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REVIEW

Current Evidence on Voriconazole Exposure and Individualized Therapy for Aspergillosis

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Abstract: With emerging global antifungal resistance, voriconazole is a preferred first-line antifungal agent for the treatment of aspergillosis, and therapeutic drug monitoring (TDM) is frequently utilized during therapy. This review examines evidence from international guidelines, clinical studies, case reports, and population pharmacokinetic analyses to investigate the multifactorial drivers influencing voriconazole therapy. Current guidelines demonstrate variability in recommended target trough concentrations, though a range of 1.0–5.5 mg/L appears as a frequently cited reference interval; however, these recommendations are often derived from heterogeneous populations rather than being specific to aspergillosis. Plasma voriconazole concentration alone may not fully account for the variability in clinical outcomes. Efficacy and safety are influenced by multiple factors, including CYP2C19 polymorphisms, disease severity, host immune status, and infection site. Consequently, the interpretation of a single concentration threshold may be limited. A multidimensional approach—considering genotype, host factors, inflammatory status, and dynamic clinical context—is a component of individualized therapy for characterizing treatment response and toxicity risk. Within this framework, TDM is an established tool for assessing systemic exposure, and its integration with clinical and biological information is relevant for clinical assessment. Altogether, these observations underscore the value of integrated clinical assessment while identifying remaining evidence gaps for further investigation.

Keywords: voriconazole, *Aspergillus*, therapeutic drug monitoring, individualized dosing, pharmacokinetics

Introduction

Aspergillosis is a clinically significant fungal infection caused by species of the genus *Aspergillus*. It predominantly affects immunocompromised individuals, as well as critically ill patients in intensive care units (ICUs), particularly those with severe viral infections.[1,2] The incidence of invasive aspergillosis (IA) varies considerably across different patient populations and geographic regions.[1–7] In certain areas of Africa, prevalence rates as high as 27% have been reported, with associated mortality exceeding 60%.[8] Globally, IA is estimated to affect more than 2 million individuals annually, with crude mortality rates surpassing 85% in high-risk populations, including patients with chronic obstructive pulmonary disease, those admitted to ICUs, individuals with lung cancer, and patients with hematological malignancies.[9]

Due to environmental selection pressure and the agricultural use of azole fungicides, azole resistance in *Aspergillus* spp. has shown an upward trend[10] with regional variability in resistance rates.[11,12] The underlying mechanisms of azole resistance are multifactorial and include mutations in the *CYP51A* gene, overexpression of efflux transporters, and alterations in non-target genes,[13,14] thereby further complicating antifungal therapy.

Current international guidelines recommend triazole antifungals, such as voriconazole, isavuconazole, and posaconazole, as first-line agents for the treatment of aspergillosis.[15,16] Voriconazole, a second-generation triazole, has been consistently endorsed as the preferred first-line therapy by multiple clinical practice guidelines.[17–21] However, voriconazole is characterized by nonlinear pharmacokinetics, leading to pronounced interindividual and intraindividual variability in systemic exposure.[22] Key determinants of voriconazole pharmacokinetics include CYP2C19 genetic polymorphisms, body weight, hepatic function, concomitant medications, and inflammatory status.[23] Notably, the

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prevalence of CYP2C19 poor metabolizer phenotypes is significantly higher in East Asian, Southeast Asian, and Indigenous Oceanian populations compared with Caucasians, whereas rapid metabolizers are more commonly observed in Europe, the Middle East, and Africa.[24]

Despite its established role as a first-line antifungal agent, voriconazole has a narrow therapeutic window. Most guidelines recommend a target trough concentration range of 1.0–5.5 mg/L, (IDSA;[18] ESCMID-ECMM[20]), whereas Takesue et al[25] specify a narrower target of 2.0–4.0 mg/L for Asian patients with aspergillosis. While TDM is frequently utilized to achieve therapeutic levels, consensus remains lacking regarding optimal target concentrations, site-specific therapeutic thresholds, and individualized dosing strategies across diverse patient populations.

This review aims to summarize target concentration ranges, dosing regimens, and individualized TDM practices for site-specific infections in the treatment of aspergillosis from the existing literature.

Methods

Literature Search and Screening

PubMed and Web of Science databases were searched for literature published between January 2002 and July 2025. The objective was to identify studies concerning voriconazole treatment for *Aspergillus* infections in the context of therapeutic drug monitoring. Search terms included "voriconazole", "aspergillosis", "invasive aspergillosis", "pharmacokinetics", and "therapeutic drug monitoring", as well as site-specific terms such as "brain", "intracranial", and "CNS", utilizing Boolean operators (AND/OR). Search terms also included "dose adjustment" and "dose optimization" to capture relevant literature. A manual search of references within the included studies and relevant guidelines was also performed. Following the removal of duplicates, potential literature was screened based on titles and abstracts, followed by a full-text review.

Inclusion Criteria

A literature search was conducted to identify relevant studies on voriconazole for the treatment of aspergillosis. Inclusion criteria comprised randomized controlled trials (RCTs), cohort studies, case-control studies, case series, case reports, retrospective studies, and population pharmacokinetic (PopPK) studies. Specifically, case reports were included for patients meeting the criteria for proven or probable diagnosis as defined by the EORTC/MSG guidelines. Clinical and PopPK studies included patients categorized as proven, probable, or possible cases according to the EORTC/MSG guidelines.[26] Eligible studies were required to document voriconazole therapy for aspergillosis in conjunction with TDM and definitive blood concentration measurements.

Guidelines concerning aspergillosis management and voriconazole TDM were included if they provided target concentration ranges, dosing regimens, and dose adjustment strategies.

Data Extraction

Efficacy and safety outcomes of voriconazole at various plasma concentration levels were extracted from the included clinical studies and case reports. Additionally, relevant recommendations for voriconazole therapy in aspergillosis were collected from the identified guidelines.

