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Molecular diagnosis of onychomycosis: Outcomes from a retrospective study of 306 patients at an academic center in New York City

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To the Editor:

Onychomycosis, the most common nail disorder encountered in clinical practice, may cause pain and decreased quality of life.¹ Since about half of nail conditions are not onychomycosis, diagnosis is essential before initiating treatments that may be costly or cause side effects.² Unlike potassium hydroxide with microscopy and histopathology, culture and polymerase chain reaction (PCR) can identify the causative pathogen¹; however, real-world data comparing these techniques' utility are lacking. We aimed to compare culture and PCR for onychomycosis diagnosis and potential impact on patient outcomes.

A retrospective analysis was conducted on Weill Cornell Dermatology patients with onychodystrophies (4/20/2017-6/22/2023) with both PCR and fungal culture performed. Accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of PCR were calculated using culture as the standard. Discordant results were compared with histopathology data. χ^2 tests compared PCR versus culture in identifying dermatophytes and nondermatophytes ($\alpha < 0.05$).

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Patient consent: Not applicable.

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Note: This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy (eg, 45 C F R. part 46, 21 C F R. part 56; 42 U S C. §241(d); 5 U S C. §552a; 44 U S C. §3501 et seq).

Conflicts of interest

Dr Bakotic serves as Chief Medical Officer of Bako Diagnostics. Dr Lipner has served as a consultant for Ortho-Dermatologics, Moberg Pharmaceuticals, Eli Lilly, and BelleTorus Corporation. Author Katsiaunis and Dr Gold have no conflicts of interest to declare.

Three-hundred-six patients were included; mean age was 53.3 years (range: 8-89) and 63.4% were male (Supplementary Table I, available via Mendeley at <https://data.mendeley.com/datasets/9v6bb7dv9f/1>). Percent positivity for PCR (vs culture) was higher for dermatophytes (42.8% vs 14.7%, $P < .01$) and similar for nondermatophytes (12.4% vs 9.2%, $P = .193$) (Table I). Culture and PCR results agreed in 218 (71.2%) instances for dermatophytes and 280 (93.3%) instances for nondermatophytes. For dermatophytes, PCR's sensitivity and specificity were 97.8% and 66.7%; for nondermatophytes, PCR's sensitivity and specificity were 71.4% and 93.5%.

In 87 patients, dermatophytes were detected by PCR but not culture (Table II), with histopathology identifying hyphae in 84 (96.6%). Among 87 patients with dermatophyte PCR-positive/culture-negative testing, 77 received treatment; of those, 47 completed follow-up, 37 (78.8%) of whom improved. Findings were similar among 18 patients with nondermatophyte PCR-positive/culture-negative testing. In 44 PCR-positive/culture-positive dermatophyte cases there was agreement in 40 cases (Table I).

We showed that PCR more often diagnosed dermatophytes and nondermatophytes from nail samples than fungal culture, corroborating prior smaller studies. In a retrospective study of 121 patients with toenail onychodystrophy, diagnosis of onychomycosis was made more often using PCR (52.1%) versus culture (33.1%, $P < .001$).³ In a prospective study of 177 nail samples from patients with onychodystrophies, onychomycosis diagnosis was more often positive using PCR (78/177, 44%) than with culture (59/177, 34%, no P value reported).⁴ In a retrospective study of 35,257 fungal nail cultures, only half were positive, and the proportion of nondermatophytes exceeded dermatophytes, which might suggest potential contaminants.⁵ Of the 105 cases (34.3%) in our study where PCR was positive for fungal organism but culture was negative, strong concordance with histopathological findings and clinical improvement with treatment suggest that these are true onychomycosis cases (rather than colonization) that were missed by culture. Theoretically, these patients would not have been treated had they been evaluated using culture alone.

Limitations include small sample size and single-center/physician/retrospective design. Antifungal resistance was not assessed. Microscopy was not performed.

Our findings suggest culture may be inadequate for diagnosing onychomycosis. Although costlier than culture and potentially less accessible, PCR might help improve diagnosis and treatment outcomes. Larger prospective trials are needed to validate these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclaimer:

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

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Table I.

Culture and PCR results of 306 patients tested for dermatophytes and nondermatophyte molds

Test		Dermatophyte*		Nondermatophyte mold†	
Culture	PCR	No.	%	No.	%
+	+	44‡	14.4	20	6.5
+	–	1	0.3	8	2.6
–	+	87	28.4	18	5.9
–	–	174§	56.9	260	85.0
Total		306	100.0	306	100.0
Agreement		218	71.2	280	93.3
Disagreement		88	28.8	26	8.5
PCR sensitivity		97.8		71.4	
PCR specificity		66.7		93.5	
PCR NPV		99.4		97.0	
PCR PPV		33.6		52.6	

NPV, Negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value.

* Dermatophytes identified include *T rubrum* complex and *T mentagrophytes* complex by PCR, and *T rubrum*, *T mentagrophytes*, and *Trichophyton interdigitale* by culture.

† Nondermatophyte molds identified by PCR and culture include: *Aspergillus*, *Fusarium*, *Scytalidium*, and *Curvularia*. Nondermatophyte molds identified by culture alone include *Cladosporium*, *Arthrographis kalrae*, *Paecilomyces*, and *Penicillium*.

‡ Among the 44 cases where both culture and PCR were positive for dermatophytes, there was agreement in 40 cases. In the 44 discordant cases: (1) PCR identified *Trichophyton mentagrophytes* in addition to *Trichophyton rubrum* detected by both methods; (2) culture identified *Trichophyton* spp., but PCR specified *T mentagrophytes*; (3) culture identified *Trichophyton* spp., but PCR specified *T rubrum*; (4) culture identified *T rubrum*, while PCR detected an unspecified dermatophyte.

§ Among 174 cases where both culture and PCR were negative for dermatophytes, there was agreement in 106 cases at the genus and species levels (16, 15.1%) or genus alone (10, 9.4%) when species identification was not possible, or if both methods were negative (80, 75.5%). The same species/genera were as follows: *Aspergillus* (8, 7.5%), *Candida albicans* (8, 7.5%), *Candida parapsilosis* (7, 6.6%), *Candida tropicalis* (1, 1.0%), and *Fusarium* (2, 1.9%).

Table II.

Confirmatory histopathology results and outcomes of 105 patients with negative culture and positive PCR results for dermatophytes and nondermatophyte molds

PCR diagnosis	Total cases	Histopathology agreement	Treatment received	Patients completing follow-up	Improved	Did not improve	Discontinued treatment
Dermatophyte	87	84 (96.6%)	77 (88.5%)	47	37 (78.7%) *	9 (19.1%) *	1 (2.1%) *
Nondermatophyte mold	18	17 (94.4%)	16 (88.9%)	12	10 (83.3%) *	2 (16.7%) *	0 (0%) *

Percentages marked with an asterisk (*) represent the proportion of patients who completed follow-up.