PKPD & TDM of antifungals

Clinical case based discussion

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Disclaimer

- Research grants from Pfizer, MSD
- Travel grants from Pfizer, MSD, Gilead

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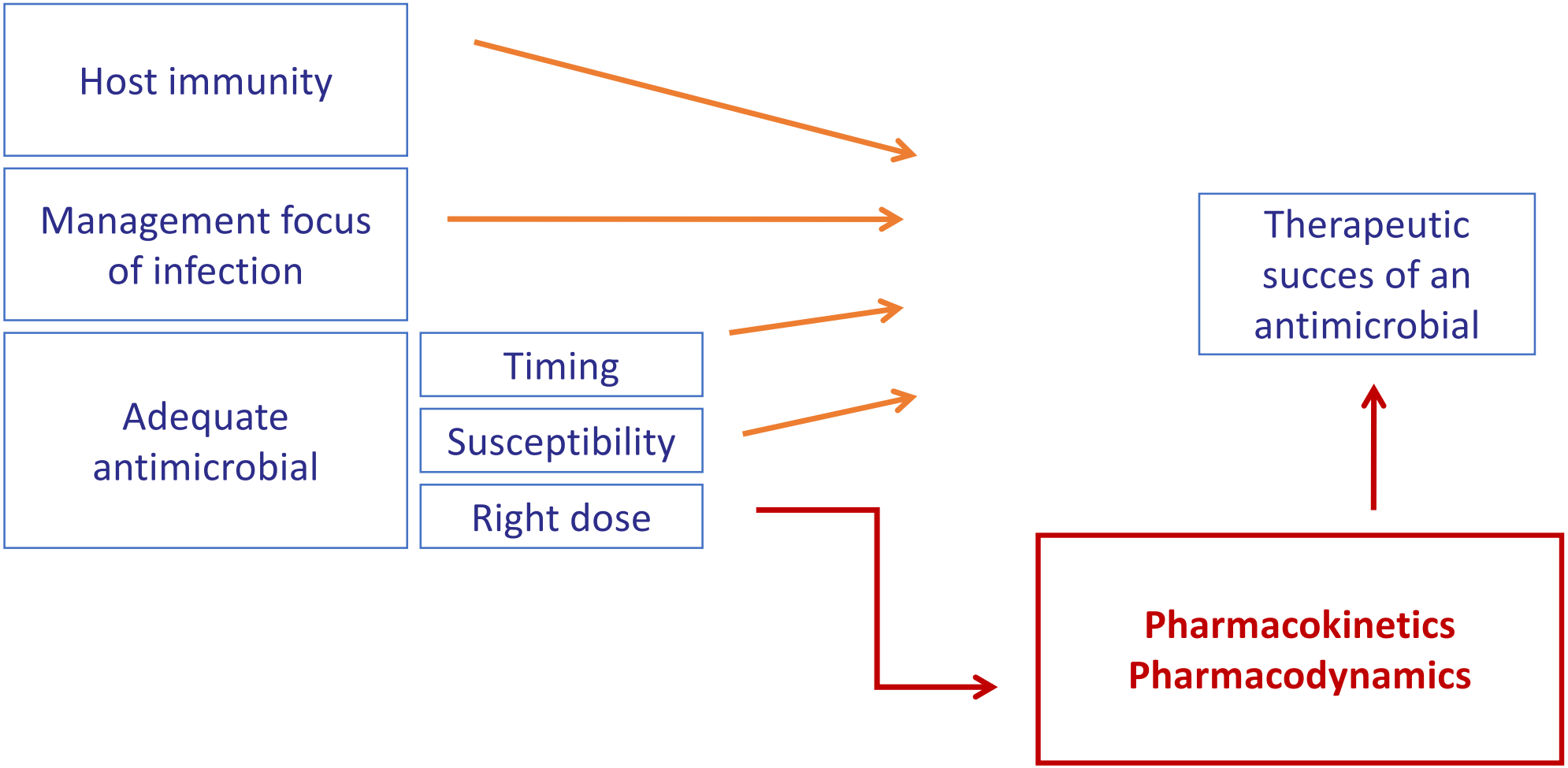
INTRODUCTION

PKPD & TDM: what's in a name?

Why is research in PKPD & TDM important for antibiotics and antifungals?

PKPD – what's in a name?

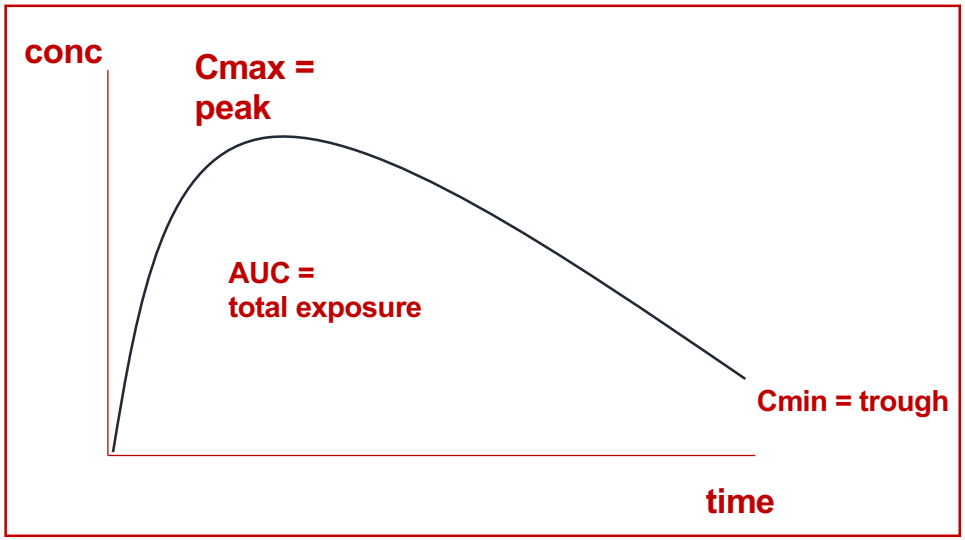


PKPD: what's in a name?

Administered dose → Serum concentrations varying in function of time

Serum concentrations varying in function of time → Concentrations in non- target tissues

Serum concentrations varying in function of time → Concentrations at the level of focus of infection



Pharmacokinetics

PKPD: what's in a name?

Pharmacodynamics

Administered dose

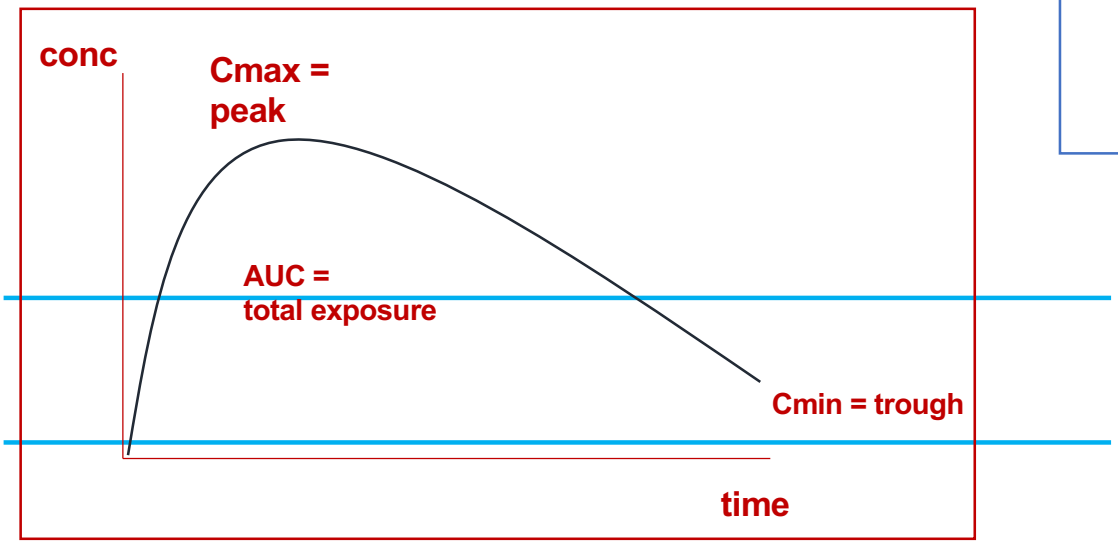
Serum concentrations varying in function of time

Concentrations in non-target tissues

Toxic effects

Concentrations at the level of the focus of infection

Therapeutic effects



THERAPEUTIC DRUG MONITORING

Textbook criteria supporting TDM

Significant PK variability	• **No clear relationship** between dose and plasma exposure • Wide **inter- and intrapatient variability**
Narrow therapeutic window	• Narrow window between concentrations that produce **therapeutic vs. toxic effects**
Clear relation between exposure and efficacy or toxicity	• **Minimal exposure** should be attained to warrant **efficacy** • **Maximal exposure** should be taken into account to avoid **toxicity**
TDM only way to assess/predict effect	• Effect (pharmacodynamics) **not clinically evaluable** • Dosing can not be optimized by routine biochemical tests or based on clinical observation

Schumacher GE, ed. Therapeutic drug monitoring. Norwalk, CT: Appleton and Lange, 1995.
Ensom et al. Clinical Pharmacokinetics in the 21st century. Clin Pharmacokin 1998;34:265-79

PKPD & TDM for antimicrobials: why is it important?

Host + Pathogen = Infection

AB concentrations should be

✓ **sufficient <u>to kill the bug</u>**

✓ **sufficient <u>to attain the infected tissue</u>**

(e.g. lung, brain, abdomen…)

✓ **not to be too <u>high to avoid toxic effects</u>**

→ **<u>Targets for TDM : integration of PK parameters and MIC value</u>**

PKPD & TDM for antimicrobials: why is it important?

- For most drugs: clinical effect is readily clinically or biochemically/radiologically observable….
  - Sedatives
  - Antihypertensives
  - insulin and other antidiabetics
  - Vasopressors

… but this is **not the case for antibiotics/antifungals**

PKPD & TDM for antimicrobials: why is it important?

Antimicrobial PKPD – targets & magnitude - knowledge anno 2019

	Preclinical studies		Clinical studies	
Concentration-dependent				
Aminoglycosides	Maximum killing[43]	AUC_{0-24}/MIC 80–100	Clinical cure[82–86]	C_{max}/MIC 8–10; AUC/MIC >70
	Resistance suppression[87]	C_{max}/MIC 10–30	Microbiological cure	..
Time-dependent				
Carbapenems	Maximum killing[88]	40% $T_{>MIC}$	Clinical cure[89]	75% $T_{>MIC}$; C_{min}/MIC 5
	Resistance suppression[90, 91]	16 × MIC; C_{min}/MIC >6·2	Microbiological cure[17]	54% $T_{>MIC}$
Cephalosporins	Maximum killing[11]	60–70% $T_{>MIC}$	Clinical cure[92]	100% $T_{>MIC}$
	Resistance suppression	..	Microbiological cure[16,93]	60–100% $T_{>MIC}$; 95% $T_{>4·3×MIC}$
Penicillins	Maximum killing[11]	40–50% $T_{>MIC}$	Clinical cure	..
	Resistance suppression[94]	40–50% $T_{>MIC}$	Microbiological cure[95]	40–50% $T_{>MIC}$
Concentration-dependent and time-dependent				
Fluoroquinolones	Maximum killing[11,96]	AUC_{0-24}/MIC >30–100	Clinical cure[15,86,96,97,98]	AUC_{0-24}/MIC ≥125–250; C_{max}/MIC ≥8
	Resistance suppression[99,100,101]	AUC_{0-24}/MIC >160; AUC_{0-24}/MPC ≥22	Microbiological cure[14,86,102]	AUC_{0-24}/MIC ≥34–125; C_{max}/MIC ≥8
Vancomycin	Maximum killing[103]	AUC_{0-24}/MIC 86–460	Clinical cure[20,21]	AUC_{0-24}/MIC ≥400–450
	Resistance suppression[104]	AUC_{0-24}/MIC >200	Microbiological cure[20]	AUC_{0-24}/MIC ≥400
Linezolid	Maximum killing	..	Clinical cure[22]	AUC_{0-24}/MIC ≥85; 85% $T_{>MIC}$
	Resistance suppression	..	Microbiological cure[22]	AUC_{0-24}/MIC 80–120; 85% $T_{>MIC}$
Tigecycline	Maximum killing[105]	50% $T_{>MIC}$	Clinical cure[106,107,108]	AUC_{0-24}/MIC >12·8–17·9; *f* AUC_{0-24}/MIC ≥0·9
	Resistance suppression	..	Microbiological cure[109,110]	AUC_{0-24}/MIC 6·9–17·9
Daptomycin	Maximum killing[111,112]	AUC_{0-24}/MIC 38–442	Clinical cure	..
	Resistance suppression[104]	AUC_{0-24}/MIC >200	Microbiological cure	..
Colistin	Maximum killing[113,114]	AUC_{0-24}/MIC 7–23	Clinical cure	..
	Resistance suppression	..	Microbiological cure	..

