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Antimykotische Therapie und TDM: ECIL 6 Guidelines

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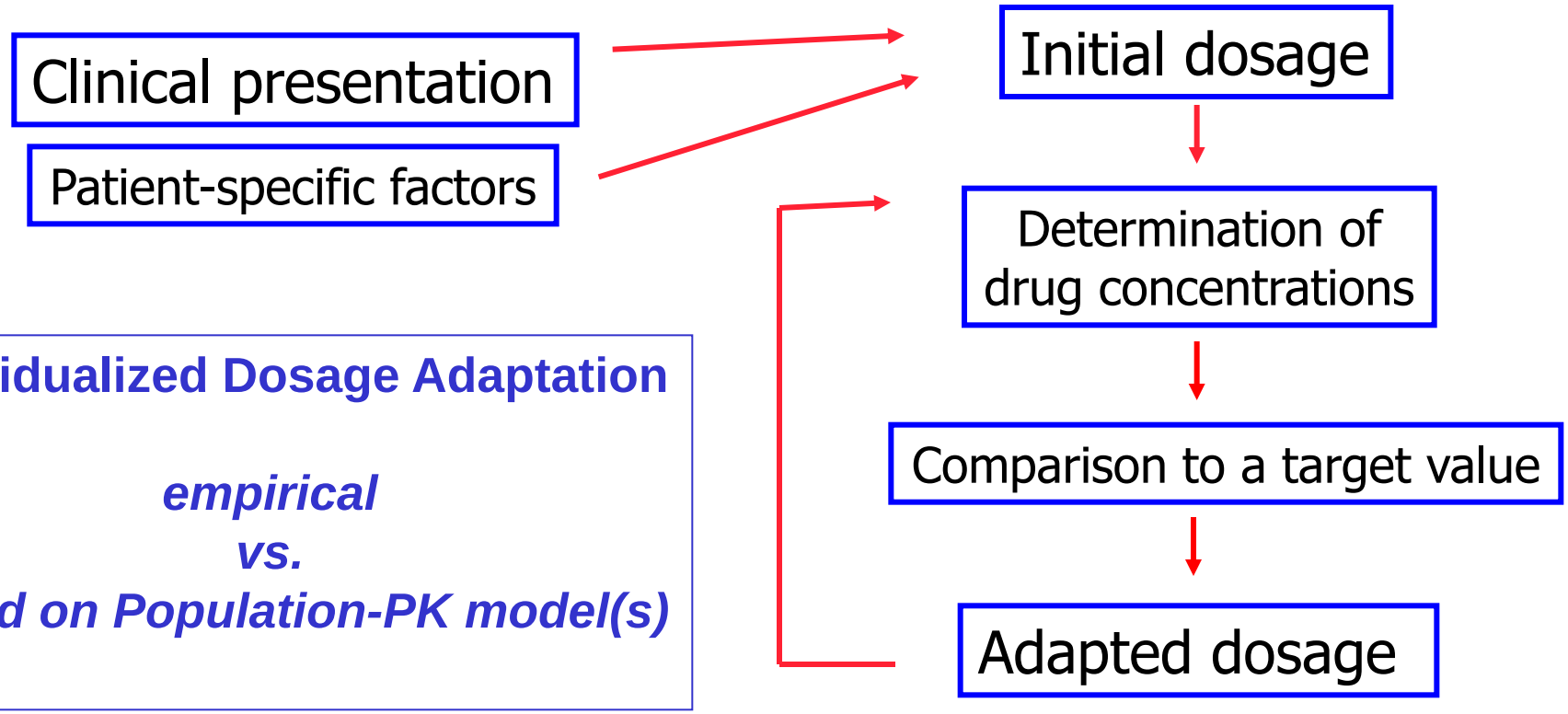
Disclosures

- **Grants**
  - **Gilead, Merck, Sharp & Dohme, Pfizer**
- **Consultant**
  - **Amplyx, Astellas, Basilea, Gilead, Merck, Sharp & Dohme and Schering-Plough**
- **Speakers' bureau**
  - **Astellas, Basilea, Gilead, Merck, Sharp & Dohme, Pfizer, Schering-Plough and Zeneus/Cephalon**

What is Therapeutic Drug Monitoring (TDM) ?

Computation **of individual dosing recommendations based on drug concentrations in body fluids**



Individualized Dosage Adaptation

empirical
vs.
based on Population-PK model(s)

When does TDM make sense ?

- **if there is no readily available parameter of efficacy**
- **in drugs with high pharmacokinetic variability**
- **in drugs with small therapeutic window**
- **in populations at risk for increased toxicity**

- ***established concentration/effect relationships***
- ***established PK/PD target parameter / surrogate (i.e., C_{min})***

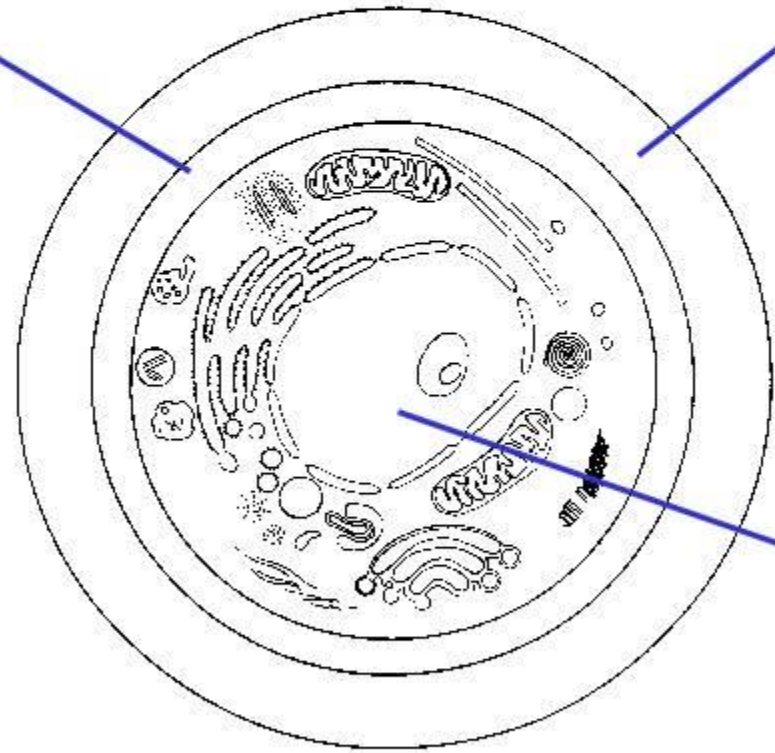
- **validated, robust and rapid analytical method**

