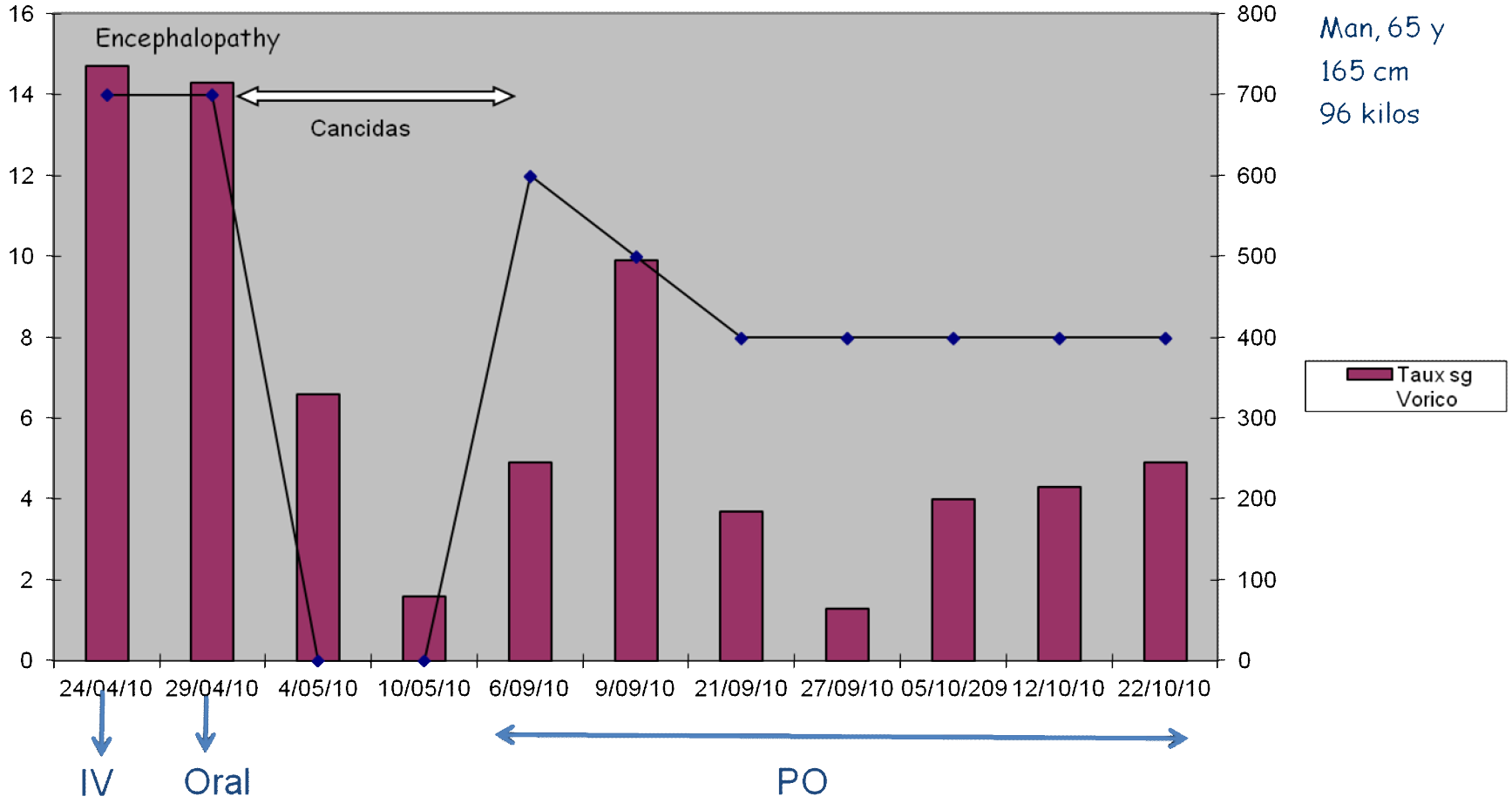
11-févr
21-févr
3-mars
13-mars

Neurological toxicity



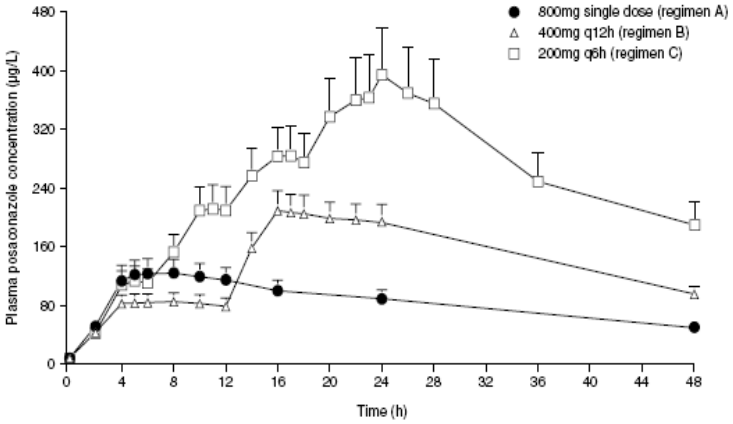
Man, 65 y
165 cm
96 kilos

Posaconazole: absorption

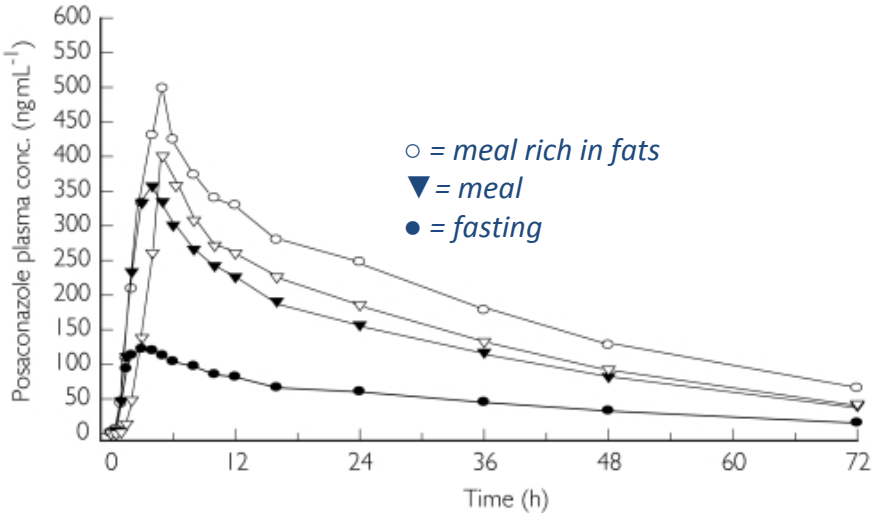
- Only oral formulation available:
  - Dose-proportionnal PK with dose-related increases in exposure up to a total dose of 800mg/d (saturable absorption)
  - **Optimally administered in divided daily doses** (2-4 times/d)

- Administration
  - with food →mean AUC x 2.6 and Cmax x 3
  - With high-fat meal: bioavailability x 4 as compared with the fasting state

