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# Trichophyton indotineae is an emerging pathogen in India: A review article

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## Abstract

**Background:** A superficial fungal infection that affects the skin, hair, and nails is called dermatophytosis. It is brought on by dermatophytes, which are filamentous fungi that live by eating keratin and are members of the genera Trichophyton, Microsporum, and Epidermophyton. Tinea corporis (trunk), tinea cruris (groin), tinea faciei (face), tinea manuum (hands), and tinea pedis (foot) are dermatophytosis variations that impact the epidermis. Both tinea barbae (beard) and tinea capitis (scalp) can be caused by infections that affect the hair follicle. **Emergence of Antifungal Resistance:** Numerous topical and oral antifungal medications can be used as solo or combination therapy to treat dermatophytosis, depending on its severity and extent. Because of its safer profile and fewer side effects, topical treatment is the recommended choice whenever possible and can effectively handle the majority of tinea corporis cases. **Terbinafine Resistance:** Clinical evidence of T. indotineae's terbinafine resistance was first noted when the dermatophytosis worsened despite receiving appropriate oral antifungal therapy and did not improve with treatment. This could be because the corresponding dermatophytes are less sensitive in vitro or have developed resistance to it. **Conclusions:** The mutations that might make T. indotineae, and mycotic strains in general, more resistant to the treatments that are currently accessible are still mostly unknown. Essentially, the goal for the future is to provide individualized care for every patient by customizing therapy as much as feasible.

**Key words:** Trichophyton indotineae**,** superficial fungal infection, Terbinafine resistance, and AFST.

## INTRODUCTION

A superficial fungal infection that affects the skin, hair, and nails is called dermatophytosis. It is brought on by dermatophytes, which are filamentous fungi that live by eating keratin and are members of the genera Trichophyton, Microsporum, and Epidermophyton. Tinea corporis (trunk), tinea cruris (groin), tinea faciei (face), tinea manuum (hands), and tinea pedis (foot) are dermatophytosis variations that impact the epidermis. Both tinea barbae (beard) and tinea capitis (scalp) can be caused by infections that affect the hair follicle. Finally, tinea unguium, also known as onychomycosis, is a term used to describe fungal infections of the nails. Approximately 20–25% of people worldwide suffer from dermatophytosis, which is extremely common (1). As evidenced by significant outbreaks of severe, resistant dermatophytosis in South Asia over the past ten years, dermatophytes that do not respond to standard antifungal treatment dosages and durations have emerged as a global public health concern. The development of a newly identified species, Trichophyton indotineae (previously Trichophyton mentagrophytes genotype VIII), has been the primary cause of these epidemics. Extensive, itchy plaques, usually on the trunk, limbs, and groin, are the hallmark of tinea cruris. These plaques are frequently mildly inflammatory, do not go away with topical antifungals alone, and usually do not respond to oral terbinafine treatment at the same dosages and durations as tinea infections (2).

In several regions of South Asia, outbreaks of dermatophytosis have recently been reported to have escalated to epidemic proportions (3). Globally, the number of dermatophytosis cases brought on by the newly discovered pathogen Trichophyton indotineae is rising. Terbinafine is the first-line therapy choice, although many people are resistant to it, making cases challenging to treat. In Ontario, Canada, we report the rise in T. indotineae infection cases (4). The global spread of T. indotineae infections could therefore provide new therapeutic challenges. Furthermore, although initially

being limited to the Indian subcontinent, dermatophytoses caused by T. indotineae have been observed in more nations across the world, primarily because of migration and travel (5). In addition, dermatophytosis caused by T. indotineae has been reported in China, Australia, Canada, France, Belgium, Switzerland, Greece, Denmark, and most recently, Vietnam (6). More than 76% of T. indotineae isolates were terbinafine resistant in vitro, according to a multicentre study conducted in India, and a sizable portion of patients infected with this newly discovered species no longer react well to topical or oral terbinafine treatment.