Antifungal Agents and TDM

Cell membrane

- **Polyenes**
  - > D-AmB
  - > L-AmB
  - > ABLC

- **Triazoles**
  - > Fluconazole
  - > Itraconazole
  - > Voriconazole
  - > Posaconazole
  - > Isavuconazole



Cell wall

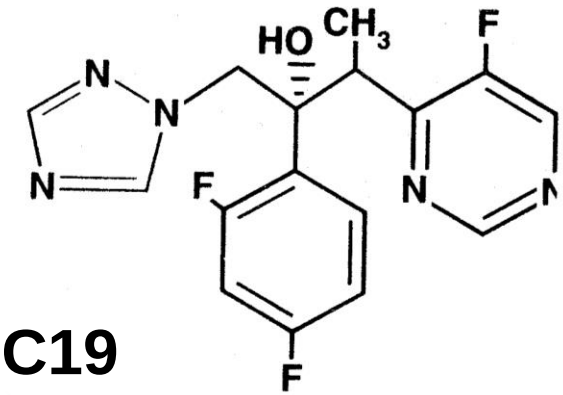
- **Echinocandins**
  - > Caspofungin
  - > Micafungin
  - > Anidulafungin

Nucleic acid synthesis

- > Flucytosine

Voriconazole

Voriconazole



– ***Non-linear pharmacokinetics***

– ***Complex metabolization***

- **Substrate/inhibitor of CYP2C9, 3A4, 2C19**
- ***Genetic polymorphisms of CYP2C19***
- ***Changing metabolism rates (autoinduction)***
- ***Children: intestinal first-pass metabolism ****

– ***Number of relevant pharmacokinetic interactions***

➡ ***High variability in exposure***

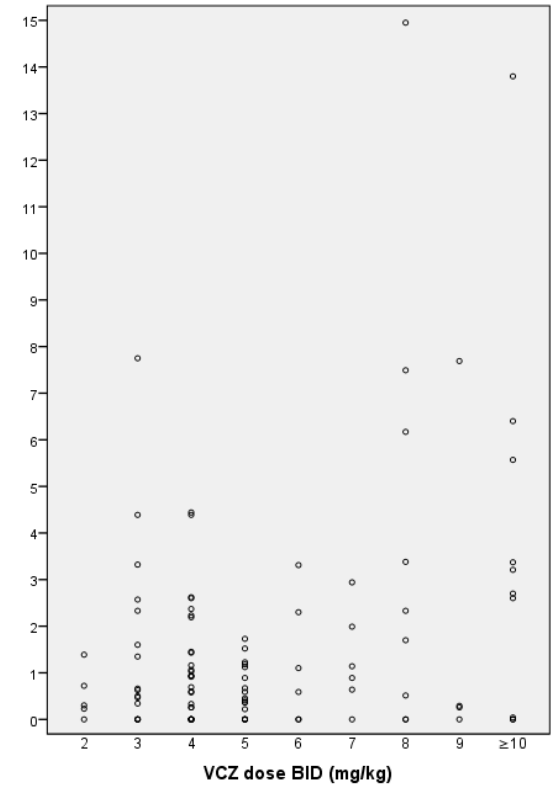
➡ ***Toxicity issues with link to exposure***

** Zane et al., Clin Pharmacokinet 2014*

VCZ – Relationship of Dose and Exposure

74 pts (0.2-18y; mean: 10.2y) / 101 courses of VCZ IV (4) and (15)/or (82) PO at median of 4.8 mg/kg BID (r, 2.2-17.4) for a median of 40 days (r, 6-1002)

Voriconazole trough [mg/L]	No. (%) of samples
< 0.2	*56 (22.3)*
0.2 – 0.5	*50 (19.9)*
> 0.5 – 1.0	39 (15.5)
> 1.0 – 2.0	36 (14.3)
> 2.0 – 5.0	50 (19.9)
> 5.0	20 (8.0)

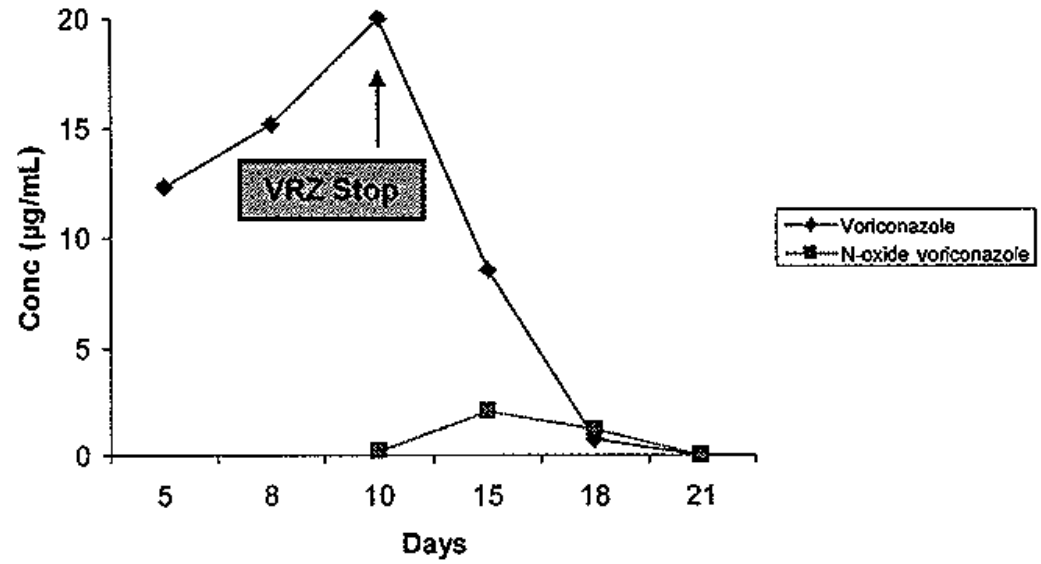


- ***no predictable dose-concentration relationships***
- ***high intra-individual variability in concentrations***
- ***quarter of samples with undectable levels***

