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Review Article

Expert opinion on current and emerging treatments in dermatophytosis

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ABSTRACT

Dermatophytosis continues to be a worldwide public health problem, predominantly in developing countries like India. Early diagnosis and appropriate management are imperative to enhance patient outcomes and improve quality of life of individuals with dermatophytosis. Multiple focused group discussions involving 76 dermatologists across 36 cities in India were conducted to provide a consensus clinical viewpoint of expert dermatologists to gain insights toward effective diagnosis and management of Indian subjects with dermatophytosis. These discussions mainly aimed at reviewing current literature on prevalence, etiology, diagnosis and management of dermatophytosis and highlighting variations in diagnostic and treatment approaches in routine clinical practice. The current article summarizes the experts' clinical viewpoint on overall management of dermatophytosis. Diagnosis of dermatophytosis involves clinical observation, microscopic examination and dermoscopy. Molecular techniques have certain advantages over conventional microscopy and culture methods but are associated with issues of cost and technique complexity. Oral itraconazole 200 mg–400 mg daily and terbinafine 500 mg/day could be considered for recalcitrant tinea infections. Topical azoles like luliconazole, sertaconazole, and terbinafine could be beneficial. A combination of oral and topical antifungal drugs is effective in patients with steroid-modified and difficult-to-treat tinea infections. Also, patient counselling and use of adjunctive therapies like antihistamines, retinoids, and moisturizers are essential for managing tinea infections.

Keywords: Dermatophytosis, Tinea infection, Antifungal

INTRODUCTION

Dermatophytosis is a common superficial fungal infection of the skin and nails. Recently, there has been a surge in the occurrence of dermatophytosis with unusual clinical presentations including large and multiple lesions. Steroid-modified dermatophytosis is the most commonly observed clinical presentation in the current scenario.[1] Moreover, there has been a large increase in the number of chronic and recurrent dermatophytosis cases in India in recent

years.[2] This has led to an increased awareness of the seriousness of the condition and has called for a strategic action plan at curbing the increased rates of tinea infections. Although a wide range of antifungal drugs are available for effective and safe management of dermatophytosis, a practical approach to treating tinea cases based on the prevalent clinical types and sensitivity of the commonly found dermatophyte isolate in a particular area are needed. The objective of this review is to provide an overview of diagnosis and management of dermatophytosis in current clinical practice in India.

Multiple focused groups discussions were held among 76 dermatologists across 36 cities in India. The main purpose of the meetings was to review the currently available literature on prevalence, etiological factors, diagnosis, and management of dermatophytosis and to discuss the variations in diagnostic and treatment approach in current clinical practice.

Table 1: Types of tinea infections.

Infection	Presentation/description
Tinea corporis (ringworm)	Red, annular, scaly, pruritic patch with central clearing and an active border
Tinea cruris (Jock itch)	Involves the portion of the upper thigh opposite the scrotum
Tinea pedis (Athlete's foot)	Typically involves the skin between the toes, but can spread to sole, sides, and dorsum of involved foot *Acute form:* Erythema and maceration between the toes, sometimes accompanied by painful vesicles *Chronic form:* Scaling, peeling, and erythema between the toes; however, it can spread to other areas of the foot
Tinea unguium (Onychomycosis)	Frequently seen in individuals with dystrophic toenails; it is characterized by thickened, brittle, and discolored nails
Tinea capitis	Ringworm of the scalp

For compilation of this article, a literature search was conducted using PubMed and Google to identify relevant articles using Boolean operators and/or the search terms/keywords dermatophytosis, fungal infections, relapse, recurrent, diagnosis, treatment, and management. Data were accessed from 40 published research articles, systematic reviews, or meta-analyses and along with expert discussions and recommendations were used to summarize experts' clinical viewpoint on overall management of dermatophytosis.

TYPES AND NATURE OF DERMATOPHYTOSIS

Tinea (fungal) infections, caused by dermatophytes, are classified by the involved site of infection (Table 1).[3] Tinea corporis or ringworm presents as a red, annular, scaly, pruritic patch with central clearing and an active border. Tinea cruris involves the upper thigh areas. It mostly affects adolescents and young adult males. Tinea pedis involves the skin between the toes; the infection can spread to the sole and the sides of the foot. Tinea unguium or onychomycosis is a nail infection. Tinea capitis is ringworm of the scalp and it affects mostly children.[3] The different clinical definitions based on the nature/stage of the infection are summarized in Table 2.[1]

Table 2: Definitions of nature of tinea infections.

