Pharmacokinetics Modeling and Simulation of Voriconazole Dosing and Safety in Patients with Liver Cirrhosis

Taotao Wang¹, Miao Yan², Dan Tang^{2,3}, Yuzhu Dong¹, Li Zhu⁴, Qian Du¹, Dan Sun¹,
Jianfeng Xing⁵, Yalin Dong^{1*}

¹ Department of Pharmacy, The First Affiliated Hospital of Xi'an Jiaotong University,
Xi'an 710061, China.

² Department of Pharmacy, the Second Xiangya Hospital, Central South University,
Changsha 410008, China

³ School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University,
Nanjing 210009, China

⁴ Department of infectious disease, The First Affiliated Hospital of Xi'an Jiaotong
University, Xi'an 710061, China.

⁵ School of Pharmacy, Xi'an Jiaotong University, Xi'an 710061, China.

Running title: Voriconazole doses in cirrhotic patients

***Corresponding author: Yalin Dong, Ph.D.**

Department of Pharmacy, The First Affiliated Hospital of Xi'an Jiaotong University,
Xi'an 710061, China.

Phone : +86-29-85323241; Fax: +86-29-85323240

E-mail : dongyalin@mail.xjtu.edu.cn

26 **Abstract**

27 Voriconazole is used to treat invasive fungal disease and the optimal dose regimens
 28 are still unknown in cirrhotic Patients. The aim of this study was to determine the
 29 safety, to describe pharmacokinetics characteristics, and to optimize dosage regimens
 30 of voriconazole in cirrhotic patients. Data pertaining to voriconazole were collected
 31 retrospectively and analyzed using a population pharmacokinetics model. A total of
 32 219 trough concentrations (C_{min}) from 120 patients were analyzed.
 33 Voriconazole-related adverse events developed in 29 patients, with 69.0% of AEs
 34 developing within the first week after voriconazole treatment. The threshold C_{min} for
 35 AEs was 5.12 mg/L. A one-compartment model with first-order absorption and
 36 elimination adequately described the data. The Child-Pugh class was the only
 37 covariate in final model. Voriconazole clearance in patients with Child-pugh A and B
 38 cirrhosis (CP-A/CP-B) and Child-pugh C cirrhosis (CP-C) were 1.79 L/h and 0.99 L/h,
 39 respectively, the volume of distribution was 159.6 L, and the oral bioavailability was
 40 91.8%. The elimination half-life was significantly extended for up to 61.8 - 111.7 h in
 41 cirrhotic patients. Model-based simulations showed that the appropriate maintenance
 42 doses are 75 mg/12 h and 150 mg/24 h intravenously or orally for CP-A/CP-B
 43 patients, and 50 mg/12 h and 100 mg/24 h intravenously or orally for CP-C patients.
 44 The results support voriconazole maintenance doses in LC patients should be reduced
 45 to one-fourth for CP-C patients and to one-third for CP-A/CP-B patients compared to
 46 that for patients with normal liver function. Monitoring C_{min} early could be a useful
 47 strategy to ensure the safety.

48 **Key words:** Voriconazole; Liver cirrhosis; Population Pharmacokinetics; Invasive
 49 fungal disease; Therapeutic drug monitoring; Adverse events;

50 1. Introduction

51 Liver cirrhosis is a late stage of hepatic fibrosis and is a leading cause of death
52 worldwide (1). Due to the immunocompromised state of cirrhotic patients and their
53 requirement for use of steroids and broad-spectrum antimicrobial agents, as well as
54 invasive procedures, invasive fungal disease (IFD) constitutes an important cause of
55 morbidity in patients with liver cirrhosis (2-4). Voriconazole is a triazole antifungal
56 agent with activity against a broad spectrum of clinically significant fungal pathogens,
57 and it is used to treat and prevent IFD in clinical practice (5, 6).
58 Voriconazole is metabolized primarily by the *CYP2C19* isoenzyme while *CYP2C9*
59 and *CYP3A4* contribute to a minor extent, and the large inter- and intra-individual
60 variabilities of voriconazole pharmacokinetics are associated with *CYP2C19* genetic
61 polymorphisms, liver dysfunction, drug-drug interaction and food intake (7-9). The
62 voriconazole trough concentration (C_{min}) is associated with treatment efficacy and
63 safety (10, 11), and voriconazole C_{min} ranging from 1 - 5 mg/L was identified as the
64 therapeutic target with appropriate clinical efficacy and safety (12). However, the
65 reduced hepatic blood flow and enzyme activity in patients with liver cirrhosis can
66 theoretically lead to voriconazole accumulation and make patients at risk of adverse
67 events (AEs). Therefore, the voriconazole package insert recommends that while the
68 standard loading dose regimens should be used, the maintenance dose should be
69 halved in patients with Child-pugh A and B cirrhosis (CP-A/CP-B) (13). However,
70 there is no recommended voriconazole regimen for patients with Child-pugh C

71 cirrhosis (CP-C). Meanwhile, our previous study demonstrated that the halved dose
72 still leads to a supratherapeutic level in the majority of cirrhotic patients, with a
73 voriconazole $C_{\min}$ of 4.02 ± 2.00 mg/L (14, 15).

