Content available at: https://www.ipinnovative.com/open-access-journals

IP Indian Journal of Clinical and Experimental Dermatology

Journal homepage: www.ijced.org/

Review Article

Rising burden of superficial fungal infections in India and the role of Clotrimazole for optimal management

Shashank Bhargava[1], Siddhartha Chakrabarty[2], Rajan T Damodaran[3], Prasanna Kumar Saikia[4], Manjunath Shenoy[5], Nikhil Bangale[6], Poonam Shah[7,*]

[1]*R. D. Gardi Medical College, Ujjain, Madhya Pradesh, India*
[2]*Royal Regency, Malibagan, Kaikhali, Kolkata, West Bengal, India*
[3]*Private Practitioner, Mumbai, Maharashtra, India*
[4]*Cutis, Marwari Patty, Bank of Baroda complex, M G Road, Nagaon, Assam, India*
[5]*Dept. of DVL, Yenepoya Medical College, Mangalore, Karnataka, India*
[6]*Medical Affairs, Bayer Consumer Health, Bayer House,Central Avenue, Hiranandani Estate, Thane, Mumbai, Maharashtra, India*
[7]*Medical and Regulatory Affairs, Bayer Consumer Health, Bayer House, Central Avenue, Hiranandani Estate, Thane, Mumbai, Maharashtra, India*

ARTICLE INFO

Article history:
Received 10-02-2023
Accepted 24-03-2023
Available online 04-04-2023

Keywords:
Dermatophytosis
Superficial fungal infection
Tinea infections
Topical therapy
Antifungal agents
Clotrimazole

ABSTRACT

Cutaneous dermatophytosis are among the most common infections seen in clinical practice. Over the past few years there has been a rising trend in the prevalence with change in spectrum of infection and isolation of some uncommon species. Recognition and appropriate treatment of these infections is important to reduce the morbidity and discomfort and also reduce the possibility of transmission. Azoles are the antifungal agents used extensively to treat dermatophytosis. Clotrimazole is mainly used locally in the treatment of skin fungal infections due to dermatophytes and yeasts. It is known to provide a broad-spectrum antifungal coverage against dermatophytes, moulds, yeasts and some bacteria, and is an efficient, safe and well accepted treatment for skin fungal infections in children and adults. This review provides an overview of the role of topical clotrimazole available as cream and powder and in combination with topical steroid for the optimal management of skin fungal infections.

1. Introduction

Fungal infections of keratinised tissues i.e., the skin, hair and nails is caused by dermatophytes, which are the most common organisms that belong mainly to the 3 genera: the Trichophytons, Epidermophytons and Microsporum. The yeasts and other unrelated filamentous fungi can cause opportunistic dermatomycoses that sometimes resembles the cutaneous fungal infections caused by dermatophytes. Fungal infections caused by dermatophytes are called "Tinea" and the infections are typically named according to the anatomical location that is involved.[1]

Dermatophytes are generally confined to the skin because of their inability to penetrate the deeper tissues or organs.[1] Dermatophytosis or tinea is predominant in about 20–25% of the population worldwide. Some of the factors associated with increased rate of infection are high temperature and humidity (tropical and sub-tropical regions); type of geographical regions (most common in rural than in urban areas); chronic diseases or disorders (patients with diabetes); people in community living (low socioeconomic conditions); those using antibiotics and

* *Corresponding author*.
E-mail address: poonam.shah@bayer.com (P. Shah).

https://doi.org/10.18231/j.ijced.2023.001

steroids; those receiving immunosuppressive drugs (for AIDS); and those with close contact with animals.[2]

Although the most common causative agents of superficial fungal infections (SFIs) are dermatophytes, it may also be caused by non-dermatophytic moulds and commensal yeasts.[3] SFIs, especially in the intertriginous areas (groin, sub mammary folds, gluteal clefts) are common and increasingly seen in clinical practice and the most common pathogens are dermatophytes and Candida spp. in general population.[4]

SFIs can also affect various parts of the body. The treatment is mainly topical antifungal agents and oral systemic medications. Until a decade ago, most cases were managed with only topical antifungal agents and oral antifungal therapy was needed only when the topical agents proved ineffective.

An inaccurate diagnosis can lead to inappropriate treatment and also the inappropriate use of topical corticosteroids can worsen the clinical picture. It is important for the primary care providers to be aware of the various presentations of dermatophytic infections and the treatment options available for its accurate management[5] i.e., both clinical and mycological cure, prevent relapses, prevent spread to untreated patients and also limit morbidity in those affected.[6] Fungal infections of the skin, hair and nails usually respond to treatment within a few weeks and persisting symptoms and signs will need referral to a dermatologist.[7]

SFI of the skin represent a significant disease burden. They were ranked 4^{th} highest in the incidence of disease i.e. 2.1 billion cases when compared to 328 different diseases and injuries globally in 2016. SFIs also contribute to a considerable amount to the total DALYs (disability-adjusted life years) and in 2017, they accounted for almost 10% of the total DALYs caused by all skin disorders.[8] Although the prevalence of cutaneous dermatophytosis is increasing worldwide, the research in this area is often neglected and the management guidelines that are not so recent may not be relevant to the current scenario.[9]

