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REVIEW

Global Emergence of *Trichophyton mentagrophytes* ITS Genotype VIII (*Trichophyton indotineae*): A Scoping Review of Epidemiology, Clinical Features, and Antifungal Resistance, 2019–2025

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Abstract: Over the past decade, reports of difficult-to-treat, antifungal-resistant superficial fungal infections have increased markedly, raising global concern among clinicians and public health authorities. *Trichophyton mentagrophytes* ITS genotype VIII, more recently classified as *T. indotineae*, has emerged as a principal driver of this shift, with infections often presenting as inflammatory, extensive dermatophytoses that are prone to persistence and relapse despite antifungal therapy. This scoping review synthesizes literature published between 2019 and 2025 to provide a comprehensive overview of emerging trends in epidemiology, clinical features, antifungal susceptibility, molecular resistance mechanisms, and management strategies. Resistance in *T. indotineae* contributes not only to prolonged disease courses and recurrent infections but also to intrafamilial and community outbreaks, highlighting the species' capacity for rapid and widespread transmission. These challenges are compounded by diagnostic limitations, variable correlation between squalene epoxidase gene mutations and terbinafine susceptibility, and the continued reliance on terbinafine as a first-line systemic therapy in many regions. Together, these factors underscore the urgent need for integrated diagnostic and management approaches, combining phenotypic susceptibility testing, genotypic analysis, and careful clinical assessment. Moreover, updated treatment guidelines and coordinated public health interventions are critical to mitigate transmission, optimize therapeutic outcomes, and address the growing clinical and epidemiological burden posed by resistant *T. indotineae* infections worldwide.

Keywords: dermatomycoses, *Trichophyton indotineae*, *Trichophyton mentagrophytes* ITS genotype VIII, tinea, antifungal drug resistance, terbinafine, itraconazole

Introduction

Dermatophytosis represents one of the most prevalent infectious diseases worldwide, affecting an estimated 20–25% of the global population.[1,2] Although dermatophytosis has historically been regarded as a relatively uncomplicated infection responsive to standard topical or systemic therapy, the clinical landscape has changed considerably. Increasing reports now describe chronic, extensive, and treatment-refractory disease, representing a significant departure from the traditional pattern of localized and readily controlled tinea infections.[3,4]

This emerging form of dermatophytosis was first described in detail in India, where reports of unusually persistent, inflammatory, and rapidly spreading infections began to draw attention.[5,6] Similar patterns have since been documented across multiple world regions, including Asia, Europe, North America, South America, and Africa,[7,8] indicating that this phenomenon is no longer geographically confined. The expanding distribution of these cases reflects a broader shift in dermatophyte epidemiology and underscores the growing clinical and public health importance of this issue globally.

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At the center of this emergence is *Trichophyton (T.) indotineae* (formerly *T. mentagrophytes* ITS genotype VIII), a dermatophyte recently designated as a distinct species following its formal description in 2020.[9–11] However, its taxonomic status remains under discussion.[12,13] Initially described as *T. mentagrophytes* ITS genotype VIII, it was later proposed to be renamed *T. indotineae* by De Hoog,[14] while more recently Švarcová et al[15] more recently proposed the alternative classification of *T. mentagrophytes* var. *indotineae*. For consistency, the term *T. indotineae* is used throughout this review.

Historically, dermatophyte species within the *T. mentagrophytes/T. interdigitale* complex have been challenging to differentiate using conventional phenotypic or morphological methods, which show significant overlap in colony appearance and microscopic characteristics. As a result, accurate species-level identification depends on molecular tools, particularly sequencing of the internal transcribed spacer (ITS) region.[9,12] Although *T. indotineae* differs from *T. mentagrophytes* and *T. interdigitale* by only two to three nucleotides in the ITS region, these subtle differences are essential for correct classification and have important implications for both treatment and epidemiologic tracking.[9]

In this review, we synthesize the available evidence on *T. indotineae* to provide a comprehensive overview of its molecular characteristics, antifungal susceptibility patterns, and clinical implications. By integrating data from studies published between 2019 and 2025, this review aims to clarify current knowledge gaps, contextualize resistance trends, and support evidence-based clinical decision-making in the management of *T. indotineae* infections.

Methods

A scoping review was conducted in October 2025 to identify and consolidate available evidence related to *T. mentagrophytes/interdigitale* ITS genotype VIII published between 2019 and 2025. PubMed, Embase (Ovid), and Web of Science were systematically searched using the terms "*Trichophyton indotineae*", "*Trichophyton mentagrophytes* ITS genotype VIII", "antifungal drug resistance", "squalene epoxidase", and "14-alpha-demethylase", All search results were imported into Covidence (https://www.covidence.org/) for deduplication and structured screening.

Eligibility criteria focused on clinical reports and laboratory studies involving *T. indotineae* that had been confirmed through molecular diagnostic screening tests (particularly ITS sequencing). Studies based on isolates of uncertain origin, non-English publications, review articles, and expert opinion pieces were excluded. Title and abstract screening, followed by full-text review, and data extraction were performed independently by AL with discrepancies resolved in consultation with AKG. Extracted variables included study characteristics (author, year, and location), patient characteristics when available (age, sex, recent travel, intrafamilial contact, and sexual contact), diagnostic approaches, therapeutic approaches and outcomes, molecular or phenotypic resistance mechanisms, and antifungal susceptibility results.

Results

A total of 543 studies were obtained from the database search. Of the 225 articles remaining after deduplication, title and abstract screening yielded 182. Following full-text screening, data was extracted from 112 articles published between 2019 and 2025. Of the extracted studies, there were 27 studies that reported data from *T. indotineae* isolates only, with minimal or no patient data, totaling 1128 isolates. The remaining 85 articles included case reports, case series, prospective observation, and retrospective observation studies, totaling 974 patients.

Analysis of publication trends reveals a progressive increase in studies reporting on *T. indotineae* over time (Figure 1). Between 2019 and 2020, only a few studies were published annually (2 and 4, respectively), potentially reflecting the early phase of scientific recognition and reporting of this pathogen in the literature. Publication activity accelerated from 2021 onward, with 10 studies, followed by 14 in 2022, and 17 in 2023, indicating growing recognition and research interest. The number of publications surged further in 2024 and 2025, reaching 37 and 28 published studies, respectively. These data highlight a clear upward trajectory in global research on *T. indotineae* ITS genotype VIII, reflecting increasing clinical awareness, improved diagnostic capabilities, and heightened concern regarding terbinafine-resistant infections.