74 The present study aimed (1) to describe the pharmacokinetics characteristics and
75 safety of voriconazole, and identify the factors influencing pharmacokinetics
76 variability; and (2) to establish the optimal intravenous and oral voriconazole doses
77 with an appropriate efficacy and safety profile in patients with liver cirrhosis.

78

79 **2. Results**

80 **2.1 Patient characteristics**

81 The demographic and clinical characteristics of the study population are presented in
82 Table 1. The distributions of the initial voriconazole $C_{\min}$, as sampled before dosage
83 adjustment, in relation to the different dosage regimens are shown in Figure 1. There
84 were 40 CP-A/CP-B patients and 80 CP-C patients. Voriconazole $C_{\min}$ was measured
85 in 219 samples (median of 1 per patient; range 1 - 7), and the median sampling time
86 was 6 days (range 3 - 37 days) after the first dose. The initial voriconazole $C_{\min}$ was
87 measured at a median time of 5 days (range, 3 - 27 days) after voriconazole was
88 administered.

89 **2.2 Voriconazole $C_{\min}$ and adverse events**

90 Voriconazole-related AEs appeared in 29 (24.2%) patients. The most common AEs
91 were neurotoxicity, visual disturbances and hallucination. The median voriconazole

92 $C_{\min}$ in patients with AEs was 5.98 mg/L (range, 2.37 - 15.10 mg/L), and the median
 93 time from voriconazole treatment initiation to the development of AEs was 6 days
 94 (range, 2 - 15 days) (Table 2). Additionally, 69.0% (20/29) of voriconazole-related
 95 AEs developed within the first week after voriconazole treatment. The voriconazole
 96 $C_{\min}$ at the time of AEs emerging differed significantly from the initial $C_{\min}$ among
 97 patients without AEs (median 5.98 mg/L vs 4.76 mg/L, $P = 0.045$). The CART
 98 analysis showed that voriconazole-related AEs were more likely to occur in patients
 99 with $C_{\min} > 5.12$ mg/L ($P = 0.014$). The incidence rates of AEs for patients achieving
 100 $C_{\min}$ values of >5.12 mg/L and ≤ 5.12 mg/L were 32.8% and 16.1%, respectively.

101 **2.3 Population pharmacokinetics analysis**

102 When each covariate was tested separately, the Child-Pugh class, total bilirubin
 103 (TBIL), Child-Pugh score, international normalized ratio (INR), MELD score,
 104 gamma-glutamyl transferase (GGT), aspartate transaminase (AST), alkaline
 105 phosphatase (ALP), platelet (PLT), age, and alanine transaminase (ALT) showed
 106 significant impacts on the CL of voriconazole. The type of cirrhosis, body weight and
 107 CYP inducer or inhibitor did not significantly influence voriconazole parameters in
 108 this population. The incorporation of the Child-Pugh class as a covariate in the basic
 109 model on CL resulted in a significant reduction in OFV ($\Delta\text{OFV} = 28.1$). The
 110 Child-Pugh class was the only significant covariate in the final PPK model. The
 111 parameters of final PPK model and bootstrap results are summarized in Table 3, and
 112 most of the parameters in the final model were reliably estimated and with relatively

113 small RSEs. The model was associated with the variability of CL decreasing from
 114 67.2% to 59.2%. The typical value and variability of CL in CP-A/CP-B and CP-C
 115 patients were calculated using an IF-THEN coding structure in the control model. The
 116 estimated typical values of CL for CP-A/CP-B and CP-C patients were 1.79 L/h and
 117 0.99 L/h, respectively, and the corresponding average elimination $t_{1/2}$ values were 61.8
 118 h and 111.7 h.

119 The goodness-of-fit plots of models are shown in Figure 2. The final model described
 120 the data very well, where observed concentrations were close to the population and
 121 individual model-based predictions. The bootstrap analysis showed that for the final
 122 model, 786 out of 1000 runs converged successfully. The mean values and 95%
 123 confidence interval (CI) of parameters from bootstrap results are presented in Table 3.
 124 The parameters of the final PPK model were close to the mean bootstrap values and
 125 all included in the 95% CI. The VPC showed that most of the observed data were fell
 126 within the 90% prediction interval (Figure S1).

127 **3.4 Simulations**

128 The lack of effect of weight on voriconazole pharmacokinetics parameters does not
 129 support weight-adjusted dosing in patients with liver cirrhosis. Figure 3 and Figure S2
 130 show the simulated concentration–time profiles between 0 h and 420 h calculated for
 131 the different dosage regimens. The probabilities of simulated voriconazole $C_{\min}$ values
 132 of <1 mg/L, 1–5 mg/L, and >5 mg/L with different oral and intravenous regimens in
 133 liver cirrhotic patients are presented in Table 4 and Table S1. The results of the

134 simulations showed that the halved dose in CP-A/CP-B and CP-C patients could lead
135 to a majority of cases for $C_{\min}$ over the supratherapeutic target (5 mg/L). Regarding
136 the $C_{\min}$ target for efficacy and safety, the results of the simulations suggested that
137 maintenance dosage regimens of 75 mg/12 h and 150 mg/24 h intravenously or orally
138 for CP-A/CP-B patients, and of 50 mg/12 h and 100 mg/24 h intravenously or orally
139 for CP-C patients are appropriate, since the predicted probability of achieving the
140 therapeutic target concentration in the steady state was 59.0% - 68.2% for these
141 optimal regimens in patients with liver cirrhosis.

