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# Monte Carlo Analysis of Different Administration Regiments for Isavuconazole against *Candida spp.* and *Aspergillus spp.*

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## Abstract

In our study, we aimed to optimize the dosage regimen of Isavuconazole against *Candida spp.* and *Aspergillus spp.* by Monte Carlo simulation (MSC). Pharmacokinetic parameters and microbiological data of Isavuconazole were collected. Then we used MSC to simulate 10,000 patients analyzed by Crystal Ball to calculate probability of target attainment (PTA) and cumulative fraction of response (CFR). With dosages of 100 mg, 200 mg, and 400 mg in oral group and dosages of 100 mg, and 200 mg in intravenous administration, all have different degrees of antifungal effect. But when the dosage regimen was 50 mg IV, the therapeutic effect of Isavuconazole against *Aspergillus spp.* and *Candida spp.* were not good.

## Keywords

Monte Carlo Simulation (MSC), Isavuconazole, *Candida spp.*, *Aspergillus spp.*

## 1. Introduction

At present, invasive fungal infection is one of the major infectious diseases in the world, and its main pathogenic bacterias are *Aspergillus* and *Mucor*, which is the main cause of high morbidity and mortality, and is one of the most serious disease burdens in the world [1]. At present, due to the safety and effectiveness of therapeutic drugs and other reasons, the treatment is less selective [2]. Isavuconazole is a triazole antifungal drug that inhibits the conversion of lanosterol to ergosterol by inhibiting cytochrome P450 (CYP)-dependent 14-$\alpha$-demethylase in fungal cell membranes, thereby affecting the growth and replication of fungal cells. And thus play a pharmacological role [3]. The antimicrobial spectrum of

Isavuconazole is broad, and in vitro activity tests have confirmed that Isavuconazole has inhibitory effects on mold, yeast, and dimorphic fungi [4] [5] [6], which was currently approved by the FDA for the treatment of primary treatment of invasive aspergillosis (IA) and mucormycosis, available in oral and intravenous forms [7]. In this study, combined with antifungal pharmacokinetics (PK)/pharmacodynamics (PD) and microbial information, Monte Carlo simulation was used to analyze the treatment regiments for Isavuconazole against *Candida spp.* and *Aspergillus spp.*, so as to obtain the best treatment regiments for each pathogen, and also provide basis for early antifungal therapy (**Figure 1**).

## 2. Materials and Methods

### 2.1. Pharmacokinetic Parameters

PK parameters are derived from published research [8]. In adult study subjects, there are two administration routes of Isavuconazole, oral administration and intravenous administration, with dosages of 100 mg, 200 mg, and 400 mg in oral group and dosages of 50 mg, 100 mg, and 200 mg in intravenous administration. PK parameters of each administration regimen are shown in **Table 1**.

### 2.2. Microbial Information

MIC distributions of Isavuconazole against *Aspergillus spp.* derived from EUCAST website (https://mic.eucast.org/search/, MIC distributions for Isavuconazole, 2021-7-13). The MIC distribution of Isavuconazole against *Candida spp.* is derived from the published literature of Rybak *et al.* [9] (shown in **Table 2**).

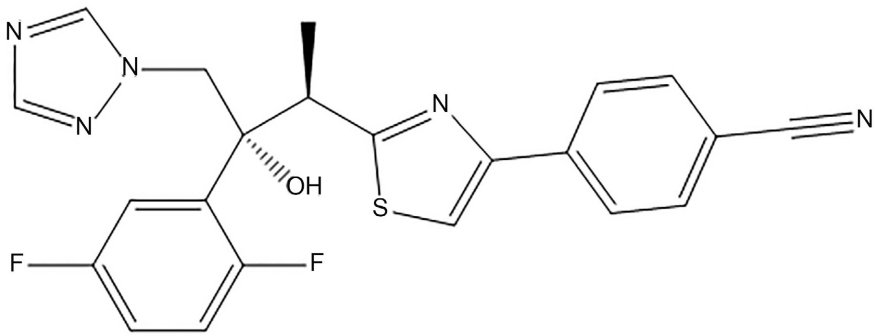



**Figure 1.** The chemical structure of Isavuconazole.

**Table 1.** Pharmacokinetic parameters of Isavuconazole estimated after single oral administration and intravenous infusion.