Of the 112 studies identified, 79 enrolled participants or isolates within a single calendar year, 11 recruited over a two-year period, and 22 spanned three years or longer. The earliest reported recruitment was by Klinger et al,[16] who

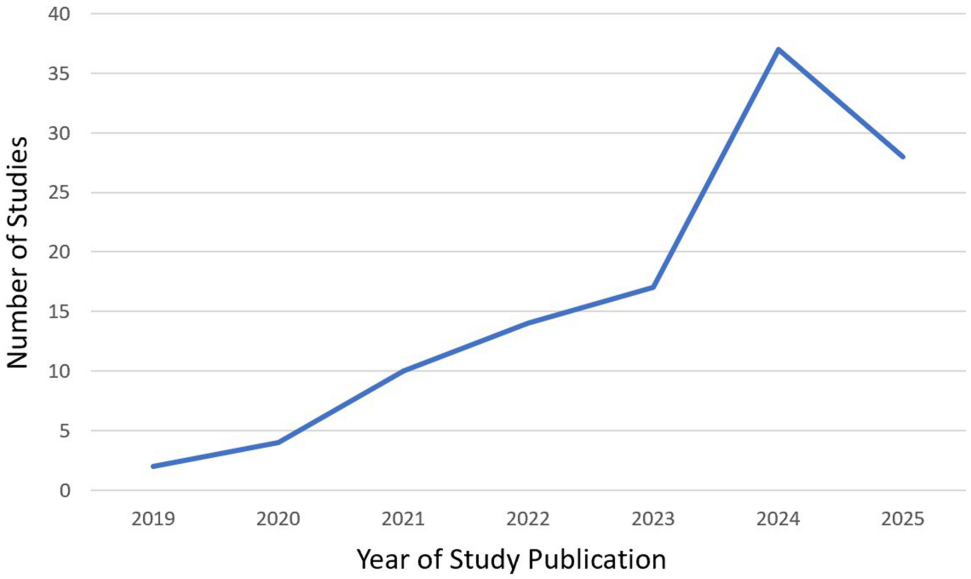

Figure 1 Trends in published studies on *T. indotineae* by year, 2019–2025.

enrolled patients between 2009 and 2016. Differences in study duration likely reflect variations in case burden, study design, and the availability of diagnostic or surveillance resources across regions.

Epidemiology

The prevalence of *T. indotineae* has increased exponentially since its formal identification, transitioning from a localized regional outbreak to a significant global public health concern. This rise is defined by a major epidemiological shift, in which this genotype has largely displaced *T. rubrum* as the dominant strain in endemic regions like India.[17–19] This displacement suggests that *T. indotineae* possesses a distinct evolutionary and competitive advantage, characterized by high environmental resilience and a multidrug-resistant profile that allows it to thrive under modern selective pressures. Consequently, its geographical footprint has expanded across six continents, with our literature search identifying its presence across 41 countries.

Analysis of the current literature underscores a significant concentration of the pathogen within specific epicenters, yet reveals a burgeoning presence in non-endemic regions. Among the 131 country-specific entries reviewed, India remains the most frequently reported source of isolates (15/131), followed by Japan (13/131), Germany (10/131), and Iran (9/131) (Figure 2). While nearly half of all identified isolates originated from the India subcontinent (48.2%; 920/1908 isolates), a substantial paradigm shift toward European establishment is evident. Notably, studies performed in European countries, including the United Kingdom, Germany, France, Poland, Spain, and Belgium, collectively accounted for 24.3% (464/1908) of *T. indotineae* isolates. Data from the UK National Mycology Reference Laboratory indicate that *T. indotineae* has consistently represented over 30% of all referred dermatophyte isolates between 2024 and 2025, underscoring its substantial integration into the dermatophyte epidemiology of Western nations.[20]

Collectively, these epidemiological trends suggest that *T. indotineae* affects individuals across a broad range of ages and both biological sexes. Among the 1014 reported cases identified in this review, 260 (25.6%) were female, 366 (36.0%) were male, and biological sex was not reported in 388 (38.2%). Age-related data, where available, indicate that individuals aged 20–50 years are most commonly affected (516/1014; 50.1%). Additionally, published reports also document *T. indotineae* infections in infants and children, highlighting susceptibility across the lifespan.[21–26]

The transmission dynamics of *T. indotineae* is characterized by high infectivity, particularly within close-contact networks. It is suggested that transmission occurs primarily through a variety of proximal ways, including the sharing of beds and towels, as well as direct skin-to-skin contact.[20] Despite many studies reporting high rates of intrafamilial cases,

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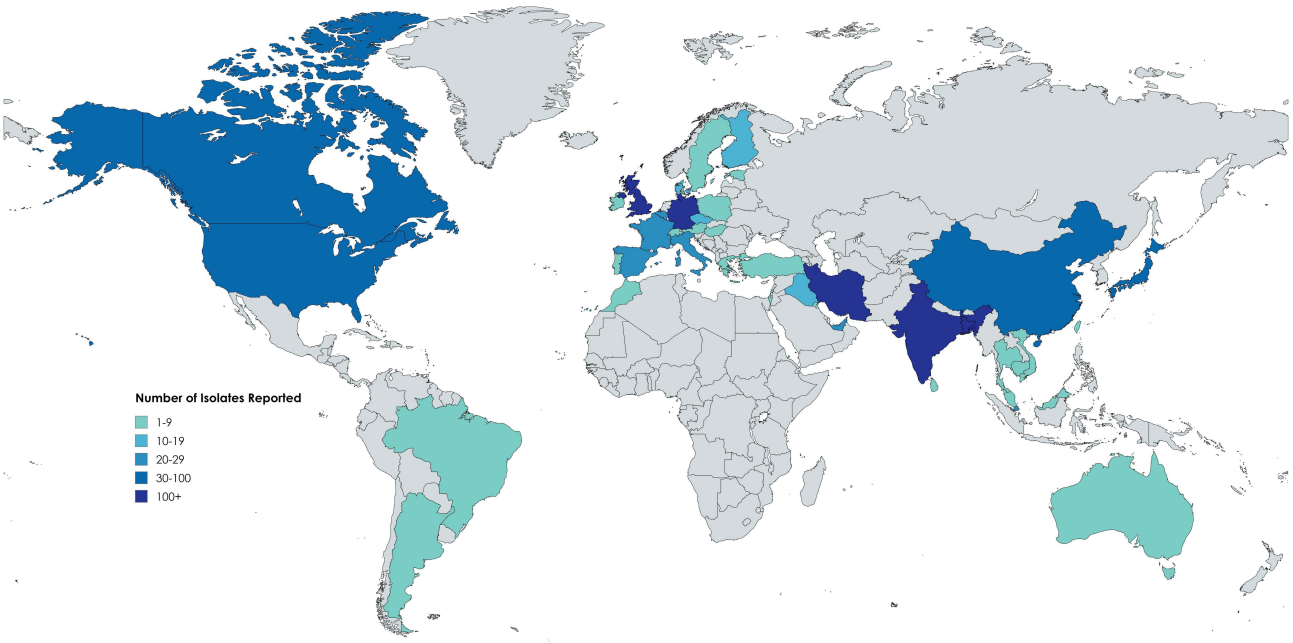