Results

Associations Between Voriconazole Concentrations and Clinical Outcomes in Patients with Aspergillosis Reported in Clinical Studies

This review integrates the results of six clinical studies[27–32] involving voriconazole treatment for aspergillosis. Three of these studies identified associations between voriconazole plasma concentrations and clinical safety or efficacy.[29,31,32] Specifically, adverse reactions such as skin rash and elevated liver enzymes, alongside an increased risk of cardiotoxicity, were reported in patients with trough concentrations exceeding established thresholds. Regarding efficacy, subtherapeutic concentrations (< 1.0 mg/L or < 2.0 mg/L) were associated with treatment failure rates ranging from 45% to 83.33%. Conversely, clinical success rates of 32% to 85.7% were observed when trough concentrations remained within the range

of 1.0–5.0 mg/L (or 1.0–5.83 mg/L).[31,32] Notably, Lee et al[31] reported that in patients with chronic pulmonary aspergillosis, the lower trough concentration limit was observed at 0.5 mg/L, which was associated with a 41.7% efficacy rate and mitigated hepatotoxicity. Data extracted from these clinical studies are summarized in Table 1.

Table 1 Data on the Efficacy and Safety of Voriconazole in Clinical Studies Related to Aspergillosis

First Author	Study Design	Research Countries or Regions/Number of Centers	Study Sample Size	Effectiveness and Safety
Kim[28]	Prospective observational study	South Korea, multicenter	25 people (no explicit mention of the number of people with TDM data)	Adverse Events: For patients experiencing SAEs, the median trough concentration was 6.32 mg/L. For patients without SAEs, the median trough concentration was 2.15 mg/L. Receiver-operating characteristic (ROC) curve analysis determined a trough concentration of 5.83 mg/L as the cutoff for predicting serious adverse events. Multivariate analysis showed that a trough concentration ≥5.83 mg/L was the only independent risk factor for serious adverse events.
Teng[30]	Retrospective cohort study	China, single center (Xuanwu Hospital)	12 people (reduced dose group) + 25 people (standard dose group) (the number of people with TDM data was not clearly mentioned)	By reducing the trough concentration of voriconazole to above 0.5 mg/L, it is possible to alleviate hepatotoxicity while maintaining a certain clinical efficacy. There was no statistical difference in the therapeutic efficacy between the reduced-dose group and the standard-dose group.
Denning[29]	Open, non-controlled multicenter study	Multiple European countries, multiple centers	141 people (initially included), 116 people (evaluable for efficacy), 137 people (evaluable for safety)	Low Concentration (<0.25 mg/mL): Number of Patients: Mean blood concentrations consistently below <0.25 mg/mL were observed in 5 patients. Response: Infections in 3 patients were unresponsive to treatment. One patient's disease stabilized. One patient's disease worsened but ultimately achieved a partial response after dose escalation.
				Intermediate Concentration (500–1250 ng/mL): Number of Patients: 6. Response: Infections in 1 patient were completely responded to. In 2 patients, there was a partial response. In 2 patients, there was stable disease. In 1 patient, infection was unresponsive to treatment.

(*Continued*)

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Table 1 (Continued).

First Author	Study Design	Research Countries or Regions/Number of Centers	Study Sample Size	Effectiveness and Safety
Lee[31]	Retrospective study	Seoul, South Korea, single center	52 people	At 2 weeks, the successful clinical response rate was 45% (5/11) among patients with voriconazole trough concentrations ≤2.0 mg/L, compared with 51% (21/41) among those with trough concentrations >2.0 mg/L. There was no statistically significant difference between the two groups (P = 0.73). At 4 weeks, the successful clinical response rate was 45% (5/11) among patients with voriconazole trough concentrations ≤2 mg/L, compared with 63% (26/41) among those with trough concentrations >2.0 mg/L. There was no statistically significant difference between the two groups (P = 0.32). At 8 weeks, the successful clinical response rate was 45% (5/11) among patients with voriconazole trough concentrations ≤2.0 mg/L, compared with 61% (25/41) among those with trough concentrations >2 mg/L. There was no statistically significant difference between the two groups (P = 0.50). Clinical successful response at week 12: The successful response rate was 45% (5/11) in patients with voriconazole trough concentration ≤2.0 mg/L and 54% (22/41) in patients with trough concentration >2.0 mg/L.
Yousefian[32]	Prospective studies	Iran, single center	24 people were initially included, and 22 people were finally included	Overall treatment failure rate: subtherapeutic group: 83.33%. Supratherapeutic group: NR. Overall mortality rate: subtherapeutic group: 62.50%. Therapeutic group: 28.57%. Supratherapeutic group: NR.
Neofytos[27]	Prospective, randomized, open-label, multicenter trial (early termination)	North America (Johns Hopkins University in the United States, University of Montreal in Canada, and other 4 centers)	29 people (15 in the standard group and 14 in the TDM group)	In the TDM group, the treatment failure rate was reduced to 7.1%, P=0.17, and the clinical success rate was 85.7%, P=0.05.

Clinical Observations of Voriconazole Concentrations and Outcomes in Aspergillosis Case Reports

Twenty-four clinical cases[33–56] provide a supplementary perspective on voriconazole treatment for aspergillosis in real-world settings (detailed in Supplementary Table 1). Analysis of these cases indicates that clinical improvement was observed within a trough concentration range of 1.0–3.0 mg/L, while concentrations below 2.0 mg/L or above 5.0 mg/L were associated with treatment failure and toxicity, respectively. Individual cases showed clinical improvement at relatively low trough concentrations, such as 0.6 mg/L.[51] However, some patients did not exhibit favorable clinical responses despite maintaining concentrations within recommended ranges (eg., 2.87 mg/L,[49] 3.8 mg/L,[44] and 4.22 mg/L[57]). Reflecting the limitations of case-level evidence, these observations remain hypothesis-generating and provide exploratory insights rather than definitive causality or universal therapeutic thresholds.

