Triazole Antifungal Therapeutic Drug Monitoring

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ECIL 6 meeting

September 11-12, 2015
Sophia Antipolis, France

Previous ECIL recommendations:
ECIL-4 2011: Pediatric fungal diseases
ECIL-5 2013: Antifungal recommendations

- **TDM was not extensively addressed for antifungal <u>treatment</u>**
- **TDM was recommended for <u>primary antifungal prophylaxis</u>***

- **Voriconazole → to improve efficacy, safety**
  - Target trough: 1-5 mg/L
- **Posaconazole → to improve efficacy**
  - Target trough: > 0.7 mg/L
- **Itraconazole → to improve efficacy, safety**
  - Target trough: > 0.5 mg/L; toxicity 17.0 mg/L (bioassay)

***No evidence grading was applied in this section**

Available: http://www.kobe.fr/ecil/program2013.htm, accessed 24 June 2015
Groll et al. Lancet Oncology 2014:e327-e340.

ECIL 6 charges:

- **Identify key questions concerning azole therapeutic drug monitoring (TDM) in patients with haematological malignancies /allogeneic HSCT**
- **Provide evidence-based recommendations or expert opinion addressing key questions (ESCMID/EFISG scoring system)**

Pharmacology	Haematology / Infectious diseases	Clinical reference laboratory
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Evidence grading- ESCMID/EFISG scoring system

Strength of Recommendation (SoR)	Definition
Grade A	ECIL strongly supports a recommendation for use
Grade B	ECIL moderately supports a recommendation for use
Grade C	ECIL marginally supports a recommendation for use
Grade D	ECIL supports a recommendation against use
Quality of Evidence (QoE)	Definition
Level I	Evidence from at least 1 properly* designed randomized, controlled trial (orientated on the primary endpoint of the trial)
Level II	Evidence from at least 1 well-designed clinical trial (including secondary endpoints), without randomization; from cohort or case-controlled analytic studies (preferably from > 1 centre; from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
Added Index	Source of Level II Evidence
r	Meta-analysis or systematic review of RCT
t	Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trials
a	Published abstract presented at an international symposium or meeting

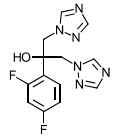
*poor quality of planning, inconsistency of results, indirectness of evidence etc.... would lower the SoR

Key questions-Pharmacology

- **What are the specific azole PK/PD considerations that support the need for TDM?**

- **Which triazoles should be monitored?**

Standard TDM criteria

Triazole	Significant PK variability?	Therapeutic range defined in humans?	Narrow therapeutic window?
Fluconazole 	✔ yes	✔ yes	✘

TDM needed for fluconazole?

- **Substantial PK variability (>30% CV) in some populations may result in subtherapeutic exposures**
  - Critically-ill patients with sepsis[1,2]
  - Hemodialysis (CVVH or CVVHD, CVVHDF)
  - Pediatrics[3]
- **Fluconazole has a broad therapeutic index → possibly more practical to empirically administer higher weight-based doses (e.g., 8-12 mg/kg/day)**
- **Uncertainty regarding best monitoring strategy:**
  - Estimate AUC/MIC (target > 100)…1, 2 and 4hr sample?

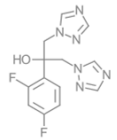
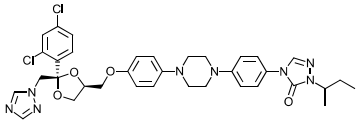
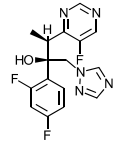
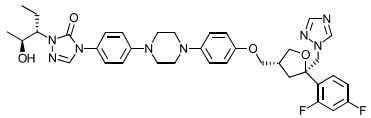
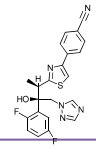
continuous venovenous hemofiltration (CVVH)
continuous venovenous hemodialysis (CVVHD)
continuous venovenous hemodiafiltration (CVVHDF)

1. Ashbee et al. J Antimicrob Chemother 2014;69:1162-76.
2. Sinnollareddy et al. Crit Care 2015;19:33
3. van der Elst et al. Clin Infect Dis 2014;59:1527-1533

TDM may be beneficial for fluconazole in special circumstances ?

- **Hemodialysis/hemofiltration +/- sepsis**
- **CNS infections**
- **Pediatrics**
- **Infections cause by pathogens with elevated MICs (>2-4 mg/L)**
- **Patients at risk for QTc prolongation (especially in setting of renal disease)?**

Fluconazole TDM may be helpful to guide dosing for rare treatment circumstances to target:
AUC/MIC > 100; AUC 400 mg·h/L; or trough of > 10 to 15 mg/L **(BIII)**

Parameter	Substantial PK variability?	Therapeutic range defined in humans?	Narrow therapeutic window?
Fluconazole 	✔ yes	✔ yes	✘ no
Itraconazole 	✔ yes	✔ yes	✔ yes
Voriconazole 	✔ yes	✔ yes	✔ yes
Posaconazole * 	✔ yes	✔ yes	? not well defined
Isavuconazole ** 	✔ yes	✘ no	? not well defined

*Limited data for new posaconazole formulations
**Limited data

Key questions-Pharmacology

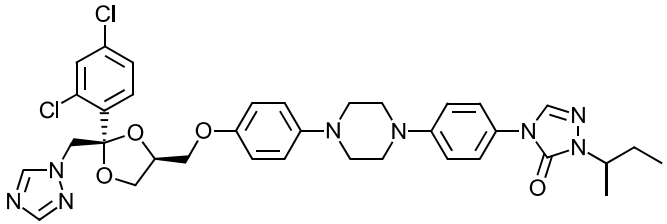
- What are the specific azole PK/PD considerations that support the need for TDM?
- Which triazoles should be monitored?
- **What target levels are recommended for each triazole?**
- **When should azole concentrations be evaluated and re-evaluated? How is dosing adjusted?**

Limitations of an evidence-based triazole target ranges

- **A proportion of TDM evidence is derived from single-centre, retrospective, and/or statistically underpowered studies**
- **Many studies do not provide 95% CI when describing concentration-effect or toxicity relationships**
- **Current evidence supports an *approximate* TDM target range to maximize efficacy, and in some cases, safety**
  - Ultimate dosing target is dictated by clinical situation (prophylaxis vs. treatment, severity or duration of infection, level of immunosuppression, susceptibility of pathogen…etc.)

Itraconazole-PK variability

- **Oral bioavailability**[1]
  - Capsule has variable, pH-dependent oral bioavailability (55%)→ must give with food
  - Solution (cyclodextran): 30% higher bioavailability vs. capsule- absorption is pH independent but reduced with food → increased GI adverse effects
  - Mucositis, diarrhea associated with decreased blood levels; compliance with solution challenging[2]
- **Substrate and inhibitor of CYP3A4**[1]
  - Saturable, non-linear elimination
  - Complex chemistry (4 *cis* isomers with different affinity for CYP 3A4, PgP)
  - Active metabolite (OH-itra), 1 to 1.59-fold higher conc. then itraconazole → impacts interpretation of bioassay (2-10x higher than HPLC measurement, depending on calibration standards used) [3]



logP 5.48
pka 3.92

1. Dolton & McLachlan. Current Opinion Infect Dis 2014;27:493-500.
2. Marr KA,et al. Blood 2004; 103: 1527–1533.
3. Wiederhold et al. Antimicrob Agent Chemother 2014;58:424-431.
4. Odds et al. J Antimicrob Chemother 1999; 43:723-727.

Itraconazole concentration-efficacy relationship

- **Prophylaxis in neutropenic patients or other underlying conditions:** Breakthrough fungal infections are more frequent when trough itraconazole plasma levels < 0.25-0.5 mg/L (HPLC assay)[1-4]

- **Aspergillosis treatment:** improved outcomes with mean itraconazole plasma concentration of approximately 5-8 mg/L (bioassay) [5]

- **Meta-analysis of 3,957 patients**: significant relationship between itraconazole dose and incidence of breakthrough IFI [6]

Efficacy target:
Prophylaxis: > 0.5 mg/L (parent compound only, HPLC assay method) (AII)
Treatment: > 1 mg/L (parent compound only, HPLC assay method) (AII)

1. Tricot G, et al. Rev Infect Diseases, 9, S94-S95.
2. Morgenstern GR,et al. Br J Haematol 1999; 105: 901–911.
3. Glasmacher A, et al. Mycoses 1999; 42: 591–600.
4. Boogaerts M, et al. Ann Intern Med 2001; 135: 412–422.
5. Denning DW, et al. Am J Med 1994; 97: 135–144.
6. Glasmacher et al. J Clin Oncol 2003;21:4615-4626

Itraconazole concentration-toxicity relationship

- **Decreased rates of toxicity (fluid retention and GI adverse effects) at concentrations < 17 mg/L (bioassay) [1]**
    - CART analysis: 86% vs. 31%
- **Estimation of HPLC safety target: < 3-4 mg/L (~ 5 fold lower than bioassay)[3]**

Safety target:
Prophylaxis and treatment (HPLC, parent compound): < 4 mg/L (BIII)
Bioassay method : < 17 mg/L (BII)

1. Lestner JM et al. Clin Infect Dis 2009; 49: 928–930..
2. Law D. et al. Antimicrob Agents Chemother 1994; 38: 1561–1566.

