Current challenges in triazole TDM

Société Belge d'Infectiologie et de Microbiologie Clinique
Belgische Vereniging voor Infectiologie en Klinische Microbiologie

Isabel Spriet, PharmD PhD
Clinical Pharmacology and Pharmacotherapy,
University Hospitals Leuven & KU Leuven, Belgium

Background

- Triazoles are the most widely prescribed antifungals for prophylaxis and treatment of IFI, especially in patients with hematological malignancies

- Triazoles exhibit substantial inter- and intrapatient variability in exposure and PK, especially in patients with mucositis, diarrhea, hypoalbuminemia, sepsis, altered renal function, CYP450 DDIs….

- A growing body of evidence has identified a relationship between triazole plasma exposure and clinical outcome which suggests a benefit for **therapeutic drug monitoring (TDM)**

ECIL-6 guidelines

(*https://www.ebmt.org/Contents/Resources/Library/ECIL/Documents/2015%20ECIL6/ECIL6-Triazole-TDM-07-12-2015-Lewis-R-et-al.pdf*)

Summary of TDM plasma target level recommendations

Triazole	Recommended plasma range[a]	SOR	Timing of first trough sample
Voriconazole	Prophylaxis and treatment: Acceptable: 1-6 mg/L; Optimal: 2-5 mg/L	AII (efficacy) AII (toxicity)	After 2-5 days; (repeat sampling recommended)
Posaconazole	Prophylaxis: > 0.7 mg/L Treatment: > 1.0 mg/L	BII (efficacy) AII (efficacy)	Tablet/IV: after 3 days: Suspension: 5-7 days.*
Itraconazole	Prophylaxis: 0.5-4 mg/L Treatment: 1-4 mg/L	AII (efficacy) BII (toxicity)	7-15 days;*

[a] values from a chromatography assay: i.e. high performance liquid chromatography (HPLC), liquid chromatography mass spectroscopy (LC/MS) of LC/MS/MS

[b] patients without symptoms of clinical toxicity may not warrant dosage adjustment, decisions should be individualised to the patient

[c] higher troughs (≥ 2) are advocated for severe infections or treatment of pathogens with potentially or documented elevated MICs (around 1 mg/L or higher)

*earlier sampling possible and may be desirable during treatment

* Earlier sampling possible using lower targets

→ 1st line IA treatment

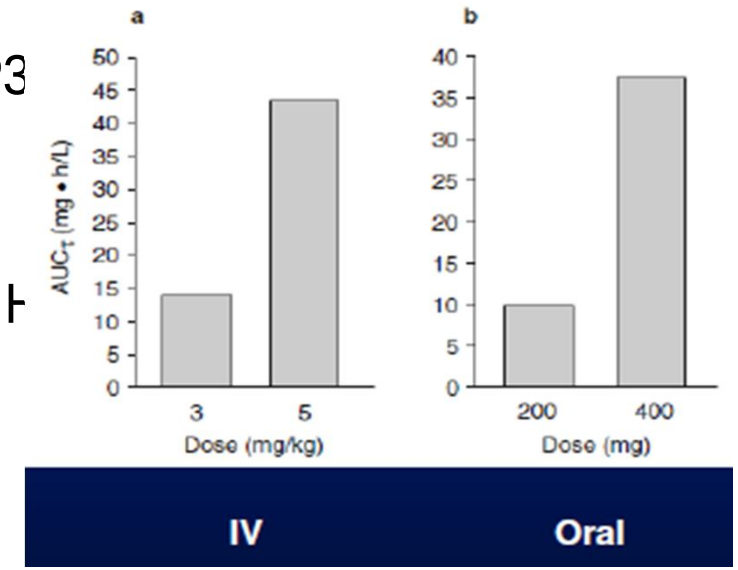
→ 1st line IFI prophylaxis

1. PK variability?
2. Narrow therapeutic window?
3. Clear relation between exposure and efficacy/safety?

→ **Current challenges are highlighted in red**

Voriconazole – PK variability?

1) Reduced oral bio-availability (60-65%) in some populations
   - co-administration with food/enteral feeding decreases absorption (AUC↓35%)
2) 100- fold intrapatient variability in metabolism/clearance
   - Non-linear saturable elimination in adults
   - Metabolism mediated by CYP2C9, CYP2C19 & CYP3
     - Involved in many drug-drug interactions
     - Genetic polymorphism described for CYP2C19
3) Children < 12 yrs: 3-5 fold greater clearance (FMO3). H

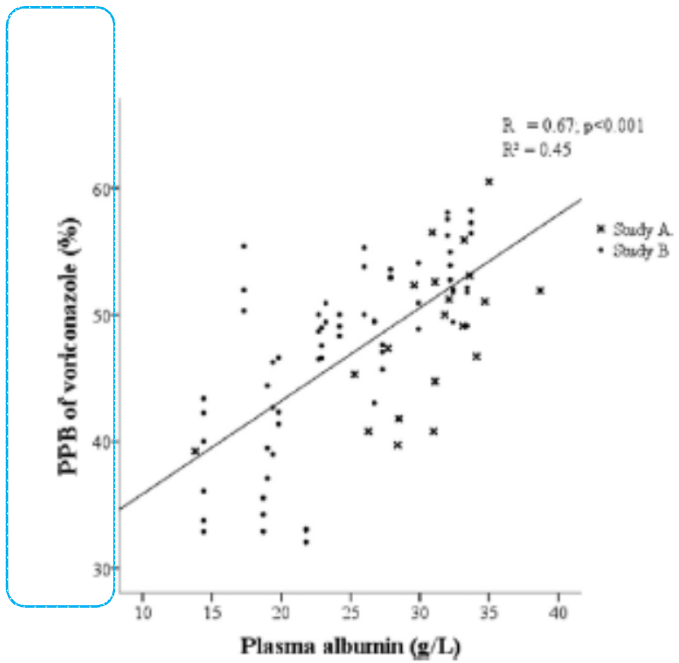


Pascual A et al. CID 2012; 55: 381-90. Scholz I et al. Br J Clin Pharmacol 2009; 68:906-15. Levin M-D et al. JAC 2007; 60:1104-7. Yanni SB et al. Drug Metab Dispos 2010; 38: 25-31. Trifilio S et al. BMT 2007; 40: 451-6. Dolton MJ et al. AAC 2012; 56: 4793-99.