142

143 **3. Discussion**

144 The rationality of halving the voriconazole dose in CP-A/CP-B patients has not been
145 validated widely in clinical practice, and the optimal dose in CP-C patients remains to
146 be established. The present study used a PPK analysis to identify the potential source
147 of pharmacokinetics variability and to optimize the dosage regimens in patients with
148 liver cirrhosis.

149 To our knowledge, this is the first time that voriconazole PPK properties have been
150 characterized in patients with liver cirrhosis. In the present study, single- or
151 multiple-trough samples were collected from patients. These features restricted the
152 ability to estimate k_a and V_d accurately, which may have an impact on the simulated
153 peak concentration of voriconazole. In the process of constructing the basic model,
154 the OFV value of the model was 532.6 and 535.5, respectively, when k_a was fixed to a

155 value of 0.5 h^{-1} (16) or 1.1 h^{-1} (17), as reported elsewhere. However, we found that the
 156 variabilities of k_a and F were very small when the NONMEM software was used to
 157 calculated k_a instead of giving a fixed value, and a OFV value of 508.6 was observed
 158 in the process. Thus, the basic model in this study did not include k_a and F variability,
 159 and a k_a value of 0.25 h^{-1} was calculated, which is similar to previously reported
 160 values (0.53 h^{-1} to 1.1 h^{-1}) (16-18). Actually, delayed gastric emptying in cirrhotic
 161 patients could delay the absorption of drugs by the small intestine (19). The estimated
 162 bioavailability of voriconazole in this study was 91.8%, which was slightly higher
 163 than previously reported values for adult patients (63.0% - 89.5%) (17, 18, 20, 21).
 164 Theoretically, the reduced liver blood flow and enzyme activity in cirrhotic patients
 165 can substantially reduce the first-pass effect, which results in greater systemic
 166 availability (22).

167 Like the Child-Pugh class, the nine potential covariates (TBIL, Child-Pugh score, INR,
 168 MELD score, GGT, AST, ALP, PLT, and ALT) are also indicators of liver function,
 169 and so these nine covariates and the Child-Pugh class were not incorporated in a
 170 model simultaneously. Additionally, the simultaneous addition of Child-Pugh class
 171 and age did not lead to a further significant decrease in OFV. Thus, the Child-Pugh
 172 class was found to influence voriconazole CL and was the only covariate included in
 173 the final model. As the samples were trough values, the CL can be accurately
 174 estimated using PPK method. The estimated typical values of CL for CP-A/CP-B and
 175 CP-C patients were 1.79 L/h and 0.99 L/h , respectively, which suggest that different

dosing regimens need to be administered depending on the Child-Pugh class. The calculated CL in cirrhotic patients is much lower than that in patients with normal liver function (17, 21). Actually, the Child-Pugh class is the most-common method used to classify liver impairment and to adjust the dose of drugs in patients with liver cirrhosis (23, 24), which mainly due to liver disease being clearly associated with reduced liver blood flow and enzyme activity (22). The elimination $t_{1/2}$ value of voriconazole is significantly prolonged in patients with liver cirrhosis, and so we believe that it is sufficient to administer voriconazole once daily in cirrhotic patients. The final PPK model appeared to describe the data very well and to be reliably validated, making it adequate for further dosing simulations. The results of the simulations showed that 32.5 - 36.7% and 60.7 - 66.2% of CP-A/CP-B and CP-C patients, respectively, had a $C_{\min}$ exceeding the supratherapeutic target on at day 14 after they had received the halved dose (Table 4 and Table S1). Thus, the halved dose may be inappropriate in cirrhotic patients for an amount of supratherapeutic voriconazole $C_{\min}$ emerged. For CP-C patients, only Yamada *et al.* (25). has provided an optimal voriconazole maintenance dose in CP-C patients; those authors used clinical data from six CP-C patients and concluded that the oral voriconazole maintenance doses should be reduced to one-third of the normal dose. However, the results obtained in the present model-based simulations indicate that voriconazole maintenance doses in cirrhotic patients should be reduced to one-fourth for CP-C patients and to one-third for CP-A/CP-B patients compared to that for patients with

197 normal liver function. These optimal dosage regimens could ensure that >60% of
 198 patients will achieve a $C_{\min}$ within the therapeutic target. Notably, TDM was also
 199 necessary in patients who received the optimal dosage regimens, since 20 - 30% of
 200 them exhibited $C_{\min}$ values that exceeded the supratherapeutic target. Furthermore,
 201 further clinical studies are needed to investigate the safety and efficacy of these
 202 optimal dosage regimens in adequate numbers of cirrhotic patients.

