# Management of Dermatophytosis: Real-World Indian Perspective

#### **Abstract**

Background: In spite of the availability of multiple consensus statements on dermatophytosis management, different treatment approaches have been experienced in India and require more scrutiny to further update guidelines and improve patient care. Aim: To determine the different approaches in dermatophytosis diagnosis and management among dermatologists in India. Materials and Methods: A web-based questionnaire was created and validated by five panelists with experience of >15 years in dermatophytosis and then circulated to about 2,000 dermatologists in India in September 2021 for a real-world management scenario. Results: Out of 2,000 dermatologists, 459 responded. About half of the dermatologists (51%) routinely conduct potassium hydroxide mount (KOH) at the initiation of therapy. Similarly, about 53% of dermatologists initiate the management of dermatophytosis with combination therapy in all types of dermatophytosis for 4-6 weeks depending upon severity. Different types of combinations are being practiced, such as either two systemic and one topical, two topicals and one systemic, but the combination of one systemic and one topical (69%) is the most commonly practiced. Itraconazole (100 mg twice a day) and luliconazole are the most commonly prescribed antifungal medications. In case of non-response to routine dose of systemic anti-fungals, about 72% of dermatologists up dose them. Most of them continue these drugs for additional 1-2 weeks after clearance of the disease. Additionally, keratolytics and moisturizers are commonly prescribed. Additionally, 62% advise liver function tests (LFTs) at the initiation of therapy, whereas 72% advise monitoring adverse effects due to systemic antifungal drugs during treatment. Conclusion: Combination therapy stood out as the need of the hour in the current menace of dermatophytosis with timely monitoring of laboratory tests for adverse events due to the use of systemic antifungals for a longer duration.

Keywords: Combination therapy, dermatophytosis, India, itraconazole, real world management

#### Introduction

comparison In yesteryears, scenario dermatophytosis India is marked by changes in epidemiological, clinical, and mycological features.[1] Infections that are chronic, non-responsive, recurrent, slowly conventional responsive to treatment regimens are becoming more common. *Trichophyton* mentagrophytes complex has emerged as the dominant pathogen, with a shifting pattern of dermatophyte isolates.<sup>[2,3]</sup> A multidrug-resistant clad different from the *T. mentagrophytes/T.* interdigitale complex has recently been discovered.[4] Additionally, the newly emerged fungus—*T*. mentagrophytes genotype VIII, now called T. indotineae, often causes pruritic and inflammatory forms of tinea infections, which are found to be terbinafine resistant.<sup>[5,6]</sup> There was a paucity of guidelines/recommendations

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for the management of dermatophytosis especially in recalcitrant Consequently, in 2018, experts created a consensus on dermatophytosis management [Expert Consensus Management of Dermatophytosis in India (ECTODERM India)[7], and 2020, the Indian Association of Dermatologists, Venereologists, Leprologists (IADVL) Task Force against Recalcitrant Tinea (ITART) published the consensus on the management of glabrous tinea (INTACT).[1]

However, further research is required to fully grasp the real-world practice regarding the management of tinea infections and to determine the influence of these guidelines on diagnostic workup and treatment strategy selection. Many concerns, such as the dermatologist's awareness of guidelines, their practical implementation in clinical practice, and the causes for divergence

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from standard recommendations, require more scrutiny to further update guidelines and improve patient care.

Consequently, expert dermatologists from India, who treat dermatophytic infections on large scale, created a questionnaire to get feedback on a wide range of topics related to the management of dermatophytosis and the perspectives related to the application of concerned national guidelines. Hence, this survey was conducted with the purpose to evaluate how well dermatologists across India know and follow the established guidelines, as well as reasons for deviation from guidelines and different treatment strategies in the real-world setup.

#### **Materials and Methods**

To assess the real-world experience of dermatophytosis management, an expert panel was formed comprising five dermatologists with a minimum experience of 15 years in management and research in the field of dermatophytosis.

A web-based multiple-choice questionnaire was created and circulated amongst panel members. The questionnaire comprised 47 questions pertaining to awareness, adherence, and/or deviation of current guidelines, laboratory work-up in dermatophytosis, and treatment options used. The survey was beta tested and approved by panelists before dissemination to other participants. The survey questionnaire was disseminated via a web link to 2,000 randomly selected dermatologists in September 2021, followed by a reminder to participate in October–December 2021. Participants were given 15 days to reply and were guaranteed complete anonymity.