AUC_{0-24}/MIC=ratio of area under the concentration time curve from 0 to 24 h to minimum inhibitory concentration. C_{max}/MIC=ratio of maximum concentration of antibiotic in a dosing interval to minimum inhibitory concentration. $T_{>MIC}$=percentage of dosing interval that the antibiotic concentration is maintained above the minimum inhibitory concentration. AUC_{0-24}/MPC=ratio of the AUC_{0-24} to the concentration that prevents mutation. C_{min}=minimum concentration of antibiotic in a dosing interval, *f*=free concentration or fraction of drug not bound to plasma proteins. *Where the index is reported as a range, data included might have been derived from different infection models with different bacteria. Specific data for the contributing values can be found in the associated references. Data for the various indices has been reported in different studies according to total and free (unbound) concentrations of drug.

***Table 1*: Studies reporting pharmacokinetic/pharmacodynamic indices from preclinical and clinical assessments, by antibiotic class**

Roberts JA, Lancet Infect Dis 2014; 14: 498-509

PKPD & TDM for antimicrobials: why is it important?

- PKPD targets are based on optimal systemic exposure in humans

- For most antimicrobials and most patients
  - standard dosing will lead to sufficient concentrations above the MIC
  - the magnitude of the PKPD index is easily reached
  - the optimal exposure is not linked to important dosedependent toxicity

  → TDM is not necessary, standard dosing is OK

- For some antibiotics/antifungals, some infections and some patient populations
  - a minimal exposure above the MIC (in the right PKPD index) is critical but difficult to reach, especially in (resistant) pathogens with an elevated MIC value
  - this minimal exposure is close to the potentially toxic exposure

  → **insights in PKPD & implementation of TDM contributes to efficacy and avoidance of toxicity**

PKPD & TDM for antiFUNGALS: why is it important?

- Incidence of IFI
  - increasing – more immunocompromised patients, better diagnostics, better knowledge of risk factors
- Disease severity of IFI:
  - ICU, hematology dpt, children with malignancies, Tx patients
  - high mortality rate
- Increasing resistance

PKPD & TDM for antiFUNGALS: why is it important?

Altered pharmacokinetics in specific patient populations

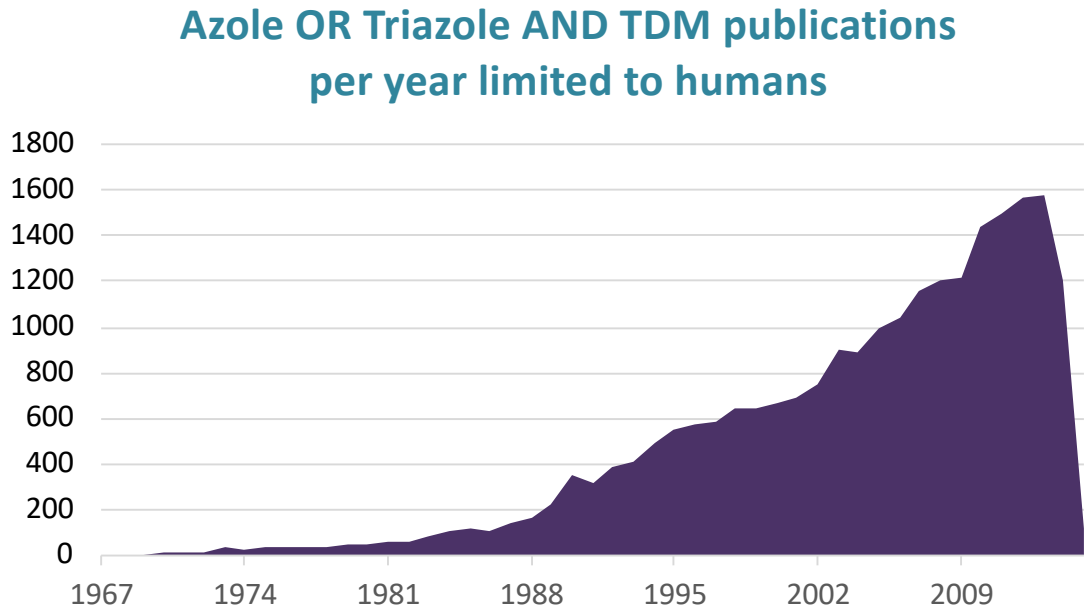
Critically ill
Pediatrics
Renal Replacement Therapy
Patients with hematological diseases

- **Impaired oral bioavailability**
  - Mucositis/stomatitis
  - Diarrhea
  - Nausea and vomiting
  - Achlorhydria, acid suppression therapy
  - Interaction with food
- **Altered drug distribution, protein binding**
  - Cachexia, hypo-albuminemia,hypo-bilirubinemia, effusions
  - Sepsis, inflammation
- **Drug clearance**
  - Impaired renal or hepatic function
  - Inflammation, malignancy
  - Drug-drug interactions

Theuretzbacher U. Clin Infect Dis 2012;54:1785-1792
Brüggemann RJM,et al. Clin Infect Dis 2009; 48: 1441–1458.
Vanstraelen et al. Antimicrob Agent Chemother 2014;58:6782-9.

PKPD & TDM for antiFUNGALS: why is it important?

Hot topic – e.g. literature on triazole TDM…



38% PK, DI studies
22% true TDM studies
20% review article
20% analytical method

Slide from ECIL-6 Triazole Antifungal Therapeutic Drug Monitoring

CASE-BASED DISCUSSION

Azoles

Echinocandines

Liposomal amphotericin B

Recommendations for triazole TDM based on ECIL-6 guideline
https://www.ebmt.org/Contents/Resources/Library/ECIL/Documents/2015%20ECIL6/ECIL6-Triazole-TDM-07-12-2015-Lewis-R-et-al.pdf

Voriconazole: PKPD & TDM – CASE 1

A 62 yr old patient, weighing 65 kg, known with COPD Gold IV (for which he was treated with low dose oral methylprednisolone at home) is admitted at the ICU with severe influenza. He is started on oseltamivir and ceftriaxone and is mechanically ventilated.

On day 3 after admission, a bronchoscopy is undertaken, BAL GM is 1.2, corresponding to probable IA for which voriconazole IV is started (LD: 2 x 400 mg, MD: 2x 260 mg) and ceftriaxone is stopped.

After 4 days a trough level is sampled which is 1.2 mg/L. Doses are increased up to 2 x 350 mg. Two days later, the trough level is 0.9 mg/L.

The patient's comedication consists out of ranitidine, PN + vitamins/micronutrients, enoxaparin, oseltamivir, midazolam, morphine, insulin, noradrenalin, IV fluids.

You are the clinical pharmacist advising the ward.

What do you recommend concerning the dose?

Voriconazole: PKPD & TDM – CASE 1 : what do you recommend?

1. I would keep on increasing the maintenance dose, again with +50% of the current dose (i.e. MD of 525 mg 2x/day)

2. I would keep the current dose, attaining a new steady state takes at least 4 days.

3. I would keep the current dose, attaining a new steady state takes at least 4 days, but I would recommend to change ranitidine into omeprazole.

4. I would ask for CYP2C19 genotyping, I guess the patient is an URM.

5. I would check for DDIs with the patient's comedication – it is strange that these doses result in low vori levels.

Case 1: What would you recommend?

I would keep on increasing the maintenance dose, again with +50% of the current dose (i.e. MD of 525 mg 2x/day)	**A**
I would keep the current dose, attaining a new steady state takes at least 4 days.	**B**
I would keep the current dose, attaining a new steady state takes at least 4 days, but I would recommend to change ranitidine into omeprazole.	**C**
I would ask for CYP2C19 genotyping, I guess the patient is an URM.	**D**
I would check for DDIs with the patient's comedication – it is strange that these doses result in low vori levels.	**E**

Voriconazole: PKPD & TDM – CASE 2

- A 54 year old woman, 60 kg, is treated on an ambulatory basis with voriconazole (LD: 2x 350 mg PO, MD: 2x 250 mg PO) for probable IA which was diagnosed 4 weeks earlier and was presumably associated with oral MTX treatment for RA.
- She is followed-up by the ID specialist in the outpatient clinic. Every 2 weeks a vori trough level is sampled. Surprisingly the trough levels were <0.2 and 0.3 mg/L.
- Her comedication consists out of pantoprazole, paracetamol and ibuprofen 3 x 600 mg (RA), carbamazepine 2 x 200 mg/day (postherpetic neuralgia). Oral MTX was temporarily interrupted because of IA.

- The treating clinician calls you to discuss the low vori levels.

  What is your recommendation?

Voriconazole: PKPD & TDM – CASE 2 - What do you recommend?

1. I would discuss compliance with her. Probably she is not taking voriconazole twice daily.

2. I would discuss intake with her. Probably she is taking voriconazole with a meal explaining decreased absorption and low bio-availability.

3. I would increase the dose with at least 50%, or even consider to double the dose.

4. I would check for DDIs, these low levels seem very strange to me.

5. I would ask for CYP2C19 genotyping, I guess the patient is an URM.

Case 2: What would you recommend?

I would discuss compliance with her. Probably she is not taking voriconazole twice daily.

I would discuss intake with her. Probably she is taking voriconazole with a meal explaining decreased absorption and low bio-availability.

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I would check for DDIs, these low levels seem very strange to me.

I would ask for CYP2C19 genotyping, I guess the patient is an URM.

Voriconazole: PKPD & TDM – Indication & Dosing

Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America

Thomas J. Walsh,[1,a] Elias J. Anaissie,[2] David W. Denning,[13] Raoul Herbrecht,[14] Dimitrios P. Kontoyiannis,[3] Kieren A. Marr,[5] Vicki A. Morrison,[6,7] Brahm H Segal,[8] William J. Steinbach,[9] David A. Stevens,[10,11] Jo-Anne van Burik,[7] John R. Wingard,[12] and Thomas F. Patterson[4,a]

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

Indications

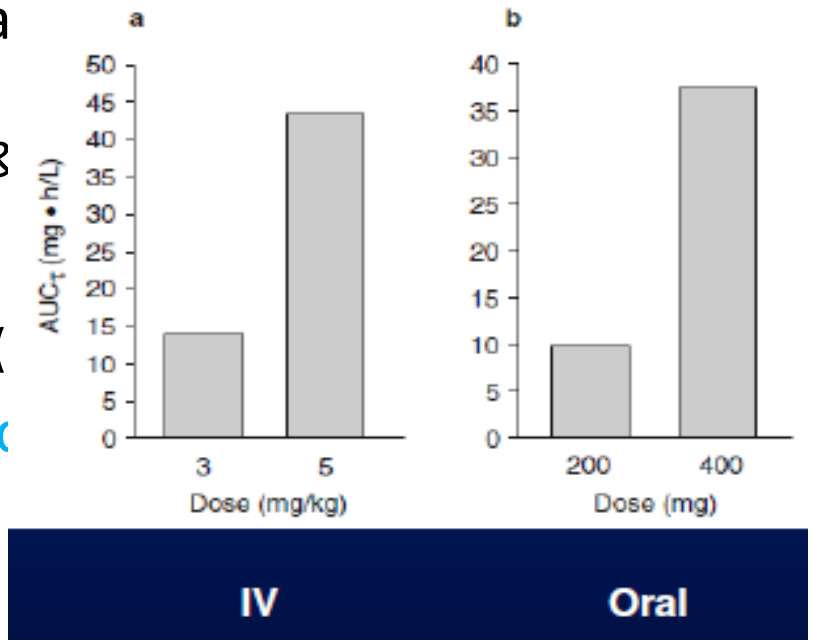
- probable or proven IA in immunocompromised patients
- proven IA in immunocompetent patients
- IC or candidemia in fluco resistant *Candida* spp
- *Scedosporium* of *Fusarium* spp.

Dosing (SmPC)

Loading	2 x 6 mg/kg
Maintenance	2 x 4 mg/kg
Adults < 40 kg	2 x 6 mg/kg – 2 x 2 mg/kg
Child A&B cirrhosis	2 x 6 mg/kg – 2 x 2 mg/kg

Voriconazole: PKPD & TDM –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 meta
   - Non-linear saturable elimination in adults
   - Metabolism mediated by CYP2C9, CYP2C19 &
     - Involved in many drug-drug interactions
     - Genetic polymorphism described for CYP2C19
   - Children < 12 yrs: 3-5 fold greater clearance (
3) Little or no correlation between dose and

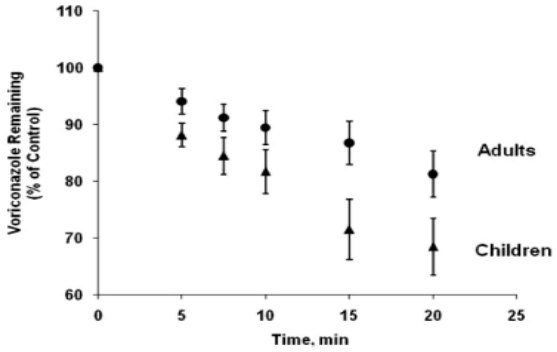


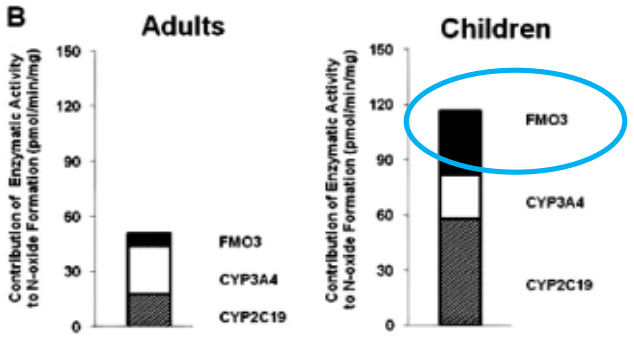
Pascual A et al. CID 2012; 55: 381-90. Scholz I et al. Br J Clin Pharmacol 2009; 68:906-15. Levin M-D et al. JAC 2007; 60:1104-7. Yanni SB et al. Drug Metab Dispos 2010; 38: 25-31. Trifilio S et al. BMT 2007; 40: 451-6. Dolton MJ et al. AAC 2012; 56: 4793-99.

