

# Burden of Chronic Dermatophytosis in a Tertiary Care Hospital: Interaction of Fungal Virulence and Host Immunity

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**Abstract** Dermatophytosis is caused by keratinophilic dermatophytes and affects the superficial skin and its appendages. The nature of infection and response to treatment is influenced by host–pathogen factors like duration and severity of disease, prior drug history and type of causative organism. In our study, the burden of dermatophytosis affecting glabrous skin saw a rise in recalcitrant and reinfection cases with only 1.6% achieving complete cure. Chronicity of dermatophytic infection was reflected in the high

serum IgE levels and immediate hypersensitivity reactions. Hence, it becomes pertinent for clinicians to identify the non-responders and modify therapy to achieve clinical cure with fungal clearance confirmed by mycological tools.

**Keywords** Chronic dermatophytosis · Reinfection/ recalcitrant dermatophytosis · *Trichophyton mentagrophytes* complex · Antifungal therapy

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## Introduction

Dermatophytosis is the most common superficial skin infection in the world, affecting millions annually

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worldwide, commonly referred to as ringworm or “tinea” infections and named with reference to the area of the infected body part, e.g., tinea capitis, tinea pedis, tinea unguium [1, 2]. Dermatophytes are a group of highly specialized keratinolytic fungi that invade the keratinized tissue. These organisms have the unique ability to infect immunocompetent people and are associated with considerable morbidity and socio-economic trauma. The epidemiological profile of dermatophytosis has observed an increase in the diversity with dynamic evolution of dermatophytes due to migration of population [3]. Despite a considerable understanding of the causative agent, the mechanistic details of the interaction between host immune system and the dermatophyte with the resultant pathogenesis are poorly understood. Consequently, effective therapeutics specific to dermatophytes are limited. Dermatophytes produce a variety of proteolytic enzymes which act in acid, alkali or neutral environments. These protease genes are variably expressed with distinct enzyme patterns as found in infection versus cultured conditions [4, 5]. In addition, other factors such as those concerned with host resistance, have a role in limiting the ability of dermatophytes to penetrate further than the stratum corneum. The trend of clinical profile of patients with tinea corporis or tinea cruris is changing towards recalcitrant condition probably owing to the development of drug resistance, misdiagnosis, suboptimal dosing or impaired cell-mediated immunity of the patient [6, 7]. There is a dearth of information regarding the burden of dermatophytic infection pertaining to the glabrous skin in Delhi. Our analysis offers insight into the burden of dermatophytosis of glabrous skin in patients attending the OPD of a large tertiary care hospital. Also, an attempt was made to correlate the fungal virulence factor and the host immune status with the clinical status.

## Materials and Methods

This hospital-based cross-sectional study was conducted from November 2015 to April 2017 in the Department of Microbiology, GTB Hospital, Dilshad Garden, Delhi, in collaboration with the Department of Dermatology from where the patients were referred for microbiological investigations. The study was conducted after obtaining institutional ethical

clearance and written informed consent from the study participants.

There were 300 patients included in the study, who were clinically diagnosed with the dermatophytic infection of the glabrous skin. They were divided into study groups based on their clinical history into naïve, reinfection and recalcitrant. “Naïve” patients presented with the characteristic lesion of tinea for the first time. “Reinfection” patient had a prior history of tinea infection with complete cure and is now presenting with skin infection either in the same lesion or in a different location. “Recalcitrant” patient is the one whose tinea infection shows no improvement or worsening with the current therapy [8]. Patients who were pregnant, immunosuppressive conditions or intake of corticosteroids (oral/systemic) were excluded.

Trichophytin intradermal skin testing was performed on the patients and the test result read within 15 min and after 48 h. Trichophytin antigen (with protein concentration 2.3 mg/ml) derived from anthropophilic *Trichophyton spp* strains was procured from All Cure Pharma Pvt. Ltd., Delhi (India); 0.01 ml each of trichophytin antigen and phosphate-buffered saline (PBS) (negative control) was injected intradermally using separate syringes at independent sites of skin of the forearm in all patients. The test was read after 15 min for immediate hypersensitivity (IH) response and 48 h for delayed-type hypersensitivity (DTH) response. Any reaction with mean wheal diameter at least 3 mm greater than the negative control was taken as positive [9].