#### Results

Out of 2,000 dermatologists from India who were sent the questionnaire, 459 (23%) completed the survey. Most dermatologists (72%) reported having clinical experience of more than 5 years and 69% had their own clinical setup. About 64% of dermatologists reported to be seeing more than 60 cases of dermatophytosis per week.

# Rising trend of recalcitrant dermatophytosis

Increased incidence of chronic/recurrent or recalcitrant dermatophytosis has been noted in the current survey. As

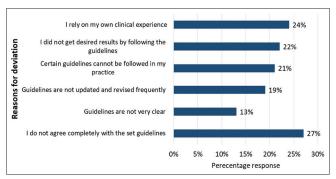


Figure 1: Various reasons for deviation from guidelines

per the results, 92% of dermatologists have noted that 50% of cases of dermatophytosis were chronic. As per the responses, there were many causes of chronicity as shown in Table 1. Additionally, 73% of dermatologists reported an increasing incidence of familial dermatophytosis in up to 25% of the total cases.

# Adherence to guidelines

More than 90% of dermatologists generally follow guidelines, but most of them deviate occasionally. Almost all dermatologists (98%) were aware of one or more dermatophytosis guidelines/treatment recommendations. Fifty-eight percent of them complied with the IADVL textbook of dermatology followed by ECTODERM India and ITART guidelines (26% each). About 18.2% of dermatologists follow other guidelines. About 87% of dermatologists who follow guidelines reported to have deviated from them occasionally due to various reasons as shown in Figure 1.

## Diagnostic test/lab workup for dermatophytosis

About half of the dermatologists (51%) often perform either potassium hydroxide mount (KOH) microscopy or fungal culture at the initiation of therapy for various reasons as shown in Figure 2. Additionally, 62% advise liver function tests (LFTs) at the initiation of therapy, whereas 72% advise them during treatment to monitor adverse effects due to systemic antifungal drugs.

Table 1: Reasons for non/poor therapy responsive or recalcitrant dermatophytosis

Reasons for non/poor therapy responsive or recalcitrant dermatophytosis	% response
Continued transmission from affected family members	37%
Poor hygiene	39%
Topical corticosteroid usage	44%
Comorbidities such as diabetes, HIV disease, malnutrition	26%
Antifungal resistance	52%
Increased virulence of dermatophytes	32%
Poor drug-quality of antifungals	24%

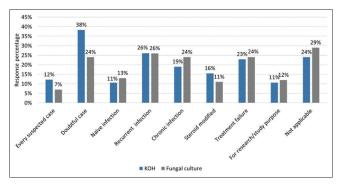


Figure 2: Indications for KOH/fungal culture in dermatophytosis management

# Treatment strategy adopted for the management of dermatophytosis

About 53% of dermatologists initiate the management of dermatophytosis with combination therapy in all types of dermatophytosis. Different types of combination therapies are prescribed by dermatologists such as the combination of systemic and topical antifungals, a combination of one systemic and two topicals, and a combination of two systemic and one topical or two topical antifungals. Of these, 69% of them prescribe a combination of systemic and topical antifungals, of which itraconazole and topical azole (33%) is the most commonly prescribed combination followed by itraconazole and a non-azole topical antifungal drug (32%). A combination of one systemic and two topical antifungals (17%) is well prescribed in chronic and relapse cases. Other combination therapies such as the combination of either two systemic and one topical or two topical antifungals (14% each) are also prescribed in these cases [Figure 3a-c]. Recurrent (50%), chronic (38%), and treatment failure (34%) are the most common indications for use of a combination of systemic and topical antifungals.

Itraconazole (79%) is the most commonly prescribed systemic antifungal followed by terbinafine (61%) in all cases of dermatophytosis. The most common regimen of itraconazole prescribed is 100 mg twice a day (39%) followed by 200 mg once a day (28%). Only 7% of dermatologists prescribe itraconazole 200 mg twice a day. About 39% of dermatologists prescribe systemic therapy for 4–6 weeks in localized infection, whereas in chronic cases, 21% prescribe up to 6–8 weeks, and 17% for more than 8 weeks [Figure 4]. In case of non-response to routine dose of systemic anti-fungals, about 72% of dermatologists updose them.

