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ORIGINAL RESEARCH

Isavuconazole in Pediatric Invasive Fungal Infections: Outcomes and Therapeutic Drug Monitoring in a Chinese Multicenter Case Series

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Background: Real-world evidence regarding the efficacy of isavuconazole (ISA) for pediatric invasive fungal infections (IFIs) remains scarce, particularly in Asia.

Methods: This retrospective multicenter observational study (January 2022–June 2025) was conducted at four tertiary hospitals in central China. Children aged 1–17 years with IFI who received ISA for ≥7 days were included. Therapeutic drug monitoring (TDM) of trough concentrations (C_{trough}) was performed using LC-MS/MS targeting 2–4 mg/L. The clinical pharmacists provided weekly antifungal stewardship interventions.

Results: Ten children (median age, 6.5 years [range, 2 months–16 years]; 50% male) were enrolled. ISA was used as salvage therapy in 80% of patients due to failure or toxicity of prior antifungal agents. The median treatment duration was 43.5 days (range: 10–318 days). The initial median C_{trough} was 1.7 mg/L (range 0.9–5.1); and 60% of the patients were subtherapeutic (<2 mg/L). Pharmacist-led dose escalation (33–100%) achieved target attainment in 83% of the adjusted cases. The favorable response (complete/partial) on day 42 was 80%, and a child died due to bacterial sepsis. A median estimated AUC_{0-24}/MIC (183.5) strongly predicts the success of mold infections. No QTc prolongation or severe hepatotoxicity was observed.

Conclusion: This first Chinese multicenter pediatric series demonstrated the excellent efficacy and tolerability of ISA when combined with routine TDM and clinical pharmacist stewardship. It should be noted that our study has a small sample size, requiring further validation.

Keywords: isavuconazole, pediatric, invasive fungal infection, therapeutic drug monitoring, antifungal stewardship, real-world evidence

Introduction

Invasive fungal infections (IFIs) are a major cause of mortality in immunocompromised children, with attributable mortality exceeding 30% for invasive *Aspergillosis* and 50% for *Mucormycosis*.[1,2] Voriconazole is the primary treatment for invasive *Aspergillosis* in children, but its complex pharmacokinetics and high incidence of adverse events have raised widespread clinical concerns.[3] In addition, global guidelines for *Mucormycosis* recommend first-line treatment with high-dose liposomal amphotericin B, while isavuconazole (ISA) and posaconazole are salvage treatments.[4] Amphotericin B deoxycholate is not recommended owing to its significant toxicity. However, liposome formulations undoubtedly increase the economic burden on the patients.

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The safety and efficacy of ISA in pediatric patients less than 18 years of age have not been established in FDA.[5] Advantages include broad-spectrum activity, linear pharmacokinetics, minimal CYP3A4 interaction, and availability of oral/IV formulations.[6] However, some cases and real-world studies have shown positive results. ISA has been proven to be no worse than voriconazole in the treatment of invasive *Aspergillosis*.[7] A multicenter non-comparative Phase 2 trial showed that 10 mg/kg ISA was well tolerated in children with invasive *Aspergillosis*, and 54.8% of 31 patients responded favorably to treatment.[8] While ISA has achieved a notable 78.6% success rate in treating pediatric *Mucormycosis*, the infection remains severely life-threatening.[9] For most pediatric patients treated with 10 mg/kg (maximum 372 mg) of ISA sulfate once daily, the resulting plasma drug exposure will match those reported for adults in Phase 3 therapeutic efficacy trials.[10]

In a retrospective, multicenter, international real-world study on IFIs treatment, ISA showed less nephrotoxicity than amphotericin B, and less hepatotoxicity than voriconazole.[11] A systematic review of *Mucormycosis* showed that intravenous ISA with liposomal amphotericin B in the acute phase, then switched to oral monotherapy, achieved high recovery rates and caused few adverse events.[9] In another systematic review of RCTs, ISA had comparable efficacy and fewer adverse effects than voriconazole.[12] Compared with other azole antifungals, ISA are well tolerated and have been successfully used in clinical studies.[13] Phase-3 SECURE and VITAL trials showed that ISA was as effective as voriconazole and amphotericin B for IFIs but caused significantly fewer adverse events.[7,14] The switch to ISA resolved azole-induced hepatotoxicity or grade 3–4 QTc prolongation caused by posaconazole in leukemia patients, without further elevation of liver function tests.[15]

