

Concerning rates of laboratory-confirmed antifungal-resistant onychomycosis and tinea pedis: An online survey of podiatrists, United States

1 | INTRODUCTION

Onychomycosis (tinea unguium) and tinea pedis are common, frequently concomitant infections of the nails and feet, respectively, and are often caused by dermatophyte fungi (*Trichophyton*, *Microsporum*, and *Epidermophyton* spp.).¹ Antifungal-resistant tinea is an emerging global public health problem.² A recent, large analysis of toenail samples from US patients with suspected onychomycosis found that nearly 4% of *Trichophyton* spp samples had squalene epoxidase gene mutations, which are associated with terbinafine resistance.³ Clinicians may be increasingly likely to encounter resistant tinea infections. Therefore, we aimed to assess diagnostic approaches, antifungal resistance testing practices, and treatment practices for treatment-resistant onychomycosis and tinea pedis.

2 | METHODS

A 12-question survey was developed in early 2023 by a working group consisting of a dermatologist with expertise in cutaneous fungal infections (BE), an infectious disease clinician (PP), infectious diseases laboratory scientists, epidemiologists, and other experts. The survey instrument was created using Qualtrics^{XM} licensed to The Ohio State University (CTJ). The survey was deemed exempt from full review by the university's Institutional Review Board. Informed consent was included as the initial segment of the survey which gave access to the subsequent survey questions when affirmed. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy (e.g., 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.).

The survey aimed to query a range of physicians, including podiatrists, who treat dermatophyte infections; the survey was emailed twice to approximately 8000 nonstudent and non-resident American Podiatric Medical Association (APMA) members in February 2023. Other distribution listservs included:

dermatologists, the Mycoses Study Group Education and Research Consortium, the [FungusCME.org](https://funguscme.org) listserv, and social media. SAS (SAS Institute, v. 9.4) was used to produce descriptive statistics.

3 | RESULTS

The survey closed on March 31, 2023, with 577 responses. Most responses ($n = 498$, 86.3%) were from podiatrists, 19 were from primary care practitioners, 23 were from dermatologists, 19 (3.3%) were from infectious diseases physicians, 13 (2.3%) from others, and 5 (0.9%) from pathology/laboratory medicine clinicians. The quantity and completeness of responses from the non-podiatry audiences were low; therefore, we focused on the responses from podiatrists to preserve statistical power. In total, 498 podiatrists began the survey; 200 respondents who did not complete the survey and 1 who did not see patients with dermatophyte infections were excluded from the analysis.

Among the 297 included respondents, 106 (36.9%) were from the South; 83 (28.9%) were from the Northeast; 55 (19.2%) were from the Midwest, and 43 (15.0%) were from the West. Most respondents ($n = 266$, 89.6%) saw > 10 patients with onychomycosis and >10 patients with tinea pedis monthly ($n = 171$, 57.6%) (Figure 1).

The most commonly reported definitions of treatment failure were terbinafine failure (72.4%), failure of multiple topical therapies (71.4%), and infection spreading during treatment (48.1%) (Table 1). Most respondents (53.2%) reported that >20% of onychomycosis cases involve treatment failure; 52.2% reported that <10% of tinea pedis cases involved treatment failure (Figure 2).

Cost was a frequently reported (59.6%) barrier to ordering diagnostic testing for dermatophyte infections. The most commonly ordered diagnostic testing included histological examination (81.5%) and molecular testing (59.5%); 21.6% ordered antifungal susceptibility testing, and 30.0% indicated that their

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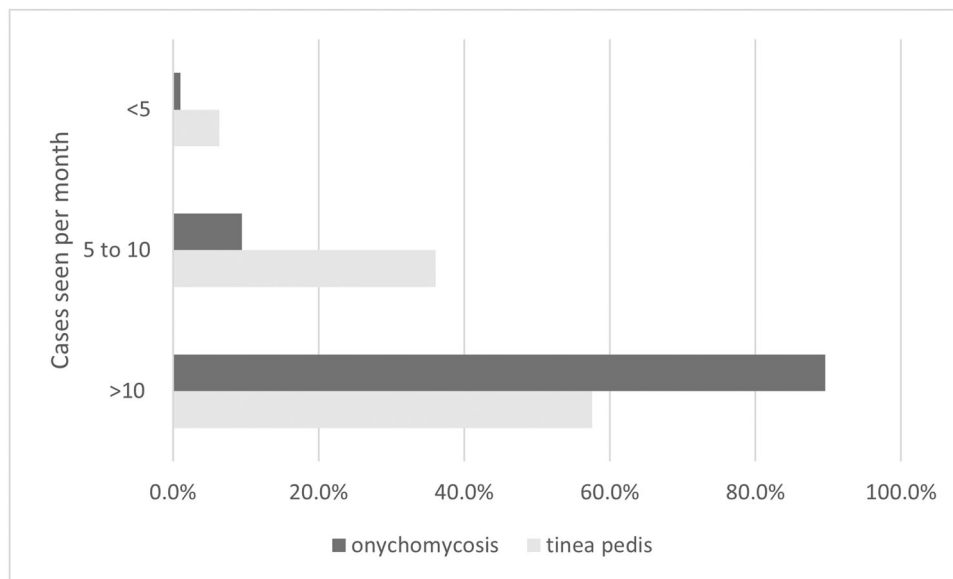


FIGURE 1 Frequency of onychomycosis and tinea pedis cases seen per month.

laboratory has reported antifungal resistance for treatment failure cases. No regional differences in antifungal resistance were observed (data not shown).

