

TDM monograph Voriconazole

Synonyms:

Vfend

Summary

Indication:	<p>Invasive aspergillosis, candidemia in non-neutropenic patients, fluconazole-resistant severe invasive candidemia, and fungal infections caused by <i>Scedosporium</i> and <i>Fusarium</i> species especially in immunocompromised patients, prophylaxis of invasive fungal infections in high-risk allogeneic hematopoietic stem cell transplantation patients.</p> <p>Off-label indications: Chronic pulmonary aspergillosis, Candida esophagitis, Candida retinitis, Candida endophthalmitis, candiduria, renal candidiasis, and empirical therapy in neutropenic patients with unexplained fever.</p> <p>Indication TDM: All patients</p>
Sample material:	Plasma or serum
Time of sampling:	Trough sample
Storage conditions:	Voriconazole is stable in plasma for 14 days at room temperature (stability data from the KKG T antifungal rounds)
Interpretation:	<p>Therapy and prophylaxis: ^{1,2} Trough concentration: 1.5 (2) - 6 mg/L; In case of abnormal liver biochemical test, trough: 1.5 (2) - 4 mg/L</p> <p>Tough penetrable area (e.g. cerebral infection, sinus infection or invasive aspergillosis): ² Trough concentration: 2 - 6 mg/L</p>
Evidence level:	1

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Introduction

Voriconazole is a broad-spectrum antifungal agent from the triazole class, registered for invasive aspergillosis, candidemia in non-neutropenic patients, fluconazole-resistant severe invasive candidemia, and for fungal infections caused by *Scedosporium* en *Fusarium* species especially in immunocompromised patients. ³ It is also registered for prophylaxis of invasive fungal infections in high-risk allogeneic hematopoietic stem cell transplantation patients. ⁴ There are several reviews which describe the role of TDM of voriconazole. ⁴⁻⁸

Dosing guidelines

Adults

See www.kennisbank.knmp.nl or Summary of Product Characteristics (SmPC) voriconazole. ³

Dosing guidelines in children and adolescents

Children 2-18 years, see www.kinderformularium.nl ⁹ or Summary of Product Characteristics (SmPC) voriconazole. ³

Dosing guidelines in CYP2C19 Poor Metabolizer (PM) or Ultrarapid Metabolizer (UM) patients

CYP2C19 Poor Metabolizer (PM) or Ultrarapid Metabolizer (UM): see www.kennisbank.knmp.nl. ¹⁰

Indications/Criteria for TDM

Due to the high inter- and intra-individual variation, the concentration efficacy relation and the concentration toxicity relation it is recommended to monitor the serum/plasma concentration of voriconazole and especially in patients with one or more of the following characteristics: ^{2,11}

- Populations with increased pharmacokinetic variability, obese patients, (neutropenic) hematologic patients, patients with impaired gastrointestinal function or hepatic dysfunction, critically ill patients, elderly and children.
- Changing pharmacokinetics such as changing hepatic function or inflammation status, intravenous to oral switch, changing gastrointestinal function, physiological-instability.
- In the presence of interacting drugs whom can influence the voriconazole concentration, such as medication known to induce cytochrome P450 enzymes.
- Poor prognosis disease, such as extensive or bulky infection, lesions contiguous with critical structures, central nervous system infection, multifocal or disseminated infection.
- Compliance concerns.
- Suspected drug toxicity (e.g. neurological side effects or abnormal liver functions).
- Suspected breakthrough infections.
- Proven or suspected reduced azole susceptibility.

Reference values

In the international literature there is no consensus regarding a reference value for voriconazole TDM. Most research suggests an reference trough value of 1.5 – 2 mg/L for the treatment for aspergillosis for children and adults. ¹²⁻¹⁷ As recommended by the Dutch working party on antibiotic policy (SWAB-guidelines) a reference trough value of 1.5 (2) to 6 mg/L is advised. ²

Efficacy

There are several studies investigating the relation between voriconazole plasma concentrations and effectivity. ^{5,12,14,15,17,18} The most reliable parameter for voriconazole effectivity is the AUC/MIC ratio, the trough level is however, a good predictor for the AUC. ¹ Until now, three randomized controlled trials were performed investigating the effect of voriconazole TDM. Two of these studies showed an significant higher response in the TDM group, and also less discontinuation of the treatment due to side effects in the TDM group. ^{12,19} One study could not demonstrate that TDM guided dosing resulted in an increase in clinical

improvement (combined response to treatment and treatment discontinuation due to an adverse drug reaction).²⁰ This may be because the initial voriconazole levels in the non-TDM population were largely within the therapeutic range (80.6%), a significantly higher number than seen in prospective studies. The positive effect of TDM effect was also shown in a meta-analysis of 24 studies.²¹ Also, several studies in pediatric patients showed a relation between the voriconazole trough concentration and effectivity.^{6,13,16} This was also confirmed in a meta-analysis of nine studies.²² Therefore several guidelines (i.e. IDSA, ECCMID, British society for Medical Mycology, and ECIL) advise to apply voriconazole TDM.^{11,23–25}

