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Review article

Pathogenesis and clinical significance of dermatophytes: A comprehensive review

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Abstract

Dermatophytes, a group of keratinophilic fungi thriving on the keratin substrate are the etiological agents responsible for causing cutaneous infections. Dermatophytosis currently treated with the commercially available topical and oral antifungal agents in spite of the existing side effects. Treatment of these cutaneous infections with secondary metabolites produced by marine microorganisms considered as a novel approach. For many years, these organisms explored with the view of developing antibacterial, antifungal, antiviral, anticancer and antiparasitic drugs. Exploring the unexplored aspect of actinobacteria for developing anti-dermatophytic drugs is a novel attempt, which needs further investigation. The prevalence of superficial mycotic infection worldwide is 20–25% of which dermatophytes are the most common agents. Recent developments in understanding the path physiology of dermatophytosis have confirmed the central role of cell-mediated immunity in countering these infections. Hence, a lack of delayed hypersensitivity reaction in presence of a positive immediate hypersensitivity (IH) response to trichophytin antigen points toward the chronicity of disease. Diagnosis, though essentially clinical should be confirmed by laboratory-based investigations. Several new techniques such as polymerase chain reaction (PCR) and mass spectroscopy can help to identify the different dermatophyte strains. Management involves the use of topical antifungal in limited disease, and oral therapy is usually reserved for more extensive cases. The last few years have seen a significant rise in the incidence of chronic dermatophyte infections of skin which have proven difficult to treat. However, due to the lack of updated national or international guidelines on the management of *tinea corporis*, cruris, and pedis, treatment with systemic antifungal is often empirical. The present review aims to revisit this important topic and will detail the pathogenesis and clinical significance of Dermatophytes: *tinea corporis*, *tinea cruris*, and *tinea pedia* while highlighting the lack of clarity of certain management issues.

Keywords: Dermatophytes, Cutaneous infection, Polymerase chain reaction, Mass spectroscopy, Pathogenesis.

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1. Introduction

Dermatophytes

Dermatophytes are fungi that invade and multiply within keratinized tissues (skin, hair, and nails) causing infection [1]. Based upon their genera, Dermatophytes can be classified into three groups: *Trichophyton* (which causes infections on skin, hair, and nails), *Epidermophyton* (which causes infections on skin and nails), and *Microsporum* (which causes infections on skin and hair). Based upon the mode of transmission, these are been classified as anthropophillic, zoophilic, and geophilic. Finally, based upon the affected site, these are been classified clinically into *tinea capitis* (head), *tinea faciei* (face), *tinea barbae* (beard), *tinea corporis* (body), *tinea manus* (hand), *tinea cruris* (groin), *tinea pedis* (foot), and *tinea unguium* (nail). Other clinical variants include *tinea imbricata*, *tinea pseudoimbricata*, and *Majocchi granuloma*.

Despite the increasing prevalence of cutaneous dermatophytosis across the world, and especially in tropics, research in this area has often been neglected. In fact, one has to go back nearly two decades to find guidelines on the management of *tinea corporis* and cruris (by the American Academy of Dermatology) [2] and these at best, appear inadequate in today's world. The more recent guidelines published by the British Association of Dermatology and in the British Medical Journal have largely focused on *tinea capitis* and tinea unguium with scarce reference to *tinea corporis*/cruris [3-5]. Cochrane reviews have been updated on the use of topical therapy in *tinea corporis*, cruris, and pedis. Few on oral therapies have helped to bridge this knowledge gap but still well designed trials, national and/or

international evidence based guidelines and recommendations on the dose and duration of the use of systemic antifungal in *tinea corporis*/*cruris* are conspicuous by their absence [6-8]. The primary hosts of anthropophilic species are human beings but they may also cause infection in animals. Transmission of infection is from man to man. Examples include *Trichophyton rubrum, Trichophyton kanei, Trichophyton schoenleini, Trichophyton concentricum, Trichophyton tonsurans, Micropsorum gypseum, audouinii, Microsporum ferrugineum* and *Epidermophyton floccosum* [9, 10].