1.1. Types of skin fungal infections

SFI of the skin (Figure 1) are common worldwide which affects about 20-25% of population with an estimated lifetime risk of 10-20%. Dermatophytes are fungal organisms that infect keratinized superficial layers of the skin (stratum corneum) and use keratin as a source of nutrients.[10]

There are about 100,000 species of fungi worldwide and about 40 different species of dermatophytes (Trichophyton, Microsporum and Epidermophyton). Majority of SFI of the skin are caused by 5 to 6 species of dermatophytes, and the most common of them is the *Trichophyton rubrum*. Dermatophytes usually thrive at surface temperatures of 25–28°C and the infection of human skin is mainly due to

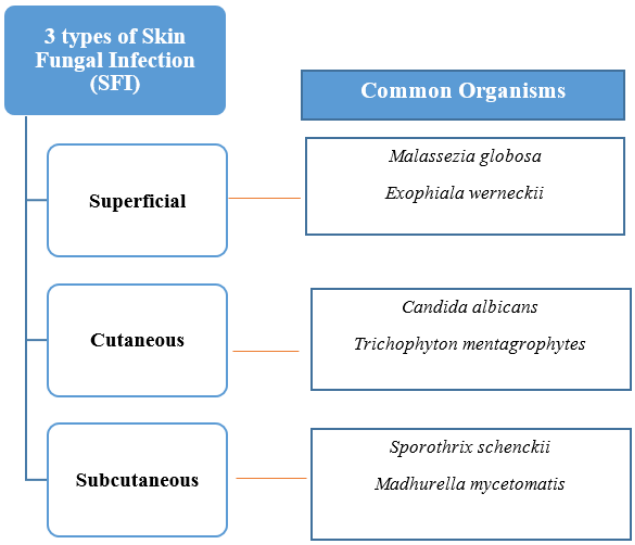


Fig. 1: Types of skin fungal infections[11–14]

warm and humid conditions. That's why SFIs are relatively common in the tropical countries and is exacerbated by the wearing occlusive clothing. Also the less common or the forgotten species are being imported and disseminated with the booming mass tourism, international sports activities and increasing migration. The superficial fungal skin infections are not just more prevalent in the tropical and subtropical regions they are also more distinctive and more frequent, particularly in Asia (especially India) and Africa. Superficial skin infections have a low tendency to self-limitation, and its spread may be increased with poor or absence of medical care.[15]

2. Epidemiology of Skin Fungal Infections (SFIs) in India

SFIs in India are among the most common skin infections and their incidence is growing.[16] The current scenario of dermatophytosis is characterised by many atypical manifestations (epidemiological, clinical and mycological) compared to the earlier times. There has been an increase in chronic, recurrent and partially responding infections, a changing pattern of the dermatophyte isolates i.e. *T. mentagrophytes* emerging as the major pathogen and also *T. mentagrophytes/T. interdigitale* complex with multidrug resistance.[13]

The recent prevalence of dermatophytosis in India is between 36.6–78.4% and the most predominant isolate are *T. mentagyrophyte* and *T. rubrum*.[3] The newly emerged fungus *T. mentagrophytes* genotype VIII which is now called *T. indotineae* causes inflammatory and pruritic forms of difficult-to-treat tinea cruris, tinea corporis, and tinea faciei.[17] The emergence of this new and more virulent *T. mentagrophytes* subspecies (genotype VIII) is in response

to a high use of antifungal agents possibly facilitated or enhanced by an animal reservoir and also the challenges in infection control due to crowded housing conditions.[18]

Although dermatophytes are assuming high significance in India[3] the data on the incidence of dermatophyte infections is very limited as it is not a reportable disease.[19] There have been cases with unusually large lesions, ring within ring lesions, lesions at multiple site and corticosteroid modified lesions making diagnosis difficult.[3] About 15–20% of the patients presenting to dermatology OPDs/ clinics are recalcitrant cases.[20] This is possibly the outcome of a complex and intrigued interplay between the host, the fungus, the drug and the environment, due to multiple factors such as more humid and warmer climate, irrational use of topical corticosteroid based combinations, increased use of broad spectrum antibiotics, increasing burden of immuno-compromised population, widespread use of antifungals in the agricultural industry, and also the drug resistance to antifungals.[3]

The exact incidence and prevalence is difficult to calculate owing to the scarcity of community-based surveys. The prevalence recorded in south India is between 6.09% to 27.6%, whereas it is 61.5% in north India, most of which is from hospital-based studies over a period of 1- 2 years. Although dermatophytosis is expected to be more prevalent in the hot and humid climates of south India and less so in north India, no such association seems to be apparent and in the last 5–7 years there has been a rising trend all over the country. There is also a steady increase in the incidence of chronic, relapsing and recurrent dermatophytosis with disease durations running into months or years.[21]