203 This study found a clear association between voriconazole $C_{\min}$ and AEs, and that the
 204 threshold $C_{\min}$ for identifying patients with a higher risk of AEs was 5.12 mg/L, which
 205 is similar to the supratherapeutic target of voriconazole treatment recommended by
 206 the guideline from the British Society for Medical Mycology (12). The rate of AEs
 207 was higher in this study than previously reported in liver transplant patients (26). A
 208 particularly interesting finding was that 69.0% (20/29) of cases of
 209 voriconazole-related AEs developed within the first week after voriconazole treatment,
 210 and that the elimination $t_{1/2}$ was prolonged, which suggested that implementing
 211 accurate initial dose or plasma concentration monitoring as early as possible could
 212 avoid the occurrence of AEs.

213 This study was subject to some limitations. First, it couldn't evaluate the
 214 hepatotoxicity according to the criteria of the National Cancer Institute in cirrhotic
 215 patients. Additionally, this study had a retrospective design. These two factors would
 216 reduce the incidence of voriconazole-related AEs. Second, most of patients did not
 217 detect *CYP2C19* polymorphisms in this study. Our previous study showed that

218 voriconazole had a $C_{\min}$ of 3.13 ± 2.68 mg/L in poor metabolizers of *CYP2C19* with
 219 normal liver function who received the recommended dosage regimens (27). This
 220 suggests that the effect of liver cirrhosis on voriconazole pharmacokinetics parameters
 221 may exceed the effect of the *CYP2C19* polymorphism. Third, the number of
 222 Child-Pugh Class A patient was too small ($n = 6$), and further studies are needed to
 223 optimize voriconazole dosage regimens in these patients.

224

225 **4. Conclusion**

226 We have firstly explored the PPK parameters of voriconazole in patients with liver
 227 cirrhosis, with the findings suggesting that the optimal voriconazole dosages are 75
 228 mg/12 h and 150 mg/24 h intravenously or orally for CP-A/CP-B patients, and 50
 229 mg/12 h and 100 mg/24 h intravenously or orally for CP-C patients. To reduce the
 230 incidence of voriconazole-related AEs, it is critical to ensure voriconazole $C_{\min}$ is
 231 <5.12 mg/L by monitoring voriconazole $C_{\min}$ early. Clinically, TDM is also needed in
 232 liver patients who receive the optimal dosage regimens because $C_{\min}$ exceeded the
 233 supratherapeutic target in some patients. The present study represents a substantial
 234 step forward in determining the optimal dosing regimens in cirrhotic patients, and
 235 should be complemented by future clinical studies.

236

237 **5. Materials and methods**

238 **5.1 Patients**

239 We reviewed the laboratory information system from May 2014 to May 2018 at two
 240 tertiary hospitals. Patients who treated by voriconazole and therapeutic drug
 241 monitoring (TDM) had been performed during antifungal therapy were identified and
 242 then screened by applying inclusion criteria of (1) presence of liver cirrhosis,
 243 including CP-A, CP-B and CP-C patients and (2) age >18 years, and exclusion criteria
 244 of (1) the initial TDM after dose adjustment and (2) missing the values of key
 245 covariates. This study was approved by all participating institutional review boards.
 246 Finally, we retrospectively collected 120 cirrhotic patients into the analysis. Among
 247 these patients, four initial dosage regimens were administered: (1) patients received
 248 the recommended dosage regimen based on package insert or a fixed dose of 200 mg
 249 twice daily orally or intravenously; (2) patients received the loading dose of 200 mg
 250 twice daily on day 1, following by 100 mg twice daily orally or intravenously or a
 251 fixed dose of 100 mg twice daily orally or intravenously; (3) patients received loading
 252 dose of 200 mg twice daily on day 1, following by 200 mg daily orally or
 253 intravenously or a fixed dose of 200 mg daily orally or intravenously; (4) patients
 254 received a fixed dose of 100 mg daily orally or intravenously.

255 **5.2 Data collection**

256 Data were extracted from laboratory information system and medical records,
 257 including voriconazole-related information (C_{min} , timing, amount, route),
 258 demographics (age, gender and bodyweight), the type of cirrhosis, laboratory data (the
 259 liver, kidney and coagulation function) and concomitant medications (CYP2C19

260 inhibitors and inducers). The Child-Pugh score, Child-Pugh class and MELD (Model
261 for end-stage liver disease) score were calculated based on previous criteria (28, 29).
262 The types of AEs were extracted from medical records, and the causal relationship of
263 AEs with voriconazole treatment was defined according to the CTCAE criteria over
264 the treatment period (30).

265 **5.3 Blood sampling and analytical assays**

266 A $C_{\min}$ was defined as a level obtained after 3 days of voriconazole therapy with a
267 loading dose or 5 days of voriconazole treatment without a loading dose, and samples
268 were collected at interval windows of 10 - 12 h post-dose. The validated
269 high-performance liquid chromatography (HPLC) assays from participating hospital
270 were used to measure voriconazole concentrations (9, 31). We use blank plasma to
271 dilute the plasma whose concentration was beyond the upper limit of quantification
272 and then measured by HPLC.

273 **5.4 Population pharmacokinetics model and simulations**

274 **5.4.1 Population pharmacokinetics model construction**

275 A population pharmacokinetics (PPK) analysis was conducted using the data to
276 estimate the typical values and the variabilities of pharmacokinetics parameters in the
277 population, and to identify the factors influencing these parameters.