Voriconazole Dosing and TDM Guidance Within Aspergillosis Treatment Guidelines and Pharmacotherapy TDM Guidelines

Guidelines for both aspergillosis treatment and voriconazole TDM emphasize the importance of conducting TDM.[15–21,58–62] While a clinical framework of "loading-maintenance-TDM-readjustment" is widely recognized, specific recommendations regarding dosing and target thresholds vary among different clinical and TDM-specific organizations. For adults, the initial loading dose is typically 6 mg/kg every 12 hours (two doses), followed by a maintenance dose of 4 mg/kg every 12 hours, with TDM initiation recommended during the early phase of treatment (days 4–7).[15,18,19,21,58,63] Guidelines state that special populations, such as individuals with hepatic impairment, those undergoing continuous renal replacement therapy (CRRT), or CYP2C19 poor metabolizers, require early monitoring to facilitate individualized dosing and reduce dose-related toxicities. However, the recommended trough concentration ranges are not standardized, with values including 1.0–5.5 mg/L,[18–21] 1.0–6.0 mg/L,[60] and 1.0–5.0 mg/L.[17,18] Notably, Takesue et al[25] specify a target range of 2.0–4.0 mg/L for Asian patients with aspergillosis. Furthermore, dose adjustment strategies differ, with some guidelines suggesting 50% increments or reductions based on target attainment.[58,63] Detailed comparisons of dosing ranges, adjustment schemes, and considerations for special populations are provided in Table 2.

Voriconazole Treatment for *Aspergillus* Infections in Specific Sites

Clinical guideline recommendations for voriconazole therapy are differentiated by the anatomical site of infection (Table 3).[15,18,19,21] For extrapulmonary manifestations, the currently available guidelines specify protocols that diverge from standard pulmonary management across three primary variables: therapeutic duration, the timing of surgical adjuncts, and individualized TDM targets. Specifically, the clinical recommendations include prolonged treatment courses for osteoarticular and chronic pulmonary infections, alongside mandatory early surgical debridement for sinonasal and ocular involvements. TDM trough targets for central nervous system (CNS) and disseminated disease are adjusted to higher ranges relative to pulmonary protocols to ensure adequate tissue penetration.

Summary of PopPK Studies of Voriconazole in Patients with Aspergillosis

This review summarizes 4 PopPK studies involving patients with aspergillosis.[66–69] The authors of these investigations made use of a variety of diverse modeling approaches to investigate and explore the factors that are associated with voriconazole exposure variability and the clinical implications that they identified.

Chantharit et al[69] reported that for patients with serum albumin (SA) levels ≤ 30.0 g/L, a maintenance dose of 200 mg po q12h enabled 64% of the cohort to reach the target concentration of ≥ 2.0 mg/L. The researchers noted that patients with SA > 30.0 g/L appeared to require higher dosages to achieve the same therapeutic target. They observed no significant influence from the CYP2C19 genotype, suggesting that inflammation-related factors might mask its potential effects, and they identified serum albumin and GGT as parameters for routine clinical monitoring.

In their evaluation, Duangpraphat et al[66] found that intravenous administration resulted in higher AUC:EC50 ratios compared to oral dosing. The authors indicated that critically ill patients requiring intubation exhibited significantly elevated AUC:EC50 ratios. They also pointed out that individuals with higher EC50 values might face risks of

Table 2 Comparison of Voriconazole Dosing and TDM Recommendations in Aspergillosis Management and TDM-Specific Guidelines

Author (Year)	Adult Dosing Regimen	Pediatric Dosing Regimen	Target Trough Concentration (mg/L)	Dose Adjustment Strategy	Special-Population Considerations
Agarwal et al[16] (2024)	PO 400 mg/day in two divided doses; max 600 mg/day. Administer on an empty stomach; TDM target trough ≥1 mg/L.	NA	>1.0	NA	Avoid in pregnancy.
Husain et al[21] (2019)	IV/PO: loading 6 mg/kg q12h on day 1, then 4 mg/kg q12h; target trough >1 mg/L.	2–14 y & <50 kg: 9 mg/kg q12h day 1 → 8 mg/kg q12h; ≥15 y or ≥50 kg: same as adults.	1.0–5.5; 2.0–6.0 in severe infection	Increase dose if trough below target; reduce if above.	Higher doses needed in cystic fibrosis; ECMO/ critically ill require routine TDM because of unstable clearance; renal impairment—no dose reduction, but TDM advised.
Walsh et al[58] (2008)	IV 6 mg/kg q12h day 1 → 4 mg/ kg q12h; step-down to PO 200 mg q12h when stable	7 mg/kg IV/PO q12h	1.0–5.5	<1.0: ↑50%; >5.5: ↓50%; re-check after 2–3 d.	Avoid prolonged IV in renal impairment; HSCT/ severe immunosuppression: 4–6 mg/kg IV q12h or 200 mg PO q12h.
Epelbaum et al[17] (2024)	IV 6 mg/kg q12h day 1 → 4 mg/ kg q12h; step-down PO 200 mg q12h.	2–14 y & <50 kg: 50% higher than adult (9 mg/kg q12h day 1 → 8 mg/ kg q12h).	NA	NA	NA
Patterson et al[18] (2016)	IV 6 mg/kg q12h day 1 → 4 mg/ kg q12h; step-down PO 200 mg q12h; trough target >1.0–1.5 mg/L.	2–14 y & <50 kg: IV 9 mg/kg q12h day 1 → 8 mg/kg q12h; PO 9 mg/kg q12h.	>1.0–1.5; <5.0–6.0	<1.0 mg/L: ↑daily dose 50% or add omeprazole; >5.0–6.0 mg/L or toxicity: interrupt and restart at lower dose when 1–5 mg/L.	Hepatic impairment: dose reduction; immunosuppressed & elderly: TDM recommended.
Douglas et al[15] (2021)	IV 6 mg/kg q12h day 1 → 4 mg/ kg q12h; step-down PO 300 mg bid; TDM target 1.0–6.0 mg/L.	<50 kg: 9 mg/kg q12h day 1 → 8 mg/ kg q12h; ≥50 kg: as adults; PO 9 mg/kg q12h.	NA	NA	NA
Garcia-Vidal[60] et al (2018)	IV 6 mg/kg q12h day 1 → 4 mg/ kg q12h; step-down PO 300 mg bid; TDM target 1.0–6.0 mg/L.	NA	1.0–6.0	Increase if below range; reduce if above.	NA

