

Impact of Dose Adaptations Following Voriconazole Therapeutic Drug Monitoring in Pediatric Patients

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Complete List of Authors:	Lempers, Vincent; Radboudumc Meuwese, Edme; Erasmus MC Mavinkurve-Groothuis, Annelies; Princess Máxima Center for Pediatric Oncology Henriet, Stefanie; Radboudumc van der Sluis, Inge; Princess Máxima Center for Pediatric Oncology Hanff, Lidwien; Princess Máxima Center for Pediatric Oncology Warris, Adilia; MRC Centre for Medical Mycology University of Aberdeen, Institute of Medical Sciences Koch, Birgit; Erasmus MC Brüggemann, Roger; Radboud University Medical Center, Pharmacy;
Keyword:	voriconazole, therapeutic drug monitoring, pediatrics, azoles, pharmacokinetics
Abstract:	Voriconazole is a broad-spectrum triazole antifungal agent which has emerged as the preferred treatment of invasive aspergillosis in both children (≥ 2 years of age) and adults (1, 2). Increased voriconazole exposure has been associated with improved treatment outcome in adults, with suggested provisional cut-off points for voriconazole trough plasma concentrations (C_{min}) of 1-6 mg/L (3-6). An exposure-response relationship was also established for pediatric patients, in which a voriconazole $C_{min} > 1$ mg/L was associated with improved outcomes (7-11). Based on the relationship between voriconazole exposure and efficacy and the high inter- and intra-patient variability in pediatric patients (12-15), the importance of voriconazole therapeutic drug monitoring (TDM) in pediatric patients has been acknowledged (1, 2, 16, 17). Although TDM-based dose adjustments are performed to optimize plasma concentrations, it remains unclear if these dose adaptations in pediatric patients correspond with target attainment. We conducted a retrospective analysis in a cohort of pediatric oncology patients (both leukemia as well as lymphoma) with difficult to manage

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	voriconazole concentrations and assessed the result of TDM-based dose adaptations on target attainment.

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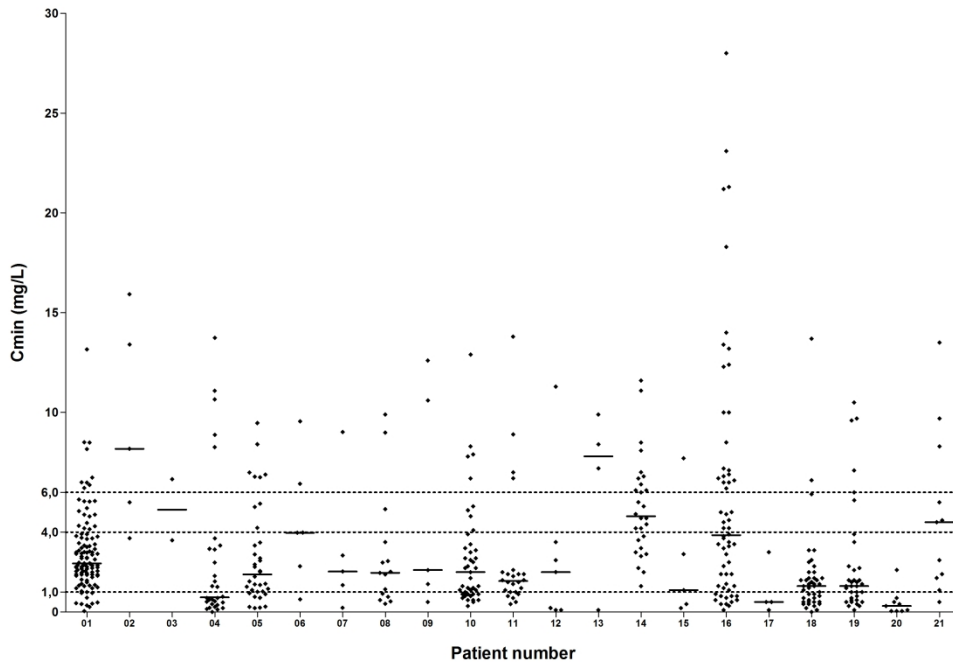
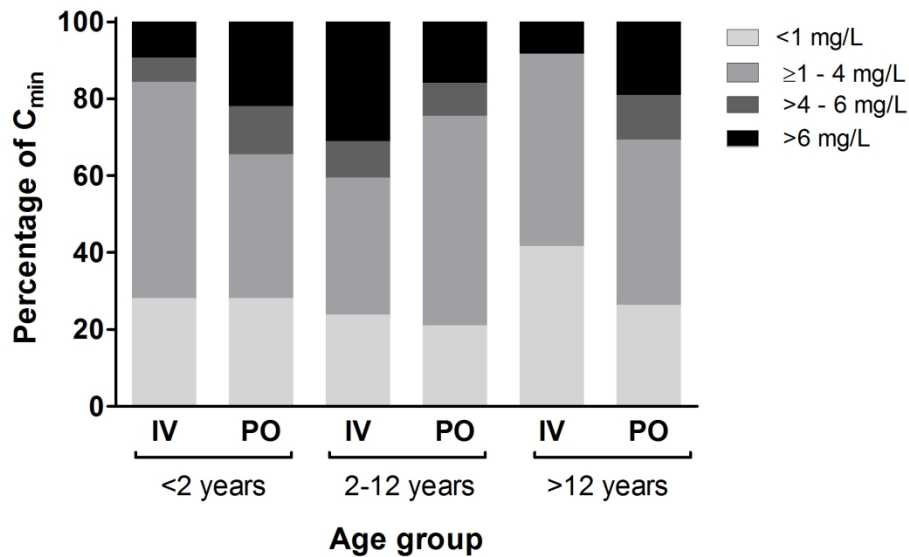


Figure 1

285x195mm (300 x 300 DPI)



Age group	Formulation	C_{min} (% of total)			
		< 1 mg/L (n)	1 - 4 mg/L (n)	>4 - 6 mg/L (n)	> 6 mg/L (n)
< 2 years	IV	28.1 (9)	56.3 (18)	6.3 (2)	9.4 (3)
	PO	28.1 (9)	37.5 (12)	12.5 (4)	21.9 (7)
2-12 years	IV	23.8 (10)	35.7 (15)	9.5 (4)	31.0 (13)
	PO	21.1 (52)	54.5 (134)	8.5 (21)	15.9 (39)
>12 years	IV	41.7 (5)	50.0 (6)	0.0 (0)	8.3 (1)
	PO	26.3 (32)	43.0 (52)	11.6 (14)	19.0 (23)

Age group	Formulation	Median dose administered (mg/kg/day)			
		< 1 mg/L	1 - 4 mg/L	>4 - 6 mg/L	> 6 mg/L
< 2 years	IV	12.2	11.9	N/A	12.9
	PO	12.2	12.3	22.0	12.6
2-12 years	IV	17.1	24.5	15.7	57.9
	PO	24.0	25.9	22.9	28.2
>12 years	IV	10.0	11.1	N/A	N/A
	PO	18.4	15.7	11.0	10.4

Figure 2

173x209mm (300 x 300 DPI)

Impact of Dose Adaptations Following Voriconazole Therapeutic Drug Monitoring in Pediatric Patients

Vincent J. Lempers¹, Edmé Meuwese², Annelies M. Mavinkurve-Groothuis³, Stefanie Henriët⁴, Inge M van der Sluis^{3,5}, Lidwien M. Hanff³, Adilia Warris⁶, Birgit C.P. Koch², Roger J. Brüggemann^{1,7*}

Affiliations

¹ Radboud university medical center, Department of Pharmacy and Radboud Institute for Health Sciences, Nijmegen, The Netherlands

² Erasmus Medical Center, Department of Pharmacy, Rotterdam, The Netherlands

³ Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

⁴ Radboud university medical center, Department of Pediatric Infectious Diseases & Immunology, Nijmegen, The Netherlands

⁵ Erasmus Medical Center-Sophia Children's Hospital, Department of Pediatric Haematology-Oncology, Rotterdam, The Netherlands

⁶ MRC Centre for Medical Mycology, Aberdeen Fungal Group, Institute of Medical Sciences, University of Aberdeen, United Kingdom