Most studies have focused on voriconazole treatment rather than prophylaxis, resulting in limited reference values for prophylactic use. An observational study found reduced colonization and fewer invasive fungal infections at trough levels above 1.5 mg/L.²⁶ Guidelines therefore recommend using the same reference values for prophylaxis as for therapy.^{2,11} For sanctuary sites, such as the brain and sinus, higher reference values are proposed. Voriconazole penetration is adequate in liquor (~30-60% of the plasma concentration).²⁷

Relationship with occurrence of side effects & toxicity

Several studies report an association between the voriconazole plasma concentration and toxicity.

^{12,14,15,17,28} Most non-randomized studies reported increased toxicity at drug levels exceeding 5.0-5.5 mg/L.

^{17,29–31} A meta-analysis concluded that voriconazole levels exceeding 6.0 mg/L were the best predictor of toxicity.²¹ Higher voriconazole trough levels (>4 – 6 mg/L) are associated with neurological side effects. The relation between neurological side effects and the trough concentration is confirmed in several studies.

^{17,32,33} These neurological side effects (such as hallucinations and changes in color perception) are typically transient and self-limiting, resolving within 2-7 days when voriconazole levels are within the therapeutic range, and usually do not require discontinuation of treatment.

Voriconazole can also cause elevated liver function enzymes (ASAT, ALAT, AP, and GGT). In the Caucasian population, no upper limit for the voriconazole trough level is established for liver toxicity.^{17,34} However, the likelihood of elevated liver enzymes rises with increased exposure to voriconazole. Thus, an upper limit of 4 mg/L for the voriconazole trough concentration is recommended for patients with elevated hepatic enzymes.² Additionally, in patients with reduced liver function, higher voriconazole trough levels are often observed. For patients with hepatic impairment, switching to an alternative treatment, such as isavuconazole (which has lower hepatotoxicity) or liposomal amphotericin b, may be considered where appropriate.^{11,23,35} Otherwise, an upper limit of 4 mg/L is advised.

Sampling & storage conditions

It is recommended to obtain a voriconazole trough sample two or three days after the start of the voriconazole treatment. ² After dose adjustments, pseudo-steady state is reached after the third dose, obtain a trough sample before the fourth dose. After achieving adequate trough levels, it is advised to monitor voriconazole trough concentrations once weekly in patients with any of the characteristics described under 'Indications/Criteria for TDM'. In stable patients, less frequent monitoring (once every 2-4 weeks) may be sufficient. Following a switch from intravenous to oral administration, it is recommended to measure a voriconazole trough level after two or three days. When using Model-Informed Precision Dosing (MIPD), sampling can be carried out earlier.

Additional information concerning the interpretation of results

Table 1 can be used to guide dose adjustments after obtainment of trough samples. This table is, however, not validated and dose adjustments should be made with the clinical situation of the patient taken into account.

Table 1: suggested dose adjustments for adults and for children over 12 years old or weighting more than 40 kg* (based on expert opinion)

	Current intravenous dose (mg/kg ever other 12 hours)				Trough level	Current oral dose (mg every other 12 hours)				
	4	5	6	7		200	250	300	400	
New intravenous dose (mg/kg ever other 12 hours)	6	7	8	8.5	< 0.1 mg/L	400	400	400	500	New oral dose (mg every other 12 hours)
	6	7	8	8.5	0.1 – 0.4 mg/L	400	400	400	500	
	5	6	7	8	0.5 – 0.9 mg/L	300	350	400	450	
	5	6	6.5	7.5	1.0 – 1.4 mg/L	250	300	350	450	
	4 - 4.5	5 - 5.5	6 - 6.5	7 - 7.5	1.5 – 1.9 mg/L [#]	200 - 250	250 - 300	300 - 350	400 - 450	
	NA	NA	NA	NA	2.0 – 5.4 mg/L	NA	NA	NA	NA	
	2	3	3	4	> 5.5 mg/L [†]	100	150	150	200	

NA: Not applicable.

* This table is not validated, keep in mind that there are other factors which can influence the voriconazole trough level and follow-up TDM is necessary. This table cannot be used in children <12 years old / <40 kg.

[#] For sanctuary sites or in infections caused by less susceptible species, it is advised achieve a trough level ≥2 mg/L.