Pieper et al. JAC 2012

VCZ – Relationship of Dose and Exposure

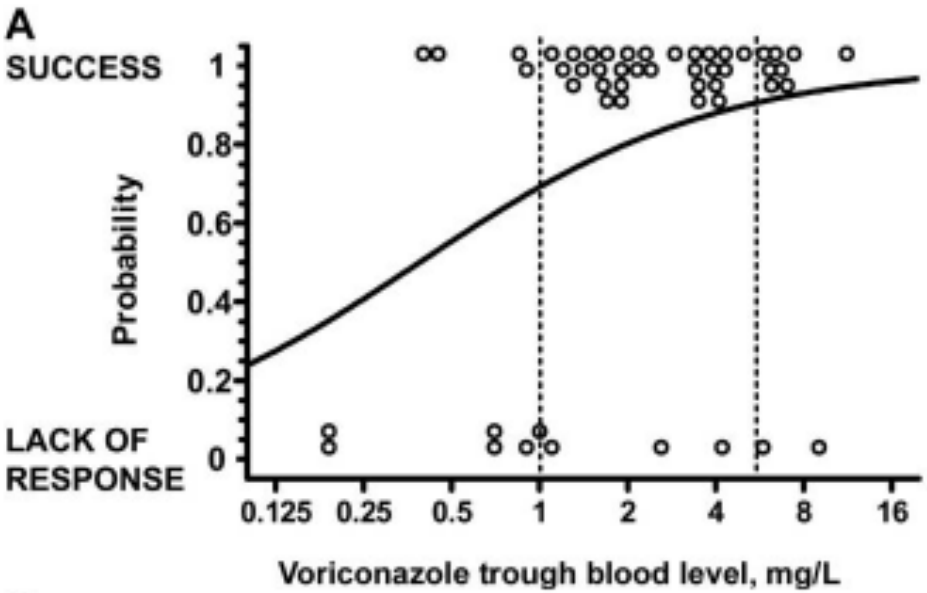
Unpredictable accumulation of VCZ in a patient without any genetic risk factor in CYP2C19 / CYP 2C9 resulting in hallucinations and coma

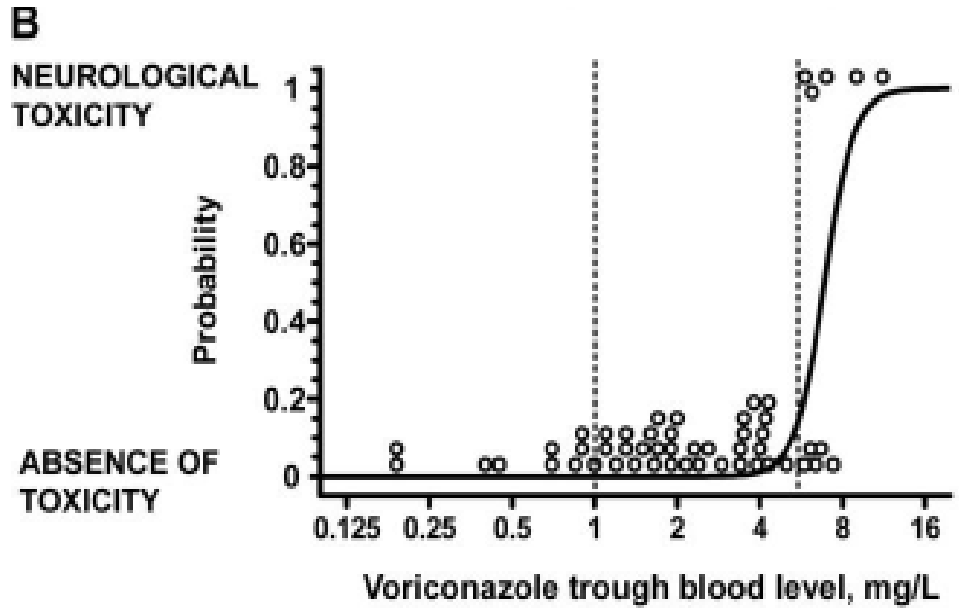


Lemaitre et al, Drug Metab. Pharmacokinet 2013

VCZ TDM – Correlation with Outcome in Patients with IFIs

- *trough levels ≤1mg/L associated with treatment failure*
- *trough levels ≥5.5 mg/L assoc. with neurological toxicity*



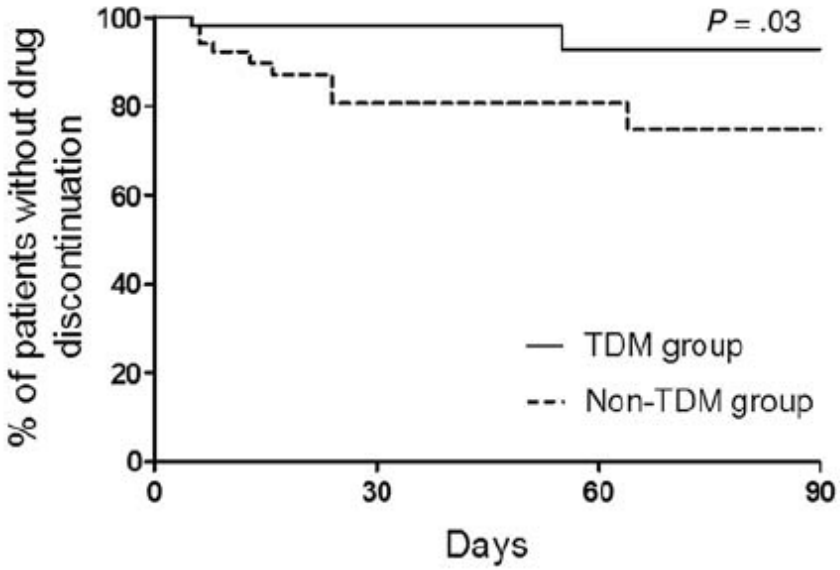


- *Blood levels >1 mg/L reached after increasing the dosage with complete resolution of infection in all 6 cases*

