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BRIEF REPORT

Antifungal Therapeutic Drug Monitoring Practices: Results of an Emerging Infections Network Survey

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In a survey of 523 infectious disease specialists, a moderate to high percentage reported using any antifungal therapeutic drug monitoring (TDM) during itraconazole (72%), posaconazole (72%), and voriconazole (90%) treatment, and a low to moderate percentage reported using any antifungal TDM during prophylaxis (32%, 55%, and 65%, respectively). Long turnaround times for send-out TDM testing and logistical difficulties were frequent barriers.

Keywords. antifungal agents; drug monitoring; itraconazole; posaconazole; voriconazole.

The Infectious Diseases Society of America (IDSA) recommends antifungal therapeutic drug monitoring (TDM) during itraconazole, voriconazole, or posaconazole treatment for invasive fungal infections (IFIs) [1–6]. Clinical practice guidelines for aspergillosis also recommend TDM during prolonged azole prophylaxis, which is indicated for certain patients with hematologic malignancies or transplantation [2]. Itraconazole, voriconazole, and posaconazole have narrow therapeutic indices, frequent interactions with other drugs, and variable pharmacokinetic profiles, making TDM particularly important for pediatric patients and patients with critical illness, obesity, or liver or kidney dysfunction [7]. TDM for itraconazole, voriconazole, or posaconazole might improve patient outcomes by minimizing toxicity associated with supratherapeutic antifungal levels and preventing treatment failure due to subtherapeutic levels [8–10]. Guidance for TDM use for fluconazole and isavuconazole is limited, but some data suggest that it should be used for certain critically ill patients [3, 7, 11].

Studies based on medical charts and administrative data suggest that TDM for itraconazole, posaconazole, and voriconazole is underused [12]. Few published data exist regarding the benefits of TDM use for isavuconazole or fluconazole, and challenges associated with performing TDM have not been previously explored in-depth. Therefore, we conducted a survey of infectious disease specialists to better understand TDM practices and potential barriers.

METHODS

The Emerging Infections Network (EIN; https://ein.idsociety.org/) is a provider-based network supported by the Centers for Disease Control and Prevention and IDSA. EIN emailed a link to an online survey 3 times during March 2023 to 1903 network members who are infectious disease physicians and other health care professionals in North America. The survey questions (http://www.int-med.uiowa.edu/Research/EIN/AntifungalTherapeuticDrugMonitoringquery_final.pdf) covered the use of systemic azole antifungals (itraconazole, posaconazole, voriconazole, isavuconazole, and fluconazole) for the treatment and prophylaxis of IFI, the estimated proportion (collected as "none," "1%–20%," "21%–50%," "51%–75%," and ">75%," which we dichotomized into "none" vs "any" for analysis) of patients for whom TDM was used by drug and indication, perceived utility of hydroxyitraconazole testing, and barriers to TDM use. We conducted descriptive analyses and bivariate comparisons using chi-square tests ($\alpha = .05$) to evaluate practice-related factors associated with any TDM use by drug and indication.

RESULTS

In total, 715 (38%) surveyed EIN members responded; of these, 192 (27%) did not complete the survey because they do not routinely care for patients with IFI. The remaining 523 respondents who completed the survey were mostly infectious disease physicians (91%), mostly cared for adult patients (75%), and mostly practiced at university or teaching hospitals (73%) (Table 1). Most respondents treated ≤10 patients for infection with each antifungal in the past year (Supplementary Table 1). Among 364 (70%) respondents who routinely care for patients receiving antifungal prophylaxis, most cared for ≤5 patients per drug in the past year (Supplementary Table 2).

Among respondents who treated patients receiving each antifungal, 90% reported any TDM use during treatment with voriconazole, 72% for posaconazole, 72% for itraconazole, 40% for isavuconazole, and 10% for fluconazole. When asked whether hydroxyitraconazole testing is helpful in a patient's clinical care, 32% said "always" or "often," 20% said "sometimes" or "rarely," and 47% said "never" or "do not use" hydroxyitraconazole testing.