† When the voriconazole trough level is >7 mg/L, it is advised to temporary discontinue voriconazole. Duration of discontinuation depends on clinical situation and trough level.

Background information [extended]

Pharmacokinetics

Voriconazole is absorbed within two hours of oral administration. In adults, the bioavailability is high (>90%). However the bioavailability can be lower in (critically) ill adults compared to healthy volunteers.³⁶ In pediatric patients, particularly children with malabsorption and low body weight, bioavailability can also be reduced.³

Voriconazole is mainly metabolized by CYP2C19, and to a lesser extent by CYP3A4 and CYP2C9. The inactive metabolites are mostly secreted by urine (80%) and less than 2% is secreted unchanged.³⁷

Voriconazole is for 59% bound to proteins, and shows nonlinear pharmacokinetics due to its capacity-limited elimination in adults and children >12 years old.³⁷ As a result, the AUC and C_{max} change disproportional with increasing dosages. In children <12 years (and/or <40 kg) voriconazole pharmacokinetics seems to be linear, with a higher rate of drug elimination.^{13,38,39}

Effect of food

In the presence of food, voriconazole absorption is reduced. When multiple doses of voriconazole are co-administrated with high fat meals, the C_{max} and AUC are reduced by 34% and 24% respectively.⁴⁰ Therefore it is advised to administer voriconazole at least one hour before a meal to ensure adequate absorption. Voriconazole absorption is not affected by changes in gastric pH.⁴¹

Due to the possible limited gastro-intestinal transit time in pediatric patients, the absorption of tablets can be aberrant in children compared to adults. The pediatric dose recommendations are based on studies where voriconazole is administrated as an oral suspension. Also, the bio-equivalence for tablets and oral suspension is only studied in an adult population.³ Therefore it is recommended to administer voriconazole oral suspension in children from 2 - 12 years old.⁹

Renal impairment

The pharmacokinetics of voriconazole are not affected by renal impairment. Therefore, no dose adjustment is necessary in patients with mild to severe renal impairment. It is advised in the SmPC of voriconazole to

monitor renal function and to switch to oral therapy when inexplicable deterioration occurs due to accumulation of the intravenous vehicle sulfobutylated beta-cyclodextrin (SBECD).³ However, a systematic review showed that intravenous administration of voriconazole did not lead to deterioration in renal function in patients with normal renal function as well in patients with impaired renal function.⁴² Therefore, in cases of pre-existing renal impairment, there is no rationale for choosing oral administration over intravenous administration. A 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.³ Also, CVVH does not significantly influence the voriconazole concentration.^{43,44} Dose adjustments are therefore not needed for patients undergoing hemodialysis, peritoneal dialysis, CVVH, or those with renal impairment.

Three recent case reports showed variable voriconazole concentrations during extracorporeal membrane oxygenation (ECMO).^{45–47} An ex-vivo study showed sequestration of voriconazole in the ECMO circuit.⁴⁸ In an large multi-center retrospective study, there was however no significant effect of ECMO on the voriconazole trough concentration. Subtherapeutic concentrations (<2 mg/L) were observed in 56% of the samples during ECMO and in 39% without ECMO ($p = 0.80$).⁴⁹ Also, the median voriconazole trough concentration, for a similar daily dose, was 2.4 (1.2–4.7) mg/L under ECMO and 2.5 (1.4–3.9) mg/L without ECMO ($p = 0.58$).

Liver function

Voriconazole is largely eliminated by the liver, and therefore dependent on liver function for its elimination. After an oral single-dose (200 mg), the AUC was 233% higher in subjects with mild to moderate hepatic cirrhosis (Child-Pugh A and B) compared with subjects with normal hepatic function.³ For patients with a Child-Pugh C score, one study showed that voriconazole serum concentrations were prone to vary, showing accumulation of voriconazole over time, and implying the need for repeated TDM.⁵⁰ For adults and pediatric patients >12 years old with a Child-Pugh A or B score, the SmPC of voriconazole advises administering a standard loading dose followed by 50% of the maintenance dose. For patients with a Child-Pugh C score, no dose recommendation is available due to a lack of data.³ Therefore, the use of voriconazole should be carefully evaluated in patients with liver failure, and switching to a less hepatotoxic drug should be considered.