| Parameter | Oral administration | | | Intravenous infusion | | |
|---|---|---|---|---|---|---|
| | 100 mg | 200 mg | 400 mg | 50 mg | 100 mg | 200 mg |
| $AUC_{0-\infty}$ (μg·h/ml) | 37.0 ± 6.75 | 78.5 ± 10.8 | 215 ± 42 | 11.3 ± 4.43 | 26.6 ± 6.25 | 73.2 ± 12.4 |
| CL (liters/h) | 2.8 ± 0.548 | 2.59 ± 0.363 | 1.91 ± 0.418 | 5.03 ± 1.99 | 3.69 ± 1.04 | 2.80 ± 0.519 |
| $t_{1/2\alpha}$ (h) | 1.70 ± 0.34 | 2.05 ± 0.53 | 2.06 ± 0.59 | 1.57 ± 0.52 | 1.53 ± 0.59 | 0.42 ± 0.31 |
| $t_{1/2\beta}$ (h) | 36.1 ± 21.7 | 77.1 ± 12.8 | 56.0 ± 2.49 | 76.2 ± 32.0 | 104 ± 56.7 | 80.4 ± 33.0 |

**Table 2.** MIC distributions of Isavuconazole against *Aspergillus spp.* and *Candida spp.*

| Species | n | MIC (μg/ml) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.001 | 0.002 | 0.004 | 0.008 | 0.016 | 0.032 | 0.064 | 0.125 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 |
| *Aspergillus spp.* | | | | | | | | | | | | | | | | |
| *A. flavus* | 434 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 5 | 44 | 285 | 96 | 3 | 0 | |
| *A. fumigatus* | 426 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 21 | 199 | 174 | 12 | 9 | 5 | 3 |
| *A. nidulans* | 156 | 0 | 0 | 0 | 0 | 0 | 1 | 19 | 95 | 36 | 5 | 0 | 0 | 0 | 0 | 0 |
| *A. niger* | 224 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 8 | 53 | 118 | 35 | 7 | |
| *A. terreus* | 349 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 8 | 83 | 165 | 75 | 9 | 1 | 7 | 0 |
| *Candida spp.* | | | | | | | | | | | | | | | | |
| *C. albicans* | 744 | 66 | 24 | 62 | 233 | 315 | 40 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *C. glabrata* | 312 | 0 | 0 | 0 | 0 | 0 | 3 | 12 | 30 | 75 | 110 | 50 | 13 | 11 | 8 | |
| *C. krusei* | 56 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 3 | 14 | 28 | 9 | 0 | 0 | 0 | |
| *C. parapsilosis* | 285 | 0 | 0 | 2 | 7 | 15 | 61 | 108 | 70 | 12 | 4 | 4 | 0 | 2 | | |
| *C. tropicalis* | 155 | 0 | 0 | 3 | 3 | 14 | 53 | 51 | 19 | 5 | 4 | 2 | 0 | 1 | | |