278 Firstly, a basic model, including structural model and statistical model, was developed
279 to describe the PK properties of voriconazole without consideration of covariate
280 effects. A one compartment model with first-order elimination was found to be

appropriate as the structural model. The pharmacokinetics parameters, clearance (CL), volume of distribution (V_d), absorption rate constant (k_a) and bioavailability (F) were calculated in this model. An exponential model described the inter-individual variability with a mean of zero and a variance of ω^2 , and a combined error model described residual variability with a mean of zero and a variance of σ^2 . The elimination half-life, $t_{1/2}$, was calculated by the form of $\ln(2)/(CL/V_d)$.

Next, the effect of each covariate on a single pharmacokinetics parameter was tested in a single functional form separately, with a reduction of the objective function value (OFV) greater than 3.84 considered statistically significant. These retained covariates were then used to construct the PPK model in the forward selection process. A backward elimination process was not used in this study since only one covariate was incorporated in the forward selection process. All of these processes were followed the standard procedure of model building (32). The most appropriate PPK model had to meet the following criteria: (1) the minimal OFV; (2) A reduction in OFV of > 6.83 in the process of forward selection; (3) the diagnostic plots were improved compared to the basic model. (4) the covariate should be physiologically plausible.

5.4.2 Model validation

The precision of voriconazole parameters and the robustness of the final model were evaluated using non-parametric bootstrap. A total of 1000 runs were carried out. The visual predictive check (VPC) was used to evaluated the predictive performance of the final voriconazole PPK model. A total of 1000 replicates were simulated, and the

302 90% prediction intervals were generated. The simulated results were compared with
303 these observed concentrations in the present study visually.

304 **5.4.3 Model-based simulations for optimizing voriconazole doses**

305 The final PPK model was used to simulate the voriconazole plasma
306 concentration–time profile over 420 h by considering the variability of
307 pharmacokinetics parameters and covariate. This was used to generate 50,000
308 pharmacokinetics profiles of voriconazole for each candidate regimen in CP-A/CP-B
309 and CP-C patients, and the dosing schedules were set to 30, 50, 75, or 100 mg twice
310 daily orally or intravenously, and 60, 100, 150, or 200 mg daily orally or
311 intravenously. All of the simulated virtual patients received a loading dose of 400 mg
312 twice daily orally or intravenously. The concentration–time profiles of the simulated
313 virtual patients were summarized and compared using their median and 5%, 25%,
314 75%, and 95% percentile values. These simulations aimed at predicting the
315 achievement of the voriconazole therapeutic target of 1 - 5 mg/L (12).

316 In the present study, PPK analysis and model-based simulations were performed using
317 NONMEM software (version 7.20) and subroutine ADVAN6 and the first-order
318 conditional estimation with interaction algorithm, and Wings for NONMEM (Version
319 743). The voriconazole plasma concentration-time curve were drew with R software
320 (version 3.4.4).

321 **5.5 Statistical analysis**

322 The Child-Pugh class was included as a dichotomous variable in this study, with a

323 value of 0 indicating CP-A/CP-B patients and a value of 1 indicating CP-C patients.

324 Student's *t*-test was used to compare voriconazole troughs. A classification and

325 regression tree (CART) analysis was used to identify the threshold for a continuous

326 variable that would maximize the difference in outcome between two groups. A *P*

327 value of < 0.05 was considered statistically significant.

328 **Funding**

329 This work was supported by the National Natural Science Foundation of China (grant
330 no. 81703618).

331 This work was supported by the Clinical Research Award of the First Affiliated
332 Hospital of Xi'an Jiaotong University (grant no. XJTU1AF-CRF-2017-023).

333

334 **Transparency declarations**

335 None to declare.

336

337 **Ethical approval**

338 This study was approved by all participating Hospital Ethics Committee.

339 **Reference**

- 340 1. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. 2019. Burden of liver diseases
341 in the world. *J Hepatol* 70:151-171.
- 342 2. Verma N, Singh S, Taneja S, Duseja A, Singh V, Dhiman RK, Chakrabarti A,
343 Chawla YK. 2018. Invasive fungal infections amongst patients with
344 acute-on-chronic liver failure at high risk for fungal infections. *Liver Int*
345 doi:10.1111/liv.13981.
- 346 3. Hassan EA, Abd El-Rehim AS, Hassany SM, Ahmed AO, Elsherbiny NM,
347 Mohammed MH. 2014. Fungal infection in patients with end-stage liver
348 disease: low frequency or low index of suspicion. *Int J Infect Dis* 23:69-74.
- 349 4. Gao J, Zhang Q, Wu Y, Li Y, Qi T, Zhu C, Liu S, Yu R, He Q, Wen W, Zhou F,
350 Chen Y, Chen J, Hou J. 2018. Improving survival of acute-on-chronic liver
351 failure patients complicated with invasive pulmonary aspergillosis. *Sci Rep*
352 8:876.
- 353 5. Patterson TF, Thompson GR, 3rd, Denning DW, Fishman JA, Hadley S,
354 Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal
355 BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young JA, Bennett JE.
356 2016. Practice Guidelines for the Diagnosis and Management of Aspergillosis:
357 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*
358 63:e1-e60.
- 359 6. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA,

360 Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ,
361 Zaoutis TE, Sobel JD. 2016. Clinical Practice Guideline for the Management
362 of Candidiasis: 2016 Update by the Infectious Diseases Society of America.
363 Clin Infect Dis 62:e1-e50.