Voriconazole: PKPD & TDM – PK in children

Linear PK!

- **Additional enzyme system (FMO3)** compensates for saturable P450 metabolism





- Consequences
  - Faster clearance and lower levels
  - Non homogeneuous group: TDM is important
    - Underlying morbidity: CF vs. hemato …
    - **Age: FMO 3 activity ↓ if age ↑**

Matching Dose (q12h)	IV Loading Dose	IV Maintenance Dose		Oral Maintenance Dose
Children (2 to <12 years old) & young adolescents (12 to 14 years old weighing <50 kg)	9 mg/kg	8 mg/kg	4 mg/kg	9 mg/kg (maximum dose of 350 mg)
Other adolescents (12 to 14 years old weighing ≥50 kg and 15-16 years old) & adults	6 mg/kg	4 mg/kg	3 mg/kg	200 mg

Voriconazole: PKPD & TDM – PK variability

Potential Factors for Inadequate Voriconazole Plasma Concentrations in Intensive Care Unit Patients and Patients with Hematological Malignancies

Martin Hoenigl,[a,b] Wiebke Duettmann,[b] Reinhard B. Raggam,[c] Katharina Seeber,[b] Katharina Troppan,[d] Sonja Fruhwald,[a] Florian Prueller,[c] Jasmin Wagner,[b] Thomas Valentin,[b] Ines Zollner-Schwetz,[b] Albert Wölfler,[d] Robert Krause[b]

- Re… 21 V… 5…
- Or… hera…
- 56… % tox…
- M… fac… nc…

Factors associated with subtherapeutic levels:

- Young age
- DDIs (carbamazepine, rifampine, rifabutine, phenytoin, ..)
- Ultra Rapid Metabolism

Factors associated with toxic levels:

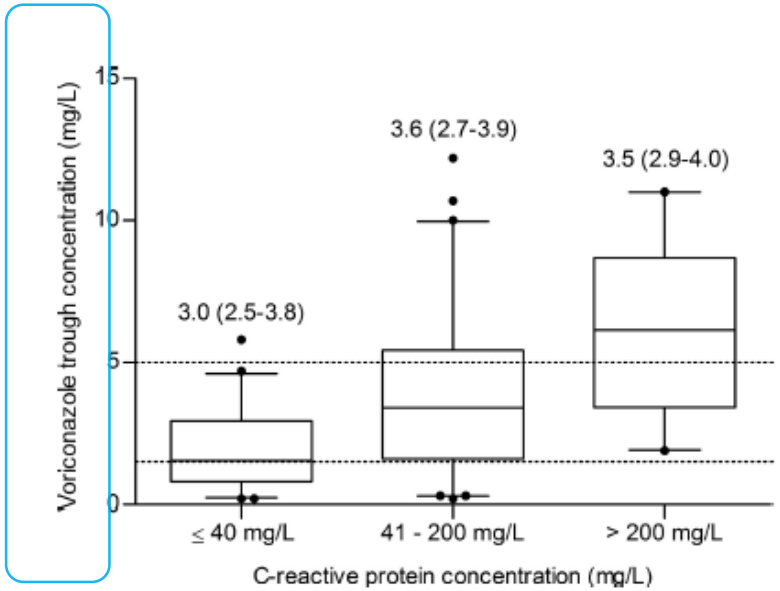
- higher BMI
- combination with PPI (CYP2C19 inhibition)

Antimicrobial Agents and Chemotherapy p. 3262-3267 July 2013 Volume 57 Number 7

Voriconazole: PKPD & TDM – PK variability

Inflammation Is Associated with Voriconazole Trough Concentrations

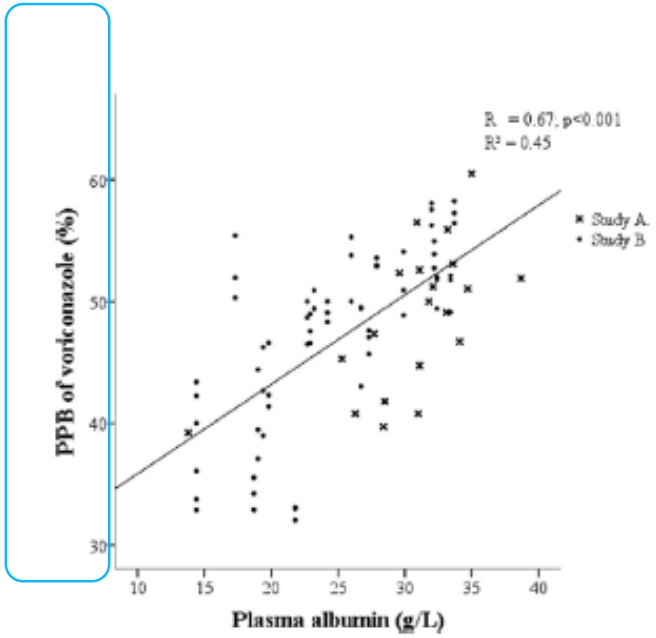
Marjolijn J. P. van Wanrooy,[a] Lambert F. R. Span,[b] Michael G. G. Rodgers,[c] Edwin R. van den Heuvel,[d] Donald R. A. Uges,[a] Tjip S. van der Werf,[e] Jos G. W. Kosterink,[a,f] Jan-Willem C. Alffenaar[a]



AAC 2014; 58: 7098-101

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

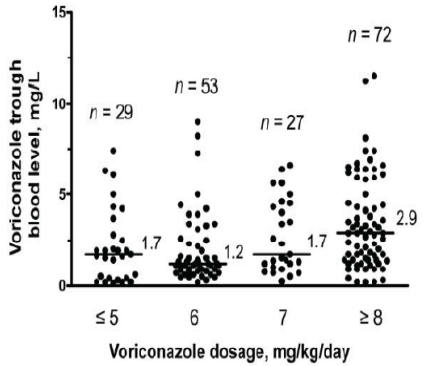
Voriconazole: PKPD & TDM – Relation with efficacy

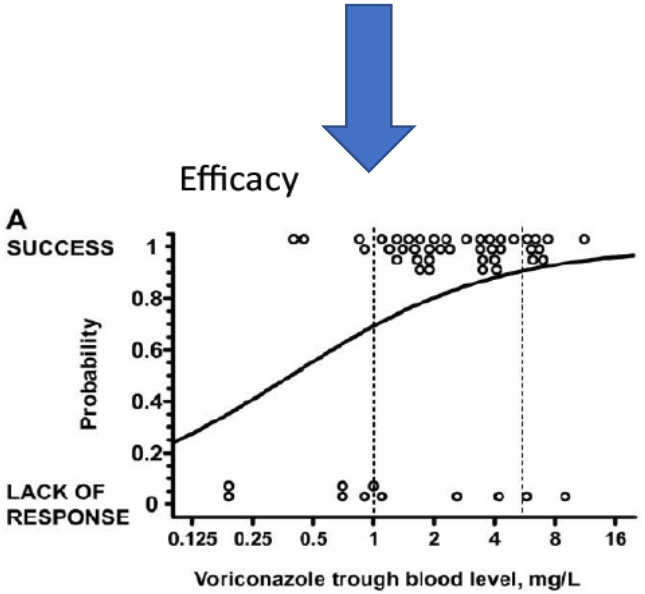
- Several retrospective and prospective studies have reported vori Cmin > 1,5 – 2 mg/L to be associated with maximal clinical response

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,[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





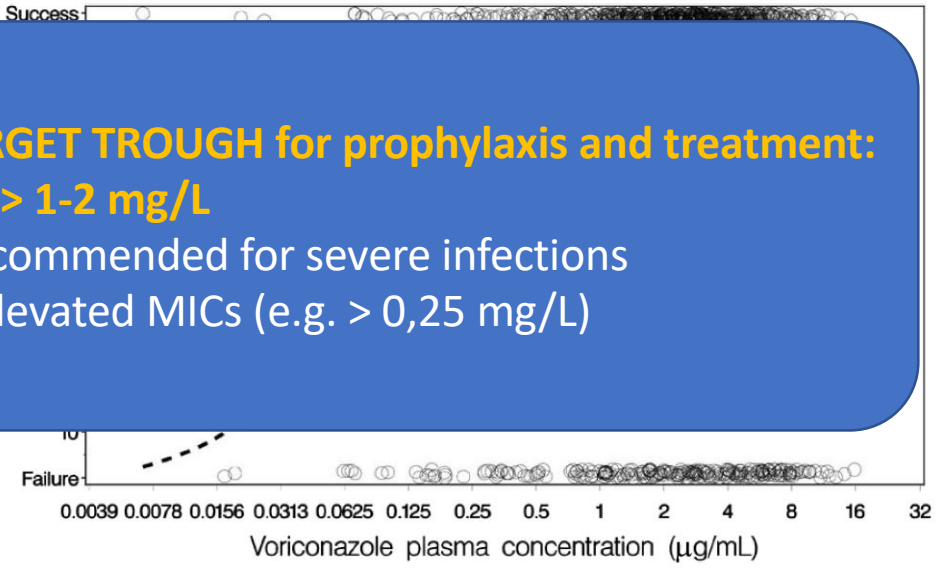
Pascual A et al. CID 2008; 46 (2): 201-11.

Voriconazole: PKPD & TDM – Relation with efficacy

- Several retrospective and prospective studies have reported vori Cmin > 1,5 – 2 mg/L to be associated with maximal clinical response
- Post-hoc analysis of phase II/III clinical efficacy trials
  - Cavg/MIC target > 2, or C avg plasma concentration 2-5 mg/L
  - Response rate 74%

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)



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

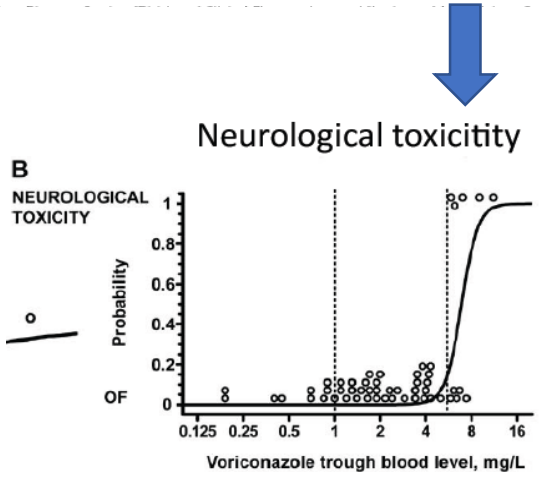
Voriconazole: PKPD & TDM – Relation with toxicity

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

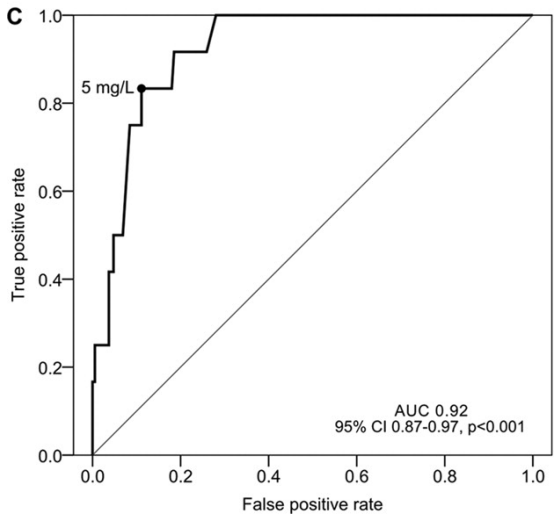
Andres Pascual,[1] Thierry Calandra,[1] Saskia Bolay,[1] Thierry Buclin,[2] Jacques Bille,[3] and Oscar Marchetti[1]



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]