Figure 2 World map of reported *T. indotineae*, with shading representing total isolates per country.

our literature search yielded only 12 studies that reported intrafamilial contact with *T. indotineae* infections, totaling 135 patients (12.5%), there were 7 studies that reported no intrafamilial contact.

More recently, sexual contact has emerged as an increasingly reported mode of transmission for other *T. mentagrophytes*/*interdigitale* complex members (eg *T. mentagrophytes* ITS genotype VII). However, reports of sexual transmission of *T. indotineae* are uncommon. We identified four studies involving ten patients explicitly linking *T. indotineae* to sexual networks, with reports being from France,[27] the United States,[28] Italy,[29] and Denmark.[30] High-risk behaviors, specifically those that increase opportunities for transmission within sexual networks, including contexts such as sex work, certain groups of men who have sex with men, or sex-related travel, may play a role in the dissemination of sexually transmissible dermatophyte infections.

While *T. indotineae* has been primarily characterized as an anthropophilic pathogen, recent evidence suggests the potential for an expanding host range, indicating the potential for zoonotic transmission. Thakur et al demonstrated through whole genome sequencing that there were low single nucleotide protein differences between isolates from animals and humans potentially indicating the transmission of the disease from animals to humans.[31,32] This highlights a critical shift in the epidemiological understanding of the species, suggesting that domestic animals may act as reservoirs, potentially complicating efforts to contain outbreaks in household settings. Across four studies,[19,33–35] 46 patients reported contact with animals. While these findings raise the possibility that animals could contribute to transmission dynamics, the current evidence is insufficient to determine whether such contact represents a meaningful risk factor or merely coincidental exposure.

Although *T. indotineae* was likely introduced to non-endemic regions through travel or migration from endemic countries, increasing evidence indicates that domestic (autochthonous) transmission is occurring. In our review, 49 studies reported travel to another country (180 patients, 17%), eight studies reported no travel (27 patients, 2%), and 55 studies did not specify travel history. Of the cases that reported travel, travel to a country located in South Asia, notably India (57/180) and Bangladesh (54/180), accounted for 72.7% (131/180). These findings align with regional data, where multi-center surveillance in India attributes up to 78% of all dermatophyte cases to this genotype,[19] and studies in Bangladesh report a prevalence as high as 96.2%.[24] Beyond these primary epicenters, travel-related cases were also linked to Europe (7/180, 3.8%), Southeast Asia (9/180, 5.0%), the Middle East (9/180, 5.0%), and South America (5/180,

2.7%). Collectively, these findings underscore both the expanding geographic reach of *T. indotineae* and the potential for local transmission beyond imported cases.

Presentation

In contrast to classical, localized tinea infections (that is *T. rubrum*), disease caused by this organism frequently extends beyond a single anatomical location and presents as extensive or multifocal dermatophytosis.[36,37] Across reported cases, *T. indotineae* infections demonstrate a wide anatomical distribution, affecting nearly all major cutaneous sites (Table 1). While localized infection was observed in some patients, multifocal disease predominated, with 36.9% (360/974) of cases exhibiting involvement of multiple body regions, making disseminated or multifocal dermatophytosis the most frequently reported clinical pattern in the literature. Among single-site infections, tinea corporis (137/974 patients) and tinea cruris (174/974 patients) were the most commonly reported presentations. These findings are consistent with the organism's tropism for soft keratinized tissue and its association with extensive, inflammatory dermatophytosis.

T. indotineae causes a distinctive form of dermatophytosis characterized by variable degrees of inflammation, lack of central clearing, rapid dissemination, and a prolonged, often treatment-refractory clinical course (Figures 3–5).[10,37–41] In contrast to the relatively slow-paced progression characteristic of *T. rubrum, T. indotineae* is associated with a protracted and recalcitrant clinical course, frequently persisting for months or years despite the administration of standard antifungal therapy.[17,38] Consistent with this, Ebert et al reported a median disease duration of six months, with cases ranging from as short as two weeks to as long as seven years.[19] As disease becomes more extensive, classic annular morphology may be obscured, resulting in atypical clinical appearances.

The rapid spread and morphologic variability of *T. indotineae* infection may lead to diagnostic uncertainty. Lesions may clinically mimic inflammatory dermatoses such as eczema, psoriasis, or seborrheic dermatitis,[37,42] particularly in patients with prior exposure to topical or systemic corticosteroids, which can further modify lesion

Table 1 Anatomical Distribution of *T. indotineae* Infections Reported in the Literature

Site of Infection	Number of Patients (n=974)
Tinea Corporis	137
Tinea Cruris	174
Onychomycosis	6
Tinea capitis	1
Tinea faciei	12
Tinea pedis	21
Tinea manuum	3
Tinea mammae	1
Tinea genitalis	1
Tinea unguium	5
Tinea universalis	1
Tinea barbae	1
Tinea axillaris	1
Multiple body sites	360
Not reported	250