The present review aims to detail the pathogenesis and clinical significance of Dematophytes and management of *tinea corporis*, *tinea cruris*, and *tinea pedis* while highlighting the lack of clarity of certain management issues.

Trichophyton

The genus *Trichophyton* includes 24 species. The colonies on agar media are powdery, velvety or waxy. The predominant spore type is micro conidia with sparse macro conidia [11]. Reverse side pigmentation is characteristic of the species and is used for the identification of the species within the genus [12, 13]. The macro conidia are thin walled with smooth surface and variable shape [14]. Some of the *Trichophyton* species are fastidious in their requirement for amino acid as nitrogen source. *Trichophyton* tonsurans requires ornithine, citrul-line and Arginine whereas *Trichophyton* mentagrophytes requires methionine. This nutritional specificity used by many authors in the identification of the *Trichophyton* species [14].

Microsporum

The genus *Microsporum* includes 16 species. The colony morphology of *Microsporum* species on agar surface is either velvety or powdery with white to brown pigmentation [11]. Both macro and micro conidia produce but the predominant conidial structures are macro conidia. Micro conidia are less abundant. The macro conidia are multi septate with thick wall and rough surface [15]. Rarely some species produce neither micro nor macro conidia [16]. They do not have any special nutritional requirements.

Epidermophyton

The genus *Epidermophyton* includes only 2 species. The colonies are slow-growing, powdery and unique brownish yellow in colour. This genus is devoid of micro conidia. Macro conidia are abundant and produced in clusters [11]. These macro conidia are thin walled with smooth surface [15].

Distribution frequency of dermatophytes and dermatophytosis

All the three genera of Dermatophytes namely *Trichophyton*, *Microsporum* and *Epidermophyton* are worldwide in geographical distribution. The predominant cause of Dermatophytic infections is *Trichophyton* followed by *Epidermophyton* and *Microsporum*. Within the genus *Trichophyton*, *Trichophyton rubrum* is the predominant etiological agent accounting for 69.5% followed by *Trichophyton mentagrophytes*, *Trichophyton verrucosum* and *Trichophyton tonsurans* [17-19]. According to the World Health Organization (WHO) survey on the incidence of dermatophytic infection, about 20% the people worldwide present with cutaneous infections [20]. The disease does not spare people of any age [21]. Among the tinea infections, the most predominant type of infection is *tinea corporis* or *tinea circinata* followed by *tinea cruris*, *tinea pedis (*Figure 1) and *Onychomycosis*. *Tinea corporis* accounts for about 70% of the dermatophytic infection [21].

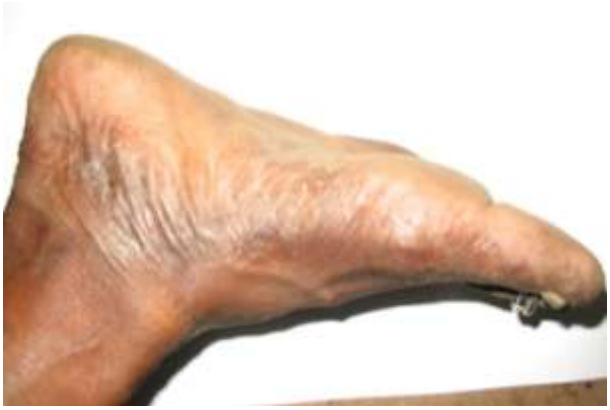

Figure 1 *TINEA PEDIS*

Pathogenesis and clinical presentation

The possible route of entry for the Dermatophytes into the host body is injured skin, scars and burns. Infections caused by arthrospores or conidia. Resting hairs lack the essential nutrient required for the growth of the organism. Hence, these hairs not invaded during the process of infection [22]. The pathogen invades the uppermost, non-living, keratinized layer of the skin namely the stratum corneum, produces exo-enzyme keratinase and induces inflammatory reaction at the site of infection [23-26]. The customary signs of inflammatory reactions such as redness (ruber), swelling (induration), heat and alopecia (loss of hair) are seen at the infection site. Inflammation causes the pathogen to move away from the site of infection and take residence at a new site. This movement of the organism away from the infection site produces the classical ringed lesion [27] (Figure 2)