**Treatment of Dermatophytosis and Emergence of Antifungal Resistance**

Numerous topical and oral antifungal medications can be used as solo or combination therapy to treat dermatophytosis, depending on its severity and extent. Because of its safer profile and fewer side effects, topical treatment is the recommended choice whenever possible and can effectively handle the majority of tinea corporis cases. Dermatophytosis can be well treated with topical azoles (such as clotrimazole, bifonazole, sulconazole, miconazole, sertaconazole, eberconazole, econazole, oxiconazole, and luliconazole) and topical allylamines (such as terbinafine and naftifine). In contrast to topical azoles, topical allylamines—specifically, terbinafine—have shown better cure rates and shorter treatment durations (1).

Systemic medication is required when there are widespread infections or when topical medicines are not working well. Itraconazole (50–200 mg/day), fluconazole (50 mg/day–150 mg/week), terbinafine (250 mg/day), and griseofulvin (500–1000 mg/day) are often prescribed oral therapies, and results are usually anticipated in a few weeks (8 & 9). Randomized controlled trials have underscored their efficacy, particularly noting better outcomes for terbinafine and itraconazole compared to griseofulvin (10 & 11). Topical antifungal medications can be used in addition to oral systemic therapy for severe infections. A recent review suggests that combining antifungal agents may enhance both clinical and microbiological healing of a superficial infection, potentially expediting the recovery process (12).

**Resistance mechanism of T. indotineae**

Compared to the wild-type, T. indotineae isolates with Phe397Leu and Leu393Ser SQLE mutations demonstrate reduced susceptibility to terbinafine in vitro (13). Conversely, the Ala448Thr mutant exhibits higher susceptibility to terbinafine, although it is subject to debate whether this mutant may be less sensitive to azoles (14, 15). The double mutation Phe397Leu/Ala448Thr is linked to decreased susceptibility to terbinafine and azoles (11). Similarly, the double mutant Leu393Ser/Ala448Thr shows reduced susceptibility to terbinafine, as well (13). SQLE mutations are significant and well-known contributors to antifungal resistance in T. indotineae. However, resistance to azoles has also been recently observed in mutants with upregulation of ABC transporters or mutation in the ERG11/CYP51 gene. The ERG11 gene, which is the target of azoles, encodes the lanosterol 14-α-demethylase enzyme involved in the ergosterol biosynthesis pathway (13,14).

Epidemiological studies in India have shown a trend towards an increased occurrence of T. mentagrophytes (16). T. mentagrophytes surprisingly turned out to be the most common dermatophyte with a prevalence of up to 75.9 to 77.5% (17), followed by T. rubrum, but sometimes also by other Trichophyton species. At the same time, parallel to the emergence of morphologically new, therapy-refractory forms of tinea in India, a pathogen change from T. rubrum to T. mentagrophytes has taken place. This dermatophyte prevails against the pathogens previously found in India, primarily T. rubrum, and largely displaces them as the cause of tinea cruris, tinea corporis, and tinea faciei (18). In our own multicentre experience on tinea cruris, tinea corporis, and tinea faciei in India, T. mentagrophytes was detectable in 138 (92.62%) of all culture-positive skin samples. T. rubrum, however, was isolated in only 11 (7.38%) samples (19).

**Sources of Infection and Routes of Transmission of Trichophyton indotineae**

As of right now, T. indotineae is primarily spread from person to person. In Iran, a family instance of T. indotineae infection was reported to have spread (20). Infection by the species is currently found in numerous Iranian areas, and none of the afflicted family members had ever visited India. On the other hand, at least one German couple who were originally from Iraq showed signs of intra-familial transmission (21). In Germany, T. indotineae was reported to have been transmitted from a Libyan to his female partner and their kid, from a Bahraini baby with tinea corporis and other family members, and from a German woman and her Saudi Arabian spouse. Only six cases (Poland, Egypt, and India) have been reported to involve animal diseases or sources of infection (22). There have also been suggestions of a so-called obligate "anthropozation" of this species through host adaptation, i.e., away from animals into humans (23).