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Table 1. Factors Associated With Any Reported Antifungal Therapeutic Drug Monitoring Use During Antifungal Treatment Among Emerging Infections Network Survey Respondents, 2023

Characteristic	Total (n = 523), No. (%)	Itraconazole (n = 402)		Posaconazole (n = 419)		Voriconazole (n = 488)		Isavuconazole (n = 373)		Fluconazole (n = 437)	
		Yes (n = 291), No. (%)	No (n = 111), No. (%)	Yes (n = 300), No. (%)	No (n = 119), No. (%)	Yes (n = 439), No. (%)	No (n = 49), No. (%)	Yes (n = 149), No. (%)	No (n = 224), No. (%)	Yes (n = 42), No. (%)	No (n = 395), No. (%)
Member type											
Infectious diseases physician	474 (91)	262 (90)	96 (86)	259 (86)[a]	112 (94)[a]	392 (89)	48 (98)	128 (86)	197 (88)	40 (95)	351 (89)
Other health care professional	49 (9)	29 (10)	15 (14)	41 (14)[a]	7 (6)[a]	47 (11)	1 (2)	21 (14)	27 (12)	2 (5)	44 (11)
Population served											
Adult	393 (75)	223 (77)	82 (74)	203 (68)[b]	105 (88)[b]	325 (74)	41 (84)	102 (68)[a]	186 (83)[a]	30 (71)	298 (75)
Pediatric	130 (25)	68 (23)	29 (26)	97 (32)[b]	14 (12)[b]	114 (26)	8 (16)	47 (32)[a]	38 (17)[a]	12 (29)	97 (25)
Main practice setting											
University or nonuniversity teaching hospital	383 (73)	213 (73)	79 (71)	254 (85)[b]	66 (55)[b]	333 (76)[a]	28 (57)[a]	129 (87)[b]	150 (67)[b]	32 (76)	283 (72)
City, county, community hospital or other setting	140 (27)	78 (27)	32 (29)	46 (15)[b]	53 (45)[b]	106 (24)[a]	21 (43)[a]	20 (13)[b]	74 (33)[b]	10 (24)	112 (28)
Years of experience since fellowship											
<15	300 (58)	186 (64)[a]	56 (50)[a]	186 (62)[a]	54 (45)[a]	270 (62)[b]	14 (29)[b]	91 (61)	129 (58)	23 (55)	225 (57)
≥15	221 (42)	104 (36)[a]	55 (50)[a]	113 (38)[a]	65 (55)[a]	168 (38)[b]	35 (71)[b]	57 (38)	95 (42)	19 (45)	169 (43)
Region											
Midwest	164 (31)	136 (47)[b]	14 (13)[b]	91 (30)[b]	38 (32)[b]	140 (32)[b]	11 (22)[b]	52 (35)	58 (26)	8 (19)[b]	129 (13)[b]
Northeast	91 (17)	23 (8)[b]	29 (26)[b]	40 (13)[b]	25 (21)[b]	73 (17)[b]	12 (24)[b]	23 (15)	43 (19)	2 (5)[b]	68 (17)[b]
South	141 (27)	81 (28)[b]	34 (31)[b]	84 (28)[b]	34 (29)[b]	119 (27)[b]	17 (35)[b]	35 (23)	69 (31)	4 (10)[b]	120 (30)
West	122 (23)	51 (18)[b]	30 (27)[b]	85 (28)[b]	18 (15)[b]	105 (24)[b]	6 (12)[b]	39 (26)	52 (23)	27 (64)[b]	74 (19)[b]
Canada and Puerto Rico	5 (1)	0 (0)[b]	4 (4)[b]	0 (0)[b]	4 (3)[b]	2 (0.5)[b]	3 (6)[b]	0 (0)	2 (1)	1 (2)[b]	4 (1)[b]

[a] $P < .05$.

[b] $P < .001$.