When liver function enzymes are elevated (3-5 times above the upper limit of normal) and liver function is not impaired,⁵¹ it is advised to monitor the voriconazole trough concentration closely (one or two times per week) to prevent liver toxicity.⁵² Also, there are some indications that oral voriconazole might lead to more liver function disturbances than intravenous therapy.^{13,53,54}

Inflammation

Inflammation, and subsequently a rise in C-reactive Protein (CRP) concentration as marker for inflammation, may be of influence on the voriconazole levels in adults and children. Inflammation can cause a decrease in voriconazole metabolism due to CYP-enzyme inhibition, which subsequently can cause increase voriconazole trough levels. The cause of inflammation is not of influence. After clinical improvement of the inflammation, the metabolism of voriconazole may increase and the trough levels can subsequently decrease. CRP is frequently used as a marker of inflammation severity.^{55–60} However, the correlation between inflammation and voriconazole is weak and only moderately accounts for the variability in voriconazole exposure.⁶¹

Pediatric population

In a study of Neely *et al.* 66% of 46 children reached a voriconazole trough level of >1 mg/L at a dose of 7 mg/kg two times daily.¹³ It is possible that in the pediatric population several dose adjustments are needed to reach target attainment, also leading to higher doses than described in the SmPC.⁶² In most patients <12 years old, it is possible to adjust the dose linear, however, at higher doses nonlinear pharmacokinetics can play a role. A step by step approach to reach target attainment can be used.⁶³ In pediatric patients where the voriconazole trough level is not detectable, it is advised to measure a voriconazole peak concentration (15 minutes after intravenous infusion or 2 hours after oral ingestion) to distinguish between malabsorption and a high rate of elimination.

Pharmacogenetics

In vivo studies show that CYP2C19 is highly involved in the metabolism of voriconazole.^{64,65} It can be considered to perform CYP2C19 genotyping to clarify aberrant voriconazole trough concentrations.¹⁰ In a meta-analysis of 10 studies with a total of 262 CYP2C19 IM patients, voriconazole trough levels increased significantly with an average of 0.6 mg/L.¹⁰ Dosage recommendations are available when the CYP2C19 genotype is known.¹⁰ The main metabolite of voriconazole is the inactive voriconazole N-oxide. Measuring the voriconazole N-oxide concentration to determine the metabolic ratio of voriconazole has been suggested.⁵⁶ However, the added value of measuring voriconazole N-oxide remains uncertain.

Interactions

If possible, it is advised to avoid prescribing drugs which interact with voriconazole. Correcting voriconazole trough levels can take some time, causing a delay in reaching therapeutic levels.

Voriconazole is a substrate and inhibitor of CYP2C9, CYP3A4, and CYP2C19, which may lead to several interactions.^{3,10} CYP inhibitors or inducers (e.g. phenytoin, phenobarbital, carbamazepine, rifampicine, rifabutine, ritonavir, efavirenz, and St. John's Wort) can influence the voriconazole concentrations. Strong CYP inducers can lead to not detectable trough levels of voriconazole. Also, evidence suggest an interaction between voriconazole and flucloxacillin, with subtherapeutic plasma voriconazole concentrations as a result.^{66,67}

Voriconazole is a strong CYP3A4 inhibitor and can influence the exposure of other drugs (e.g. immunosuppressive drugs and tyrosine kinase inhibitors). When voriconazole increases the plasma concentration of drugs which might influence prolongation of the QTc-interval, caution is warranted.^{65,68}

PK parameters

	F (%)	Cl (L/h⁻¹)	Vd (L/kg)	t_{1/2} (h⁻¹)	Protein binding	Tmax (h)	Ref.
Adults	90-96% in healthy volunteers 46-83% in patients	5.25-7 L/h in healthy adults for the linear portion of the drug kinetics	4.6	6-12*	42-58%	1-2	³
Children (≥2 and ≤17 years old)	44-90%	0.1-1.5 (l/h/kg)	1-3	3-30	42-58%	1-4	⁶⁹

* This value is usually not useful due to the non-linear pharmacokinetics.

The PK of voriconazole in neonates and children <2 years old is lacking. Patients <12 years show an higher CL and Vd (and linear pharmacokinetics) in comparison to patients >12 years old. Also, in comparison to adults, no bioequivalence is shown between the intravenous and oral formulations.⁶⁹

Population models

Model-Informed Precision Dosing (MIPD) software tools can support voriconazole TDM. Several PK models have been published.^{70,71} However, it is important to select an appropriate population PK model which is as similar as possible to the local population.