Infection	Definition
Naïve infection	The patient has not been exposed to a particular infection of a given disease or treatment for that disease
Chronic dermatophytosis	Chronic dermatophytosis is when the patient suffers from the disease for more than 6 months to 1 year, with or without recurrence, in spite of being adequately treated
Recurrent dermatophytosis	Recurrent dermatophytosis is when the disease re-occurs within few weeks (<6 weeks) after completion of the treatment
Relapse	Relapse indicates the occurrence of dermatophytosis, after a longer period of infection-free interval of 6-8 weeks in a patient who was clinically cured
Tinea incognito	Infection has been modified by improper use of steroids and topical immunomodulators that it is no longer diagnostic

PREVALENCE OF DERMATOPHYTOSIS IN INDIA

In India, the prevalence of dermatophytosis ranges from 36.6%–78.4%.[1] The common age-group affected with dermatophytosis is 21-60 years. According to published epidemiological studies from India, the most common clinical types of dermatophytosis are tinea corporis and onychomycosis. Trichophyton mentagrophyte and T. rubrum were the most commonly isolated dermatophytes.[1] About 90% of cases of chronic dermatophytosis have been attributed to T. rubrum infections.[2]

ETIOLOGY OF DERMATOPHYTOSIS

A complex interaction between the host, the causative agent, and the environment is involved in the development of dermatophytosis.[4] Although various species including Trichophyton and Microsporum have been isolated, a recent study reported a shift in the trend of predominant causative agent, from T. rubrum to T. mentagrophytes, for superficial dermatophytosis in India.[4,5]

Table 3: Recommendations for oral and topical antifungal drugs for dermatophytosis.

	Dose
Oral drugs	
Itraconazole	100-200 mg/day
Terbinafine	250 mg/day
Fluconazole	150-300 mg/week
Griseofulvin	250–500 mg twice daily
Topical drugs	
Luliconazole	Once or twice a day for 2-6 weeks
Sertaconazole	Once or twice a day for 2-6 weeks
Terbinafine	Twice daily for 2 weeks
Amorolfine	Twice daily for 4 weeks

Table 4: Newer antifungal agents and their implication.

Mode of therapy	Antifungal agent	Comment
Topical	Efinaconazole Tavabarole Lanoconazole	Modest cure rate
	Butenafine	Cost factor should be considered for butenafine
	Naftifine	Naftifine is not available in India
Oral	Posaconazole Voriconazole	Limited clinical use

Occlusive footwear and tight-fitted clothing have also been associated with higher prevalence of infection.[4,6] Specific regions of the body like web spaces and groins are prone to fungal infections due to excessive sweating, maceration, and alkaline pH.4 Other predisposing factors include overcrowding, occupational exposure (outdoor work/activities), sharing of clothes, and poor hygiene.[2,7,8] The primary reason for spread of infection is direct contact from other people or indirect acquisition from fomites (clothes, upholstery, hairbrushes, hats, etc.).9 In addition, re-infection from contact or fomites may contribute to persistence of infection.[2]

Another major causative factor of increasing trends of dermatophytosis is extensive use/abuse of irrational fixed-dose combinations of topical steroids in combination with antifungal and antibacterial agents.5,6 There have been increased reports of temporal association of changes in the clinical pattern of tinea infections with the duration of steroid use.[6] Studies have reported increased prevalence of dermatophytosis in India in the months of April to July due to favorable high temperature and humidity during summer and monsoon.[10-12]

DIAGNOSTIC INVESTIGATIONS

Nowadays, diagnosis of dermatophytosis has become challenging due to prevalent atypical morphological variants as a result of steroid abuse.[13] Laboratory diagnosis becomes important to confirm infection and initiate appropriate treatment.[1] Direct microscopic examination of skin scrapings with 10% potassium hydroxide (KOH) mount is routinely performed to confirm dermatophytosis. KOH mount is a simple, rapid, inexpensive, and efficient screening technique.[1] Although fungal culture provides definitive identification of fungal species1, it was not recommended by experts for routine diagnosis of dermatophytosis. Culture takes time and is less sensitive.[1] Similarly, antifungal susceptibility test is also a tedious procedure requiring trained manpower. In addition, there is lack of reference data on minimum inhibitory concentration (MIC) of antifungal drugs against dermatophytosis.[13] Involvement of vellus hair has shown therapeutic implication in tinea infections.[1] Identification of vellus hair involvement by dermoscopy is considered an adjunctive diagnostic approach for management of dermatophytosis.[1] Molecular techniques have advantages over conventional microscopy and culture methods in terms of specificity, sensitivity, and shorter time for identification of causative agent. However, there are concerns associated with cost and complexity of the technique.[14]

TREATMENT AND MANAGEMENT OF DERMATOPHYTOSIS

Management of dermatophytosis includes non-pharmacological and pharmacological methods. Skin surface should be completely dried before wearing clothes, and loose-fitting cotton or synthetic garments are advised. It is advisable to avoid walking barefoot or to share garments or other tools with family members.[4]