Itraconazole-TDM approach

- **Itraconazole concentrations reach steady state after 2 weeks of therapy (if no loading doses administered)** [1,2]
- **Check first trough level on day 5-7 or soon thereafter**
  - Earlier determinations may be indicated in the treatment of active disease: target > 0.25 mg/L
  - Due to long half-life, concentrations drawn in middle of dosing interval should not differ substantially from trough (essentially no plasma half-life)
- **Recheck trough sample in 7 days if:**
  - Changes affecting oral absorption
  - Change in dose
  - New interacting drug is started or stopped
  - Changes in clinical condition of patient

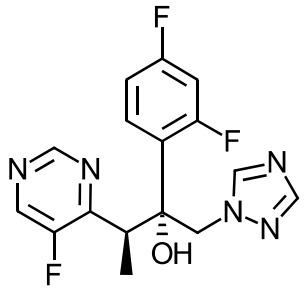
1. Marr KA,et al. Blood 2004; 103: 1527–1533.
2. Bogaerts M, et al. Ann Intern Med 2001; 135: 412–422.

Itraconazole-TDM approach

- **If trough concentration is low (< 0.5 mg/L):**
  - Consider clinical scenarios that could be addressed to improve bioavailability (i.e. drug interactions, compliance, poor GI function, gastric pH)
  - Stop protein pump inhibitors, administer with Cola or other acidic beverage
  - Switch patient to oral solution or IV formulation if taking capsules
  - If capsules continued →increase dose by 100 mg twice daily
  - See specific recommendations for pediatric dosing
- **If trough concentration is high (> 4 mg/L by HPLC, > 17 mg/L bioassay assay method):**
  - Consider dose reduction if patient experiencing adverse effects or patient cannot be switched to alternative antifungal

Voriconazole PK variability

- **Bioavailability 85-92% in healthy volunteers, but can be reduced (60-65%) in some populations, including pediatrics** [4,6]
  - Co-administration with food decreases absorption (AUC ↓ 35%)
- **Metabolism/clearance pathways associated with up to 100-fold intrapatient PK variability**
  - Patient CYP2C19 metabolic capacity (pharmacogenetics)[1,2]
  - Non-linear saturable elimination in adults, changing metabolism rates (autoinduction)[2]
  - Children < 12 years: 3-5 fold greater rate of CYP 2C19 metabolism. Adolescent clearance at ages 12-14 years depends on weight (50 kg)[5-10]
  - Drug interactions- Substrate of CYP2C19 , inhibitor of CYP3A4 [7]
- **Little or no correlation between voriconazole dose and measured plasma level** [11-12]



logP 1.82
pka 2.27

1. Levin M-D, et al. J Antimicrob Chemother 2007; 60: 1104–1107.
2. Eiden C, et al. Xenobiotica 2010; 40: 701–706.
3. Hassan A, et al.Ther Drug Monit 2011; 33: 86–93.
4. Pascual A, et al. Clin Infect Dis 2012; 55: 381–390.
5. Neely M, et al. Clin Infect Dis 2010; 50: 27–36.
6. Scholz I, et al. Br J Clin Pharmacol 2009; 68: 906–915.
7. Brüggemann RJM, et al. Clin Infect Dis 2009; 48: 1441–1458.
8. Weiss J, et al. J Clin Pharmacol 2009; 49: 196–204.
9. Yanni SB et al. Drug Metab Dispos 2010; 38: 25–31.
10. Friberg et al. Antimicrob Agent Chemother 2012;56:3032-3042.
11.Trifilio S et al. Bone Marrow Transplant 2007; 40: 451–456.
12. Dolton MJ et al. Antimicrob Agents Chemother 2012; 56: 4793–4799

Voriconazole concentration-efficacy relationship

- **Retrospective studies have identified a relationship between voriconazole trough concentrations in adult and paediatric patients and clinical outcome during <u>prophylaxis</u> or <u>treatment</u>**
- **Some retrospective studies *did not* identify a relationship[10-12]**

1. Choi S-H et al. Pediatr Blood Cancer 2013; 60: 82–87.
2. Dolton MJ et al. Antimicrob Agents Chemother 2012; 56: 4793–4799.
3. Lee Y-J et al. Med Mycol 2013; 51: 324–330.
4. Smith J et al. Antimicrob Agents Chemother 2006; 50: 1570–1572.
5. Soler-Palacín P et al. J Antimicrob Chemother 2011; 67: 700–706.
6. Trifilio S et al. Bone Marrow Transplant 2007; 40: 451–456.
7. Tucker L et al. J Pediatr Pharmacol Ther 2015; 20: 17–23.
8. Ueda K et al. Int J Hematol 2009; 89: 592–599.
9. Gómez-López A et al. Med. Mycol. 50, 439–445 (2011).
10. Pieper S, et al. J Antimicrob Chemother 2012; 67: 2717–2724.
11. Racil Z,et al. Mycoses 2012; 55: 483–492.
12. Barreto JN,et al. Am J Hematol 2013; 88: 283–288.

Voriconazole concentration-efficacy relationship

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

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

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

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

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

Voriconazole concentration-toxicity relationship

- **Patients with voriconazole trough concentrations > 5-6 mg/L have a higher probability of neurotoxic events and visual hallucinations; which may lead to premature discontinuation or interruption of therapy, and worse treatment outcome**[1-4]

- **Post-hoc phase II/III safety data analysis:**[5]
  - Some evidence of relationship between increased risk of hepatotoxicity at higher voriconazole exposures
  - No reliable upper "cut-off" concentration can be identified to minimize risk of hepatotoxic effects[1,5]
  - Possible exception: Japanese patients hepatotoxicity was more common (34.5%) if voriconazole trough concentrations ≥ 3.9 mg/L[6-8]

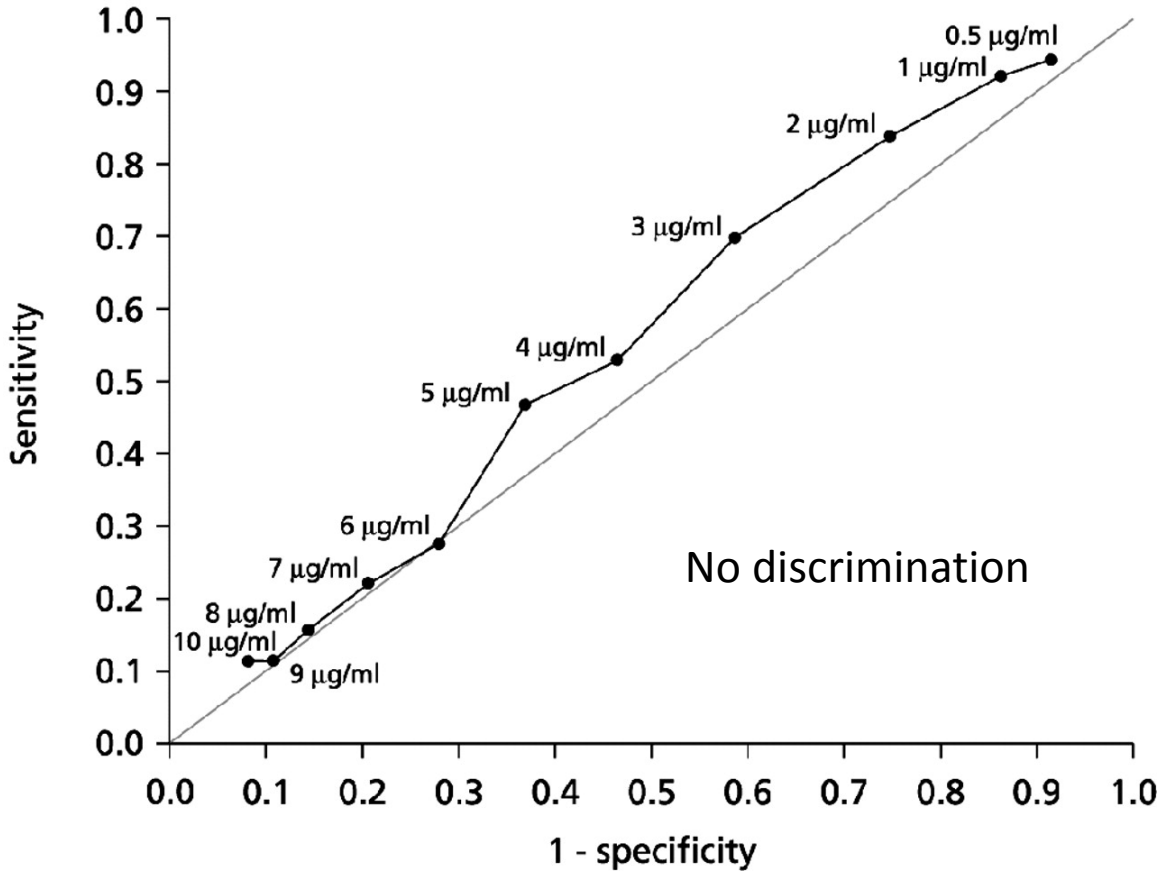
1. Pascual A,et al. Clin Infect Dis 2012; 55: 381–390.
2. Pascual A, et al. Clin Infect Dis 2008; 46: 201–211.
3. Dolton MJ et al. Antimicrob Agents Chemother 2012; 56: 4793–4799
4. Zonios D et al. J Infect Dis 2014;209:1941-1948.
5. Tan K et al. J Clin Pharmacol 2006; 46: 235–243.
6. Matsumoto K, et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