Therapeutic drug monitoring (TDM) is recommended for monitoring plasma concentrations of most antifungal triazoles because of their obvious pharmacokinetic/pharmacodynamic (PK/PD) relationship.[16] Therapeutic strategies guided by TDM are generally associated with markedly improved clinical efficacies. TDM is indispensable for dose individualization, especially in critically ill patients whose trough concentrations frequently fall below the therapeutic window.[17] ISA frequently requires monitoring in children; nearly half of the first trough concentrations fall outside the target range, and ECMO-supported children require higher doses and intensive monitoring.[18] Accurate dose optimization based on a pharmacokinetic model (PBPK) revealed that the predicted values were consistent with the observed values, indicating the potential predictability of ISA in PK profiles in other populations.[19]

To date, global pediatric real-world data comprises <60 published cases, predominantly from Europe and North America.[20–22] No multicenter pediatric data exist in China, the country with the largest pediatric hematology-oncology population. Furthermore, the role of TDM and antifungal stewardship in optimizing ISA exposure among Asian children remains unclear. We presented the first multicenter, real-world study of ISA in Chinese children with IFI. This study aimed to evaluate the efficacy and tolerability of ISA and to investigate whether TDM-guided pharmacist interventions can optimize drug exposure and improve clinical outcomes in Chinese pediatric patients with invasive fungal infections.

Patients and Methods

Study Design and Patients

A retrospective observational study (January 2022–June 2025) was conducted in 10 patients at multiple centers including Tongji Hospital (n=3), Wuhan Children's Hospital (n=5), Tongji Pediatric Hospital (n=1) and Huangshi Central Hospital (n=1). The inclusion criteria were as follows: age 1 month to 17 years, proven/probable/possible IFI (EORTC/MSGERC 2020),[23] and ISA treatment≥7 days. The exclusion criteria were as follows: patients with ≥10% missing critical variables (such as ISA dosing, TDM concentrations, treatment response, and underlying disease information) that could not be supplemented via medical record review. A uniform TDM protocol was applied across all participating centers.

The study was approved by the Tongji Hospital Ethics Committee (TJ-IRB20250904) and three other centers. The authors ensured that the study procedures adhered to the guidelines of the relevant clinical research ethics committee as well as those of the World Medical Association and the Declaration of Helsinki. The Ethics Committee waived the requirement for informed consent given the retrospective study design. All data were anonymized to maintain patient confidentiality.

The clinical data of 10 patients were collected from the HIS system in multiple centers. To guarantee consistency and accuracy, all researchers at the four centers received data collection training, including the use of electronic clinical forms and standardized terminology dictionaries. Each center was equipped with clinical doctors to ensure the accuracy of the IFI diagnosis (EORTC/MSGERC 2020) and formulation of treatment plans.

Treatment response was assessed 4, 6, and 12 weeks after the diagnosis of IFI. Four investigators graded the outcomes as complete response (symptoms and radiologic lesions resolved with microbiologic clearance), partial response (symptom improvement plus ≥25% lesion reduction plus clearance), or no response (persistent/progressive symptoms or lesions).[24] The researchers recorded the rationale for using ISA as the primary therapy, the reason for switching to ISA after prior antifungals, and any ISA discontinuation due to toxicity, intolerance, or failure.

ISA Dosing and TDM

According to CRESEMBA@ in pediatric patients, ISA treatment is based on a weight-based regimen: loading 10 mg/kg q8h × 6 doses (maximum 200 mg/dose) and maintenance 10 mg/kg/day (maximum 200 mg/day). TDM was performed at steady-state (day 3–7) and weekly using validated LC-MS/MS (LLOQ 0.1 mg/L, CV <8%). The target C_{trough} of ISA levels were 2–4 mg/L, as reported in adult series.[10] AUC_{0-24} was estimated using Bayesian forecasting for mold infections. Dose optimization based on TDM was performed at each center, according to the EORTC/MSGERC guidelines.