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Ullmann et al[19] (2018)	IV 6 mg/kg q12h day 1 → 4 mg/kg q12h; PO 200–300 mg q12h; severe infection trough 2.0–6.0 mg/L.	<50 kg: 18 mg/kg/day divided q12h → 16 mg/kg/day; ≥15 y or ≥50 kg: as adults.	1.0–5.5; 2.0–6.0 in severe infection	Adjust dose if outside range; re-check within 1 week.	Moderate hepatic/renal impairment: halve dose; severe: further reduction + close TDM.
Denning et al[59] (2016)	150–200 mg q12h; trough 1.0–5.0 mg/L.	NA	NA	NA	Lower doses advised in elderly (>70 y), low-weight patients, severe hepatic disease, and North-East Asian ethnicity.
Koehler et al[61] (2021)	IV 6 mg/kg q12h day 1 → 4 mg/kg q12h.	NA	2.0–6.0	NA	Routine TDM performed.
Wichmann et al[62] (2025)	IV 6 mg/kg q12h (total 12 mg/kg day 1); from day 2: 4 mg/kg q12h; step-down PO 200–300 mg q12h (300 mg if ≥40 kg, 200 mg if <40 kg).	NA	2.0–6.0	NA	Hepatic impairment (Child A/B): loading 6 mg/kg q12h, then 2 mg/kg q12h from day 2.
Warris et al[20] (2019)	NA	NA	1.0–5.5; 2.0–6.0 in severe infection	NA	NA
Takesue et al[25] (2022)	IV 300 mg q12h.	NA	2.0–4.0	Increase if low; reduce if high.	Dose by ideal/adjusted weight in obesity/low weight; Child-Pugh A/B: half maintenance after standard load, C: quarter; TBil ≥3 mg/dL: load 200 mg q12h → 50 mg q12h; TBil ≥10 mg/dL: 100 mg q24h/50 mg q24h; CrCl<50 mL/min: avoid IV; PPI co-administration—adjust after TDM.
Ashbee et al[64] (2014)	IV 6 mg/kg q12h day 1 → 4 mg/kg q12h.	9 mg/kg load → 8 mg/kg maintenance.	1.0–5.5; 2.0–6.0 in severe infection	NA	NA
Chen et al[63] (2018)	4 mg/kg or 200 mg twice daily.	NA	0.5–5.0	<0.5 mg/L or poor response: ↑50%; 5–10 mg/L without ≥grade-2 AE: ↓20%; >10 mg/L or ≥grade-2 AE: skip one dose then ↓50%; repeat TDM after any change.	Routine TDM in special populations.

(*Continued*)

Table 2 (Continued).

Author (Year)	Adult Dosing Regimen	Pediatric Dosing Regimen	Target Trough Concentration (mg/L)	Dose Adjustment Strategy	Special-Population Considerations
Chau et al[65] (2021)	Without pantoprazole: 500–600 mg q12h; with pantoprazole: 400–450 mg q12h.	12 mg/kg q12h	1.0–5.5; >2.0–3.0 in severe infection	If low: ↑25–50%; after two adjustments consider CYP2C19 ultra-rapid metabolizer (UM) genotyping or increase frequency/add PPI; if >5.5 mg/L: asymptomatic ↓25%, toxic ↓50% after one skipped dose.	Base dose on total body weight in obesity; CYP2C19 UM: 500–600 mg q12h (no PPI) or 400–450 mg q12h (with PPI); renal impairment—adjust by eGFR, acknowledging limited reliability; CNS/severe infection target >2.0–3.0 mg/L.

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Table 3 Summary of Clinical Guideline Recommendations for Voriconazole Therapy Across Different Sites of Aspergillosis Infection

Infection Site	Recommended Duration (Author)	Adjunctive Therapy: Surgical/ Local (Author)	Notes
Pulmonary (IPA)	6–12 weeks;[18,19] 12 weeks[15,21]	Surgery generally not required[19]	Douglas et al: First follow-up CT no earlier than Day 14.[15]
Chronic Pulmonary (CPA)	≥6 months[18,19,61]	Single aspergilloma resectable[19]	Patterson et al: Long-term monitoring of resistance and toxicity required.[18]
Airway (TBA)	12 weeks;[18] 12–20 weeks[21,58]	Inhaled AmB;[18,21,58] Bronchoscopic debridement[18]	Husain et al: Confirm mucosal healing via bronchoscopy before discontinuation.[21]
Sinonasal/Orbital	4–8 weeks;[19] 6–12 weeks;[15,18] 4–8 weeks for acute invasive, extend to 8–12 weeks if lesions/ immunosuppression persist[20]	Surgical debridement within 24h;[15] Mandatory surgery[18,19,62]	Douglas et al: Intraoperative frozen section recommended.[15] Warris et al: Evaluation of residual lesion status is critical.[20]
CNS	>8–12 weeks;[19,58] ≥12 weeks, extend to 16–24 weeks if lesions remain or CSF-GM positive;[15,21] 200mg q12h lifelong post-op[58]	Surgery for single lesion;[15] Surgical debridement;[19,21,58] 7 mg/kg IV q12h post-op for resectable lesions[58]	Douglas et al: Discontinuation requires MRI stability/reduction and CSF-GM <0.5.[15,21] Walsh: MRI every 6 months for lifelong cases.[58]
Disseminated (Multifocal)	≥12 weeks;[15] 16–24 weeks[21,58]	Aspiration drainage;[21,58] Imaging follow-up for each organ[15]	Husain et al: Initial combination VCZ + L-AmB favored for multi-organ involvement.[21]
Bone/Osteoarticular	≥6–12 months until bone healing/ normal inflammatory markers/immune recovery;[18,19] ≥3–6 months post-debridement, longer for CGD/ vertebral;[15] ≥12 weeks, extend to 16–24 weeks if defects/implants remain;[21] ≥6–8 weeks[58]	Thorough debridement/ sequestrectomy; Hyperbaric oxygen[21,58]	Douglas et al: Monitor CRP/ESR. Husain: Target trough same as CNS (2–6 mg/L).[21] Patterson: Requires evidence of immune recovery.[18]
Skin/Soft Tissue	Post-op ≥4–6 weeks until wound healing and immunosuppression stops;[18,19] ≥4–6 weeks, >12 weeks for burns/disseminated;[15] ≥12 weeks;[21] 4–6 weeks[58]	Surgical debridement (Consensus); Debridement for large-area burns[18]	Husain et al: Follow-up imaging and wound culture required every 4 weeks.[21] Patterson et al: Focus on total cessation of immunosuppressive therapy.[18]
Endophthalmitis	6–12 weeks;[15,21] ≥8–10 weeks[58]	Intravitreal 50–100μg (Consensus); 1–3 injections at 48–72h intervals;[21] 50μg/0.1 mL once, repeat at 48h if needed;[58] 100μg/0.1 mL[18]	Husain et al: Stop-criteria include resolved fundus inflammation and negative vitreous culture.[21] Patterson et al: 24h post-injection OCT for retinal toxicity.[18]
Keratitis	Local therapy ≥2 weeks[15]	Local Natamycin;[15,18] Corneal transplant for deep/perforated cases[15]	Douglas et al: Systemic therapy not proven beneficial; corticosteroids strictly prohibited.[15]
Cardiovascular	≥6 weeks[19,61]	Valve/Lesion replacement and excision[19,61]	Koehler et al: If surgery is not possible, extend duration to ≥6 months.[61]