Voriconazole-hepatotoxicity

- **Voriconazole plasma trough levels are not predictive of hepatotoxicity in Caucasian patients…** [1-5]
- **However, voriconazole levels can be elevated in patients with liver dysfunction** [7]
- **Oral therapy may be more hepatotoxic than IV due to first-pass effect** [8,9]
- **CYP2C19 genotype not independently associated with hepatotoxicity risk**
- **In Japanese patients hepatotoxicity was more common (34.5%) if voriconazole trough concentrations ≥ 3.9 mg/L** [10-12]
  - CYP2C19 HET or HOM poor metaboliser genotype frequency 60-70%:
  - Proposed therapeutic range 2-4 mg/L

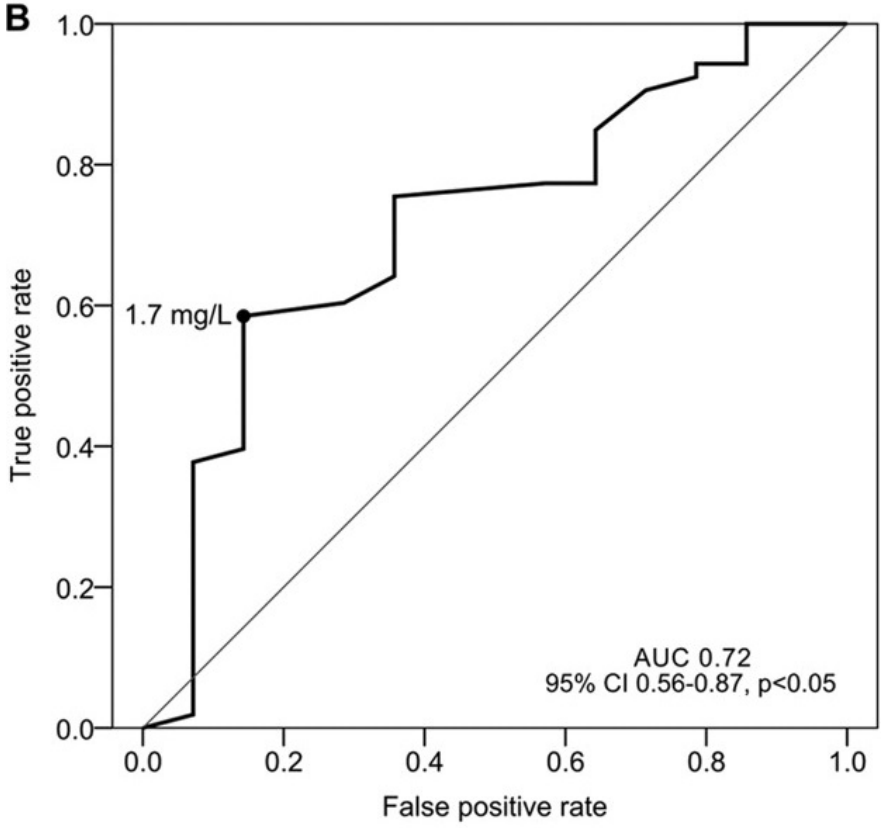
1. Pascual A,et al. Clin Infect Dis 2012; 55: 381–390.
2. Pascual A, et al. Clin Infect Dis 2008; 46: 201–211.
3. Dolton MJ et al. Antimicrob Agents Chemother 2012; 56: 4793–4799.
4. Tan K et al. J Clin Pharmacol 2006; 46: 235–243.
5. Gorski et al. Antimicrob Agents Chemother 2011; 55: 184–189
6. Saini L, et al. Can J Infect Dis Med Microbiol 2014; 25: 271–276.
7. Denning DW et al. Clin Infect Dis 2002; 34: 563–571.
8. Levin M-D, et al. . J Antimicrob Chemother 2007; 60: 1104–1107.
9. Den Hollander JG,et al. J Antimicrob Chemother 2006; 57: 1248–1250.
10. Matsumoto K, et al. Int J Antimicrob Agents 2009; 34: 91–94.
11. Suzuki Y,et al.Clin Chim Acta 2013; 424: 119–122.
12. Atsushi et al. J Ped Oncol 2013;35:p e219–e223

Voriconazole plasma concentrations did not predict hepatotoxicity in Phase II/III clinical trials

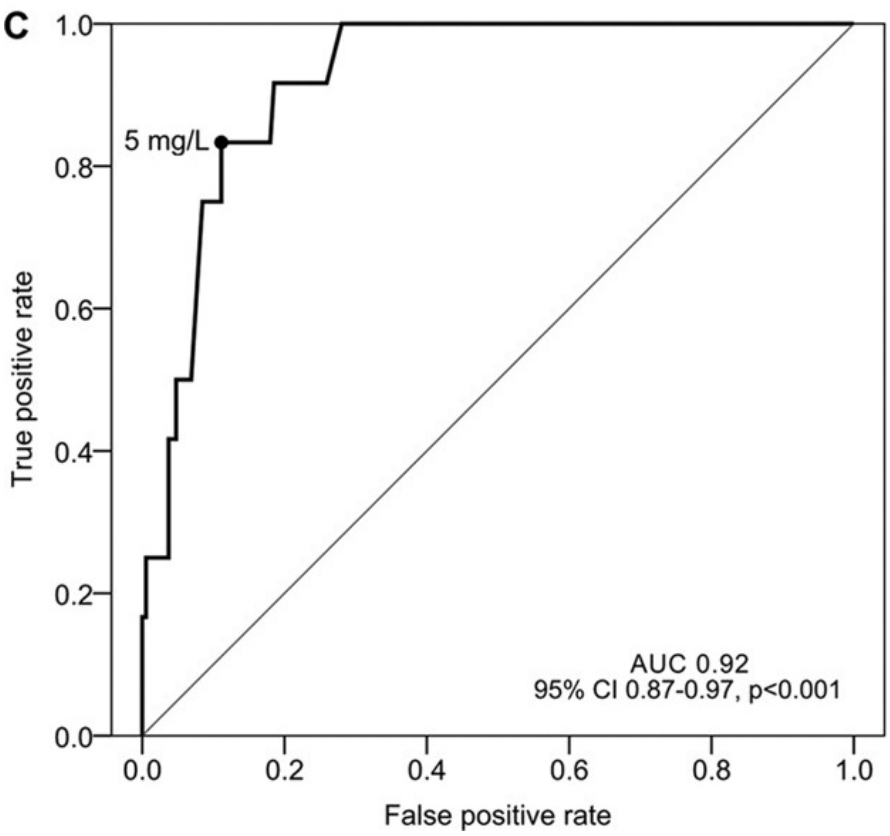


Voriconazole plasma concentrations are associated with clinical response and neurotoxicity

Clinical response, IFI



Neurotoxic AE, IFI



Voriconazole concentration-toxicity relationship

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

Patients without symptoms of clinical toxicity may not require dose reductions, however the risk versus benefit must be weighed for each patient

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

Lower trough < 4 mg/L in Japanese patients may be associated with lower hepatotoxicity risk (CYP2C19 genotype/higher exposures)

Voriconazole TDM approach

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

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

Recheck trough 3-5 days if:

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

Voriconazole TDM approach

- **If pre-dose trough concentration is low (< 1 mg/L)**
  - Check to ensure if dose was adequate (including loading dose)
  - Screen for clinical scenarios affecting voriconazole PK (e.g., compliance, drug interactions)
  - If recently switched from IV to oral, administer same weight-based (mg/kg) oral dose
    - lower levels often associated with fixed 200 mg BID oral dose
  - If receiving oral therapy, consider switch to IV
  - If plasma levels are very low (< 0.5 mg/L), consider dose IV or oral dose increase daily dose by 50%. Adjust subsequent doses based on TDM results **(see nomogram on slide # 28)**
  - If receiving IV therapy, increase daily dose **(see nomogram on slide # 28)** and recheck plasma level after 2-5 days.
  - Computerized dosing assistance programs: e.g., DoseMe®, Insight Rx® can aid dosage selection and probability of target attainment
  - See specific slides for recommended pediatric dosing

Voriconazole TDM approach

- **If pre-dose trough concentration is high (> 6 mg/L)**
  - Double check the sample is indeed a pre- and not post- dose sample
  - Screen for clinical scenarios affecting voriconazole PK (e.g., drug interactions, appropriate dose per weight)
  - Dose reduction may not be necessary if patient is tolerating voriconazole- However, the risk versus benefit is a decision individualised for each patient
  - CYP2C19 genotyping not currently recommended for patients monitored with routine TDM [2]
  - Dose reduction protocol (Park et al CID 2012):[1]
    - Reduced drug discontinuation, but not adverse effects
    - Reduce dose by 50% if level elevated, no adverse effect
    - If adverse effect and elevated level, or trough > 10 mg/L: hold one dose and reduce subsequent doses by 50%
    - Alternative approach: Dose by TDM results and nomogram (see slide #30)
    - Computerized dosing assistance programs may be helpful: e.g., DoseMe®, Insight Rx®

1. Park et al. Clin Infect Dis 2012;55:1081-1087.
2. Clin Pharm Ther 2001;89:662-672.

Voriconazole TDM-guided dosing algorithm

voriconazole trough level	dosage each 12 hrs (oral) 200mg*	250mg*	300mg*	400mg*
<0,1mg/L	400mg	400mg	400mg	500mg
0.1-0.4mg/L	400mg	400mg	400mg	500mg
0.5-1mg/L	300mg	300mg	400mg	450mg
1-1,5mg/L	250mg	300mg	450mg	450mg
1.5-2mg/L	250mg	300mg	350mg	450mg
2-3.5mg/L	200mg	250mg	300mg	400mg
3.5-5mg/L	150mg	200mg	250mg	300mg
> 5mg/L	100mg	150mg	150mg	200mg

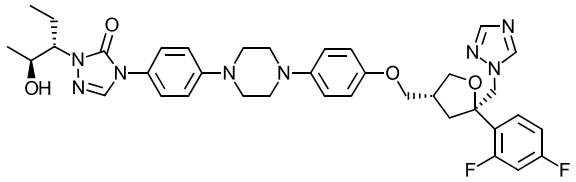
voriconazole trough level	dosage each 12 hrs (intravenous) 4mg/kg*	5mg/kg*	6mg/kg*	7mg/kg*
<0,1mg/L	6mg/kg	7mg/kg	8mg/kg	8,5mg/kg
0.1-0.4mg/L	6mg/kg	7mg/kg	8mg/kg	8,5mg/kg
0.5-1mg/L	5mg/kg	6mg/kg	7mg/kg	8mg/kg
1-1,5mg/L	5mg/kg	6mg/kg	7mg/kg	8mg/kg
1.5-2mg/L	4,5mg/kg	5,5mg/kg	6,5mg/kg	7,5mg/kg
2-3.5mg/L	4mg/kg	5mg/kg	5mg/kg	6mg/kg
3.5-5mg/L	3mg/kg	4mg/kg	4mg/kg	5mg/kg
> 5mg/L	2mg/kg	3mg/kg	3mg/kg	4mg/kg

* = dosage given to patient at time of concentration measurement

Slide courtesy of Roger Brüggemann

Posaconazole PK variability

- **Oral bioavailability (suspension)**
  - Affected by gastric pH, frequency of dosing, and administration with (fatty) food
  - Decreased when administered with proton pump inhibitors
  - Decreased by GI disease (diarrhea, mucositis)
  - Decreased absorption when administered by NG tube
- **PK problems in past compounded by lack of IV formulation**



logP 5.50
pka 3.93

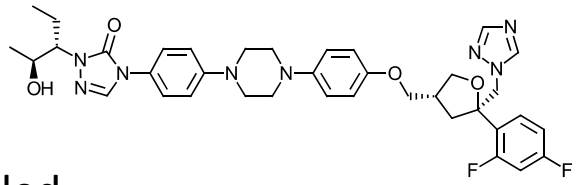
Absorption of new tablet formulation does not depend on low gastric pH, and less affected by food → <u>preferred oral formulation if patients can take tablets</u> (AII)

33% higher bioavailability in fasted subjects versus suspension in fed subjects

1- Dolton & McLachlan. Current Opinion Infect Dis 2014;27:493-500.
2-Wiederhold et al. Antimicrob Agent Chemother 2014;58:424-431.
3-Dolton et al. Antimicrob Agent Chemother 2014;58:6879-6885

Posaconazole PK variability

- **Distribution:**
  - Large Vd, highly protein bound (> 98%, mostly albumin)
  - Vd increased in neutropenic patients, during active fungal disease vs. healthy volunteers[1]
- **Metabolism/Clearance:**
  - Hepatic metabolism by UDP pathway to a monoglucoronide of posaconazole (18 - 28% of profiled radioactive dose). Only minor metabolites are formed by CYP450-mediated pathways
  - **Non-linear clearance observed with escalating IV doses[2]**



logP 5.50
pka 3.93

1-Dolton et al. Antimicrob Agent Chemother 2014;58:6879-6885
2-Kersemaekers et al. Antimicrob Agent Chemother 2015;59:1246-1251.

Posaconazole concentration- prophylaxis efficacy

- **Pharmacokinetic analysis of two pivotal prophylaxis trials utilizing suspension formulation did not report significant concentration-effect relationships** [1,2]
  - Median posaconazole 0.61 mg/L (breakthrough IFI) vs. 0.92 mg/L (no breakthrough)
- **FDA pharmacodynamic analysis:** [3]
  - Inverse relationship between POS plasma levels and clinical failure by logistic regression
  - Proposed efficacy target: 0.7 mg/L
  - Definition of clinical failure used in this analysis was different than original studies (resulted in a greater number of treatment failures)

1. Krishna G et al. Pharmacotherapy:2008; 28: 1223–1232.
2. Krishna G, et al. Journal of Clin Pharmacol 2007; 27: 1627–1636.
3. Jang SH et al. Clinical Pharmacology & Therapeutics 2010; 88: 115–119.
4. Dolton et al. Antimicrob Agetn Chemother 2012;56:2806-2813.

Posaconazole concentration- prophylaxis efficacy

- **Other monocentric studies reported concentration-response relationship between posaconazole plasma trough levels and risk of breakthrough infection** [1-5]

  > 0.5 or 0.7 mg/L

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

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

1. Lebeaux D. Antimicrob Agents Chemother 2009; 53: 5224–5229.
2. Bryant AM, . Int J Antimicrob Agents 2011; 37: 266–269.
3. Eiden C, Eur J Clin Microbiol Infect Dis 2012; 31: 161–167.
4. Hoenigl M, Int J Antimicrob Agents 2012; 39: 510–513.
5. Cattaneo et al. Mycoses 2015; 58, 362–367

Posaconazole concentration –treatment efficacy

- **Open-label salvage study of posaconazole salvage therapy in patients with invasive aspergillosis refractory or intolerant to other antifungals[1]**

Patient Quartile	Cavg Range mg/L	Clinical Failure
Q1	**0.055 – 0.277**	**76%**
Q2	**0.290 – 0.544**	**47%**
Q3	**0.550 – 0.861**	**47%**
Q4	**0.877 – 2.010**	**29%**
Hist. Control	**--**	**74%**

Recommendation: treatment efficacy trough > 1 mg/L (AII)
(defined for invasive aspergillosis)

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

Posaconazole concentration- toxicity

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

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

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

Posaconazole gastroresistant tablet and IV formulations

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

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

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

additional data are needed

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

Posaconazole TDM approach

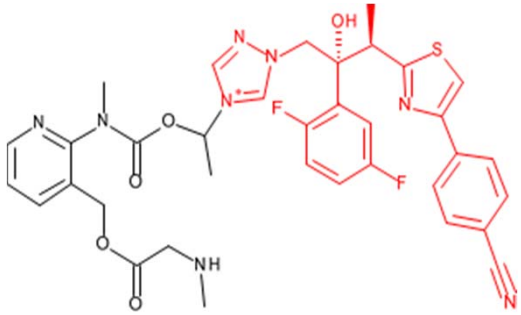
- **If pre-dose trough concentration is low (< 0.7 mg/L prophylaxis or < 1 mg/L treatment):**
  - Assess clinical scenarios affecting bioavailability and compliance.
  - Switch patient to the gastro-resistant tablet or IV formulation if receiving suspension
  - If patient requires suspension formulation, increase dose from 600 to 800 mg daily administered in 4 divided doses with food or acidic beverage, stop acid suppression therapy if feasible
  - Recheck trough after 5-7 days
  - Safety of dose escalation with gastro-resistant tablets above 300 mg day is not well defined

1. Green MR, Woolery JE. Ther Drug Monit 2012; 34: 118–119.
3. Duarte RF, et al. Antimicrob Agents Chemother 2014; 58: 5758–5765.
4. Maertens J, et al. Antimicrob Agents Chemother 2014; 58: 3610–3617.