⁷ Center of Expertise in Mycology Radboudumc / CWZ, Nijmegen, The Netherlands

*Corresponding author

Dr. Roger JM Brüggemann

Department of Pharmacy 864

Radboud university medical center

Geert Grooteplein 10

6525 GA Nijmegen

The Netherlands

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Word count: 2500

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3 34 Abstract (243/250 words)
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7 36 Voriconazole is the mainstay of treatment for invasive aspergillosis in immunocompromised pediatric
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9 37 patients. Although Therapeutic Drug Monitoring (TDM) of voriconazole is recommended, it remains
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11 38 unknown if TDM-based dose adaptations result in target attainment.
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13 39 Patients < 19 years from two pediatric hematologic-oncology wards were retrospectively identified
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15 40 based on unexplained high voriconazole trough concentrations ($C_{min} > 6\text{mg/L}$). Patient demographics,
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17 41 clinical characteristics, treatment, voriconazole dosing information, voriconazole C_{min} before and
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19 42 after adjustment based on TDM were obtained.
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22 43 Twenty-one patients, median (range) age 7.0 (1.2-18.5) years, were identified in two centres. First
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24 44 C_{min} (3.1mg/L [0.1-13.5]) was obtained after 3 days (1-27) of treatment. The median of all C_{min} (n=485,
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26 45 median 11 per patient) was 2.16mg/L (0.0 (undetectable)–28.0), with 24.1% of $C_{min} < 1\text{mg/L}$, 48.9% 1-
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28 46 4mg/L, 9.3% 4-6mg/L and 17.7% $> 6\text{mg/L}$. Inpatient variability was large (94.1% for IV, 88.5% for
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30 47 PO). Dose increases at $C_{min} < 1\text{ mg/L}$ resulted in an increased C_{min} in 76.4%, with 60% between 1-4
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32 48 mg/L. Dose decreases at $C_{min} > 6\text{ mg/L}$ resulted in a decreased C_{min} in 80%, with 51% between 1-4
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34 49 mg/L. Overall in 45% of the cases (33 out of 55 and 12 out of 45) therapeutic targets were attained
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36 50 after dose adjustment.
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38 51 Fifty-five percent of initial C_{min} was outside the therapeutic target of 1-4mg/L, with multiple dose
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40 52 adaptations required to achieve therapeutic concentrations. Only 60% and 51% of dose adaptations
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42 53 following sub- and supra-therapeutic C_{min} , respectively, did result in target attainment. Intensive and
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44 54 continuous TDM of voriconazole is a prerequisite for ensuring adequate exposure in pediatric
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46 55 patients.
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3 58 Introduction
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8 60 Voriconazole is a broad-spectrum triazole antifungal agent which has emerged as the preferred
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10 61 treatment of invasive aspergillosis in both children (≥ 2 years of age) and adults ^(1, 2).
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12 62 Increased voriconazole exposure has been associated with improved treatment outcome in adults,
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14 63 with suggested provisional cut-off points for voriconazole trough plasma concentrations (C_{\min}) of 1-6
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16 64 mg/L (3-6). An exposure-response relationship was also established for pediatric patients, in which a
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18 65 voriconazole $C_{\min} > 1$ mg/L was associated with improved outcomes ⁽⁷⁻¹¹⁾. Based on the relationship
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20 66 between voriconazole exposure and efficacy and the high inter- and intra-patient variability in
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22 67 pediatric patients ⁽¹²⁻¹⁵⁾, the importance of voriconazole therapeutic drug monitoring (TDM) in
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24 68 pediatric patients has been acknowledged ^(1, 2, 16, 17). Although TDM-based dose adjustments are
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26 69 performed to optimize plasma concentrations, it remains unclear if these dose adaptations in
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28 70 pediatric patients correspond with target attainment.
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32 71 We conducted a retrospective analysis in a cohort of pediatric oncology patients (both leukemia as
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34 72 well as lymphoma) with difficult to manage voriconazole concentrations and assessed the result of
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36 73 TDM-based dose adaptations on target attainment.
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7 77 *Study design and patients*
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10 78 This retrospective analysis was carried out in the pediatric hematology-oncology wards of two
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12 79 university hospitals in the Netherlands (Radboud university medical centre, Nijmegen and Sophia
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14 80 Children's Hospital, Erasmus Medical Center, Rotterdam). From August 2007–May 2014, the results
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16 81 from routinely performed TDM of voriconazole in both hospitalized and ambulant pediatric patients
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18 82 were evaluated. Patients < 19 years who received voriconazole orally (PO) or intravenously (IV) were
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20 83 included if more than one voriconazole C_{\min} was determined, of which at least one concentration was
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22 84 >6 mg/L during treatment. Due to the retrospective nature of the study, written informed consent
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24 85 was deemed not necessary.
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30 87 *Data collection*
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32 88 Data was collected from the patients' medical records and included patient demographics (e.g. age,
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34 89 gender, body weight), voriconazole treatment data (e.g. route of administration, treatment duration,
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36 90 total daily dose, dose adjustments) and TDM data (e.g. plasma trough concentrations [C_{\min}], number
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38 91 of samples per patient, number of sub- and supra-therapeutic C_{\min}). Concomitant medications with or
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40 92 without a known or suspected interaction with voriconazole exposure were reported.
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45 94 *Voriconazole dosing and dose adjustments*
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48 95 Initial dosing and administration of voriconazole was according to the Summary of Product
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50 96 Characteristics (SmPC) of voriconazole, but could be increased or decreased based on clinical
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52 97 indications and TDM results. End of treatment was defined by successful clinical response, or by
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54 98 discontinuation due to a lack of clinical response, or adverse events. Consistent with institution
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56 99 guidelines during the study period, adequate voriconazole exposure was defined as C_{\min} between 1-4
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58 100 mg/L. If the patient showed no signs of hepatotoxicity (*i.e.* liver function tests no more than three
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3 101 times the upper limit of normal), C_{\min} up to 6 mg/L were accepted. The 4 mg/L target concentration to
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5 102 prevent hepatotoxicity has been established in Asian patients particularly(18, 19). In Caucasian
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7 103 people this relation has not been established with a clear cut-off value. Rather an increase in drugs
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9 104 concentration, results in an increased chance of encountering hepatotoxicity(20). In case of
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12 105 sanctuary infection sites or disseminated disease, the lower threshold was set to 2 mg/L (*i.e.* 2-4
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14 106 mg/L or 2-6 mg/L). Target concentrations remain subject to debate but our target concentrations are
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16 107 in line with the recently published ESCMID guideline(2) and the ECIL guideline [available online via
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18 108 www.ecil-leukaemia.com]

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21 109 In case of a sub- or supra-therapeutic voriconazole C_{\min} (< 1 or > 6 mg/L), dose adjustments, assuming
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23 110 near-linear pharmacokinetics in children ⁽¹⁴⁾, to reach adequate C_{\min} were subsequently made. A
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25 111 follow-up sample within 1 week was recommended. Dosing frequency was initially two times daily,
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27 112 but could be increased to three times daily in an attempt to reach adequate voriconazole exposure.
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32 115 *Therapeutic Drug Monitoring*

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35 116 TDM was performed as standard of care, but frequency of sampling was dependent on individual
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37 117 decisions made for each patient. First TDM sample was recommended at steady state concentrations
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39 118 of the drug, which is at least two days after initiation of voriconazole therapy or following dose
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41 119 adaptations. Only blood samples withdrawn within a 1 hour period prior to the next dose were
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43 120 included in the analysis to ascertain a trough concentration. Decisions on dose adaptations were
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45 121 made by experts in the field with knowledge on PK of voriconazole taking in mind the clinical
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47 122 condition of the patient.
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52 124 *Analytical assay*

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3 125 Voriconazole plasma concentrations were measured twice weekly using an in-house, validated ultra-
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5 126 performance liquid chromatography (HPLC) method with either a fluorescence or MSMS detection
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7 127 method (Waters).
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12 129 *Data analysis*

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14 130 A Spearman rank-order correlation was run to determine the relationship between voriconazole dose
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16 131 and C_{\min} using SPSS 20.0 (SPSS inc., IL, USA). A p-value of <0.05 was considered statistically significant.
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18 132 Intra-patient variability of voriconazole C_{\min} was analyzed in patients who had at least three
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21 133 voriconazole C_{\min} at similar doses and formulations.
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135 RESULTS

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137 *Patients*

138 Twenty-one patients (8 male, 13 female) were eligible for analysis. Median (range) age at first dose
139 was 7.0 years (1.2–18.5 years), of which 3 patients (14.3%) were <2 years, 11 (52.4%) between 2 and
140 12 years, and 7 (33.3%) between 12 and 19 years. Median (range) weight and BMI were 21.9 kg (9.5–
141 65) and 17.7 kg/m² (14–25.4), respectively (Table 1).