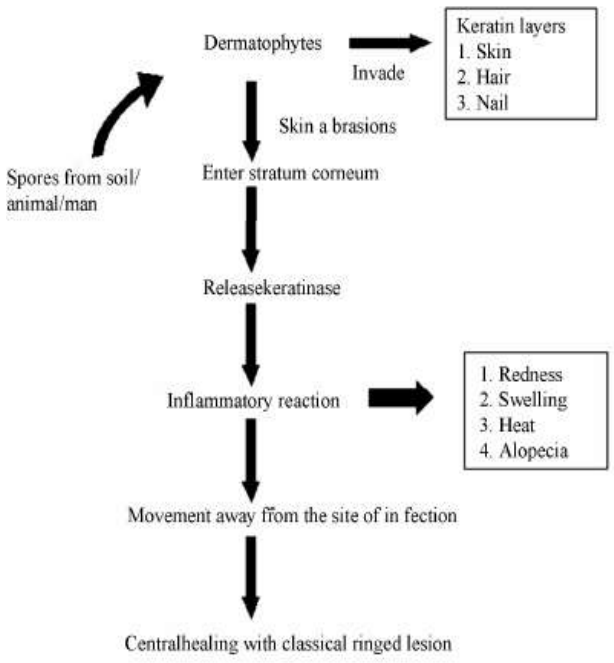

Figure 2: The schematic route of entry of dermatophytes into the host system and onset of immune response in the host when pathogen entry.

The infections caused by Dermatophytes commonly referred to as "*tinea*" or "ring-worm" infections due to the characteristic ringed lesions [28]. Based on the site of infection, the tinea infections are referred to as *tinea capitis* (scalp), *tinea corporis* or *tinea circinata* (non-hairy, glaborous region of the body), *tinea pedis* ("Athletes' foot"; foot), *tinea ungium* ("*Onychomycosis*"; nail), *tinea mannum* (hands) (Figure 3), *tinea barbae* ("Barbers' itch"; bearded region of face and neck), *tinea incognito* (steroid modified), *tinea imbricata* (modified form of *tinea corporis*), tinea gladiatorial (common among wrestlers') and *tinea cruris* ("Jocks' itch"; groin) [29].

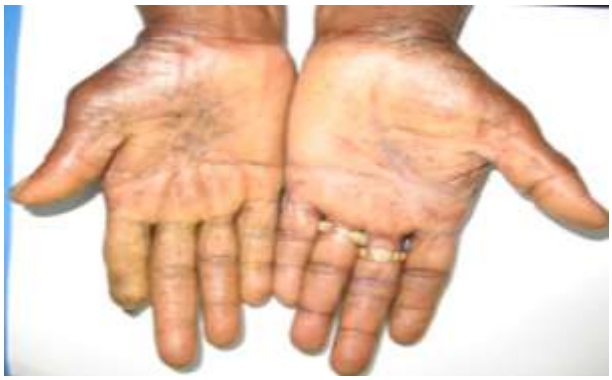

Figure 3: Tinea mannum

Innate immune response

Dermatophytes contain cell wall carbohydrate molecules (β‑glucan) that are recognized by innate immune mechanisms, such as Dectin‑1 and Dectin‑2, which activate toll‑like receptor 2 and 4 (TLR‑2 and TLR‑4). Dectin‑1 amplifies the production of tumor necrosis factor‑α and IL‑17, IL‑6, and IL‑10, all of which stimulate the adaptive immunity [30, 31]. Keratinocytes in the presence of dermatophyte antigens, such as trichophytin, release IL‑8, a potent neutrophillic chemo‑attractant. A recent study shows the involvement of TLR‑2 and TLR‑4 in localized and disseminated dermatophytosis due to *T. rubrum*. A reduced expression of TLR‑4 in the lower and upper epidermis of both localized and disseminated dermatophytosis patients was found compared to controls; TLR‑2 expression was preserved in the upper and lower epidermis of all three groups [32, 33].