All the cases of dermatophytosis were mycologically diagnosed and identified based on KOH wet mount examination, fungal culture on Sabouraud’s Dextrose Agar (SDA) (with cycloheximide/cycloheximide + 0.04% gentamicin + 0.005% chloramphenicol), urease test and morphological identification by using lactophenol cotton blue preparation under microscopy. From the growth on culture media, the fungal pathogen was assessed for protease activity using Staib agar method and calculated by the ratio method, i.e. the ratio of the diameter of the well to the zone of growth around the well. Protease activity of dermatophyte isolates was analysed and grouped into the following categories: null ( $\geq 1$ ), mild (0.8–1.0), moderate (0.6–0.8) and high ( $< 0.6$ ).

Serum total IgE levels were estimated from blood samples of all the patients (using Calbiotech IgE

ELISA Kit). IL-4 cytokine analysis was also performed on blood samples (using ELISA Kit from Genprobe, Diaclone, France). Thirty age-matched healthy controls were also included to analyse IL-4 levels.

A follow-up assessment was done to assess mycological cure by microscopy, and growth on culture media after 4–6 weeks of treatment. Patients received either griseofulvin/terbinafine/itraconazole monotherapy, or a combination therapy of two different antifungals.

The isolates which were identified as *Trichophyton mentagrophytes* complex by conventional phenotypic methods were subjected to molecular confirmation by sequencing the internal transcribed spacer (ITS) region of rDNA [10]. DNA was extracted from the cultures grown on SDA by using the commercially available DNA extraction kit (HiYield Genomic DNA Kit, RBC, Taiwan). The extracted DNA was subjected to PCR using primers [3]: ITS1 (5'-TCCGTAGGTGAACCTGCGG-3') and ITS4 (3'-TCCTCCGCTTATTGATATGC-5') to amplify the internal transcribed spacer (ITS) region of 18S rRNA. The samples were amplified by using the following thermal cycling parameters: 95 °C for 5 min; 40 cycles of 95 °C for 30 s, 56 °C for 30 s, and 72 °C for 45 s; and 72 °C for 10 min. Purification of the PCR products and DNA sequencing was done commercially. The sequence analysis was performed and compared with the sequences deposited in GenBank by using the BLAST program (<https://www.ncbi.nlm.nih.gov/blast/Blast.cgi>). Sequence analysis of the ITS region showed > 99% identity with *Trichophyton interdigitale*, and the representative isolates ( $n = 14$ ) were submitted to GenBank database and assigned accession numbers MG889846-59.

Statistical analysis of the collected data was performed using SPSS 20.0 statistical software (SPSS Inc., Chicago, IL, USA; version 20.0). Tests of significance like Chi-square were applied, and the  $p$ -value less than 0.05 was taken as significant. Unpaired  $t$  test was performed to compare the serum levels of cytokine IL-4 amongst study subjects versus healthy controls. Data were expressed as mean  $\pm$  SD unless stated otherwise.

## Results

The study conducted during 2015–2017 observed that a majority of patients with dermatophytosis were males (66.3%) with the male-to-female ratio as 1.97:1 as shown in Table 1. Most of the patients belonged to the age group of 15–30 year (66.33%) residing in East Delhi (58.3%) as well as in adjoining Delhi NCR—Uttar Pradesh (36%).

Recruited patients were categorized as naïve (6.7%), reinfection (49%) and recalcitrant (44.3%). Variability was observed in the diagnosis of the patients with most being diagnosed with both tinea corporis and tinea cruris 159/300 (53.0%) followed by tinea cruris 50/300 (16.7%) alone, tinea corporis 44/300 (14.7%) alone and cases of tinea incognito 15/300 (5.0%) (as given in Table 1—Supplementary material). Patients presented with either inflamed 206 (68.6%) or non-inflamed 94 (31.3%) lesions.