142

143 *Voriconazole therapy*

144 Patients received voriconazole therapy for a median (range) of 118 days (17–866; Table 1). The
145 median total daily dose per kg (range) was 23.1 mg/kg (6.1–109.6). Initial voriconazole administration
146 was IV in 15 (71.4%) and PO in 6 (28.6%) of patients. Five patients received voriconazole orally only, 2
147 only IV, and 14 received a combination of both. In four patients voriconazole was given TID at some
148 time as part of their management strategy for a median (range) of 60 days (6–397) with a median
149 total daily dose of 34.4 mg/kg (13.6–109.6). Median intra-individual variability of voriconazole dose
150 was 94.1% during IV therapy (dose range: 12.2–16.0 mg/kg/day) and 88.5% during PO therapy (dose
151 range: 10.5–44.1 mg/kg/day).

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153 *Therapeutic drug monitoring – initial C_{min}*

154 The first measurement of voriconazole C_{min} was performed at a median (range) of 3 days (1–27) after
155 start of treatment, with a median (IQR) C_{min} of 3.1 mg/L (1.34–7.0; Table 1). Upon first measurement,
156 11 out of 21 (52.4%) patients reached a C_{min} between 1–6 mg/L (7 of these patients received
157 voriconazole IV, 4 PO). Of the remaining 10 patients who had a voriconazole concentration <1 mg/L
158 or >6 mg/L at first measurement, 5 out of 9 patients (55.5%) required only 1 dose adaptation to
159 achieve a C_{min} between 1–6 mg/L. Target concentrations in these 9 patients were attained after a
160 median (range) of 15 days (8–123). One patient was unable to achieve target values during the entire

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3 161 length of voriconazole therapy despite TDM-based dose adaptations. After the first suboptimal C_{min} ,
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5 162 TDM-based dose adaptations were performed within a median of 2 days. A very weak positive
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7 163 correlation between voriconazole dose and initial C_{min} was calculated, which was not statistically
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9 164 significant ($r^2=0.05$, $p=0.82$).
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14 166 *Therapeutic drug monitoring – all C_{min}*

16 167 In total, 485 samples were obtained with a median (range) concentration of 2.16 mg/L (undetectable
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18 168 -28; Table 1). Four concentrations (0.8%) were reported as below the lower limit of quantification. A
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20 169 median (range) of 11 samples (2-109) were drawn per patient, of which 117 (24.1%) were <1 mg/L,
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22 170 237 (48.9%) between 1-4 mg/L, 45 (9.3%) between 4-6 mg/L and 86 (17.7%) >6 mg/L. An overview of
23
24 171 all C_{min} per patient is shown in Figure 1. There was no significant correlation between voriconazole
25
26 172 dose and all C_{min} , ($r_s(485)=0.02$, $p=0.59$). A C_{min} <1 mg/L was most frequently encountered in patients
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28 173 >12 years receiving voriconazole IV, whereas patients 2-12 years suffered most frequently from C_{min}
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30 174 >6 mg/L (Figure 2).
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36 176 *Voriconazole dose adaptations*

38 177 A total of 108 dose increases and 135 dose decreases were made, of which 50.9% when C_{min} < 1,
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40 178 and 33.3% C_{min} > 6 (see table 1). Out of a 117 cases with a C_{min} <1mg/L prompted a dose increase in
41
42 179 47.0% (n=55) of occurrences, which resulted in an increased C_{min} at follow-up sampling in 76.4%
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44 180 (n=42) of cases. In 60% (n=33) of dose increases following a concentration of <1 mg/L, this led to a
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46 181 therapeutic C_{min} between 1–4 mg/L (median 1.7 mg/L). In these 33 cases, the total daily dose was
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48 182 increased from a median of 18.3 mg/kg/day to 22.7 mg/kg/day (24.0%).
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52 183 Out of 86 cases with a C_{min} of >6 mg/L (median 8.29 mg/L) this prompted a dose decrease in 52.3%
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54 184 (n=45) of cases, of which 80.0% (n=36) resulted in a subsequent lower C_{min} at follow-up sampling.
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56 185 These dose decreases resulted in a C_{min} of <6mg/L in 51.1% (n=23) of cases and even led to
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3 186 concentrations between 1-4 mg/L (median 2.3 mg/L) in 26.7% (n=12). In these 12 cases, the total
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5 187 daily dose was decreased from a median of 23.5 mg/kg/day to 16.8 mg/kg/day (39.9%).
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For Peer Review Only

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3 190 Discussion
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7 192 Here, we present our experience with voriconazole TDM in a cohort of 21 pediatric patients with
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10 193 difficult to control voriconazole C_{min} , characterized by at least one $C_{min} >6$ mg/L, enabling us to assess
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12 194 the result of TDM-based dose adaptations on voriconazole target attainment.
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14 195 Overall, 18.5 % of all doses adjustments made, based on TDM, resulted in target concentrations (1-4
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16 196 mg/L). The vast majority (95.2%) of the patients in our study were able to achieve at least one
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18 197 therapeutic concentration (1-4 mg/L) after TDM-based dose adjustments. This is in a similar range of
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20 198 the reported value of 80% in a study from Bartelink *et al.*, although voriconazole target values of 1-5
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22 199 mg/L were used in this study ⁽²¹⁾.
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25 200 Of the total number of 485 voriconazole C_{min} , 24.1% was <1 mg/L, which is correlated with increased
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27 201 likelihood of treatment failure in children ⁽⁷⁻⁹⁾. In case of such a subtherapeutic C_{min} , voriconazole
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29 202 dose was increased in 47.0% of cases. Accordingly, 60% of dose increases resulted in the desired
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31 203 therapeutic C_{min} of 1-4 mg/L, with a median dose increase from 18.3 mg/kg/day to 22.7 mg/kg/day.
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34 204 Previous studies have reported that dose adjustments to median doses of 20–40 mg/kg/day were
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36 205 required to obtain therapeutic plasma concentrations of >1 mg/L ^(9, 10, 22). In addition, 17.7% of the
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38 206 total number of voriconazole C_{min} were >6 mg/L, which is regarded as a cut-off concentration for
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40 207 hepatotoxicity in adults (23), although no clear correlation is seen in pediatric patients ^(7, 24, 25). At
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42 208 these supratherapeutic concentrations, voriconazole dose was lowered in 52.3% of cases, resulting in
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44 209 a C_{min} between the target range of 1-4 mg/L in 26.7% of cases (decreasing the median dose from 23.5
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46 210 mg/kg/day to 16.8 mg/kg/day).
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49 211 Age is one of the most important factors influencing voriconazole plasma exposure, as voriconazole
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51 212 clearance has been shown to be much higher in children under the age of 12, and oral bioavailability
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53 213 of voriconazole is lower in children (65%), compared to adults (96%) ^(14, 26). As a result, several studies
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55 214 reported similar voriconazole exposure in children (<12 years) compared to adults with IV doses of 7-
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57 215 9 mg/kg BID ^(13, 14, 26). This prompted higher dosing regimens in children compared to adults. Although
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3 216 voriconazole has been reported to display near-linear pharmacokinetics in children receiving multiple
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5 217 doses of 3 mg/kg and 4 mg/kg BID IV⁽¹⁵⁾ (i.e. doses that have been found effective in clinical trials
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7 218 with adults), increasing evidence suggests saturated (non-linear) pharmacokinetic behavior is
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9 219 observed in children receiving doses higher than 7 mg/kg BID. We found no predictable relationship
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11 220 between dose and C_{min} (Figure 1,2) and it remains unclear from current literature if such a
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13 221 relationship exists. Given the high maintenance doses in our study (median 23.1 mg/kg/day), this
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15 222 could explain the absence of a dose/concentration relationship. Another explanation could be found
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17 223 in the high intra-subject variability in voriconazole C_{min} both after IV and PO dosing (figure 1), which is
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19 224 consistent with other pediatric studies ^(12-14, 26).
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25 226 Due to the retrospective nature of this study, laboratory data on the majority of our patients was
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27 227 limited and often obtained only on the day of voriconazole TDM. In addition, markers for hepatic
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29 228 function were not always investigated in parallel. It was therefore not possible to draw any
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31 229 conclusions on the yet unclear relationship between voriconazole C_{min} and hepatotoxicity in pediatric
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33 230 patients. Because the focus of our study on the relationship between dose adjustments and target
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35 231 attainment, we did not monitor for voriconazole-related adverse events (e.g. neurological adverse
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37 232 events, phototoxic skin reactions and potentially proarrhythmic conditions) in relation to dose or
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39 233 exposure.
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45 235 Despite rapid dose adaptations after the first subtherapeutic C_{min} in our study (median of 2 days), a
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47 236 median of 15 days were required to obtain an adequate C_{min} , increasing the risk of inadequately
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49 237 treated fungal infections and unfavourable outcome. Of all dose adaptations following both sub –and
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51 238 suprathereapeutic C_{min} , only 45% resulted in a therapeutic C_{min} between 1-4 mg/L at the following
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53 239 concentration measurement. If we would stretch the therapeutic targets to 1-6 mg/L (assuming all
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55 240 C_{min} between 4-6 mg/L were acceptable based on adequate liver function tests), 56% of dose
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57 241 adaptations would result in target attainment.
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243 Dose adaptations were done by experts with expertise in the field of antifungal pharmacology but
244 without a nomogram. For purposes of personalized dosing, there is an urgent need to implement
245 advanced pharmacometric models with "clinician-proof" software, that can take into account all
246 important determinants for treatment response. Nowadays model-informed precision dosing (MIPD)
247 can be deployed as a technique to forecast dosing in the individual. Programs such as InsightRx,
248 DoseMe and Best Dose fulfil this need and are being tested in the clinic. To take advantage of this
249 approach, solid pharmacokinetic models must be available to be used in MIPD. Here we can still gain
250 knowledge for this specific drug and the current population as the unexplained inter-individual
251 variability in published models remains very large. Before implementation in routine patient
252 management these models must be prospectively validated to demonstrate its value. In addition the
253 software must comply to relevant legislation (for instance CE label in Europe) when deployed outside
254 of a research scope. Nevertheless this is the way forward taking advantage of a platform for
255 individualized treatment with visual feedback.