suboptimal outcomes similar to those observed with elevated minimum inhibitory concentrations (MIC). Consequently, the investigators discussed the possibility of adjusting target concentrations within a range up to 6.0 mg/L, using galactomannan levels as an indirect measure to evaluate therapeutic response and inform dose adjustments.

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Wang et al[66] stated that patients undergoing CRRT required increased loading doses (≥5 mg/kg q12h) and maintenance doses (4 mg/kg q12h) to reach target levels. For non-CRRT patients, the authors found that 2 mg/kg q12h was sufficient to achieve the target range of 2.0–5.0 mg/L. They also highlighted the influence of CRP, GGT, and AST on drug clearance, suggesting that dosage adjustments be made based on the dynamic changes of these markers.

Liu and Mould[67] focused on the concurrent use of voriconazole and anidulafungin, noting a synergistic effect of combined exposure on hepatic adverse events. The authors observed that during monotherapy, dose adjustments might be guided by clinical response and tolerance rather than strict adherence to fixed concentration thresholds. However, in the context of combination therapy, they emphasized that monitoring exposure served as a method to mitigate the risk of cumulative toxicities, such as hepatotoxicity and psychiatric symptoms. The primary findings and characteristics of these four investigations are summarized in Table 4.

Discussion

Clinical Utility of Trough Concentration Thresholds in Voriconazole Therapy for Aspergillosis

Currently, it is widely accepted that the clinical efficacy and safety of voriconazole are closely linked to its systemic exposure levels. Accordingly, major clinical guidelines unanimously recognize the pivotal role of voriconazole in aspergillosis treatment and advocate for the implementation of TDM.[15,18,20,59] Notably, a seminal 2008 study by Pascual et al[70] recommended a target trough concentration range of 1.0–5.5 mg/L, a threshold that has since been extensively cited in the literature. Moreover, multiple meta-analyses have confirmed that maintaining voriconazole plasma concentrations within specific thresholds is significantly associated with improved clinical outcomes.[71–74] Corroborating these observations, preclinical mouse models validate that voriconazole efficacy is exposure-dependent, providing a pharmacological foundation for clinical target concentrations.[75–77]

Although current guidelines offer differing perspectives on the target plasma concentration for voriconazole, most are categorized as strong recommendations based on low-level evidence. An integration of existing guidelines reveals that these recommended concentrations are not entirely consistent. Even regarding the target concentration intervals, descriptions vary among guidelines: most employ closed intervals, whereas others use ranges defined by inequalities; for instance, the guidelines by Patterson et al[18] specify a target of >1.0 mg/L and <5.0–6.0 mg/L. Furthermore, multiple aspergillosis treatment guidelines[20,21,61,62] cite the 2017 ESCMID guidelines in their plasma concentration recommendations. However, several studies cited by the ESCMID guidelines to establish these targets included patients with various fungal infections,[70,78–81] rather than being specifically designed for patients with aspergillosis.

Regarding real-world data, an analysis of select case reports[33–56] on voriconazole treatment for aspergillosis found that the range of effective trough concentrations for successful treatment is narrower than the standard reference intervals

Table 4 Summary of Population Pharmacokinetic Studies of Voriconazole in Patients with Aspergillosis

Author	Population Characteristics	Target Concentration Range	Key Covariates	Research Focus
Duangpraphat et al (2024)[68]	Severe aspergillosis	1.0–6.0 mg/L	Route of administration, intubation status	Relationship between AUC/EC50 and efficacy
Liu & Mould (2014)[67]	Combination with anidulafungin	1.0–6.0 mg/L	Combination therapy	Exposure-efficacy in combination therapy
Wang et al (2025)[66]	CAPA, CRRT	2.0–5.0 mg/L	CRRT, CRP, GGT, AST, PLT	Critical illness and renal replacement therapy
Chantharit et al (2020)[69]	Adult IPA	2.0–5.0 mg/L	Albumin, GGT, body weight	Clearance prediction models

recommended by major guidelines. Given the limitations of case reports in terms of study design and sample size, these observations should be interpreted with caution; their primary value lies in providing clues to understand the heterogeneity of the voriconazole exposure-response relationship, rather than serving as a basis for establishing a uniform therapeutic threshold. However, a clinical study by Teng et al[30] suggested that maintaining voriconazole trough concentrations above 0.5 mg/L can sustain efficacy in chronic pulmonary aspergillosis (CPA). This suggests that CYP2C19 poor metabolizers may also achieve safe, long-term therapy by initially halving the dose and implementing TDM.