The Trichophytin skin intradermal testing showed immediate hypersensitivity reaction in 96.7% of cases. Delayed hypersensitivity reaction was not exhibited by any patient. The serum IgE levels were found to be high in 77% cases of dermatophytosis. Serum levels of IL-4 were significantly ( $p = 0.01$ ) raised in cases (mean  $\pm$  SD: 9.31  $\pm$  1.24 pg/ml) compared to healthy controls (as given in Table 2—Supplementary material). Amongst the study groups, 50% of naïve patients, 80.3% of reinfection patients and 76.6% of recalcitrant patients showed high serum IgE levels as shown in Table 1.

Of the 300 clinically diagnosed patients of dermatophytosis, 294 samples (98.0%) were positive for hyphal elements on KOH mount. Culture positivity amongst study groups showed 50% growth in the naïve group, 70.07% in the reinfection group and 74.44% in the recalcitrant group of patients, as shown in Table 1. *Trichophyton mentagrophytes* complex (TM, *T. mentagrophytes*) was the major dermatophyte isolated (97.2%). Five isolates of *Trichophyton rubrum* (TR) and one isolate of *Trichophyton violaceum* were also noted. Molecular identification revealed *Trichophyton interdigitale* as the predominant species amongst the isolates sequenced. Of the 212 dermatophytes obtained from culture, protease activity was performed on 172 isolates. Protease activity was elicited in 110/172 dermatophytes while 62 isolates showed null activity. Forty isolates (out of 212) were not subjected to protease activity. The

**Table 1** Clinical mycological profile of study groups

|  | Naïve<br>(n = 20)<br>(6.7%) | Reinfection<br>(n = 147)<br>(49%) | Recalcitrant<br>(n = 133)<br>(44.3%) | Total<br>(n = 300) |
|--|-----------------------------|-----------------------------------|--------------------------------------|--------------------|
| Gender                                       |                             |                                   |                                      |                    |
| Male   | 13                          | 102                               | 84                                   | 199 (66.3)         |
| Female                                       | 7                           | 45                                | 49                                   | 101 (33.7)         |
| Age (in years)                               |                             |                                   |                                      |                    |
| 0–15   | 1                           | 7                                 | 2                                    | 10 (3.3)           |
| 15–30  | 12                          | 94                                | 82                                   | 188 (62.6)         |
| 30–45  | 6                           | 31                                | 35                                   | 72 (24)            |
| 45–60  | 0                           | 12                                | 8                                    | 20 (6.7)           |
| ≥ 60   | 1                           | 3                                 | 6                                    | 10 (3.3)           |
| KOH positivity                               | 20 (100)                    | 141 (95.9)                        | 133 (100)                            | 294 (98)           |
| Culture positivity                           | 10 (50)                     | 103 (70.1)                        | 99 (74.4)                            | 212 (70.6)         |
| Protease activity of dermatophytes (n = 172) |                             |                                   |                                      |                    |
| Total of protease producers                  | 4                           | 51                                | 55                                   | 110                |
| High   | 1                           | 17                                | 17                                   | 35                 |
| Serum IgE levels                             |                             |                                   |                                      |                    |
| High   | 11 (55)                     | 118 (80.3)                        | 102 (76.7)                           | 231 (77)           |
| Low  | 9 (45)                      | 29 (19.7)                         | 31 (23.3)                            | 69 (23)            |
| Trichophytin skin test                       |                             |                                   |                                      |                    |
| Immediate hypersensitivity                   | 20                          | 141                               | 129                                  | 290 (96.7)         |
| Delayed-type hypersensitivity                | 0                           | 0                                 | 0                                    | 0                  |
| No reaction                                  | 0                           | 6                                 | 4                                    | 10 (3.3)           |

test could not be recorded due to plate contamination making the interpretation invalid. In this study, the in-vitro protease activity of the major isolate *T. mentagrophytes* complex suggested it to be a moderate to high producer of protease enzyme as shown in Table 2.

At the time of recruitment, 199 patients were prescribed antifungal griseofulvin as monotherapy in all the groups irrespective of their category of infection (as shown in Table 3). Other modalities of

monotherapy were terbinafine prescribed to 38 patients, fluconazole to 8 patients and itraconazole to 6 patients (5 belonging to recalcitrant and 1 to reinfection group). Combination therapy was also noted with a majority being a combination of griseofulvin with either triazoles or allylamines. Twenty-five patients were prescribed only topical antifungal application (either clotrimazole, miconazole, terbinafine, or sertaconazole).