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257 Given the difficulty of target attainment despite dose adaptations, together with the prior observed
258 relationship between voriconazole exposure and efficacy and adverse events and the large inter -and
259 inpatient variability in children, this study underscores the indispensable need for voriconazole
260 TDM in severely immunocompromised pediatric patients early in the course of treatment with
261 multiple follow-up samples during therapy when aiming to optimize treatment outcomes.

263 Table 1. Baseline characteristics (n=21).

264

Demographics

Gender	
Male (n [%])	8 (38.1)
Female (n [%])	13 (61.9)
Median age at first VCZ ^a dose (yrs [range])	7.0 (1.2 – 18.5)
Age class (yrs)	
0 – <2 (n [%])	3 (14.3)
2 – <12 (n [%])	11 (52.4)
12 – 18 (n [%])	7 (33.3)
Race	
Caucasian (n [%])	18 (85.7)
Negroid (n [%])	2 (9.5)
Asian (n [%])	1 (4.8)
Median weight (kg [range])	21.9 (9.5 – 65)
Median BMI (kg/m ² [range])	17.7 (14 – 25.4)

Voriconazole therapy

Median days of VCZ ^a therapy (n [range])	118 (17-866)
Intravenous administrations (%)	12.5
Oral administrations (%)	87.5
Median total daily dose (mg [range])	400 (120-2400)
Median total daily dose per kg (mg/kg [range])	23.1 (6.1 – 109.6)
Patients on temporarily TID ^b dosing (n [%])	4 (19)
Median days of TID ^b dosing (n range)	60 (6 – 397)
Median total daily dose during TID dosing (mg/kg [range])	34.4 (13.6 – 109.6)
TID dosing administrations (% of total)	11.1

Therapeutic drug monitoring

Median days until first measurement of VCZ ^a C _{min} ^c (n [range])	3 (0 – 27)
Median plasma concentration of first C _{min} ^c (mg/L [IQR ^d])	3.1 (1.34 – 7.0)
Initial C _{min} adequate (% of all patients) ^e	11 (52.4)
Intravenous administration (%)	7 (63.6)
Oral administration (%)	4 (36.4)
Initial C _{min} below therapeutic range (% of all patients)	4 (19)
Intravenous administration (%)	3 (75)
Oral administration (%)	1 (25)
Initial C _{min} above therapeutic range (% of all patients)	6 (28.6)
Intravenous administration (%)	4 (66.7)
Oral administration (%)	2 (33.3)
Total C _{min}	485
<1 mg/L (n [%])	117 (24.1)
1 – 4 mg/L (n [%])	237 (48.9)
4 – 6 mg/L (n [%])	45 (9.3)
>6 mg/L (n [%])	86 (17.7)

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4 Median concentration of all C_{\min} (mg/L; range) 2.16 (0 – 28.0)
5

6 *Dose adaptations*

7 Dose adaptations (n [%]) 243 (50.1)
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9 Dose increases (total) 108

10 Dose increase at $C_{\min} < 1$ mg/L (n [%]) 55 (47)

11 Resulted in increase in C_{\min} 42 (76.4)

12 Resulted in C_{\min} 1 – 4 mg/L 33 (60)
13

14 Dose decrease (total) 135

15 Dose decrease at $C_{\min} > 6$ mg/L 45 (33.3)

16 Resulted in decrease in C_{\min} 36 (80.0)

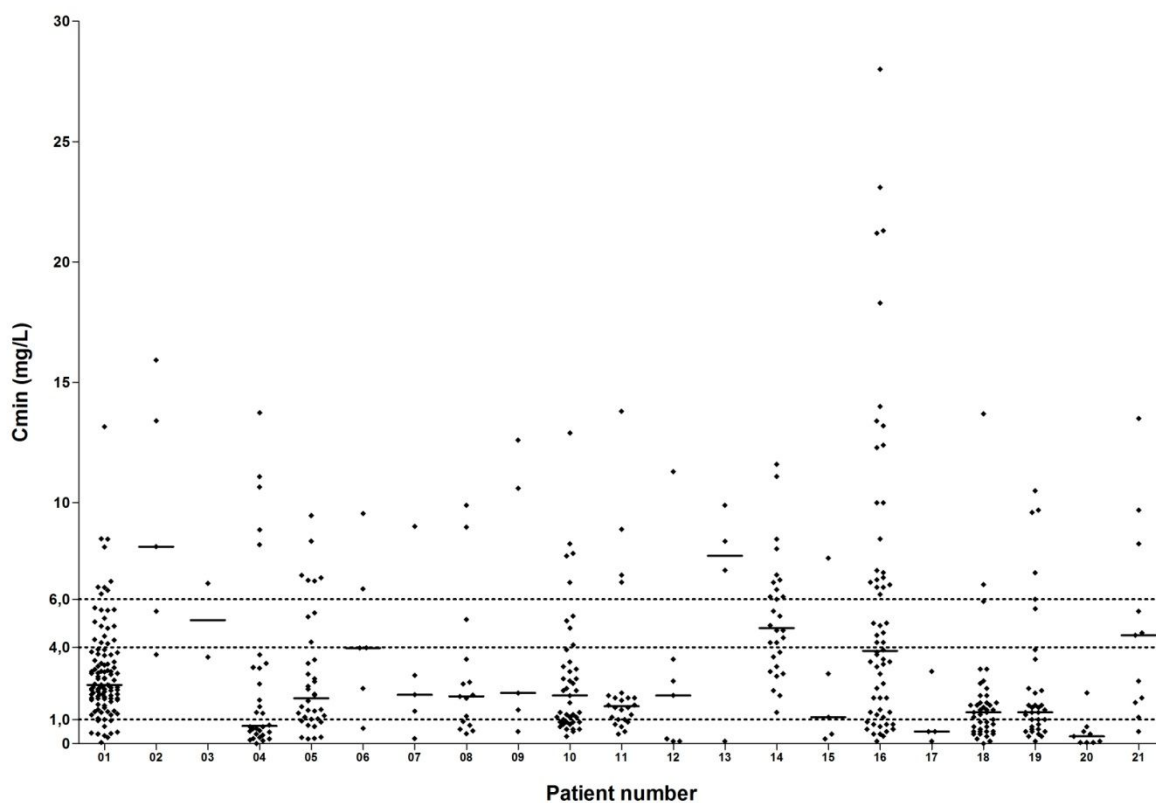
17 Resulted in $C_{\min} < 6$ mg/L 23 (51.1)