Adaptive immune response

- Humoral immunity: Humoral immunity to dermatophytes is not protective. High levels of specific IgE and IgG4 are detected in patients with chronic dermatophytosis which is responsible for positive (IgE mediated) IH tests to *Trichophyton*. On the other hand, Ig levels are low in patients that present positive delayed type hypersensitivity (DTH) skin test. The IH skin test for *Trichophyton* is associated with the presence of serum IgE and IgG (mostly IgG4) against *Trichophyton* antigens, hallmarks of a Th2 response. Here, IL‑4 produced by CD4 T‑cells (Th2 cells) induces antibody isotype switching to IgG4 and IgE
- Cell‑mediated immunity: Several experiments have shown that the resolution of dermatophytosis mediated by DTH. Immunity to pathogens could be regulated by Th1 or Th2 subsets, which would ultimately determine the outcome of the infection. An acute inflammatory response correlates with a positive DTH skin test to trichophytin and clearing of the infection whereas chronic infection is associated with high IH and low DTH [34].

Non-specific response

Unsaturated transferrin found to be inhibitory to dermatophytes by binding to its hyphae. Commensal pityrosporum aids lipolysis and increases the pool of fatty acid available for inhibiting growth of fungi.

Treatment

Nonpharmacologic measures

Patients should be encouraged to wear loose‑fitting garments made of cotton or synthetic materials designed to wick moisture away from the surface. Socks should have similar properties. An area likely to become infected has to be dried completely before being covered with clothes. Patients should be advised to avoid walking barefoot and sharing garments

Medical management with antifungal

A variety of traditional agents without specific antimicrobial function are still in use, including Whitfield's ointment and Castellani's (Carbol fuchsin solution) paint. The efficacy of these preparations has not been well quantified [35]. Table 1 summarizes the classification of commonly employed antifungal [36-38]. Lesions covering a large body surface area fail to clear with repeated treatment using different topical agents should be considered for systemic therapy [35]. There is no definite comparative study on combination of systemic and topical versus monotherapy with systemic antifungal treatment.

Table 1: Classification of antifungal therapy based on their structure

Antifungal	class Examples
Antibiotics Polyenes Heterocyclic benzofuran	Amphotericin B, nystatin, natamycin Griseofulvin
Antimetabolite	Flucytosine
Azoles Imidazoles Triazoles	Topical - clotrimazole, econazole, miconazole, bifonazole, fenticonazole, oxiconazole, tioconazole, sertaconazole, berconazole, luliconazole, eberconazole Systemic - ketoconazole Itraconazole, fluconazole (also topical), voriconazole, posaconazole, isavuconazole, posoconazole, ravuconazole, pramiconazole, albaconazol
Allylamines	Terbinafine, butenafine, naftifine
Echinocandins	Caspofungin, anidulafungin, micafungin, aminocandin
Sordarin derivatives	GR135402, GM237354
Cell wall antagonist	Capsofungin, micafungin
Other agents	Tolnaftate, ciclopirox, amorolfine, undecylenic acid, buclosamide, Whitfield's ointment, benzoyl peroxide, zinc pyrithione, selenium sulfide, azelaic acid etc., nikkomycins, icofungipen
Newer and potential therapies	Demcidin, macrocarpal C

Topical medications have better pharmacokinetics than their systemic counterparts do. Hence, combinations expected to have better mycological clearance than systemic and topical alone. Combination should be from different groups for wide coverage to prevent emergence of resistance. Drugs given for shorter duration with higher dose there has a less chance of development of resistance compared to lower dose for longer duration. Drug with keratophilic and lipophilic property, when given in higher doses will have reservoir effect and will lead to better mycological clearance.