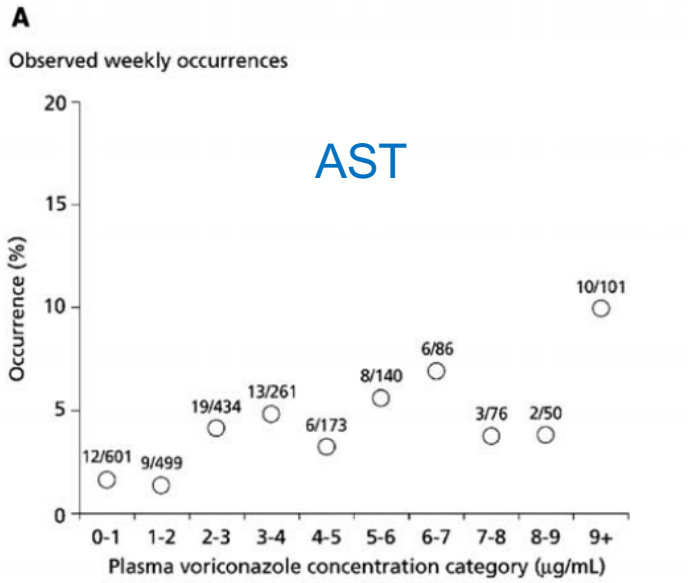


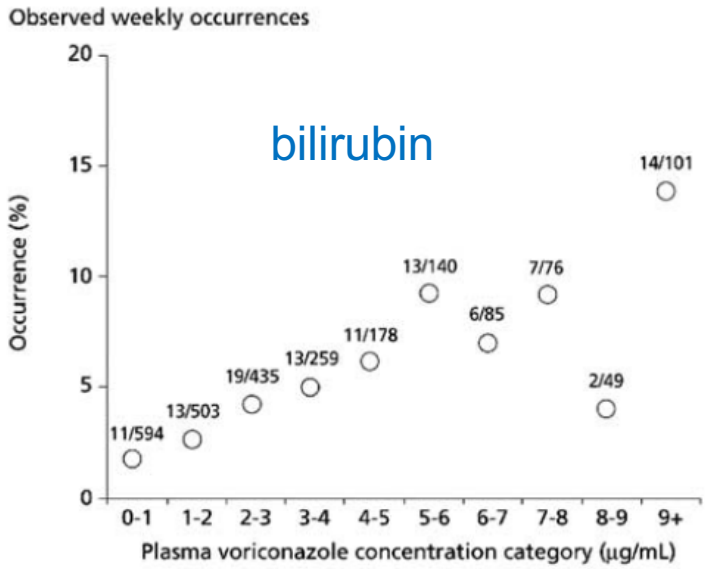
Dolton M J et al. AAC 2012;56:4793-4799

Voriconazole: PKPD & TDM – Relation with toxicity

HEPATOTOXICITY

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





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

Voriconazole: PKPD & TDM – Relation with toxicity

HEPATOTOXICITY

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

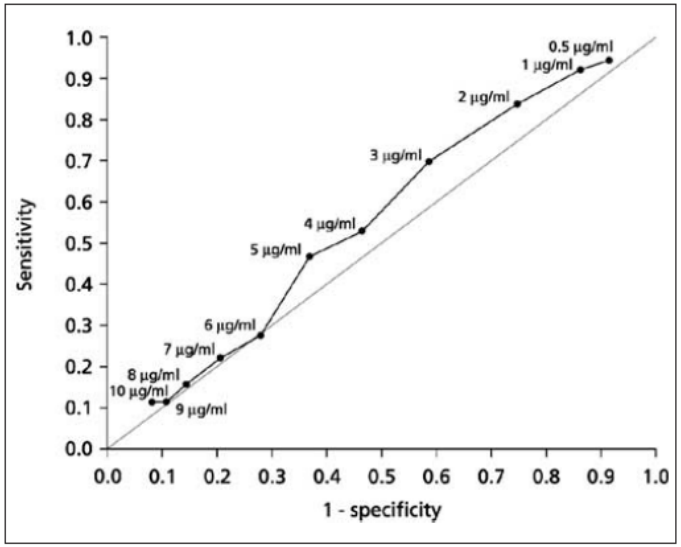


Figure 6. ROC curve for predicting AST abnormalities from plasma voriconazole concentrations.

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**

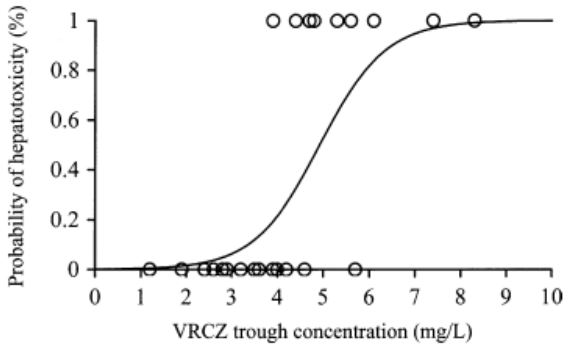


Fig. 1. Voriconazole (VRCZ) trough concentration and logistic regression model for hepatotoxicity (absence, $n = 19$; presence, $n = 10$).

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

Voriconazole: PKPD & TDM – Relation with 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.

s (CNS)

Voriconazole: Is TDM useful?

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

Voriconazole: PKPD & TDM – CASE 1 : what do you recommend?

(influenza patient on IV treatment for IA in the ICU, low levels)

1. I would keep on increasing the maintenance dose, again with +50% of the current dose (i.e. MD of 525 mg 2x/day)

2. I would keep the current dose, attaining a new steady state takes at least 4 days.

3. I would keep the current dose, attaining a new steady state takes at least 4 days, but I would recommend to change ranitidine into omeprazole.

4. I would ask for CYP2C19 genotyping, I guess the patient is an URM.

5. I would check for DDIs with the patient's comedication – it is strange that these doses result in low vori levels.

Voriconazole: PKPD & TDM – CASE 2 - What do you recommend?

(ambulatory patient with RA, treated for IV, low levels, CBZ taken at home)

1. I would discuss compliance with her. Probably she is not taking voriconazole twice daily.

2. I would discuss intake with her. Probably she is taking voriconazole with a meal explaining decreased absorption and low bio-availability.

3. I would increase the dose with at least 50%, or even consider to double the dose.

4. I would check for DDIs, these low levels seem very strange to me.

5. I would ask for CYP2C19 genotyping, I guess the patient is an URM.

Posaconazole: PKPD & TDM – Case 3

A 33 yr old man is admitted with acute leukemia in the hematology dpt. As part of the standard treatment scheme he is treated with posaconazole (Noxafil) tablet, LD: 2 x 300 mg, MD: 1 x 300 mg. This is used as prophylaxis during the neutropenic phase following chemotherapy.

The comedication exists, next to chemotherapy, out of omeprazole, levofloxacin (SDD), cotrimoxazole (PJP), paracetamol and enteral nutrition, as the patient is too weak to eat sufficiently by mouth.

Once per week posaconazole trough levels are monitored, the result was 0.2 mg/L.

The hematologist is calling you for advice. What do you recommend?

Posaconazole: PKPD & TDM – Case 3 – What do you recommend?

1. You advice to increase the dose up to 400 mg/day as the target for prophylaxis in the hematology setting is 0.7 mg/L.

2. You advice to stop the enteral nutrition, as enteral feeding will decrease the oral absorption of posaconazole.

3. You recommend to switch to IV treatment. When the tabs are crushed to be given via the nasogastric tube, the gastro-resistant formulation is broken and absorption will be comparable to that of the suspension, explaining the low levels.

4. You recommend to add cola when posa tabs are administered. Posaconazole tabs need an acidic pH in the stomach to warrant absorption, which is not present because of cotreatment with omeprazole.

Case 3: What would you recommend?

You advice to increase the dose up to 400 mg/day as the target for prophylaxis in the hematology setting is 0.7 mg/L.

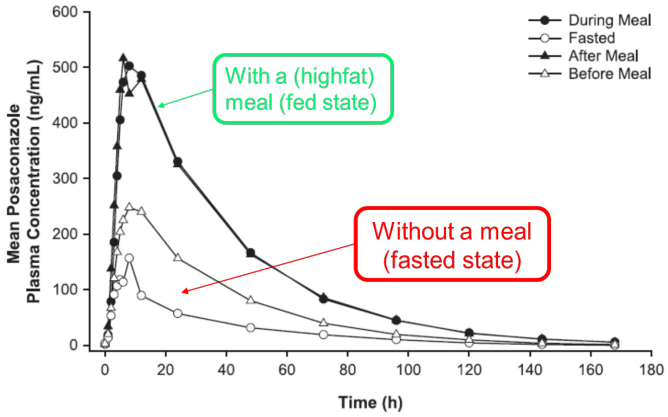
You advice to stop the enteral nutrition, as enteral feeding will decrease the oral absorption of posaconazole.

You recommend to switch to IV treatment. When the tabs are crushed to be given via the nasogastric tube, the gastro-resistant formulation is broken and absorption will be comparable to that of the suspension, explaining the low levels.

You recommend to add cola when posa tabs are administered. Posaconazole tabs need an acidic pH in the stomach to warrant absorption, which is not present because of cotreatment with omeprazole.

Posaconazole: PKPD & TDM – PK properties & formulations

- 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

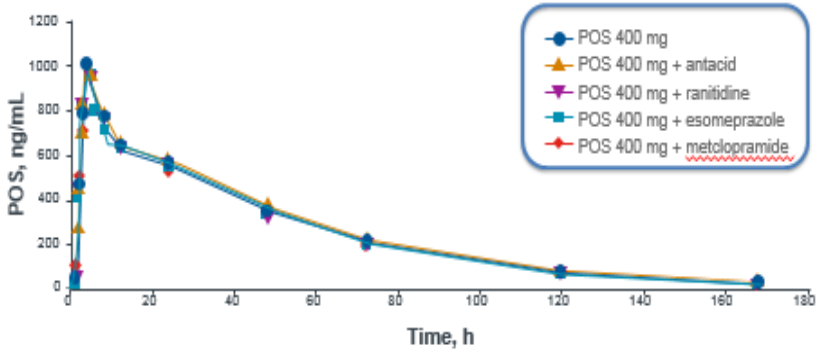
→ In some patients posaconazole concentrations not measurable

AAC 2009; 2223-4

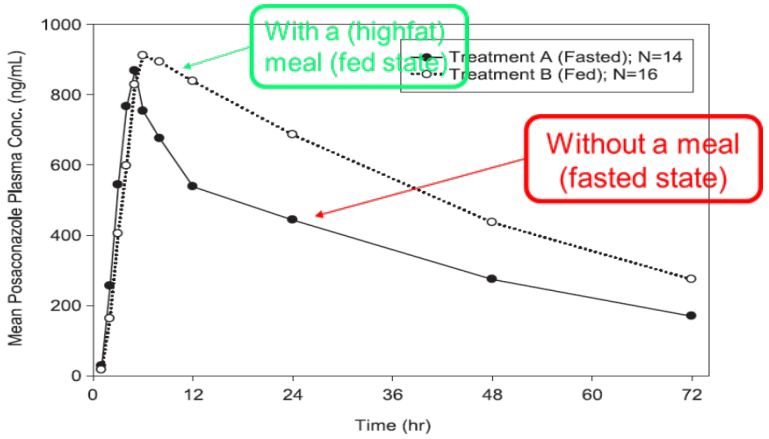
Krishna G et al. AAC 2009; 958-966.

Posaconazole: PKPD & TDM – PK properties & formulations

- 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

→tablets can not be crushed (e.g. to be given via a NG), absorption will be comparable to that of the suspension

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

Posaconazole: Is TDM useful?

- Discussed in ECIL-6 guidelines and based on a selection 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	11 (48%)
Multicentre studies	1 (4%)
Prospective	
Single-centre studies	6 (26%)
Multicentre studies	3 (13%)
Randomized for TDM intervention	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

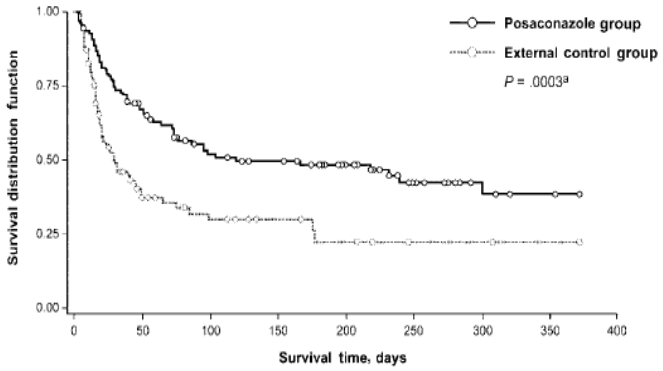


Table 8. Posaconazole plasma concentration versus global response in patients with invasive aspergillosis (MITT subset).

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**

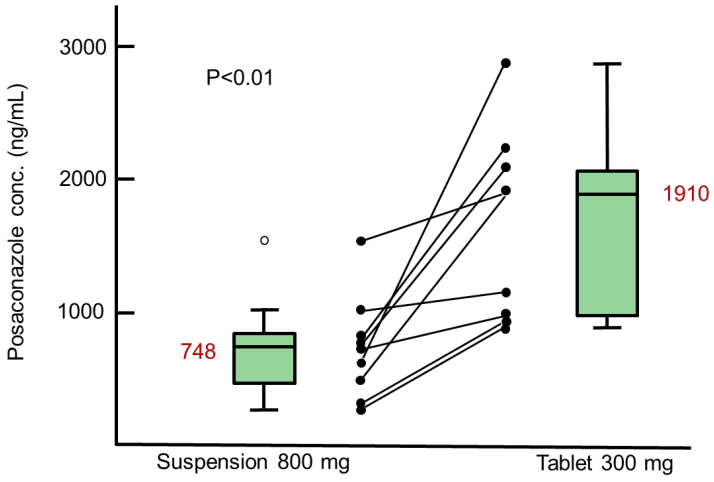
Walsh TJ et al. Clin Infect Dis 2007; 44:2-12.

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?