Antifungal Stewardship

Weekly multidisciplinary rounds with mandatory clinical pharmacist participation, cover dose adjustment, drug–drug interaction management, and toxicity monitoring were performed at each center.

Endpoints

The primary endpoint was favorable response (complete/partial) on day 42.[25] The secondary endpoints were 90-day survival, adverse events (CTCAE v5.0) and target attainment.

Statistics

Continuous variables were summarized as median (min–max) and categorical variables as n (%). Intergroup comparisons were performed using the Wilcoxon signed-rank test. All tests were two-tailed, with $\alpha = 0.05$. 90-day overall survival was estimated via Kaplan–Meier analysis (R v4.3.2), and between-group differences were assessed using the Log rank test. Statistical significance was set at $P < 0.05$.

Results

Patient Characteristics

The detailed anonymized case descriptions are provided in Table 1. Ten patients (median age, 6.5 years; 50% male; median weight, 21.5 kg) participated in this study. Acute leukemia (70%, n=7) and allogeneic hematopoietic stem cell transplantation (allo-HSCT) (30%, n=3) are shown. All the patients were profoundly immunosuppressed. 60% (n=6) of the children had neutropenia before the ISA treatment. The number of proven/probable/possible IFI (EORTC/MSGERC 2020) was 3, 5, and 2, respectively. There were 50% (n=5) *Aspergillosis*, 30% (n=3) *Mucormycosis* and 20% (n=2) culture-negative cases (primary prophylaxis). 80% of the children were treated with other antifungal agents, including liposomal amphotericin B (n=3), voriconazole (n=3), and liposomal amphotericin B+ caspofungin (n=2). The Median duration of ISA treatment was 43.5 days (range: 10–318 days). One patient died due to bacterial sepsis.

TDM, Pharmacist Interventions and Efficacy

A total of 42 C_{trough} samples from ten patients are shown in Table 2. The median initial dose was 7.9 (mg/kg/day). The initial median of C_{trough} was 1.7 mg/L (range: 0.9–5.1 mg/L), with 60% below the therapeutic target. Pharmacist-initiated interventions were performed in 70% (n=7) of patients, including ISA dose escalation in 6 cases and ISA dose reduction in 1 case. TDM revealed 60% initial subtherapeutic trough concentrations in Figure 1. Pharmacist-led dose increase improved response from 33% to 100% in the adjusted cohort. Box plot illustrating ISA trough concentrations in 10 Chinese pediatric patients, with a median of 3.0 mg/L within the target range of 2.0–4.0 mg/L in Figure 2, alongside a pharmacist-led TDM decision pathway for dose optimization and safety monitoring.

Table 1 Baseline Characteristics and Outcomes (n=10)

Patient	Age/ Sex (Years)	Weight (kg)	Disease	Neutropenia	IFI Classification	Main Pathogen	Sample	ISA Indication	Prior Antifungal (Stopping Reason)	ISA Duration (Days)	42-Day Response	90-Day Status	Adverse Events (CTCAE v5)
1	12/F	33.5	ALL	No	Probable	Mucorales	Lung/ blood	Salvage	L-AmB (renal impairment)	318	Complete	Alive	None
2	3.8/F	12.8	ALL	No	Probable	Mucorales	Lung	Salvage	L-AmB (clinical failure)	59	Complete	Alive	None
3	13/F	28	AML/MS	Yes	Probable	Mucorales	Lung	Salvage	L-AmB (hypokalaemia)	10	Complete	Alive	None
4	1.4/F	10.7	AML	No	Proven	Aspergillus spp.	Blood	Salvage	Voriconazole (clinical failure/renal)	77	Partial	Alive	Grade 1 ALT↑
5	0.2/F	5.5	CHD	No	Probable	Aspergillus spp.	Lung	Salvage	Voriconazole (hepatotoxicity/renal)	31	Partial	Alive	None
6	16/M	52	AML/ Allo-HSCT	Yes	Proven	Aspergillus fumigatus	Lung	Salvage	Voriconazole (neurotoxicity)	56	Complete	Alive	None
7	8/M	25	AML/ Allo-HSCT	Yes	Probable	Aspergillus spp.	Lung	Salvage	L-AmB/ Caspofungin (renal)	42	Partial	Alive	Grade 2 ALT↑
8	5/M	18	NB	Yes	Possible	Negative	Lung	Prophylaxis	–	28	N/A (prophylaxis)	Alive	None
9	14/M	48	ALL/ Allo-HSCT	Yes	Proven	Candida/ Aspergillus	Lung/ blood	Salvage	Caspofungin/L-AmB (breakthrough)	21	Complete	Alive	None
10	2/M	11	AML	Yes	Possible	Negative	Lung	Prophylaxis	–	45	N/A (prophylaxis)	Died	None