Compared with respondents with ≥15 years of experience, those with <15 years of experience more frequently reported any TDM use during treatment for infections using itraconazole (77% vs 65%; $P = .012$), posaconazole (78% vs 63%; $P = .002$), and voriconazole (95% vs 83%; $P < .001$) treatment (Table 1). Compared with other practice settings, respondents practicing at university or nonuniversity teaching hospitals were more likely to report TDM use during posaconazole (79% vs 46%; $P < .001$), voriconazole (92% vs 83%; $P = .005$), and isavuconazole treatment (46% vs 21%; $P < .001$). Respondents caring for pediatric patients were more likely to report TDM use during posaconazole (87% vs 66%; $P < .001$) and isavuconazole treatment (55% vs 35%; $P = .001$) than those caring for adult patients. Regional differences in TDM use occurred for all antifungals except isavuconazole, including higher itraconazole TDM use in the Midwest ($P < .001$) and higher fluconazole TDM use in the West ($P < .001$).

Among respondents who routinely care for patients on antifungal prophylaxis, 65% reported any TDM use during prophylaxis with voriconazole, 55% for posaconazole, 32% for itraconazole, 27% for isavuconazole, and 4% for fluconazole. Practice-related factors associated with TDM use during antifungal prophylaxis were generally similar to those associated with TDM use during treatment (Table 2).

Reported barriers to performing TDM included long turnaround times for send-out tests (74%), difficulty coordinating testing logistics (48%), uncertainty around TDM recommendations (39%), difficulty interpreting results (28%), uncertainty about TDM benefits (18%), cost (14%), and challenges with insurance coverage (11%); 10% reported no barriers. We did not identify meaningful differences in barriers to TDM use by practice characteristics.

DISCUSSION

This nationwide survey of infectious disease specialists revealed moderate to high reported use of any TDM (72%–90%) during itraconazole, posaconazole, and voriconazole treatment and low to moderate use of any TDM (32%–65%) during prophylaxis with these antifungals. These estimates are higher than previously described TDM use rates (during treatment or prophylaxis) among eligible patients: 41% in a study at 55 academic

Table 2. Factors Associated With Any Reported Antifungal Therapeutic Drug Monitoring Use During Antifungal Prophylaxis Among Emerging Infections Network Survey Respondents, 2023

Characteristic	Itraconazole (n = 183)		Posaconazole (n = 274)		Voriconazole (n = 261)		Isavuconazole (n = 200)		Fluconazole (n = 289)	
	Yes (n = 59), No. (%)	No (n = 124), No. (%)	Yes (n = 151), No. (%)	No (n = 123), No. (%)	Yes (n = 170), No. (%)	No (n = 91), No. (%)	Yes (n = 53), No. (%)	No (n = 147), No. (%)	Yes (n = 10), No. (%)	No (n = 279), No. (%)
Member type										
Infectious diseases physician	50 (85)	104 (84)	128 (85)	110 (89)	144 (85)	82 (90)	44 (83)	127 (86)	8 (80)	245 (88)
Other health care professional	9 (15)	20 (16)	23 (15)	13 (11)	26 (15)	9 (10)	9 (17)	20 (14)	2 (20)	34 (12)
Population served										
Adult	35 (59)	80 (65)	97 (64)	91 (74)	104 (61)	63 (69)	30 (57)[a]	109 (74)[a]	5 (50)	95 (34)
Pediatric	24 (41)	44 (35)	54 (36)	32 (26)	66 (39)	28 (31)	23 (43)[a]	38 (26)[a]	5 (50)	184 (66)
Main practice setting										
University or nonuniversity teaching hospital	53 (90)	98 (79)	132 (87)[a]	89 (72)[a]	147 (86)	71 (78)	49 (92)	120 (82)	7 (70)	222 (80)
City, county, community hospital or other setting	6 (10)	26 (21)	19 (13)[a]	34 (28)[a]	23 (14)	20 (22)	4 (8)	27 (18)	3 (30)	57 (20)
Years of experience since fellowship										
<15	33 (56)	47 (38)	99 (66)	68 (55)	106 (62)	56 (62)	35 (66)	86 (59)	4 (40)	160 (57)
≥15	26 (44)	77 (62)	52 (34)	55 (45)	64 (38)	34 (37)	18 (34)	60 (41)	6 (60)	117 (42)
Region										
Midwest	30 (51)[b]	30 (24)[b]	50 (33)	35 (28)	55 (32)	26 (29)	20 (38)	37 (25)	1 (10)	83 (30)
Northeast	1 (2)[b]	21 (17)[b]	19 (13)	22 (18)	18 (11)	19 (21)	7 (13)	25 (17)	2 (20)	46 (16)
South	16 (27)[b]	41 (33)[b]	38 (25)	38 (31)	51 (30)	30 (33)	11 (21)	50 (34)	1 (10)	82 (29)
West	12 (20)	32 (26)[b]	44 (29)	28 (23)	46 (27)	15 (16)	15 (28)	35 (24)	6 (60)	66 (24)
Canada and Puerto Rico	0 (0)[b]	0 (0)[b]	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	2 (1)

[a] $P < .05$.

