The Rise of Antifungal-Resistant Dermatophyte Infections: What Dermatologists Need to Know

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PRACTICE **POINTS**

- Recently emerged dermatophyte species pose a global public health concern because of infection severity, frequent resistance to terbinafine, and easy person-to-person transmission.
- Prolonged itraconazole therapy is considered the first-line treatment for infections caused by *Trichophyton indotineae*, a globally emerging and frequently terbinafine-resistant dermatophyte.
- Dermatologists can educate nondermatologists on the importance of mycologic confirmation and avoidance of the use of topical antifungal/corticosteroid products, which are hypothesized to contribute to emergence and spread of resistance.

The landscape of dermatophytosis is changing rapidly due to the global emergence of severe dermatophyte infections that frequently are resistant to first-line antifungal medications. We aimed to review the epidemiology of emerging dermatophyte infections and provide dermatologists with information needed for effective diagnosis and management. We emphasize the importance of proper diagnosis using mycological confirmation and judicious antifungal prescribing, and we review resources for obtaining laboratory testing to confirm the diagnosis of dermatophytosis caused by emerging species.

Worldwide, it is estimated that up to 1 in 5 individuals will experience a dermatophyte infection (commonly called ringworm or tinea infection) in their lifetime.[1] Historically, dermatophyte infections have been considered relatively minor conditions usually treated with short courses of topical antifungals.[2] Oral antifungals historically were needed only for patients with nail or hair shaft infections or extensive cutaneous fungal infections, which typically occurred in immunosuppressed patients.[2] However, the landscape is changing rapidly due to the global emergence of severe dermatophyte infections that frequently are resistant to first-line antifungal medications.[3-5] In this article, we aimed to review the epidemiology of emerging dermatophyte infections and provide dermatologists with information needed for effective diagnosis and management.

Emergence of *Trichophyton indotineae*

In recent decades, public health officials and dermatologists have noted with concern the spread of the recently emerged dermatophyte species *Trichophyton indotineae* in South Asia.[3,6] This species (previously known as *Trichophyton mentagrophytes* genotype VIII) usually is transmitted from person to person, either through direct skin-to-skin contact or by fomites.[4,6] Potential sexual transmission of *T indotineae* infections also has been reported,[7] and it is possible that animals may serve as reservoirs for this pathogen, although there are no known reports of direct spread from animals to humans.[8,9] Major outbreaks of *T indotineae* are ongoing in South Asia, and cases have been documented in 6 continents.[10-12] In the United States, most but not all cases have occurred in immigrants from or recently returned travelers to South Asia.[6,13] The emergence and spread of *T indotineae* is

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hypothesized to be promoted by the misuse and overuse of topical antifungal products, particularly those containing combinations of potent corticosteroids with other antimicrobial drugs.[14,15]

Cutaneous manifestations of *T indotineae* infections tend to cover large body surface areas, recur frequently, and pose substantial treatment challenges.[6,13,16] Several clinical presentations have been documented, including erythematous, scaly concentric plaques; papulosquamous lesions; pustular forms; and corticosteroid-modified disease (Figure 1).[6,16] Affected patients seldom are immunocompromised and often have a history of multiple failed courses of topical or oral antifungals, including oral terbinafine.[13] Many also have been prescribed topical corticosteroids or have used over-the-counter topical corticosteroids, which worsen the rash.[17]

Direct microscopy with potassium hydroxide could be used to confirm the diagnosis of dermatophyte infection, but it does not distinguish *T indotineae* from other dermatophyte species.[2,6] Importantly, culture-based testing usually will misidentify *T indotineae* as other *Trichophyton* species such as the more common *T mentagrophytes* or *Trichophyton interdigitale*. Definitive identification of *T indotineae* requires advanced molecular techniques that are available only at select laboratories.[6] Unfortunately, availability of such testing is limited (Table), and results may take several weeks; therefore, it is suggested that dermatologists who suspect *T indotineae* infections based on the patient's history and clinical presentation begin antifungal treatment after confirmation of dermatophyte infection but not wait for definitive confirmation of the causative organism.[16]

Itraconazole is considered the first-line therapy for *T indotineae* infection, as terbinafine usually is ineffective due to mutations in the squalene epoxidase gene.[16] Dermatologists should be aware that itraconazole is available in different formulations that can affect absorption. The oral solution has greater bioavailability and should be taken on an empty stomach, whereas the capsules are required to be taken with food for effective absorption; the capsules also should be taken with an acidic beverage such as orange juice. Dermatologists should

