Derma Chronicles
Issue 1, 2016

Dermatophytosis: An increasing problem

Introduction

Dermatophytosis is a fungal infection of the keratinized structures of the body such as skin, hair and nails by a group of keratinophilic fungi known as dermatophytes.[1] These are filamentous fungi, which can cause mycosis due to their ability to degrade keratin.[2] Dermatophytes can be divided into anthropophilic, zoophilic, and geophilic species on the basis of their primary habitat, with anthropophilic species being primarily associated with humans. Fungi of the genera *Microsporum, Trichophyton,* and *Epidermophyton* are commonly known to cause dermatophytosis.[3] These superficial fungal infections, as estimated may affect about 20-25% of the world population and are of great concern because of increasing prevalence of conditions causing reduction in immunity such as diabetes, HIV and use of immunosuppressive drugs.[1,4] Dermatophytic infections are also a common clinical problem accounting for more than 50% of patients enrolling in the dermatology outpatient departments. Various contributing factors such as overcrowding, poor hygiene, low standards of living, and increased humidity increasing the frequency of these infections.[2]

Transmission and clinical presentation

Transmission of dermatophytic infection can be direct due to contact with infected humans or animals, and may be indirect by acquiring it from the contaminated fomites.[4] Clinical spectrum of dermatophytosis may range from mild to severe. The mildness and severity depend on a variety of factors such as the virulence of infecting species, the host immune response, anatomical location of the infection, and other local environmental factors.[2] In majority of cases it manifests as pruritus, however, infection may also present itself as blistering, fissures, scales, or spots, which may last for months or years depending upon host reaction to various metabolic products of these fungal infections.[4] Clinical signs and symptoms of dermatophytosis depend on the site affected and are named accordingly (table 1).[3] The most common infections seen in prepubertal children are tinea corporis and tinea capitis, whereas tinea cruris, tinea pedis, and tinea unguium (onychomycosis) are more commonly encountered in adolescents and adults, while tinea rubrum is regarded as the major global etiologic agent.[3,5] It has also been seen that several anatomic sites may be infected by a single dermatophyte species, and different species may produce clinically similar lesions.[3]

Table 1: Common dermatophytic fungal infections and their manifestations

Dermetophytosis	Site of infection	Clinical signs and symptoms
Tinea barbae	Usually mild and superficial infection of the bearded area	May present as a severe inflammatory pustular folliculitis
Tinea capitis	An infection of the scalp	Presentation may vary from subclinical, mild symptoms (minor erythema and few patches) to extensive scarring, folliculitis, and kerion formation. Generalized manifestations such as fever, malaise, and regional lymphadenopathy may be present
Tinea corporis	Commonly referred to as ringworm of the body, usually spreads to trunk, shoulders, limbs, and occasionally the face	Characterized by presence of annular, scaly patches with sharp raised erythematous margins
Tinea pedis or the Athlete's foot	Feet, toes and soles	Manifested as peeling and fissuring of the feet, peculiar to areas such as soles and toe webs. Acute infection may present as vesiculobullous lesions and pustules formation
Tinea cruris	Infection of the groin, perianal, and perineal areas, and occasionally the upper thighs	Lesions are bilaterally asymmetrical, erythematous to tawny brown in color, masked with thin and dry scales. The margins are raised and well defined commonly found studded with small vesicles
Tinea favosa	Severe infection commonly involving scalp	Presents as naked skin with scutula (yellowish, cupshaped crusts) constituted by epithelial debris and dense masses of mycelium
Tinea imbricata	Specialized chronic manifestation of tinea corporis, involving almost the whole body	Lesions present as concentric rings of overlapping scales
Tinea manuum	Palmar and interdigital areas of the hand	Commonly characterized by unilateral involvement, diffuse hyperkeratosis and accentuation of the flexural creases
Tinea unguium (Onychomycosis)	Infection of the nail	Characterized by thickening of nail with superficial white spots

Source: Weitzman I, Summerbell RC. The dermatophytes. *Clin Microbiol Rev.* 1995 Apr;8(2):240-59.

