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# An Emerging Fungal Pathogen: *Trichophyton Indotineae*


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## Introduction

Dermatophytoses are common fungal infections of the skin and other keratinized structures such as hair and nails. These infections, caused by the dermatophyte fungi, affect approximately 25% of people worldwide.[1] Dermatophyte fungi include species from three genera: *Trichophyton, Epidermophyton*, and *Microsporum*, and may be categorized as anthropophilic, zoophilic, or geophilic. Most cases of dermatophytosis in Canada are attributable to *T. rubrum*.

Over the past decade, there have been an increasing number of reports of terbinafine-resistant dermatophyte infections. Most of these cases are attributable to *Trichophyton indotineae*, a newly described pathogen. Initially described in South and South-East Asia, *T. indotineae* has quickly become a worldwide health concern, with isolates detected in more than 40 countries.[2,3] Epidemiological data reviews have revealed that *T. indotineae* had been circulating in Oman, Iran, India, and Australia as early as 2004, with an increasing number of cases occurring after 2014 due to an outbreak in India.[4]

Recent reports suggest that most new dermatophyte infections in India are attributable to this new pathogen.[5] The development of terbinafine resistance has been attributed to overuse of topical medications containing fixed-dosed combinations of corticosteroids and antifungal agents, which are widely available over-the-counter in parts of Asia and Africa.[6,7] This highly virulent, treatment-resistant fungus may present with chronic, extensive disease and atypical presentations, resulting in significant difficulties for both diagnosis and treatment.

## Diagnosis

Initially classified as *Trichophyton mentagrophytes* genotype VIII within the *T. mentagrophytes/interdigitale* complex, *T. indotineae* was reclassified as its own species in 2020.[8] Due to its morphologic similarity, *T. indotineae* may be misidentified as *T. interdigitale* or *T. mentagrophytes*. Screening tests such as urease and hair perforation can aid differentiation, as *T. indotineae* typically yields a negative result, while both *T. mentagrophytes* and *T. interdigitale* are usually positive.[5] Definitive identification of *T. indotineae* requires advanced diagnostics, such as sequencing of the internal transcribed spacer region, matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS), or quantitative PCR.[3,6]

Given the difficulty of identifying *T. indotineae* via traditional methods, physicians should maintain a high degree of suspicion in patients not responding to standard antifungal therapies or who present with atypical features. Potassium hydroxide (KOH) smears offer a rapid and cost-effective method for the identification of fungal infections in patients with atypical presentations, especially in the setting of topical corticosteroid usage. Additionally, KOH smears offer a method of assessing treatment response.

## Clinical Presentation

*T. indotineae* can present with several atypical features compared to the more common dermatophyte infections. Skin infections may be extensive, with generalized or widespread skin lesions. The lower extremities, groin, and buttocks are the most common sites of infection, and cases of erythroderma have also been described, especially in immunocompromised hosts.[9-11] The majority of patients exhibit involvement of multiple sites simultaneously, and may present with concurrent tinea corporis, tinea cruris, tinea manuum, tinea pedis, and tinea unguium.[3,12] Less commonly, *T. indotineae* may present with facial and scalp infections, with the ear being a particularly frequently affected area. Involvement of the face may be subtle, showing only minimal scaling or poorly defined borders. Newborns and infants have been observed with both tinea corporis and tinea cruris.

Lesions may display a wide range of morphologies. Some may lack characteristic features classically associated with tinea corporis, including an absence of erythema, lack of central clearing, or may show significant hyperpigmentation. Patients may also present with eczematous, pustular, pityriasis rosea-like, or pseudo-imbricata type lesions. Atypical presentations have been associated with topical corticosteroid use. Patients report severe pruritus, often accompanied by a burning sensation.[3] Pruritus may persist even after clinical and mycological cure.[12]

Transmission of *T. indotineae* occurs via person-to-person contact.[7,13] In contrast to other dermatophytes, *T. indotineae* appears to spread quickly within households, often affecting multiple household members simultaneously. Although fomites have been proposed as a mechanism of intra-household transmission, this link is not yet firmly established.[5,7,12] Sexual transmission has also been described as a method of infection.[5] While *T. indotineae* is considered anthropophilic, several reports of infections in animals, such as dogs, have been documented, suggesting that animals may serve as reservoirs and contribute to human transmission.[13]

In Ontario, most *T. indotineae* cases have been associated with recent travel and/or contact with persons who have travelled to endemic regions such as South Asia.[5] While comorbidities such as diabetes mellitus and immunosuppression are typically associated with extensive or recurrent dermatophytosis, these patient factors do not appear to be strongly associated with *T. indotineae* infections, and have been described only in a small proportion of cases.[1]

## Drug Resistance

The rapid spread of *T. indotineae* has resulted in significant therapeutic challenges due to its resistance to typical treatment regimens for superficial fungal infections. Dermatophytes typically demonstrate high rates of sensitivity to terbinafine, which combined with its excellent

penetration of keratinized structures such as skin, hair, and nails, has resulted in topical or oral terbinafine being recommended as first-line therapy in the management of dermatophytosis. *T. indotineae*'s resistance to terbinafine is a public health crisis.