Literatuur

1. Seyedmousavi S, Mouton JW, Melchers WJG, Brüggemann RJM, Verweij PE. The role of azoles in the management of azole-resistant aspergillosis: From the bench to the bedside. *Drug Resistance Updates*. 2014;17(3):37-50. doi:10.1016/j.drug.2014.06.001
2. Dutch Working Party on Antibiotic Policy SWAB Guidelines for the Management of Invasive Fungal Infections. *Published online*. 2008;(Revised version released: 14 December 2017). Accessed May 23, 2022. www.swab.nl
3. CHMP. ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS. Accessed May 23, 2022. https://www.ema.europa.eu/en/documents/product-information/vfend-epar-product-information_en.pdf.
4. Andes D, Pascual A, Marchetti O. Antifungal Therapeutic Drug Monitoring: Established and Emerging Indications. *Antimicrob Agents Chemother*. 2009;53(1):24-34. doi:10.1128/AAC.00705-08
5. Brüggemann RJM, Donnelly JP, Aarnoutse RE, et al. Therapeutic Drug Monitoring of Voriconazole. *Ther Drug Monit*. 2008;30(4):403-411. doi:10.1097/FTD.0b013e31817b1a95
6. Hope WW, Billaud EM, Lestner J, Denning DW. Therapeutic drug monitoring for triazoles. *Curr Opin Infect Dis*. 2008;21(6):580-586. doi:10.1097/QCO.0b013e3283184611
7. Smith J, Andes D. Therapeutic Drug Monitoring of Antifungals: Pharmacokinetic and Pharmacodynamic Considerations. *Ther Drug Monit*. 2008;30(2):167-172. doi:10.1097/FTD.0b013e318167d0e0
8. Hussaini T, Rüping MJGT, Farowski F, Vehreschild JJ, Cornely OA. Therapeutic Drug Monitoring of Voriconazole and Posaconazole. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2011;31(2):214-225. doi:10.1592/phco.31.2.214
9. Kinderformularium, voriconazol. Accessed October 25, 2024. <https://www.kinderformularium.nl/geneesmiddel/96/voriconazol>
10. KNMP Kennisbank. Accessed October 29, 2024. <https://kennisbank.knmp.nl/>
11. Ullmann AJ, Aguado JM, Arikan-Akdogli S, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clinical Microbiology and Infection*. 2018;24:e1-e38. doi:10.1016/j.cmi.2018.01.002
12. Park WB, Kim NH, Kim KH, et al. The Effect of Therapeutic Drug Monitoring on Safety and Efficacy of Voriconazole in Invasive Fungal Infections: A Randomized Controlled Trial. *Clinical Infectious Diseases*. 2012;55(8):1080-1087. doi:10.1093/cid/cis599
13. Neely M, Rushing T, Kovacs A, Jelliffe R, Hoffman J. Voriconazole Pharmacokinetics and Pharmacodynamics in Children. *Clinical Infectious Diseases*. 2010;50(1):27-36. doi:10.1086/648679
14. Troke PF, Hockey HP, Hope WW. Observational Study of the Clinical Efficacy of Voriconazole and Its Relationship to Plasma Concentrations in Patients. *Antimicrob Agents Chemother*. 2011;55(10):4782-4788. doi:10.1128/AAC.01083-10
15. Dolton MJ, Ray JE, Chen SCA, Ng K, Pont LG, McLachlan AJ. Multicenter Study of Voriconazole Pharmacokinetics and Therapeutic Drug Monitoring. *Antimicrob Agents Chemother*. 2012;56(9):4793-4799. doi:10.1128/AAC.00626-12
16. Soler-Palacin P, Frick MA, Martin-Nalda A, et al. Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: a prospective study. *Journal of Antimicrobial Chemotherapy*. 2012;67(3):700-706. doi:10.1093/jac/dkr517
17. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole Therapeutic Drug Monitoring in Patients with Invasive Mycoses Improves Efficacy and Safety Outcomes. *Clinical Infectious Diseases*. 2008;46(2):201-211. doi:10.1086/524669
18. Butler-Laporte G, Langevin M, Lemieux C, et al. Voriconazole therapeutic drug monitoring among lung transplant recipients receiving targeted therapy for invasive aspergillosis. *Clin Transplant*. 2022;36(8). doi:10.1111/ctr.14709