The overuse of certain antifungal preparations like itraconazole in unconventional forms such as tablets and in combination with isotretinoin, preparations compounded with beta cyclodextrin and sustained release preparations or topical antifungals like amorolfine and luliconazole with penetration enhancers has led to loss of effectiveness and lower cure rates.[16] A recent Indian study found terbinafine to have very low effectiveness in treating jock itch and ringworm with 2% cure rates at 2 weeks. The effectiveness of terbinafine was abysmal in dermatophytosis.[22] The spectre of dermatophytosis is haunting Indian dermatologists. The infection is apparently much more resilient, with a tendency to recur more frequently and the overall number of patients presenting with chronic/recurrent/recalcitrant dermatophytosis is also much more.[16]

2.1. Unprecedented epidemic-like scenario of SFI in India

There has been an alarming increase in the overall number of case and also the number of difficult to treat chronic and recurrent dermatophytosis in India over the past few years.[20] At present there is an ongoing epidemic of dermatophytosis in India and other neighbouring countries in the Indian subcontinent.[17] There has been an increase in number of atypical presentations with 5–10% of the new cases, being recurrent and chronic cases with diverse clinical presentations such as larger sized and greater number of lesions, more than 1 lesion of tinea in more than 1 anatomical location.[23]

More and more children are also presenting with dermatophytosis. There has been an increasing number of lesions with multiple concentric circles i.e., tinea pseudoimbricata in those with immune suppression and those using corticosteroids.[23] The many characteristics of current epidemic of dermatophytosis in India is due:[24]

1. Increased incidence of recurrent dermatophytosis i.e., re-occurrence of the signs and symptoms within few weeks of apparent cure and chronic dermatophytosis i.e., persistence of the infection despite treatment for more than 6 months to 1 year).
2. Deviation in the clinical patterns i.e., patients presenting with extensive and morphologically atypical lesions.
3. Increased trends of potent topical steroid misuse to treat the disease.
4. Failure of systemic antifungals and lack of adequate response.
5. Emergence of *T. mentagrophytes* as the dominant or a co-dominant pathogen.

The recent upsurge in incidence of dermatophytosis and its myriad of atypical presentations in India is due to a complex interplay of:[25]

1. Agent factors: True resistance, parasitism of vellus hair.
2. Host factors: Changing clothing habits, ping pong effect within the family, untreated sanctuary sites, casual health-seeking attitude, lack of adherence to standard therapy.
3. Social factors: Hesitation to seek medical advice due to involvement of groins, gluteal region, or the infra-mammary regions.

The treatment of dermatophytosis which was once an easily curable infection is becoming challenging in India due to changing climatic conditions, westernization, and casual health-seeking attitude. Also due to indiscriminate use of irrational topical fixed drug combinations (FDCs) that is altering the clinical presentation, evoking an irritant response, and contributing to resilience of fungi, which is resulting in recurrences, chronicity, and also resistance to antifungal agents.[25]

2.2. Increasing incidence in women

The dermatophytosis which was found to occur more frequently in men than women because of outdoor work

predisposing them to hot, humid and sweaty conditions favourable for the growth of dermatophytes is changing. The male: female ratio is < 2 in the recently published studies which is in contrast to 3-5 in the earlier studies which is clearly indicative of the rising prevalence in women.[21]

Tinea cruris et corporis is more common, and more number of women have active tinea corporis, tinea cruris, and tinea corporis et tinea cruris often presenting secondary to the index case which is most often a male. This is also due to the change in fashion trends, and increasing preference for tight fitting clothing such as figure hugging denims, leggings, and jeggings without any heed to the practical aspects of its non-suitability to the hot and humid climate. Increased prevalence of tinea cruris and tinea corporis is not only among overweight but also seen in otherwise hygiene conscious, young, slim women with no other risk factors. Many women present with a sub mammary infection that involves the infra mammary fold more than the skin of the breasts which underscores the role of friction and maceration from moisture of perspiration.[23]

Superficial dermatophytosis which was once considered an innocuous, easy-to-treat infection of tropical and subtropical countries which was mainly seen during the summer and rainy seasons has now become a perennial and difficult to treat entity in India.[21]

3. SFI and its Impact on Quality of Life (QoL)

Dermatophytosis can become widespread and have a significant negative social, psychological, and occupational health effects, compromising the quality of life (QoL) of the individual affected.[3] Superficial dermatophytosis may cause significant distress and can affect patients socially, physically, and financially.[26]

Patients presenting with widespread, atypical lesions require prolonged therapy and may have frequent relapses. Most patients have household contacts and at times the entire family is affected which not just leads to impairment in quality of life, but also adds to morbidity and huge financial burden due to frequent and prolonged courses of antifungal therapy.[20]

Cutaneous fungal infections can negatively affect psychosocial well-being by lowering self-esteem, causing embarrassment and social withdrawal. The discomfort and inflammation can lead to disability and inability to perform daily activities.[8] Many patients with chronic recalcitrant dermatophytosis develop feelings of hopelessness, shame and anger; a few even express suicidal ideation.[21]