Indication of systemic antifungal in dermatophytosis

- *Tinea* capitis
- *Tinea* affecting the nails
- *Tinea* involving more than one body region simultaneously, for example, *tinea cruris* and *corporis*, or *tinea cruris* and *tinea pedis*
- *Tinea corporis* in which lesions are particularly extensive. However, there is no accepted definition of extensive disease
- *Tinea pedis* when there is extensive involvement of the sole, heel, or dorsum of the foot or when there is recurring and troublesome blistering.

Topical antifungal therapy for *tinea cruris*, corporis, and pedis

Reviewing the evidence on the use of existing topical antifungal

Various topical antifungal agents are available for the treatment of localized *tinea corporis*, *tinea cruris*, *tinea faciei*, and *tinea pedis*. It may used as an adjunct to oral antifungal for more extensive infection. Most of the studies in the treatment of *tinea corporis* and *cruris* have looked at the efficacy of topical antifungal with very few studies on the use of oral antifungal. A meta-analysis [39] evaluated the efficacy of antifungal treatment involving 14 different topical antifungal and included 65 randomized controlled trials (RCTs), comparing topical antifungal with one another or with placebo. Efficacy evaluated in the form of mycological cure at the end of treatment and sustained cure. They found no statistically significant differences among the antifungal concerning the outcome of mycologic cure at the end of treatment. For sustained cure, butenafine and terbinafine each were found to be superior to clotrimazole. Pair wise comparison of topical antifungal for the outcome of fungal cure showed butenafine and terbinafine each to be superior to clotrimazole, oxiconazole, and sertaconazole; terbinafine to be superior to ciclopirox, and naftifine to be superior to oxiconazole.

Similarly, Cochrane review [40] on the topical antifungal treatments for *tinea cruris* and *tinea corporis* suggests that the individual treatments with terbinafine and naftifine are effective with few adverse effects. Other topical antifungal like azoles treatments are also effective in terms of clinical and mycological cure rates. Regarding combinations therapy of topical steroids and antifungal though there is no standard guideline [41-43]. There is insufficient evidence to confidently assess relapse rates in the individual or

combination treatments. Difference between the different antifungal is mostly regarding fewer application and shorter duration of treatment with some class of topical antifungal compared to others. Topical antifungal are usually given once or twice daily for 2–4 weeks as illustrated in Table 2. The end point of treatment is clinical resolution in most of the cases.

Table 2: Summary of the use of topical antifungal used in the treatment of *tinea corporis, cruris and pedis*

Azole	Preparations	Site	Frequency of application	Duration of use
Imidazoles (%) Clotrimazole (1) Econazole (1) Miconazole (1) Oxiconazole (2) Sertaconazole (2) Luliconazole (1) Eberconazole (1)	Cream, lotion Cream Cream, lotion Cream, lotion Cream Cream, lotion Cream	*T. corporis/cruris/pedis* *T.corporis/cruris/pedis* *T.corporis/cruris/pedis* *T.corporis/cruris/pedis* *T.corporis/cruris/pedis* *T.corporis/cruris/pedis* *T.corporis/cruris/pedis*	BD OD-BD BD OD-BD BD OD OD	4-6 weeks 4-6 weeks 4-6 weeks 4 weeks 4 weeks 2 weeks 2-4 weeks
Triazoles (%) Efinaconazole (10)	Solution	*T. pedis*	OD	Up to 52 weeks in co-existing tinea unguium
Allylamines Terbinafine	Cream, powder	*T. corporis* *T. cruris* *T. pedis* *T. manum*	BD BD BD BD	2 weeks 2 weeks 4 weeks 4 weeks
Naftifine 1%	Cream	*T.corporis/cruris/pedis*	OD-BD	Use 2 weeks beyond resolution of symptoms
Butenafine 1%	Cream	*T.corporis/cruris/pedis*	OD-BD	2-4 weeks
Others Amolorfine 0.25% Amphotericin B (1 mg) 0.1%	 Cream Lipid based gel	 *T. corporis* *T. corporis*	 BD BD	 4 weeks 2 weeks