Limitations of Fixed Trough Concentration Thresholds and TDM Strategies

Lee et al[31] noted that an individual trough concentration may not accurately reflect true systemic exposure, pointing out that host factors such as neutrophil counts and immunosuppression status are more predictive of acute efficacy than drug concentrations alone. This underscores the profound impact of individual patient factors on clinical outcomes. Consequently, several studies have raised dissenting views regarding the sole reliance on voriconazole TDM. For instance, Tan et al[82] utilized a probability model to suggest that monitoring liver function is more effective than monitoring voriconazole blood levels. Furthermore, a clinical trial by Veringa et al[83] evaluated hematology patients with IA. This study found that a passive TDM strategy maintaining trough concentrations between 1 to 6 mg/L failed to improve the 28-day composite outcome compared to standard dosing. The strategy did not significantly reduce mortality rates or treatment discontinuation caused by toxicity, yielding a P value of 0.93.Troke et al[78] further observed that at high concentrations, the efficacy of voriconazole in aspergillosis patients was significantly lower than in those with *yeast* infections. They contended that efficacy does not monotonically increase with plasma concentration. Instead, it must be integrated with pathogen MIC and host factors, proposing a trough to MIC ratio of 2 to 5 as an individualized TDM target. Similarly, Ueda et al[84] found that in non-refractory hematological patients with IA, a trough concentration of 2.0 mg/L or greater was associated with clinical response, while failure rates rose significantly below this threshold. However, in refractory cases, concentrations exceeding 2.0 mg/L yielded no additional benefit. This indicates that simply escalating drug concentrations is insufficient to overcome therapeutic challenges in refractory patients, thereby highlighting the necessity of individualized assessment.

Influence of *Aspergillus* Resistance on Voriconazole Efficacy

A review indicates that *Aspergillus* resistance has spread globally, with resistant strains detected in clinical and environmental isolates across numerous countries.[85] Mechanisms of voriconazole resistance in *Aspergillus* include *CYP51A* mutations,[86–91] efflux pump overexpression,[92] off-target mutations,[93] environmental stress, and genomic instability.[94–96] A retrospective study by Lestrade et al[97] indicated that voriconazole-resistant *Aspergillus* infections significantly increased mortality rates. Uluç et al[98] suggested that in patients with multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacterial infections in respiratory intensive care units, antimicrobial resistance classification alone is insufficient to predict mortality, with outcomes being more influenced by host factors and disease severity.

Shifting Guidelines from Fixed Plasma Concentration Thresholds to Individualized Approaches

In the 2008 IDSA guidelines by Walsh et al,[58] a unified dosing regimen was formally recommended to serve as the initial approach for the clinical management of IA TDM was suggested to be applied within limited scenarios involving treatment failure, signs of toxicity, or special patient populations. In subsequent guidelines, routine TDM has been observed as a standard recommendation. Multiple meta-analyses[71,99,100] have reported the influence of individual factors on plasma concentrations.

Recent guidelines, including the 2016 IDSA update[18] and the 2021 guidelines by Chau et al,[65] maintain reference ranges for voriconazole while emphasizing the integration of multi-dimensional clinical factors such as CYP2C19 genotype, body weight, concomitant medications, and infection site These documents describe dynamic individualized

adjustments through TDM to maintain clinical efficacy and limit toxicity. Chau et al[65] further noted higher initial dosing regimens for ultra-rapid or rapid metabolizer phenotypes, which may be supplemented with genetic testing or medication switching, and reported the use of pharmacokinetic modeling software for dose prediction. Some guidelines suggest minimum plasma concentrations exceeding 2.0 mg/L for severe invasive pulmonary aspergillosis or CNS involvement,[19–21,62] suggesting that severe infections are associated with higher target concentrations.

Japanese guidelines suggest a target plasma concentration of 2.0–4.0 mg/L for Asian patients.[25] Meta-analyses by Asian authors further reported an increased neurotoxicity risk when concentrations exceeded 4.0 mg/L.[71,73] These observations likely relate to Asian CYP2C19 genetic backgrounds, particularly poor-metabolizer prevalence, potentially limiting their direct application to more diverse global cohorts. Similarly, the CPIC guideline[101] noted that treatment failure or toxicity may occur even within conventional concentration ranges due to CYP2C19 genotype variations. This suggests that fixed thresholds may not fully account for individual pharmacodynamic variability. The guideline supports a framework led by CYP2C19 phenotyping and integrated with TDM, age, developmental status, hepatic and renal function, drug interactions, and infection site characteristics. This approach is intended to achieve a balance between efficacy and safety in the treatment of IA.

Clinical Utility and Pre-Emptive Screening of CYP2C19 Polymorphisms

Current mainstream aspergillosis treatment guidelines do not include routine CYP2C19 genotyping as a standard recommendation. The CPIC guideline[101] describes CYP2C19 genotyping as an adjunct strategy for voriconazole therapy rather than a routine monitoring measure. In this context, treatment adjustments based on genotype results are noted for specific scenarios, such as therapeutic failure, a high risk of adverse reactions, special populations, or patients identified as ultra-rapid or poor metabolizers.

A meta-analysis[102] reported the potential utility of pre-screening CYP2C19 genotypes prior to individualized voriconazole therapy, primarily for patients with invasive fungal infections, particularly within Asian populations. This study also noted the application of screening in high-risk patients requiring voriconazole prophylaxis or treatment, including those with hematologic malignancies, post-hematopoietic stem cell transplantation, or febrile neutropenia. Regarding pediatric patients, the influence of genotype on drug metabolism was reported to be potentially diminished due to more rapid hepatic metabolism, and careful evaluation was suggested for this population.