Itching, peeling, and redness associated with SFIs can have a significant impact on wellbeing and QoL of the patients. Persistent itching may lead to tissue damage, delayed healing and secondary infections.[27] The average workdays lost per hospitalization due to dermatophytosis is 3.7 and the productivity losses from workdays lost due to hospitalizations is $ 6,77,644 in the United States of America.[28] Chronic widespread dermatophytosis affects those from the lower socioeconomic strata of society more often and most of them have many household contacts who are similarly afflicted, that magnifies the financial burden of treatment.[21] Hence recognition and proper treatment of SFI of the skin is important to not just reduce the burden of the disease, but to also reduce the physical, psychological, and social aspects associated with it.[4]

4. Cardinal feature – Itch and its Characteristics

One of the cardinal features of superficial dermatophytosis is itching that can be very bothersome. Patients complain of paroxysms of pruritus that lasts for a few minutes, few times a day and some may have it for longer periods of time.[21]

A recent study in India found itch to be a major concern in patients suffering from superficial SFI that drastically affects QoL if it is severe and for a long duration of time.[29] A study in Turkey that looked at the impact of itch in patients with athlete's foot, reported QoL to be negatively affected with increasing level and severity of itch.[30]

Itching (with burning) can get aggravated by sweating, heat, hot water and after disrobing (atmokinesis), and can disturb sleep in many patients. Nocturnal exacerbation of pruritus is common. Even fully treated patients complain of persistent itching that is often due to xerosis or impaired barrier function due to scratching. Post tinea, eczema/ dryness can lead to persistence of itch. There has been a change in the clinical behaviour of dermatophytosis with moderate or severely itchy, peripherally spreading, flat, whitish or brownish lesions without erythema which yield profuse powdery scales when scraped which is common. Topical antifungal agents like luliconazole have been anecdotally observed to cause xerosis that can contribute to itching.[21]

5. Guideline Recommendations

The treatment approach for dermatophytosis of skin is usually topical treatments especially for "localized" infections or those with limited spread. Oral medication is for more extensive infections.[31]

Topical therapies work well for topical fungi and yeasts. Azoles (clotrimazole, miconazole, ketoconazole) are basically fungistatic, which limit fungal growth depending on epidermal turnover to shed the still-living fungus from the skin surface. Azoles and imidazoles differ from allylamines and benzylamines in their mode of action i.e., they are fungistatic (except at very high concentrations) and not fungicidal. They interfere with synthesis of the fungal cell wall. The fungistatic effect is enough to clear the infection, with the help of skin desquamation. The azoles also have inherent anti-inflammatory properties.[32]

The choice of therapy will depend on the clinical appearance of lesions, prior treatment, and knowledge of

pharmacological properties of antifungal agents. The area of the skin involved (dry/sebum-rich) and the age of the patients also influence the choice of treatment. An ideal topical treatment is the one with high cure rate, low relapse rate, and short duration of action, and one with minimal adverse effects. It is very important to have a treatment regimen which is satisfactory to the patient to ensure compliance. Majority of the experts recommended the use of topical therapy in the management of naive cases of tinea cruris and corporis (localised lesion) whereas combination therapy is recommended in recalcitrant tinea cruris. The choice of topical antifungal agents will vary as per the region and also the personal experience of the individuals. Combination therapy is recommended in cases of naive tinea corporis with extensive skin involvement or lesions with papules. Topical azoles are the empiric agent of choice in the management of naive and recalcitrant cases as per expert recommendations. As per the Expert consensus on the management of dermatophytosis in India (ECTODERM India) topical azoles should be the drug of choice, due to their anti-inflammatory, antibacterial and broad spectrum antimycotic activity.[3]

6. Clotrimazole in SFI

Azoles are the 1^{st} line treatment option for many fungal infections, including dermatomycoses and candidiasis and systemic mycoses.[33] They are the most widely used class of clinical antimycotics that is sub classified into imidazoles (clotrimazole, miconazole, econazole and ketoconazole) and triazoles (fluconazole and itraconazole) depending on their chemical structure.[34] Azoles are the drug of choice because of the anti-inflammatory, antibacterial and broad spectrum activity.[3] Imidazoles (clotrimazole, miconazole, econazole, and ketoconazole) are now well established effective treatments in SFIs.[31]

Clotrimazole is the first imidazole derivative that is used for dermatophytosis, tinea versicolor and oral or mucocutaneous candidiasis with a cures rate of 60-100% for dermatophyte infections and 80-100% in cutaneous candidiasis.[35] Clotrimazole is a chlorinated tritylimidazole that was first synthesised in Germany in 1967. It is known to inhibit most strains of Trichophyton, Microsporum and Epidermophyton *in vitro*. It is as active as nystatin against Candida spp. and also inhibits some strains of Gram-positive bacteria. It is a broad spectrum imidazole that is to be applied twice daily to treat superficial dermatomycoses, and cutaneous Candida infections.[1]

Clotrimazole is the drug of choice for the topical treatment of tinea pedis (athlete's foot), tinea cruris and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis* and *C. albicans.*[36]

It has a fungistatic antimycotic activity by targeting the biosynthesis of ergosterol thereby inhibiting the fungal growth.[36] It inhibits biosynthesis of sterols, particularly ergosterol, which is an essential component of the fungal cell membrane, thereby damaging and affecting the permeability of the cell membrane. This results in leakage and loss of essential intracellular compounds that eventually causes cell lysis[37] (Figure 2).