364 7. Kadam RS, Van Den Anker JN. 2016. Pediatric Clinical Pharmacology of
365 Voriconazole: Role of Pharmacokinetic/Pharmacodynamic Modeling in
366 Pharmacotherapy. Clin Pharmacokinet 55:1031-43.

367 8. You H, Dong Y, Zou Y, Zhang T, Lei J, Chen L, Wang X, Dong Y, Wang T.
368 2018. Voriconazole therapeutic drug monitoring: Factors associated with
369 supratherapeutic and subtherapeutic voriconazole concentrations. Int J Clin
370 Pharmacol Ther 56:239-246.

371 9. Li ZW, Peng FH, Yan M, Liang W, Liu XL, Wu YQ, Lin XB, Tan SL, Wang F,
372 Xu P, Fang PF, Liu YP, Xiang DX, Zhang BK. 2017. Impact of CYP2C19
373 Genotype and Liver Function on Voriconazole Pharmacokinetics in Renal
374 Transplant Recipients. Ther Drug Monit 39:422-428.

375 10. Jin H, Wang T, Falcione BA, Olsen KM, Chen K, Tang H, Hui J, Zhai S. 2016.
376 Trough concentration of voriconazole and its relationship with efficacy and
377 safety: a systematic review and meta-analysis. J Antimicrob Chemother
378 71:1772-85.

379 11. Luong ML, Al-Dabbagh M, Groll AH, Racil Z, Nannya Y, Mitsani D, Husain
380 S. 2016. Utility of voriconazole therapeutic drug monitoring: a meta-analysis.

381 J Antimicrob Chemother 71:1786-99.

382 12. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW.

383 2014. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines

384 from the British Society for Medical Mycology. J Antimicrob Chemother

385 69:1162-76.

386 13. Pfizer Inc. VFEND U.S. Physician Prescribing Information.

387 <http://labeling.pfizer.com/ShowLabeling.aspx?id=618>. Revised May 2018.

388 14. Wang T, Yan M, Tang D, Xue L, Zhang T, Dong Y, Zhu L, Wang X, Dong Y.

389 2018. Therapeutic Drug Monitoring and Safety of Voriconazole Therapy in

390 Patients with Child-Pugh Class B and C Cirrhosis: A Multicenter Study. Int J

391 Infect Dis 72:49-54.

392 15. Wang T, Yan M, Tang D, Xue L, Zhang T, Dong Y, Zhu L, Wang X, Dong Y.

393 2018. A retrospective, multicenter study of voriconazole trough concentrations

394 and safety in patients with Child-Pugh class C cirrhosis. J Clin Pharm Ther

395 43:849-854.

396 16. Dolton MJ, Mikus G, Weiss J, Ray JE, McLachlan AJ. 2014. Understanding

397 variability with voriconazole using a population pharmacokinetic approach:

398 implications for optimal dosing. J Antimicrob Chemother 69:1633-41.

399 17. Pascual A, Csajka C, Buclin T, Bolay S, Bille J, Calandra T, Marchetti O. 2012.

400 Challenging recommended oral and intravenous voriconazole doses for

401 improved efficacy and safety: population pharmacokinetics-based analysis of

402 adult patients with invasive fungal infections. Clin Infect Dis 55:381-90.

403 18. McDougall DA, Martin J, Playford EG, Green B. 2016. Determination of a
404 suitable voriconazole pharmacokinetic model for personalised dosing. J
405 Pharmacokinet Pharmacodyn 43:165-77.

406 19. Gallagher J, Biesboer AN, Killian AJ. 2016. Pharmacologic Issues in Liver
407 Disease. Crit Care Clin 32:397-410.

408 20. Veringa A, Geling S, Span LF, Vermeulen KM, Zijlstra JG, van der Werf TS,
409 Kosterink JG, Alffenaar JC. 2017. Bioavailability of voriconazole in
410 hospitalised patients. Int J Antimicrob Agents 49:243-246.

411 21. Wang T, Chen S, Sun J, Cai J, Cheng X, Dong H, Wang X, Xing J, Dong W,
412 Yao H, Dong Y. 2014. Identification of factors influencing the
413 pharmacokinetics of voriconazole and the optimization of dosage regimens
414 based on Monte Carlo simulation in patients with invasive fungal infections. J
415 Antimicrob Chemother 69:463-70.

416 22. Palatini P, De Martin S. 2016. Pharmacokinetic drug interactions in liver
417 disease: An update. World J Gastroenterol 22:1260-78.

418 23. Albarmawi A, Czock D, Gauss A, Eehalt R, Lorenzo Bermejo J, Burhenne J,
419 Ganten TM, Sauer P, Haefeli WE. 2014. CYP3A activity in severe liver
420 cirrhosis correlates with Child-Pugh and model for end-stage liver disease
421 (MELD) scores. Br J Clin Pharmacol 77:160-9.

422 24. Pena MA, Horga JF, Zapater P. 2016. Variations of pharmacokinetics of drugs

423 in patients with cirrhosis. *Expert Rev Clin Pharmacol* 9:441-58.