18 Resulted in C_{\min} 1 – 4 mg/L 12 (26.7)
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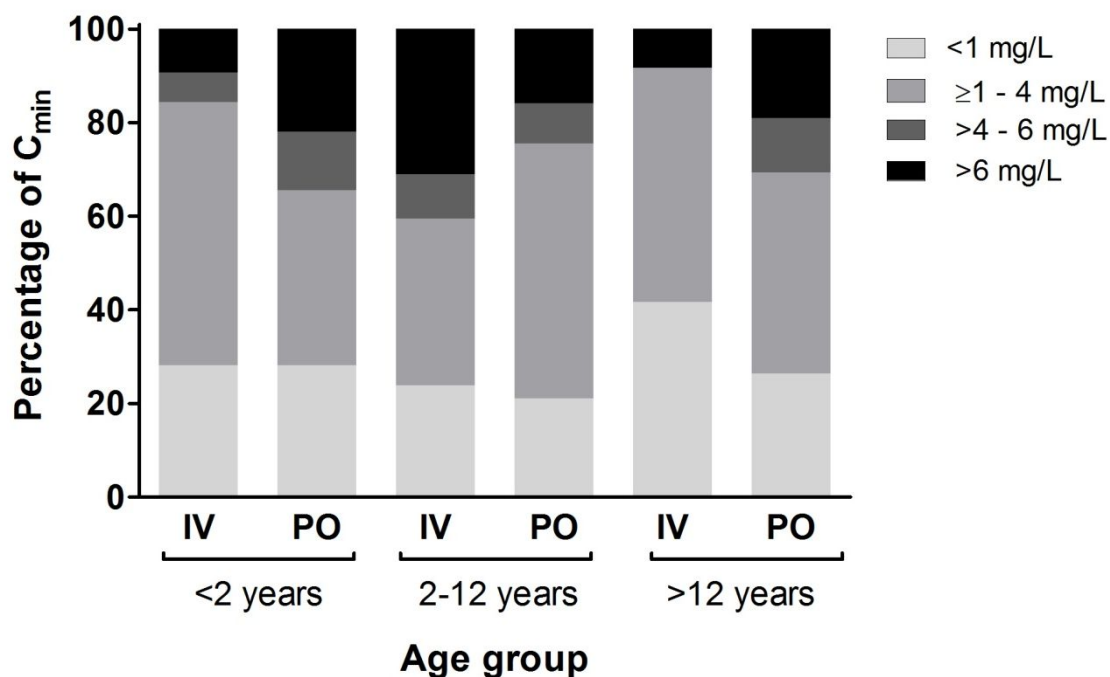
20 265
21 266 ^aVCZ = voriconazole, ^bTID = three times per day, ^c C_{\min} = trough concentration, ^dIQR = Interquartile range, ^eAdequate
22 267 therapeutic range of voriconazole C_{\min} is considered to be between 1 and 4 mg/L (1-6 if adequate liver function tests).
23 268 Subtherapeutic C_{\min} at < 1 mg/L, supratherapeutic C_{\min} at > 6 mg/L.
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270 Figure 1. Overview of all voriconazole trough concentrations at varying doses (n=485) in 21 patients

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274 Figure 2. Voriconazole C_{min} distribution (%) per formulation per age group

Age group	Formulation	C_{min} (% of total)			
		< 1 mg/L (n)	1 - 4 mg/L (n)	>4 - 6 mg/L (n)	> 6 mg/L (n)
< 2 years	IV	28.1 (9)	56.3 (18)	6.3 (2)	9.4 (3)
	PO	28.1 (9)	37.5 (12)	12.5 (4)	21.9 (7)
2-12 years	IV	23.8 (10)	35.7 (15)	9.5 (4)	31.0 (13)
	PO	21.1 (52)	54.5 (134)	8.5 (21)	15.9 (39)
>12 years	IV	41.7 (5)	50.0 (6)	0.0 (0)	8.3 (1)
	PO	26.3 (32)	43.0 (52)	11.6 (14)	19.0 (23)

Age group	Formulation	Median dose administered (mg/kg/day)			
		< 1 mg/L	1 - 4 mg/L	>4 - 6 mg/L	> 6 mg/L
< 2 years	IV	12.2	11.9	N/A	12.9
	PO	12.2	12.3	22.0	12.6
2-12 years	IV	17.1	24.5	15.7	57.9
	PO	24.0	25.9	22.9	28.2
>12 years	IV	10.0	11.1	N/A	N/A
	PO	18.4	15.7	11.0	10.4

C_{min} : trough concentration. IV: intravenous. PO: Oral.

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1 Impact of Dose Adaptations Following Voriconazole Therapeutic Drug 2 Monitoring in Pediatric Patients

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4 *Vincent J. Lempers¹, Edmé Meuwese², Annelies M. Mavinkurve-Groothuis³, Stefanie Henriët⁴,*
5 *Inge M van der Sluis^{3,5}, Lidwien M. Hanff³, Adilia Warris⁶, Birgit C.P. Koch², Roger J.*
6 *Brüggemann^{1,7*}*

7 8 9 Affiliations

10 ¹ Radboud university medical center, Department of Pharmacy and Radboud Institute for Health Sciences,
11 Nijmegen, The Netherlands

12 ² Erasmus Medical Center, Department of Pharmacy, Rotterdam, The Netherlands

13 ³ Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

14 ⁴ Radboud university medical center, Department of Pediatric Infectious Diseases & Immunology, Nijmegen,
15 The Netherlands

16 ⁵ Erasmus Medical Center-Sophia Children's Hospital, Department of Pediatric Haematology-Oncology,
17 Rotterdam, The Netherlands

18 ⁶ MRC Centre for Medical Mycology, Aberdeen Fungal Group, Institute of Medical Sciences, University of
19 Aberdeen, United Kingdom