**Table 2** Distribution of protease activity amongst isolated dermatophytes (n = 172)

| Dermatophyte (n = 172)                     | Protease non-producers (n = 62) |      | Protease producers (n = 110) |      |          |      |      |      |
|--|---------------------------------|------|------------------------------|------|----------|------|------|------|
|  | Null                            |      | Mild                         |      | Moderate |      | High |      |
|  | No.                             | %    | No.                          | %    | No.      | %    | No.  | %    |
| <i>Trichophyton mentagrophytes</i> complex | 58                              | 33.7 | 33                           | 19.2 | 42       | 24.4 | 35   | 20.3 |
| <i>Trichophyton rubrum</i>                 | 4                               | 2.3  | 0                            | 0    | 0        | 0    | 0    | 0    |
| Total                                      | 62                              | 36   | 33                           | 19.2 | 42       | 24.4 | 35   | 20.3 |

**Table 3** Treatment profile of study groups initiated at the time of recruitment ( $n = 300$ )

| Antifungal treatment at the time of recruitment | Total | Naïve | Reinfection | Recalcitrant |
|---|-------|-------|-------------|--------------|
| Monotherapy                                     |       |       |             |              |
| Griseofulvin                                    | 199   | 14    | 101         | 84           |
| Terbinafine                                     | 38    | 1     | 15          | 22           |
| Itraconazole                                    | 6     | 0     | 5           | 1            |
| Fluconazole                                     | 8     | 1     | 2           | 5            |
| Combined therapy                                |       |       |             |              |
| Griseofulvin + fluconazole                      | 11    | 2     | 7           | 2            |
| Griseofulvin + terbinafine                      | 5     | 0     | 1           | 4            |
| Griseofulvin + itraconazole                     | 3     | 0     | 1           | 2            |
| Terbinafine + fluconazole                       | 3     | 0     | 2           | 1            |
| Terbinafine + itraconazole                      | 2     | 0     | 1           | 1            |
| Only topical application                        | 25    | 2     | 12          | 11           |
| Total   | 300   | 20    | 147         | 133          |

On follow-up of study groups at 4–6 weeks of antifungal therapy, 8 (40%) out of 111 patients belonged to the naïve group, 51 (39.9%) patients represented the recalcitrant group while 52 (34.6%) patients belonged to the reinfection group. On mycological testing of the 111 follow-up patients, 63

isolates on culture were identified as *T. mentagrophytes* complex, while 48 isolates had no growth.

Of the follow-up cases, 3 cases showed only clinical cure with improvement in lesions with antifungal monotherapy/combination therapy as shown in Table 4. Complete cure was documented in only 5

**Table 4** Clinico-mycological outcome profile of follow-up cases initiated at the time of recruitment ( $n = 111$ )

| Antifungal treatment at the time of recruitment | No. of cases <sup>a</sup> | Complete cure <sup>b</sup> | Only clinical cure <sup>c</sup> | Only mycological cure <sup>d</sup> |
|---|---------------------------|----------------------------|---------------------------------|------------------------------------|
| Monotherapy                                     |                           |                            |                                 |                                    |
| Griseofulvin                                    | 66                        | 4                          | 0                               | 3                                  |
| Terbinafine                                     | 21                        | 1                          | 2                               | 2                                  |
| Itraconazole                                    | 3                         | 0                          | 0                               | 0                                  |
| Fluconazole                                     | 2                         | 0                          | 0                               | 0                                  |
| Combined therapy                                |                           |                            |                                 |                                    |
| Griseofulvin + fluconazole                      | 4                         | 0                          | 1                               | 0                                  |
| Griseofulvin + terbinafine                      | 2                         | 0                          | 0                               | 0                                  |
| Griseofulvin + itraconazole                     | 2                         | 0                          | 0                               | 0                                  |
| Terbinafine + fluconazole                       | 3                         | 0                          | 0                               | 0                                  |
| Terbinafine + itraconazole                      | 1                         | 0                          | 0                               | 0                                  |
| Only topical application                        | 7                         | 0                          | 0                               | 0                                  |
| Total   | 111                       | 5 (4.5%)                   | 3 (2.7%)                        | 5 (4.5%)                           |