Voriconazole – PK variability is not fully explained

Impact of Hypoalbuminemia on Voriconazole Pharmacokinetics in Critically Ill Adult Patients

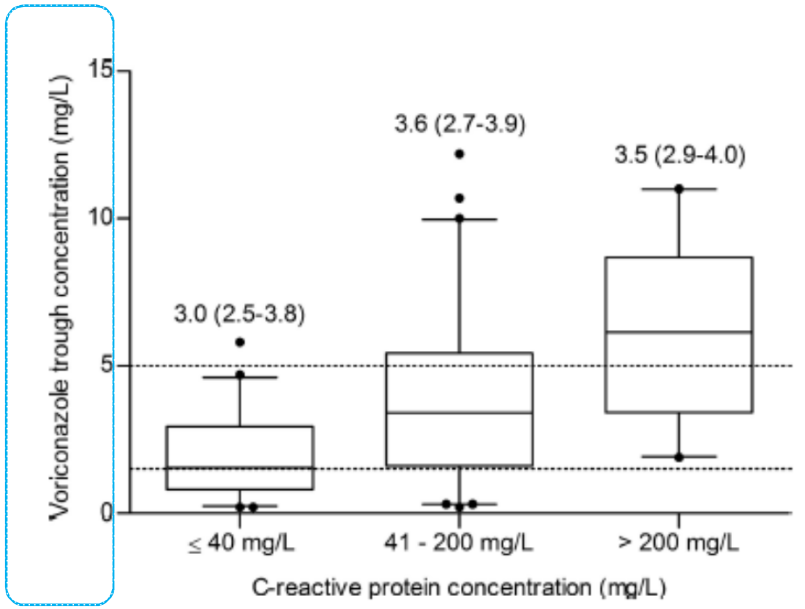
Kim Vanstraelen,[a] Joost Wauters,[b] Ine Vercammen,[a] Henriette de Loor,[c] Johan Maertens,[d] Katrien Lagrou,[e] Pieter Annaert,[f] Isabel Spriet[a]



AAC 2014; 58: 6782-9

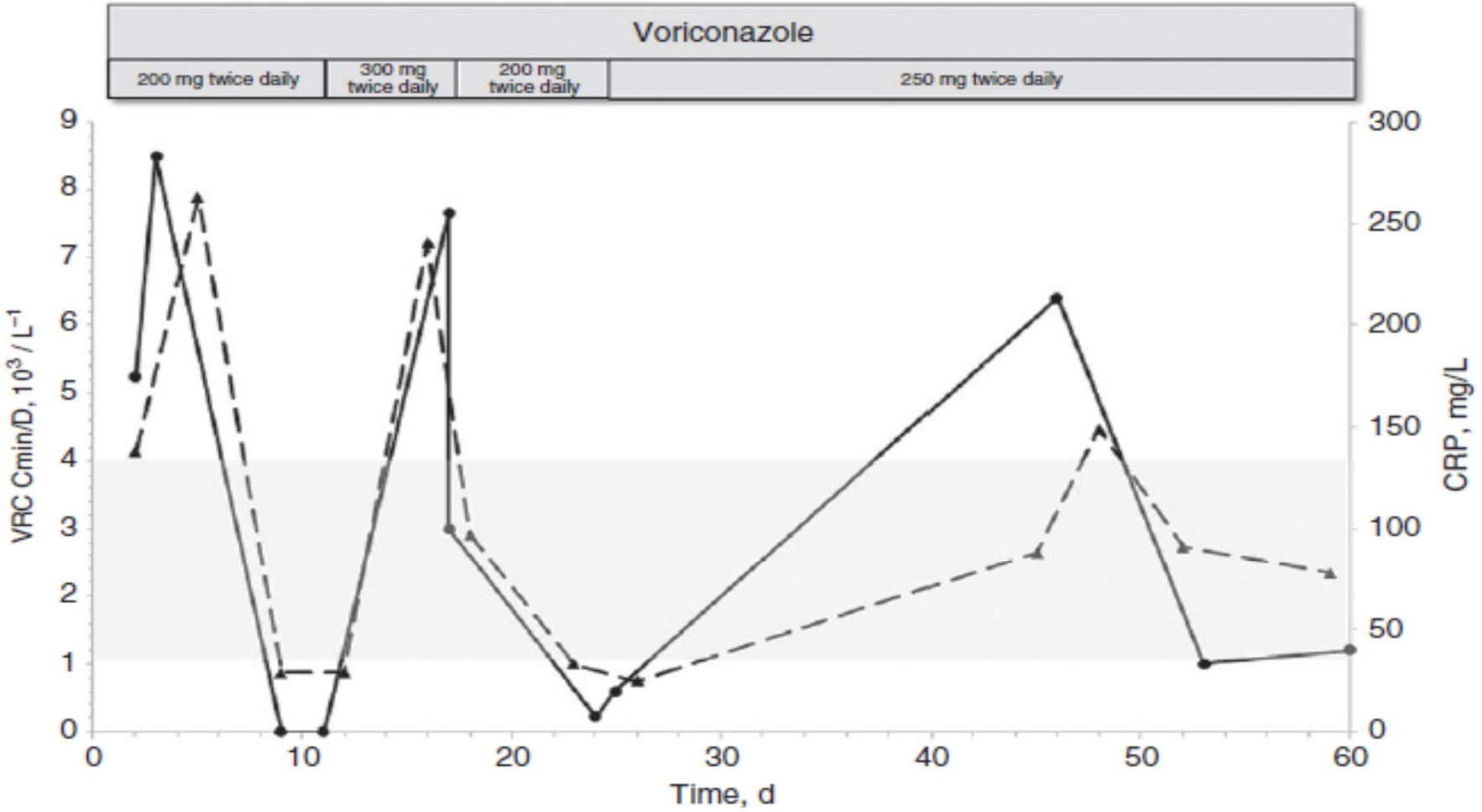
Inflammation Is Associated with Voriconazole Trough Concentrations

Marjolijn J. P. van Wanrooy,[a] Lambert F. R. Span,[b] Michael G. G. Rodgers,[c] Edwin R. van den Heuvel,[d] Donald R. A. Uges,[a] Tjip S. van der Werf,[e] Jos G. W. Kosterink,[a,f] Jan-Willem C. Alffenaar[a]