### 2.3. Monte Carlo Simulation

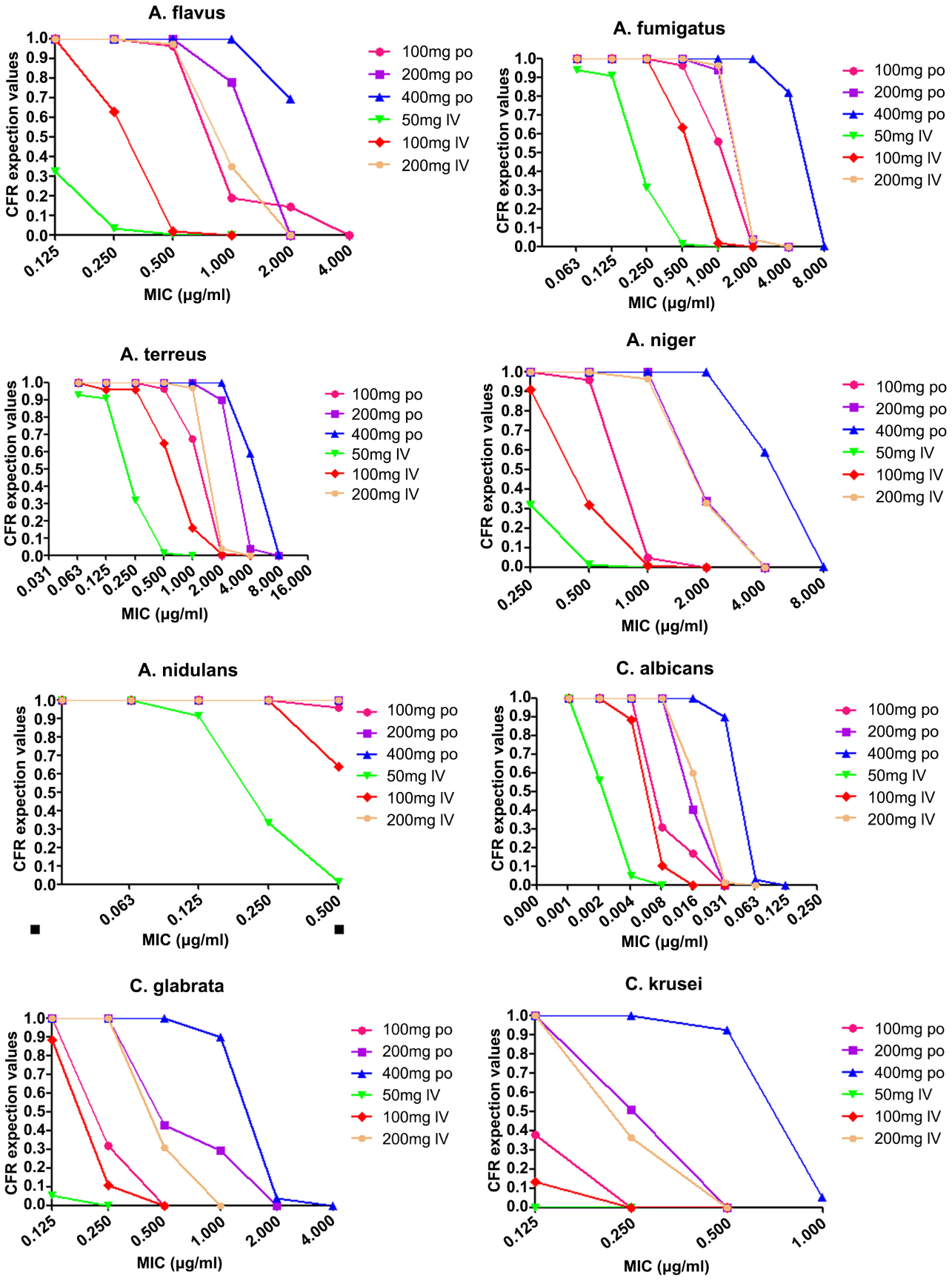
MCSs combines PK parameters of antibiotics with MIC distribution information of pathogenic bacteria to evaluate the probability of achieving each PD target in reality. Isavuconazole is a concentration-dependent antimicrobial agent, and the target value is expressed as AUC/MIC [10]. *f*AUC/MIC = ($f$× dose)/(CL × MIC). In the formula, $f$ = 1 − PBs represents the free drug fraction. The plasma protein binding rate for Isavuconazole is 99% representative [11], so its $f$ value is 1%; and CL is drug clearance rate. In our study, Crystal Ball (Version 11.1.2.4.600, Oracle) was used to simulate 10000 patients, which was used to calculate Probability of Target Attainment (PTA) and Cumulative Fraction of Response (CFR). A target value of ≥90% is considered to be an appropriate administration regimen for the microflora. The target value of PD was 0.51 for *Aspergillus spp.*, 6.2 for *C. tropicalis*, 1.6 for *C. glabrata*, 50.5 for *C. albicans*, and 3.1 for other strains [12] [13]. CFR calculation formula is as follows:

$$\mathrm{CFR} = \sum_{i=1}^{n} \mathrm{PTAi} \times \mathrm{Fi}$$

## 3. Results

### 3.1. PTA

We used MCS analyzed the dosage regimen of Isavuconazole in the treatment of *Candida spp.* and *Aspergillus spp.* infection included 100 mg Po, 200 mg Po, 400 mg Po, 50 mg IV, and 100 mg IV, respectively. The PTA ≥ 90% of 200 mg IV was as follows (shown in **Figure 2**): *A. flavus* was 0.5 μg/ml, 1 μg/ml, 2 μg/ml, 0.125 μg/ml, 0.25 μg/ml, 1 μg/ml; *A. fumigatus* was 0.5 μg/ml, 1 μg/ml, 2 μg/ml, 0.125 μg/ml, 0.25 μg/ml, 1 μg/ml; *A. nidulans* was 0.5 μg/ml, 0.5 μg/ml, 0.5 μg/ml,


A. flavus
CFR expection values
MIC (μg/ml)
0.125
0.250
0.500
1.000
2.000
4.000
A. fumigatus
0.063
0.125
0.250
0.500
1.000
2.000
4.000
8.000
A. terreus
0.031
0.063
0.125
0.250
0.500
1.000
2.000
4.000
8.000
16.000
A. niger
0.250
0.500
1.000
2.000
4.000
8.000
A. nidulans
0.063
0.125
0.250
0.500
C. albicans
0.000
0.001
0.002
0.004
0.008
0.016
0.031
0.063
0.125
0.250
C. glabrata
0.125
0.250
0.500
1.000
2.000
4.000
C. krusei
0.125
0.250
0.500
1.000
100mg po
200mg po
400mg po
50mg IV
100mg IV
200mg IV