<sup>a</sup>Number of cases who have received the specific antifungal treatment at the time of recruitment

<sup>b</sup>Complete cure—defined as both clinical and mycological cure achieved in a patient with the healing of lesion and KOH- and culture-negative mycological assessment

<sup>c</sup>Only clinical cure—defined as a reduction in symptoms; demonstration of a healed lesion or a reduction in the size of the lesion but with the culture positive for dermatophyte

<sup>d</sup>Only mycological cure—defined as KOH- and culture-negative mycological assessment in a patient with no clinical cure

**Table 5** Distribution of study groups and their outcome ( $n = 300$ )

| Outcome measures of study groups     | Naïve (%)<br>( $n = 20$ ) | Reinfection (%)<br>( $n = 147$ ) | Recalcitrant (%)<br>( $n = 133$ ) | Total (%)<br>( $n = 300$ ) |
|--------------------------------------|---------------------------|----------------------------------|-----------------------------------|----------------------------|
| Follow-up ( $n = 111$ )              | 8 (40)                    | 51 (34.7)                        | 52 (39.1)                         | 111 (37)                   |
| Compliance to treatment ( $n = 91$ ) | 7 (35)                    | 42 (28.6)                        | 42 (31.6)                         | 91 (30.3)                  |
| Complete cure                        | 1 (5)                     | 2 (1.4)                          | 2 (1.5)                           | 5 (1.6)                    |

patients, receiving either griseofulvin (4) or terbinafine (1) monotherapy, as shown in Tables 4 and 5.

## Discussion

Dermatophytosis is the most common superficial fungal infection worldwide. Chronicity of infection has changed the epidemiology of dermatophytosis over the past few years with the widespread use of antifungal drugs. Though the disease does not cause mortality, it severely affects the socio-economic condition of the patient. There has been an increase in cases of dermatophytosis in India in the past 5 years [11]. Lack of standardised guidelines has led to extensive misuse of topical and systemic antifungals. Hence, it becomes important to analyse the burden of this disease and its geographical distribution.

In our cross-sectional observational study with follow-up, we observed an alarming rise in dermatophytic cases with 49% of patients presenting as reinfection and 44.3% as recalcitrant dermatophytosis. A male preponderance with glabrous skin dermatophytosis in proportion to females belonged to educated strata where lifestyle, clothing, habits and contacts appeared to be important underlying associated factors. The predominant gender and age group in this study belonged to active and social population engaged in outdoor activities, subjecting themselves to the hot and humid environment favourable to survival and persistence of the dermatophytes on the skin surface. Dual infection with tinea corporis and tinea cruris was observed in 53.0%. The clinical patterns seen in this study were similar to a study conducted by Peerapur et al. in Bijapur where tinea corporis with cruris constituted the majority of clinical cases followed by tinea cruris alone [12]. In the study by Surendran et al. from Mangalore, tinea corporis with cruris was the most common type amongst the

mixed clinical types [13]. The study demonstrated 97.2% isolated dermatophyte as *T. mentagrophytes complex* with most significant species as *T. interdigitale*. A similar pattern of isolation was seen in studies conducted in Lucknow by Sahai et al. with *T. mentagrophytes* (25%) more than *T. inter* (20%) [14]. In another study by Shukla et al., *T. mentagrophytes* (19.17%) was also observed as the predominant isolate than *T. rubrum* (3.0%) [15]. In a recent study by Singh et al., 94% ( $n = 63$ ) isolates were identified as *T. interdigitale* and two as *T. rubrum* by ITS region sequencing [16].

Several virulence factors are excreted by dermatophyte during its invasion into the host tissue which induces host immune responses. Antigens derived from *Trichophyton* exhibit unusual immunologic properties based on their ability to induce distinct skin test reactions in different individuals. IH skin tests to *Trichophyton* extract are immunoglobulin E (IgE) antibody (Ab)-mediated reactions which are frequently observed in subjects with chronic dermatophytosis [17]. The patients with high levels of total serum IgE demonstrated immediate hypersensitivity reaction to trichophytin antigen. This finding convinces us to speculate that a predominant Th2 response leading to IH, with a probable high interleukin 4 production (as demonstrated in our study) by CD4 + T cells, may enable an antibody isotype switch to IgE and IgG4 [17]. The skin response to Trichophytin antigen can be considered as a marker of immune status in fungal infections and aid as a prognostic indicator of treatment outcome [9]. Though a non-specific marker, IgE indicates early or prior and continual sensitization to fungal antigens similar to other fungal infections.