T. corporis: Tinea corporis, T. pedis: Tinea pedis, T. manum: Tinea manum, T. cruris: Tinea cruris

A study also emphasized upon the use of topical therapy in treating *tinea corporis, cruris* and *pedis.* They also enlist the common reasons of failure of therapy namely, poor adherence to treatment, re-infection from close contact, drug resistance, misdiagnosis, and infection with uncommon species. Such patients should be referred to a higher center for appropriate management. They also suggest use of topical hydrocortisone for a short time in inflamed lesions. Studies have also shown that addition of topical steroid also increases the bioavailability of topical antifungal mostly imidazole groups in addition to better symptomatic relief in early inflammatory stage [43]. While it may be of benefit to patients with inflammatory lesions, such practice should be strongly discouraged in countries like India where easy over the counter availability of topical steroids render then to frequent misuse by patients who finally end up with tinea incognito. Steroids may helpful in initial improvement in symptoms but chronic use lead to a complication like atrophy, telangiectasia which is more prominent when lesions are present in flexures. Topical antifungal with potent anti-inflammatory action such as sertaconazole or luliconazole may be a better option than an antifungal steroid combination.

Tinea pedis is usually treated with a topical antifungal cream for 4 weeks; interdigital *tinea pedis* may only require 1 week of therapy. Various topical antifungal effective against *tinea pedis* include azoles, allylamines, butenafine, ciclopirox, tolnaftate, and amorolfine as evidenced by a metaanalysis finding strong evidence of superiority of topical antifungal agents over placebo [7]. A metaanalysis of 11 randomized trials concluded that treatment with terbinafine or naftifine produces a slightly higher cure rate than treatment with an azole [44]. Nystatin is not effective for the treatment of dermatophyte infections. Naftifine hydrochloride gel was also found to be effective both for interdigital and moccasin type of *tinea pedis* [45].

Newer topical antifungal

Luliconazole, an azole antifungal has fungicidal action against *Trichophyton* species similar to or more than that of terbinafine. Available in 1% cream formulation, it is effective as once daily application for 1–2 weeks for dematophytic infection. Approved by the US Food and Drug Administration for the treatment of interdigital *tinea pedis*, *tinea cruris*, and *tinea corporis*, it has a favorable

safety profile [46]. Econazole nitrate foam preparation has also shown its efficacy over foam vehicle for *tinea pedis* [47]. However, these newer drugs are costlier which in turn may lead to issues of adherence to treatment in resource-poor settings, and may predispose to development of resistance.

Finally, use of special carrier system where parent drug attached to carriers such as micelle or use of nanostructure lipid‐based carrier, micro emulsions, and vesicular systems such as liposomes, niosomes, transfersomes, ethosomes, or penetration enhancer vesicles is promising as it helps in better bioavailability to attain better therapeutic response [48]. More recently, lipid-based amphotericin B gel has shown encouraging pharmacologic properties and clinical results in the treatment of various mucocutaneous fungal infections including dermatophytosis, with no adverse effect [49] Amphotericin B incorporated in microemulsion shows a 100% increase in skin retention with better in vitro antifungal activity against T. Rubrum [50]. One valid concern is whether use of topical amphotericin may promote its resistance in the community, thereby limiting its use for more invasive fungal infections. Microemulsion formulations of griseofulvin have shown good cure rates in dermatophytosis [51]. Adding to this is a novel formulation of terbinafine known as terbinafine film forming solution which forms a thin film forming topical application and fungicidal effect maintained for about 13 days following single application [52]. Successful treatment of *tinea corporis* with combination of topical isoconazole with diflucotolone (apotent topical steroid) has also been reported [53].