AAC 2014; 58: 7098-101

Voriconazole – not all drug interactions are known

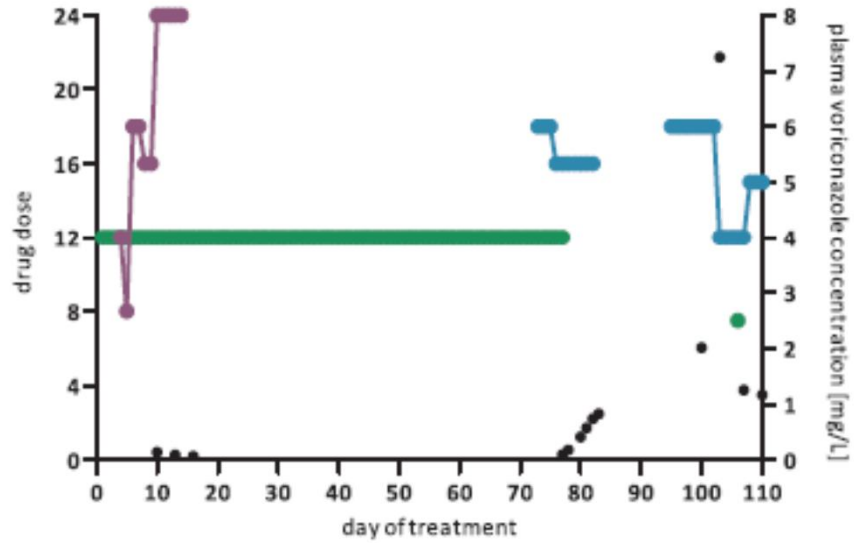


Voriconazole – not all drug interactions are known

Flucloxacillin Results in Suboptimal Plasma Voriconazole Concentrations

Elino W. Mulwijk,[a,b] Bart G. J. Dekkers,[c] Stefanie S. V. Henriet,[b,d] Paul E. Verweij,[b,e] Bregje Wittes,[f] Astrid M. L. Oude Lashof,[g] Geert H. Groeneveld,[h] Johannes van der Hoeven,[i] Jan Willem C. Alffenaar,[c] Frans G. M. Russel,[j] Frank van de Veerdonk,[b,k] Roger J. M. Brüggemann[a,b]

VORICONAZOLE AND FLUCLOXACILLINE?



- voriconazole iv [mg/kg/day]
- voriconazole po [mg/kg/day]
- flucloxacillin iv [g/day]
- plasma voriconazole concentration [mg/L]

In conclusion, the often prescribed combination of flucloxacillin and voriconazole leads to unmanageably low plasma voriconazole concentrations in half of the patients with primary and secondary immune deficiencies.

Evidence on **usefulness of TDM** and **targets** for voriconazole

- Discussed in ECIL-6 and based on a selection of 40 studies on TDM for voriconazole
- Typically for knowledge on TDM: evidence base is relatively weak
  - Most studies on TDM are retrospectively designed
  - Limited number of prospective studies are often single centre and characterized by small sample sizes
- However, specifically for voriconazole
  - Also 1 RCT
  - 5 post-hoc/meta-analysis

Study type	n (%) studies
Retrospective	
Single-centre studies	21 (53)
Multicentre studies	3 (8)
Prospective	
Single centre studies	10 (25)
Multicentre studies	2 (5)
Randomized for TDM intervention	1 (2)
Post-hoc analysis of Phase II/III RCT	2 (5)
Meta-analysis	1 (2)

https://www.ebmt.org/Contents/Resources/Library/ECIL/Documents/2015%20ECIL6/ECIL6-Triazole-TDM-07-12-2015-Lewis-R-et-al.pdf

Voriconazole – target exposure definition for **efficacy**?

- Several retrospective and prospective studies have consistently reported that vori Cmin > 1,5 – 2 mg/L is associated with maximal clinical response

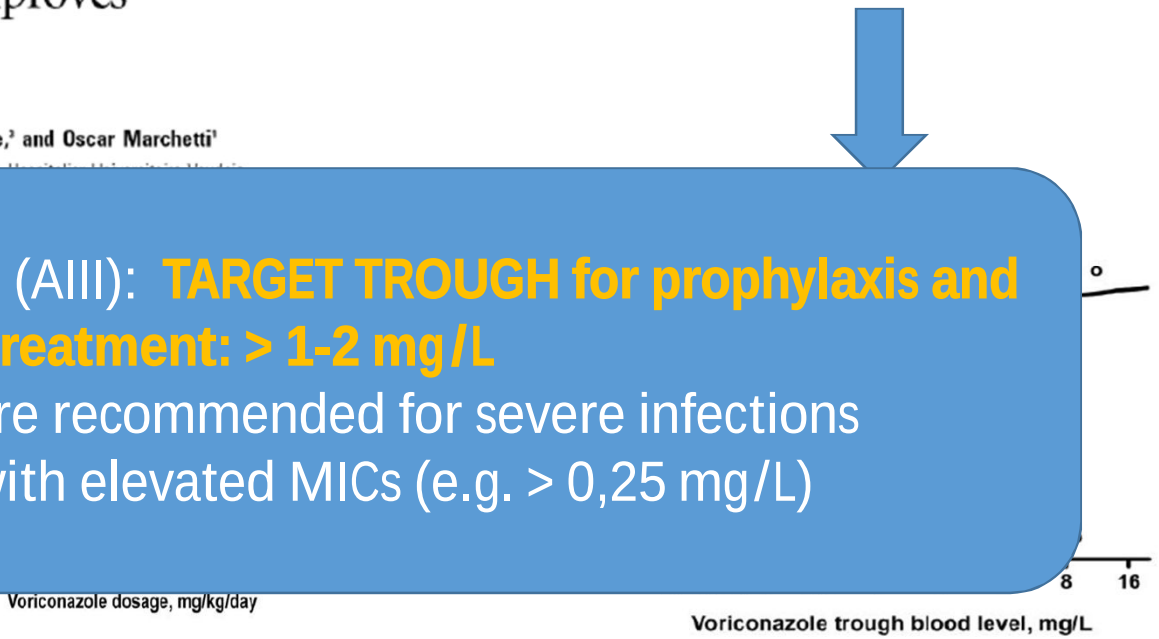
Voriconazole Therapeutic Drug Monitoring in Patients with Invasive Mycoses Improves Efficacy and Safety Outcomes

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

[1]Infectious Diseases Ser... and University of La...

ECIL-6 recommendation (AIII): **TARGET TROUGH for prophylaxis and treatment: > 1-2 mg/L**

Higher troughs are recommended for severe infections or treatment with elevated MICs (e.g. > 0,25 mg/L)



*Pascual **A et al. CID 2008; 46 (2): 201-11.***

Troke P et al. AAC 2011, 55(10):4782.

Voriconazole – target exposure definition for **toxicity**?