20 ⁷ Center of Expertise in Mycology Radboudumc / CWZ, Nijmegen, The Netherlands

21
22 *Corresponding author

23 Dr. Roger JM Brüggemann

24 Department of Pharmacy 864

25 Radboud university medical center

26 Geert Grooteplein 10

27 6525 GA Nijmegen

28 The Netherlands

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3 34 Abstract (243/250 words)
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7 36 Voriconazole is the mainstay of treatment for invasive aspergillosis in immunocompromised pediatric
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9 37 patients. Although Therapeutic Drug Monitoring (TDM) of voriconazole is recommended, it remains
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11 38 unknown if TDM-based dose adaptations result in target attainment.
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14 39 Patients < 19 years from two pediatric hematologic-oncology wards were retrospectively identified
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16 40 based on unexplained high voriconazole trough concentrations ($C_{\min} > 6\text{mg/L}$). Patient demographics,
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18 41 clinical characteristics, treatment, voriconazole dosing information, voriconazole C_{\min} before and
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20 42 after adjustment based on TDM were obtained.
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23 43 Twenty-one patients, median (range) age 7.0 (1.2-18.5) years, were identified in two centres. First
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25 44 C_{\min} (3.1mg/L [0.1-13.5]) was obtained after 3 days (1-27) of treatment. The median of all C_{\min} (n=485,
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27 45 median 11 per patient) was 2.16mg/L (0.0 (undetectable)–28.0), with 24.1% of $C_{\min} < 1\text{mg/L}$, 48.9% 1-
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29 46 4mg/L, 9.3% 4-6mg/L and 17.7% $> 6\text{mg/L}$. Inpatient variability was large (94.1% for IV, 88.5% for
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31 47 PO). Dose increases at $C_{\min} < 1\text{ mg/L}$ resulted in an increased C_{\min} in 76.4%, with 60% between 1-4
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33 48 mg/L. Dose decreases at $C_{\min} > 6\text{ mg/L}$ resulted in a decreased C_{\min} in 80%, with 51% between 1-4
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35 49 mg/L. Overall in 45% of the cases (33 out of 55 and 12 out of 45) therapeutic targets were attained
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37 50 after dose adjustment.
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40 51 Fifty-five percent of initial C_{\min} was outside the therapeutic target of 1-4mg/L, with multiple dose
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42 52 adaptations required to achieve therapeutic concentrations. Only 60% and 51% of dose adaptations
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44 53 following sub- and supra-therapeutic C_{\min} , respectively, did result in target attainment. Intensive and
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46 54 continuous TDM of voriconazole is a prerequisite for ensuring adequate exposure in pediatric
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48 55 patients.
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3 58 Introduction
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8 60 Voriconazole is a broad-spectrum triazole antifungal agent which has emerged as the preferred
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10 61 treatment of invasive aspergillosis in both children (≥ 2 years of age) and adults ^(1, 2).
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12 62 Increased voriconazole exposure has been associated with improved treatment outcome in adults,
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14 63 with suggested provisional cut-off points for voriconazole trough plasma concentrations (C_{\min}) of 1-6
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16 64 mg/L (3-6). An exposure-response relationship was also established for pediatric patients, in which a
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18 65 voriconazole $C_{\min} > 1$ mg/L was associated with improved outcomes ⁽⁷⁻¹¹⁾. Based on the relationship
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20 66 between voriconazole exposure and efficacy and the high inter- and intra-patient variability in
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22 67 pediatric patients ⁽¹²⁻¹⁵⁾, the importance of voriconazole therapeutic drug monitoring (TDM) in
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24 68 pediatric patients has been acknowledged ^(1, 2, 16, 17). Although TDM-based dose adjustments are
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26 69 performed to optimize plasma concentrations, it remains unclear if these dose adaptations in
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28 70 pediatric patients correspond with target attainment.
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32 71 We conducted a retrospective analysis in a cohort of pediatric oncology patients (both leukemia as
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34 72 well as lymphoma) with difficult to manage voriconazole concentrations and assessed the result of
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36 73 TDM-based dose adaptations on target attainment.
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3 75 Materials and Methods
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7 77 *Study design and patients*
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10 78 This retrospective analysis was carried out in the pediatric hematology-oncology wards of two
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12 79 university hospitals in the Netherlands (Radboud university medical centre, Nijmegen and Sophia
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14 80 Children's Hospital, Erasmus Medical Center, Rotterdam). From August 2007–May 2014, the results
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16 81 from routinely performed TDM of voriconazole in both hospitalized and ambulant pediatric patients
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18 82 were evaluated. Patients < 19 years who received voriconazole orally (PO) or intravenously (IV) were
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20 83 included if more than one voriconazole C_{\min} was determined, of which at least one concentration was
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22 84 >6 mg/L during treatment. Due to the retrospective nature of the study, written informed consent
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24 85 was deemed not necessary.
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30 87 *Data collection*
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32 88 Data was collected from the patients' medical records and included patient demographics (e.g. age,
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34 89 gender, body weight), voriconazole treatment data (e.g. route of administration, treatment duration,
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36 90 total daily dose, dose adjustments) and TDM data (e.g. plasma trough concentrations [C_{\min}], number
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38 91 of samples per patient, number of sub- and supra-therapeutic C_{\min}). Concomitant medications with or
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40 92 without a known or suspected interaction with voriconazole exposure were reported.
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45 94 *Voriconazole dosing and dose adjustments*
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48 95 Initial dosing and administration of voriconazole was according to the Summary of Product
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50 96 Characteristics (SmPC) of voriconazole, but could be increased or decreased based on clinical
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52 97 indications and TDM results. End of treatment was defined by successful clinical response, or by
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54 98 discontinuation due to a lack of clinical response, or adverse events. Consistent with institution
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56 99 guidelines during the study period, adequate voriconazole exposure was defined as C_{\min} between 1-4
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58 100 mg/L. If the patient showed no signs of hepatotoxicity (*i.e.* liver function tests no more than three
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3 101 times the upper limit of normal), C_{\min} up to 6 mg/L were accepted. The 4 mg/L target concentration to
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5 102 prevent hepatotoxicity has been established in Asian patients particularly(18, 19). In Caucasian
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7 103 people this relation has not been established with a clear cut-off value. Rather an increase in drugs
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9 104 concentration, results in an increased chance of encountering hepatotoxicity(20). In case of
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11 105 sanctuary infection sites or disseminated disease, the lower threshold was set to 2 mg/L (*i.e.* 2-4
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13 106 mg/L or 2-6 mg/L). Target concentrations remain subject to debate but our target concentrations are
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15 107 in line with the recently published ESCMID guideline(2) and the ECIL guideline [available online via
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17 108 www.ecil-leukaemia.com]
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21 109 In case of a sub- or supra-therapeutic voriconazole C_{\min} (< 1 or > 6 mg/L), dose adjustments, assuming
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23 110 near-linear pharmacokinetics in children ⁽¹⁴⁾, to reach adequate C_{\min} were subsequently made. A
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25 111 follow-up sample within 1 week was recommended. Dosing frequency was initially two times daily,
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27 112 but could be increased to three times daily in an attempt to reach adequate voriconazole exposure.
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32 115 *Therapeutic Drug Monitoring*

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36 116 TDM was performed as standard of care, but frequency of sampling was dependent on individual
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38 117 decisions made for each patient. First TDM sample was recommended at steady state concentrations
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40 118 of the drug, which is at least two days after initiation of voriconazole therapy or following dose
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42 119 adaptations. Only blood samples withdrawn within a 1 hour period prior to the next dose were
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44 120 included in the analysis to ascertain a trough concentration. Decisions on dose adaptations were
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46 121 made by experts in the field with knowledge on PK of voriconazole taking in mind the clinical
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48 122 condition of the patient.
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51 124 *Analytical assay*

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3 125 Voriconazole plasma concentrations were measured twice weekly using an in-house, validated ultra-
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5 126 performance liquid chromatography (HPLC) method with either a fluorescence or MSMS detection
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7 127 method (Waters).
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12 129 *Data analysis*

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14 130 A Spearman rank-order correlation was run to determine the relationship between voriconazole dose
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16 131 and C_{\min} using SPSS 20.0 (SPSS inc., IL, USA). A p-value of <0.05 was considered statistically significant.
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18 132 Intra-patient variability of voriconazole C_{\min} was analyzed in patients who had at least three
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21 133 voriconazole C_{\min} at similar doses and formulations.
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135 RESULTS

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137 *Patients*

138 Twenty-one patients (8 male, 13 female) were eligible for analysis. Median (range) age at first dose
139 was 7.0 years (1.2–18.5 years), of which 3 patients (14.3%) were <2 years, 11 (52.4%) between 2 and
140 12 years, and 7 (33.3%) between 12 and 19 years. Median (range) weight and BMI were 21.9 kg (9.5–
141 65) and 17.7 kg/m² (14–25.4), respectively (Table 1).

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143 *Voriconazole therapy*

144 Patients received voriconazole therapy for a median (range) of 118 days (17–866; Table 1). The
145 median total daily dose per kg (range) was 23.1 mg/kg (6.1–109.6). Initial voriconazole administration
146 was IV in 15 (71.4%) and PO in 6 (28.6%) of patients. Five patients received voriconazole orally only, 2
147 only IV, and 14 received a combination of both. In four patients voriconazole was given TID at some
148 time as part of their management strategy for a median (range) of 60 days (6–397) with a median
149 total daily dose of 34.4 mg/kg (13.6–109.6). Median intra-individual variability of voriconazole dose
150 was 94.1% during IV therapy (dose range: 12.2–16.0 mg/kg/day) and 88.5% during PO therapy (dose
151 range: 10.5–44.1 mg/kg/day).

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153 *Therapeutic drug monitoring – initial C_{min}*

154 The first measurement of voriconazole C_{min} was performed at a median (range) of 3 days (1–27) after
155 start of treatment, with a median (IQR) C_{min} of 3.1 mg/L (1.34–7.0; Table 1). Upon first measurement,
156 11 out of 21 (52.4%) patients reached a C_{min} between 1–6 mg/L (7 of these patients received
157 voriconazole IV, 4 PO). Of the remaining 10 patients who had a voriconazole concentration <1 mg/L
158 or >6 mg/L at first measurement, 5 out of 9 patients (55.5%) required only 1 dose adaptation to
159 achieve a C_{min} between 1–6 mg/L. Target concentrations in these 9 patients were attained after a
160 median (range) of 15 days (8–123). One patient was unable to achieve target values during the entire

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3 161 length of voriconazole therapy despite TDM-based dose adaptations. After the first suboptimal C_{min} ,
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5 162 TDM-based dose adaptations were performed within a median of 2 days. A very weak positive
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7 163 correlation between voriconazole dose and initial C_{min} was calculated, which was not statistically
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10 164 significant ($r^2=0.05$, $p=0.82$).

