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Editor's Pick | Commentary

Trichophyton indotineae and other terbinafine-resistant dermatophytes in North America

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ABSTRACT Dermatophyte infections (a.k.a. ringworm, tinea) affect an estimated 20%–25% of the world's population. In North America, most dermatophytoses are caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes* species complexes. Severe and antifungal-resistant dermatophytoses are a growing global public health problem. A new species of the *T. mentagrophytes* species complex, *Trichophyton indotineae*, has recently emerged and is notable for the severe infections it causes, its propensity for antifungal resistance, and its global spread. In this issue of the *Journal of Clinical Microbiology*, C. F. Cañete-Gibas, J. Mele, H. P. Patterson, et al. (J Clin Microbiol 61:e00562-23, 2023, https://doi.org/10.1128/JCM.00562-23) summarize the results of speciation and AFST performed on North American dermatophyte isolates received at a fungal diagnostic reference laboratory. Within their collection, 18.6% of isolates were resistant to terbinafine (a first-line oral antifungal for dermatophytoses), and similar proportions of *T. rubrum* and *T. indotineae* demonstrated terbinafine resistance. The authors also found that *T. indotineae* has been present in North America since at least 2017. These findings highlight the importance of increased surveillance efforts to monitor trends in severe and antifungal-resistant dermatophytoses and the need for antifungal stewardship efforts, the success of which is contingent upon improving laboratory capacity for dermatophyte speciation and AFST.

Dermatophytoses (a.k.a. ringworm, tinea) affect an estimated 20%–25% of the world's population (1). These superficial skin infections are characterized by pruritic, annular lesions and spread easily among humans and animals by skin-to-skin contact or from fomites (2). In North America, most dermatophytoses are caused by molds of the genus *Trichophyton*, specifically *Trichophyton rubrum* and *Trichophyton mentagrophytes* species complexes (3). Although often considered a minor ailment, dermatophytoses can cause severe discomfort, stigma, work absenteeism, and decreased quality of life (4, 5). Excluding nail and hair shaft infections, dermatophytoses are ordinarily treatable using over-the-counter topical antifungals, with systemic antifungals such as oral terbinafine (first-line systemic therapy) and itraconazole generally reserved for patients suffering extensive lesions (2, 6, 7).

In the past decade, *Trichophyton indotineae* (formerly *T. mentagrophytes* genotype VIII) has caused an epidemic across the Indian subcontinent of severe, recalcitrant dermatophytoses. A species within the *T. mentagrophytes* species complex (8–10), *T. indotineae* causes extensive, highly inflammatory plaques of tinea corporis, cruris, and faciei (11, 12). *T. indotineae* isolates are frequently terbinafine-resistant, and infections may require prolonged treatment (e.g., ≥2 months) with second-line therapies such as itraconazole or other antifungals typically reserved for invasive fungal infections (11, 13). It is hypothesized that the emergence and spread of *T. indotineae* are driven by inappropriate use and overuse of over-the-counter topical creams containing combinations of antifungals, antibacterials, and high-potency corticosteroids (e.g., clobetasol) (14, 15).

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T. indotineae infections have been reported across Asia, Europe, North America, and Oceania (11, 16). A review of DNA sequences submitted to the National Center for Biotechnology Information suggests that *T. indotineae* has been in Australia since at least 2008 and in Germany since 2010, long before it was recognized in Asia (17). In addition, cases of severe dermatophytoses caused by *T. mentagrophytes* genotype VII have been reported in Europe as the etiologic agent of severe dermatophytoses likely transmitted during sexual activity (18, 19).

Until recently, North American reports of severe and antifungal-resistant dermatophytoses have been uncommon (20). Dermatologists recently reported *T. indotineae* infections in two U.S. patients and eight Canadian patients (7, 21). Antifungal-resistant *T. rubrum* infections in the United States have also been reported (20, 22, 23). Antifungal-resistant dermatophytoses are likely underreported because antifungal susceptibility testing (AFST) of dermatophytes is rarely performed, and *T. indotineae* can only be distinguished from *T. mentagrophytes/interdigitale* using molecular methods available at select specialized laboratories (7). Antifungal-resistant dermatophytoses are generally suspected in instances of unusually severe infection or failure of terbinafine primary therapy, and systemically collected data are lacking in North America on the prevalence of such infections (7).