19. Li H, Li M, Yan J, et al. Voriconazole therapeutic drug monitoring in critically ill patients improves efficacy and safety of antifungal therapy. *Basic Clin Pharmacol Toxicol*. 2020;127(6):495-504. doi:10.1111/bcpt.13465
20. Veringa A, Brüggemann RJ, Span LFR, et al. Therapeutic drug monitoring-guided treatment versus standard dosing of voriconazole for invasive aspergillosis in haematological patients: a multicentre, prospective, cluster randomised, crossover clinical trial. *Int J Antimicrob Agents*. 2023;61(2):106711. doi:10.1016/j.ijantimicag.2023.106711
21. Luong ML, Al-Dabbagh M, Groll AH, et al. Utility of voriconazole therapeutic drug monitoring: a meta-analysis. *Journal of Antimicrobial Chemotherapy*. 2016;71(7):1786-1799. doi:10.1093/jac/dkw099
22. Hanai Y, Hamada Y, Kimura T, et al. Optimal trough concentration of voriconazole with therapeutic drug monitoring in children: A systematic review and meta-analysis. *Journal of Infection and Chemotherapy*. 2021;27(2):151-160. doi:10.1016/j.jiac.2020.11.014
23. Patterson TF, Thompson GR, Denning DW, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2016;63(4):e1-e60. doi:10.1093/cid/ciw326
24. Schelenz S, Barnes RA, Barton RC, et al. British Society for Medical Mycology best practice recommendations for the diagnosis of serious fungal diseases. *Lancet Infect Dis*. 2015;15(4):461-474. doi:10.1016/S1473-3099(15)70006-X
25. Groll AH, Castagnola E, Cesaro S, et al. 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. *Lancet Oncol*. 2014;15(8):e327-e340. doi:10.1016/S1470-2045(14)70017-8
26. Mitsani D, Nguyen MH, Shields RK, et al. Prospective, observational study of voriconazole therapeutic drug monitoring among lung transplant recipients receiving prophylaxis: Factors impacting levels of and associations between serum troughs, efficacy, and toxicity. *Antimicrob Agents Chemother*. 2012;56(5):2371-2377. doi:10.1128/AAC.05219-11
27. Lutsar I, Roffey S, Troke P. Voriconazole Concentrations in the Cerebrospinal Fluid and Brain Tissue of Guinea Pigs and Immunocompromised Patients. *Clinical Infectious Diseases*. 2003;37(5):728-732. doi:10.1086/377131
28. Karthaus M, Lehrnbecher T, Lipp HP, Kluge S, Buchheidt D. Therapeutic drug monitoring in the treatment of invasive aspergillosis with voriconazole in cancer patients—an evidence-based approach. *Ann Hematol*. 2015;94(4):547-556. doi:10.1007/s00277-015-2333-z
29. Ueda K, Nannya Y, Kumano K, et al. Monitoring trough concentration of voriconazole is important to ensure successful antifungal therapy and to avoid hepatic damage in patients with hematological disorders. *Int J Hematol*. 2009;89(5):592-599. doi:10.1007/s12185-009-0296-3
30. Hoenigl M, Duettmann W, Raggam RB, et al. Potential factors for inadequate voriconazole plasma concentrations in intensive care unit patients and patients with hematological malignancies. *Antimicrob Agents Chemother*. 2013;57(7):3262-3267. doi:10.1128/AAC.00251-13
31. Kim SH, Yim DS, Choi SM, et al. Voriconazole-related severe adverse events: Clinical application of therapeutic drug monitoring in Korean patients. *International Journal of Infectious Diseases*. 2011;15(11). doi:10.1016/j.ijid.2011.06.004
32. Boyd AE, Modi S, Howard SJ, Moore CB, Keevil BG, Denning DW. Adverse Reactions to Voriconazole. *Clinical Infectious Diseases*. 2004;39(8):1241-1244. doi:10.1086/424662
33. Imhof A, Schaer DJ, Schanz U, Schwarz U. Neurological adverse events to voriconazole: evidence for therapeutic drug monitoring. *Swiss Med Wkly*. 2006;1(45-46):739-42. doi:10.4414/smw.2006.11547
34. Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N. Investigation of the Potential Relationships Between Plasma Voriconazole Concentrations and Visual Adverse Events or Liver Function Test