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14 166 *Therapeutic drug monitoring – all C_{min}*

16 167 In total, 485 samples were obtained with a median (range) concentration of 2.16 mg/L (undetectable
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18 -28; Table 1). Four concentrations (0.8%) were reported as below the lower limit of quantification. A
19 168 median (range) of 11 samples (2-109) were drawn per patient, of which 117 (24.1%) were <1 mg/L,
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21 169 237 (48.9%) between 1-4 mg/L, 45 (9.3%) between 4-6 mg/L and 86 (17.7%) >6 mg/L. An overview of
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23 170 all C_{min} per patient is shown in Figure 1. There was no significant correlation between voriconazole
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25 171 dose and all C_{min} , ($r_s(485)=0.02$, $p=0.59$). A C_{min} <1 mg/L was most frequently encountered in patients
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27 172 >12 years receiving voriconazole IV, whereas patients 2-12 years suffered most frequently from C_{min}
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29 173 >6 mg/L (Figure 2).

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36 176 *Voriconazole dose adaptations*

38 177 A total of 108 dose increases and 135 dose decreases were made, of which 50.9% when C_{min} < 1,
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40 178 and 33.3% C_{min} > 6 (see table 1). Out of a 117 cases with a C_{min} <1mg/L prompted a dose increase in
41
42 179 47.0% (n=55) of occurrences, which resulted in an increased C_{min} at follow-up sampling in 76.4%
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44 180 (n=42) of cases. In 60% (n=33) of dose increases following a concentration of <1 mg/L, this led to a
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46 181 therapeutic C_{min} between 1–4 mg/L (median 1.7 mg/L). In these 33 cases, the total daily dose was
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48 182 increased from a median of 18.3 mg/kg/day to 22.7 mg/kg/day (24.0%).

50 183 Out of 86 cases with a C_{min} of >6 mg/L (median 8.29 mg/L) this prompted a dose decrease in 52.3%
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52 184 (n=45) of cases, of which 80.0% (n=36) resulted in a subsequent lower C_{min} at follow-up sampling.
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54 185 These dose decreases resulted in a C_{min} of <6mg/L in 51.1% (n=23) of cases and even led to
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3 186 concentrations between 1-4 mg/L (median 2.3 mg/L) in 26.7% (n=12). In these 12 cases, the total
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5 187 daily dose was decreased from a median of 23.5 mg/kg/day to 16.8 mg/kg/day (39.9%).
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190 Discussion

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192 Here, we present our experience with voriconazole TDM in a cohort of 21 pediatric patients with
193 difficult to control voriconazole C_{min} , characterized by at least one $C_{min} >6$ mg/L, enabling us to assess
194 the result of TDM-based dose adaptations on voriconazole target attainment.

195 Overall, 18.5 % of all doses adjustments made, based on TDM, resulted in target concentrations (1-4
196 mg/L). The vast majority (95.2%) of the patients in our study were able to achieve at least one
197 therapeutic concentration (1-4 mg/L) after TDM-based dose adjustments. This is in a similar range of
198 the reported value of 80% in a study from Bartelink *et al.*, although voriconazole target values of 1-5
199 mg/L were used in this study ⁽²¹⁾.

200 Of the total number of 485 voriconazole C_{min} , 24.1% was <1 mg/L, which is correlated with increased
201 likelihood of treatment failure in children ⁽⁷⁻⁹⁾. In case of such a subtherapeutic C_{min} , voriconazole
202 dose was increased in 47.0% of cases. Accordingly, 60% of dose increases resulted in the desired
203 therapeutic C_{min} of 1-4 mg/L, with a median dose increase from 18.3 mg/kg/day to 22.7 mg/kg/day.
204 Previous studies have reported that dose adjustments to median doses of 20–40 mg/kg/day were
205 required to obtain therapeutic plasma concentrations of >1 mg/L ^(9, 10, 22). In addition, 17.7% of the
206 total number of voriconazole C_{min} were >6 mg/L, which is regarded as a cut-off concentration for
207 hepatotoxicity in adults (23), although no clear correlation is seen in pediatric patients ^(7, 24, 25). At
208 these supratherapeutic concentrations, voriconazole dose was lowered in 52.3% of cases, resulting in
209 a C_{min} between the target range of 1-4 mg/L in 26.7% of cases (decreasing the median dose from 23.5
210 mg/kg/day to 16.8 mg/kg/day).

211 Age is one of the most important factors influencing voriconazole plasma exposure, as voriconazole
212 clearance has been shown to be much higher in children under the age of 12, and oral bioavailability
213 of voriconazole is lower in children (65%), compared to adults (96%) ^(14, 26). As a result, several studies
214 reported similar voriconazole exposure in children (<12 years) compared to adults with IV doses of 7-
215 9 mg/kg BID ^(13, 14, 26). This prompted higher dosing regimens in children compared to adults. Although

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3 216 voriconazole has been reported to display near-linear pharmacokinetics in children receiving multiple
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5 217 doses of 3 mg/kg and 4 mg/kg BID IV⁽¹⁵⁾ (i.e. doses that have been found effective in clinical trials
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7 218 with adults), increasing evidence suggests saturated (non-linear) pharmacokinetic behavior is
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9 219 observed in children receiving doses higher than 7 mg/kg BID. We found no predictable relationship
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11 220 between dose and C_{min} (Figure 1,2) and it remains unclear from current literature if such a
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13 221 relationship exists. Given the high maintenance doses in our study (median 23.1 mg/kg/day), this
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15 222 could explain the absence of a dose/concentration relationship. Another explanation could be found
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17 223 in the high intra-subject variability in voriconazole C_{min} both after IV and PO dosing (figure 1), which is
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19 224 consistent with other pediatric studies ^(12-14, 26).
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25 226 Due to the retrospective nature of this study, laboratory data on the majority of our patients was
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27 227 limited and often obtained only on the day of voriconazole TDM. In addition, markers for hepatic
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29 228 function were not always investigated in parallel. It was therefore not possible to draw any
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31 229 conclusions on the yet unclear relationship between voriconazole C_{min} and hepatotoxicity in pediatric
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33 230 patients. Because the focus of our study on the relationship between dose adjustments and target
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35 231 attainment, we did not monitor for voriconazole-related adverse events (e.g. neurological adverse
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37 232 events, phototoxic skin reactions and potentially proarrhythmic conditions) in relation to dose or
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39 233 exposure.
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45 235 Despite rapid dose adaptations after the first subtherapeutic C_{min} in our study (median of 2 days), a
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47 236 median of 15 days were required to obtain an adequate C_{min} , increasing the risk of inadequately
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49 237 treated fungal infections and unfavourable outcome. Of all dose adaptations following both sub –and
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51 238 suprathereapeutic C_{min} , only 45% resulted in a therapeutic C_{min} between 1-4 mg/L at the following
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53 239 concentration measurement. If we would stretch the therapeutic targets to 1-6 mg/L (assuming all
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55 240 C_{min} between 4-6 mg/L were acceptable based on adequate liver function tests), 56% of dose
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57 241 adaptations would result in target attainment.
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5 243 Dose adaptations were done by experts with expertise in the field of antifungal pharmacology but
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7 244 without a nomogram. For purposes of personalized dosing, there is an urgent need to implement
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9 245 advanced pharmacometric models with "clinician-proof" software, that can take into account all
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11 246 important determinants for treatment response. Nowadays model-informed precision dosing (MIPD)
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13 247 can be deployed as a technique to forecast dosing in the individual. Programs such as InsightRx,
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15 248 DoseMe and Best Dose fulfil this need and are being tested in the clinic. To take advantage of this
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17 249 approach, solid pharmacokinetic models must be available to be used in MIPD. Here we can still gain
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19 250 knowledge for this specific drug and the current population as the unexplained inter-individual
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21 251 variability in published models remains very large. Before implementation in routine patient
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23 252 management these models must be prospectively validated to demonstrate its value. In addition the
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25 253 software must comply to relevant legislation (for instance CE label in Europe) when deployed outside
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27 254 of a research scope. Nevertheless this is the way forward taking advantage of a platform for
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29 255 individualized treatment with visual feedback.
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34 257 Given the difficulty of target attainment despite dose adaptations, together with the prior observed
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36 258 relationship between voriconazole exposure and efficacy and adverse events and the large inter -and
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38 259 inpatient variability in children, this study underscores the indispensable need for voriconazole
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40 260 TDM in severely immunocompromised pediatric patients early in the course of treatment with
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43 261 multiple follow-up samples during therapy when aiming to optimize treatment outcomes.
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263 Table 1. Baseline characteristics (n=21).