Pascual et al. CID 2008

VCZ TDM – Correlation with Outcome in Patients with IFIs

- *randomized assessor-blinded single center study in 110 pts (75% IFDs)*
- *no TDM vs. TDM (target conc.1.0-5.5 mg/L) based on trough on day 4*



	TDM (n = 37)	Non-TDM (n = 34)	*P* Value
Treatment success	30 (81)	20 (59)	.04
Complete response	21 (57)	13 (38)	.12
Partial response	9 (24)	7 (21)	.71
Stable response	1 (3)	2 (6)	.60
Treatment failure	6 (16)	12 (35)	.07

Abbreviation: TDM, therapeutic drug monitoring.

Routine TDM of VCZ may reduce discontinuation due to AEs and improve the treatment response in invasive fungal infections

Park et al. CID 2012

Utility of voriconazole therapeutic drug monitoring: a meta-analysis

Me-Linh Luong[1]*, Mona Al-Dabbagh[2,3], Andreas H. Groll[4], Zdenek Racil[5], Yasuhito Nannya[6], Dimitra Mitsani[7] and Shahid Husain[2]

Journal of Antimicrobial Chemotherapy

- **Meta-analysis of 24 studies assessing relationship btwn. VCZ serum concentration and success / toxicity**
- **Pooled analysis demonstrated that**
  - ***72.4% of pts. with therapeutic serum concentrations vs. 63.1% in those with sub-therapeutic concentrations had successful outcome*** **(P=0.001)**
  - **Pts. with therapeutic conc. (1.0–2.2 mg/L)** ***more likely to have successful outcomes*** **(OR 2.30; 95% CI 1.39–3.81)**
  - **Pts. with supratherapeutic serum VCZ levels had 4-fold increased likelihood of toxicity (OR 4.17; 95% CI 2.08–8.36)**

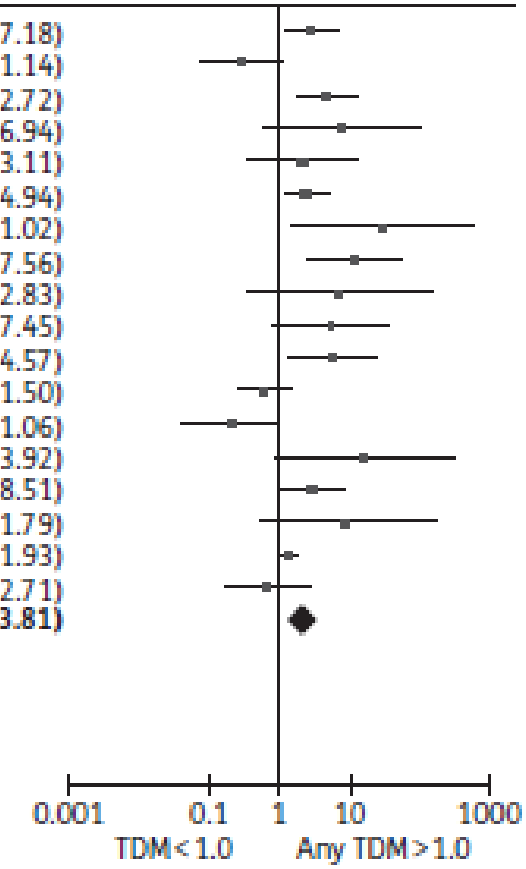
Luong et al., JAC 2016

Luong et al.: Relationship between VCZ concentrations and successful outcome

Study or subgroup	Any TDM > 1.0 Events	Total	TDM < 1.0 Events	Total	Weight	OR, 95% CI
Choi et al.[17]	53	75	13	29	8.1%	2.97 (1.22, 7.18)
Chu et al.[33]	13	33	9	13	6.0%	0.29 (0.07, 1.14)
Dolton et al.[27]	83	89	55	74	7.7%	4.78 (1.80, 12.72)
Gomez-Lopez et al.[16]	6	7	3	7	2.8%	8.00 (0.60, 106.94)
Lee et al.[18]	24	46	2	6	4.6%	2.18 (0.36, 13.11)
Mitsani et al.[28]	56	73	48	84	9.0%	2.47 (1.23, 4.94)
Miyakis et al.[5]	9	9	6	16	2.2%	30.69 (1.52, 621.02)
Neely et al.[19]	26	29	7	17	5.4%	12.38 (2.66, 57.56)
Okuda et al.[25]	6	20	0	8	2.2%	7.62 (0.38, 152.83)
Park et al.[31]	49	62	2	5	4.3%	5.65 (0.85, 37.45)
Pascual et al.[5]	34	39	7	13	5.8%	5.83 (1.38, 24.57)
Pieper et al.[30]	34	49	41	52	8.1%	0.61 (0.25, 1.50)
Racil et al.[29]	22	36	15	17	5.1%	0.21 (0.04, 1.06)
Smith et al.[14]	10	10	10	18	2.3%	17.00 (0.87, 333.92)
Soler-Palacin et al.[32]	26	35	16	33	7.5%	3.07 (1.11, 8.51)
Trifilio et al.[15]	27	27	38	44	2.3%	9.29 (0.50, 171.79)
Troke et al.[7]	465	663	103	162	10.3%	1.35 (0.94, 1.93)
Ueda et al.[26]	22	31	14	18	6.1%	0.70 (0.18, 2.71)
Subtotal (95% CI)		**1333**		**616**	**100.0%**	**2.30 (1.39, 3.81)**
Total events	965		389			