While one study suggested routine genotyping,[103] such observations are often limited to specific populations or based on individual clinical experience. Mangal et al[104] emphasized the importance of integrating multiple factors, including the pathogen MIC for voriconazole, the CYP2C19 phenotype, and concomitant proton pump inhibitor use, through the utilization of a PopPK model. Routine CYP2C19 genotyping is generally not described for the general patient population. Instead, it is suggested to serve as an adjunct to guide initial dosing in high-risk populations when feasible, while TDM remains the primary approach for individualized voriconazole clinical management.

Variation in Treatment Recommendations for Specific Sites of *Aspergillus* Infection

Multiple studies reported that pulmonary and upper respiratory tract infections constitute the largest proportion of aspergillosis sites.[105–107] Voriconazole has been observed to exhibit varying tissue penetration rates across different physiological compartments.[108,109] Heterogeneity in the evidence for aspergillosis treatment primarily manifests in guideline recommendations regarding treatment duration, administration routes, and surgical intervention strategies. These discrepancies reflect the diversity of clinical evidence and the contextual factors present during the development of each guideline (Table 3). Potential drivers of this heterogeneity include the timing of guideline formulation, specific target populations, advances in diagnostic technology, reliance on distinct epidemiological data, and variations in prognostic assessment metrics. Notably, current PK/PD evidence for various infection sites remains limited and is currently insufficient to support the establishment of clear or extrapolatable site-specific quantitative exposure-response thresholds.

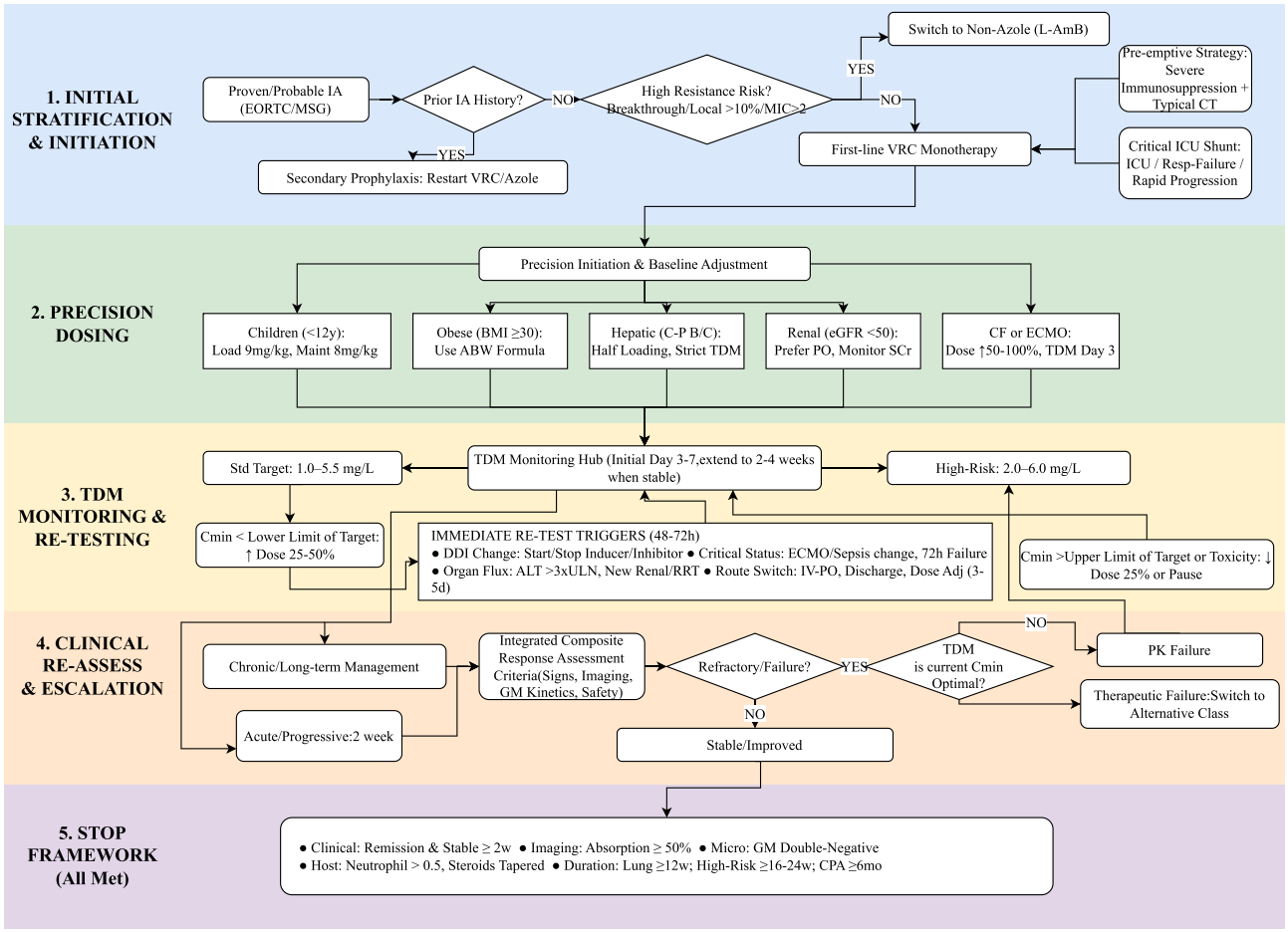

Figure 1 A Proposed Flow Diagram for the Management of Aspergillosis Using Voriconazole.

Notes: This flowchart provides a general overview based on a review of major clinical guidelines and literature. It is intended for educational and reference purposes to support the treatment of aspergillosis with Voriconazole. Treatment strategies should be individualized, taking into account patient-specific factors such as underlying conditions, comorbidities, and organ function, as well as local resistance patterns and institutional protocols. The parameters and logic described are meant to supplement, rather than replace, professional clinical judgment or the latest laboratory findings.