Cañete-Gibas et al. summarize the results of dermatophyte isolate speciation and AFST performed on North American isolates at the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio, one of the world's premier fungal diagnostic reference laboratories. Of concern, the authors found that 18.6% of isolates tested during 2020–2021 (21 *T. rubrum* and 21 *T. indotineae* isolates during 2020–2021; 3 additional *T. indotineae* isolates identified during 2017–2019) were resistant to terbinafine, including resistant isolates from at least 11 U.S. states and two Canadian provinces (16). The authors also found that *T. indotineae* has been present in the United States since at least 2017. As the authors note, the isolates received at this specialized laboratory often represent cases involving suspected antifungal resistance or severe clinical presentation, so the analysis likely overestimates the prevalence of antifungal-resistant dermatophytes. Nonetheless, this laboratory serves as a sentinel site to detect the emergence of new species or resistance patterns, and their findings suggest that antifungal-resistant dermatophytoses may be a more widespread concern in North America than previously appreciated (16).

Multiple factors limit current knowledge about the epidemiology and clinical features of antifungal-resistant dermatophytoses. First, diagnostic testing to confirm suspected dermatophytoses is infrequently ordered by clinicians, with AFST ordered even less frequently (24, 25). Clinicians may be dissuaded from confirming suspected dermatophytoses with laboratory testing because of low reimbursement rates, long turnaround times, and a lack of access to laboratories that identify dermatophytes to species and perform AFST (25, 26). Furthermore, neither FDA-approved testing platforms nor clinical breakpoints for resistance exist. Dermatophytoses, including antifungal-resistant dermatophytoses, are not nationally notifiable conditions in the United States and are not reportable in any U.S. state (https://www.cdc.gov/fungal/fungal-disease-reporting-table.html). Increased surveillance efforts and clinical studies, ideally integrating epidemiologic, laboratory, and clinical data, could help monitor the spread of antifungal-resistant dermatophytes and detect unusual clusters of severe or antifungal-resistant infections. Professional organizations such as the Infectious Disease Society of America or the American Academy of Dermatologists could consider developing registries to which clinicians could report unusual dermatophytosis cases (27). Specialty clinics, like sexually transmitted diseases clinics, could consider performing sentinel surveillance in their communities for clusters of dermatophytoses potentially transmitted during sex (28). Detailed case investigations by state and local public health departments could help better understand risk factors and treatment outcomes in patients with antifungal-resistant or severe dermatophytosis (7).

Antifungal stewardship efforts are critical to addressing the emergence of antifungal-resistant dermatophytosis and hinge on accurate laboratory diagnosis and AFST to guide therapy (6). Expanding clinician access to dermatophyte testing and AFST, particularly through the development of rapid, affordable point-of-care testing for dermatophytoses and antifungal resistance, could help improve clinical practice and minimize inappropriate antifungal prescribing that drives resistance (23, 29). Addressing the emergence of antifungal-resistant dermatophytoses will require a multidisciplinary approach that includes laboratorians, primary care providers (PCPs), infectious disease specialists, dermatologists, and community pharmacists. PCPs are often the first-line providers to encounter patients with suspected dermatophytoses and should practice judicious prescribing of antifungals while educating patients about the appropriate use of over-the-counter antifungals and corticosteroids (30). As experts in conditions of the skin, dermatologists may receive referrals for difficult-to-treat dermatophytoses, and in coordination with infectious disease specialists, they can lead research efforts to better understand optimal management and develop treatment guidelines (6). Community pharmacists can also educate patients about appropriate over-the-counter antifungal and corticosteroid use and can guide other healthcare providers in navigating potential side effects, therapeutic drug monitoring, drug-drug interactions, and variable insurance coverage related to the antifungals used to treat antifungal-resistant dermatophytoses (31, 32).

Although the isolates tested by Cañete-Gibas et al. do not compose a nationally representative sample, the high prevalance of resistance they identified underscores an urgent need for a better understanding of the epidemiology and clinical features of antifungal-resistant dermatophytoses in the United States, given the potential for rapid spread. Cañete-Gibas et al.'s manuscript can raise awareness about the emerging public health concern posed by antifungal-resistant dermatophyte infections and catalyze the necessary actions to address this significant public health concern.

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