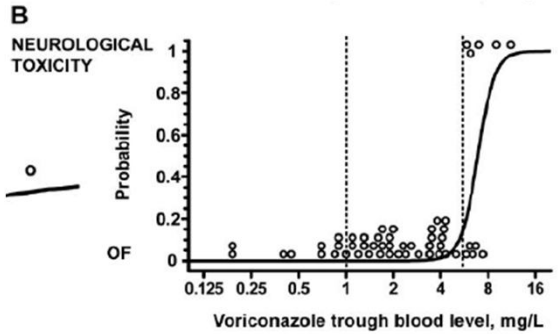
NEUROTOXICITY

- Patients with **vori Cmin > 5-6 mg/L** have a higher probability of neurotoxicity and visual hallucinations

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]

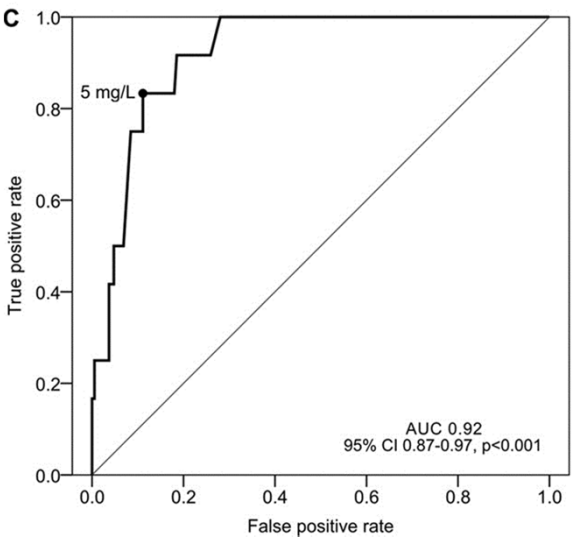
Neurological toxicitity



Pascual A et al. CID 2008; 46 (2): 201-11.

Multicenter Study of Voriconazole Pharmacokinetics and Therapeutic Drug Monitoring

Michael J. Dolton,[a] John E. Ray,[b] Sharon C.-A. Chen,[c] Kingsley Ng,[d] Lisa G. Pont,[a] and Andrew J. McLachlan[a,e]

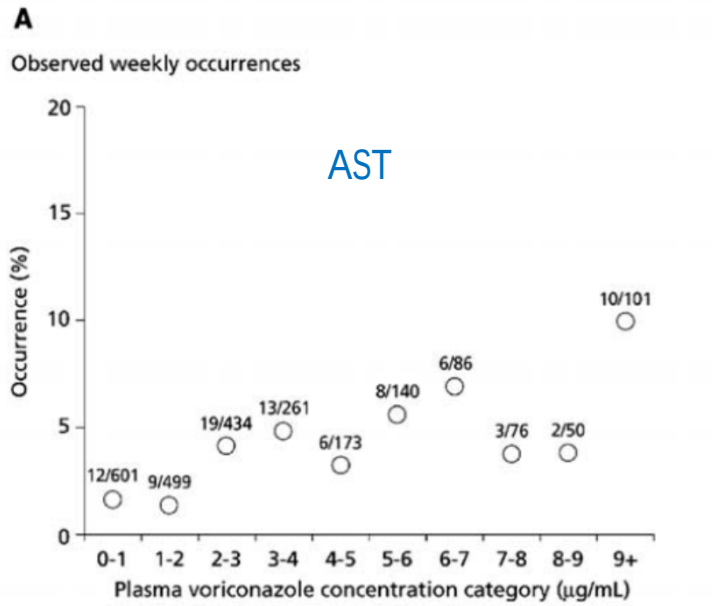


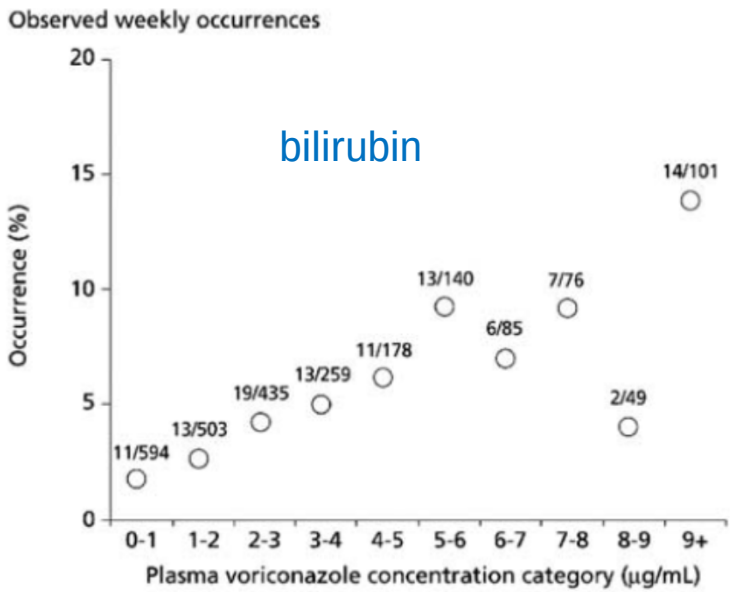
Dolton M J et al. AAC 2012;56:4793-4799

Voriconazole – target exposure definition for **toxicity**?

HEPATOTOXICITY

- Some evidence shows relationship between **higher vori exposure and hepatotoxicity**





Tan K et al. J Clin Pharmacol 2006; 46: 235-43.

Voriconazole – target exposure definition for **toxicity**?

HEPATOTOXICITY

- Despite the presumed association between higher exposure & altered LFT
- No reliable cutoff can be identified to minimize hepatotoxic effects

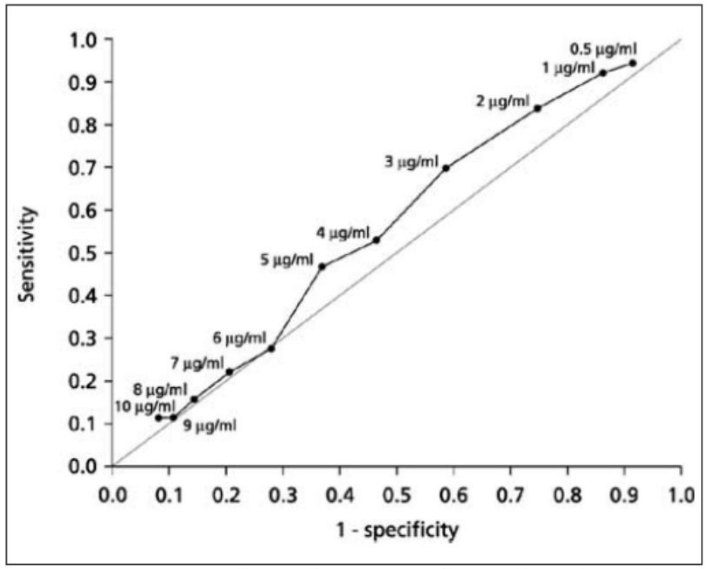


Figure 6. ROC curve for predicting AST abnormalities from plasma voriconazole concentrations.

Tan K et al. J Clin Pharmacol 2006; 46: 235-43.