Heterogeneity: $\tau^2 = 0.61$; $\chi^2 = 49.56$, df = 17 ($P < 0.0001$); $I^2 = 66\%$

Test for overall effect: $Z = 3.24$ ($P = 0.001$)



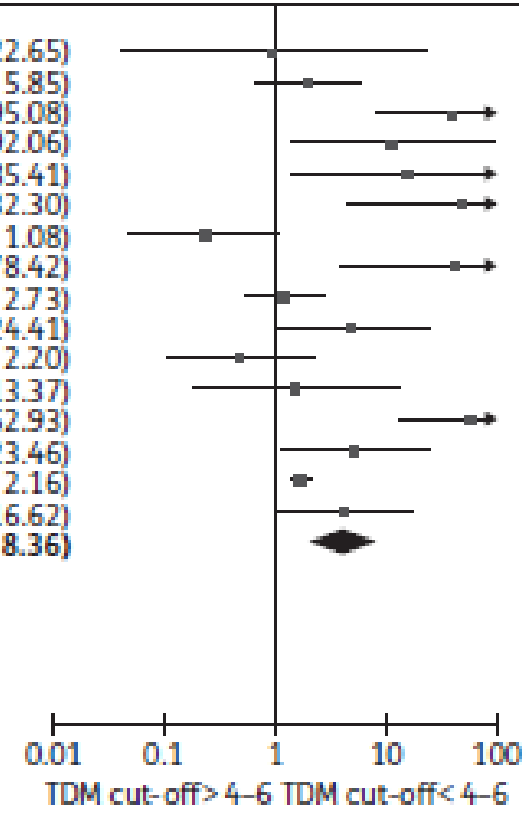
Luong et al., JAC 2016

Luong et al.: Relationship between VCZ concentrations and toxicity

Study or subgroup	TDM cut-off > 4–6 Events	Total	TDM cut-off < 4–6 Events	Total	Weight	OR, 95% CI
Bruggemann et al.[22]	0	2	6	37	3.2%	0.97 (0.04, 22.65)
Chu et al.[33]	9	16	36	92	7.9%	2.00 (0.68, 5.85)
Dalton et al.[27]	10	31	2	170	6.5%	40.00 (8.20, 195.08)
Imhof et al.[20]	4	7	2	19	5.2%	11.33 (1.40, 92.06)
Kim et al.[21]	4	5	4	20	4.4%	16.00 (1.38, 185.41)
Matsumoto et al.[23]	9	12	1	17	4.5%	48.00 (4.33, 532.30)
Mitsani et al.[28]	2	19	25	74	6.6%	0.23 (0.05, 1.08)
Okuda et al.[25]	8	9	3	19	4.5%	42.67 (3.81, 478.42)
Park et al.[31]	18	39	26	63	8.6%	1.22 (0.55, 2.73)
Pascual et al.[5]	5	16	3	36	6.5%	5.00 (1.02, 24.41)
Pieper et al.[30]	5	77	3	24	6.7%	0.49 (0.11, 2.20)
Racil et al.[29]	1	7	25	257	5.0%	1.55 (0.18, 13.37)
Soler-Palacin et al.[32]	8	14	4	182	6.9%	59.33 (13.92, 252.93)
Suzuki et al.[24]	7	14	4	25	6.7%	5.25 (1.18, 23.46)
Tan et al.[8]	145	486	417	2116	9.7%	1.73 (1.39, 2.16)
Ueda et al.[26]	8	20	4	29	7.0%	4.17 (1.04, 16.62)
Subtotal (95% CI)		**774**		**3180**	**100.0%**	**4.17 (2.08, 8.36)**
Total events	243		565			

Heterogeneity: $\tau^2 = 1.29$; $\chi^2 = 71.15$, df = 15 ($P < 0.00001$); $I^2 = 79\%$

Test for overall effect: $Z = 4.02$ ($P < 0.0001$)



Luong et al., JAC 2016

Voriconazole concentration-efficacy relationship

- ***Prospective*** **studies have reported trough concentrations of ≥ 1.5-2 mg/L are associated with near maximal clinical response in treatment of IFI** [1-6]

- **Post-hoc analysis of Phase II/III clinical trials:**[4]
  - Vori C_{avg} /MIC target > 2, or vori plasma 2-5 mg/L
  - Response rate: 74%

Recommendation: voriconazole prophylaxis and treatment target: > 1-2 mg/L **(AII);**

higher troughs (> 2) are recommended for severe infections or when there are concern of treating fungi with elevated MICs

1. Pascual A,et al. Clin Infect Dis 2012; 55: 381–390.
2. Pascual A, et al. Clin Infect Dis 2008; 46: 201–211.
3. Park WB et al. Clin Infect Dis 2012; 55: 1080–1087.
4. Troke PF, et al. Antimicrob Agents Chemother 2011; 55: 4782–47
5. Trifilio S et al. Bone Marrow Transplant 2007; 40: 451–456.
6. Dolton MJ et al. Antimicrob Agents Chemother 2012; 56: 4793–4799

Voriconazole concentration-toxicity relationship

Recommendation: voriconazole safety target: < 5.0-6.0 mg/L (AII);

Patients without symptoms of clinical toxicity may not require dose reductions

Maintenance of exposures near this threshold may be needed for severe infections (e.g., CNS infection) or when treating fungi with elevated MICs

1. Pascual A,et al. Clin Infect Dis 2012; 55: 381–390.
2. Pascual A, et al. Clin Infect Dis 2008; 46: 201–211.
3. Dolton MJ et al. Antimicrob Agents Chemother 2012; 56: 4793-4799
4. Zonios D et al. J Infect Dis 2014;209:1941-1948.
5. Tan K et al. J Clin Pharmacol 2006; 46: 235–243.
6. Matsumoto K, et al. Int J Antimicrob Agents 2009; 34: 91-94.
7. Suzuki Y,et al.Clin Chim Acta 2013; 424: 119-122.
8.Atsushi et al. J Ped Oncol 2013;35:p e219-e223

Voriconazole TDM approach

First trough sample 2-5 days
(or after 5th dose including loading doses):