→ **Administration of posa with high-fat meal or nutritionnal supplement**

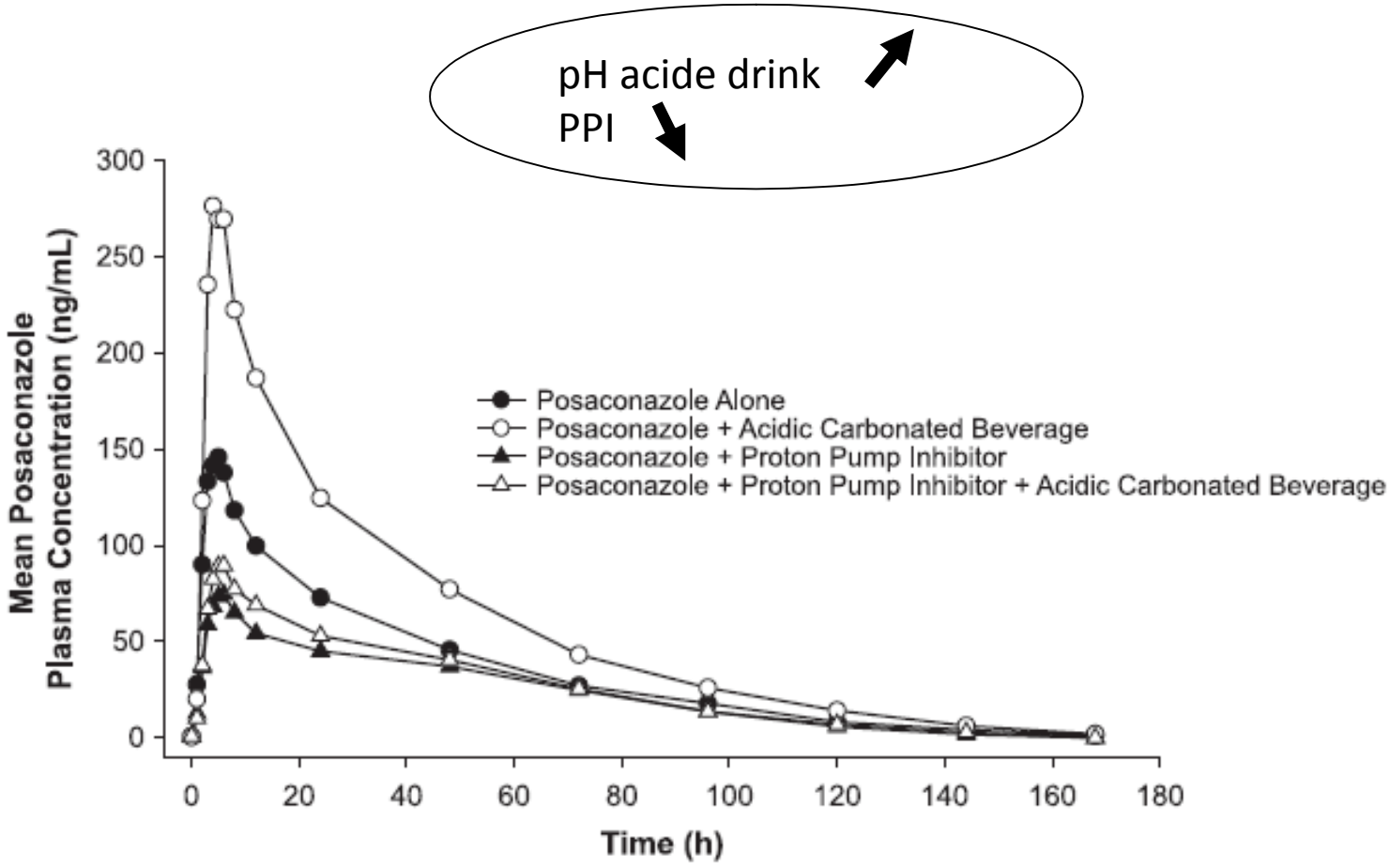


Ezzet F et al. Clin Pharmacokinet 2005



Courtney R et al. Br J Clin Pharmacol 2004

Posaconazole: absorption



Krishna G et al. Antimicrob Agents Chemother 2009

PK of posaconazole

- Great inter-individual and inter-patient variability of plasma posaconazole concentrations

- Plasma concentrations are lower when:
  - Proton pump inhibitors are administered concomitantly
  - Patients are compared to healthy individuals
  - Allogeneic hematopoietic stem cell transplant recipients are compared to non-transplant recipients
  - Patients have diarrhea

Courtney R et al. Br J Clin Pharmacol 2004
Krishna G et al. Antimicrob Agents Chemother 2009
Ezzet F et al. Clin Pharmacokinet 2005
Gubbins PO et al. Antimicrob Agents Chemother 2006
Ullman AJ et al. Antimicrob Agents Chemother 2006
Krishna G et al. Pharmacotherapy 2007
Krishna G et al. Pharmacotherapy 2008