Diagnosis and differential diagnosis of dermatophytosis

Diagnosis can be made based on the history and clinical appearance of the lesion, but the clinical diagnosis may not be solely reliable sometimes because of the wide range of differential diagnosis of tinea infections (table 2), such as tinea corporis can be confused with eczema, tinea capitis with alopecia areata, and onychomycosis can be misdiagnosed as dystrophic toe nails due to repeated trauma.[5] The diagnosis of dermatophytosis can be confirmed with available diagnostic tests such as potassium hydroxide (KOH) preparation with mycologic examination under a light microscope, and occasionally, culture and histologic examination may be required in establishing the diagnosis. Cultures may require one to four weeks for growth of organisms, results of which may be confirmed by clinical expertise. Sabouraud's peptone glucose agar is the most common medium used for isolating dermatophytes, with various commercially available formulations of this medium having additives that can inhibits the growth of other non-dermatophyte and bacterial species present. A dermatophyte test medium (DTM) indicator can also be used, but has been associated with a high rate of false-positive and false-negative results. In cases which are difficult to diagnose or those refractory to treatment, a biopsy may be performed before initiating the pharmacological treatment.[6]

Prevention, control and management: Focus on terbinafine

Various prophylactic measures for tinea infections such as practicing good personal hygiene, keeping the skin dry and cool, avoiding sharing towels, clothing, and hair accessories with the infected individuals, can be used to prevent spread of infection.[7] Despite the advancements of science and technology, the need of an efficient antifungal

Table 2: Differential diagnosis of tinea infections

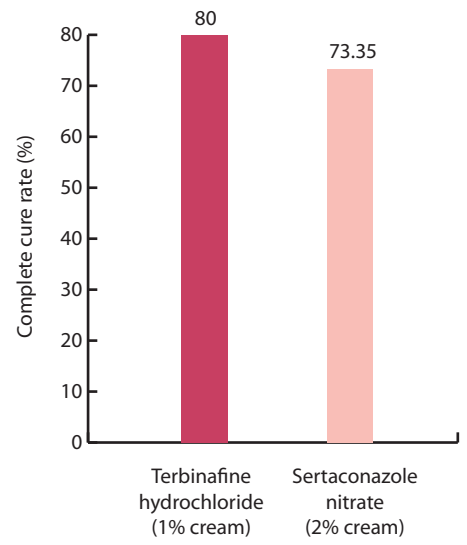
	Tinea corporis	Tinea cruris	Tinea pedis	Tinea capitis	Onychomycosis
Differential diagnosis	◆ Annular psoriasis ◆ Atopic dermatitis ◆ Erythema multiforme ◆ Fixed drug eruption ◆ Granuloma annulare ◆ Lupus erythematosus ◆ Nummular eczema ◆ Pityriasis rosea herald patch ◆ Seborrheic dermatitis	◆ Candidal intertrigo ◆ Erythrasma ◆ Inverse psoriasis ◆ Seborrheic dermatitis	◆ Contact dermatitis ◆ Dyshidrotic eczema ◆ Foot eczema ◆ Juvenile plantar dermatosis ◆ Psoriasis	◆ Alopecia areata ◆ Atopic dermatitis ◆ Bacterial scalp abscess ◆ Psoriasis ◆ Seborrheic dermatitis ◆ Trichotillomania	◆ Repeated lowgrade trauma ◆ Psoriasis ◆ Lichen planus

Source: Ely JW, rosenfeld S, stone MS. Diagnosis and Management of Tinea Infections. *Am Fam Physician.* 2014 Nov 15;90(10):702-711.

agent is still unmet due to an important reason that fungi being eukaryotic have biological mechanisms similar to humans. Hence, it is difficult to develop an antifungal agent that is more specific in targeting the fungal structure without damaging that of human beings. The treatment protocol depends on the infection site, etiological agent, and penetration ability of the drug. Since the dermatophytes are found in the keratinized structures, the antifungal agents should have good penetration ability and retention at the site of infection, which determines its efficacy and frequency of use.[8] An appropriate antifungal agent should provide mycological cure, symptomatic relief, and reduced relapse rate. Topical therapy of antifungal agent is usually recommended unless the infection covers extensive area or is resistant to initial topical application, where systemic therapy may be required. A number of antifungal agents are available such as polyenes, hydroxypyridones, azoles, and allylamines, with the latter two being the common agents used against dermatophyte infections. Terbinafine is an allylamine and is a commonly used antifungal agent.[6] It has a broad coverage of fungal species and its strong lipophilic nature accounts for its better absorption into hair, skin, and nails. Terbinafine demonstrates the fungicidal activity in contrast to fungistatic action of other antifungals, low minimum inhibitory concentration value, high selectivity for fungal squalene epoxidase, and good efficacy in superficial fungal infections. Moreover, it has been shown to be effective and tolerable in children.[9] Due to the high cure rates and better tolerability oral terbinafine may be considered as a first-line therapy for tinea capitis and onychomycosis.[5]