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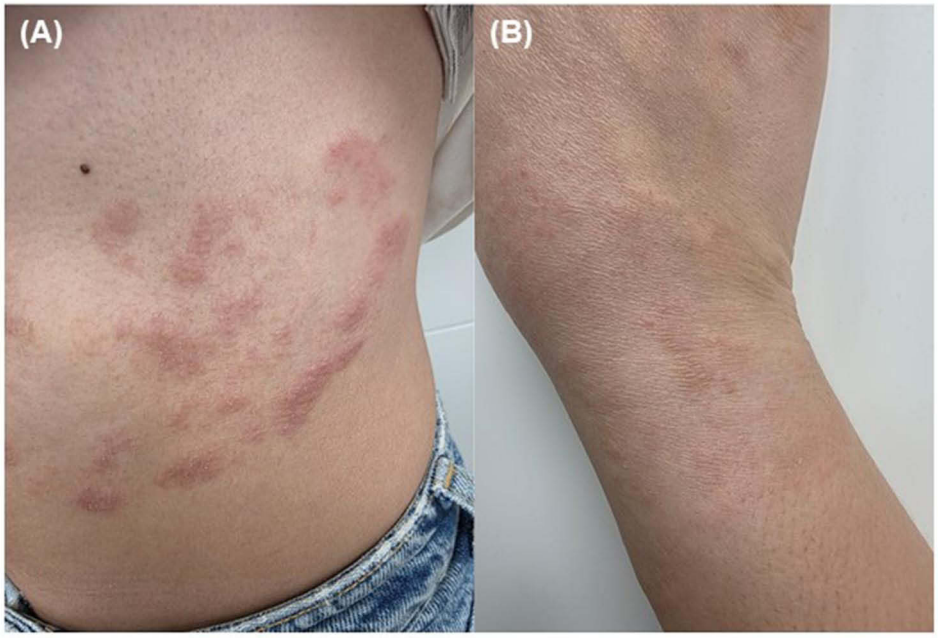

Figure 3 Tinea corporis due to *T. indotineae* in a 30-year-old female presenting with a 6-month history of pruritic, eczematous plaques on the (**A**) trunk and (**B**) wrist. Diagnosis was confirmed by ITS sequencing. The patient did not respond to terbinafine 250 mg/day x 6 weeks. Clinical improvement was observed following the administration of itraconazole 200 mg once daily x 6 weeks. Patient provided written informed consent for the publication of clinical photographs.

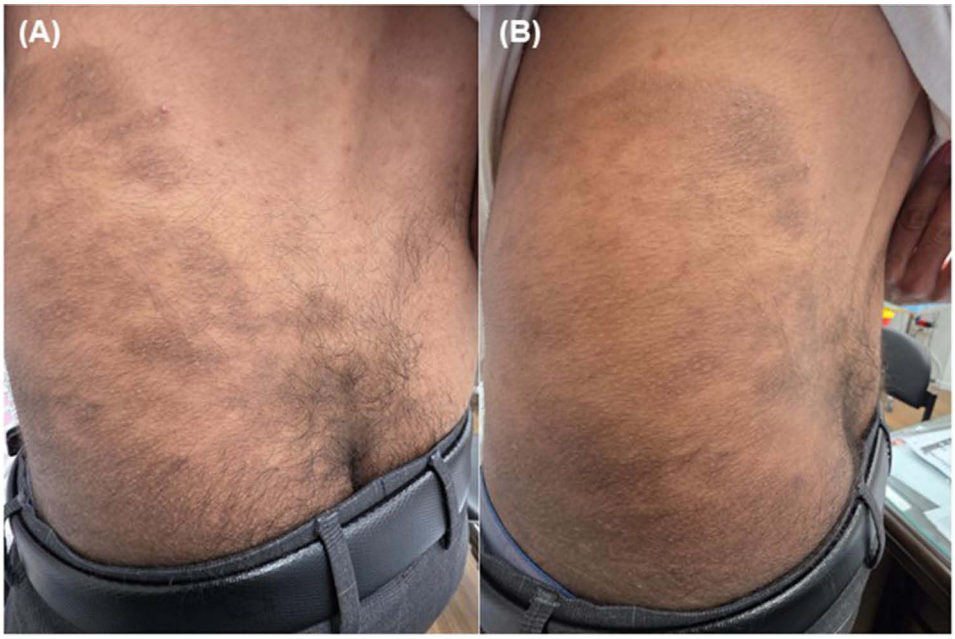

Figure 4 Tinea corporis and faciei in a 44-year-old male presenting with a 10-month history of pruritus involving the face, wrist, and waist. (**A**) Posterior and (**B**) lateral views of the trunk demonstrating scaly, hyperpigmented lesions. Differential diagnosis includes lichen planus pigmentosus and mycosis fungoides. *T. indotineae* diagnosis was confirmed by ITS sequencing. The patient had no response to terbinafine 250 mg/day for 2 months and was switched to itraconazole 200 mg once daily, with only mild improvement. He is currently receiving voriconazole 200 mg once daily, with ongoing treatment due to a good clinical response. Patient provided written informed consent for the publication of clinical photographs.

appearance (Figures 6–7).[18,38,43] These factors contribute to delayed recognition, for example, the central clearing that is often seen in tinea infections is no longer present, and underscores the importance of mycological or molecular confirmation in patients with chronic, extensive, or treatment-refractory tinea infections.

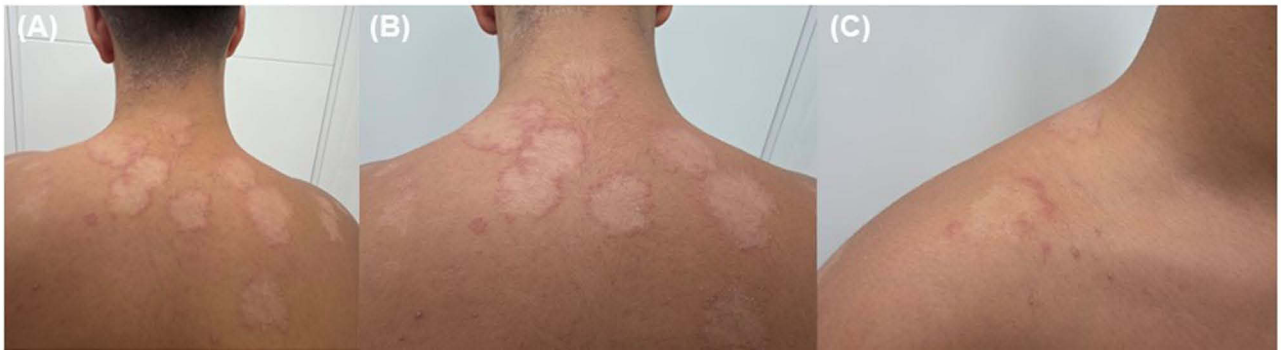

Figure 5 Tinea corporis in a 22-year-old male presenting with a 9-month history of pruritus involving the trunk (upper back, shoulders, and upper chest). Multiple annular lesions were observed on the (**A**) upper back, with additional lesions present on the (**B**) upper back and (**C**) shoulders, exhibiting inflammatory borders and central clearing with post-inflammatory hypopigmentation. *T. indotineae* diagnosis was confirmed by ITS sequencing. The patient had no response to terbinafine 250 mg/day for 2 months. He is currently receiving itraconazole 200 mg once daily, with treatment ongoing due to a good clinical response. Patient provided written informed consent for the publication of clinical photographs.