....except in Japanese patients in which hepatotoxicity was more common (34,5%) when **Cmin > 3,9 mg/L**

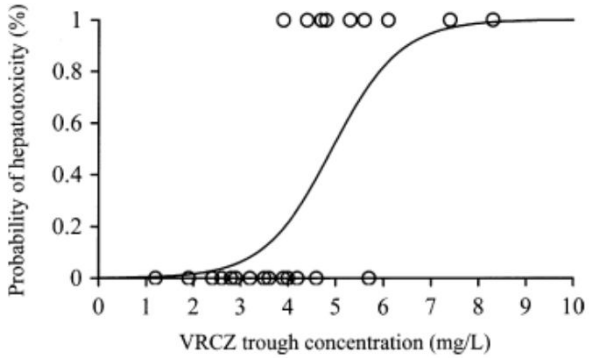


Fig. 1. Voriconazole (VRCZ) trough concentration and logistic regression model for hepatotoxicity (absence, $n = 19$; presence, $n = 10$).

Matsumoto K et al. IJAA 2009; 34: 91-94

Voriconazole – target exposure definition for **toxicity**?

How common is subsequent central nervous system toxicity in asymptomatic patients with haematologic malignancy and supratherapeutic voriconazole serum levels?

S.T. Heo [1, 3], S.L. Aitken [2], F.P. Tverdek [2], D.P. Kontoyiannis [1, *]

- (

> In summary, we have detected subsequent CNS toxicity unfrequently, in only 16 patients (5%) of 324 receiving VRC therapy with supratherapeutic levels. Given these findings, automatic VRC dose reduction out of concern for impending CNS toxicity may not be justified. However, in elderly patients or those with concomitant neurotoxic agents, vigilant monitoring for CNS toxicity needs to be performed.

(CNS)

Is TDM useful for voriconazole?

Drug	Substantial PK variability?	Therapeutic window defined in humans?	Narrow therapeutic window?
Voriconazole	✔ yes	✔ yes	✔ yes

Start Cmin monitoring at day 2-5 in every patient treated with vori

Cmin should be repeated after 7 days to confirm if patient is in target range (1-6 mg/L)

Recheck every 3-5 days if

- Change in dose
- IV to oral switch
- Change in clinical condition
- Potential DDI

If Cmin < 1 mg/L:

- Check if dose was adequate
- Screen for DDI or low compliance
- If oral R/: weight based dosing
- Consider oral to IV switch or increase dose with 50%

If Cmin > 6 mg/L:

- Check if dose was appropriate
- Screen for DDI
- Consider dose continuation if patient is tolerating vori, under close monitoring
- If dose reduction is needed: reduce with 50% if level is elevated, hold one dose if level is > 10 mg/L

Posaconazole – PK variability?

- Posaconazole – the molecule: favorable PK properties
  - Wide distribution
    - Highly protein bound (98%), large Vd
    - High intracellular concentrations
  - 'Easy' metabolism/clearance
    - No major metabolism by CYP450 enzymes
    - 30% glucuronidation followed by biliary excretion

- Posaconazole – **suspension: difficult absorption**
  - Highly dependent on gastric pH, frequency of dosing, administration with (fatty) food
  - TDM highly recommended in patients treated with the suspension

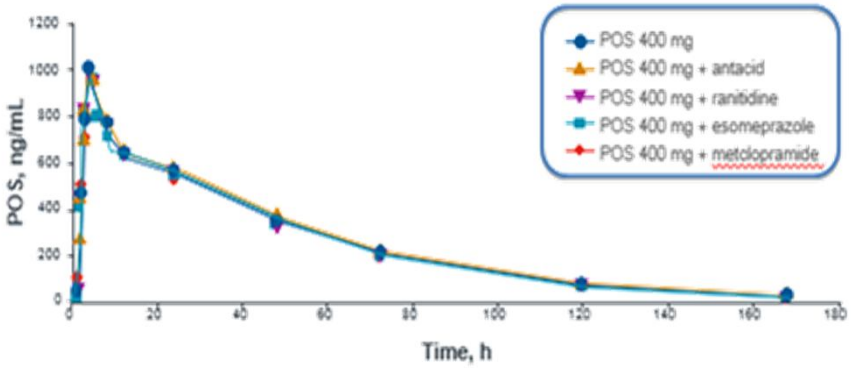
→ In some patients posaconazole concentrations not measurable

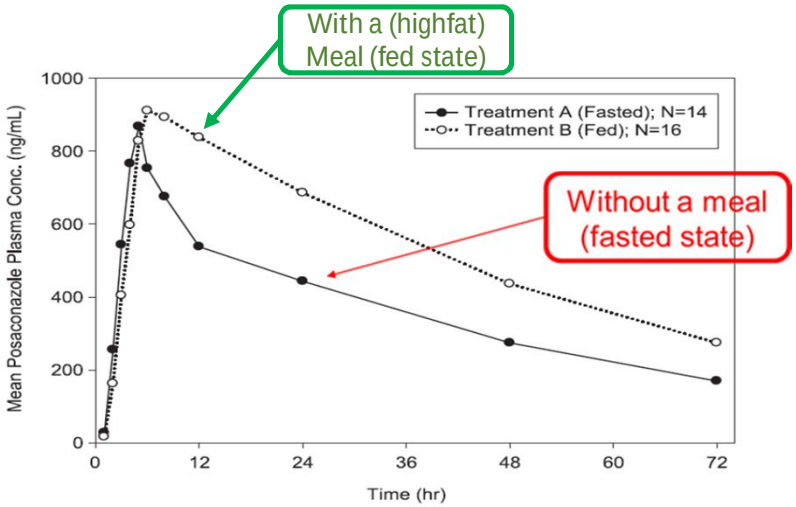
Posaconazole – PK variability?

- Posaconazole – new formulations
  - Tablets: 100 mg, dosing: 300 mg BD as LD, followed by 300 mg OD as maintenance dose
  - IV: 300 mg, dosing: 300 mg BD as LD, followed by 300 mg OD as maintenance dose

  - Tablet shows major improvement in absorption
    - not dependent on gastric pH
    - less affected by food

→tablets are the preferred oral formulation





Kersemaeckers et al. AAC 2015; 59: 3385-9.
Kraft W et al. AAC 2014; 58: 4020-5.

Evidence on usefulness of TDM and targets for posaconazole

- Discussed in ECIL-6 guidelines and based on a selection of 23 studies
- Many real life exposure studies have now been published
- Knowledge is rapidly evolving, gaining new insights on a quick basis

- Unfortunately, none of the real life studies have an ideal design (no RCTs or meta-analyses so far)

Study type	n (%) studies
Retrospective Single-centre studies Multicentre studies	 11 (48%) 1 (4%)
Prospective Single-centre studies Multicentre studies Randomized for TDM intervention	 6 (26%) 3 (13%) 0 (0%)
Post-hoc analysis of Phase II/III RCT	2 (9%)
Meta-analysis	0 (0%)

https://www.ebmt.org/Contents/Resources/Library/ECIL/Documents/2015%20ECIL6/ECIL6-Triazole-TDM-07-12-2015-Lewis-R-et-al.pdf

Posaconazole suspension – target exposure for **efficacy** in prophylaxis?