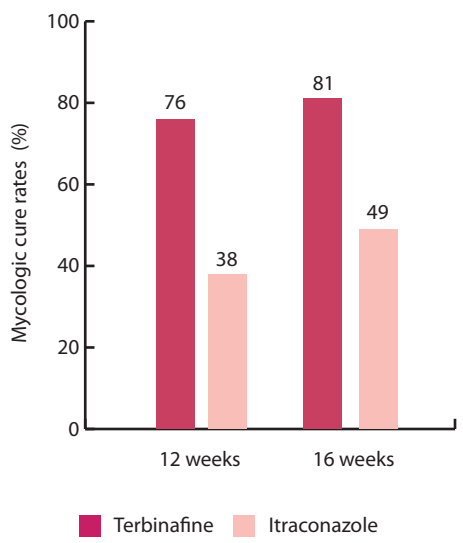
A plethora of evidences supports the clinical efficacy of terbinafine in the management of dermatophytosis. According to a study[10] conducted on 1200 patients with tinea infections, a complete mycological cure was observed in 70-90% of cases when treated topically with terbinafine (1% cream) for tinea corporis, cruris, and pedis. While it was documented as 75-90% in tinea corporis and pedis, and 90-100% in onychomycosis when treated systemically with oral terbinafine (125 mg twice daily). Despite of frequent relapse associated with these infections, a low rate of relapse was reported with terbinafine therapy. The outcomes of the study validated the effectiveness of drug in short duration therapy without any significant hematological, hepatic or renal effects.[10] As already been reported that terbinafine can be administered in children, its use in elderly patients can be shown by an open-label, randomized trial, IRON-CLAD (Improving Results in ONychomycosis-Concomitant Lamisil and Debridement) conducted on a total of 504 patients (with 75 among these older than 65 years). Many of them were taking antihypertensives, antidiabetics, or lipid-lowering agents, with no history of drug interactions. The tolerability and efficacy of terbinafine in these elderly patients with moderate to severe toenail onychomycosis were well-established.[11]Another trial compared the efficacy of topical terbinafine hydrochloride 1% cream (group A, n=15) and sertaconazole nitrate 2% cream (group B, n=15) in localized tinea corporis and tinea cruris. Patients were asked to apply the respective agents twice in a day for a total duration of three weeks. Although, at the end, both terbinafine and sertaconazole groups had 100% complete cure. But when compared for complete cure, at the end of 2nd week, complete cure rate for terbinafine was 80% as compared to 73.35% for sertaconazole (figure 1).[12] Moreover, in case of immunocompromised states as seen in patients with HIV, dermatophytoses may be reported more extensively and thereby affected and a lot may require oral antifungal therapy. Terbinafine has proven its tolerability with no significant drug interactions in the high-risk cohort studies.[13] A yet another study compared the efficacy of 1-week topical terbinafine with 4-week miconazole therapy in the treatment of tinea pedis. A total of 48 patients were studied, half of the individuals were treated with terbinafine and placebo and the other half

Figure 1: Complete cure rate of tinea corporis and tinea cruris after 2 weeks of topical treatment with terbinafine hydrochloride (1% cream) and sertaconazole nitrate (2% cream)



Source: Choudhary SV, Bisati S, Singh AL, Koley S. Efficacy and Safety of Terbinafine Hydrochloride 1% Cream vs. Sertaconazole Nitrate 2% Cream in Tinea Corporis and Tinea Cruris: A Comparative Therapeutic Trial. *Indian J Dermatol.* 2013 Nov-Dec; 58(6): 457–460.