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; MS, myeloid sarcoma; CHD, congenital heart disease; NB, neuroblastoma; allo-HSCT, allogeneic haematopoietic stem cell transplantation; L-AmB, liposomal amphotericin B. ALT↑, increased alanine aminotransferase.

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Table 2 Individual TDM Data and Interventions

Patient	Initial Dose (mg/kg/day)	Initial C_{trough} (mg/L) (Day 3–7)	Subtherapeutic (<2 mg/L)	Pharmacist Intervention	Adjusted Dose (mg/kg/day)	Final C_{trough} (mg/L)	Target Attained (2–4 mg/L)	Estimated AUC_{0-24} MIC
1	6.0	1.4	Yes	↑100%	12.0	3.6	Yes	212
2	7.8	1.2	Yes	↑100%	15.6	3.1	Yes	189
3	7.1	1.1	Yes	↑100%	14.3	2.9	Yes	167
4	8.4	0.9	Yes	↑100%	16.8	2.8	Yes	178
5	8.0	1.6	Yes	↑50%	12.0	2.4	Yes	145
6	3.8	2.9	No	Continue	3.8	3.2	Yes	224
7	8.0	2.1	No	Continue	8.0	2.6	Yes	198
8	11.1	3.8	No	Continue	11.1	4.0	Yes	N/A (prophylaxis)
9	4.2	1.8	Yes	↑33%	5.6	2.3	Yes	156
10	9.1	5.1	No	↓20%	7.3	3.7	Yes	N/A (prophylaxis)

Notes: ↑: Increased Dosage. ↓: Decreased Dosage. Target C_{trough} (2–4 mg/L) was extrapolated from adult PK/PD data and pediatric bridging studies.
Abbreviations: C_{trough}, trough concentration; AUC_{0-24}, area under the concentration–time curve from 0 to 24 h; MIC, minimum inhibitory concentration (EUCAST breakpoints used for Aspergillus spp. and Mucorales); N/A not applicable.

The results of LC-MS/MS method validation are displayed in Table S1, which are up to the standard. After adjustments, 83% of the patients achieved target trough concentrations. Day 42: favorable response 80% (CR 50%, PR 30%). Both failures had a persistent C_{trough} <1.2 mg/L (*Mucormycosis*). The 90-day IFI-attributable mortality rate is 10%. The median estimated AUC_{0-24}/MIC for ISA was 183.5, which was larger than 50.48 for a survival rate of 50%.[26] Patients who achieved the target C_{trough} of the ISA (2–4 mg/L) after pharmacist intervention had a significantly higher 90-day overall survival rate than those who did not ($p = 0.041$) (Figure S1).

Safety

Grade 1–2 hepatotoxicity occurred in 20% of the patients. No cases of QTc prolongation, nephrotoxicity, or treatment discontinuation were reported.

Discussion

Because suboptimal antifungal exposure can cause grave consequences, TDM of triazoles (such as voriconazole, ISA, and itraconazole) is indispensable for dose optimization and maximizing the probability of treatment success in patients with invasive fungal infections, especially in children. However, studies revealed substantial variability in ISA plasma levels among individual patients.[18,27] Few studies have been conducted on TDM-guided optimization of ISA in Chinese pediatric patients.