Trough should be repeated during second week of therapy to confirm patient in therapeutic range (1-6 mg/L):

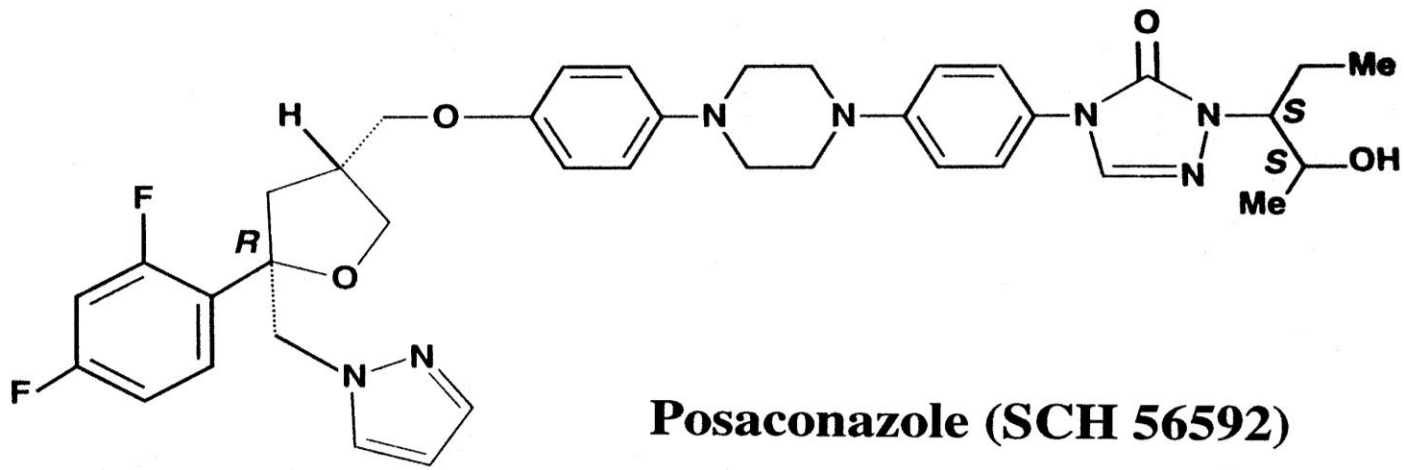
Recheck trough 3-5 days if:

- Change in dose or IV to oral switch
- Change in clinical condition (e.g., uncontrolled IFI or suspected toxicity)
- New interacting drug is started or stopped

Detailed recommendations for dose adjustments
Population-Pk based computer programs at the door

Posaconazole

Posaconazole



Posaconazole (SCH 56592)

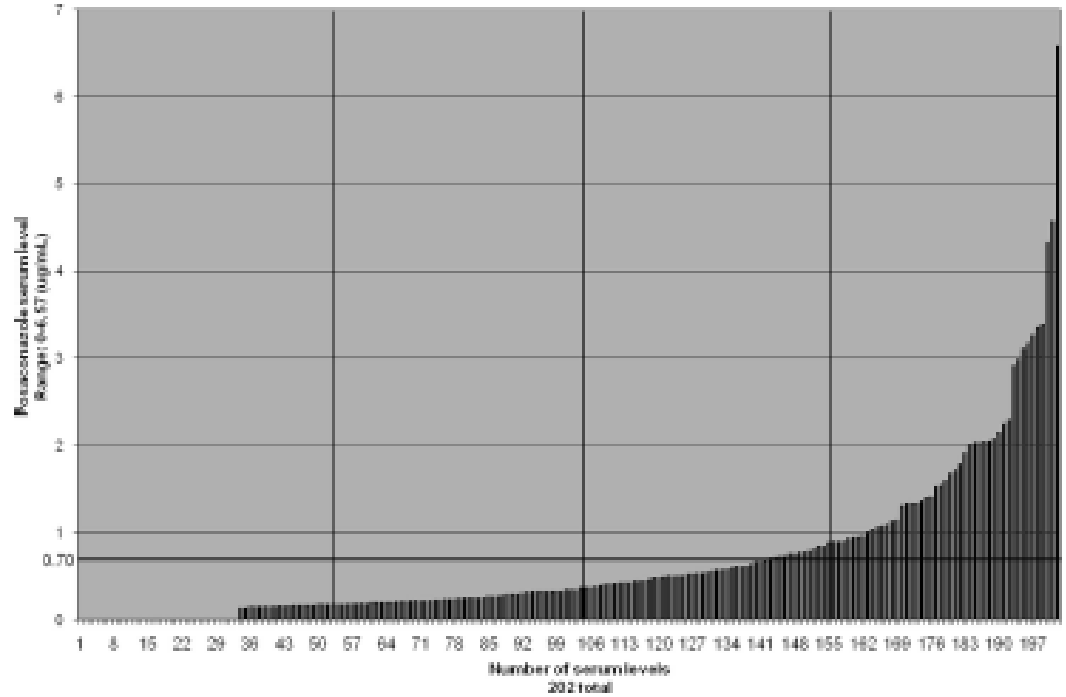
- ***linear pharmacokinetics up to 800 mg (S)***
  no CYP-mediated hepatic metabolization
  inhibitor, but no substrate of CYP 3A4
- ***No toxicity issues, but issues with absorption***

Posaconazole Suspension: Inter-Patient Variability

- **Retrospective review of all PCZ concentrations measured between 12/07 and 12/08 by a reference laboratory**

  - **No information on dose, timing of the sample, and indication**

    - **60% <500**
    - **70% <700**
    - **80% <1000 ng/mL**



Thompson et al. 09

TDM for Posaconazole: Clinical Data, Prophylaxis

- **Food, gastric pH, gastric motility, mucosal disease (muco-sitis, diarrhea) weight and concomitant chemotherapy all affect PK and explain PK variability of the suspension**

➡ **No significant relationship between exposure and preventative efficacy in large prophylaxis studies**