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Demographics

Gender	
Male (n [%])	8 (38.1)
Female (n [%])	13 (61.9)
Median age at first VCZ ^a dose (yrs [range])	7.0 (1.2 – 18.5)
Age class (yrs)	
0 – <2 (n [%])	3 (14.3)
2 – <12 (n [%])	11 (52.4)
12 – 18 (n [%])	7 (33.3)
Race	
Caucasian (n [%])	18 (85.7)
Negroid (n [%])	2 (9.5)
Asian (n [%])	1 (4.8)
Median weight (kg [range])	21.9 (9.5 – 65)
Median BMI (kg/m ² [range])	17.7 (14 – 25.4)

Voriconazole therapy

Median days of VCZ ^a therapy (n [range])	118 (17-866)
Intravenous administrations (%)	12.5
Oral administrations (%)	87.5
Median total daily dose (mg [range])	400 (120-2400)
Median total daily dose per kg (mg/kg [range])	23.1 (6.1 – 109.6)
Patients on temporarily TID ^b dosing (n [%])	4 (19)
Median days of TID ^b dosing (n range)	60 (6 – 397)
Median total daily dose during TID dosing (mg/kg [range])	34.4 (13.6 – 109.6)
TID dosing administrations (% of total)	11.1

Therapeutic drug monitoring

Median days until first measurement of VCZ ^a C _{min} ^c (n [range])	3 (0 – 27)
Median plasma concentration of first C _{min} ^c (mg/L [IQR ^d])	3.1 (1.34 – 7.0)
Initial C _{min} adequate (% of all patients) ^e	11 (52.4)
Intravenous administration (%)	7 (63.6)
Oral administration (%)	4 (36.4)
Initial C _{min} below therapeutic range (% of all patients)	4 (19)
Intravenous administration (%)	3 (75)
Oral administration (%)	1 (25)
Initial C _{min} above therapeutic range (% of all patients)	6 (28.6)
Intravenous administration (%)	4 (66.7)
Oral administration (%)	2 (33.3)
Total C _{min}	485
<1 mg/L (n [%])	117 (24.1)
1 – 4 mg/L (n [%])	237 (48.9)
4 – 6 mg/L (n [%])	45 (9.3)
>6 mg/L (n [%])	86 (17.7)

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4 Median concentration of all C_{\min} (mg/L; range) 2.16 (0 – 28.0)

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6 *Dose adaptations*

7 Dose adaptations (n [%]) 243 (50.1)

8 Dose increases (total) 108

9 Dose increase at $C_{\min} < 1$ mg/L (n [%]) 55 (47)

10 Resulted in increase in C_{\min} 42 (76.4)

11 Resulted in C_{\min} 1 – 4 mg/L 33 (60)

12 Dose decrease (total) 135

13 Dose decrease at $C_{\min} > 6$ mg/L 45 (33.3)

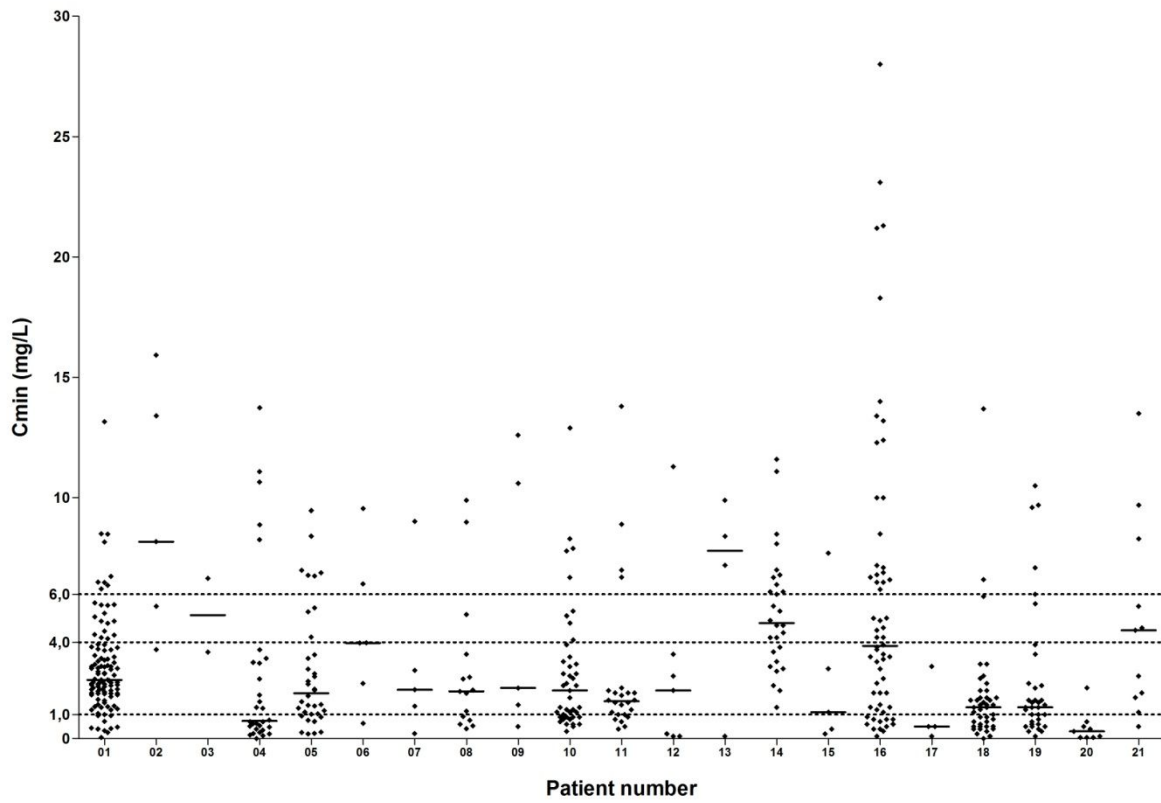
14 Resulted in decrease in C_{\min} 36 (80.0)

15 Resulted in $C_{\min} < 6$ mg/L 23 (51.1)

16 Resulted in C_{\min} 1 – 4 mg/L 12 (26.7)

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20 266 ^aVCZ = voriconazole, ^bTID = three times per day, ^c C_{\min} = trough concentration, ^dIQR = Interquartile range, ^eAdequate
21 267 therapeutic range of voriconazole C_{\min} is considered to be between 1 and 4 mg/L (1-6 if adequate liver function tests).
22 268 Subtherapeutic C_{\min} at < 1 mg/L, suprathereapeutic C_{\min} at > 6 mg/L.

270 Figure 1. Overview of all voriconazole trough concentrations at varying doses (n=485) in 21 patients
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274 Figure 2. Voriconazole C_{min} distribution (%) per formulation per age group

Age group	Formulation	C_{min} (% of total)			
		< 1 mg/L (n)	1 - 4 mg/L (n)	>4 - 6 mg/L (n)	> 6 mg/L (n)
< 2 years	IV	28.1 (9)	56.3 (18)	6.3 (2)	9.4 (3)
	PO	28.1 (9)	37.5 (12)	12.5 (4)	21.9 (7)
2-12 years	IV	23.8 (10)	35.7 (15)	9.5 (4)	31.0 (13)
	PO	21.1 (52)	54.5 (134)	8.5 (21)	15.9 (39)
>12 years	IV	41.7 (5)	50.0 (6)	0.0 (0)	8.3 (1)
	PO	26.3 (32)	43.0 (52)	11.6 (14)	19.0 (23)

Age group	Formulation	Median dose administered (mg/kg/day)			
		< 1 mg/L	1 - 4 mg/L	>4 - 6 mg/L	> 6 mg/L
< 2 years	IV	12.2	11.9	N/A	12.9
	PO	12.2	12.3	22.0	12.6
2-12 years	IV	17.1	24.5	15.7	57.9
	PO	24.0	25.9	22.9	28.2
>12 years	IV	10.0	11.1	N/A	N/A
	PO	18.4	15.7	11.0	10.4

C_{min} : trough concentration. IV: intravenous. PO: Oral.

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39 393 Sciences, Merck Sharp & Dohme Corp., and Pfizer, Inc., and has received unrestricted and research
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41 394 grants from Astellas Pharma, Inc., Gilead Sciences, Merck Sharp & Dohme Corp., and
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44 395 Pfizer, Inc. All contracts were through Radboudumc, and all payments were invoiced by
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46 396 Radboudumc.
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