Dermatophytes survive against host defence mechanism by expressing various virulent enzymes [4, 5]. The pattern of proteases secreted by dermatophytes possibly determines the survival of the fungus in the

host tissue and evolution of infection. The proteases also help in the breakdown of the keratin barrier, triggering and modulating the immune response. In our study, though we were able to demonstrate the *in vitro* protease activity of isolates, the method lacked in quantitative analysis and its association with the clinical spectrum of the disease. It is also well documented that the degree of inflammation is far more intense by a zoophilic variant compared to the anthropophilic variety which has adapted to the host tissue over the years. So often in chronic dermatophytosis caused by anthropophilic variants (*T. mentagrophytes* complex, *T. interdigitale*) unlike the zoophilic and geophilic variants, the inflammatory response may not be intense.

Antifungal agents used in the treatment of dermatophytosis can be used either topically or systemically. As in many cases of cutaneous fungal infection, topical therapy is adequate, but systemic treatment is necessary when large areas of the body are involved, when the incidence is chronic or recurrent, or when the infection is in immunocompromised patients [18]. Due to the lack of consensus about the guidelines for the management of these cases, clinicians are attempting various combinations of oral antifungals, or using a higher dose of antifungals, for the treatment of recalcitrant tinea. Oral therapy is preferred by patients as repeated application to large areas of the skin may not always be feasible or convenient to them [18]. In our tertiary care hospital, clinicians are often constrained by the availability of drugs as per the drug dispensing policy. Hence, easily affordable and gold standard drugs for *T. capitis* like griseofulvin, which have good anti-mitotic activity, are still favoured as primary cure of treatment for resource-limited health centre.

As per the hospital protocol and drug availability, the patients were initially started on griseofulvin (66.3%) for 2 months. The decision for prescribing griseofulvin monotherapy is probably taken in view of its cost-effectiveness in treating patients with no prior drug exposure in the public health sector. It is also prescribed in the cases with underlying comorbidities associated with deranged systemic functions like liver function tests which are done prior to prescribing itraconazole. We observed terbinafine monotherapy was prescribed in a single naïve case in view of its fungicidal activity and early healing of lesions. The patients of reinfection and recalcitrant infection

receiving monotherapy with no response or worsening in lesions were prescribed itraconazole after normal baseline investigations. However, some patients belonging to the same group who were found compliant to monotherapy (griseofulvin or terbinafine) but showing a non-healing lesion, the addition of itraconazole or fluconazole combination was initiated to hasten recovery. Despite such vigorous regimens, such patients on combination therapy failed to show any significant improvement in lesions as observed up to 4–6 weeks. For a good clinical response, it is necessary to draw a conclusion to the use of combination therapy with a prolonged follow-up, while taking into consideration the drug-to-drug interactions and pharmacodynamics and bioavailability of the different antifungals.

On follow-up analysis at 4–6 weeks of therapy, only 35% of patients in the naïve group had verified compliance to treatment with griseofulvin or terbinafine. Complete cure was observed in only one case who received griseofulvin. Rest in the group had either an increase in the lesions, or no change, and direct microscopy was positive for hyphal elements. Similarly, we observed 28.6% and 31.6% follow-up in the reinfection and recalcitrant group.

Clinical cure was defined as a reduction in symptoms: demonstration of a healed lesion or a reduction in the size of the lesion. The sense of well-being in patients often misleads clinicians to discontinue therapy, allowing the previously inhibited fungal propagules to regenerate again. At follow-up, a majority of patients in reinfection (81%) as well as recalcitrant groups (73.8%) showed no change in nature of lesion with either monotherapy or combination therapy, suggesting an overall poor response to the treatment advocated.