Clotrimazole is one of the 2 topical azole antifungal agents (other was and miconazole) introduced in 1969.[39] Clotimazole is effective, safe and well-tolerated with an unusual chemistry that is widely used in the treatment of skin fungal infections. It is the drug of choice for the topical treatment of tinea pedis (athlete's foot), tinea cruris and tinea corporis caused by isolates of *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis* and *Candida albicans*.[34,36] Topical application can effectively treat skin infections caused by dermatophytes or Candida. Clotrimazole cream has been found to be as effective as Whitfield's ointment and tolnaftate in the treatment of dermatophytoses, and as effective as nystatin in cutaneous candidiasis in comparative trials.[38,40]

Clotrimazole is available as topical cream and powder (Table 1) and is also formulated with steroids. Topical forms of clotrimazole are considered reasonably safe and is without any serious side effects.[36] The topical route of administration is with minimum systemic absorption.

Table 1: Application of clotrimazole in cream and dusting powder[4,38,41]

Clotrimazole cream	Clotrimazole dusting powder
• Works by preventing the boom of fungi that causes the contamination.	• Used for prevention of fungal infections due to accumulation of sweat and moisture.
• Effective in treatment of athlete's foot, jock itch, ringworm, pityriasis versicolor, intertrigo, and erythrasma.	• It is a remedy for prickly warmness at the back, neck, and shoulder.
	• Used to prevent itching in intimate parts, underarms, internal thighs, waistline, and feet.
	• As an adjuvant therapy and possibly preventive agent for superficial fungal cutaneous infection in intertriginous areas.

Clotrimazole may be even used in combination with corticosteroid for inflammatory tinea due to *Epidermophyton floccosum* and Trichophyton in adults and children > 12 years of age. It is an effective treatment for skin infections like athlete's foot, jock itch, ringworm, pityriasis versicolor, intertrigo, and erythrasma.[41] It is indicated for symptomatic inflammatory

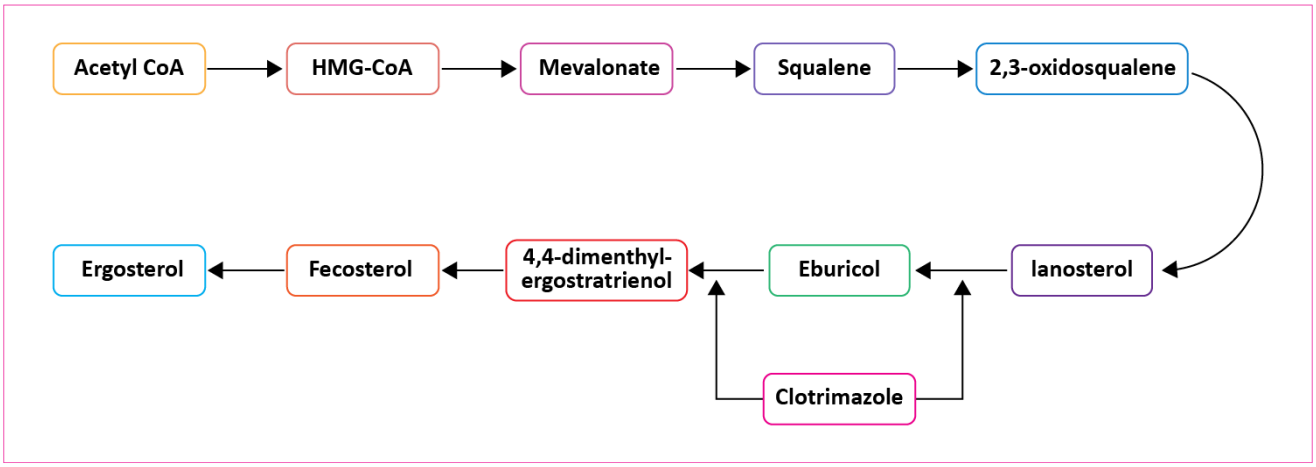


Fig. 2: Mechanism of action of clotrimazole[36,38]

dermatophytosis with erythema, pruritus, and burning. The steroid component provides rapid symptomatic relief while the slower-acting antifungal agent eradicates the causative organism.[42]

Clotrimazole is typically given topically has only modest systemic absorption and because there is minimal systemic absorption, its concentrations may not reach levels that could cause significant liver injury.[43] After topical administration the serum concentrations of clotrimazole is below the detection limit of 0.001 μg/ml which is not clinically relevant and no treatment-related systemic effects are observed clinically with topical application.[44] There are no interactions known with other substances and also the systemic concentrations are very low for any drug interactions to occur following topical application of clotrimazole.[45]

Topical formulations of clotrimazole (1% concentration) are indicated for the treatment of dermatophytic infections, yeasts, moulds, and erythrasma to be applied 2-3 times daily on the affected area that should be continued for at least 1 month for dermatophyte infections, or for at least 2 weeks for candida infections.[44]

Drug interactions are not a major issue with topical clotrimazole as it is not systemically absorbed. It is also safe for use in the elderly population and in breast-feeding mothers.[34] Topical clotrimazole cream can be used in most adults and children with fungal infections.[46,47] In infants and children with common fungal infections, clotrimazole 1% cream is to be applied times daily for 7 days (maximum 14 days).[48] Use of clotrimazole and steroid combination cream is not recommended in children <17 years of age.[49]