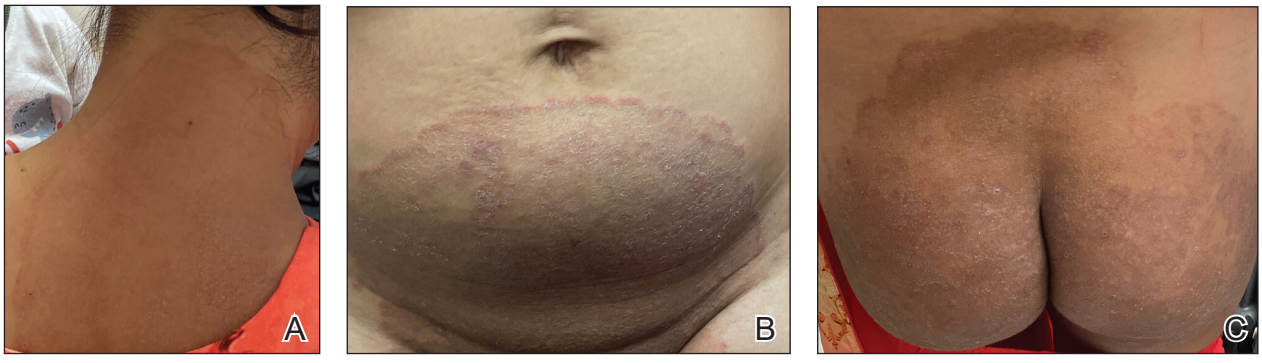

FIGURE 1. A-C, Erythematous scaly plaques on the neck, back, abdomen, and buttocks of 2 different patients with the first reported cases of tinea infection caused by *Trichophyton indotineae* in the United States. Images courtesy of Lu Yin, MD/The Ronald O. Perelman Department of Dermatology, NYU Grossman School of Medicine, New York, New York.

TABLE. Online Resources for Dermatologists and Nondermatologists From the AAD's Emerging Infections Task Force

Resource[a]	Description
https://www.aad.org/member/clinical-quality/clinical-care/emerging-diseases/dermatophytes	Provides resources on recognizing and treating antifungal-resistant dermatophyte infections
https://www.aad.org/member/clinical-quality/clinical-care/emerging-diseases/dermatophytes/recognizing-trichophyton-indotineae#testing	Provides information on laboratories that offer the specialized testing needed to identify certain emerging dermatophyte species
https://www.aad.org/member/clinical-quality/clinical-care/emerging-diseases/dermatophytes/registry	Registry through which dermatologists and other health care professionals are encouraged to report cases of antifungal resistance to help track and improve understanding of these infections

Abbreviation: AAD, American Academy of Dermatology.

[a]These resources are freely available regardless of AAD membership status.

carefully assess for drug-drug interactions when prescribing itraconazole, given its extensive interaction profile with numerous other medications. Patients may require treatment with itraconazole (100 mg/d or 200 mg/d) for a minimum of 6 to 8 weeks until complete clearance has been achieved and ideally a negative potassium hydroxide preparation of skin scrapings has been obtained. A longer treatment period (eg, ≥3 months) frequently is needed, and relapses are common.[6,16,18] Regular follow-up is needed to monitor for infection clearance and recurrences. It is important to note that cases of itraconazole resistance have been reported, although this currently appears to be uncommon.[19,20]

Other Emerging Dermatophytes to Watch

Trichophyton rubrum is the most common cause of dermatophyte infections among humans,[21] and cases of terbinafine-resistant *T rubrum* infections have been reported increasingly in the United States and Canada.[5,22-24] Onychomycosis caused by terbinafine-resistant *T rubrum* has been documented, and patients may have infections that do not respond to terbinafine given at the standard dose and duration.[22,23] Case reports have indicated successful treatment using itraconazole 200 mg/d and posaconazole 300 mg/d.[5,23]