Topical treatment

Topical therapy is usually recommended in the management of naïve tinea cases or localized infections.[1] It is highly effective for localized infections and naïve infections.[1,15] A topical agent should possess properties such as broad-spectrum activity, high mycological cure rate, convenient application, and low incidence of side effects.[16] The number of applications and duration of treatment are the deciding factors to choose between available topical antifungal drugs.[4] Azoles have anti-inflammatory, antibacterial and broad spectrum anti-mycotic activity.[1] Topical treatment usually should be continued for 2 weeks post clinical cure.1 In addition, topical antifungal agents are preferred in elderly patients, children, and pregnant women.[1]

Various topical antifungal agents like luliconazole, oxiconazole, sertaconazole, and amorolfine have been in use.[4] Luliconazole has fungicidal action against Trichophyton species similar to or more than that of terbinafine.[4] It is effective as once daily application for 1–2 weeks for dermatophytic infections.[4] Moreover, amorolfine was found to be as effective as clotrimazole in tinea corporis.[16]

Systemic/oral treatment

The choice of the antifungal agent depends on the pharmacological properties of the drug, history of prior exposure to antifungals, the site and extent of the lesion, skin area involved, and the age of patient.[1] Treatment with oral antifungal drugs is considered when repeated treatment with topical agents fail to clear the lesions on a large body surface area.[4] Systemic therapy is considered in vellus hair involvement.[1]

Terbinafine and itraconazole are commonly prescribed systemic antifungal drugs. They have demonstrated better mycological cure rates than other drugs. Griseofulvin and fluconazole are also effective but they require long-term treatment.4 Griseofulvin (250–500 mg twice daily) and fluconazole (150–300 mg/week) should be considered in patients who showed inadequate response to terbinafine or itraconazole (Table 3).[1,4] Higher doses of systemic agents can be considered in case of deep inflammatory lesions, lesions covering multiple sites, or in case of non-response to previous dose.[1] Itraconazole 200–400 mg daily and terbinafine 500 mg/day can be considered for recalcitrant cases of tinea.[1] Treatment with high dose for short duration has lower risk of resistance development compared to lower doses for longer duration.[4] The minimum duration of treatment should be 2–4 weeks in naïve cases and >4 weeks in recalcitrant cases.[1]

Combination of oral antifungal drugs

Majority of the studies have evaluated combination of oral antifungal drugs in the management of deep and invasive fungal infections. In vitro data show synergistic effect of terbinafine and itraconazole against a wide range of non-dermatophyte fungi. Sharma et al demonstrated that maximum mycological and clinical cure rates were achieved by combination of itraconazole and terbinafine (90%) compared to respective monotherapies. The combination treatment was also found to be as safe as the individual treatments.[17] However, additional evidence is needed to comment on synergistic effect of two combination drugs.[13]

Combination of oral and topical drugs

Combination of oral and topical drugs is used for extensive and recalcitrant tinea infections.[4] Given the better pharmacokinetic properties of topical agents than systemic drugs, combination of oral and topical therapy demonstrate better mycological clearance than individual therapies.[4] Most of the patients usually require longer duration of combination of oral and topical antifungal agents, especially patients with steroid-modified and difficult-to-treat tinea infections.[13]

Current emerging treatment alternatives

Itraconazole: Unconventional formulations: The bioavailability of conventional itraconazole (100 mg) is suboptimal (55%). An unconventional formulation of itraconazole, called 'super bioavailability itraconazole' is said to have ~1.8 times more bioavailability than conventional itraconazole at steady-state. This formulation is suggested to cause less variability if patients are not adherent to dietary requirements when taking itraconazole.[18]

Itraconazole oral solution is easier to administer than capsules.[19] It has been shown to improve the availability of the drug in patients with reduced stomach acidity, who are at high risk for systemic fungal infections.[19] Oral solution of itraconazole has also demonstrated efficacy in chronic and recurrent dermatophytoses in children.[20] It should be used at a lesser dose of 3 mg/kg/day for better absorption.[21]

The mycological cure rate and clinical efficacy at 18 months from the start of itraconazole pulse therapy were 62.7% and 60.8%, respectively. Elderly patients with toenail onychomycosis showed high compliance to itraconazole pulse therapy.[22]

Pelletization is currently used by most manufacturers to improve the bioavailability of drugs. The bioavailability of itraconazole is inconsistent with inter-individual variations. One of the factors influencing the absorption profile and therapeutic effect is the quality of pellet.[23] The pellet number and size analysis are important for clinicians to make informed decision for choosing an itraconazole formulation.[23] However, cost cannot be a substitute for superiority of formulation.[23]

Daily dose of fluconazole: Fluconazole 50-400 mg/day has not been associated with dose-dependent adverse effects in immunocompromised people.[24] Daily treatment with fluconazole for 12 weeks was observed to be similar to ketoconazole and superior to griseofulvin in patients with onychomycosis.[25]