Isavuconazole-PK variability

- **Absorption**
  - Administered as prodrug (isavuconazolium sulfate)
  - 98% bioavailability, not affected by food or gastric pH
- **Distribution**
  - Vd 450 L (high tissue distribution)
  - Requires loading dose 200 mg q8h x 48h then 200 mg daily
- **Metabolism**
  - Metabolized via CYP3A4 → UGT
  - Moderate inhibitor of CYP3A4
  - Very long half-life (60-130 hours, increased in hepatic impairment)
  - Less pharmacokinetic variability versus voriconazole

Isavuconazole (active drug BAL 4815)



logP 3.92
pka 2.70

1- Dolton & McLachlan. Current Opinion Infect Dis 2014;27:493-500.
2-Wiederhold et al. Antimicrob Agent Chemother 2014;58:424-431.

Isavuconazole-concentration efficacy

Isavuconazole package labelling:

12.2 Pharmacodynamics

Pharmacokinetic/Pharmacodynamic Relationship

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

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

additional data are needed

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 warrent 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

Recommended prophylaxis plasma target ranges- Guideline comparisons

	Fluconazole (mg/L)	Itraconazole (mg/L)	Voriconazole (mg/L)	Posaconazole (mg/L)
ECIL-6	TDM not routinely recommended	0.5-4 (HPLC)	1-6	> 0.7
Ashbee et al. 2014	TDM not routinely recommended	0.5-4 (HPLC)	1-6	> 0.7
Hamada et al. 2013 (VOR specific)	TDM not routinely recommended	--	1-5	--
Scodavolpe et al. 2014	AUC/MIC > 25	> 0.5 (HPLC, MIC dependent)	1-6	> 0.5
Chau et al. 2014	TDM not routinely recommended	> 0.5-1 (HPLC, MIC dependent)	1-6	> 0.7

1. Ashbee HR, Barnes RA, Johnson EM et al. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother 2014; 69: 1162–1176.
2. Hamada Y, Tokimatsu I, Mikamo H, Kimura M. Practice guidelines for therapeutic drug monitoring of voriconazole: a consensus review of the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. Journal of Infection and 2013;
4. Scodavolpe S, Quaranta S, Lacarelle B, Solas C. [Triazole antifungal agents: practice guidelines of therapeutic drug monitoring and perspectives in treatment optimization]. Ann Biol Clin 2014; 72: 391–404.
5. Chau MM, Kong DCM, van Hal SJ, Urbancic K, et al. Consensus guidelines for optimising antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy, 2014. Internal Med Journal 2014;44:1364-1388.

Recommended treatment plasma target ranges- Guideline comparisons

	Fluconazole (mg/L)	Itraconazole (mg/L)	Voriconazole (mg/L)	Posaconazole (mg/L)
ECIL-6	TDM not routinely recommended	1-4 (HPLC)	1-6	> 1
Ashbee et al. 2014	TDM not routinely recommended	1-4 (HPLC) recommended higher MIC	1-6	> 1
Hamada et al. 2013. (vori specific)	--	--	1-5	--
Scodavolpe et al. 2014	AUC/MIC > 25	>1-2 mg/L (HPLC)	1-5	0.5-1.5
Chau et al. 2014	TDM not routinely recommended	> 0.5-1 (HPLC)	1-6	> 1

1. Ashbee HR, Barnes RA, Johnson EM et al. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother 2014; 69: 1162–1176.
2. Hamada Y, Tokimatsu I, Mikamo H, Kimura M. Practice guidelines for therapeutic drug monitoring of voriconazole: a consensus review of the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. Journal of Infection and 2013;
4. Scodavolpe S, Quaranta S, Lacarelle B, Solas C. [Triazole antifungal agents: practice guidelines of therapeutic drug monitoring and perspectives in treatment optimization]. Ann Biol Clin 2014; 72: 391–404.
5. Chau MM, Kong DCM, van Hal SJ, Urbancic K, et al. Consensus guidelines for optimising antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy, 2014. Internal Med Journal 2014;44:1364-1388.

Key questions-Pharmacology

- What are the specific azole PK/PD considerations that support the need for TDM?
- Which triazoles should be monitored?
- What target levels are recommended for each triazole?
- When should azole concentrations be evaluated and re-evaluated? How is dosing adjusted?
- **What is the role for TDM in managing drug interactions?**

Drug interactions affecting azole levels

- **Patient receiving co-medication that induces CYP-P450 enzymes:**
  - Change in therapy to non-interacting antifungal recommended **(AII)**
- **Patient receiving co-medication that induces UGT enzymes:**
  - TDM recommended for posaconazole **(AII)**
- **Patient receiving antacids and PPI with itraconazole capsules or posaconazole suspension**
  - TDM recommended **(AII)**

Azole affects on metabolism of other drugs

- **Patients should have medication records screened using suitable computerized screening database before starting and stopping antifungals (AIII)**
  - Examples: www.fungalpharmacology.org; www.aspergillus.ork.uk/content/antifungals-drug-interactions, or commerical products such as Lexi-comp Lexi Interact®
- **Patient receiving co-medication metabolized through CYP P450 →esp. CYP3A4:**
  - Consult drug interactions database or clinical pharmacologist **(AIII)**
- **Medications inducing UGT enzymes**
  - Consult drug interactions database or clinical pharmacologist **(AIII)**

Key questions- Haematology / Infectious diseases

- What clinical scenarios in patients with haematological malignancies or HSCT receiving triazoles benefit from TDM assessment?
- How should TDM be used to optimize triazole use in paediatric patients with haematological malignancy or HSCT ?
- Who should advise, interpret and follow-up on TDM results?

Scenarios where routine azole TDM should be considered	Examples, comment	SOR
Populations with diseases or underlying risk factors for pharmacokinetic variability	Impaired GI function ; hepatic dysfunction (voriconazole, posaconazole, itraconazole, isavuconazole); pediatric patients, elderly patients, obese patients, malnourished, malignancy-associated cachexia, critically-ill patients; Intravenous to oral switch, changing GI function, changing hepatic function, physiological-instability	**All**
Interacting medications that could reduce or increase triazole clearance	Patient receiving medication that induces CYP3A4 (antiretroviral medications, anti-epileptic, or rifamycins), antacids, proton-pump inhibitors (itraconazole capsules, posaconazole suspension)	**All**

Haematology & ID: Which clinical scenarios will benefit from TDM ?

Scenarios where azole TDM is likely to be useful in patients with hematologic malignancies	Examples, comment	SOR
Severe infections	Extensive or bulky infection, lesions contiguous with critical structures, CNS infection, multifocal or disseminated infection	**All**
Compliance	Important issue with longer-term consolidation therapy or secondary prophylaxis (outpatient)	**All**
Suspected breakthrough infection	TDM can establish whether fungal disease progression occurred in the setting of inadequate antifungal exposure	**All**
Suspected drug toxicity, especially neurotoxicity (voriconazole)	Although exposure-response relationships are described for other toxicities (e.g., hepatotoxicity), the utility of TDM to prevent their occurrence is less well established	**All**

Haematology & ID: Which clinical scenarios will benefit from TDM ?

Scenarios where azole TDM is likely to be useful in patients with hematologic malignancies	Examples, comment	SOR
Treatment of a pathogen with reduced susceptibility	Consequences of pharmacokinetic variability are more severe with increasing MIC	**AII**

1. Andes D, Pascual A, Marchetti O. Antimicrob Agents Chemother 2009; 53.
2. Ashbee HR,et al. J Antimicrob Chemother 2014; 69: 1162–1176.
3. Hamada Y,et al. Journal of Infection and Chemotehrapy 2013;
4. Karthaus M,et al. Ann Hematol 2015; 94: 547–556.
5. Laverdiere M,et al. Can J Infect Dis Med Microbiol 2014; 25: 327–343.
6. Myers and Dodds-Ashley. Curre Clin Micro Report 2015;2:55-66.

Key questions- Haematology / Infectious diseases

- What clinical scenarios in patients with haematological malignancies or HSCT receiving triazoles benefit from TDM assessment?
- **How should TDM be used to optimize triazole use in paediatric patients with haematological malignancy or HSCT ?**
- Who should advise, interpret and follow-up on TDM results?

Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation

Andreas H Groll, Elio Castagnola, Simone Cesaro, Jean-Hugues Dalle, Dan Engelhard, William Hope, Emmanuel Roilides, Jan Styczynski, Adilia Warris, Thomas Lehrnbecher, on behalf of the Fourth European Conference on Infections in Leukaemia, a joint venture of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT-IDWP), the Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer (EORTC-IDG), the International Immunocompromised Host Society (ICHS), and the European Leukaemia Net (ELN)

ECIL 4: TDM included with all recommendations for use of voriconazole, posaconazole, and itraconazole in children

ECIL 6: TDM targets and approach harmonized with adult recommendations

Routine TDM is recommended in pediatric heme malignancy / HSCT patients treated with itraconazole, voriconazole or posaconazole (AII)

Background and Principles [1,2]

- **Key issue relative to adults is different PK / dosing**
  - ≤ 12 years: Greater clearance / larger doses
  - > 13 years: PK / dosing mostly similar vs. adults
- **Pharmacodynamics and PK/PD relationships can be considered similar in management of IFDs**

> ➢ **PK/safety studies in all pediatric age groups are prerequisite for safe and effective use**
> ➢ **No larger pediatric PK/PD studies required, adult data can be used to support PK/PD principles**

1. Groll et al. Lancet Oncology 2014;15:e327-40.
2. European Medicines Agency. CPMP/ICH/2711/99

Pharmacological considerations

Antifungal Agent	Approved Indications *	Ped. Dosage Range **	Specific Comments
Fluconazole	Treatment / prevention of superficial / invasive Candida infections; treatment of cryptococcosis and coccidioidomycosis	8-12 mg/kg/d IV/PO in one single dose; no routine TDM	Increased weight-normalized plasma clearance relative to adults; optimal dose uncertain. ECIL 4 recommends 8-12 mg/kg/d (max. 400 mg/d) for prophylaxis and 8-12 mg/kg/d (max. 800 mg/d) for targeted treatment. Recent retrosepctive PK/PD analyses suggest to use the maximum approved dose of 12 mg/kg/d (max. 800mg/d) for targeted treatment. Potential for drug-drug interactions.
Itraconazole	Treatment of superficial Candida infections; 2nd line treatment of invasive candidiasis, aspergillosis and cryptococcosis; prophylaxis in granulocytopenic patients	5 mg/kg/d PO in two divided doses plus TDM	Limited pediatric PK data in 2 to 17 year old subjects for oral suspension, no principal differences relative to adults. Similar problems with absorption. ECIL 4 recommends 5 mg/kg/d in two divided doses for prophylaxis and treatment. Only single dose PK data available for the IV formulation. Not licensed in the EU in subjects <18 years, no PK data for children <2 years. High potential for relevant drug-drug interactions.
Posaconazole	2nd line treatment of aspergillosis, fusariosis, chromoblasto- and coccidioidomycosis; treatment of oropharyngeal candidiasis; prophylaxis in AML/MDS and allogeneic HSCT patients	600-800 mg/d PO in 2 to 4 divided doses plus TDM	Limited pediatric PK data for the oral suspension; no principal differences relative to adults in adolescents ≥ 13 years . Similar problems with absorption. Not licensed in subjects <18 years in the EU but licensed in adolescents ≥ 13 years in the US for prophylaxis. ECIL 4 recommends 600 mg/d in three divided doses for prophylaxis and 800 mg/d in 2 or 4 divided doses for treatment in subjects ≥ 13 years. No pediatric PK data exist for the novel tablet- and the IV formulation; however, PK (and dosing) in adolescents ≥ 13 years are expected to be similar relative to adults. High potential for relevant drug-drug interactions.
Voriconazole	Treatment of invasive aspergillosis, fusariosis, scedosporiosis; treatment of candidaemia in non-granulocytopenic patients; prophylaxis in allogeneic HSCT patients	2- <12 yrs /12-14 yrs and <50kg: 8 mg/kg BID (day 1: 9 mg/kg) IV and 9 mg/kg BID PO; ≥15 yrs and 12-14 yrs and ≥50kg: 4 mg/kg BID (day 1: 6 mg/kg) IV; 200 mg BID PO plus TDM (all)	Increased age-dependent weight-normalized plasma clearance and lower oral bioavailability relative to adults; similar, if not higher PK variability. Similar doses recommended for prophylaxis and treatment. Not licensed in subjects < 2 years of age. High potential for relevant drug-drug interactions and relevant potential for hepatic, cutaneous, and neurological adverse events

* Summarised; or specific wording, please refer to the summary of product characterics (SPCs); ** as recommended by ECIL 4

IV, intravenously; PO, orally; TDM, therapeutic drug monitoring; PK, pharmacokinetics; for referencesplease refer to the appendix

Pediatric patients-ECIL 4 recommendations[1]

- **Voriconazole**
  - **Children 2-12 years > 50 kg:**
    - IV: 9 mg/kg twice daily day1, then 8 mg/kg twice daily
    - Oral: 9 mg/kg twice daily
  - **Children ≥ 15 years or 12-14 > 50 kg:**
    - Use adult dosing
  - **TDM is recommended, dosing target trough (same as adults):**
    - Efficacy > 1-2 mg/L
    - Safety < 5-6 mg/L
  - **Increased mortality OR 2.6 (1.4-4.8) if VRC < 1 mg/L[2]**

Routine TDM is recommended in pediatric cancer / HSCT patients treated with voriconazole (AII)

1. Groll et al. Lancet Oncology 2014;15:e327-40.
2. Neely et al. Clin Infect Dis 2010; 50: 27–36.
3. Friberg et al. Antimicrob Agents Chemother 2012; 56: 3032–42

Pediatric patients-ECIL 4 recommendations[1]

- **Posaconazole prophylaxis**
- No pediatric data on the tablet or IV formulations in pediatrics < 12 years; limited data for suspension (off-label)
  - **Children > 12 years**
    - 600 mg/d of the susp. in 3 divided doses with food
    - TDM is recommended, dosing target trough >0.7 mg/L
- **Posaconazole primary or salvage therapy**
  - **Children > 12 years**
    - 800 mg/d of the susp. in 2 or 4 divided doses with food
    - TDM is recommended, dosing target trough >1 mg/L

Routine TDM is recommended in paediatric haematology patients treated with posaconazole (AII)

1. Groll et al. Lancet Oncology 2014;15:e327-40.

Pediatric patients-ECIL 4 recommendations[1]

- **Itraconazole prophylaxis**
  - **Children > 2 years**
    - 5 mg/kg/d of the suspension orally in two divided doses
    - TDM is recommended, dosing trough target > 0.5 mg/L

- **Itraconazole salvage treatment**
  - **Children > 2 years**
    - 5 mg/kg/d of the suspension orally in two divided doses
      - Consider loading dose 10 mg/kg/day (two divided doses days 1-2) in patients with severe disease
    - TDM is recommended, dosing trough target > 1 mg/L

Routine TDM is recommended in pediatric haematology patients treated with itraconazole (AII)

1. Groll et al. Lancet Oncology 2014;15:e327-40.

TDM-approach in pediatric patients

- **Similar general principles/strategies as adults**

- **If dose adjustments are indicated:**
  - **In the absence of specific data, dose adjustments of at least 50% of the last total daily dose are recommended if plasma levels are low (posaconazole suspension: administer in 4 daily doses)**
  - **Recheck trough levels after 5 (voriconazole, posaconazole) to 7 (itraconazole) days (AII)**

Key pediatric references

Fluconazole:

1. Lee JW, Seibel NL, Amantea M, Whitcomb P, Pizzo PA, Walsh TJ. Safety and pharmacokinetics of fluconazole in children with neoplastic diseases. J Pediatr 1992; 120: 987–93.
2. Brammer KW, Coates PE. Pharmacokinetics of fluconazole in pediatric patients. Eur J Clin Microbiol Infect Dis 1994; 13: 325–29.
3. Novelli V, Holzel H. Safety and tolerability of fluconazole in children. Antimicrob Agents Chemother 1999; 43: 1955–60.
4. van der Elst KC, Pereboom M, van den Heuvel ER, Kosterink JG, Schölvinck EH, Alffenaar JW. Insufficient fluconazole exposure in pediatric cancer patients and the need for therapeutic drug monitoring in critically ill children. Clin Infect Dis. 2014 Dec 1;59(11):1527-33.