Luliconazole (65%) is the most commonly prescribed topical antifungal drug followed by ciclopirox olamine (38%) [Figure 5]. All topical antifungals are prescribed for up to 4–6 weeks depending upon the severity of the disease. Additionally, both systemic and topical antifungal drugs are prescribed for additional 2 weeks for better clearance of lesions as reported by 82% and 89% of the respondents, respectively.

#### Adjuvant treatment in dermatophytosis

Moisturizers are prescribed by 78% of dermatologists, whereas keratolytics are prescribed by 73% in various phases of dermatophytosis management. H2 antihistamines are also commonly prescribed, whereas 57% prescribe immunomodulators. Topical tacrolimus is the most commonly prescribed immunomodulator (23%), followed by isotretinoin (17%). Dapsone and zinc are less commonly prescribed. All these adjuvant therapies are prescribed for 2–4 weeks depending on the clinical response [Figure 6].

# Topical corticosteroid applications

As per 36% of dermatologists' responses, topical corticosteroids (TCS) are useful in some of the patients at the initiation of therapy. According to them, TCS are useful in inflamed or severe tinea infection and eczematization or severe dermatitis due to previous topical medications. Amongst dermatologists who prescribe TCS, 52% prescribe two-drug combinations (antifungal + topical steroid combination), whereas 38% prescribe three-drug combinations (antifungal + antibacterial + topical steroid combination). Most of them (84%) prescribe these combinations for the first 1–2 weeks, whereas the rest prescribe for more than 2 weeks.

#### **Discussion**

In India, very few recommendations and consensus papers for the treatment of dermatophytosis have been developed. However, several studies have been conducted nationwide to guide dermatologists in their routine clinical practice. This is the first survey that we are aware of that looked at the real-world management of dermatophytosis in India in reference to the established guidelines, adherence, and reasons for poor adherence if any.

# **Epidemiology**

In the last 6–7 years, Indian dermatologists have seen an increase in chronic and recurrent dermatophytosis cases. Although there is no data on the prevalence of this infection at the population level, multiple hospital-based investigations have found disease burdens ranging from 36.6% to 78.4%<sup>1-4,7</sup> This was in corroboration with findings of the present survey, wherein 42% of the dermatologists responded that they encounter >30 patients, with dermatophytosis per week, out of which 10% encounter >100 patients per week. These figures are simply the tip of the iceberg, given that they come from highly specialized skin care clinics.

The chronicity and recurrence of dermatophytosis are two conspicuous features of this epidemic. [8] Any chronic skin ailment has a significant psychological and social impact on the patient. [2,9,10] Another notable aspect of the current outbreak is the extensive dermatophytosis covering a substantial body surface area (BSA). Tinea corporis, alone or in conjunction with tinea cruris, has surpassed tinea cruris as the most common dermatophytosis presentation. [11] A worrying increase in instances of resistant dermatophytosis has been reported in several studies in India. [2-4] For cases that cannot be classified as chronic or recalcitrant, a new term called "unresponsive dermatophytosis" has been coined. [12] It is unclear if people with this illness have relapsed owing to an undiscovered nail infection or if there is undetected intra-family transmission. [3]

Apart from the obvious explanations for such a rise, the increased importance of familial dermatophytosis