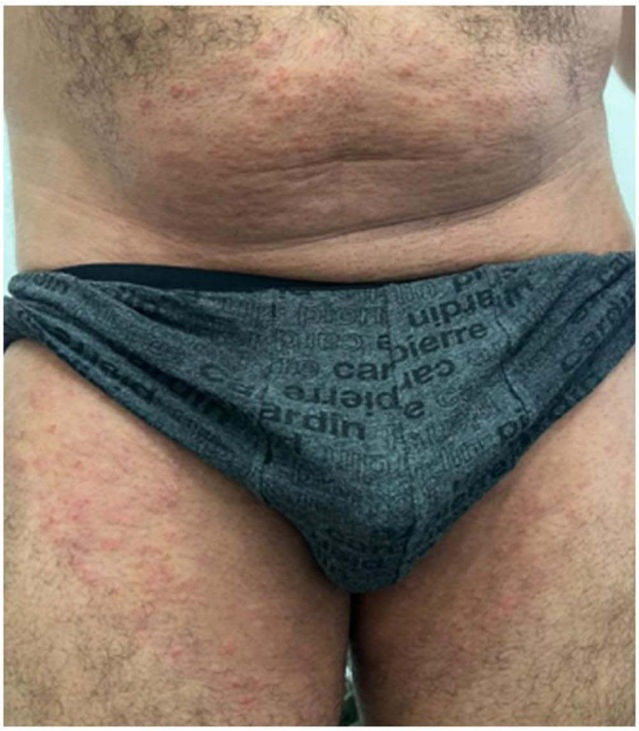

Figure 6 A 54-year-old male with a 10-year history of recalcitrant tinea corporis presented with lesions clinically resembling eczema. Molecular identification via Sanger sequencing of the ITS region confirmed *T. indotineae*. Initial therapy with oral terbinafine 250 mg/day resulted in only minimal and transient improvement after 2 months. The patient was subsequently treated with itraconazole 200 mg/day for 4 weeks, followed by a maintenance regimen of 200 mg twice weekly, achieving substantial clinical resolution within 10 days. Figure was adapted with permission from Gupta et al, 2024., Expert Rev Anti Infect Ther, 22:739–751.

Hypopigmentation in *T. indotineae* infection is uncommon and is most often attributed to post-inflammatory melanocyte dysfunction (Figure 5); however, some patients exhibit reduced pigmentation without clinically evident preceding inflammation. In such cases, superficial epidermal invasion may disrupt keratinocyte–melanocyte signaling and impair melanosome transfer, resulting in altered pigment distribution rather than melanocyte loss.[44,45] Subclinical inflammation may also suppress melanocyte enzymatic activity, including tyrosinase function, leading to decreased melanin synthesis. Unlike *Malassezia* species,[46,47] dermatophytes including *T. indotineae* have not been shown to produce established tyrosinase-inhibiting metabolites such as azelaic acid, suggesting that pigmentary changes are more likely secondary to host–pathogen interactions than to direct fungal depigmenting compounds.