**Terbinafine Resistance of Trichophyton indotineae**

Clinical evidence of T. indotineae's terbinafine resistance was first noted when the dermatophytosis worsened despite receiving appropriate oral antifungal therapy and did not improve with treatment. This could be because the corresponding dermatophytes are less sensitive in vitro or have developed resistance to it (24). However, terbinafine treatment failure is mostly observed in Indian strains of T. indotineae (25). The approximate timing of the mutation or mutations that led to the formation of T. indotineae cannot be accurately estimated. In vitro terbinafine resistance was

first reported in India in 2017. Multicentre research in India found that at least 57.1% of the T. rubrum isolates investigated and up to 76% of the isolates of this species were resistant to terbinafine in vitro (26). It is well established that topical or oral treatment with this allylamine no longer produces satisfactory results for a considerable proportion of individuals with dermatophytoses caused by T. indotineae (23)

**Treatment of Dermatophytoses Caused by Trichophyton indotineae**

As previously stated, topical and oral terbinafine do not work for a considerable portion of chronic recurrent dermatophytosis (23). In vitro, T. indotineae mostly exhibits resistance to terbinafine. This is in line with the identification of one or more point mutations involving amino acid substitutions in the squalene epoxidase gene's position L393F or F397L (26, 27). Itraconazole is the preferred medication for treating dermatophytosis caused by this pathogen. Itraconazole 100 mg twice daily is the recommended dosage for 4–8 weeks, and in certain cases, up to 12 weeks (23). Itraconazole produced using SUBA (super bioavailability) technology has recently been shown to be effective (28) when taken twice daily in a dosage of 50 mg for the same amount of time as regular itraconazole. The minimum inhibitory concentration (MIC) of other medications, such as fluconazole and griseofulvin, against T. indotineae is also elevated (29).

Regretfully, no breakpoint value has been found, and some workers employ the epidemiologic cut-off value (ECOFF) in situations when there is a lack of clarity regarding the relationship between the in vitro MICs and the clinical response (30). In cases of tinea corporis and tinea cruris caused by T. indotineae, strains collected from several sites throughout India showed elevated MICs that corresponded with clinical non-response to fluconazole and griseofulvin. According to a study by Singh et al. from Banaras Hindu University in Varanasi, India, oral fluconazole, griseofulvin, and terbinafine are not as efficient as itraconazole in treating the current dermatophytosis epidemic in India (31)

## CONCLUSIONS

In conclusion, the relatively abrupt epidemiologic shift from T. rubrum to T. indotineae, which has led to an epidemic-like situation in the Indian subcontinent, particularly in India, as well as neighbouring countries like the United Arab Emirates, Oman, Iran, and others, and is currently spreading to Europe, is not only a bothersome disease but has also turned into a public health issue because of the suffering it causes and the sheer number of people afflicted. To have a better understanding of this disease, population-based research from the Indian subcontinent is required. Although molecular diagnosis of the implicated T. indotineae is crucial, most hospitals, particularly large teaching hospitals, do not have easy access to it. The quality of antimycotic medications, particularly itraconazole, must be closely monitored. Lastly, laws favouring prescription-only medications must be strictly enforced, antifungal medications sold over the counter must be restricted, and FDCs containing antifungal agents and strong topical steroids, particularly clobetasol propionate, must be strictly prohibited.

The mutations that might make T. indotineae, and mycotic strains in general, more resistant to the treatments that are currently accessible are still mostly unknown. Essentially, the goal for the future is to provide individualized care for every patient by customizing therapy as much as feasible. Standardizing the use of squalene epoxidase (SQLE) mutational analysis and in vitro antifungal susceptibility testing (AFST) may be a successful approach for precise diagnosis and successful treatment in the event of persistent dermatophytosis. Treatment results for T. indotineae infections may also be enhanced by examining the safety and effectiveness of novel therapeutic approaches, such as combination therapy.

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