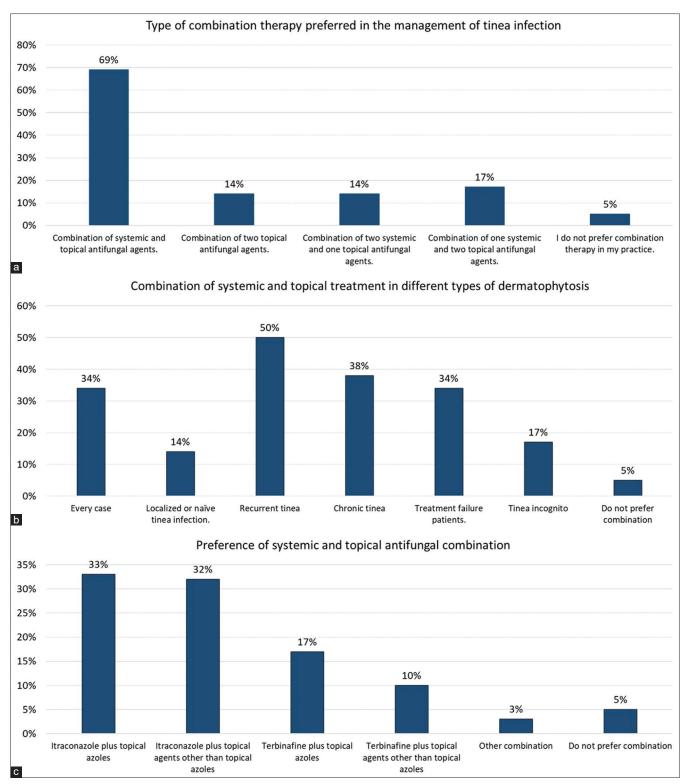


Figure 3: (a-c) Treatment approach for the management of dermatophytosis

transmission has emerged as one of the most important factors in the current survey. Undetected/untreated cases of dermatophytosis have been linked to recurrent infections in a particular family, according to research.<sup>[1-3]</sup> In patients with recurring or chronic dermatophytosis, therapeutic failure cases frequently tend to have more than one afflicted family member, according to research.<sup>[3,4]</sup> The entire family

is put in a financial bind as a result of this. Because it is an infectious disease, fomites play a significant part and their implication might differ depending on the traditional culture and behaviors. The practice of hand-washing garments in a single vessel in India, as opposed to using high-temperature washing machines in the West, is thought to have a significant influence on the spread of infection. [3,4,7-9] In

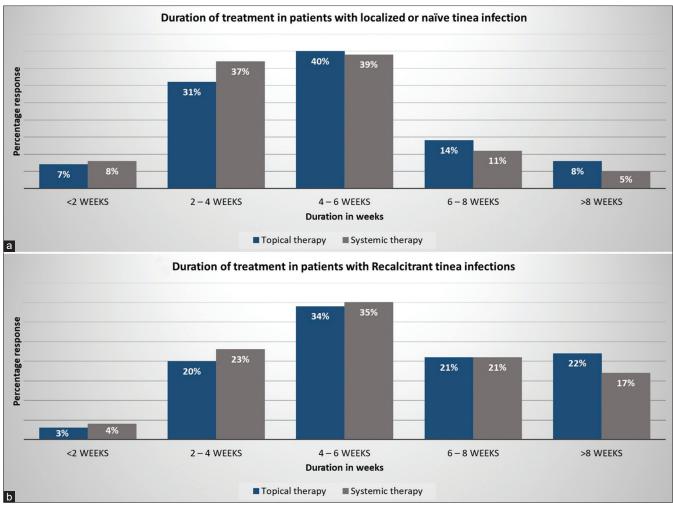


Figure 4: (a and b) Duration of treatment in different types of dermatophytosis

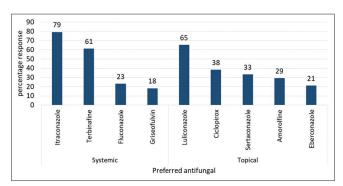


Figure 5: Preferred antifungal in management of dermatophytosis

India, sharing a bathing stool for sitting while taking a bath is quite common unlike showering in the West.

The majority of physicians are aware of and follow recommendations in their clinical practice on a regular basis, yet they occasionally diverge

Approximately 98% of dermatologists opined that they are aware of dermatophytosis guidelines and follow them in their clinical practice. However, several of them

have reported that they deviate from it for a variety of reasons. Non-agreement with current recommendations and dependence on own clinical expertise were the most common explanations mentioned. The number of patients with chronic/recalcitrant dermatophytosis has increased dramatically in the last 6–7 years across the country. The widespread usage of creams containing a mix of antifungals, ultra-potent corticosteroids, and antibiotics, either by self-medication or owing to prescription by the misguided practitioner, has exacerbated or possibly created this problem.<sup>[2,8-11]</sup>

As a result, existing treatment protocols are no longer relevant. [2] This indicates that the rules need to be restructured to reflect the present reality in India.

#### Impact on diagnostic tests

Although dermatophytosis is usually diagnosed clinically, atypical presentations, which often mimic other dermatoses, have become more widespread in recent years, making diagnosis more challenging at times.<sup>[11,13,14]</sup> As a result, at the start of therapy, either KOH microscopy or fungal culture is indicated for confirmation.