- PK analysis of 2 Phase III trials (suspension) : no statistically significant difference in Cavg in patients with vs. without breakthrough IFI

Population	Cavg in patients with breakthrough IFI	Cavg in patients without breakthrough IFI
HSCT-GvHD	0,61 mg/L (n=5)	0,92 mg/L (n=241)
AML-MDS	0,457 mg/L (n=6)	0,586 mg/L (n=188)

- FDA pharmacodynamic analysis (suspension) – combined endpoint for clinical failure

→ Higher probability for clinical failure with low posa plasma concentrations
→ 0,7 mg/L was proposed as target Cmin for efficacy when used in prophylaxis

Krishna G et al. Pharmacotherapy 2008; 28:1223-32.
Krishna G et al. Pharmacotherapy 2007; 27: 1627-36.
Jang SH et al. Clin Pharmacol Ther 2010; 88: 115-9.

Posaconazole suspension – target exposure for **efficacy** in prophylaxis?

- Several monocentric studies, all investigating PK and TDM using the suspension, reported a relationship between posa plasma trough levels and risk of breakthrough infection –

  all proposing a cutoff for Cmin levels of 0,5-0,7 mg/L

  - *Lebeaux D et al. AAC 2009; 53:5224-9.*
  - *Bryant AM et al. IJAA 2011; 37: 266-9.*
  - *Elden E et al. EJCMID 2012; 31: 161-7.*
  - *Hoenigl M et al. IJAA 2012; 39-510-3.*
  - *Cattaneo et al. Mycoses 2015; 58: 362-7.*

ECIL-6 recommendation (BII): **TARGET Cmin for efficacy in PROPHYLAXIS: > 0,7 mg/L**

Posaconazole suspension– target exposure for **efficacy** in treatment?

- Open label, externally controlled, study with posaconazole as salvage treatment in patients with IA refractory or intolerant to other antifungals
  - Clinical response improved with increasing Cavg
  - Highest response (75%) observed with Cavg >1,250 mg/L

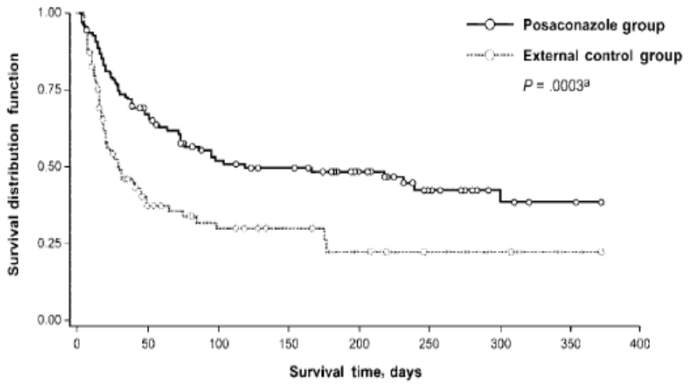


Table 8. Posaconazole plasma concentration versus global response in patients with invasive aspergillosis (MITT subset).

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)

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.

ECIL-6 recommendation (AII): **TARGET Cmin for efficacy in TREATMENT: > 1 mg/L**

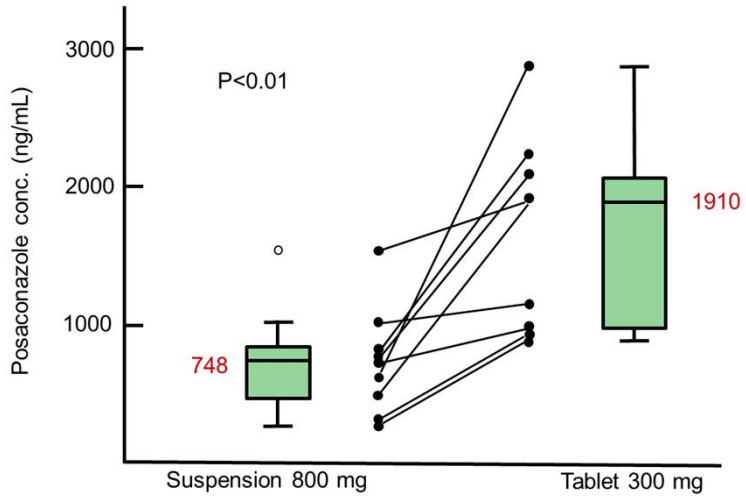
Walsh TJ et al. Clin Infect Dis 2007; 44:2-12.

Should these TDM recommendations, derived from the suspension, also be applied for the **new formulations**?

Yes – efficacy has been extrapolated from the suspension data by aiming comparable exposure (90% of patients with Cavg 0,5-2,5 mg/L) for the new formulations

However…. important remaining questions before recommending TDM for the new formulations:

- In how many patients treated with the new formulations is the exposure < 0,7 mg/L?
- Is serum the right matrix to evaluate posa exposure?
- Should we think about an upper threshold for toxicity as exposure with the new formulations is now much higher?