Distribution of serum posaconazole levels

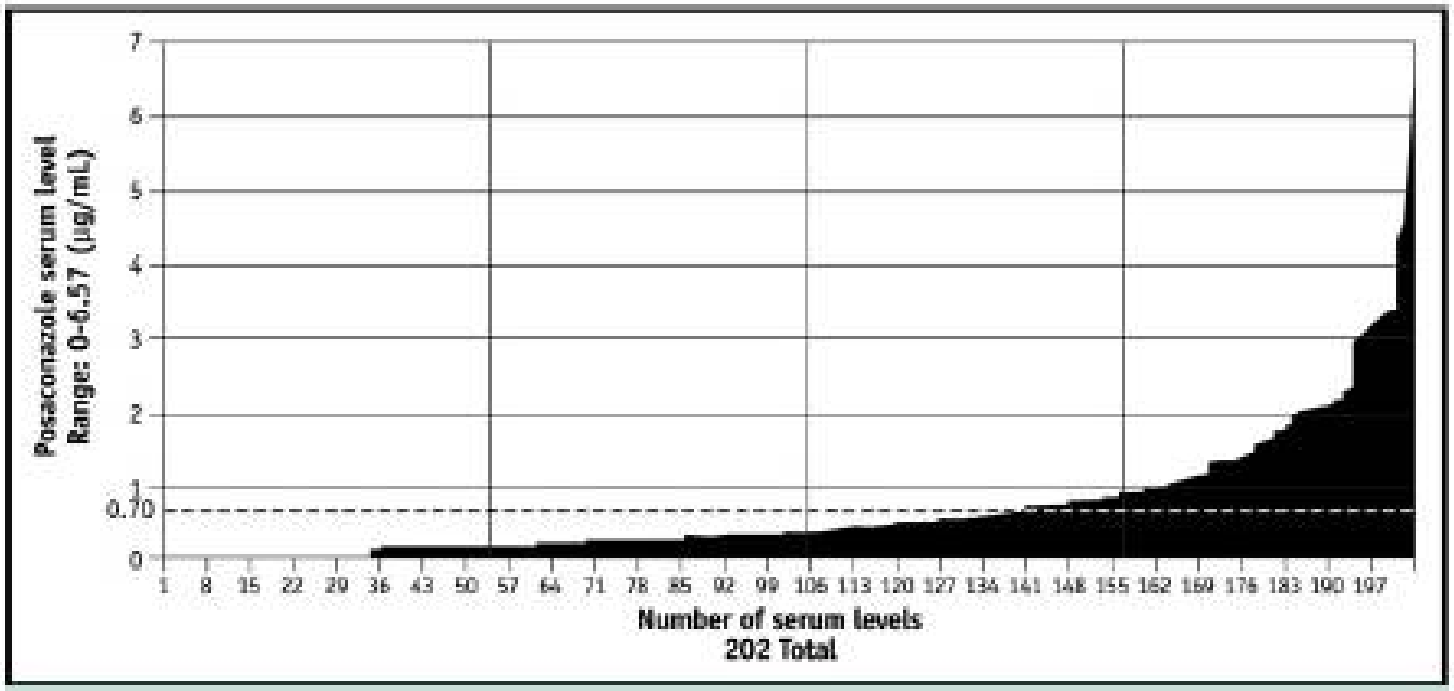


Figure 2 Distribution of serum posaconazole levels obtained by The Fungus Testing Laboratory, San Antonio, Texas, from December 26, 2007 through December 30, 2008. Reproduced from Thompson et al, 2009.[104]

Kontoyiannis Am J Medicine 2012; 125:825

Treatment of invasive fungal infections
Relationship between plasma concentrations and efficacy

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

		Plasma C_{max}		Plasma C_{avg}		
Quartile	No. of subjects[a]	Mean ng/mL	CV, %	Mean ng/mL	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)

NOTE. C_{avg}, average plasma concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation.

[a] Data were available for 67 patients with available plasma concentrations of posaconazole.