Terbinafine is a fungicidal agent that inhibits squalene epoxidase, an enzyme that catalyzes a key step in the ergosterol biosynthesis pathway necessary for the fungal cell membrane. Multiple single nucleotide variants in the SQLE gene have been detected in *T. indotineae* isolates. These mutations modify terbinafine's binding site on squalene epoxidase, reducing the size and hydrophobicity of the binding pocket.[10] In vitro testing has shown that *T. indotineae* had an increase in the mean inhibitory concentration (MIC) of terbinafine consistent with clinical reports of high rates of failure to standard doses. However, the absence of clearly defined breakpoints limits the usefulness and generalizability of MIC values, as even low MICs have not reliably predicted clinical responses.[3,10,11]

*T. indotineae* has also demonstrated resistance to azole antifungals including fluconazole, with consistently high MIC values reported. Similar to terbinafine, azole antifungals block ergosterol biosynthesis, inhibiting lanosterol 14-α demethylase. Resistance to fluconazole has been attributed to an overexpression of drug-efflux pumps and duplication of the CYP51B gene.[3,5] Resistance to other azole antifungals, such as itraconazole and voriconazole, have been more rarely described, but have also been attributed to amplification via tandem repeats of the CYP51B gene.[13]

## Management

*T. indotineae* poses a unique challenge for dermatologists, given its atypical presentations, multiple drug resistances, and high relapse rates. Standard therapies, including topical antifungals and oral terbinafine, are not effective, and thus effective management requires new strategies.[14]

Terbinafine has historically been the first-line topical and systemic agent for dermatophytosis, typically administered at 250 mg daily. Increasing resistance to terbinafine standard regimens for tinea corporis was first noted in 2016. To address this, Increasing the dose to 250 mg twice daily and extending the treatment duration has been posited.[3,12] Given the rapidly rising incidence of terbinafine-resistant infections, a twice-daily 250 mg regimen of terbinafine is now recommended as the standard dose therapy.[12]

Itraconazole has been found to be the most effective oral antifungal agent for managing *T. indotineae*.[11,12,14] When prescribed for the treatment of either tinea cruris or tinea corporis, itraconazole is typically administered at a dose of 100 mg per day for 7 days. However, due to the increase in treatment failures and frequent relapses associated with *T. indotineae* infection, higher doses and longer treatment durations have been explored.[12] Despite this, a 2022 randomized clinical trial in India found no significant difference in treatment response rates between 100 mg and 200 mg daily dosing.[15] Higher response rates were noted with itraconazole regimens of 400 mg per day; however, these are relatively contraindicated due to the increased associated costs and a higher risk of adverse effects, including hepatotoxicity.[15] As adequate serum levels and skin penetration are achieved with 100 mg daily itraconazole, higher doses are rarely indicated. Additionally, super-bioavailable formulations have been developed to improve absorption without requiring an acidic environment for absorption, which also has been demonstrated to be effective in the management of *T. indotineae*.[12]

When treating *T. indotineae* with itraconazole, extended treatment lengths are recommended given the high rate of relapse rates associated with fixed-length regimens. Patients typically require a minimum of 6 weeks of therapy to achieve both clinical and mycological cure, and treatment courses of up to 20 weeks have been described.[12,15] Treatment should continue until there is a complete cure with resolution of all clinical lesions and confirmation of a negative KOH smear.

Fluconazole has been reported to be ineffective in the management of *T. indotineae*, consistent with in vitro data demonstrating high MIC values. Cure rates have reported to be as low as 42% after an 8-week course of daily dosed fluconazole.[14] Given the published data,

fluconazole is not recommended for the treatment of terbinafine-resistant dermatophytoses.

Resistance to itraconazole has been documented in over 20% of *T. indotineae* cases.[16] In infections resistant to both terbinafine and itraconazole, voriconazole or posaconazole may be effective options.[9,12,13,17] However, optimal dosing and treatment lengths for these agents is not known.[13] Studied voriconazole regimens include 200–800 mg per day for up to 3 months,[17] though the use of voriconazole should be limited to reduce the risk of resistance. Voriconazole is associated with adverse effects such as visual disturbances and option neuropathy, requiring ophthalmologic monitoring for long-term use.[13] Posaconazole has been reported to be effective in recalcitrant cases of *T. indotineae* at a dose of 300 mg per day for 1–3 months.[3,13,17]

While topical therapy is typically ineffective against *T. indotineae*, topical voriconazole 1% has demonstrated efficacy after systemic terbinafine failure.[18] Topical antifungals may also serve as adjunctive therapies in combination with systemic agents. *In vitro* studies have demonstrated significant synergy when itraconazole is combined with other antifungal agents; however, early evidence suggests no additional benefit from combining topical luliconazole with systemic itraconazole in the management of disseminated tinea corporis.[12] Additionally, keratolytic agents such as Whitfield's' ointment may aid in the treatment of hyperkeratotic lesions.[3]

Even with effective therapy, *T. indotineae* infections demonstrate high rates of relapse. Data suggests that most patients experience relapse after treatment, regardless of the agent or regimen used. The underlying cause has not been fully determined, but has been theorized to be due to a novel virulence factor.[10] Predicting which patients will experience a relapse is challenging, as factors such as lesion count, sites affected, total affected body surface area, and comorbidities have not been associated with increased risk.[10,12] Relapses should be treated with the same regimen as prescribed for the initial infection.[12]

## Conclusion

*Trichophyton indotineae* represents a significant and growing global public health concern due to its atypical clinical presentations, chronic relapsing infections, and high rates of antifungal resistance. Its rapid worldwide spread has heralded a shift in the management of dermatophytosis, with increased reliance on second- and third-line agents such as itraconazole, voriconazole, and posaconazole, as well as prolonged treatment courses. New antimicrobial stewardship programs are needed to help guide clinicians in accurate diagnosis and effective treatment, while mitigating emerging resistance.

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