Itraconazole:

1. de Repentigny L, Ratelle J, Leclerc JM et al. Repeated-dose pharmacokinetics of an oral solution of itraconazole in infants and children. Antimicrob Agents Chemother 1998; 42: 404–08.
2. Groll AH, Wood L, Roden M et al. Safety, pharmacokinetics, and pharmacodynamics of cyclodextrin itraconazole in pediatric patients with oropharyngeal candidiasis. Antimicrob Agents Chemother 2002; 46: 2554–63.
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4. Foot AB, Veys PA, Gibson BE. Itraconazole oral solution as antifungal prophylaxis in children undergoing stem cell transplantation or intensive chemotherapy for haematological disorders. Bone Marrow Transplant 1999; 24: 1089–93
5. Abdel-Rahman SM, Jacobs RF, Massarella J, Kauffman RE, Bradley JS, Kimko HC, Kearns GL, Shalayda K, Curtin C, Maldonado SD, Blumer JL. Single-dose pharmacokinetics of intravenous itraconazole and hydroxypropyl-beta-cyclodextrin in infants, children, and adolescents. Antimicrob Agents Chemother. 2007 Aug;51(8):2668-73

Key pediatric references

Voriconazole:

1. Walsh TJ, Karlsson MO, Driscoll T et al. Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. Antimicrob Agents Chemother 2004; 48: 2166–72
2. Walsh T, Driscoll T, Milligan P et al. Pharmacokinetics, safety, and tolerability of voriconazole in immunocompromised children. Antimicrob Agents Chemother 2010; 48: 4116–23.
3. Driscoll TA, Yu LC, Frangoul H et al. Pharmacokinetics and safety of intravenous voriconazole to oral switch in immunocompromised children compared to adults. Antimicrob Agents Chemother 2011; 55: 5770–79
4. Driscoll TA, Yu LC, Frangoul HL et al. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised adolescents and healthy adults. Antimicrob Agents Chemother 2011; 55: 5770–79
5. Friberg LE, Ravva P, Karlsson MO, Liu P. Integrated population pharmacokinetic analysis of voriconazole in children, adolescents, and adults. Antimicrob Agents Chemother 2012; 56: 3032–42.
6. Zane NR, Thakker DRA physiologically based pharmacokinetic model for voriconazole disposition predicts intestinal first-pass metabolism in children. Clin Pharmacokinet. 2014 Dec;53(12):1171-82
7. Yanni SB1, Annaert PP, Augustijns P, Ibrahim JG, Benjamin DK Jr, Thakker DR. In vitro hepatic metabolism explains higher clearance of voriconazole in children versus adults: role of CYP2C19 and flavin-containing monooxygenase 3. Drug Metab Dispos. 2010 Jan;38(1):25-31
8. Pieper S, Kolve H, Gumbinger HG et al. Monitoring of voriconazole plasma concentrations in immunocompromised paediatric patients. J Antimicrob Chemother 2012; 67: 2717–24.
9. Neely M1, Rushing T, Kovacs A, Jelliffe R, Hoffman J. Voriconazole pharmacokinetics and pharmacodynamics in children. Clin Infect Dis. 2010 Jan 1;50(1):27-36
10. Gerin M1, Mahlaoui N, Elie C, Lanternier F, Bougnoux ME, Blanche S, Lortholary O, Jullien V. Therapeutic drug monitoring of voriconazole after intravenous administration in infants and children with primary immunodeficiency. Ther Drug Monit. 2011 Aug;33(4):464-6

Key pediatric references

11. Bartelink IH1, Wolfs T, Jonker M, de Waal M, Egberts TC, Ververs TT, Boelens JJ, Bierings M. Highly variable plasma concentrations of voriconazole in pediatric hematopoietic stem cell transplantation patients. Antimicrob Agents Chemother. 2013 Jan;57(1):235-40
12. Neely M, Margol A, Fu X, van Guilder M, Bayard D, Schumitzky A, Orbach R, Liu S, Louie S, Hope W. Achieving target voriconazole concentrations more accurately in children and adolescents. Antimicrob Agents Chemother. 2015 Jun;59(6):3090-7

Posaconazole:

1. Krishna G, Sansone-Parsons A, Martinho M et al.: Posaconazole plasma concentrations in juvenile patients with invasive fungal infection. Antimicrob Agents Chemother 2007; 51: 812–18.
2. Welzen ME, Brüggemann RJ, Van Den Berg JM et al. A twice daily posaconazole dosing algorithm for children with chronic granulomatous disease. Pediatr Infect Dis J 2011; 30: 794–7.
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4. Döring M, Müller C, Johann PD et al. Analysis of posaconazole as oral antifungal prophylaxis in pediatric patients under 12 years of age following allogeneic stem cell transplantation. BMC Infect Dis 2012; 12: 263.
5. Yunus S, Pieper S, Kolve H, Goletz G, Jürgens H, Groll AH. Azole-based chemoprophylaxis of invasive fungal infections in paediatric patients with acute leukaemia: an internal audit. J Antimicrob Chemother. 2014 Mar;69(3):815-20
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Key questions- Haematology / Infectious diseases

- What clinical scenarios in patients with haematological malignancies or HSCT receiving triazoles benefit from TDM assessment?
- How should TDM be used to optimize triazole use in paediatric patients with haematological malignancy or HSCT ?
- **Who should advise, interpret and follow-up on TDM results?**

Therapeutic drug monitoring process

Pre-analytical phase

Clinical question

Test selected

Test ordered

Specimen collected

Analytical phase

Sample prepared

Analysis performed

Results verified

Post-analytical phase

Results reported

Clinical answer

Action taken

Effect on patient care

TDM process recommendations

- **Multidiciplinary approach to TDM is recommended**
  - Should include involvement of nursing staff, physicians (haematologist and infectious diseases), analytical staff, pharmacologist, and microbiologist with clearly-defined responsibilities (AIII)
- **Pre-analytical phase**
  - Patient sampling schemes should be standardized when possible to minimize errors (AIII)
  - Trough concentrations are generally the least-error prone and most convienent approach to measure patient azole exposure

1. Ashbee HR, et al. J Antimicrob Chemother 2014; 69: 1162–1176.
2. Hamada Y, et al. Journal of Infection and 2013;
3. Laverdiere M, et al. Can J Infect Dis Med Microbiol 2014; 25: 327–343.

TDM process recommendations

- **Analytical phase**
  - An accurate, precise, sensitive, and selective analytical method for the quantitative determination of azole antifungal drugs in plasma/serum is recommended (AIII)
  - Assays should be validated according according to the current requirements for validation of bioanalytical assays[1] (AIII)
  - To help identify sources of errors and to further improve analytical methods, participation in an ongoing proficiency testing program is recommended (AIII)
    - Standards and controls should be externally validated at a certified centre by HPLC

TDM process recommendations

- **Post-analytical phase**
  - Interpretation of results should be performed by clinical pharmacist/ pharmacologist, physician or microbiologist with expertise in antifungal therapy familar with the sampling time, patient clinical parameters, and likely pathogen if not identified (AIII)

  - Results should be communicated with responsible physician by someone with expertise in TDM and interpretation (BIII)

  - Repeat sampling should be considered once-or twice weekly in patient strongly suspected or proven to have invasive fungal disease or clinical instability, or concentration otside target range
    - Need for resampling is individualized to the clinical scenario o the patient

Key questions-laboratory

- What samples are suitable for analysis?
- How should antifungal drugs be analysed?
- What are the external quality assurance/ assessment (EQA) schemes for laboratories analysing TDM samples?

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Measure parent drug only or parent + metabolites?

- **Itraconazole**
  - Parent drug
  - OH-itraconazole metabolite (active)
- **Voriconazole**
  - Parent drug
  - Optional: Voriconazole –N-oxide metabolite (inactive)
- **Posaconazole**
  - Parent drug only
- **Isavuconazole**
  - Parent drug only

When analysed with parent drug could provide information on compliance, metabolic phenotype…

1. Yamada T,et al. Clin Biochem 45:134–138.
2. Eiden C,et al. Xenobiotica 40:701–706.
3. Meletiadis J, et al. Pharmacogenomics 9:561–584.
4. Meletiadis J, et al. Clin Microbiol Rev 19:763–787.
5. Cowen EW, et al. J Am Acad Dermatol 62:31–37.
6. Denning DW, et al. Clin Exp Dermatol 26:648–653.
7. Epaulard O,et al. Clin Infect Dis 57:e182–8.

Reporting antifungal drug levels:

- Levels should be reported as mg/L to one decimal place for microbiological methods and two decimal places for instrumental methods
- Very low levels may have to be reported as < whatever value has been obtained as the lower limit of detection for that method
- Very high levels can be reported as > whatever value has been obtained as the upper limit of detection but, are more useful for dosage adjustment when diluted and repeated to calculate an absolute value
- It is important to include an interpretation with the drug level i.e. low level, high level or satisfactory level and an indication of normal ranges and efficacy and toxicity cut offs if known

What samples are suitable for analysis?