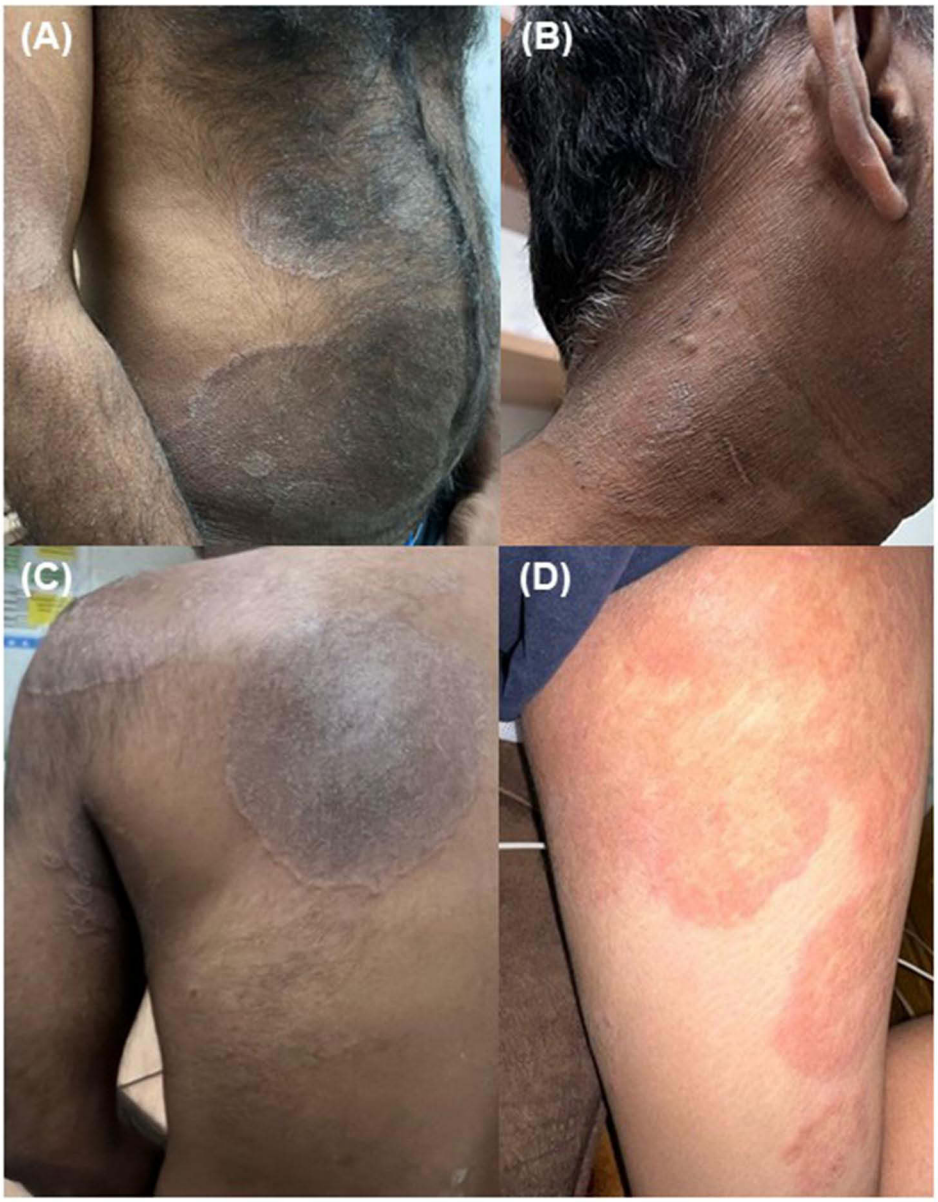

Figure 7 A 44-year-old male with a 20-year history of treatment-refractory tinea corporis of the (**A**) trunk, (**B**) neck, and (**C**) back demonstrated persistent lesions unresponsive to terbinafine, itraconazole, and fluconazole. Symptomatic relief was achieved with voriconazole 200 mg/day for 6 weeks, followed by 200 mg three times weekly for 4 weeks, with pruritus improvement noted after 2 weeks. (**D**) A 36-year-old male with a 13-year history of chronic, refractory tinea corporis, unresponsive to multiple systemic antifungals, experienced rapid symptom relief within 2 weeks of starting posaconazole 300 mg/day for 4 weeks, followed by 300 mg twice weekly for 4 weeks. Figure was adapted with permission from Gupta et al, 2024., Expert Rev Anti Infect Ther, 22:739–751.[42]

While the trunk and groin are the primary targets,[41,48] *T. indotineae* exhibits an expanding anatomical range. In our literature search, less commonly affected sites included the face (tinea faciei, 12 patients), feet (tinea pedis, 21 patients), nails (onychomycosis/tinea unguium, 11 patients), and hands (tinea manuum, 3 patients). In line with previous studies,[19,26,38,49] Very infrequent presentations include tinea barbae, tinea capitis, tinea genitalis, tinea axillaris, tinea mammae, and tinea universalis, each reported in only one patient, highlighting that this infection has been documented in nearly all cutaneous sites.

Despite the growing number of reported cases, heterogeneity in clinical reporting remains a limitation of the available literature. Within our literature search, 21 studies did not specify the anatomical site of infection, accounting for 250

patients with unreported localization. This variability in reporting underscores differences in study design and reporting practices and highlights ongoing gaps in the standardized clinical characterization of *T. indotineae* infections.

Treatment

The management of *T. indotineae* presents challenges due to its high rates of antifungal resistance, particularly to terbinafine, and its tendency for incomplete clinical response, relapse (lesion reappearance within less than 6-weeks after treatment completion),[50,51] and recurrence (lesion reappearance after a longer disease-free period of 6–8 weeks).[50,51] When reasonable clinical suspicion is raised, it is imperative to begin treatment promptly to avoid worsening of the infection and transmission of the infection to household members. It is strongly suggested that assessment of the patient's close contacts occur to determine if transmission has occurred. Additionally, given the recent documentation of potential zoonotic transmission links,[31,32] household pets should be considered potential reservoirs for *T. indotineae*. Systematic evaluation of animals in close contact with infected patients is therefore warranted to prevent reinfection and community spread.[52]

Typically, terbinafine 250 mg/day x 4 weeks continues to be the recommended first-line treatment for dermatophyte infections in many geographical locations due to its favorable safety profile and efficacy. Within our literature search, terbinafine was the most common single-agent therapy documented (51/391, 13.0%), followed by itraconazole (42/391, 10.7%). Importantly, the frequent reporting of terbinafine as a prescribed agent in the literature does not necessarily equate to clinical effectiveness. A recent meta-analysis evaluating clinical terbinafine resistance in *Trichophyton* infections found that 82% of isolates with available MIC data demonstrated concordant clinical resistance.[53] The analysis incorporated studies from multiple geographic regions, including India, Japan, Canada, China, and several European countries. Consistent with these findings, country-specific investigations have shown substantial geographic variability in terbinafine resistance rates, with particularly high prevalence reported in India (up to 72%),[19] followed by Canada (71.4%),[54] Germany (45%),[25] and Greece (37.5%).[22] In the case of terbinafine-resistant *T. indotineae* infections, subsequent clinical failure with persistent or recurrent disease often prompted escalation to alternative systemic therapy. Extended durations of terbinafine (6–12 weeks) have been used in clinical practice, but evidence for improved efficacy in the setting of documented resistance remains limited.

Alternatively, itraconazole (100–400 mg daily) is the most frequently employed alternative to terbinafine and has demonstrated in vitro activity against *T. indotineae* isolates. Clinical series report favorable outcomes with continuous itraconazole therapy for 4–6 weeks or longer in superficial infections. In a clinical series reported by Khurana et al,[55] successful treatment with itraconazole often required extended therapy, with patients achieving complete clinical resolution after an average of approximately 6.6 weeks of therapy. Notably, higher itraconazole doses were associated with more rapid treatment responses, with shorter mean durations observed at daily doses of 400 mg compared with lower dosing regimens of 100 mg and 200 mg.[55] Despite its clinical utility, diminished susceptibility and therapeutic failure with itraconazole have been increasingly reported.[41] Recent studies from Canada[54] and India[19] have documented itraconazole resistance rates of 23.7% and 14%, respectively.

Super-bioavailable (SUBA) itraconazole has been proposed as an alternative formulation in selected cases, particularly in patients with recalcitrant disease or those at risk for subtherapeutic drug exposure. However, the use of SUBA itraconazole for dermatophytosis represents off-label prescribing in many jurisdictions and should be individualized based on clinical response, pharmacokinetic considerations, and antifungal stewardship principles. In refractory *T. indotineae* infections, SUBA itraconazole may be administered at 130 mg once daily for approximately 6–8 weeks. Contrary to conventional itraconazole capsules, which demonstrate variable absorption due to their pellet-based formulation, SUBA itraconazole utilizes a solid dispersion technology that improves dissolution and enhances bioavailability, resulting in more consistent systemic exposure.[56,57] At a dose of 130 mg, SUBA itraconazole provides pharmacokinetic equivalence to conventional itraconazole 200 mg, achieving comparable therapeutic exposure while demonstrating significantly greater bioavailability and reduced interpatient variability.[57,58]

Other antifungal agents such as voriconazole and posaconazole may be considered if infection continues to persist. For voriconazole, limited literature evidence reports cure rates similar to itraconazole, and posaconazole, another extended-spectrum triazole, has also demonstrated in vitro activity and emerging clinical utility in refractory

cases.[37,59,60] However, given their broad antifungal activity, potential toxicity, and drug–drug interaction profiles, the use of voriconazole and posaconazole should be reserved for select cases and guided by antifungal stewardship principles. Specialist consultation is advised when considering these agents, and therapeutic drug monitoring may be warranted to ensure adequate exposure while minimizing adverse effects with voriconazole and posaconazole. In contrast, older agents such as griseofulvin and fluconazole have generally shown poor activity against *T. indotineae*, with consistently elevated MICs and limited clinical efficacy reported.[37,38,61]