424 25. Yamada T, Imai S, Koshizuka Y, Tazawa Y, Kagami K, Tomiyama N,
425 Sugawara R, Yamagami A, Shimamura T, Iseki K. 2018. Necessity for a
426 Significant Maintenance Dosage Reduction of Voriconazole in Patients with
427 Severe Liver Cirrhosis (Child-Pugh Class C). *Biol Pharm Bull* 41:1112-1118.

428 26. Hashemizadeh Z, Badiie P, Malekhoseini SA, Raeisi Shahraki H,
429 Geramizadeh B, Montaseri H. 2017. Observational Study of Associations
430 between Voriconazole Therapeutic Drug Monitoring, Toxicity, and Outcome in
431 Liver Transplant Patients. *Antimicrob Agents Chemother* 61:e01211-1217.

432 27. Wang T, Zhu H, Sun J, Cheng X, Xie J, Dong H, Chen L, Wang X, Xing J,
433 Dong Y. 2014. Efficacy and safety of voriconazole and CYP2C19
434 polymorphism for optimised dosage regimens in patients with invasive fungal
435 infections. *Int J Antimicrob Agents* 44:436-42.

436 28. Rockville (MD). 2003. Guidance for industry: pharmacokinetics in patients
437 with impaired hepatic function: study design, data analysis, and impact on
438 dosing and labeling. Center for Biologics Evaluation and Research, Food and
439 Drug Administration (US).

440 29. Northup PG, Wanamaker RC, Lee VD, Adams RB, Berg CL. 2005. Model for
441 End-Stage Liver Disease (MELD) predicts nontransplant surgical mortality in
442 patients with cirrhosis. *Ann Surg* 242:244-51.

443 30. Bethesda M. 2010. National Cancer Institute, National Institutes of Health.

444 Common terminology criteria for adverse events (CTCAE), version 4.03. U.S.
 445 Department of Health and Human Services.

446 31. Wang T, Xie J, Wang Y, Zheng X, Lei J, Wang X, Dong H, Yang Q, Chen L,
 447 Xing J, Dong Y. 2015. Pharmacokinetic and Pharmacodynamic Properties of
 448 Oral Voriconazole in Patients with Invasive Fungal Infections.
 449 Pharmacotherapy 35:797-804.

450 32. Owen J S, Fiedler-Kelly J. 2014. Introduction to population
 451 pharmacokinetic/pharmacodynamic analysis with nonlinear mixed effects
 452 models. Hoboken: Wiley & Sons.

453

454 **Figure legends**

455 **Figure 1** The distributions of the initial voriconazole $C_{\min}$ in relation to the different
456 dosage regimens. The solid lines represent interquartile range ($Q_{25} - 75$). The dashed
457 lines represent the voriconazole target trough plasma concentrations of 1 mg/L and 5
458 mg/L.

459 **Figure 2** The goodness-of-fit of the basic model (left) and final model (right). OBS:
460 observed concentrations; PRED, population predicted concentrations; IPRED,
461 individual predicted concentrations; WRES: weighted residuals.

462 **Figure 3** The concentration–time profiles of different voriconazole oral dosing
463 regimens in CP-C (left) and CP-A/CP-B (right) patients based on 50000 simulations.
464 The dashed lines represent the voriconazole target trough plasma concentrations of 1
465 mg/L and 5 mg/L. The solid line is the 50% of simulated data, and the dark grey area
466 and the light gray area are the 50% ($Q_{25} - 75$) and 90% ($Q_5 - 95$) prediction intervals,
467 respectively.

468 **Table 1** Demographic and baseline clinical characteristics of patients

Parameters	Group A
Child-pugh class (A:B:C)	6:34:80
Child-pugh score	10.0 ± 1.8 (5 - 13)
MELD score	18.3 ± 7.3 (6.2 – 40.1)
Demographic	
Age (year)	50.5 ± 13.2 (22 - 82)
Gender (male/female)	95:25
Weight (kg)	63.1 ± 9.6 (40.5 - 88)
Type of cirrhosis, no. (%) of patients	
Viral hepatitis	93 (77.5%)
Alcoholic	5 (4.2%)
Autoimmune hepatitis	6 (5%)
Cholestasis	2 (1.7%)
Hepatotoxic drugs	5 (4.2%)
Cryptogenic	9 (7.5%)
The laboratory data	
RBC (10 ¹² /L)	3.1 ± 0.7 (1.7 - 5.3)
WBC (10 ⁹ /L)	7.5 ± 4.8 (1.2 - 24.6)
PLT (10 ⁹ /L)	96.4 ± 85.6 (3 - 542)
ALT (U/L)	101.3 ± 305.0 (3.0 - 3157.0)
AST (U/L)	137.5 ± 277.0 (11.0 - 2718.0)
ALP (U/L)	144.5 ± 100.3 (8 - 564)
Total bilirubin (μmol/L)	243.7 ± 202.9 (5.1 - 901.6)
Albumin (g/L)	31.9 ± 5.2 (19.1 - 45.4)
Serum creatinine (μmol/L)	85.7 ± 77.5 (2.9 - 528.0)
INR	1.9 ± 0.7 (1.0 - 4.2)
Concomitant medication, no. (%) of patients	
<i>CYP2C19</i> inhibitor	4 (3.3%)
<i>CYP2C19</i> inducer	73 (60.8%)
<i>CYP3A4</i> inducer	27 (22.5%)

469 Note: continuous variables were expressed as mean ± standard deviation (range); ALT,
470 alanine aminotransferase; AST, aspartate transaminase; ALP, alkaline phosphatase;
471 INR, international normalized ratio.