Sample types validated for separate or simultaneous TDM for itraconazole, posaconazole, voriconazole (+/-more antifungals) by HPLC/LC-MS

	HPLC / LC-MS	References (examples)
Serum	yes	Mistretta doi: 10.1179/0001551213Z.00000000018 Decostard doi:10.1128/AAC.00404-10
Plasma	yes	Decostard doi:10.1128/AAC.00404-10 Verweij-van Wissen
Dried Blood Spot	yes	Reddy doi:10.1016/j.jchromb.2011.10.008 van der Elst doi:10.1128/AAC.00707-13
Dried Plasma Spot	yes	Baietto doi: 10.1093/jac/dks285
CSF	yes	Wiederhold doi:10.1128/AAC.01558-13 voriconazole (and some data also on posaconazole though less clinically relevant)

What samples are suitable for analysis?

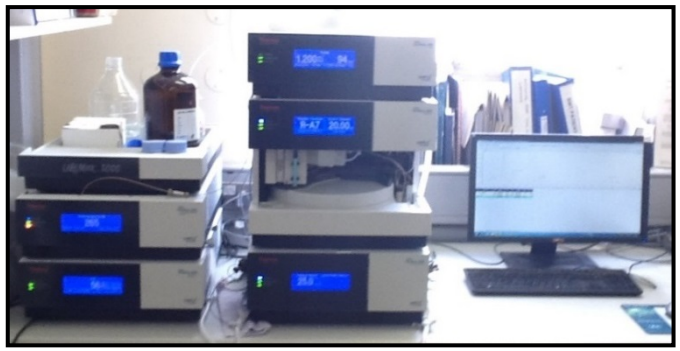
Sample types validated for TDM for itraconazole, posaconazole, voriconazole (separately) by bioassay.

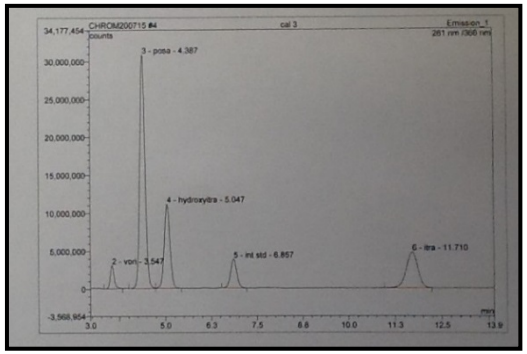
	Bioassay	References (examples)
Serum	yes	Cendejas-Bueno doi:10.1128/AAC.00323-13 (voriconazole) Cendejas-Bueno doi:10.1111/j.1469-0691.2011.03732.x (posaconazole) Odds doi: 10.1093/jac/43.5.723 (itraconazole) Pascual doi:10.1128/AAC.00957-06 (voriconazole) Pascual doi 10.1128/AAC.00022-10 (posaconazole)
Plasma	yes	Pascual doi:10.1128/AAC.00957-06 (voriconazole) Pascual doi 10.1128/AAC.00022-10 (posaconazole)
Dried Blood Spot		No data
Dried Plasma Spot		No data
CSF		No data

Two main types of analytical method for measuring antifungal drug levels:

1. **Microbiological method:** plate assay / bioassay
   - plate seeded with susceptible organism
   - known standard concentrations placed in triplicate wells / discs
   - patient samples placed in triplicate wells /discs
   - plate incubated and zones of inhibition measured
   - standard curve constructed to interpolate unknowns

2. **Instrumental techniques:** although there are a large number of potential electrophoretic and chromatographic methods for antifungal drug analysis high-performance liquid chromatography (HPLC), ultra-HPLC and HPLC with mass spectrophotometry (HPLC-MS) have become the reference methods.
   ARK Diagnostics, Inc. has developed an enzyme immunoassay test for Voriconazole TDM that can be run on various biochem lab robots like Roche's Cobas 8000 instrument. (Cattoir et al Clin Chem Lab Med 2015; 53(5):e135-9)





Laboratory: How should antifungal drugs be analysed?

Method	Advantages	Disadvantages
Bioassay	Inexpensive to conduct Acquisition costs minimal Minimal training Quick set up Suitable for small sample volumes Good for resource limited environments and when access to HPLC/uHPLC/HPLC-MS is limited	Long incubation (24h) Sensitivity variable Range limited **Lack of standardisation of methodology** Reading imprecision (subjective) Unsuitable for combination therapy unless developed to incorporate tester organisms with drug-specific resistance Unable to distinguish native drug from active metabolite Itraconazole: semi-quantitative only (1) Generally poorer EQA performance (2)
HPLC/uHPLC/HPLC-MS	Good precision Objective measurement Quick turnaround time (3 -4 h) Can measure several drugs simultaneously May already be established in a centre and adapted for antifungal assay	High equipment acquisition costs High maintenance costs High reagent costs Limited availability of instruments in clinical micro labs For some - time consuming sample preparation steps Best performed in batches – may increase TAT Requirement for skilled operator Need for technical support Possible peak interference from compounds with identical retention time (HPLC/uHPL)
ARK Diagnostics (3) (immunoassay)	Commercially available Can be run on random access chemistry analysers Quick turn around time (5 min)	High equipment acquisition costs Requirement for ± 120 requests/month (kit stability) Equipment available in biochemistry labs which lack experience on sample interpretation Currently only available for voriconazole

1. Laverdiere M, *et al*. Can J Infect Dis Med Microbiol 2014; 25: 327–343
2. Darville *et al.* Abstract P1693 24th ECCMID 2014
3. Cattoir et al Clin Chem Lab Med 2015; 53(5):e135-9

In-house laboratory validation and verification of the performance characteristics of the chosen method should be undertaken to include:

- Analytical specificity
- Linearity, working range and limits of detection and quantification (LOD and LOQ)
- Precision: repeatability (intra-day precision)
  reproducibility (intra-day precision)
- Stability of analyte on storage
- Extraction recovery (for HPLC methods)
- System suitability (for HPLC methods)
- Ongoing Internal Quality Control (IQC)
- Ongoing Internal Quality Assessment (IQA)
- **External Quality Assessment / Assurance (IQA)**

1. Shabir GA Journal of Validation Technology 2004
2. Honour J W Ann Clin Biochem 2011; **48**: 97-111
3. BS EN ISO 15189:2012 Medical Laboratories – Requirements for quality and competence
4. Validation of Analytical Methods. Agilent Technologies 2010

Rationale for participation in EQA schemes:

- Confirms a laboratory's analytical method is fit for purpose
- Ensures continuing analytical competence
- Monitors ongoing accuracy
- Allows intra and inter-laboratory comparison
- Enables post-marketing vigilance for commercial test components
- Allows early recognition of potential problems
- Important to reduce potential bias in PK/PD studies
- Enhances laboratory users confidence in results

1. James *et al*. J. Clin. Pathol 2014;10.1136/jclinpath-2013-201621.
2. Brüggemann *et al*. Antimicrob. Agents Chemother. 2009;53:303-305

Laboratory: What are the external quality assurance (EQA) schemes for laboratories analysing TDM samples?

Features to consider when selecting an EQA test	Ideal	SOR
Accreditation status	Scheme accredited to ISO 17043 or equivalent	AIII
Frequency of distribution	Sufficient to identify perfomance issues in a timely manner (monthly?)	AIII
Range of analytes included in panel	itraconazole / hydroxy itraconazole voriconazole posaconazole	AIII
Range of concentrations included	Clinically relevant challenges that mimic patient samples	AIII
Test materials	Commutable materials	AIII
Handling of performance issues	Mechanism in place for managing poor performance	AIII
Number of participants	Sufficient to allow significant result analysis and peer comparison	AIII
Management / development	Competent professionals Independent oversight committee	AIII

Key Questions - Laboratory: What are the external quality assurance/assessment (EQA) schemes for laboratories analysing TDM samples?

Scheme organisation	INSTAND e.V.	KKGT	UKNEQAS
Accreditation status	Reference laboratory accredited to ISO standards		CPA accredited
Frequency of distribution	2 panels per year	2 x 2 samples per year	Monthly
Range of analytes included in panel	Itra / hydroxyitraconazole Voriconazole Posaconazole Fluconazole	Itra / hydroxyitraconazole Voriconazole Posaconazole Fluconazole	Itra / hydroxyitraconazole Voriconazole Posaconazole
Single analyte samples suitable for bioassay	No	No	Yes
Range of concentrations	Clinically relevant	Clinically relevant	Clinically relevant
Test materials	Commutable materials	Commutable materials	Commutable materials
Handling of performance issues	Certificate awarded for satisfactory performance	Comprehensive report provided	Poor performance letters / referral to oversight panel
Number of participants	??	63	24

EQA unmet need:

There is no interpretative EQA scheme to ensure that the correct advice is being given regarding the levels that are achieved. Or to assess any advice given on ways to attempt to rectify low or high levels.