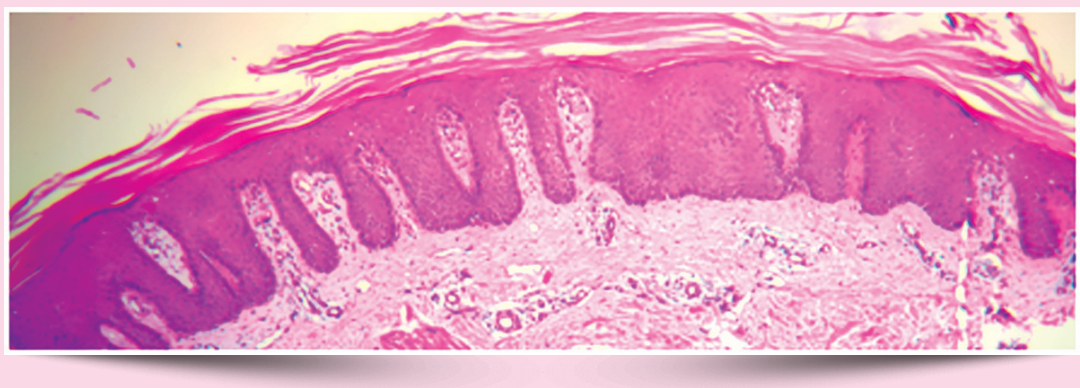
Figure 2: Mycologic cure rates with terbinafine and itraconazole oral therapies at 12 and 16 weeks



Source: Darkes MJ, Scott LJ, Goa KL. Terbinafine: a review of its use in onychomycosis in adults. *Am J ClinDermatol.* 2003;4(1):39-65.

Dermatopathology Quiz Section

Q: HOW WOULD YOU DESCRIBE THE FINDINGS IN THE EPIDERMIS?



Skin biopsy from a well-defined itchy and scaly plaque on the back

(For answer please see the last page.)

with miconazole. After 10 weeks, mycological cure was seen in about 52.6 % and 55%, and clinical efficacy in about 47% and 45% in terbinafine and miconazole treatment groups, respectively. At the end of the study, it was found that topical terbinafine cream for 1 week was as good as miconazole cream for 4 weeks in the treatment of tinea pedis.[14] Besides, in one of the randomized double-blind trials,[15] oral terbinafine 250 mg/day given for 12 or 16 weeks was documented to be more efficacious than itraconazole, fluconazole and griseofulvin in dermatophyte onychomycosis of the toenails. L.I.ON (Lamisil vs Itraconazole in ONychomycosis) study showed that mycologic cure rates were higher for terbinafine (76 vs 38% after 12 weeks treatment, 81 vs 49% after 16 weeks therapy, for terbinafine and itraconazole, respectively), while the complete cure rates seen with terbinafine were reported to be double of those with itraconazole in patients with toenail mycosis (figure2).[15] Sometimes, the fungal infections may also be associated with superadded inflammation warranting the need of combination of other agents with anti-inflammatory properties such as steroids in addition to specific antifungals. The combination therapy of antifungal and steroids may help in better management of such fungal lesion.[6]

Conclusion

The management of dermatophytic infections needs prevention such as practicing good personal hygiene, better diagnosis and proper medication. With increasing incidence of fungal infection, microbial resistance to the existing drugs, and associated side effects, there is a need for an antifungal drug that can overcome all these limitations. Terbinafine being a broad spectrum allylamine shows various desired properties. From the above mentioned studies the efficacy and tolerability of both topical and oral terbinafine can be well established in the management of various tinea infections. Although terbinafine being efficacious alone, occasionally may be combined with other agents such as steroids for the management of fungal lesions associated with inflammation.

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Chronically recurrent and widespread tinea corporis managed with combination therapy with systemic terbinafine and topically applied terbinafine cream: A case report

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Case presentation and history

A 31-year-old male presented to the dermatology outpatient department with a 4-year history of itching and reddish lesions on various surfaces of his body associated with pain and discomfort. Patient reported that lesions first appeared on his right foot and toenail, then it spread to other parts of the body like inner thighs and abdomen. The patient had been using some topical preparations (including topical corticosteroid and corticosteroid/antifungal/antibacterial creams) in the past over the lesions but the lesions reappeared after the cessation of application. No other significant medical history was reported.

Clinical examination

On examination extensive erythematous, scaly plaques involving the abdomen, gluteal and inguinal regions along with similar lesions on feet and nails were seen. The lesions were tender on palpation.

Investigations and diagnosis

Scraping of the lesion showed septate and branching hyphae on direct microscopic examination (KOH preparation). Species identification was performed by growth on Sabouraud dextrose agar. The pathogen identified was *Trichophyton rubrum*. The same fungal species was cultured from the abdominal, gluteal, foot and toenail. Diagnosis of Chronically recurrent and widespread tinea corporis with concomitant tinea pedis and onychomycosis was made and the pharmacological management was started.