Trichophyton mentagrophytes genotype VII (TMVII) is an emerging dermatophyte that recently has been reported as a cause of sexually transmitted dermatophyte infections in Europe and the United States primarily affecting men who have sex with men.[25-27] Patients may present with pruritic, annular, scaly patches and plaques involving the trunk, groin, genital region, or face (Figure 2). Although closely related to *T indotineae*, TMVII differs in that it more often affects the genital region, generally is susceptible to terbinafine, and in the United States and Europe usually is not related to travel or immigration involving South Asia.[26] Although TMVII has not been associated with antifungal resistance, awareness among dermatologists is important because patients may experience inflamed, painful, and persistent rashes that can lead to secondary bacterial infection or scarring, and physicians might mistake it for mimics including eczema or psoriasis.[25,26]

Importance of Judicious Antifungal Use

Optimizing the use of antifungals is critical to improving patient outcomes and preserving available treatment options.[28,29] A retrospective analysis of commercial health insurance data estimated that topical antifungal prescriptions were potentially unnecessary for more than half of the more than 560,000 patients who were prescribed these medications in 2023. In this study, it also was observed that only 16% of patients prescribed a topical antifungal had received diagnostic testing, with low rates across specialties.[30] This is concerning because even among board-certified dermatologists, incorrect diagnosis of suspected fungal skin infections can occur; in one survey-based study of board-certified dermatologists who were presented with dermatomycosis images, respondents categorized cases with greater than 75% accuracy in only 31% (4/13) of instances.[31] Clotrimazole-betamethasone is among the most commonly prescribed topical antifungals in the United States,[14,32] and 2 recent retrospective analyses highlighted that the majority of patients prescribed this medication did not receive any fungal diagnostic testing.[33,34]

Final Thoughts

In an era of emerging antifungal-resistant dermatophyte infections, it is important for dermatologists to educate nondermatologists about the importance of using diagnostic testing for suspected dermatophyte infections.[14,28] Dermatologists also can educate nondermatologist colleagues on the importance of avoiding the use of topical combination antifungal/corticosteroid medications and referring for dermatologic evaluation when diagnoses are

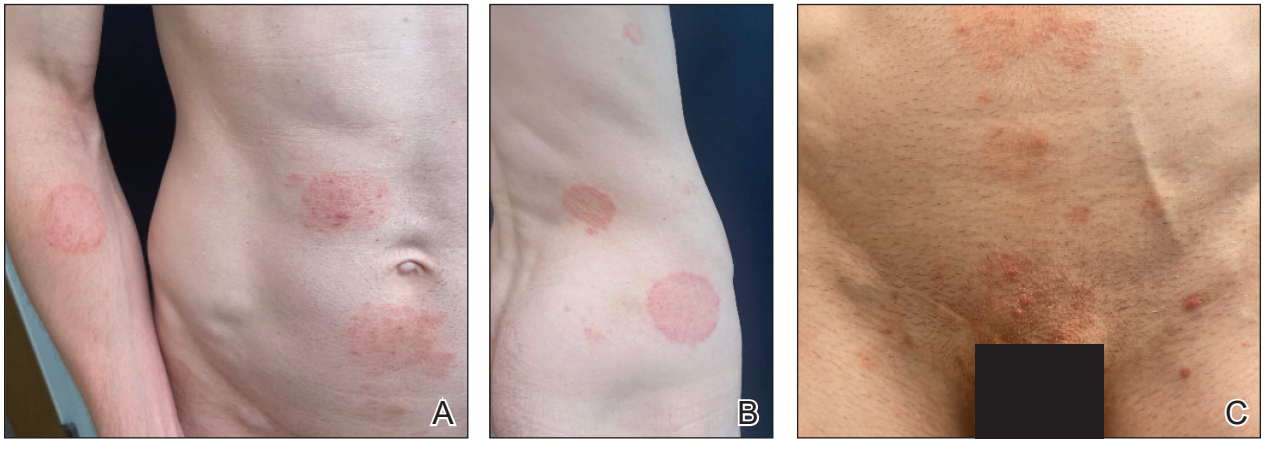

FIGURE 2. A-C, Erythematous scaly patches on the right arm, trunk, and genital region in a patient with *Trichophyton mentagrophytes* genotype VII infection. Images courtesy Avrom S. Caplan, MD/The Ronald O. Perelman Department of Dermatology, NYU Grossman School of Medicine, New York, New York.

uncertain.[33,34] Strategies for education by dermatologists could include giving workshops, creating educational materials, and fostering open communication about optimal treatment practices and referral parameters for suspected dermatophyte infections.

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