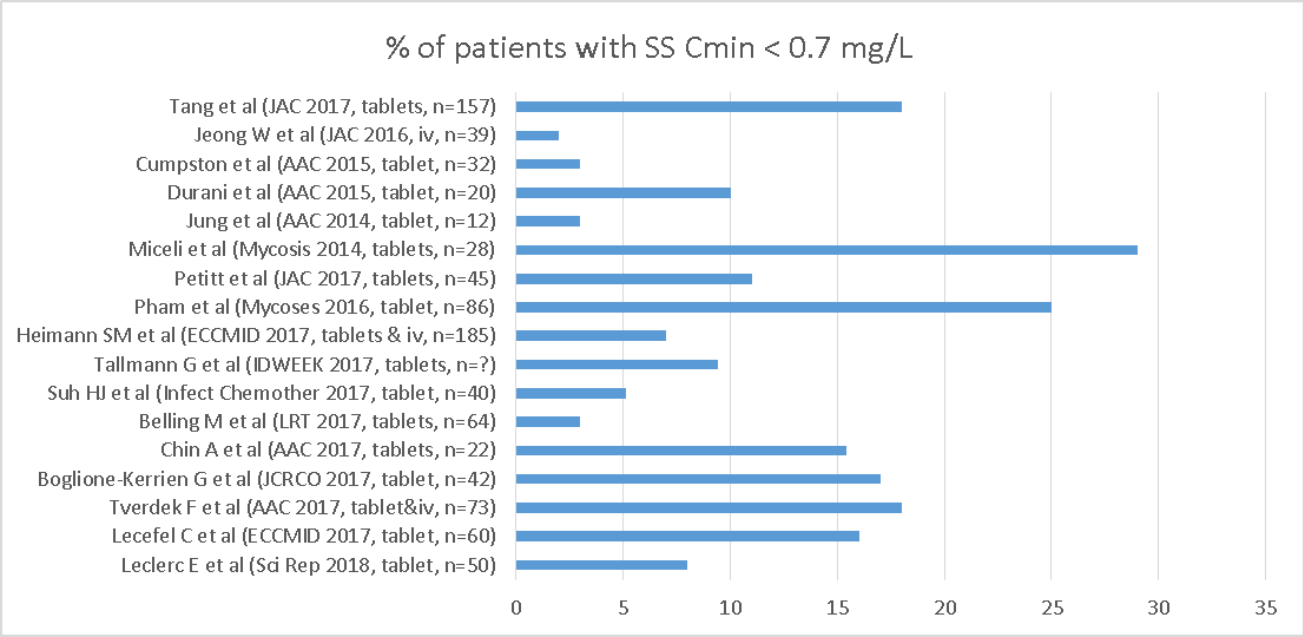


Jung et al. Antimicrob Agent Chemother 2014;58:6993-5.

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)

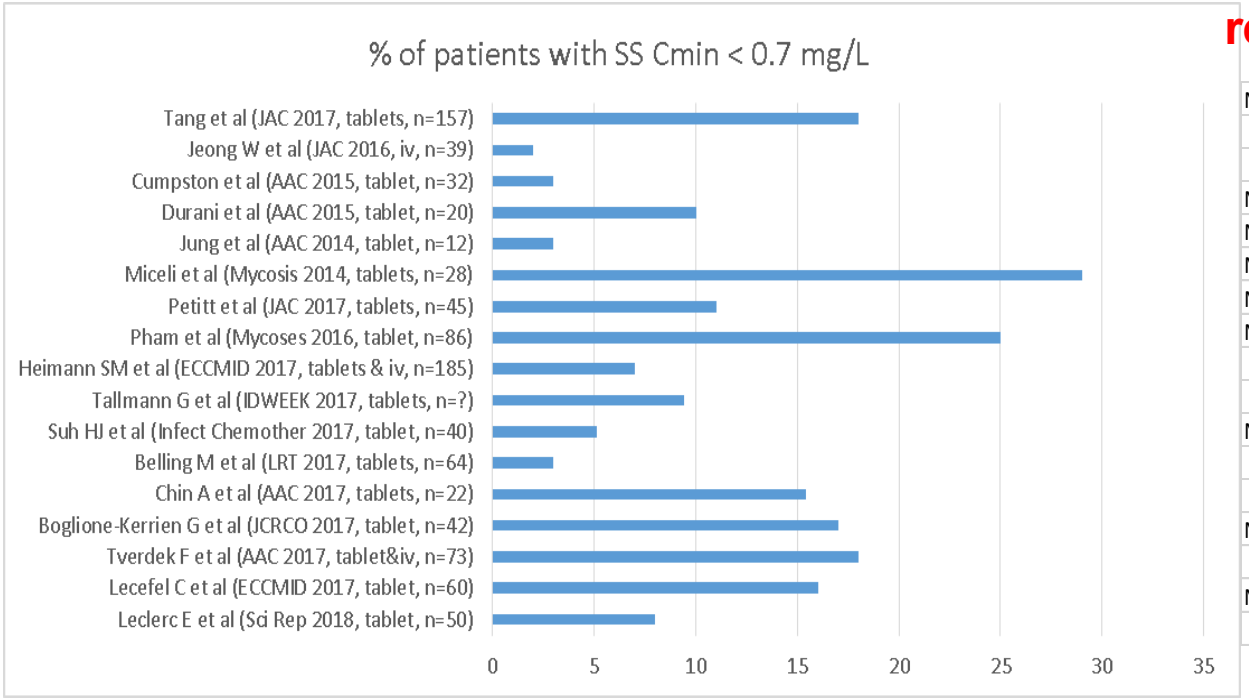
However, in other studies **no significant correlation** was found between these factors and low exposures (Lecefel et al, Jung et al, Pham et al)

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

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

Relation between low exposure and **breakthrough IFI**

Real life evidence with posa tablet & iv from 2014-2018



% patients with breakthrough infection reported in real life studies

NR
0
3
NR
NR
NR
NR
NR
1
1,7
NR
6,4
15
NR
2
NR
0

Probable IFI breakthrough rate with the tablet is approximately **1-3%**

Breakthrough infection is **not always observed** in context of low posa serum levels

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

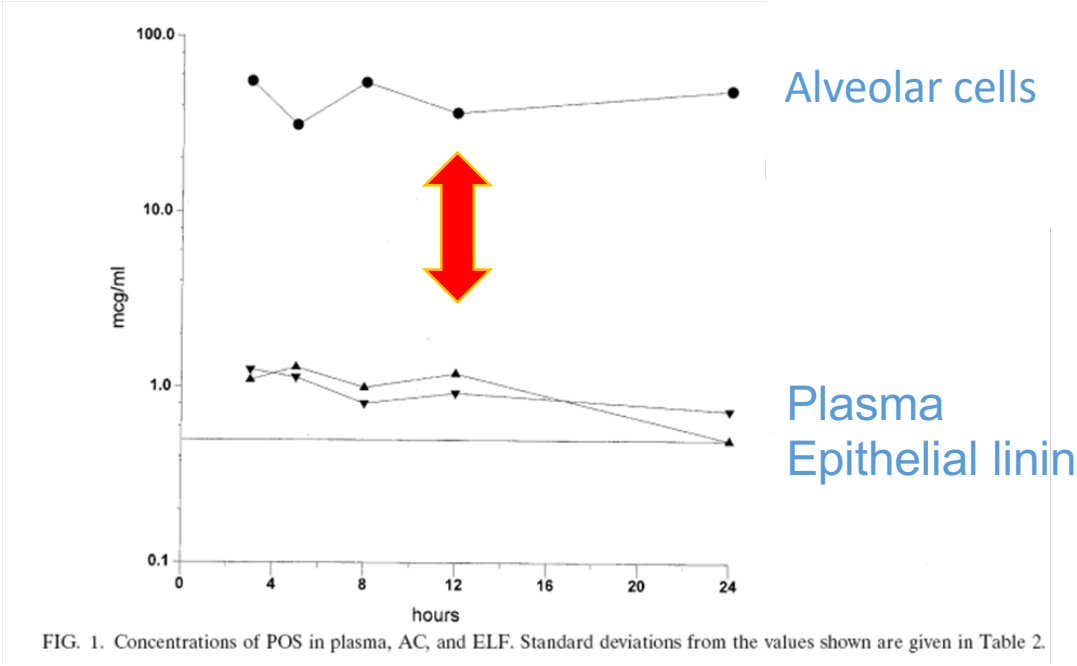


FIG. 1. Concentrations of POS in plasma, AC, and ELF. Standard deviations from the values shown are given in Table 2.

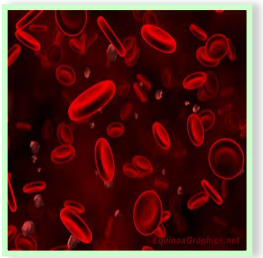
Alveolar cells

Plasma
Epithelial lining fluid

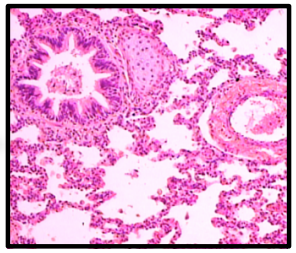
Conte JE et al. AAC 2010; 54: 3609-13.

New insights in posaconazole intracellular concentrations

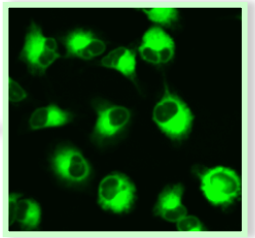
Host:



Serum
500ng/ml
x 1



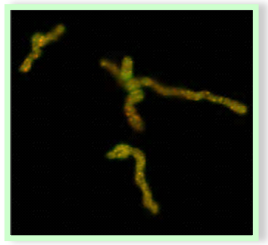
Host Cells
20µg/ml
x 40



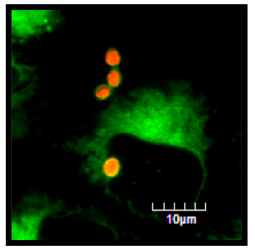
Cell Membranes
200µg/ml
x 400

Fungus:

- 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



Target Enzyme
x 400



Fungal Membranes
x 400

Campoli P et al. J Infect Dis 2013; 208: 171

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 seems 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

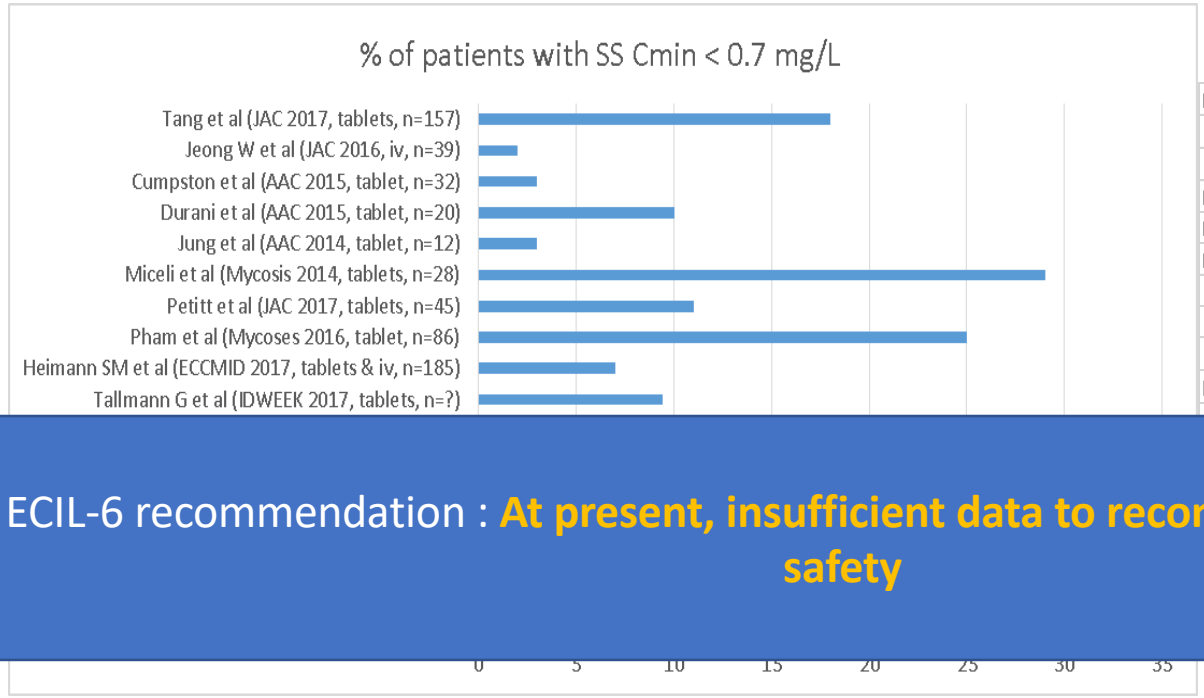
Quartile	Posaconazole pC_{avg} mean (ng/mL)	pC_{avg} range (ng/mL)	Number of subjects	Subjects reporting any treatment-related TEAEs, *n* (%)
1	860	442–1223	51	29 (57)
2	1481	1240–1710	51	19 (37)
3	1979	1719–2291	51	16 (31)
4	3194	2304–9523	52	20 (38)

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



% patients with transient liver function elevations*

*varying definitions

NR
0
3
NR
NR
NR
22,7
10,46
0
NR

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

Liver function elevations occur **relatively frequently** with posaconazole

Results are **conflicting** when looking into the relation between liver function elevations and exposure

Posaconazole: Is TDM useful?