Management

Initial treatment was carried out with topical terbinafine (1% cream), but the patient reported with recurrence after a short healing period of lesions. He was then prescribed oral terbinafine 250 mg along with the continuous application of topical terbinafine cream. Improvement was reported except for few lesions on the inguinal region which recurred after three weeks of completion of treatment. The patient was finally administered a higher dosage of terbinafine (500mg) and was successfully managed with a combination of systemic and topical terbinafine therapy. A 1 year follow-up did not show any recurrence of infection.

Discussion

- Dermatophytosis has a wide geographical distribution, with *Trichophyton rubrum* being the commonest species causing the infection of skin, hair and nails.[1]
- Males are more commonly affected than females and it is more commonly observed between age groups of 21–40 years. This can be attributed to the fact that the males because of longer vigorous outdoor activity and increased sweating, which creates an environment for the development of tinea infection, may be more prone to these infection as seen in the above reported case.[1,2]
- Recurrent dermatophytosis refers to the reappearance of the dermatophyte infection within few weeks after completion of treatment.
- The mechanism behind the chronic/recurrent dermatophytic infections is not well understood may be may be secondary to host, agent, environmental, or pharmacologic factors.
- About 90% of cases of chronic dermatophytosis have been associated with *Trichophyton rubrum* infection. Widespread *T. rubrum* dermatophytosis can be described as *T. rubrum* syndrome, generalized chronically persistent rubrophytia, and tinea corporis generalisata.[3]

- It has also been reported that *Trichophyton rubrum* may be able to suppress cell-mediated immune reactions of the host by inhibiting critical steps in antigen presentation process. Thus the ability of Trichophyton rubrum to evade host defenses may account for the high prevalence of its infections.[4]
- Antifungal resistance has also emerged over the past few years, which can be microbiologic or clinical resistance or a combination of these two.
- Microbiologic resistance refers to nonsusceptibility of a fungus to an antifungal agent. Primary resistance is found naturally among certain fungi without prior exposure, while secondary resistance develops among previously susceptible strains after exposure to the antifungal agent.
- Clinical resistance can be defined as the persistence of an infection despite appropriate antimicrobial therapy. It can be attributed to incorrect diagnosis, immunosuppression, and suboptimal dose or duration of therapy. A successful clinical response to antimicrobial therapy depends not only on the susceptibility of the pathogenic organism, but also on the host immune system, drug penetration and distribution, and patient compliance.
- Re-infection from the contacts or fomites may also be a contributing factor.[3]
- Terbinafine, an orally and topically active allylamine antifungal agent, possess fungicidal activity in vitro
- Its broad-spectrum allylamine and targets a range of dermatophyte.
- Clinical trials have suggested good tolerability profile of terbinafine, with almost 90% mycological and 80% overall cure rate of cutaneous dermatophyte infections such as tinea corporis/cruris and tinea pedis.[5]
- Clinical and mycological efficacy and tolerability of higher dose of terbinafine (500mg) is well established from the evidences reported from past studies showing its advantage over low dose regimen.[6]

References

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UPCOMING CONFERENCE CALENDAR

National Symposium on Clinical Dermatology & Bedside Investigations 2016
Dates: 11-12 June, 2016
Location: NIMHANS, Bangalore, India

AESTHETICS 2016
Dates: 19-21 August, 2016
Location: India Habitat Centre, New Delhi, India

The XXth National Conference of the Cosmetic Dermatology Society 2016
Dates: 25-28 August, 2016
Location: Mumbai, India

Annual Conference of Indian Society for Pediatric Dermatology 2016
Dates: 28th August, 2016
Location: Taj Krishna, Hyderabad, India

The 10th Asian Dermatological Congress 2016
Dates: 13-16 October, 2016
Location: Sahara Star International Convention Centre, Mumbai, India

45th National Conference of Indian Association of Dermatologists, Venereologists & Leprologists (IADVL)
Dates: 12-15 January, 2017
Location: Science City Kolkata, West Bengal

Dermatopathology Quiz Section

A: The epidermis is thickened, a process called acanthosis.
The rete ridges are elongated to almost equal length.
This pattern of acanthosis is called psoriasiform hyperplasia.
It is seen commonly in plaque lesions of psoriasis.
It is also seen in other lesions, such as, lichen simplex chronicus, seborrheic keratosis and mycosis fungoides to name a few.