6.1. Clinical evidence

6.1.1. Clotrimazole cream (1%)

An open, comparative, multicenter study conducted in Europe and the United States evaluated the efficacy and safety of oral fluconazole and topical clotrimazole in fungal infections of the skin. Patients were randomized to receive fluconazole, 50 mg/day, or clotrimazole 1% topical cream, twice daily, for up to 6 weeks. The clinical response at the end of therapy was similar in both treatment groups. Mycologic cure at the end of treatment in the European trial was 85% and 86% with oral fluconazole and topical clotrimazole respectively. A similar trend was seen in the US trial with cure rates of 66% and 72%, respectively. Both drugs were well tolerated.[50]

A study by Lucker and co-workers with a different investigational approach i.e. an intra-individual comparison between clotrimazole and bifonazole among 8 healthy male volunteers showed that following application of 5 mg 14C-labelled clotrimazole as a 1% cream to an area of 100 cm^2 the total active ingredient concentration in the epidermis was 1.5 mg after 24 hours, with a mean half-life for clotrimazole of 25 hours in the upper, 27 hours in the middle and 26 hours in the lower layers of skin. About 30% of the applied amount of active ingredient in the skin after 24 hours and a mean half-life of about 24 hours suggests that sufficiently high active ingredient concentrations (well above the MIC) can be maintained with twice daily application of clotrimazole.[51]

A Cochrane review of randomised controlled trials assessed the effects of topical antifungal treatments in tinea cruris and tinea corporis. The mycological cure rates favoured clotrimazole 1% cream compared to placebo (RR 2.87, 95% CI 2.28 to 3.62, NNT 2, 95% CI 2-3) across two studies.[52]

A retrospective study by Zhao and co-workers compared the efficacy and safety of 1% topical clotrimazole cream

Table 2: Comparison within and between the groups after 4 weeks of treatment[53]

Parameters		1% clotrimazole cream	1% butenafine cream	P value (Difference within groups)
Erythema score	Pre-treatment	1.75 (0.61)	1.68 (0.60)	<0.01
	Post-treatment	0.57 (0.62)	0.64 (0.65)	
Scaling score	Pre-treatment	1.81 (0.54)	1.75 (0.53)	<0.01
	Post-treatment	0.50 (0.55)	0.57 (0.59)	
Itching score	Pre-treatment	1.86 (0.40)	1.80 (0.41)	<0.01
	Post-treatment	0.55 (0.55)	0.64 (0.61)	
KOH-negative results	Pre-treatment	0 (0)	0 (0)	<0.01
	Post-treatment	21 (48.8)	19 (44.2)	

to 1% topical butenafine cream for the management of tinea cruris and found it to be equally effective and safe in 86 patients with confirmed tinea cruris for the presence of fungal hyphae. After treatment, patients in both groups achieved better improvements in erythema, scaling, itching and KOH-negative results compared to before the treatment and there were no significant differences in erythema, scaling, itching, and KOH-negative results between the 2 groups (Table 2).[53]

6.1.2. Clotrimazole powder (1%)

Antifungal powder is effective in keeping the skin dry due to its hygroscopic properties and can be also used in prophylaxis of tinea.[54] Use of 1% clotrimazole powder could be an adjuvant therapy and a preventive agent for superficial fungal cutaneous infection in the intertriginous areas. Desomchoke and co-workers in a preliminary, prospective, open-label, randomized, comparative study (n = 67 patients, mean age 54.6 years) evaluated the efficacy and safety of 1% clotrimazole cream (control group) and 1% clotrimazole cream plus 1% clotrimazole powder (experimental group) in patients with superficial fungal cutaneous infection (dermatophytes or Candida spp) in the intertriginous areas. The complete cure rate at 4, 8, and 12 weeks and the relapse rates during a 24-week period and patient satisfaction were assessed. The complete cure rates in experimental group were significantly higher than in the control group at 4 weeks with fungal intertriginous skin infection caused by dermatophyte or Candida spp. (p = 0.01) and dermatophyte infection (p = 0.039) (Figure 3). In both groups, relapse up to 24 weeks were not statistically different and there was no statistical significance in preference of medical application of cream over powder in both dermatophytosis and candidiasis group (Figure 4). Powder formulation with lack of sticky feeling is suitable for treatment of dermatophytes and Candida spp. infection in intertriginous areas.[4]

Antifungal dusting powder may be suitable for treatment of superficial fungal infection in moist areas such as in intertriginous areas especially in tinea pedis. A retrospective review of the medical records of patients, clinically diagnosed with tinea pedis at the Thai naval rating school

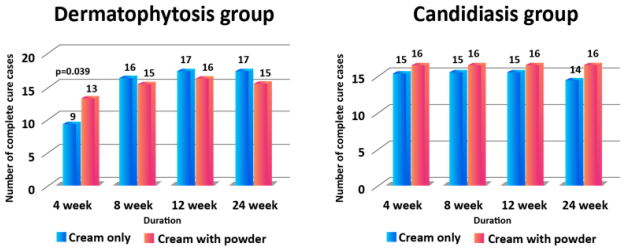


Fig. 3: Complete cure rates at 4, 8, 12 weeks and 24 weeks[4]