Novel antifungal agents

Since the last decade, increased resistance to available topical and oral antifungal drugs has led to the development and application of newer drugs in managing dermatophytosis.[26] Topical agents such as efinaconazole and tavabarole are used for onychomycosis; however they show modest cure rates. Third generation azoles like posaconazole, voriconazole, and lanoconazole have demonstrated low MICs. Evidence of their use is limited, especially in severe infections with associated immunodeficiency.[27] In addition, echinocandins have shown similar efficacy to amphotericin B and fluconazole.[28] They have also demonstrated in vitro activity against dermatophytes. Butenafine is approved for the treatment of tinea infections. It has demonstrated similar efficacy to topical azoles. Naftifine has similar efficacy as that of azoles. It has demonstrated good clinical and mycological cure rates after 2–8 weeks of use.[26] Thus, clinical use of these agents is based on evidence-based claims, their availability, and cost-effectiveness (Table 4).

Soaps, sprays, and powders

Antifungal powders and sprays may be useful in preventing reinfections.[24] A few reports support the use of antifungal powders in tinea pedis. Antifungal powders, flutrimazole 1% and bifonazole 1% (twice daily for 4 weeks), showed rapid symptom relief in patients with tinea pedis.[29] They have also demonstrated reduction in frequency of relapses in patients with recurrent tinea pedis.30 Generally, antifungal soaps and powders are not recommended in the management of tinea.[13]

Supplemental therapies

Besides antifungal agents, adjunctive therapies including salicylic acid, antihistamines, and moisturizers play an important role in the management of tinea infections. However, these therapies are not suggested for all cases.[1] Superficial dermatophytosis usually causes disrupted skin barrier structure and function, enhanced cell proliferation, thickened epidermis and scaling.[31] These skin alterations affect the absorption of topical antifungal drugs and render them ineffective.[1] Moreover, dermatophytosis is also associated with increase in transepidermal water loss and alterations in extracellular lipid bilayer of the skin. Hence, application of moisturizers is helpful to improve skin barrier function and provide symptomatic relief.[1,13]

In addition, retinoids work by modulating epidermal growth and differentiation. A 2-week course of oral isotretinoin (0.3-0.4 mg/kg) in combination with oral itraconazole (100 mg twice daily) was found to be effective in treating recalcitrant superficial dermatophytosis.[32] In addition, antibacterial agents are needed for bacterial super infections.[1]

Lasers and photodynamic therapy

Lasers and photodynamic therapy (PDT) are potential local treatment options for onychomycosis, which are devoid of systemic adverse effects.[32] The most effective lasers for onychomycosis belong to deep-red or near-infrared spectrum, including 1064 nm Nd:YAG, CO2 and near-infrared diode lasers.[33] In patients with onychomycosis, long-pulsed 1064 nm Nd:YAG laser (at one week interval and total four sessions) was associated with reduction of chromonychia, onycholysis, opacity, longitudinal striae, and jagged proximal edge.[34] In addition, combination of ablative fractional laser therapy (3 sessions at 4-week intervals) and a topical antifungal demonstrated 92% clinical response rate and 50% complete response rate in patients with toenail onychomycosis.[35] In a randomized, placebo-controlled study in 80 patients with toenail onychomycosis, a significant response ($p<0.002$) was observed with methylene blue aqueous solution irradiated with light emission diode device (MBLED/PDT) with 18 J/cm2 (interval of 15 days between each session for 6 months) compared to flucanoazole, especially in patients who required nail abrasion ($p<0.001$).[36]

Blanket antifungal therapy for family members

It is estimated that about 50% of patients with dermatophytosis have at least one other family member infected.[38] If one family member remains untreated or undetected, it may lead to recurrence in others due to sharing of clothes, towels, and combs.[7,38] A molecular study demonstrated significant association of spread of infection among household members with presence of T. rubrum strains, a history of concomitant tinea pedis and onychomycosis, and plantar scaling and/or nail discoloration ($p<0.05$).[39] Thus, if a patient presents with tinea pedis or onychomycosis, examination should include enquiry about infection in other family members or any history of tinea infections.[39] Also, close family members of patients affected with tinea infections should be examined and screened.[40]

PATIENT EDUCATION AND COUNSELLING

Patient education and counselling form an integral part of management of dermatophytosis. Patients should be made aware of the disease nature and course. They should be counselled on general management measures required for treatment adherence and compliance.[13]

CONCLUSION

Given the increased burden of dermatophytosis, especially recurrent and relapse cases, strategizing effective management approaches is of utmost importance. In this paper, the experts' panel has provided a comprehensive diagnostic and management approach for dermatophytosis. The panel highlighted the clinical use of available antifungal drugs, including itraconazole, terbinafine, and griseofulvin, along with potential clinical role of novel antifungal drugs. The panel also supported the role of adjunctive use of antihistamines, retinoids, and moisturizers in managing tinea infections.

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