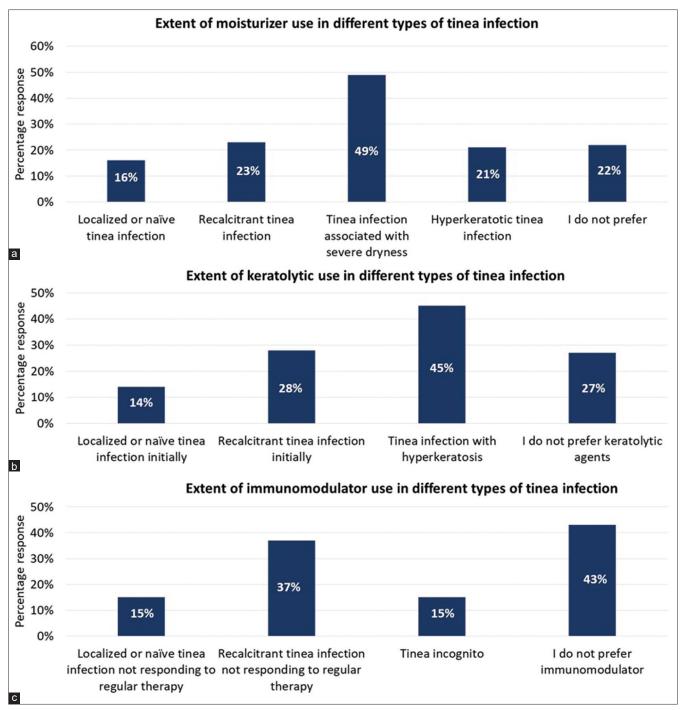


Figure 6: (a-c) Preference of moisturizers, keratolytics, and immunomodulators in the management of dermatophytosis

In our survey, only half of the dermatologists recommended a 10% KOH test to their patients. The most probable reason for this might be the lack of feasibility to order this test in each case, especially in private practice. Verma *et al.* have reported that although it is considered necessary in many countries, it is not feasible because it is time-intensive and most dermatologists do not have qualified assistants to help them.<sup>[2]</sup> Although a KOH examination is not required for the initial diagnosis of dermatophytosis unless the diagnosis is unclear, it is necessary to do the test before

continuing therapy with the newer oral antifungals after 1 month in case of partial remission.<sup>[2]</sup> Dermatologists in the current survey confirmed this by ordering KOH mount tests in patients with chronic, recurring, steroid-modified, or therapy failure dermatophytosis.

In the current Indian scenario, systemic antifungals are often used, and for longer periods than is indicated in earlier protocols. As a result, it is critical to keep the track of adverse effects of these medications. In recalcitrant dermatophytosis, ECTODERM India<sup>[5]</sup> suggested basal

LFTs with frequent monitoring. Numerous dermatologists follow these guidelines, according to our survey results.

# Combination therapy: First choice, the right choice

Dermatologists across the country have been baffled by an increase in frequent clinical failures with conventional antifungal dosage and duration (1 to 2 weeks of treatment). In the study on the management of dermatophytosis, Majid *et al.* found that regular (250 mg OD for 2 weeks) terbinafine therapy had reduced effectiveness and increased recurrence. Similarly, itraconazole monotherapy, at its standard dosage (100 mg OD) and duration of 2 weeks as mentioned in standard textbooks, appears to be ineffective in treating these infections. As a result, the use of combination regimens has increased in India in recent years.

Patients with extensive lesions or resistant tinea infections should be treated with a combination of systemic and topical antifungals, according to several evaluations.<sup>[1,7,17]</sup> When it came to using the same or different antifungal classes in combination, there was some disagreement. However, the majority of the authors suggested that when utilizing combination therapy, medications from two distinct classes be utilized for broader coverage, additive or synergistic activity, and reduced resistance risk.<sup>[7]</sup>