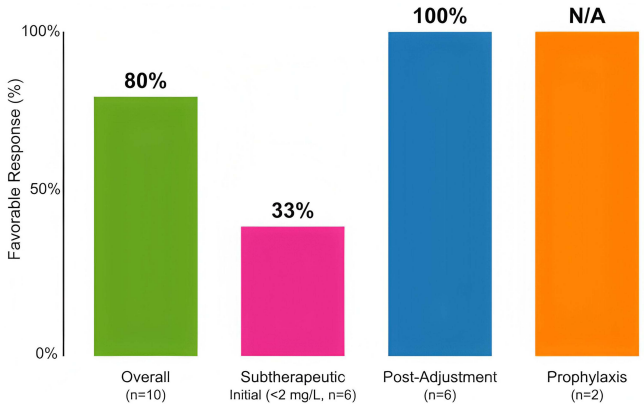

Figure 1 Clinical Response Rate of Isavuconazole in Chinese Children with IFI. TDM revealed 60% initial subtherapeutic trough concentrations. Pharmacist-led dose increase improved response from 33% to 100% in the adjusted cohort.
Abbreviations: IFIs, Invasive fungal infections; TDM, Therapeutic drug monitoring.

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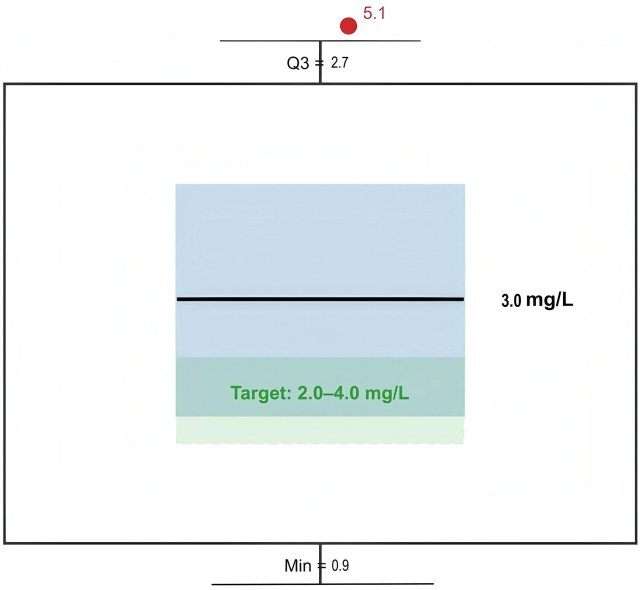

Figure 2 The Concentrations of Isavuconazole in Chinese Children. The initial C_{trough} (mg/L) (Day 3–7) was 1.7 mg/L (IQR, 1.25–2.70). The min and max initial C_{trough} were 0.9 and 5.1 mg/L. The median final C_{trough} after TDM-based dosing was 3.0 mg/L (IQR, 2.65–3.50).

Regarding mortality, a retrospective single-center review showed that patients who died from IFI had a lower average daily AUC than those who died from non-IFI causes.[3] The lower limit proposed in a pediatric ISA PK study for prophylaxis was 60 mg*h/L.[28] Although the median daily C_{trough} was also low in patients who died from IFI and significant heterogeneity was observed, the effective exposure level was associated with a target steady-state AUC >100 mg·h/L.[3] Similar to vancomycin, trough concentration alone did not correlate well with AUC.[29] In contrast to previous conclusions in adults,[30] there was no correlation between the dose and ISA plasma concentration in children or patients with a high body weight (BMI).[31,32] In contrast, low BMI, long-term use, higher doses, liver dysfunction, older age, Asian ethnicity, and combination therapy with CYP3A4/5 inhibitors are associated with increased ISA exposure.[33]

While the published pediatric cohorts are summarized in Table 3, our TDM-based strategy with little samples (n=10) resulted in the favorable outcomes: an 80% response rate and 10% 90-day mortality. In our study, the median of final C_{trough} was 3.0 mg/L within the range 2.0–4.0 mg/L which was reported in adult series.[34] Meanwhile, existing studies have suggested keeping the ISA concentration below approximately 5.0 mg/L to reduce the risk of toxicity, including gastrointestinal reactions and hepatotoxicity.[35–37] In our study, no cases of QTc prolongation, nephrotoxicity, or treatment discontinuation were reported, and grade 1–2 hepatotoxicity occurred in 20% of patients.