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

Gastroresistant tablet and iv are the preferred formulations

In observational trials **2-30%** of patients receiving the new formulations do not reach 0,7 mg/L

Suboptimal exposure can thus far not be predicted on risk factors alone

ECIL-6

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

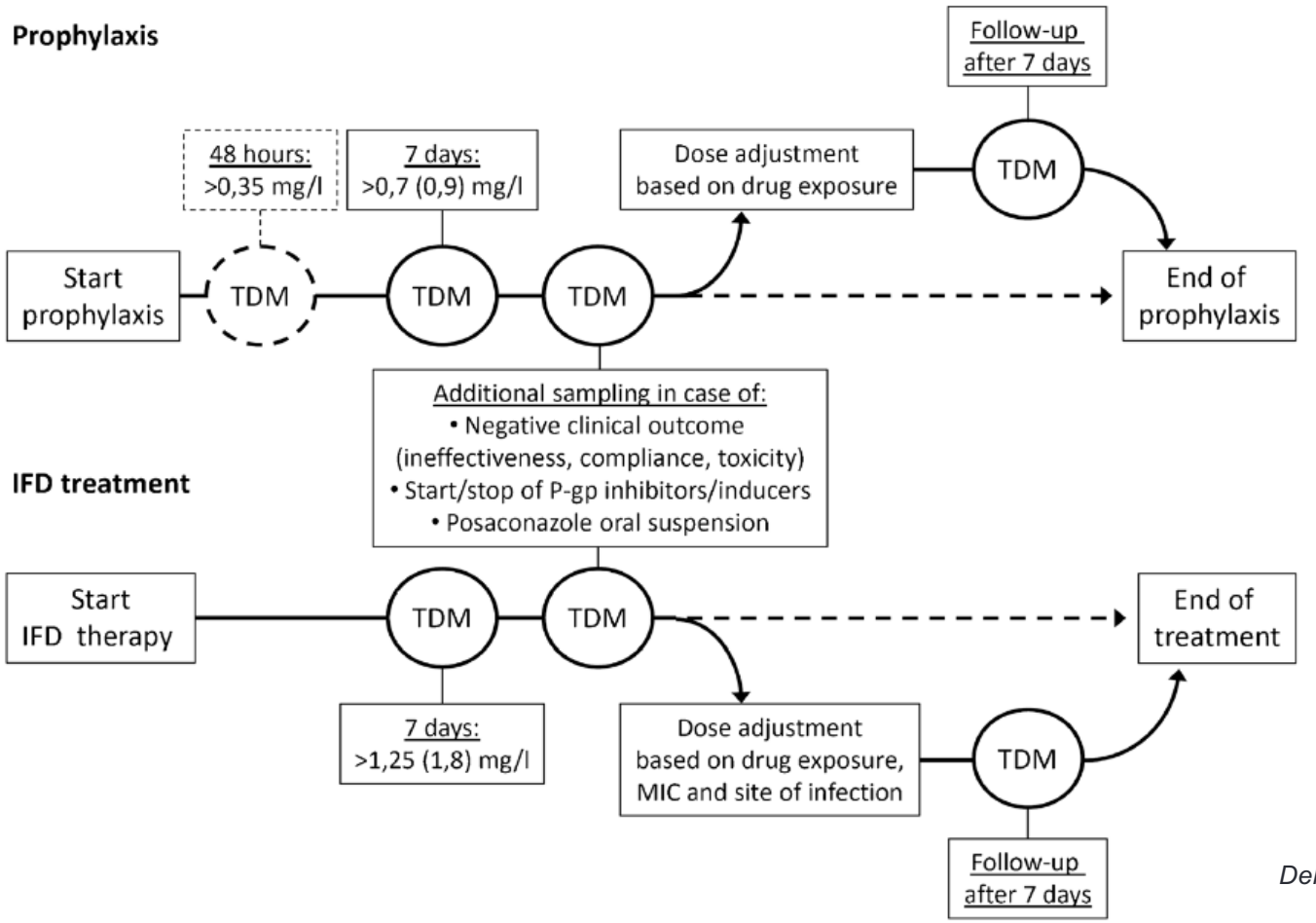
TDM **is** indicated in the setting of breakthrough infection, resistant pathogens, DDIs, therapeutic failure

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

Strategy for posa TDM



Tablet or IV
Trough sample at **day 4** after LD

Suspension
Trough sample **at day 7-8**, if earlier use target of 0,35 mg/L

Recheck after 5 days if
- Changes in dose or GI function
- Changes in clinical condition
- Therapeutic failure

If Cmin< 0.7 mg/L (for tablet)
- Check for low compliance
- Check for DDI
- Consider switch to iv in patients with diarrhea
- Increase the dose up to 400 mg/day

Dekkers et al. Curr Fungal Infect Rep. 2016;10:51–61.

Posaconazole: PKPD & TDM – Case 3 – What do you recommend?

(leukemia patient with low posa levels when treated with the tablet via NGT)

1. You advice to increase the dose up to 400 mg/day as the target for prophylaxis in the hematology setting is 0.7 mg/L.

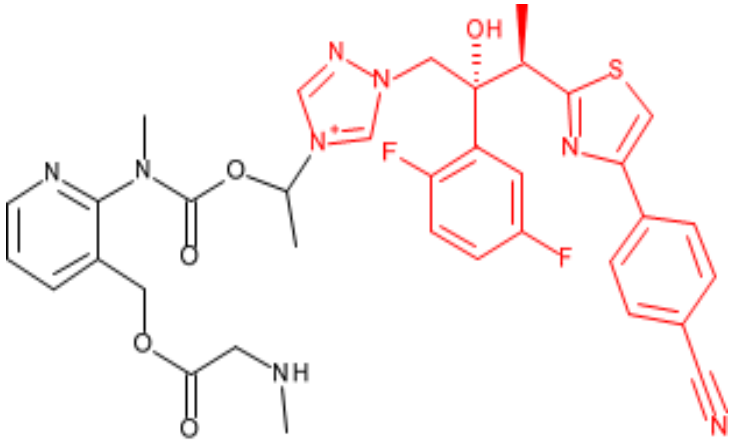
2. You advice to stop the enteral nutrition, as enteral feeding will decrease the oral absorption of posaconazole.

3. You recommend to switch to IV treatment. When the tabs are crushed to be given via the nasogastric tube, the gastro-resistant formulation is broken and absorption will be comparable to that of the suspension, explaining the low levels.

4. You recommend to add cola when posa tabs are administered. Posaconazole tabs need an acidic pH in the stomach to warrant absorption, which is not present because of cotreatment with omeprazole.

Isavuconazole: PKPD & TDM?

Isavuconazonium sulfate (prodrug BAL 8557)
Intravenous and oral formulations

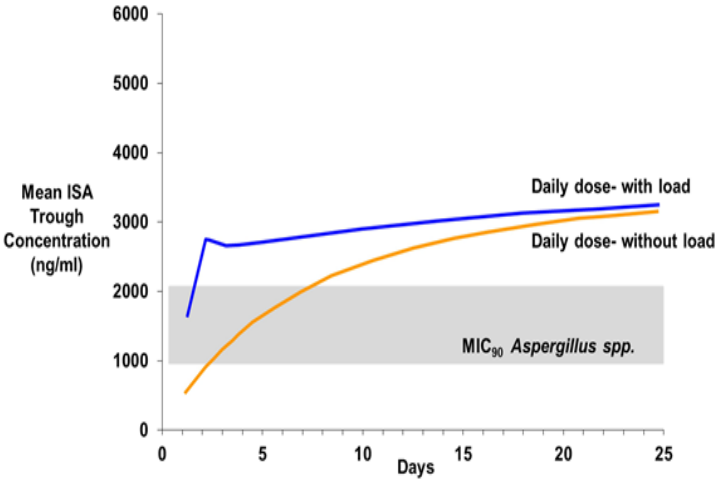


Inactive cleavage product
(BAL 8728)

Isavuconazole
(active drug BAL 4815)

Isavuconazole: favorable PKPD

Absorption	■ Rapidly absorbed, > 98% oral bioavailibility ■ Absorption not affected by food or gastric pH
Distribution	■ Vd 450 L (Very high tissue distribution) ■ Linear pharmacokinetics ■ Loading dose required (200 mg q8h x48h)
Metabolism	■ Very long half-life (approx. 130 hours) ■ Less pharmacokinetic variability versus voriconazole ■ Metabolized via CYP3A4 → UGT ■ Clearance reduced in hepatic impairment
Elimination	■ Urine→ inactive glucuronide metabolites

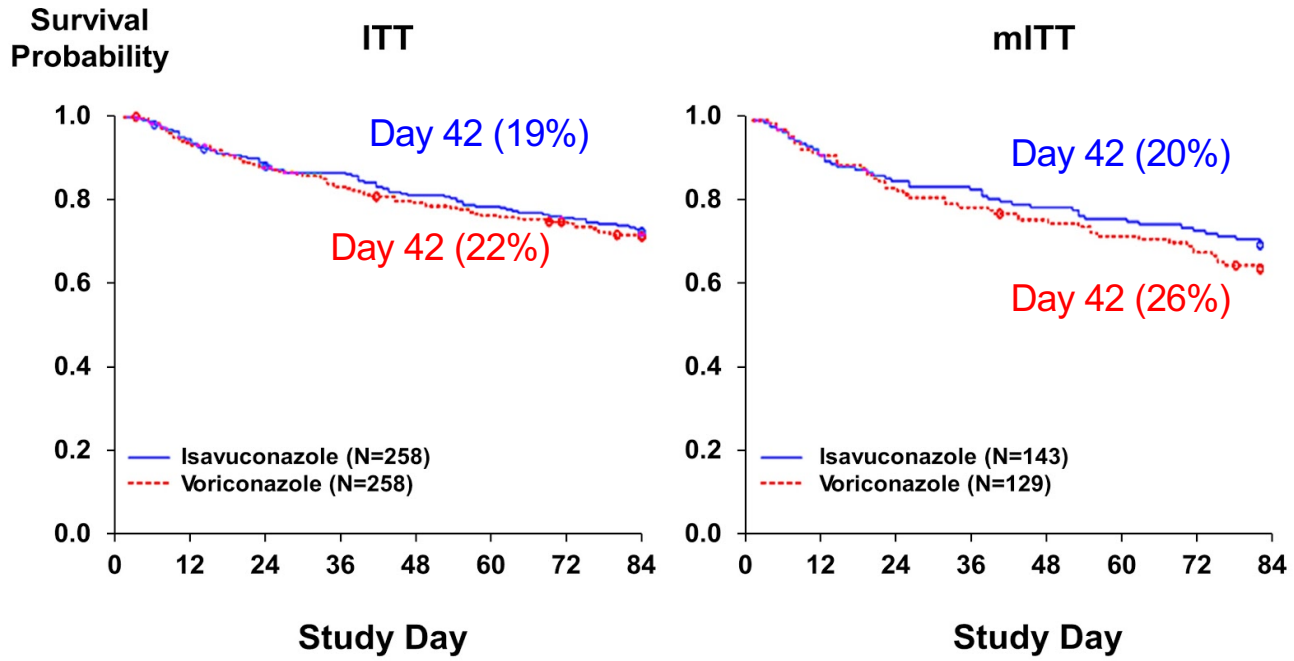


Falci & Pasqualotto. Infection and Drug Resistance. 2013:6 163–174

Isavuconazole: relation between exposure and efficacy?

- Isavuconazole vs. voriconazole for proven or probable aspergillosis (SECURE Trial)

  Kaplan Meier estimates of survival probability through day =84



No relationship between isavuconazole AUC or trough with outcome noted

Maertens JA, Raad, II, Marr KA, et al. *Lancet.* 2016;387(10020):760-769.

Isavuconazole: is TDM useful?

Parameter	Substantial PK variability?	Therapeutic window defined in humans?	Narrow therapeutic window?
Isavuconazole	yes	✗ no	?

Fluconazole: PKPD & TDM – Case 4

- You are called by an ICU physician. He is treating a 27 yr old, 90 kg weighing male patient who is recovering from polytrauma in the ICU.
- On day 7 after ICU admission, the patient develops candidemia. Hemocultures revealed *C. albicans*, susceptible to fluconazole.
- The intensivist is wondering which dose should be given as the patient shows augmented renal clearance (measured CrCl = 165 mL/min.1.73 m2).

- Which dose would you recommend?

Fluconazole– Case 4 – Which dose would you recommend?

- A standard LD of 800 mg, followed by a MD of 400 mg. Fluconazole is known for its stable and easy PK, without significant impact of patient related factors.
- A maintenance dose of 800 mg. The patient is showing hyperclearance and fluconazole is eliminated in an important manner via the kidney.
- A maintenance dose of 6 mg/kg, i.e. 540 mg.
- I would switch to an echinocandin.

Case 4: Which dose would you recommend?

A standard LD of 800 mg, followed by a MD of 400 mg. Fluconazole is known for its stable and easy PK, without significant impact of patient related factors.

A maintenance dose of 800 mg. The patient is showing hyperclearance and fluconazole is eliminated in an important manner via the kidney.

A maintenance dose of 6 mg/kg, i.e. 540 mg.

I would switch to an echinocandin

Fluconazole: PK properties

- Easy PK – once daily dosing – needs a loading dose

Absorption	BB> 90% Independent from food or pH
Distribution	Widely distributed in tissues and CSF Vd = 0.56-0.82 L/kg
Metabolism	Only minor hepatic metabolism
Excretion	80% unchanged renal elimination
Other	• Linear PK: dose proportional exposure • Halflife = 30h, allows once daily dosing • SS is reached after 5-10 days, or at day 2 after a LD • PB: 11% • Inhibits CYP2C9, CYP3A4 and CYP2C19

Fluconazole: PKPD & TDM?