For difficult-to-treat or terbinafine-resistant dermatophyte cases, reported management strategies included surgical nail avulsion (59.6%), topical therapy (45.8%), and systemic azole therapy (39.1%) (Figure 3). However, 31.0% reported that some cases remained refractory.

4 | DISCUSSION

Our study demonstrates that antifungal resistant onychomycosis and tinea pedis might be more common than previously appreciated, with nearly one-third of surveyed podiatrists reporting laboratory-confirmed resistance. This proportion might underestimate the true frequency of antifungal resistance because nearly 80% of podiatrists did not routinely order antifungal susceptibility testing. In addition, our study highlights the burden of onychomycosis, as suggested by the high percentage of onychomycosis patients who experience treatment failure, and by the substantial percentage of whom underwent surgical nail avulsion, which is painful and unlikely to be curative.

The proportion of podiatrists reporting antifungal resistance in this survey exceeded a 2022 survey in which nearly 20% of 1500 nonspecialist healthcare providers reported clinical experience with antifungal resistant tinea.⁴ These findings might be attributable to podiatrists ordering diagnostic testing for suspected tinea more frequently than nonspecialists.⁵ For all clinicians who see patients with tinea, confirmatory laboratory testing is essential for guiding appropriate therapy and avoiding unnecessary antifungal use.

Reported treatment failure in this study could be related to several factors besides resistance, including misdiagnosis, patient non-adherence to treatment, or variable definitions of treatment failure. For suspected onychomycosis, the differential is broad, and approximately half of nail disorders seen in clinical practice are not due to fungal pathogens.¹ Therefore, the American Academy of Dermatology, as part of the ABIM Foundation's Choosing Wisely campaign, recommends that suspected fungal nail infections be confirmed before starting oral antifungal therapy,⁶ which we argue should be expanded to include topical antifungals. In addition, inadequate courses of antifungal therapy can lead to treatment failure, particularly for onychomycosis, which requires a long treatment course and can be difficult to completely cure. A treat-to-terminate approach is suggested.

The high proportion of laboratory-confirmed antifungal resistance observed could also partly reflect survey response bias in which APMA members who were more familiar with dermatophytes and resistance were more likely to respond to the survey. Other study limitations include that we did not query regarding laboratory-confirmed antifungal resistance for tinea pedis and onychomycosis separately, though tinea pedis almost always precedes onychomycosis. The lack of demographic and training-related information for respondents is another notable limitation. These data could help identify more specific opportunities to address educational gaps in antifungal resistance testing practices.

Together with previous studies, our findings suggest that antifungal-resistant tinea is a growing concern. This concern merits increased attention to antifungal stewardship efforts, emphasizing diagnostic testing and judicious antifungal use for suspected superficial fungal infections of the skin and nails.

TABLE 1 Testing practices and antifungal resistance among patients with onychomycosis and tinea pedis in a survey of American Podiatric Medical Association members.

Characteristic	n = 297	%
How do you (or would you) define treatment failure for dermatophyte (tinea) infections? ^a		
Failure of normal course of terbinafine (Lamisil)	215	72.4
Failure of multiple topical therapies	212	71.4
Infection that spreads during treatment	143	48.1
Failure of multiple oral therapies	135	45.5
Multiple specialists involved, employing multiple agents with little or no disease resolution	133	44.8
Other (specify)	14	4.7
Type of diagnostic testing ordered for dermatophyte infections ^{a,b}		
PAS histological examination	211	81.5
DNA-based molecular testing (e.g., PCR)	154	59.5
Microscopic KOH examination	110	42.5
Microscopic culture for fungal identification only	91	35.1
Susceptibility testing	56	21.6
Other	9	3.5
Logistical barriers to diagnostic testing ^a		
High cost of diagnostic testing	177	59.6
No logistical barriers	83	27.9
Long turnaround time	49	16.5
Difficulty accessing the testing	37	12.5
Other	29	9.8
Difficulty interpreting MIC values	13	4.4
Has the laboratory reported back to you antifungal resistance for any of your treatment failure cases? ^a		
No	208	70.0
Yes	89	30.0
Yes, but treatment failure might be due to other factors (e.g., patient non-adherence)	51	17.2
Yes, and there appears to be a correlation between treatment failure and terbinafine resistance	49	16.5
Yes, and there appears to be a correlation between treatment failure and topical antifungal resistance	31	10.4
Yes, and there appears to be a correlation between treatment failure and itraconazole resistance	10	3.4
Yes, and there appears to be a correlation between treatment failure and fluconazole resistance	8	2.7

Abbreviations: KOH, potassium hydroxide; MIC, minimum inhibitory concentration; PAS, Periodic acid–Schiff.