Within our literature search, most patients received more than one treatment modality over the course of their infection (261/391 patients, 66.7%). Sixty studies documented patients who underwent sequential or combination therapies, reflecting the clinical complexity and treatment-refractory nature of many *T. Indotineae* infections. Topical antifungal therapy such as terbinafine cream, luliconazole, and ketoconazole may play a supportive role in localized or mild disease and in conjunction with systemic therapy. However, topical monotherapy is generally insufficient for extensive, multifocal, or treatment-refractory infections characteristic of *T. indotineae*, and evidence for topical efficacy in this genotype is limited.[4,62]

Achieving durable clinical and mycological cure in patients with *T. indotineae* is frequently difficult and often necessitates prolonged or maintenance therapy. Relapse and recurrence were variably reported across the literature. Eleven studies documented relapse in 70 patients, representing approximately 6% of all reported cases. In addition, nine studies described recurrence in 153 patients, accounting for 14% of cases. The elevated relapse rates associated with *T. indotineae* appear to arise from multiple contributing factors, including intrinsic antifungal resistance mechanisms as well as ongoing transmission within households and from contaminated fomites. These findings underscore the persistent and recurrent nature of *T. indotineae* infections and highlight the challenges associated with achieving sustained clinical and mycological cure.

MIC_{50} Values

Across both Clinical & Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodologies, terbinafine susceptibility data demonstrated a high prevalence of in vitro resistance. Using an MIC cutoff of ≥4 μg/mL, 65.4% of CLSI-tested isolates and 56.9% of EUCAST-tested isolates were classified as resistant. These findings highlight the declining reliability of terbinafine as a first-line systemic agent for *T. indotineae* infections and align with the widespread distribution of *SQLE* mutations documented globally.

In contrast to the widespread terbinafine resistance, itraconazole demonstrated comparatively favorable in vitro activity. Based on an MIC threshold of >0.125 μg/mL, only 32.0% of isolates tested using CLSI methods and 25.0% tested using EUCAST methods exhibited resistance. Although these data suggest itraconazole remains a valuable systemic treatment option, the emergence of isolates with elevated MICs signals a concerning trend that may foreshadow future resistance development, particularly in regions with high antifungal pressure and frequent therapeutic failure.

There were 48 (CLSI: 41 isolates, EUCAST: 7 isolates) isolates that had a reported MIC_{50} value for griseofulvin, with the CLSI values reporting increased resistance (34.1% of isolated being ≥4 μg/mL) compared to EUCAST values (28.5% reporting ≥4 μg/mL and 42.8% reporting 0.125 μg/mL). Additionally, the majority of isolates with reported MIC_{50} values for fluconazole demonstrated resistance, with CLSI values reporting 89.1% (99/111) of isolates being ≥4 μg/mL, and EUCAST reporting 95.5% (43/45).

SQLE Mutations and MIC_{50} Data

Squalene epoxidase (*SQLE*) mutations are the primary molecular mechanism associated with terbinafine resistance in dermatophytes, particularly within *the Trichophyton mentagrophytes/interdigitale* complex.[53,63,64] In our scoping review, 67 studies reported *SQLE* mutation results, encompassing 960 clinical isolates with confirmed *T. indotineae* infection. A variety of resistance-associated substitutions were identified, with Phe397Leu emerging as the predominant mutation (450/960, 46.8%) (Table 2). Other frequently reported genotypes included *SQLE* wildtype sequences (151/960, 15.7%), Ala448Thr (138/960, 14.3%), dual Phe397Leu/Ala448Thr mutations (90/960, 9.3%), Leu393Ser (61/960, 6.3%), and Leu393Phe (27/960, 3.9%).

Table 2 Frequency of SQLE Genotypes Identified Among *T. indotineae* Clinical Isolates, Summarizing Wild-Type and Resistance-Associated Mutations Linked to Terbinafine-Reduced Susceptibility

SQLE Mutation	Number of Isolates (n=960)
Phe397Leu	450
Wildtype	151
Ala448Thr	138
Phe397; Ala448Thr	90
Leu393Ser	61
Leu393Phe	27
Lys276Ans; Leu419Phe	10
Ser436Ala	5
Gln408Leu; Ala448	3
His440Tyr	3
Ser443Pro	3
Phe415Cys	2
Phe397Leu; Thr414	2
Gln417His	2
Gln417His; Phe397Leu	2
Asn429Asp	1
Phe397Ile	1
Gln408Asn; Ala448Thr	1
Leu393Phe; Ala448	1
Ser395Pro; Ala448	1
Ala230Thr; Tyr444His	1
Ser392Ala	1
Val444Ile; Ala448Thr	1
Phe415Val	1
Gln408Leu	1
Gly445Ser	1

These findings are consistent with a recent meta-analysis demonstrating the presence of SQLE mutations in approximately 84.8% of *T. indotineae* cases.[4] Moreover, patients harboring *SQLE*-mutant isolates experienced a substantially prolonged median time to clinical cure compared with those infected by wild-type strains (16 weeks vs 8 weeks).[4] This delay in therapeutic response supports a direct genotype–phenotype–outcome relationship, wherein specific SQLE mutations have the potential to contribute to elevated terbinafine MICs, slower clinical resolution, and an increased likelihood of treatment failure, often necessitating prolonged or alternative antifungal regimens.

To further elucidate the relationship between *SQLE* genotype and antifungal susceptibility, 44 studies reported both *SQLE* sequence data and corresponding terbinafine MIC values, yielding 791 individual susceptibility results. Among these, 25 studies employed CLSI methodology, while 19 utilized EUCAST protocols. A total of 555 MIC values were generated using CLSI methods, of which 459 were included following exclusion of non-discrete or ranged values. Similarly, 236 EUCAST-derived MICs were reported, with 172 included after applying the same exclusion criteria.

Across both testing methodologies, a strong association was observed between *SQLE* mutations and elevated terbinafine MICs. Phe397Leu was the most frequently identified mutation in both datasets (28.6% CLSI; 29.1% EUCAST) and was consistently associated with high-level resistance, with more than 90% of isolates exhibiting MICs ≥4 μg/mL. Isolates harboring Leu393Ser demonstrated a broader MIC distribution (0.5 to ≥4 μg/mL), with the largest proportion displaying MICs of 1 μg/mL, reflecting a more variable resistance phenotype. In contrast, isolates containing Ala448Thr alone predominantly exhibited low MIC values (≤0.125 μg/mL), reinforcing its limited contribution to resistance. Dual Phe397Leu/Ala448Thr mutations were uniformly associated with high MICs across both CLSI and EUCAST testing systems, underscoring the dominant resistance effect of the Phe397Leu substitution.