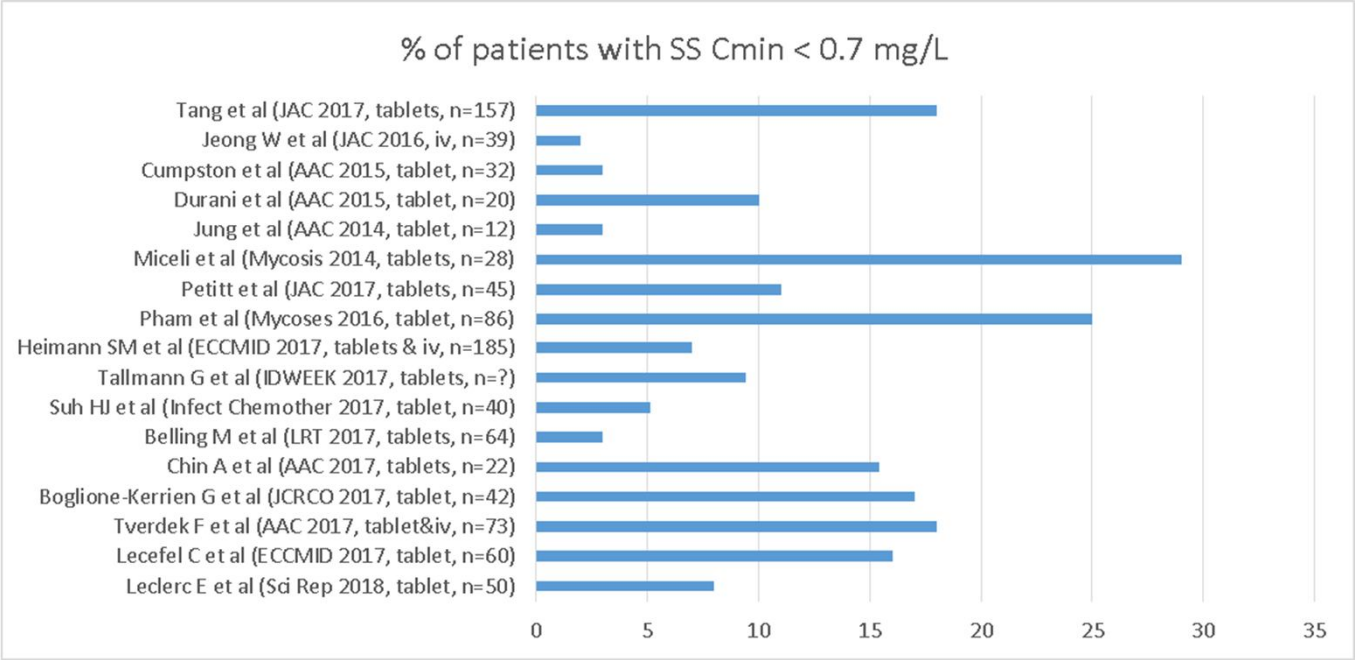


Jung et al. Antimicrob Agent Chemother 2014;58:6993-5.

Exposure < 0,7 mg/L for posa tablet and IV

Real life evidence (17 studies) with posa tablet & iv from 2014-2018

- **High interpatient variability** in exposure (Cavg, Cmin) reported with new formulations
- Proportion of patients not attaining 0,7 mg/L ranges from **3-29%**



*SS= steady state Cmin

Patients **at risk** for low exposure in prophylaxis

In some studies, **several independent risk factors** for low exposure were identified:

- Diarrhea (Tang et al, Miceli et al, Leclerc et al),
- Mucositis (Belling et al),
- Age < 60y (Belling et al),
- BW > 90 kg or BMI > 30 (Miceli et al, Tang et al),
- Treatment with a PPI (Tang et al)

However, in other studies **no significant correlation** was found between these factors and low exposures (Lecefel et al, Jung et al, Pham et al)

→ Up till now: patients at risk for low exposure can not be identified based on clinical risk factors alone

Despite the fact that Cmin is < 0.7mg/L in 3-29%:
Probable IFI breakthrough rate with the tablet is approximately **1-3%**
Breakthrough infection is **rarely observed** in context of low posa serum levels

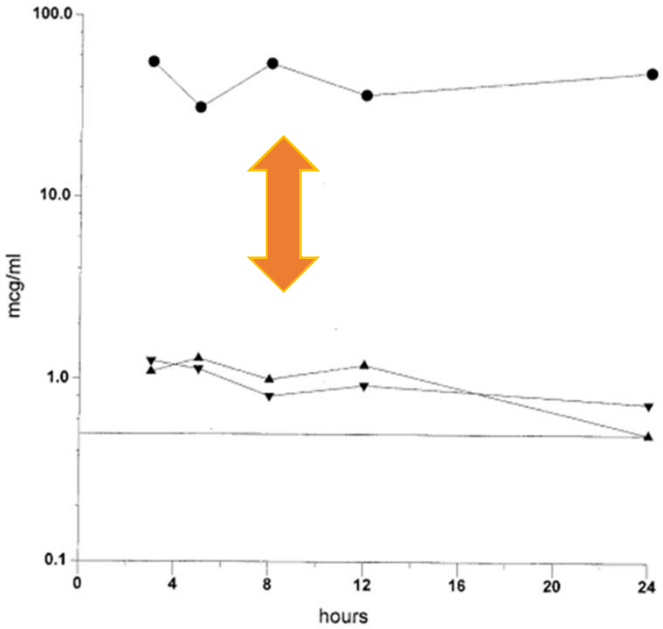
Miceli MH et al. Mycoses 2015; 58: 432-6.
Tang L et al. JAC 2017; 72: 2902-5.

New insights in posaconazole intracellular concentrations

Steady-State Intrapulmonary Pharmacokinetics and Pharmacodynamics of Posaconazole in Lung Transplant Recipients[▽]

John E. Conte, Jr.,[1,2,3]* Catherine DeVoe,[1] Emily Little,[1,3] and Jeffrey A. Golden[3]

American Health Sciences, San Francisco, California,[1] and Department of Epidemiology and Biostatistics[2] and Department of Medicine,[3] University of California, San Francisco, San Francisco, California



Alveolar cells

Plasma
Epithelial lining fluid

FIG. 1. Concentrations of POS in plasma, AC, and ELF. Standard deviations from the values shown are given in Table 2.

- Very high concentrations in host cell and fungal membrane support efficacy in prophylaxis setting, even if low serum exposure
- Questions if serum is the right matrix for TDM

Conte JE et al. AAC 2010; 54: 3609-13.

Campoli P et al. J Infect Dis 2013; 208: 1717-28

Do we need to define a target for **toxicity**?

Adverse events most commonly reported are:

- **GI: vomiting, diarrhea, nausea**
- **(Transient) liver function elevations**
- **Hypokalemia**
- **QTc prolongation**

Relation between adverse events and posaconazole exposure was addressed in the phase III trial with the tablet formulation

→Risk for adverse events does not seem to be exposure dependent

Table 7. Summary of treatment-related TEAEs by quartile of pC_{avg} values, all C_{min} PK-evaluable patients: posaconazole 200 mg and 300 mg dose groups combined

Quartile	Posaconazole pC_{avg} mean (ng/mL)	pC_{avg} range (ng/mL)	Number of subjects	Subjects reporting any treatment-related TEAEs, *n* (%)
1	860	442–1223	51	29 (57)
2	1481	1240–1710	51	19 (37)
3	1979	1719–2291	51	16 (31)
4	3194	2304–9523	52	20 (38)

pC_{avg}, predicted average concentration from C_{min}.
AEs occurring in >5% of subjects in each quartile were as follows: quartile 1—diarrhoea 12%, nausea 10%, rash 10%, abdominal pain 8%, hypokalaemia 6%, hypophosphatemia 6%, vomiting 6%; quartile 2—diarrhoea 6%, nausea 10%, abdominal pain 6%, vomiting 6%; quartile 3—diarrhoea 12%, nausea 6%, hypokalaemia 6%, increased ALT 8%, dyspepsia 6%, increased AST 6%; quartile 4—nausea 13%, vomiting 8%.