- Substantial PK variability in some populations potentially leading to subtherapeutic exposure
  - critically ill patients with sepsis, e.g. DALI results
  - hemodialysis
  - pediatrics
  - obese patients

- But:
  - Monitoring strategy unclear – AUC/MIC >100?
  - fluconazole has a **broad therapeutic window** – dose can be increased empirically (e.g. up to 12 mg/kg/day)

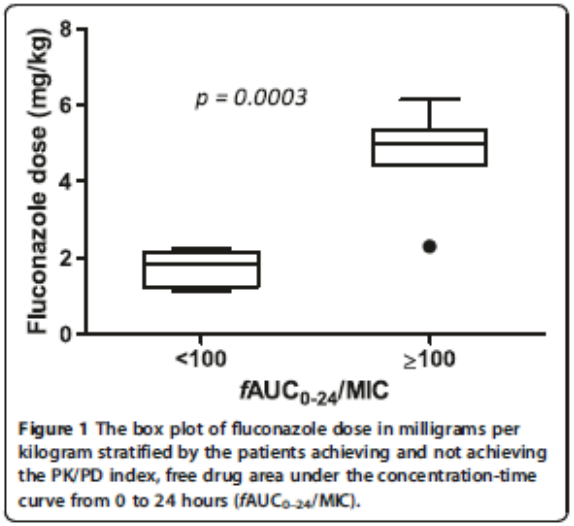


Figure 1 The box plot of fluconazole dose in milligrams per kilogram stratified by the patients achieving and not achieving the PK/PD index, free drug area under the concentration-time curve from 0 to 24 hours ($fAUC_{0-24}$/MIC).

Sinnollareddy et al. Crit Care 2015; 19-33.
Sinnollareddy et al. Exp Opin Drug Metab Toxicol 2011; 7:1431-40.

Fluconazole & TDM?

Parameter	Substantial PK variability?	Therapeutic window defined in humans?	Narrow therapeutic window?
Fluconazole	yes	/ yes	✗ no

ECIL-6 recommendation (DIII): **routine TDM for fluconazole is not recommended**

Fluconazole TDM may be helpful for rare treatment circumstances to target AUC/MIC > 100 (BIII)
e.g. hemodialysis + sepsis, CNS infection, pathogens with high MICs (>2-4 mg/L)

Fluconazole– Case 4 – Which dose would you recommend?

- A standard LD of 800 mg, followed by a MD of 400 mg. Fluconazole is known for its stable and easy PK, without significant impact of patient related factors.
- A maintenance dose of 800 mg. The patient is showing hyperclearance and fluconazole is eliminated in an important manner via the kidney.
- A maintenance dose of 6 mg/kg, i.e. 540 mg.
- I would switch to an echinocandin.

Echinocandins – Case 5

- You are participating in the multidisciplinary case discussion at the ICU.
- A 52-yr old patient (65kg) admitted in the ICU after major abdominal surgery developed candidemia (*C. albicans)* during his ICU stay. Anidulafungin was started in the recommended doses (LD: 200 mg, MD: 100 mg) 5 days ago. However, daily blood cultures keep on showing *C. albicans*.
- The question is raised if this might be due to underdosing of anidulafungin and if TDM should be started.
- The patient's APACHE score is 21, the patient's cotreatment is meropenem, vancomycin, noradrenalin, propofol, morphine, omeprazole, PN + MV/TE, insulin, IV fluids, enoxaparin.
- The patient's renal clearance is 66 mL/min.1.73m2.
- What is your advice?

Echinocandins – Case 5 – What is your advice?

- I would recommend to switch to caspofungin – it has been shown that the PK of caspo is less variable than that of anidula.
- I would recommend to double the dose. The patient is critically ill, and anidulafungin is potentially underdosed leading to uncontrolled candidaemia.
- The PK of anidulafungin is not much altered in ICU patients. The question is whether there is another focus (valves? prostheses? Septic emboli?) leading to persistent candidaemia.
- I would advice to order a trough level. Based on that, the dose might be adapted in order to warrant clinical efficacy.

Case 5: What do you recommend?

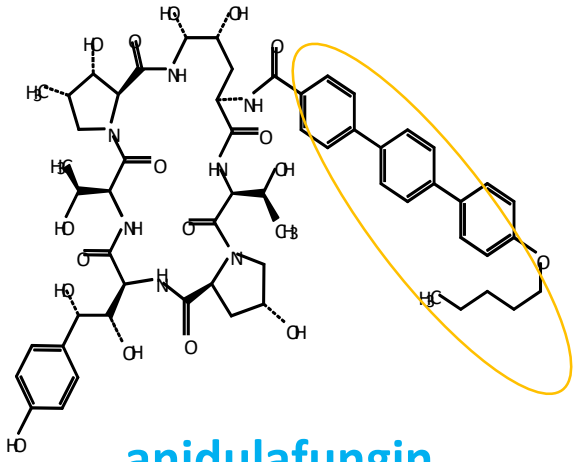
I would recommend to switch to caspofungin – it has been shown that the PK of caspo is less variable than that of anidula.

I would recommend to double the dose. The patient is critically ill, and anidulafungin is potentially underdosed leading to uncontrolled candidaemia.

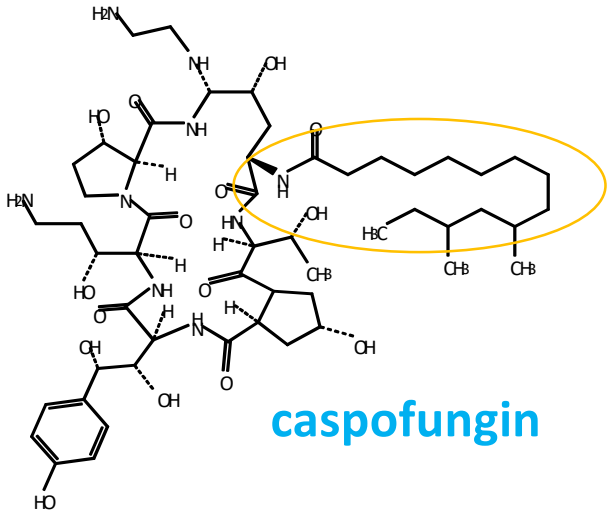
The PK of anidulafungin is not much altered in ICU patients. The question is whether there is another focus (valves? prostheses? Septic emboli?) leading to persistent candidaemia.

I would advice to order a trough level. Based on that, the dose might be adapted in order to warrant clinical efficacy.

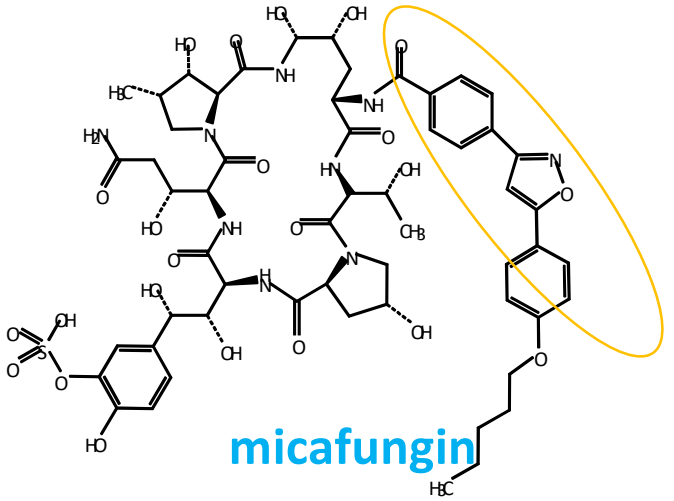
ECs: different drugs – different PK?



anidulafungin



caspofungin



micafungin

Sidechain determines

- activitity: interaction with cell wall
- pharmacokinetics: the more lipophilic, the higher Vd

EC approved indications

ADULTS

	Caspofungin	Micafungin	Anidulafungin
Treatment of invasive candidiasis	70 mg load; 50 mg QD	100 mg QD	200 mg load; 100 mg QD
Empirical therapy for presumed fungal infections in febrile neutropenic patients	70 mg load; 50 mg QD		
Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (ie, amphotericin B, lipid formulations of amphotericin B, and/or itraconazole)	70 mg load; 50 mg QD		
Prophylaxis of Candida infections in allogenic HSCT recipients		50 mg QD	

CHILDREN

	Caspofungin	Micafungin	Anidulafungin
Treatment of candidemia and the following Candida infections: intra-abdominal abscesses, peritonitis	<u>17years – 3months</u> load : 70mg/m² QD: 50mg/m² <u>< 3months</u> load : 25mg/m² QD: 25mg/m²	<u>< 40kg</u> 2mg/kg QD	
Empirical therapy for presumed fungal infections in febrile neutropenic patients			
Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (ie, amphotericin B, lipid formulations of amphotericin B, and/or itraconazole)			
Prophylaxis of Candida infections in allogenic HSCT recipients		<u>< 40kg</u> 1mg/kg QD	

Basic pharmacokinetics

Table I Pharmacokinetic parameters of echinocandins in adult subjects (Denning 2003; Deresinski and Stevens 2003; Wiederhold and Lewis 2003; Carver 2004; Murdoch and Plosker 2004; Raasch 2004; Zaas and Alexander 2005)

Variable	Caspofungin	Micafungin	Anidulafungin
C_{max} (mg/L)(50 mg single dose)	7.64	4.95	2.07–3.5
Bioavailability			2%–7%
$t_{1/2}$ (hours)	9-11	11-17	24–26
Vd (L/kg)	0.14 [9.67L]	0.215–0.242	0.5 [30–50L]
AUC (mg•h/L)	87.9–114.8	111.3	44.4–53
Protein binding (%)	96–97	99.8	84
Metabolism	Via slow peptide hydrolysis and N-acetylation. Also spontaneously degrades to inactive product	Via catechol-O-methyltransferase pathway	Not metabolised; undergoes slow chemical degradation to inactive metabolites
Cl_T (mL/min/kg)	0.15		
f_e	1.4 %		
Elimination	35% (~1.		
CSF penetration (% of plasma)	? lov		
Dosage adjustment in renal insufficiency	No		
	No		
Dosage adjustment in hepatic insufficiency	Chil		
	Chil		
	incr		
	mai		
	35 m		
	Chil		

Abbreviations: AUC, area under the plasma conc
fluid; f_e, fraction of drug excreted unchanged in the

Some PK differences, but all characterized by…

- Low interindividual variability
- Low potential for drug-drug interactions

→ Due to

- Slow degradation to inactive metabolites
- Minimal renal excretion of unchanged drug
- Poor substrates for CYP450 / P-GP

Pea F. Expert Rev Anti Infect Ther 2013; 11: 1-9
Chen S et al. Drugs 2011; 71: 11-41.

EC: Recommended dosing

	Caspofungin	**Anidulafungin**	**Micafungin**
Normal dose	LD: 70 mg MD: 50 mg, if >80 kg: 70 mg	LD: 200 mg MD: 100 mg	100 mg
Renal impairment	No dose adjustments	No dose adjustments	No dose adjustments
Liver insufficiency	Child B: 35 mg Child C: no data	No dose adjustments	100 mg No data in Child C
Children	70 mg/m2 50 mg/m2	No data	2 mg/kg
Prophylaxis	No data	No data	50 mg (1 mg/kg)

- Importance of infusion duration
  - caspofungin/micafungin: 1 hr
  - anidulafungin: LD: 3 hr – MD 1,5 hr

Chen S et al. Drugs 2011; 71: 11-41

ECs & drug-drug interactions

- Few serious drug interactions
  - Unique antifungal mode of action
  - No substrates, inhibitors or inducers of CYP450/P-GP

Table IV. Drug interactions with the echinocandins[11-13,138-142]

Drug	Caspofungin	Micafungin	Anidulafungin
CYP/P-glycoprotein interactions	Poor substrate for CYP Not an inhibitor of CYP Not a substrate/inhibitor of P-glycoprotein	Substrate for CYP3A4 Weak inhibitor CYP3A4 Not a substrate/inhibitor of P-glycoprotein	Not a substrate, inducer or inhibitor of CYP
Tacrolimus	AUC, peak and 12-hour concentrations of tacrolimus are decreased by ~20%	No significant effect on tacrolimus	No significant effect on tacrolimus
Sirolimus	No data	Increases AUC of sirolimus by 12%	No data
Ciclosporin	35% increase in the AUC of caspofungin	Decreases clearance of ciclosporin by 16%	22% increase in AUC of anidulafungin; dose adjustment not required
Rifampicin	Decreases steady-state plasma caspofungin concentrations	No significant effect on micafungin	No significant effect on anidulafungin
Voriconazole	No data	No significant effect on micafungin	No significant effect on anidulafungin
Nefidipine	No data	Increases the AUC and C_{max} of nifedipine by 18% and 43%, respectively	No data

AUC = area under the plasma concentration-time curve; $\mathbf{C_{max}}$ = maximum concentration; **CYP** = cytochrome P450.

TDM !