➡ **MIC90 values of *Aspergillus* spp and limited clinical data suggest a dosing target of ≥500 ng/mL; FDA and EMA agreed on a lower boundary of C_{avg} of 500 ng/mL for dose finding studies with new formulations**

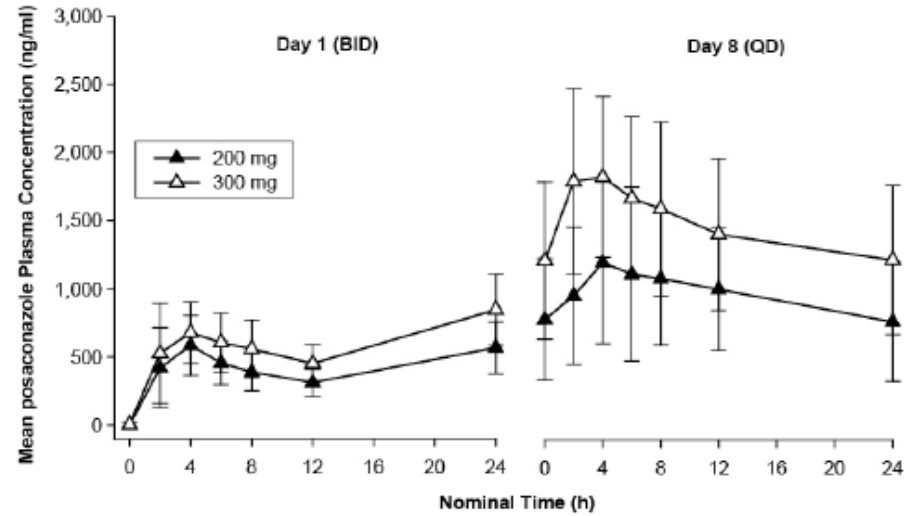
Ullmann 06; Gubbins 06; Ullmann 07; Krishna 07; Cornely 07; Krishna 08; Lebeaux 09; Jang 2010; Kohl 2010; Walravens 2011; Vehreschild 2012; Dolton 2012; Assessment report EMA/159150/2014

Posaconazole: Delayed Release Tablet

pH-sensitive, acid-resistant polymer matrix

- **enhanced bioavailability, less variability in exposure**

- **Phase 1B dose-ranging multicenter PK study in 51 pts with AML/MDS**
- **200 and 300 mg QD (d1: BID)**
  - **300 mg QD attained prespecified exposure target (≥500 and ≤2500 ng/mL, d8) in 97 % of pts (mean Cavg 1460 ng/mL; AR: 2,5)**
  - **Loading with 300 mg BID on d1 attained Cavg >500 ng/mL in all**
  - **no safety issues**



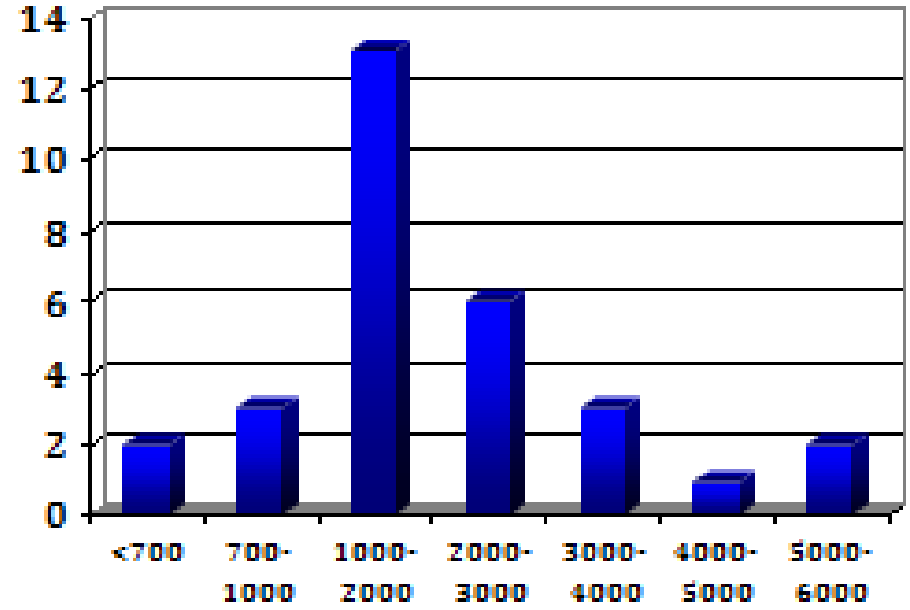
Krishna et al, AAC 2012; Krishna et al, JAC 2012; Kraft et al, AAC 2014; Duarte et al, AAC 2014

Plasma Exposures following Posaconazole Delayed Release Tablets

- 20 pts, median age 14.8 yrs (5-18;6<13), median BW 49 kg (21-85)
  - approved dose in 16, modified in 4 pts for median of 40 d (20-303)
  - total of 30 trough levels

➡ Median trough concentration 1661 +/-1459 ug/L

➡ Trough concentrations above target of 700 ug/l in 28/30 occasions



*Herbrüggen Mycoses 2016; * Neely ICAAC 2015*

Posaconazole concentration- prophylaxis efficacy

- **Pharmacokinetic analysis of two pivotal prophylaxis trials utilizing suspension formulation did not report significant concentration-effect relationships 1,2**
  - **Median POS 0.61 mg/L (breakthrough IFI) vs. 0.92 mg/L (no breakthrough)**

- **Other monocentric studies reported concentration-response relationship between posaconazole plasma trough levels and risk of breakthrough infection** [2-7]
  > 0.5 or 0.7 mg/L

Recommendation: prophylaxis target: > 0.7 mg/L (BII)

Tablet formulation (or IV formulation) are preferred formulations to maximize probability of achieving target plasma levels (AII)

1. Krishna G et al. Pharmacotherapy:2008; 28: 1223–1232.
2. Krishna G, et al. Journal of Clin Pharmacol 2007; 27: 1627–1636.
3. Lebeaux D. Antimicrob Agents Chemother 2009; 53: 5224–5229.
4. Bryant AM, . Int J Antimicrob Agents 2011; 37: 266–269.
5. Eiden C, Eur J Clin Microbiol Infect Dis 2012; 31: 161–167.
6. Hoenigl M, Int J Antimicrob Agents 2012; 39: 510–513.
7. Cattaneo et al. Mycoses 2015; 58, 362–367