[b] $P < .001$.

medical centers and 16% in a study using hospital administrative data [12, 13]. A likely explanation for these differences involves the specialist population surveyed here, who might be more aware than nonspecialty providers about TDM recommendations and benefits. Also, this convenience sample might not necessarily represent the practices of all US infectious disease professionals. Self-selection bias to participate in the survey based on interest in and perceived importance of TDM could have further increased the observed TDM use frequencies. Social desirability bias could have also led respondents to overestimate their use of TDM. Lastly, another possible explanation for the higher TDM use in this study involves our measurement of any TDM use at the provider level, whereas previous studies measured TDM use rates per patient or per hospitalization. The more frequent TDM use during both treatment and prophylaxis with itraconazole, voriconazole, and posaconazole compared with isavuconazole and fluconazole is consistent with TDM not being routinely recommended for these 2 drugs [7].

The low-to-moderate reported TDM use during antifungal prophylaxis and the lack of perceived utility of hydroxyitraconazole testing in approximately half of respondents reveal opportunities for improvement in terms of TDM practices and research. Emerging evidence suggests that monitoring combined itraconazole and hydroxyitraconazole levels might contribute to improved clinical outcomes among patients with blastomycosis [8]. Guidelines for aspergillosis management specifically recommend monitoring both itraconazole and hydroxyitraconazole levels, although further work is needed to better define target hydroxyitraconazole levels [2, 14].

The survey results revealed that TDM use for certain antifungals varied according to practice setting and years of experience, highlighting specific challenges and gaps. The higher TDM use for posaconazole, voriconazole, and isavuconazole among respondents practicing in university or teaching hospital settings could be related to ease of access to testing; however, long turnaround times for send-out testing were a commonly reported barrier regardless of hospital setting. The greater use of itraconazole, posaconazole, and voriconazole TDM among respondents with fewer years of experience postfellowship likely reflects more recent training about TDM guidelines and emerging evidence for its benefits.

Other significant and unsurprising associations emerged in this analysis. For example, the regional variations in reported TDM use likely reflect more itraconazole use in the Midwest for histoplasmosis treatment and more fluconazole use in the

West for coccidioidomycosis treatment. The higher isavuconazole TDM use reported among pediatric infectious disease specialists is consistent with isavuconazole being off-label in children, for whom dosing has not been well established [15]. Similarly, oral posaconazole formulations are only approved for patients aged >13 years; therefore, posaconazole TDM is particularly important for younger children as posaconazole suspension, approved for patients aged <13 years, has more pharmacokinetic variability [16].

Addressing barriers to antifungal TDM identified in this survey is critical to improving patient care and antifungal stewardship. Rapid, in-house TDM technology has been linked to a survival benefit in patients with fungal diseases compared with send-out tests requiring long turnaround times [17]. Currently available bioassays for triazoles can have rapid results; however, they are subject to interference from other drugs, they might measure combined parent drug and metabolite levels, and levels can be many fold higher than high-performance liquid chromatography results, making interpretation difficult [18]. Newer technology like biosensors and quantitative lateral flow assays could overcome these challenges with on-site bioassays [19]. Pharmacists in hospital settings can take an active role in antifungal TDM and might be able to navigate logistical barriers that inhibit TDM use [20]. Comprehensive guidelines for antifungal TDM use currently do not exist for the United States [21] but are available from other countries [18, 22]. Guidelines focusing on the US context (ie, to address issues such as insurance coverage, availability of TDM technology and antifungals, and health care regulations) could be useful for providers caring for patients on triazole antifungals.