According to the present report, 53% of dermatologists begin treatment with a combination of drugs. There are several variants of combinations that can be administered; however, the most frequent is a topical and systemic antifungal combination. This might be owing to the fact that topical antifungals achieve a high concentration at the action site and are hence preferable to be used in conjunction with systemic antifungal medications.[18] Various in-vitro investigations have shown varied findings of antagonism when two medicines operating on the same target are combined.[19,20] There are several research articles available that show the benefits of combination therapy. [21-27] However, there is no clarity for using medications from the same or other classes as those described above. Though some reviews advocate combining two separate classes of medicines, synergistic benefits of luliconazole and itraconazole have been demonstrated in a recent paper.[28] Even in the newly issued INTACT consensus guidelines, there was no unanimity on whether to utilize the same or different antifungal classes.[1]

In the present survey, the most often prescribed antifungals were found to be itraconazole and luliconazole. This might be because they have a lower minimum inhibitory concentration (MIC) than other drugs and hence are more effective. Both drugs were recently discovered to be the most powerful molecules in their respective medication classes, according to a recent report. [29] Sardana *et al.* suggested that both of these drugs had a synergistic

impact.<sup>[28]</sup> About 14% of respondents said that they would administer a mixture of two systemic and one topical antifungal, whereas 17% said they would prescribe one systemic and two topical antifungal combinations. Only a few studies have demonstrated that itraconazole and terbinafine can be used together; however, evidence on other combinations is very scarce.<sup>[21-25]</sup>

In the event of non-response, roughly 72% of dermatologists increase the systemic antifungal dosage. Sahoo *et al.* advocated itraconazole (200–400 mg) in split doses coupled with topical antifungals in resistant cases.<sup>[17]</sup> In tinea incognito patients, ECTODERM India guidelines<sup>[7]</sup> suggested prescribing itraconazole (200–400 mg per day) for 4–6 weeks. INTACT guidelines suggested accentuating terbinafine dosage in non-responsive cases.<sup>[1]</sup> However, some recent studies have concluded no benefits in increasing the dose but suggested prolonged treatment duration.<sup>[30,31]</sup>

# Confidence in adjuvant therapy

Prescriptions for adjuvant medicines such as keratolytics and moisturizers have skyrocketed in recent years. Because dermatophytosis causes increased epidermal thickness, hyperkeratosis, and skin scaling, topical antifungal medications alone may be ineffective. [32,33] Keratolytics were proven to be useful in these situations. [34] According to one study, a brief combined therapy of antifungal and salicylic acid was shown to be successful and safe, as well as a helpful choice for hyperkeratotic dermatophytosis to reach clinical cure sooner and with improved patient compliance. [35] In our poll, 73% of dermatologists reported that they use keratolytics to treat dermatophytosis.

In dermatophytosis, there is a substantial rise in trans-epidermal water loss, which leads to a disruption in skin barrier function.<sup>[32]</sup> As a result, it is advised that moisturizer be used in the treatment of dermatophytosis, as evidenced by the 78% response rate in the present survey. The most common recommendation for moisturizer usage was 2–4 weeks.

Itching is one of the most common symptoms of dermatophyte lesions. Itching can be so bad that it interferes with daily tasks, especially if it occurs in intimate places. Additionally, sleep may be disrupted by nocturnal itching. All these factors might have an impact on one's quality of life. [36] Antihistamines should be used in the initial phase of dermatophytosis management, according to a consensus statement titled "ECTODERM India". [7] This corresponded to the dermatologists who took part in the survey's real-world clinical practice patterns.

Due to a growth in the proportion of recalcitrant cases, dermatologists have indeed been experimenting with newer regimens that include increased doses and durations, as well as the use of unusual drugs such as isotretinoin, immunomodulator drugs, and newer systemic

antifungal drugs such as voriconazole. There have been conflicting reports available on isotretinoin.[37,38] The immunomodulatory impact of isotretinoin in resistant dermatophytosis has been attributed to enhanced epidermal cell turnover, which eliminates the dermatophyte, and an increase in skin pH, which limits dermatophyte development.<sup>[7,8]</sup> When taken in conjunction with oral itraconazole, isotretinoin has a greater favorable effect.[7] However, because isotretinoin increases cell turnover and decreases sebum production, it is probable that isotretinoin with itraconazole may result in rapid clearance of itraconazole from the skin, resulting in the decreased therapeutic efficacy of itraconazole, according to one study.[39] According to another study, adding isotretinoin to terbinafine provided no further effect in treating recurrent dermatophytosis patients.[40]