Walsh TJ, et al. Clin Infect Dis 2007

Drug interactions

Fluconazole	Inhibitor	3A4+++, 2C19++, 2C9++
Itraconazole	Inhibitor	3A4+++, 2C9+
	Inducer	3A4+++
Voriconazole	Inhibitor	2C19+++, 3A4++, 2C9++
	Inducer	2C19+++, 3A4+, 2C9+
Posaconazole	Inhibitor	3A4+++

Zaas AK, J Invasive Fungal Infec 2007;1:133

Posaconazole: drug-drug interactions

- Should not be administered with rifabutin, phenytoin, or cimetidine unless benefits outweigh risks
- Blood levels of immunosuppressive agents (ciclosporin, tacrolimus, sirolimus) should be monitored and doses adjusted as necessary
- Contraindicated for administration with: terfenadine, astemizole, cisapride, pimozide, halofantrine, quinidine, ergot alkaloids, and HMG-CoA reductase inhibitors
- Other drugs not tested but may result in significant interactions: rifampicin, carbamazepine, phenobarbital, primidone, H2 receptor antagonists and proton pump inhibitors, sirolimus, digoxin, calcium channel blockers, antiretroviral agents, vinca alkaloids, and benzodiazepines

Conclusions on efficacy

- Prophylaxis: too few patients developed IFDs to determine a plasma concentration target for prophylaxis.

Suggested concentrations targets
- 400 – 500 ng/ml for prophylaxis
- 500 – 1500 ng/ml for treatment

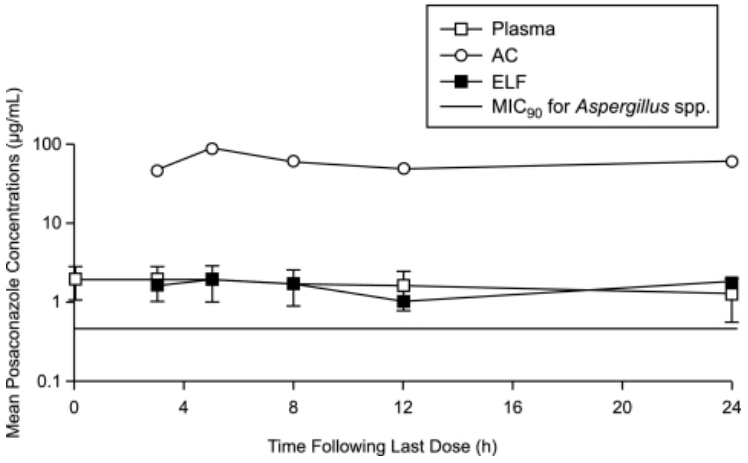
- Long elimination half-life and large volume of distribution → posaconazole accumulates in tissues, reaching concentrations far above those in plasma

Posaconazole concentrations in tissues

ELF and alveolar cells

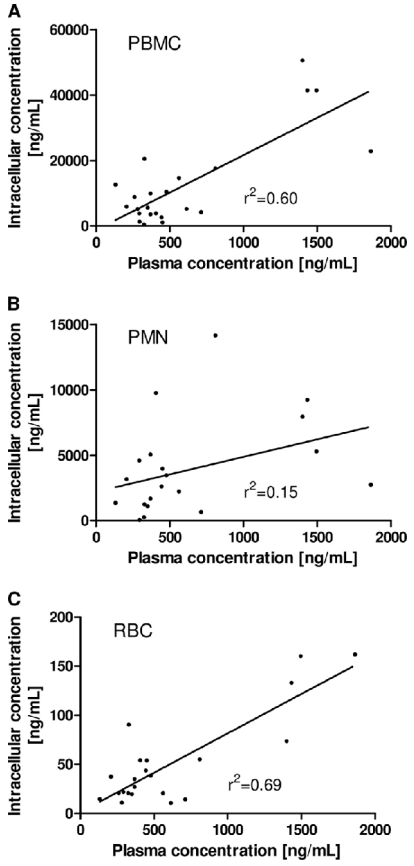
25 healthy adults (Conte):

- up 40 times higher in alveolar cells than in plasma
- The concentrations persisted above the MIC90 of Aspergillus over the 12-hour dosing interval and for 24h after the last dose



Conte. Antimicr Ag Chemother 2009; 53, 703-7

Monocytes and neutrophils



Farowski Antimicr Ag Chemother 2010; 54, 2928-31

The future?

- IV formulation of posaconazole
- Isavuconazole?