Oral antifungal therapy in *Tinea corporis*, cruris, and pedis

Reviewing the evidence on the use of existing oral antifungal

Systemic antifungal are indicated in case of extensive involvement and patients who fail topical therapy [54]. Out of the various systemic antifungal, terbinafine, and itraconazole are commonly prescribed. Griseofulvin and fluconazole are also effective but require long‐term treatment. RCTs support the efficacy of systemic antifungal [Table 3] [55‐58]. Comparative trial between itraconazole 100 mg/day with ultramicronized griseofulvin 500 mg/day for *tinea corporis* or *tinea cruris* showed significantly better clinical and mycological outcome in favor of itraconazole after 2 weeks of therapy [55]. Similar study comparing terbinafine with griseofulvin (both 500 mg daily for 6 weeks) for *tinea corporis* found mycological cure rate of about 87% in former group compared to 73% in latter.[57] A double‐blinded study between itraconazole (100 mg/day) and griseofulvin (500 mg/day) found itraconazole to be superior in providing mycological cure.[58]

Table 3: Recommended dosing of different systemic antifungal in dermatophytosis

Condition	Drug	Dose (oral)	Duration
T.corporis/ curis	Terbinafine Itraconazole Fluconazole Gresiofulvin (micro size) ultra‐micro size)	250 mg once daily, 3-6 mg/kg/day 200 mg/day 150-300 mg/week 500 mg/day (10-20 mg/kg/day) 300-375mg/day(5-10 mg/kg/day)	2-3 weeks 1-2 weeks 3-4 weeks 2-4 weeks
T. pedis	Terbinafine Itraconazole Fluconazole Gresiofulvin	250 mg once daily 100-200 mg/sday 150 mg/weeks 750-1000 mg/day (micro size) 660-750 mg/day (ultra‐micro size)	1week (interdigital type), 2 weeks (moccasin) 2-4 weeks 4 weeks 4-8 weeks

T. corporis: Tinea corporis, T. pedis: Tinea pedis

Topical therapy is less effective than oral antifungal for the treatment of *tinea pedis*, and oral treatment generally given for 4–8 weeks. In a systematic review of efficacy of oral antifungal in, terbinafine was found to be more effective than griseofulvin, whereas the efficacy of terbinafine and itraconazole were similar [8]. In addition to antifungal therapy, Burrow's (1% aluminum acetate or 5% aluminum subacetate) wet dressings, applied for 20 min 2–3 times/day may be helpful if vesiculation or maceration is present. Of various types of *tinea pedis*, hyperkeratotic variety is more recalcitrant to treatment due to thick scales leading to ineffectiveness of topical antifungal and need for longer duration of systemic antifungal. Use of keratolytic agents and topical antifungal along with systemic antifungal has been found to be more useful in early achievement of clinical and mycological cure as well as decreasing the duration of oral antifungal leading to better patient compliance [59]. Secondary bacterial infection should be treated with oral antibiotics. Other adjunctive therapies include use of antifungal powder may help to prevent maceration and avoidance of occlusive footwear.

Conclusion

Treatment of cutaneous dermatophytosis has increasingly become difficult, and dermatologists been forced to think beyond conventional wisdom to counter this menace. Although there is sufficient evidence to demonstrate the efficacy of topical antifungal in limited disease yet, there is

scarce data on the frequency of relapse once topical monotherapy discontinued. Among various options, topical terbinafine for 4 weeks appears to be the treatment of choice for limited disease (*tinea corporis*/*cruris/pedis*). For extensive disease, the choice is less clear. Both terbinafine (250–500 mg/day for 2–6 weeks) and itraconazole (100–200 mg/day for 2–4 weeks) appear to be effective. However, an appropriate dose and duration of administration that can produce mycologic cure and prevent recurrence remains elusive. This review also highlights the huge research gaps in the management of cutaneous dermatophytosis that need not plugged to provide better and effective care to the patients. RCTs that are more stringent are the need of the hour comparing the various oral antifungal therapies to give a clear idea regarding the appropriate dose and duration of therapy.

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