472 **Table 2** Voriconazole trough concentrations and the time from voriconazole treatment
 473 initiation to the development of adverse events. Data were expressed as median
 474 (range).

	Voriconazole $C_{\min}$ (mg/L)	Time (days)
Visual disturbances (n = 6)	4.69 (3.14 - 8.76)	6 (2 - 8)
Hallucination (n = 3)	3.25 (2.37 - 8.30)	4 (2 - 4)
Neurotoxicity (n = 12)	5.85 (3.30 - 15.10)	7 (2 - 12)
Rash (n = 3)	6.00 (5.14 - 10.65)	4 (4 - 7)
Nausea and vomit (n = 2)	4.12, 10.82	13, 15
Hypokalemia (n = 2)	6.71, 8.29	4, 8
Nephrotoxicity (n = 1)	6.17	7
All patients	5.98 (2.37 - 15.10)	6 (2 - 15)

475 $C_{\min}$: trough concentration.

476 **Table 3** The pharmacokinetics parameters of basic model and final model and bootstrap results.

Parameters	Basic model ^a		Final model ^b		Final model ^c		Bootstrap results		
	Typical	RSE	Typical	RSE	Typical value	RSE	Mean	95%CI-	95%CI-
	value	(%)	value	(%)		(%)		Lower	Upper
CL (L/h)	1.35	8.9	1.77	8.1	CL ₁ = 0.99	10.6	CL ₁ = 1.01	0.78	1.24
					CL ₂ = 1.79	8.3	CL ₂ = 1.80	1.49	2.12
V _d (L)	150.4	8.3	159.3	7.6	159.6	7.7	158.3	131.7	185.0
k _a (h ⁻¹)	0.25	0.3	0.25	0.2	0.25	0.2	0.21	0.07	0.35
F (%)	91.2	7.3	91.8	6.6	91.8	6.7	92.4	79.7	105.1
ω _{CL}	67.2%	20.1	59.2	25.6	ω _{CL1} = 58.4	48.9	ω _{CL1} = 55.9	33.6	78.4
					ω _{CL2} = 60.0	33.9	ω _{CL2} = 58.8	47.4	70.18
ω _{vd}	63.3%	32.8	65.8	27.1	66.4%	27.1	65.2	54.2	76.3
θ _{CPG}	/	/	0.43	14.1	/	/	/	/	/
Proportional error (%)	0.096	72.8	0.105	63.4	0.108	62.9	0.11	0.04	0.18
Additive error (mg/L)	1.10	25.8	1.03	29.6	1.03	30.4	0.98	0.59	1.37

477 CL, clearance; V_d, the volume of distribution; k_a, absorption rate constant; F, bioavailability;

478 ^a CL = θ₁ × e^{η₁}; V_d = θ₂ × e^{η₂}; k_a = θ₃; F = θ₄;

479 ^b CL = θ₁ × (1 - θ₅ × CPG) × e^{η₁}; V_d = θ₂ × e^{η₂}; k_a = θ₃; F = θ₄;

480 ^c CL₁ = θ₁ × e^{η₁} (for CP- C patients); CL₂ = θ₂ × e^{η₂} (for CP- A/CP-B patients); V_d = θ₃ × e^{η₃}; k_a = θ₄; F = θ₅.

Table 4 The probability of simulated voriconazole trough concentrations achieving or not achieving the therapeutic target for different oral dosage regimens in patients with liver cirrhosis.

Dosage regimens	Probability (%)								
	Day 3			Day 7			Day 14		
	< 1	1 - 5	> 5	< 1	1 - 5	> 5	< 1	1 - 5	> 5
	mg/L	mg/L	mg/L	mg/L	mg/L	mg/L	mg/L	mg/L	mg/L
100 mg/12 h, p.o. for CP-A/ CP-B	10.8	65.8	23.4	10.8	61.9	27.3	9.8	57.8	32.5
75 mg/12 h, p.o. for CP-A/ CP-B	13.7	68.2	18.1	15.0	66.8	18.2	15.2	64.9	19.9
150 mg/24 h, p.o. for CP-A/ CP-B	14.8	67.6	17.6	17.3	66.9	15.8	18.7	63.6	17.7
100 mg/12 h, p.o. for CP-C	5.8	53.0	41.3	4.2	45.4	50.4	2.8	36.5	60.7
50 mg/12 h, p.o. for CP-C	9.3	62.9	27.7	10.3	64.8	24.9	10.2	64.3	25.5
100 mg/24 h, p.o. for CP-C	9.4	63.5	27.1	11.3	64.5	24.2	11.6	64.0	24.4

CP-A/CP-B: Child-Pugh Class A and Child-Pugh Class B; CP-C: Child-Pugh Class C;
p.o.: orally.

Basic model