^a“Check all that apply” format; totals can exceed 100%;

^bExcluding n = 38 (12.8%) respondents who said “I am not testing.”

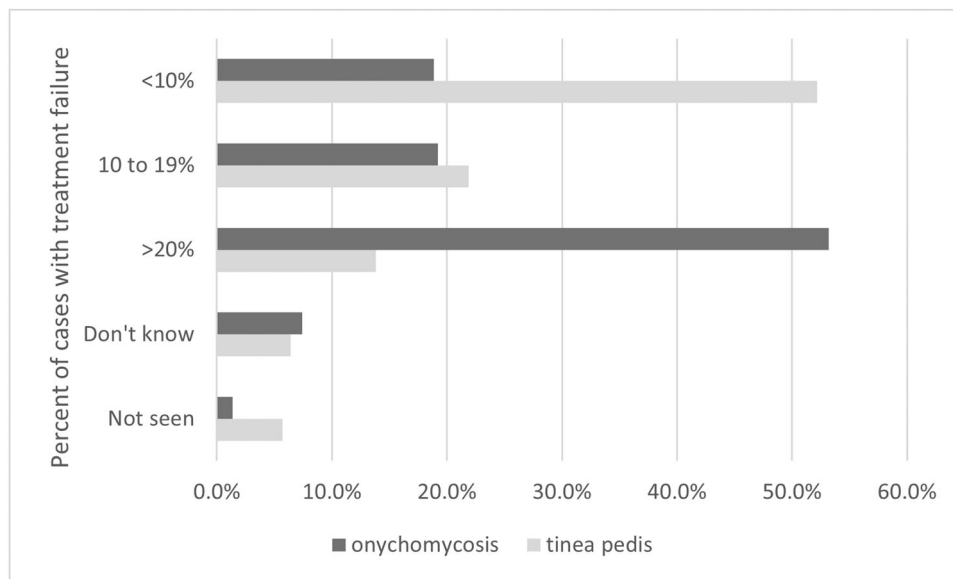


FIGURE 2 Percent of onychomycosis and tinea pedis cases seen with treatment failure.

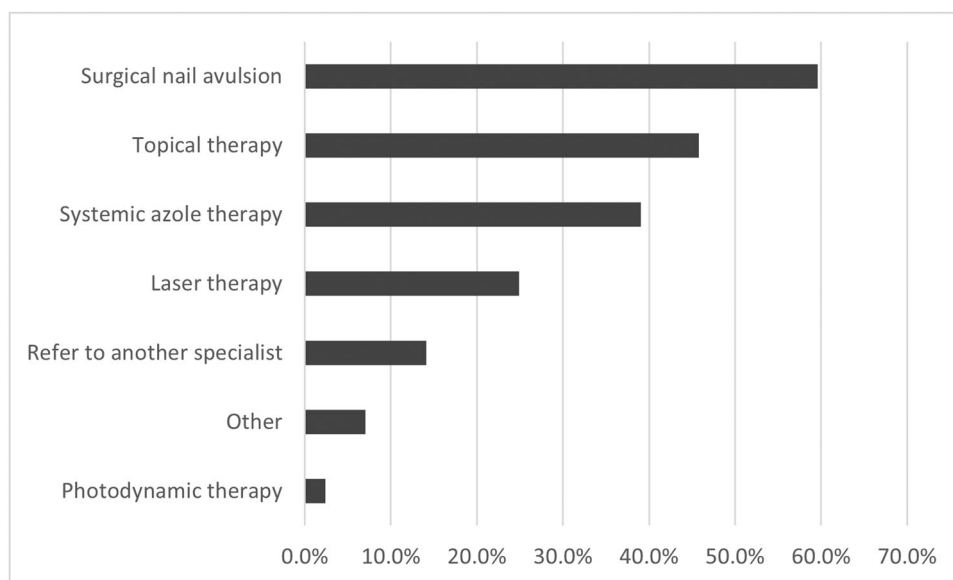


FIGURE 3 Management strategies for difficult-to-treat or terbinafine-resistant dermatophyte cases.

KEYWORDS

drug resistance, fungal; onychomycosis; podiatry; tinea pedis; United States

AUTHOR CONTRIBUTIONS

Kaitlin Benedict: Formal analysis; writing—original draft; writing—review and editing. **Jeremy A. W. Gold:** Conceptualization; methodology; writing—review and editing. **Carolynn T. Jones:** Conceptualization; methodology; writing—review and editing. **Lisa A. Tushla:** Conceptualization; methodology; writing—review and editing. **Shari R. Lipner:** Methodology; writing—review and editing. **warren s joseph:**

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CONFLICTS OF INTEREST STATEMENT

Shari Lipner has served as a consultant for Ortho-Dermatologics, Moberg Pharmaceuticals, Hoth Therapeutics, and BelleTorus Corporation. Lisa Tushla has received research grant support from Bristol Myers Squibb and Novartis in the area of skin cancer. These financial relationships were not involved with this study. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data presented in this study are primarily included in this article; however, the full data set and survey instrument may be available on request from the corresponding author.

TRANSPARENCY STATEMENT

The lead author Kaitlin Benedict affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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