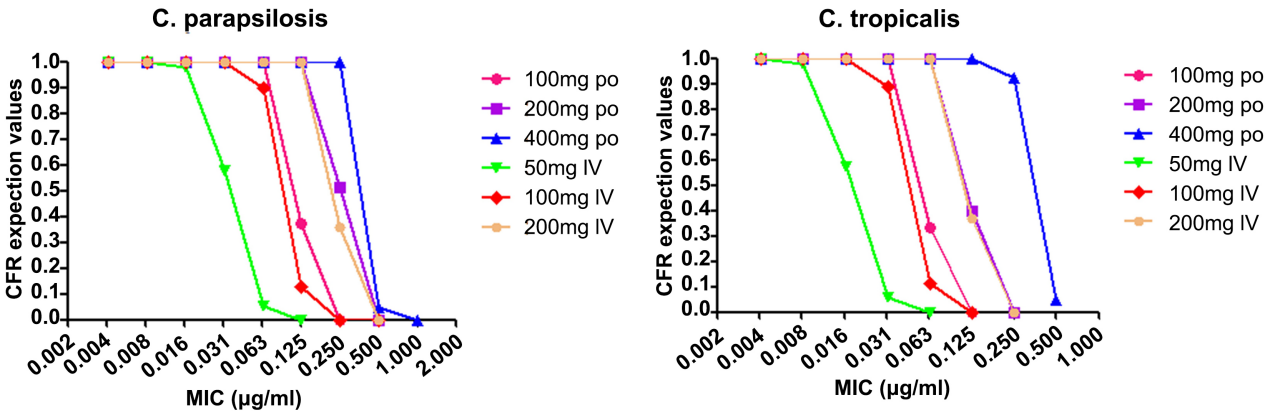



**Figure 2.** PTA of Isavuconazole estimated at different MIC values in patients with *Candida spp.* and *Aspergillus spp.* Infections.

0.125 μg/ml, 0.25 μg/ml, 0.5 μg/ml; *A. terreus* was 0.5 μg/ml, 1 μg/ml, 2 μg/ml, 0.125 μg/ml, 0.25 μg/ml, 1 μg/ml; *C. Albicans* was 0.004 μg/ml, 0.008 μg/ml, 0.016 μg/ml, 0.001 μg/ml, 0.002 μg/ml, 0.008 μg/ml; *C. glabrata* was 0.125 μg/ml, 0.25 μg/ml, 0.5 μg/ml, 0.032 μg/ml, 0.064 μg/ml, 0.025 μg/ml; *C. parapsilosis* was 0.064 μg/ml, 0.125 μg/ml, 0.5 μg/ml, 0.016 μg/ml, 0.032 μg/ml, 0.125 μg/ml; *C. tropicalis* was 0.032 μg/ml, 0.064 μg/ml, 0.25 μg/ml, 0.008 μg/ml, 0.016 μg/ml, 0.064 μg/ml; when the administration scheme of *A. niger* was 50 mg IV, PTA of all MIC values did not meet the standards, and the rest reached the standards: 100 mg po, 200 mg po, 400 mg po, 100 mg IV, 200 mg IV were 0.5 μg/ml, 1 μg/ml, 2 μg/ml, 0.25 μg/ml,1μg/ml; for *C. krusei*, when regimen were 50 mg IV and 100 mg IV, PTA was not up to the standard for MIC, and the rest were up to the standard; when regimen were 100 mg po, 200 mg po, 400 mg po, 200 mg IV were 0.064 μg/ml, 0.125 μg/ml, 0.5 μg/ml, 0.125 μg/ml.

### 3.2. CFR

CFR values of Isavuconazole dosage regimen of Isavuconazole in the treatment of *Candida spp.* and *Aspergillus spp.* infections are shown in Table 3. When the dosage regimen was 100 mg po, only the CFR value of *A. nidulans* reached the standard, and the other fungus did not reach the standard. The CFR value of *A. flavus*, *A. fumigatus*, *A. nidulans*, *A. terreus*, *C. parapsilosis* reached the standard when the dosage regimen was 200 mg po, but the other fungus did not reach the standard. The CFR values of *C. glabrata* and *C. krusei* were all up to standard when the dosage regimen was 400 mg po. When the dosage regimen was 50 mg IV, CFR of each strain was not up to the standard. When dosage regimen was 100 mg IV, only the CFR for *A. nidulans* met the standard; the CFR values for *A. fumigatus*, *A. nidulans*, *A. terreus*, *C. parapsilosis* met the standard when the dosage regimen was 200 mg IV.