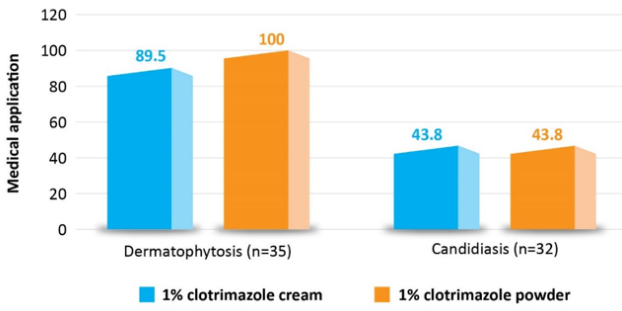


Fig. 4: Convenience of topical application of clotrimazole cream and powder[4]

medical department during August – September 2015 by Ongsri and co-workers found clotrimazole dusting powder had an advantage over boric acid and salicylic acid powder (mBS foot powder) and clotrimazole cream in decreasing excessive humidity due to its' hygroscopic properties which absorbs excess moisture in applied surfaces, especially in humid body areas.[54]

It is very important to clear up skin infection completely to make sure it does not return. A bland, absorbent powder i.e., talcum powder or an antifungal powder are often used between the toes, on the feet, and in socks and shoes once or twice a day as good health habit. Powders are not to be used as the only treatment for fungus infections like athlete's foot, jock itch or ringworm of the body. It is to be used only after antifungal cream has been applied and has disappeared into the skin.[55]

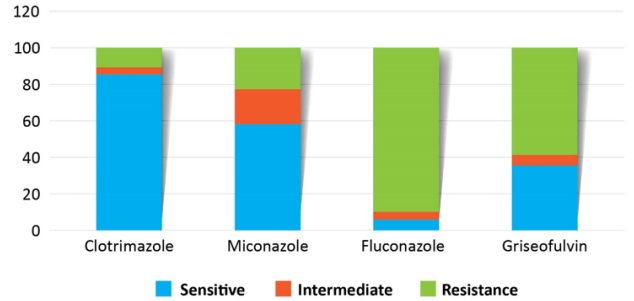
Plain talc is often used to keep the feet dry, but when hot occlusive footwear is worn periodic use of a topical antifungal agent may be required. Clotrimazole powder is an excellent dusting powder for the feet in Tinea Pedis.[56]

6.1.3. *Benefits of micronized size of cream/ powder*

Drug particles if micronized or reduced to a very small size can dissolve more quickly and can reach its site of action i.e. improved bioavailability. Micronized particles have a greater surface area that allows for better interaction with solvents like body fluids which improves the solubility of the particles and enhances its absorption. Micronization can have a positive impact on the shelf life and stability of medications; is an efficient and cost-effective process and can produce larger volumes of drugs.[57] Selection of an appropriate size of particles is a valuable factor that can impact the therapeutic outcomes of dermal drug administration.[58]

6.1.4. *Sensitivity pattern of dermatophytes to Clotrimazole vs. other antifungals*

Kadnur and co-workers evaluated the clinico-mycological pattern of dermatophytes and their *in-vitro* sensitivity to commonly used antifungals and found clotrimazole to have the highest sensitivity i.e. about 87.5% to all dermatophytes followed miconazole 60.4%, griseofulvin 37.5% and fluconazole only 8.3% (Figure 5). Among *T. mentagrophytes* which is the major species causing infection, 88% were sensitive to clotrimazole, 8% to fluconazole, 60% to miconazole, and 38% to griseofulvin. Among topical antifungals tested, 88% of the isolates were sensitive to clotrimazole vs. 60% of the isolates to miconazole.[59]



Clotrimazole			Miconazole			Fluconazole			Griseofulvin		
R	I	S	R	I	S	R	I	S	R	I	S
8.3	4.2	87.5	20.8	18.8	60.4	87.5	4.2	8.3	56.3	6.3	37.5

Fig. 5: *In-vitro* sensitivity pattern of dermatophytes to Clotrimazole vs. other antifungals[59]

6.1.5. *Clinical and mycological cure with clotrimazole*

Clotrimazole is effective in terms of clinical and mycological cure (Table 3).