In conclusion, despite the relatively high self-reported TDM use during antifungal treatment, these survey results revealed opportunities for improvement in adherence to TDM recommendations specifically regarding itraconazole, posaconazole, and voriconazole prophylaxis. Increased capacity for on-site TDM might help reduce long wait times for test results, particularly in nonacademic hospital settings, and further research is needed to inform optimal TDM practices.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Ethical conduct. This activity was reviewed by the CDC and was conducted consistent with applicable federal law and CDC policy (eg, 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.).

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References

1. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis **2016**; 62:e1–50.
2. Patterson TF, Thompson GR III, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis **2016**; 63:e1–60.
3. Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. Clin Infect Dis **2016**; 63:e112–46.
4. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis **2010**; 50:291–322.
5. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis **2007**; 45:807–25.
6. Chapman SW, Dismukes WE, Proia LA, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis **2008**; 46:1801–12.
7. John J, Loo A, Mazur S, Walsh TJ. Therapeutic drug monitoring of systemic antifungal agents: a pragmatic approach for adult and pediatric patients. Exp Opin Drug Metab Toxicol **2019**; 15:881–95.
8. Firkus D, Abu Saleh OM, Enzler MJ, et al. Does metabolite matter? Defining target itraconazole and hydroxy-itraconazole serum concentrations for blastomycosis. Mycoses **2023**; 66:412–9.
9. Yi WM, Schoeppler KE, Jaeger J, et al. Voriconazole and posaconazole therapeutic drug monitoring: a retrospective study. Ann Clin Microbiol Antimicrob **2017**; 16:60.
10. Luong M-L, Al-Dabbagh M, Groll AH, et al. Utility of voriconazole therapeutic drug monitoring: a meta-analysis. J Antimicrob Chemother **2016**; 71:1786–99.
11. Höhl R, Bertram R, Kinzig M, et al. Isavuconazole therapeutic drug monitoring in critically ill ICU patients: a monocentric retrospective analysis. Mycoses **2022**; 65: 747–52.
12. Ostrosky-Zeichner L, Nguyen MH, Bubalo J, et al. Multicenter registry of patients receiving systemic mold-active triazoles for the management of invasive fungal infections. Infect Dis Ther **2022**; 11:1609–29.
13. Benedict K, Gold JAW, Toda M, Thompson GR III, Wiederhold NP, Smith DJ. Low rates of antifungal therapeutic drug monitoring among inpatients who received itraconazole, posaconazole, or voriconazole, United States, 2019–2021. Open Forum Infect Dis **2023**; 10:XXX–XX
14. Wiederhold NP, Schwartz IS, Patterson TF, Thompson GR 3rd. Variability of hydroxy-itraconazole in relation to itraconazole bloodstream concentrations. Antimicrob Agents Chemother **2021**; 65:e02353-20.
15. Zimmermann P, Brethon B, Roupret-Serzec J, et al. Isavuconazole treatment for invasive fungal infections in pediatric patients. Pharmaceuticals (Basel) **2022**; 15:375.
16. Garner LM, Ngo S, Kaplan JB, Wilson WS, McKinzie CJ. Evaluation of posaconazole dosing in children and young adults: a single-center review. J Pediatr Pharmacol Ther **2021**; 26:834–40.
17. McCreary EK, Bayless M, Van AP, et al. Impact of triazole therapeutic drug monitoring availability and timing. Antimicrob Agents Chemother **2019**; 63:e01245–19.
18. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother **2014**; 69:1162–76.
19. Ates HC, Roberts JA, Lipman J, Cass AEG, Urban GA, Dincer C. On-site therapeutic drug monitoring. Trends Biotechnol **2020**; 38:1262–77.
20. ASHP statement on the pharmacist's role in clinical pharmacokinetic monitoring. Am J Health Syst Pharm **1998**; 55:1726–7.
21. McCreary EK, Davis MR, Narayanan N, et al. Utility of triazole antifungal therapeutic drug monitoring: insights from the Society of Infectious Diseases Pharmacists. *Pharmacother J Hum Pharmacol Drug Ther* **2023**; 00:1–8.
22. Chau MM, Daveson K, Alffenaar JC, et al. Consensus guidelines for optimising antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy and haemopoietic stem cell transplant recipients, 2021. Intern Med J **2021**; 51(Suppl 7):37–66.