## 4. Discussion

MCS combined with true fungus resistance of PK and PD information and microbes in the MIC value distribution of specific drugs, to simulate each fungus

**Table 3.** Cumulative Fraction of Response (CFR) expectation values (%).

| Species | dosage regimen of Isavuconazole | | | | | |
|---|---|---|---|---|---|---|
| | 100 mg po | 200 mg po | 400 mg po | 50 mg IV | 100 mg IV | 200 mg IV |
| *A. flavus* | 26.54 | 94.35 | 99.30 | 1.23 | 8.80 | 83.14 |
| *A. fumigatus* | 73.40 | 90.69 | 97.74 | 2.84 | 36.14 | 91.87 |
| *A. nidulans* | 99.87 | 100 | 100 | 76.23 | 98.78 | 100 |
| *A. niger* | 2.87 | 46.37 | 90.43 | 0.46 | 2.60 | 44.99 |
| *A. terreus* | 76.42 | 97.41 | 97.88 | 10.57 | 59.35 | 94.50 |
| *C. albicans* | 37.18 | 68.90 | 98.92 | 11.08 | 22.61 | 77.17 |
| *C. glabrata* | 22.08 | 58.35 | 88.26 | 3.53 | 15.92 | 49.28 |
| *C. krusei* | 5.59 | 21.67 | 81.02 | 0.22 | 3.91 | 18.03 |
| *C. parapsilosis* | 76.85 | 94.44 | 97.85 | 88.68 | 67.00 | 93.76 |
| *C. tropicalis* | 58.05 | 84.88 | 95.36 | 10.90 | 46.92 | 84.46 |

provided dosage regimen of standard, and determine the sensitivity to fold point of antifungal drugs, thus for clinical anti-infection schemes are put forward by the scientific evaluation, to improve clinical therapeutic effects of maximum likelihood, and minimize the possibility of antimicrobial resistance [14]. In this study, MCS was used to calculate in the treatment of *Candida spp.* and *Aspergillus spp.* infections. The results showed that, when 100 mg po, only the CFR value of *A. nidulans* reached the standard, and the antifungal effect on other strains was not good. The CFR value of *A. flavus*, *A. fumigatus*, *A. nidulans*, *A. terreus*, *C. parapsilosis* reached the standard when the dosage regimen was 200 mg po. The CFR values of all fungi except *C. glabrata* and *C. krusei* were all up to standard when the dosage regimen was 400 mg po. When the dosage regimen was 50 mg IV, CFR of each strain was not up to the standard. The dosage regimen was 100 mg IV, the CFR of *A. nidulans* met the standard; the CFR for *A. fumigatus*, *A. nidulans*, *A. terreus* and *C. parapsilosis* met the standard when the dosage regimen was 200 mg IV.

Isavuconazole is a concentration-dependent antimicrobial agent, whose PD index is measured by AUC/MIC ratio. A series of studies have confirmed that PD target values of Isavuconazole in the treatment of *Aspergillus spp.* and *Candida spp.* Among *Candida spp.*, the differences among species were great, *C. tropicalis* was 6.2, *C. glabrata* was 1.6, *C. albicans* was 50.5, and the others were 3.1, while the target value of *Aspergillus spp.* was generally believed to be 0.51 [12] [13]. In this study, the PD target values mentioned above were used for MCS, which was compared with non-albicans *Candida spp.* reported in the literature [14]. Compared with the AUC/MIC values of 312, the analysis results are more targeted and targeted.

PK/PD analysis combined with MCS analysis of antifungal drug dosage regimen can scientifically analyze the rationality of antibacterial drug administration regimen, provide reference for early clinical empirical drug use, and also be used

for optimization of antibacterial treatment regimen. However, there are also some limitations. First, Isavuconazole parameters are derived from adults in the study area, and differences among different races and ethnic groups are not fully considered. Secondly, MIC data are derived from EUCAST website, which lacks certain pertinence for data of regions not included in the study of EUCAST website.

## 5. Conclusion

In conclusion, different dosage regimens for Isavuconazole in different administration routes were used in this study, indicating that there are still differences in administration regimens for different strains with the same dose and different routes. However, when the dosage regimen was 50 mg IV, the therapeutic effect of Isavuconazole against *Aspergillus spp.* and *Candida spp.* were not good, which showed the treatment is not recommended.

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## Data Availability Statement

All data generated or analyzed during this study are included in this published article.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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