From a mechanistic standpoint, several resistance-associated substitutions, particularly Phe397Leu and Leu393 variants, appear to localize within or adjacent to regions of the SQLE enzyme that are critical for terbinafine binding.[65,66] Amino acid changes at these positions are thought to reduce drug–target interactions, resulting in high-level antifungal resistance.[65,66] By contrast, the Ala448Thr substitution has been repeatedly associated with little to no effect on terbinafine susceptibility, indicating that this mutation alone is largely functionally silent. However, the Ala448 residue has been linked to altered ergosterol synthesis and may contribute to reduced azole susceptibility. Several studies have reported elevated azole MICs in isolates carrying the single Ala448Thr substitution.[19,67,68] Notably, Ebert et al reported that isolates carrying the Ala448Thr substitution, alone or combined with Phe397Leu, exhibited significantly higher itraconazole and voriconazole MICs compared with strains harboring only Phe397Leu or wild-type SQLE.[19]

Notably, a substantial proportion of isolates with wild-type *SQLE* sequences nonetheless demonstrated elevated terbinafine MICs in both CLSI (57.9%) and EUCAST (54.2%) datasets. This observation suggests that terbinafine resistance in *T. indotineae* is likely multifactorial and may involve additional mechanisms beyond coding-region *SQLE* mutations, including gene overexpression, efflux pump activation, or regulatory and promoter-region alterations.[69] Overexpression of drug efflux pumps from the ATP binding cassette (ABC) and major facilitator superfamilies can decrease intracellular drug concentrations, and such efflux upregulation has been observed in *T. indotineae* isolates lacking *SQLE* mutations.[70–72] Similarly, biofilm formation may impede drug penetration and promote persistent infection, a phenomenon documented in dermatophytes in vitro.[72,73] Stress response pathways, including upregulation of heat shock proteins, likely contribute to fungal survival under antifungal pressure,[74,75] and experimental data suggest that overexpression of the salA gene, encoding for salicylate 1-monooxygenase can also modulate terbinafine tolerance.[76,77]

Discussion

T. indotineae represents an evolving global dermatological challenge, with its rapid spread across continents signaling a shift in dermatophyte epidemiology. Beyond mere incidence, its clinical and public health significance lies in its recalcitrant course, atypical clinical presentations, and increasing antifungal resistance, which collectively complicate diagnosis and management. In many cases, terbinafine resistance in isolates causes delayed treatment responses, necessitating alternative treatment modalities, such as itraconazole or SUBA-itraconazole, either as monotherapy or combination therapy with topical antifungals.[62]

The variability in *SQLE* and MIC data within the current literature has important clinical implications, as relying exclusively on *SQLE* molecular screening may fail to detect resistant isolates, potentially leading to continued terbinafine treatment despite a low probability of therapeutic success. Whenever possible, phenotypic antifungal susceptibility testing should be employed in cases of recalcitrant or extensive dermatophytosis to guide more informed treatment decisions. However, it is important to note that isolates with high MICs to terbinafine or itraconazole may still respond clinically, while isolates with low MICs may fail therapy. Similarly, the observed differences in MICs among isolates harboring identical *SQLE* mutations indicate that genotype alone is an unreliable predictor of therapeutic response.

Therefore, antifungal selection should integrate MIC data, molecular findings, patient-specific factors, and observed clinical response rather than relying solely on laboratory values.

The international spread of *T. indotineae* also underscores the need for coordinated public health strategies, particularly in endemic regions where over-the-counter corticosteroid-antifungal combinations remain widely used. In this context, antifungal stewardship becomes critical.[78] Promoting the rational use of systemic and topical antifungals can help improve treatment outcomes, reduce the emergence of resistance, and preserve the effectiveness of existing therapies. Widespread misuse of corticosteroid-containing creams, often combined with antifungals, not only masks classic dermatophytosis morphology but can also exacerbate inflammation in the long-term, facilitate atypical or disseminated infections, and contribute to recalcitrant disease. Educational initiatives targeting both healthcare providers and patients on the dangers of indiscriminate topical steroid use, alongside stewardship programs, are therefore essential to prevent prolonged or recurrent infections.[79,80]

Beyond antifungal treatment, preventing reinfection and limiting community transmission is crucial. Strict hygiene measures such as daily bathing, regular laundering of clothing and bedding, disinfecting footwear and other fomites, and avoiding the sharing of personal items are essential. Current evidence indicates that effective decontamination of textiles requires both high temperatures and the mechanical action of repeated rinsing to remove fungal conidia.[81] Household members should be assessed and treated if infected, and pets considered as potential reservoirs even though zoonotic transmission is uncommon. Additionally, as mentioned previously, household members should be assessed for signs of infection and treated promptly if positive, as close contact is a common route of transmission. Pets should also be evaluated as potential reservoirs, even though zoonotic transmission appears rare, to prevent reinfection or ongoing community spread. Educating patients on these measures, emphasizing consistent adherence, and reinforcing the rationale for these interventions is a crucial yet often underappreciated component of controlling *T. indotineae*. Implementing these strategies not only reduces the likelihood of recurrent or chronic infections in individual patients but also helps protect household members and the broader community, complementing pharmacological therapy and antifungal stewardship efforts.

Conclusion

Clinicians should suspect *T. indotineae* when patients present with widespread, atypical lesions that persist despite standard topical antifungals, oral terbinafine, and/or repeated courses of corticosteroid-containing regimens. Conventional diagnostic methods, such as KOH and routine culture, may confirm dermatophytosis but often cannot distinguish *T. indotineae* from closely related members of the *T. mentagrophytes/interdigitale* complex. Definitive identification frequently requires molecular techniques, g, which remain unavailable in many settings. Management frequently necessitates prolonged systemic therapy, most commonly itraconazole for terbinafine-refractory cases, combined with adjunctive topical antifungals. Effective control also relies on preventing reinfection and community transmission through strict hygiene measures, patient counselling, and evaluation of household contacts. Awareness of antifungal resistance, judicious use of topical corticosteroids, and adherence to antifungal stewardship principles are essential to achieving durable clinical and mycological cure and to limit the further global spread of *T. indotineae*.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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