Posaconazole concentration- toxicity

- **No relationship between adverse effects and plasma concentrations for oral suspension [1-3]**
- **Pharmacokinetic bridging studies for gastroresistant tablet and IV formulation used an upper plasma target of 3.75 mg/L[3]**

Recommendation: At present, insufficient data to recommend target trough for safety ***further data are needed***

1. Jang SH et al. Clinical Pharmacology & Therapeutics 2010; 88: 115–119.
2. Cantanzaro et al. Clinical Infectious Diseases 2007;45:562-568.
3. European Medicine Agency. Assessment report: Noxafil. 2014. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000610/human_med_000937.jsp&mid=WC0b01ac058001d124. Accessed 30 April 2015.

Posaconazole gastroresistant tablet and IV formulations

Up to 10 % of patients receiving new posaconazole formulations may not achieve plasma targets > 0.7 mg/L.[1-3] The percentage of patients not reaching treatment target (> 1 mg/L) will be higher

It is unknown whether risk for inadequate exposures can be predicted based on observable clinical risk factors alone (e.g., mucositis, aGVHD). Therefore, TDM remains the most direct approach for identifying patients with suboptimal posaconazole plasma levels

- Pending further data, TDM is still recommended in patients receiving posaconazole tablets or IV formulation for prophylaxis **(CIII)**
- TDM is recommended in patients receiving posaconazole tablets or IV formulation receiving treatment for suspected or documented fungal infection **(CIII)**
- TDM is indicated for patients receiving tablets or IV formulation in the setting of breakthrough or progressing infection unresponsive to treatment, treatment of pathogens with reduced susceptibility, or drug interactions **(CIII)**

additional data are needed

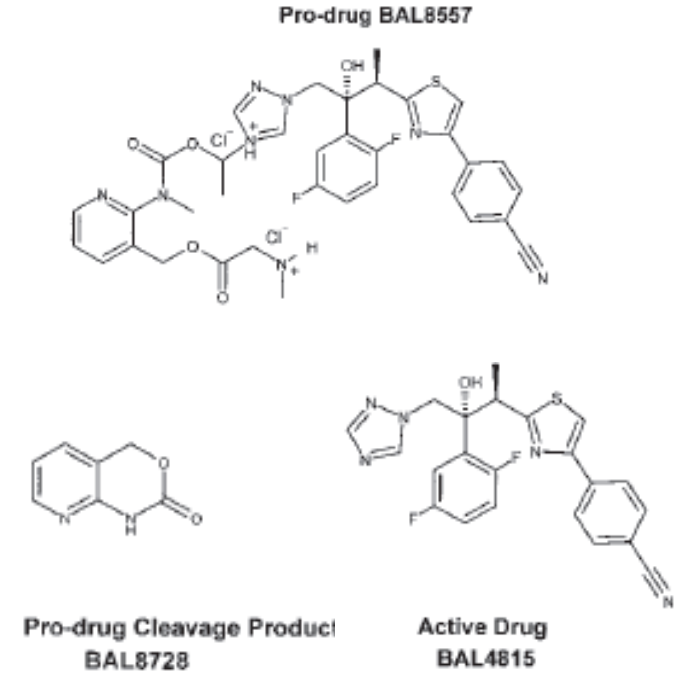
1. Cumpston et al. Antimicrob Agent Chemother 2015;59:4424-4428
2.Durani et al. Antimicrobial Agent Chemother 2015;59:4914-4918
3. European Medicine Agency. Assessment report: Noxafil. 2014. Accessed 30 April 2015.

Isavuconazole

Isavuconazole (BAL-4815)

Administered as BAL8557, a water-soluble pro-drug suitable for oral and intravenous administration

- **Favorable PK properties**
  - **linear PK, long t ½, high tissue distribution**
  - **98% bioavailability, not affected by pH or food**
  - **less PK variability versus voriconazole**
- **Interaction profile similar to other azoles**
- **Safety improved relative to voriconazole**



Approved for inv. aspergillosis and mucormycosis

[1] *Schmitt-Hoffmann et al, AAC 2006;*
[2] *Schmitt-Hoffmann et al, AAC 2006*

Isavuconazole-concentration efficacy

Isavuconazole package labelling:

12.2 Pharmacodynamics

Pharmacokinetic/Pharmacodynamic Relationship

In patients treated with CRESEMBA for invasive aspergillosis in a controlled trial, there was no significant association between plasma AUC or plasma isavuconazole concentration and efficacy.

TDM is indicated for patients receiving tablets or IV formulation in the setting of breakthrough or infection unresponsive to treatment, treatment of pathogens with reduced susceptibility, or in the setting of drug interactions **(CIII)**

additional data are needed

Conclusions

What did *Groll* say…

- **Ample room for improvement in management of IFIs**
- **There is no rationale for TDM for polyenes and echinocandins**
- **TDM is an issue for antifungal azoles**
  - **strong recommendation for itraconazole and voriconazole**
  - **weak recommendation for new formulations of posaconazole and for isavuconazole**
- ***Issues that need further clarification***
  - ***optimum sampling schedule***
  - ***models/ algorithms for dose modificati*ons**
  - **situations in which to consider alternative agents**

ECIL Guidelines 2015: Triazole Antifungal Therapeutic Drug Monitoring

Russell Lewis (Chair, Italy); Roger Brüggemann (Netherlands)
Christophe Padoin (France); Johan Maertens (Belgium)
Oscar Marchetti (Switzerland); Andreas Groll (Germany)
Elizabeth Johnson (UK); Maiken Arendrup (Denmark)

ECIL - European Conference on Infections in Leukemia
- a joint initiative of EBMT, ICHS, EORTC and European Leukemia Net

http://www.kobe.fr/ecil/program2013.htm