- Abnormalities. *The Journal of Clinical Pharmacology*. 2006;46(2):235-243. doi:10.1177/0091270005283837
35. Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): A phase 3, randomised-controlled, non-inferiority trial. *The Lancet*. 2016;387(10020):760-769. doi:10.1016/S0140-6736(15)01159-9
 36. Veringa A, Geling S, Span LFR, et al. Bioavailability of voriconazole in hospitalised patients. *Int J Antimicrob Agents*. 2017;49(2):243-246. doi:10.1016/j.ijantimicag.2016.10.010
 37. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/Pharmacodynamic Profile of Voriconazole. *Clin Pharmacokinet*. 2006;45(7):649-663. doi:10.2165/00003088-200645070-00002
 38. 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(6):2166-2172. doi:10.1128/AAC.48.6.2166-2172.2004
 39. Karlsson MO, Lutsar I, Milligan PA. Population Pharmacokinetic Analysis of Voriconazole Plasma Concentration Data from Pediatric Studies. *Antimicrob Agents Chemother*. 2009;53(3):935-944. doi:10.1128/AAC.00751-08
 40. Purkins L, Wood N, Kleinermans D, Greenhalgh K, Nichols D. Effect of food on the pharmacokinetics of multiple-dose oral voriconazole. *Br J Clin Pharmacol*. 2003;56(s1):17-23. doi:10.1046/j.1365-2125.2003.01994.x
 41. Wood N, Tan K, Purkins L, et al. Effect of omeprazole on the steady-state pharmacokinetics of voriconazole. *Br J Clin Pharmacol*. 2003;56(s1):56-61. doi:10.1046/j.1365-2125.2003.02000.x
 42. Turner RB, Martello JL, Malhotra A. Worsening renal function in patients with baseline renal impairment treated with intravenous voriconazole: A systematic review. *Int J Antimicrob Agents*. 2015;46(4):362-366. doi:10.1016/j.ijantimicag.2015.05.023
 43. Grensemann J, Pfaffendorf C, Wicha SG, et al. Voriconazole Pharmacokinetics Are Not Altered in Critically Ill Patients with Acute-on-Chronic Liver Failure and Continuous Renal Replacement Therapy: An Observational Study. *Microorganisms*. 2021;9(10):2087. doi:10.3390/microorganisms9102087
 44. Radej J, Krouzecky A, Stehlik P, et al. Pharmacokinetic Evaluation of Voriconazole Treatment in Critically Ill Patients Undergoing Continuous Venovenous Hemofiltration. *Ther Drug Monit*. 2011;33(4):393-397. doi:10.1097/FTD.0b013e3182205d93
 45. Vu T, Feih J, Juul J. Fluctuating Voriconazole Concentrations during Extracorporeal Membrane Oxygenation. *J Pharm Pract*. 2023;36(4):998-1001. doi:10.1177/08971900211060959
 46. Mathieu A, Thiboutot Z, Ferreira V, et al. Voriconazole Sequestration During Extracorporeal Membrane Oxygenation for Invasive Lung Aspergillosis: A Case Report. *ASAIO Journal*. 2022;68(3):e56-e58. doi:10.1097/MAT.0000000000001427
 47. Peterson EL, Chittick PJ, Richardson CL. Decreasing voriconazole requirement in a patient after extracorporeal membrane oxygenation discontinuation: A case report. *Transplant Infectious Disease*. 2021;23(3):2-5. doi:10.1111/tid.13545
 48. Zhang Y, Hu H, Zhang Q, et al. Effects of ex vivo Extracorporeal Membrane Oxygenation Circuits on Sequestration of Antimicrobial Agents. *Front Med (Lausanne)*. 2021;8(December):1-8. doi:10.3389/fmed.2021.748769
 49. Van Daele R, Bekkers B, Lindfors M, et al. A Large Retrospective Assessment of Voriconazole Exposure in Patients Treated with Extracorporeal Membrane Oxygenation. *Microorganisms*. 2021;9(7):1543. doi:10.3390/microorganisms9071543
 50. Zhao Y, Hou J, Xiao Y, et al. Predictors of Voriconazole Trough Concentrations in Patients with Child-Pugh Class C Cirrhosis: A Prospective Study. *Antibiotics*. 2021;10(9):1130. doi:10.3390/antibiotics10091130
 51. Liu X, Su H, Tong J, et al. Significance of monitoring plasma concentration of voriconazole in a patient with liver failure. *Medicine*. 2017;96(42):e8039. doi:10.1097/MD.0000000000008039