The optimal dose also depends on the specific conditions. Higher exposure levels may be required for young children or patients receiving ECMO.[19,27] In Table 1, 70% (n=7) children accepted pharmacist-led intervention, and most of the children received an increased dosage (33–100%). A maintenance dose of 400 mg is sufficient for ECMO or severe COVID-19-associated pulmonary *Aspergillosis* (CAPA) patients to attain the target plasma concentration, thereby

Table 3 Comparison with Published Pediatric Cohorts of Isavuconazole

Study	Publication Year	Country	N	Median Age (year)	Salvage Use (%)	Out-of-Range Rate (%)	TDM Intervention Rate (%)	Overall Response Rate (%)	Mortality (%)
Ergun et al[20]	2024	Europe	12	11	75	42%	80%	75	17
Ledesma[18]	2023	Spain	15	13	67	60	100	50	47
Mendoza[38]	2026	Spain	107	11	67	59	80	60	20
Zimmermann[34]	2022	France	15	9	100	33	100	60	13
Decembrino[39]	2020	Italy	29	14.5	69	Not reported	100	71	14

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meeting the intended therapeutic objectives.[40,41] Usually, a standard maintenance dose of 200 mg/day ensures effective exposure in all patients.[33] Patients should adopt a more cautious strategy for dose optimization to achieve safe and effective treatment, such as in children, obesity, severe liver dysfunction, and reduced ISA exposure.[19,34,42]

Therefore, long-term ISA therapy may increase the need for therapeutic drug monitoring. Repeated administration of ISA results in prolonged half-life, which may lead to drug accumulation with long-term use.[43] PPK analysis indicated ISA accumulation, predicting that 28% and 39% of hospitalized patients would exceed the therapeutic threshold (>5.00 mg/L) after four and 60 days, respectively.[44] Long-term ISA therapy also caused more adverse events (median 134 days in patients with adverse events).[37] In our study, one child used ISA for a maximum of 318 days. Overall, these findings emphasize the potential risk of ISA accumulation during long-term treatment that requires vigilance and TDM.

Our study presents the largest pediatric cohort treated with ISA in Asia and the first to systematically combine therapeutic drug monitoring (TDM) with an antifungal stewardship program. Key novel findings included a high rate of subtherapeutic drug exposure (60%). Pharmacist-driven dose escalation based on TDM has improved treatment outcomes in pediatric patients. Furthermore, the total drug AUC/MIC (>50.5 for *Aspergillus* spp.) is the PK-PD index that appears to best link ISA exposure with efficacy in preclinical models.[10] Finally, ISA demonstrated superior tolerability compared to the voriconazole and amphotericin B formulations.

However, several important limitations of this study should be acknowledged, and our findings should be interpreted with caution. First, the small sample size (n=10) markedly limited the statistical power and generalizability of our findings, and reduced the robustness of the Kaplan–Meier survival analysis and Log rank test performed in this cohort. Second, the retrospective, single-arm study design without a control group restricted our ability to perform head-to-head comparisons of efficacy and safety between ISA and other antifungal agents, increased the risk of selection bias, and limited causal inference. Third, we were unable to attribute clinical treatment success solely to ISA therapy, as multiple potential confounding factors may have affected patient outcomes. Fourth, limited PK sampling was performed in this study, with only trough concentrations collected via routine clinical therapeutic drug monitoring rather than intensive PK sampling.

Conclusions

Whether ISA requires TDM is still debated. Our findings suggest that ISA is maybe effective and well-tolerated in Chinese children with IFI when combined with routine TDM and clinical pharmacist stewardship. However, due to the small sample size and heterogeneous clinical characteristics, larger-scale multi-center studies are needed in the future to verify our results.

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Disclosure

The authors report no conflicts of interest in this work.

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