With these observations, our study highlights the evident role of unfavourable host immune status (high IgE levels and poor DTH response to Trichophytin antigen) which fails to eliminate the fungus despite the antifungals. A mycological clearance without clinical remission may often be misinterpreted and attributed to a lowered fungal load not detectable on culture (viable but not culturable under the influence of antifungals), or poor sampling may result in no growth. The need of the hour is to continue treatment with correct dosage, regular monitoring and extended periods of follow-up aided with laboratory

investigations, essential for achieving the target of a clinical and mycological cure in chronic dermatophytosis patients.

Complete cure was seen in only 5 cases with griseofulvin (4/5) and terbinafine (1/5) monotherapy. One of these was a naïve case diagnosed as tinea corporis for 2 weeks of duration, who responded to griseofulvin monotherapy. Early detection and initiation of therapy is beneficial when the fungal load is low, and the spread of fungal propagule to other sites is restricted, thus hastening early clearance of lesions. In two cases of reinfection, one case of tinea cruris with a 1-year history of incomplete griseofulvin treatment responded to the same drug when given at a dose of 250 mg twice daily for 4 weeks, while the other case of tinea corporis with cruris having periods of remission and relapses for over 1.5 years, presented currently with lesion of 1.5-month duration, responded to 500 mg griseofulvin twice daily. Similarly, the patient diagnosed as recalcitrant tinea corporis with a prior history of steroid application also responded to treatment with griseofulvin administered for 4 weeks. Partial treatment with griseofulvin often leads to partial clearance of the fungus, allowing the appearance of new lesions when the drug rapidly disappears from the stratum corneum. Griseofulvin has long been used for extensive tinea corporis, although cure rates of only up to 60% have been observed and patient's poor compliance often leads to rapid resurgence of lesions. This observation further strengthens our understanding that, though not in all, we can expect fungal clearance in recalcitrant patients, when administered antifungals for a duration long enough for the immune response to recover and promote fungal exclusion for a successful outcome.

In a recent study from India, Singh et al. have documented high-level terbinafine resistance of dermatophyte isolates (*T. interdigitale*) which is indeed a matter of great concern; however, it is also necessary to correlate these findings with patient outcome, as underlying host immune factors may also prove detrimental to treatment and tend to progress to chronicity of infection [16].

## Conclusion

The burden of dermatophytosis is evident with a large proportion of patients with reinfection and recalcitrant

patients with no cure at the period of 4–6 weeks. Of these, 96.7% of patients demonstrated immediate hypersensitivity reaction and 77% had high serum IgE levels. High IgE indicates an atopic population with a shift to Th2 response as observed in recalcitrant and reinfection/relapse cases. We demonstrated 106/300 (35.3%) patients with an incomplete cure. *T. mentagrophytes* complex with *T. interdigitale* was the predominant dermatophyte isolated with a moderate level of protease activity. The ongoing challenges in nomenclature with the different taxonomic approaches [19, 20] hinders the appropriate detection of species complicating the problem further for laboratories to make the correct identification. The complexity of survival and anthropophilic adaptation of dermatophytes in the host promote the establishment of infection by producing several enzymes which further dampen the immune response thus favourable for their persistence. Clinicians must identify the non-responders, as chronicity of infection promotes poor clearance and prolongs survival of the fungus. Therapeutically, clinicians should aim to achieve a target of mycological cure with culture negative. Particular attention should be administered for collecting quality specimen and optimize laboratory tools for precise identification of the fungus to facilitate clinicians to initiate therapy. The limitation of study is as follows: as dermatophytosis has become an entity associated with chronicity, the follow-up analysis of 4–6-week period of antifungal therapy is insufficient to observe the effect of drug as many patients showed no clinical cure during that time period. In our study, the clinical outcome of patients observed in 4–6 weeks follow-up was unsatisfactory despite being on antifungals. This emphasizes the surge in the disease severity of chronic dermatophytosis. To address the emerging threat and the predisposing factors of chronic dermatophytosis, larger multicentric studies would be beneficial with the demonstration of antifungal resistance and molecular characterisation of the dermatophytes.

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## Compliance with Ethical Standards

**Conflict of interest** The authors state no conflict of interest.



**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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