52. Alffenaar JC, De Vos T, Uges DRA, Daenen SMGJ. High voriconazole trough levels in relation to hepatic function: how to adjust the dosage? *Br J Clin Pharmacol*. 2009;67(2):262-263. doi:10.1111/j.1365-2125.2008.03315.x
53. Alffenaar JWC, van Assen S, de Monchy JGR, Uges DRA, Kosterink JGW, van der Werf TS. Intravenous Voriconazole after Toxic Oral Administration. *Antimicrob Agents Chemother*. 2010;54(6):2741-2742. doi:10.1128/AAC.01193-09
54. Roffey SJ, Cole S, Comby P, et al. The disposition of voriconazole in mouse, rat, rabbit, guinea pig, dog, and human. *Drug Metabolism and Disposition*. 2003;31(6):731-741. doi:10.1124/dmd.31.6.731
55. van Wanrooy MJP, Span LFR, Rodgers MGG, et al. Inflammation Is Associated with Voriconazole Trough Concentrations. *Antimicrob Agents Chemother*. 2014;58(12):7098-7101. doi:10.1128/AAC.03820-14
56. Veringa A, ter Avest M, Span LFR, et al. Voriconazole metabolism is influenced by severe inflammation: a prospective study. *Journal of Antimicrobial Chemotherapy*. 2017;72(1):261-267. doi:10.1093/jac/dkw349
57. Encalada Ventura MA, van Wanrooy MJP, Span LFR, et al. Longitudinal Analysis of the Effect of Inflammation on Voriconazole Trough Concentrations. *Antimicrob Agents Chemother*. 2016;60(5):2727-2731. doi:10.1128/AAC.02830-15
58. Chen J, Wu Y, He Y, Feng X, Ren Y, Liu S. Combined Effect of CYP2C19 Genetic Polymorphisms and C-Reactive Protein on Voriconazole Exposure and Dosing in Immunocompromised Children. *Front Pediatr*. 2022;10(March):1-12. doi:10.3389/fped.2022.846411
59. Valle-T-Figueras JM, Renedo Miró B, Benítez Carabante MI, et al. Voriconazole Use in Children: Therapeutic Drug Monitoring and Control of Inflammation as Key Points for Optimal Treatment. *Journal of Fungi*. 2021;7(6):456. doi:10.3390/jof7060456
60. Takahashi T, Jaber MM, Smith AR, Jacobson PA, Fisher J, Kirstein MN. Predictive Value of C-Reactive Protein and Albumin for Temporal Within-Individual Pharmacokinetic Variability of Voriconazole in Pediatric Patients Undergoing Hematopoietic Cell Transplantation. *The Journal of Clinical Pharmacology*. 2022;62(7):855-862. doi:10.1002/jcph.2024
61. Vreugdenhil B, van der Velden WJFM, Feuth T, et al. Moderate correlation between systemic IL-6 responses and CRP with trough concentrations of voriconazole. *Br J Clin Pharmacol*. 2018;84(9):1980-1988. doi:10.1111/bcp.13627
62. Lempers VJ, Meuwese E, Mavinkurve-Groothuis AM, et al. Impact of dose adaptations following voriconazole therapeutic drug monitoring in pediatric patients. *Med Mycol*. 2019;57(8):937-943. doi:10.1093/mmy/myz006
63. Friberg LE, Ravva P, Karlsson MO, Liu P. Integrated Population Pharmacokinetic Analysis of Voriconazole in Children, Adolescents, and Adults. *Antimicrob Agents Chemother*. 2012;56(6):3032-3042. doi:10.1128/AAC.05761-11
64. Hyland R, Jones BC, Smith DA. Identification of the Cytochrome P450 Enzymes Involved in the N-Oxidation of Voriconazole. *Drug Metabolism and Disposition*. 2003;31(5):540-547. doi:10.1124/dmd.31.5.540
65. Brüggemann RJM, Alffenaar JC, Blijlevens NMA, et al. Clinical Relevance of the Pharmacokinetic Interactions of Azole Antifungal Drugs with Other Coadministered Agents. *Clinical Infectious Diseases*. 2009;48(10):1441-1458. doi:10.1086/598327
66. Muilwijk EW, Dekkers BGJ, Henriët SS V., et al. Flucloxacillin Results in Suboptimal Plasma Voriconazole Concentrations. *Antimicrob Agents Chemother*. 2017;61(9). doi:10.1128/AAC.00915-17
67. Vangheluwe T, Van Hoecke F, Dumoulin A, Vogelaers D. Broad-spectrum azoles and flucloxacillin: a dangerous match. *European Journal of Clinical Microbiology & Infectious Diseases*. 2022;41(1):153-154. doi:10.1007/s10096-021-04333-z
68. Fungal pharmacology. Accessed October 25, 2024. <http://www.fungalpharmacology.org/>

69. Bury D, Tissing WJE, Mulwijk EW, Wolfs TFW, Brüggemann RJ. Clinical Pharmacokinetics of Triazoles in Pediatric Patients. *Clin Pharmacokinet.* 2021;60(9):1103-1147. doi:10.1007/s40262-021-00994-3
70. Yang P, Liu W, Zheng J, et al. Predicting the Outcome of Voriconazole Individualized Medication Using Integrated Pharmacokinetic/Pharmacodynamic Model. *Front Pharmacol.* 2021;12(October):1-7. doi:10.3389/fphar.2021.711187
71. Chaudhri K, Stocker SL, Williams KM, et al. Voriconazole: an audit of hospital-based dosing and monitoring and evaluation of the predictive performance of a dose-prediction software package. *Journal of Antimicrobial Chemotherapy.* 2020;75(7):1981-1984. doi:10.1093/jac/dkaa098

Colophon

This guideline has been constituted by dr. R.J.M. Brüggemann, dr. J.W.C. Alffenaar and drs. I. Bartelink, hospital pharmacists, under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)
Date: November 2011.

Appendices

Not applicable

Revision

This guideline has been revised by drs. L.N. van Merendonk (hospital pharmacist i.t.) and dr. K.C.M. van der Elst (hospital pharmacist – clinical pharmacologist) and drs. T. Bognår (hospital pharmacist). The guideline was updated based on most recent literature. It was translated to English by drs. J.S. Kingma (hospital pharmacist).