Abbreviations: VRC, Voriconazole; TDM, Therapeutic Drug Monitoring; L-AmB, Liposomal Amphotericin B; PK, Pharmacokinetics; GM, Galactomannan.

Management Considerations for Specific Patient Populations in Aspergillosis Therapy

In the clinical management of invasive aspergillosis, precision strategies are described for specific patient populations to address varied pharmacokinetic profiles and clinical needs. For pediatric and adolescent patients aged under 12 years or weighing 50 kg or less, higher maintenance dosing regimens are noted due to increased drug clearance, with TDM suggested as early as days 2–3 of treatment.[19,21] In critical care settings involving ECMO, severe hypoalbuminemia, or multiple organ dysfunction, an increased TDM frequency of every 3–4 days is described to address fluctuations in distribution volume and potential circuit adsorption. For severe infections or CNS involvement, an elevation of trough concentration targets to 2.0–6.0 mg/L is observed within these recommendations.[19,21] Regarding patients with organ impairment, while renal insufficiency is typically described as not requiring direct dose reduction, monitoring for excipient accumulation is suggested. Conversely, hepatic impairment represents a clear indication for dose adjustment, with TDM noted for days 3, 7, and 14, alongside potential dose reduction or transition to alternative antifungal agents based on clinical assessment.[15,21] In patients with hematologic malignancies or hematopoietic stem cell transplant recipients, continuous galactomannan monitoring is suggested to track disease progression and therapeutic response. For patients with febrile neutropenia persisting for 4–7 days, the initiation of empirical antifungal therapy is recommended.[17,18,61] Additionally, for aspergilloma cases undergoing

https://doi.org/10.2147/IDR.S579990

surgical intervention, the maintenance of antifungal therapy for at least 4 weeks both pre- and post-operatively is reported.[18]

Perspectives on Clinical Practice for Aspergillosis Management

The routine application of TDM is suggested, particularly in high-variability populations such as those in intensive care, receiving organ support therapy, or with malnutrition, to maintain effective exposure and reduce toxicity risk. While guideline-recommended trough concentration ranges serve as a reference framework, adjustments based on patient-specific factors are described. Inflammatory status, support therapy, and host immune recovery have been suggested to potentially carry more prognostic value than isolated concentration metrics.

Site-specific management involves multidisciplinary collaboration. Evidence for common sites such as the lungs is relatively sufficient, allowing for standard TDM guidance. For rare sites with lower evidence strength, awareness of penetration barriers and consideration of auxiliary interventions, such as surgery or combination regimens, are noted. Precision in dose adjustments is described in special scenarios, as exemplified by the potential benefits of higher initial doses for patients receiving CRRT, while cautious dose reductions for those with low albumin or poor metabolizer status are suggested to balance efficacy and safety.

Voriconazole exhibits non-linear pharmacokinetic characteristics (Michaelis-Menten mechanism), leading to a non-linear dose-exposure relationship and amplified individual variability. PopPK models provide reliable guidance for TDM and individualized dose adjustments by integrating multiple covariates. This approach is reported to be particularly applicable to high-risk groups, such as immunosuppressed patients, children, and those with hepatic dysfunction, helping to maintain efficacy and reduce toxicity risk.[110] For populations with a high proportion of CYP2C19 poor metabolizers, a narrower target plasma concentration range is suggested to reduce the risk of adverse reactions. The decision-making process for voriconazole treatment of Aspergillosis is shown in Figure 1.

Limitations

Due to the notable heterogeneity among the studies included in this review, a systematic analysis was not feasible, which may limit the precision and broad applicability of the conclusions. Current research on voriconazole for aspergillosis therapy is reported to involve mostly small sample sizes and single-center designs, with observed methodological variations and a lack of large-scale multicenter randomized controlled trials. The inclusion of patients without microbiological confirmation of aspergillosis in some studies is noted, which may influence the disease-specific relevance of the findings. Furthermore, given the marked variation in patient populations across case reports, statistical testing for the safety and efficacy of voriconazole has not been performed, and evaluation results are observed to involve a degree of subjectivity.

Future Research Directions

Refinement of resistance monitoring networks: Future efforts may focus on the expansion of genomic tools to further elucidate resistance mechanisms and transmission patterns, such as *CYP51A* mutations. These initiatives could provide a scientific foundation for the development of novel antifungal agents.[14]

Strategic development of pharmacokinetic and pharmacodynamic frameworks: Potential directions involve the establishment of comprehensive TDM protocols, the exploration of concentration thresholds within specific target tissues, and the systematic evaluation of multi-drug combination regimens.

Integration of clinical trials and modelling for diverse patient populations: Prioritizing randomized controlled trials may support the development of robust efficacy and safety models for special populations. For infection sites where sampling remains a challenge, such as the eyes or bone marrow, PopPK modelling could be leveraged to predict local drug exposure and inform the adjustment of therapeutic strategies.

Exploration of adjuvant immunotherapies and host response enhancement: Investigations into adjuvant therapies, such as IFN-gamma and other immunomodulatory agents, could focus on the regulation of cytokine and chemokine networks. These strategies represent a potential pathway to support antifungal outcomes by enhancing the host immune response.[111]

Conclusion

Current evidence suggests that individualized voriconazole dosing and TDM represent key components in the management of aspergillosis. Since existing target concentration ranges are primarily derived from broader invasive fungal infection populations, further validation within aspergillosis-specific cohorts remains a recognized area for clinical refinement. Individualized therapy is often associated with the integration of genetic background, infection site, and disease severity to address the complexity of host-pathogen interactions. For infections at sites with limited drug penetration, the application of site-specific strategies incorporating host factors and resistance status has been described. These approaches, combined with dose adjustment strategies and emerging immunomodulatory strategies, are suggested to potentially support clinical efficacy while limiting the risk of adverse reactions. Future high-quality research specifically targeting aspergillosis patients may further advance the development and implementation of precision antifungal therapy.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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