Cornely O et al. J Antimicrob Chemother 2016; 71:718-26.

Do we need to define a target for **toxicity**?

Real life evidence (17 studies) with posa tablet & iv from 2014-2018:

Hyperbilirubinemia and AST/ALT elevations occur **relatively frequently** with posaconazole
Results are **conflicting** when looking into the relation between liver function test elevations and exposure

ECIL-6 recommendation : **At present, insufficient data to recommend target trough for safety**

Is TDM useful for posaconazole?

Setting	Substantial PK variability?	Therapeutic window defined in humans?	Narrow therapeutic window?
Posaconazole used in **prophylaxis**	✔ yes	?	? Probably not
Posaconazole used in **treatment**	✔ yes	✔ yes	? Probably not

ECIL-6

TDM **may be** indicated in patients receiving posaconazole tablets or iv for prophylaxis (CIII) or treatment (BIII)

TDM **is** indicated in the setting of breakthrough infection, resistant pathogens, DDIs, therapeutic failure

My personal opinion

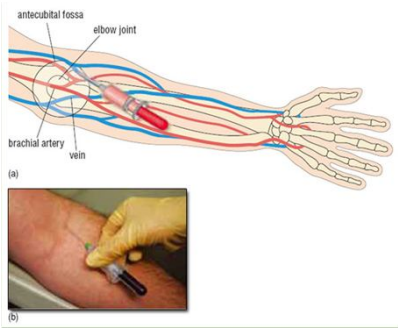
TDM when

- Used in treatment
- Used in ICU patients
- Patients with severe mucositis, diarrhea
- Patients with high BW/BMI
- Potential toxicity
- Unknown drug interactions

Importance of **correct implementation** of TDM

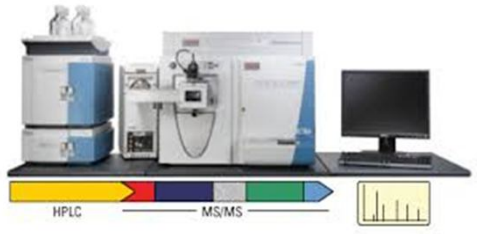
From the PATIENT

1. Prescription for TDM
2. Venipuncture
3. Correct tubes
4. Correct storage on ward
5. Sending sample to lab



to the LAB

1. Correct storage in lab
2. Sample preparation
3. Analysis
   1. Commercial IA
   2. LC-MSMS



and back to the PATIENT

1. Validation of result
2. Advice for dose adaptation based on reference values
3. Actual dose adjustment

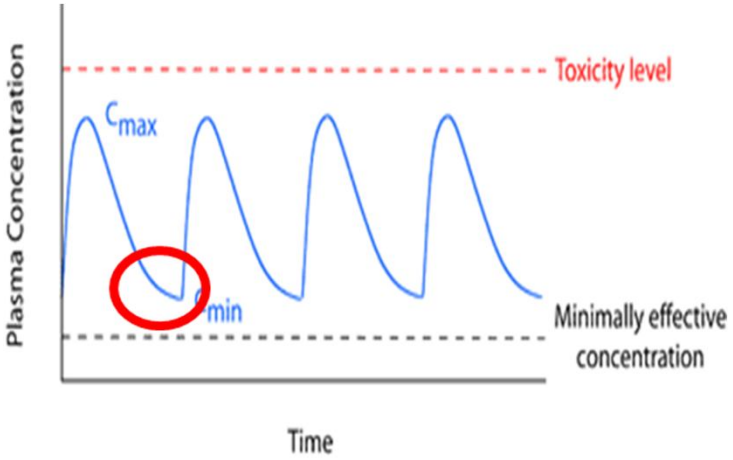
Drug	Reference
Voriconazole	1-6 mg/L
Posaconazole	> 0,7 mg/L
Itraconazole	0,5-4 mg/L

ECIL-6 (AIII) recommendation: **TDM is a multidisciplinary process**, quality should be assured in the pre-analytical, analytical and post-analytical phase

Importance of correct implementation of TDM:
when and how is the sample taken?

- **Trough** level

just before the next dose



- ✓ Not at 4 am or 6 am when all other blood samples are taken…
- ✓ Not when AF is already infused….

- **Preferably peripheral venipuncture**

Importance of correct implementation of TDM:
accuracy of the analytical method

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Five year results of an international proficiency testing programme for measurement of antifungal drug concentrations

V. J. C. Lempers[1], J. W. C. Alffenaar[2], D. J. Touw[2,3], D. M. Burger[1], D. R. A. Uges[3], R. E. Aarnoutse[1,3] and R. J. M. Brüggemann[1]*

Results: Fifty-seven laboratories (13 countries) reported 2251 results (287 fluconazole, 451 itraconazole, 348 hydroxyitraconazole, 402 posaconazole, 652 voriconazole and 111 flucytosine) in 5 years. Analyses were performed using HPLC (55.0%), LC-MS(/MS) (43.4%), UPLC (1.4%) or GC-MS (0.2%). Overall, 432 (19.2%) analyses were inaccurate. The performing laboratory was the only factor clearly associated with inaccuracies. The questionnaire results indicated that laboratories encounter significant problems analysing low concentrations (15.4% of all inaccuracies).

Conclusions: Results of the PT programme suggest that one out of five measurements is inaccurate. The performing laboratory is the main determinant of inaccuracy, suggesting that internal quality assurance is pivotal in preventing inaccuracies, irrespective of the antifungal drug measured, concentration and analytical equipment.

ECIL-6 recommendation (AIII) to participate in **ongoing proficiency testing programs** to identify sources of errors and improve analytical methods

Conclusion: current challenges for posa/vori TDM

1. **Variability** in PK and DDI is still not completely understood

2. **Evidence base** on TDM is relatively weak
   - Evidence for triazole TDM is derived from single-centre, retrospective and/or statistically underpowered studies - current evidence provides an *approximate* TDM range

3. For **voriconazole**
   - Clear relationship between exposure and efficacy: lower efficacy target for Cmin 1-2 mg/L
   - Neurotoxicity and liver injury are well known side effects: upper safety target for Cmin – 5-6 mg/L – **dose reduction?**

4. For **posaconazole**
   - Evidence for a clear relationship between exposure and efficacy when used in prophylaxis is weaker
     - **TDM might be carried out, especially in patients at risk, aiming > 0.7 mg/L**
   - When used in treatment, higher targets should be used (1-1.25 mg/L)
   - **Plasma concentrations** may not reflect antifungal activity at the site of infection

5. **Implementation** should be carried out very carefully
- Education on sampling
- Participation in quality assurance programs