Caspo: 70 mg

Chen S et al. Drugs 2011; 71: 11-41

EC Safety

Very safe agents

- most side effects very mild
- Infusion related reactions (chills, rigor, thromboflebitis) – histamine mediated: slow infusion!
- Liver abnormalities: mild, rarely > 5x ULN

Table V. The more common adverse reactions reported in clinical trials (expressed as a percentage of all adverse reactions)[11-13]

Adverse reaction	Caspofungin (%)	Micafungin (%)	Anidulafungin (%)
Pyrexia	21.2	Not documented	0.7
Diarrhoea	14.9	2.1 [gastrointestinal disorders (57.2)]	3.1 [nausea (1)]
Increased liver enzymes	ALT (14.9); AST (12.5); alkaline phosphatase (12.1)	Rare	ALT (2.3); γ-glutamyl transferase (1.3)
Hypokalaemia	11.8	1.8	3.1
Infusion-related reactions	2	45.6	Not documented
Metabolism and nutrition disorders	Not documented	42.7	Not documented
Headache	Not documented	Not documented	1.3
Neutropenia	Not documented	Not documented	1.0

Chen S et al. Drugs 2011; 71: 11-41

PK in ICU patients: anidulafungin

Pharmacokinetics of Anidulafungin in Critically Ill Patients with Candidemia/Invasive Candidiasis

Ping Liu,[a] Markus Ruhnke,[b] Wouter Meersseman,[c] José Artur Paiva,[d] Michal Kantecki,[e] Bharat Damle[f]

- Open label phase 3 study assessing efficacy/safety and PK of anidulafungin in ICU patients
- Inclusion of 21 ICU patients with documented invasive candidiasis/candidemia
- Standard dosing
- PK at steady state, 7 blood samples

→ Somewhat lower/comparable AUC (higher Vd) compared to hematological patients and healthy subjects

→High interindividual variability

→No need for dose adjustments

→No need for TDM

Liu P et al. AAC 2013; 57:1672-1676

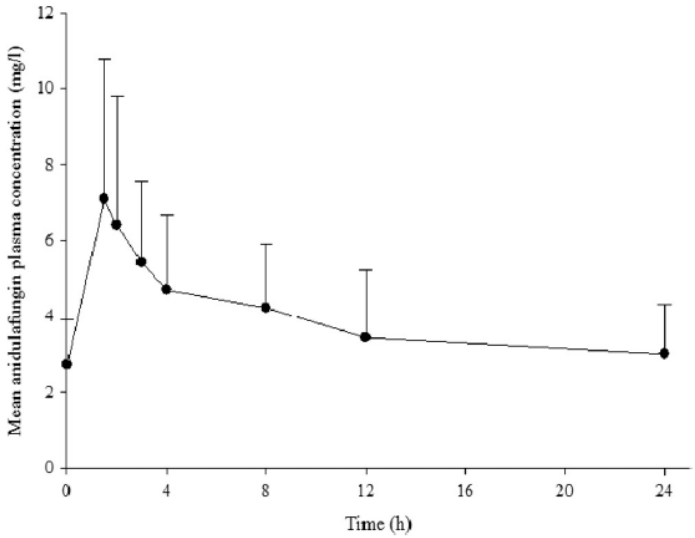


FIG 1 Mean (+ standard deviation) anidulafungin plasma concentration-time

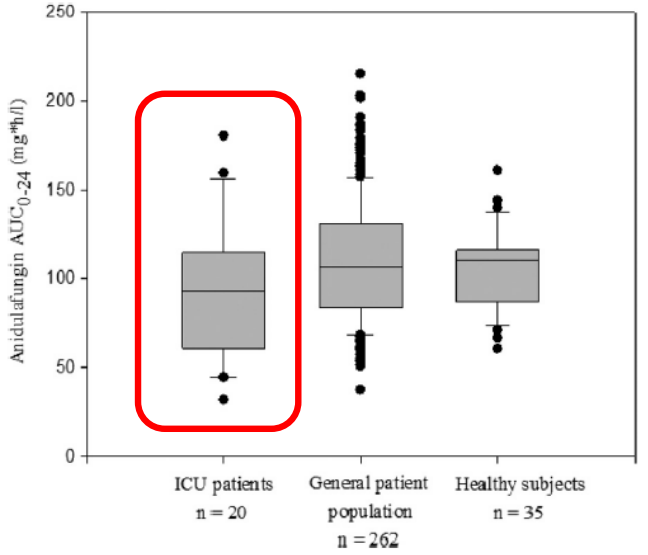


FIG 2 Comparison of anidulafungin AUC_{0-24} in ICU patients with that in the general patient population and healthy subjects at a 200/100-mg (loading dose/maintenance dose) dosing regimen. The box plot provides medians with 10th, 25th, 75th, and 90th percentiles; values outside the 10th to 90th percentiles are represented as filled circles.

PK in ICU patients: caspofungin

Pharmacokinetics of caspofungin in ICU patients

E. W. Muilwijk[1*], J. A. Schouten[2], H. J. van Leeuwen[3], A. R. H. van Zanten[4], D. W. de Lange[5], A. Colbers[1], P. E. Verweij[6,7], D. M. Burger[1,7], P. Pickkers[8] and R. J. M. Brüggemann[1,7]

- Open label, phase IV PK study
- Inclusion of 24 patients
- Standard dosing (70/50 mg < 80 kg – 70/70 mg > 80 kg)
- PK at steady state, daily trough level and 2 x full profile (11 samples)
- **Multivariable analysis** in order to identity covariates

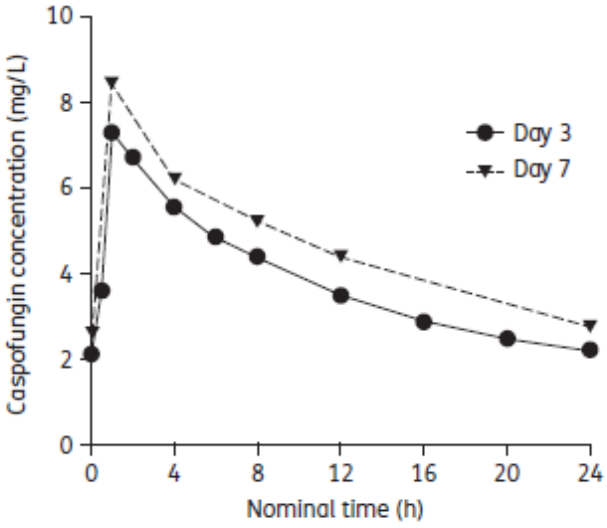


Figure 3. Overlay of caspofungin plasma concentration curves on days 3 and 7.

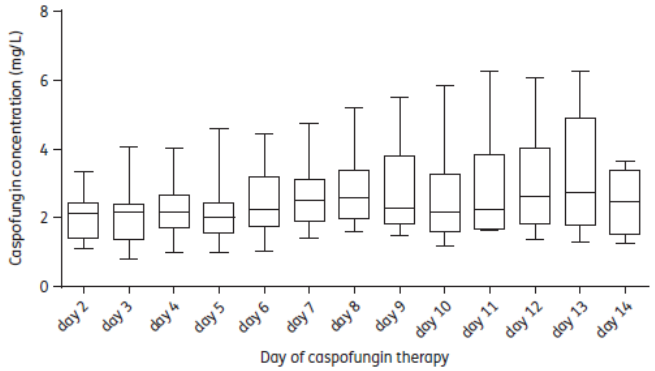


Figure 4. Daily caspofungin trough concentrations prior to infusion of caspofungin.

Trough levels are
- relatively stable/predictable
- Limited intra-individual variation
- Only moderate interindividual variation

→ No need for dose adjustments
→ No need for TDM

Muilwijk E et al. JAC 2014; 69: 3294-3299
Stone JA AAC 2002; 46:739-45

Echinocandins: is TDM useful?

Parameter	Substantial PK variability?	Therapeutic window defined in humans?	Narrow therapeutic window?
Fluconazole	+/- no	yes	✗ no

Echinocandins – Case 5 – What is your advice?

(ICU patient with persistent candidemia)

- I would recommend to switch to caspofungin – it has been shown that the PK of caspo is less variable than that of anidula.
- I would recommend to double the dose. The patient is critically ill, and anidulafungin is potentially underdosed leading to uncontrolled candidaemia.
- The PK of anidulafungin is not much altered in ICU patients. The question is whether there is another focus (valves? prostheses? Septic emboli?) leading to persistent candidaemia.
- I would advice to order a trough level. Based on that, the dose might be adapted in order to warrant clinical efficacy.

Liposomal amphotericin B: PKPD & TDM

- Amphotericin B and lipid formulations
  - PK data very scarce, 1st PK studie cAmB conducted 30 yrs after launching
  - Unclear if serum concentrations reflect efficacy
  - Difficult from analytical point of view: is free, albumin-bound or lipid-complexed/liposomal ampho B measured?
  - Studies not readily comparable!

  → utility of TDM still unclear

Liposomal amphotericin B in ICU

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1997, p. 1275–1280 Vol. 41, No. 6
0066-4804/97/$04.00+0

Pharmacokinetics of Liposomal Amphotericin B (AmBisome) in Critically Ill Patients

VOLKER HEINEMANN,* DANIEL BOSSE, ULRICH JEHN, BRIGITTE KÄHNY, KIRSTEN WACHHOLZ, ALEXANDER DEBUS, PRISKA SCHOLZ, HANS-JOCHEM KOLB, AND WOLFGANG WILMANNS

- Study dates from 1997
- Objective: to compare PK properties (Cmax, AUC, Vd) L-AmB vs. cAmB in relation to nephrotoxicity
- 22 pts
- Results:
  - Vd L-Amb 5 fold lower than Vd of cAmB
  - Cmax L-AmB 8fold higher than Vd of cAmB
  - T1/2 L-AmB 2fold shorter than T1/2 of cAmB
- L-AmB and cAmB are two completely different molecules from a PK point of view
  - L-AmB stays in the plasma
  - cAmB distributes immediately to the tissue
- Different PK profile does not lead to differences in toxicity

L-AmB: is TDM useful?

Parameter	Substantial PK variability?	Therapeutic window defined in humans?	Narrow therapeutic window?
Fluconazole	?	no	?

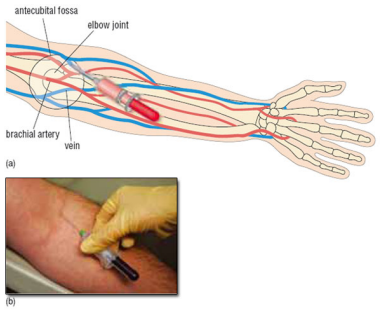
TO END UP…

Correct implementation of TDM

Importance of **correct implementation** of TDM

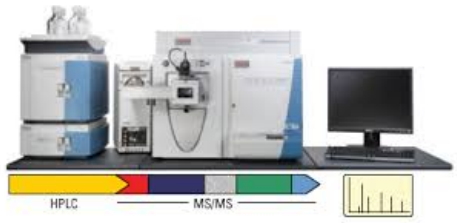
From the PATIENT

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

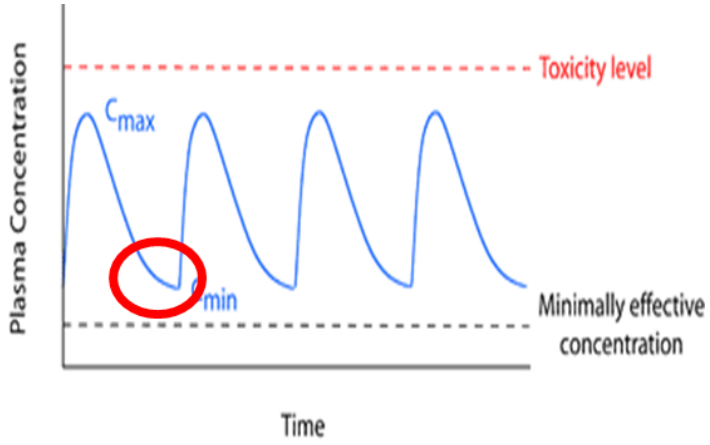
ECIL-6 (AIII) recommendation: **TDM is a multidisciplinary process**, quality should be assured in the pre-analytical, analytical and post-analytical phase

Role for the CP!

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 via peripheral venipuncture**


BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2010.03749.x

Letter to the Editors

Falsely elevated vancomycin plasma concentrations sampled from central venous implantable catheters (portacaths)

Daniel F. B. Wright,[1] Hesham S. Al-Sallami,[1] Pamela M. Jackson[2] & David M. Reith[2]

[1]School of Pharmacy, University of Otago and [2]Department of Women's and Children's Health, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

Role for the CP!

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

J Antimicrob Chemother 2014; **69**: 2988–2994
doi:10.1093/jac/dku242 Advance Access publication 7 July 2014

Journal of Antimicrobial Chemotherapy

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

Role for the CP!

CONCLUSION

Conclusion

- **Antifungal TDM is important** as
  - The effect (PKPD target attainment/clinical cure) can not be assessed directly
  - Patients with invasive fungal infections are often critically ill

- **TDM is implemented in routine for voriconazole & posaconazole**
- **TDM is probably not necessary for EC**
- **The role of TDM is unclear for isavuconazole, fluconazole and L-AmB**

- Next to clinical studies and research on TDM, paying attention to **correct implementation** is very important, otherwise wrong concentrations measured & wrong dose adaptations are carried out leading to therapeutic failure/toxicity

Conclusion

The clinical pharmacist can be a key-player in antifungal PKPD & TDM