The calcineurin pathway has been linked to the pathophysiology of dermatophytosis and other aggressive fungal infections, notably in terms of fungal cell wall integrity and medication resistance.<sup>[41,42]</sup> The suppression of calcineurin signaling has emerged as a unique method for inhibiting fungal virulence and increasing the efficacy of current antifungal medications.[43] Tacrolimus coupled with itraconazole revealed synergistic antifungal effectiveness against five strains of Trichophyton mentagrophytes in vitro using MIC testing and cell growth measurement.[41,44] Patients with persistent tinea incognito who received topical tacrolimus with oral itraconazole had 100% adherence to antifungal medication and 100% remission of lesions with no recurrence in non-randomized clinical research by Kumar et al., compared to only 60% resolution in patients who were treated with oral itraconazole.[41] However, the small sample size (n = 10) remained the major limitation of this study and hence could not be generalized.

Poor adherence to treatment has been identified as one of the reasons for poor therapeutic response. Inflammatory symptoms and lesion flare-ups in the early stages of the illness are major factors contributing to poor adherence. [41] Despite the fact that there have been a few case reports of tacrolimus-induced tinea incognito, it can be considered a "lesser evil" when compared to topical corticosteroids for reducing inflammation because it does not cause cutaneous atrophy even after long-term use. Also, it can be used on flexural areas and the face. [41] Authors found that tacrolimus improved the activity of itraconazole and fluconazole in *in vitro* research. [45] Topical tacrolimus improved adherence to antifungal treatment in persistent tinea incognito, according to one study. [41]

Twenty-eight percent of dermatologists opined that newer systemic antifungals such as voriconazole can be tried in cases that do not respond to conventional antifungal drugs. In a clinical trial done by Khondker *et al.*, it was found that patients with treatment failure dermatophytosis showed clinical cure in 68% and

improvement in 31% of patients, whereas mycological cure was seen in 99% of the cases at the end of the study period. Chandrashekhar *et al.* concluded a good efficacy and safety profile with a very low rate of recurrence with voriconazole for the treatment of recurrent and resistant dermatophytosis. In susceptibility studies done on patients of dermatophytosis, there was no resistance noted in cases of voriconazole, whereas terbinafine and fluconazole showed maximum resistance. However, the majority of the dermatologists in the present survey opined that voriconazole should not be used in the treatment of dermatophytosis as it is a very important broad-spectrum, cost-effective drug in the therapeutic armamentarium of patients with deep mycoses.

### Antifungal and steroid combination

Despite the fact that limited/no use of TCS has been highly suggested in all review articles, [1,7] in real-world practice, roughly 36% prescribe TCS in combination at the start of treatment for 1–2 weeks. TCS, alone or in conjunction with antifungals, had no role in the treatment of inflammatory dermatophytosis, according to INTACT recommendations. The anti-inflammatory properties of topical azole antifungals may be useful in individuals having inflammatory and corticosteroid-modified dermatophytic lesions. [1]

# Limitations of the study

In physician survey studies carried out on a voluntary basis, a selection bias is always likely to occur. Though the survey was performed with dermatologists only, the response rate was on the lower side (23%). However, we strongly believe that this limitation is less likely to essentially change the characteristic of our results.

#### **Conclusion**

From the findings of the present survey, combination therapy and duration of treatment play important role in the complete resolution of symptoms and it is preferred to continue antifungal medication for an additional period of 1–2 weeks. Moreover, routine monitoring of laboratory tests also plays a definitive role due to the extensive use of systemic antifungals. All these factors need to be worked upon by continuous medical education of dermatologists and the updation of guidelines to improve the clinical outcome and avoidance of unfitting treatment strategies.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

#### What this real-world survey adds

Though dermatologists are aware about consensus or guidelines, they deviate from it many times, and relying on clinical experience has emerged as one of the factors for it.

About half of the dermatologists routinely opt for KOH testing for better management of dermatophytosis.

Although combination therapy is routinely practiced in dermatophytosis management, a combination of one topical and one systemic agent is preferred in recurrent, chronic, and treatment-failure cases.

Itraconazole and luliconazole are the most commonly prescribed antifungals in the management of dermatophytosis.

Most dermatologists updose systemic antifungals in case of non-response.

In current scenario, dermatologists rely on adjuvant therapies such as moisturizer, keratolytic, or immunomodulator for better management.

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