6.2. *Clotrimazole in combination with steroid*

Corticosteroid-based combination treatment has an important role in inflammatory dermatophytosis.[3,98] The key advantage of combining an antifungal with a corticosteroid is swift resolution of the inflammatory changes and symptoms of mycoses, such as itching, burning and erythema; restoration of normal skin conditions and re-establishment of a healthy microbial flora. The rapid resolution of symptoms is likely to encourage good patient compliance with treatment. Addition of a corticosteroid to imidazole topical therapy increases the concentration of imidazole in the dermis and epidermis due to the local vasoconstrictive effects of the corticosteroid, that delays the dispersal of the imidazole via the circulation, thereby prolonging the duration of antimycotic activity compared to only antimycotic therapy. This is likely to result in faster clearance of fungal infections.[15]

The most important benefit is in inflammatory dermatophytoses i.e., the ability of the corticosteroids to produce fast relief of disturbing symptoms, which can prevent premature discontinuation of therapy before the effect of slower acting antifungal agent is seen. Treatment with antifungal and corticosteroid combination is indicated for inflammatory tinea corporis (excluding tinea faciale), inflammatory tinea cruris (sparing the inguinal folds) and inflammatory tinea pedis.[63] Addition of a corticosteroid to an antifungal agent at the initiation of treatment can lessen the inflammatory symptoms of the infection and increase patient compliance, reduce the risk of bacterial super infection and enhance the efficacy of the antifungal agent. But irrational use of antifungal-corticosteroid can lead to treatment failure and adverse effects.[23,99]

6.2.1. *Combination of clotrimazole (1%) +beclomethasone dipropionate (0.025%)*

Steroids may enhance the antifungal activity of the clotrimazole,[42] however it may be attributable to the anti-inflammatory effect. The addition of topical steroid also increases the bioavailability of topical antifungals mostly imidazole groups in addition to better symptomatic relief in early inflammatory stage.[9] Wadhwa and co-workers evaluated the efficacy and safety of the combination of clotrimazole 1% + beclomethasone dipropionate 0.025% among physicians (n = 84) pan India and found the combination to be highly effective in 822 patients suffering from candidiasis with inflammatory diseases. The reduction in severity of all symptoms/signs was >80% and scaling and lichenification was 76.05% and 66.03% respectively. Adverse reaction was noted in only 1 patient.[100] Clotrimazole with beclomethasone combination

Table 3: Clotrimazole: Clinical cure and mycological cure skin fungal infections

Indication	Study design	Treatment (n)	Clinical cure	Mycological cure
Ringworm	Double-blind, placebo-controlled study [60]	Clotrimazole 1% cream/ solution 4-6 weeks BID	96%	86%
	Double-blind comparator study [61]	Clotrimazole 1% vs. Butenafine	96% vs. 96.2 at 4 weeks	92% vs. 96.2% at 4 weeks
	Randomised controlled comparator study vs. amorolfine cream [62]	Clotrimazole 1% vs. Amorolfine cream	On Day 28: Clotrimazole vs. Amorolfine Itching subsided in 95.4% vs. 92.1; Erythema absent in 92.9% vs. 97.4%; Scaling subsided in 92.9% vs. 92.15%	On day 28 Clotrimazole vs. Amorolfine 76.2% vs. 78.9%
Jock itch	Double-blind, placebo-controlled study (n=1,361) [60]	Clotrimazole 1% cream/ solution 4-6 weeks BID	96%	86%
	Randomised study (n=391) [63]	Clotrimazole 1% cream BID vs. Oral fluconazole 150 mg once weekly	End of therapy: 88% vs. 90%.	End of therapy: 90% vs. 100%.
	Double-blind comparator study [61]	Clotrimazole 1% vs. Butenafine	96% vs. 96.2 at 4 weeks	92% vs. 96.2% at 4 weeks
Skin Candidiasis	Double-blind, placebo-controlled study (n=1,361) [60]	Clotrimazole 1% cream/solution 4-6 weeks BID	100%	78%
	Double-blind trial [64]	Clotrimazole 1% cream vs. Nystatin ointment		100% vs. 100%
	Randomised, double-blind study [65]	Clotrimazole 1% vs. Miconazole	-	100% vs. 100%
	Double-blind placebo-controlled and comparator study [66]	Clotrimazole 1% cream vs. bifonazole cream	75.0% vs. 70.1%	86.8% vs. 73.1%
	Randomised open label comparator study [63]	Clotrimazole 1% cream twice daily vs. Oral fluconazole 150 mg once weekly	End of therapy: 100% vs. 100%.	End of therapy: 71% vs. 100%.
	Double-blind phase III comparator study [67]	Clotrimazole 1% cream vs. eberconazole 1%	73% vs. 50%	-
Pityriasis versicolor	Two double-blind placebo-controlled studies of clotrimazole cream and solution [60]	Clotrimazole 1% cream/ solution for 4-6 weeks	80% vs. 38%	80% vs. 38%
	Comparator study [68]	Clotrimazole 1% vs. Whitfield's ointment	88% vs. 27% (complete cure)	100% vs. 72.7%
Erythrasma	Double-blind comparator trial [64]	Clotrimazole 1% vs. Whitfield's ointment	At 4 weeks 100% vs. 100%	-
	Double-blind comparator trial [65]	Clotrimazole 1% vs. Miconazole	At 4 weeks 100% vs. 100%	-
Athlete's foot	Double-blind, placebo-controlled study (n=1,361) [60]	Clotrimazole 1% cream 4-6 weeks BID	76%	86%
	Randomised open label comparator study [63]	Clotrimazole 1% cream BID vs. Oral fluconazole 150 mg once weekly	End of therapy: 72% vs. 81%. Long term follow-up:82% vs. 82%.	End of therapy: 91% vs. 79%. Long term follow-up: 92% vs. 69%.

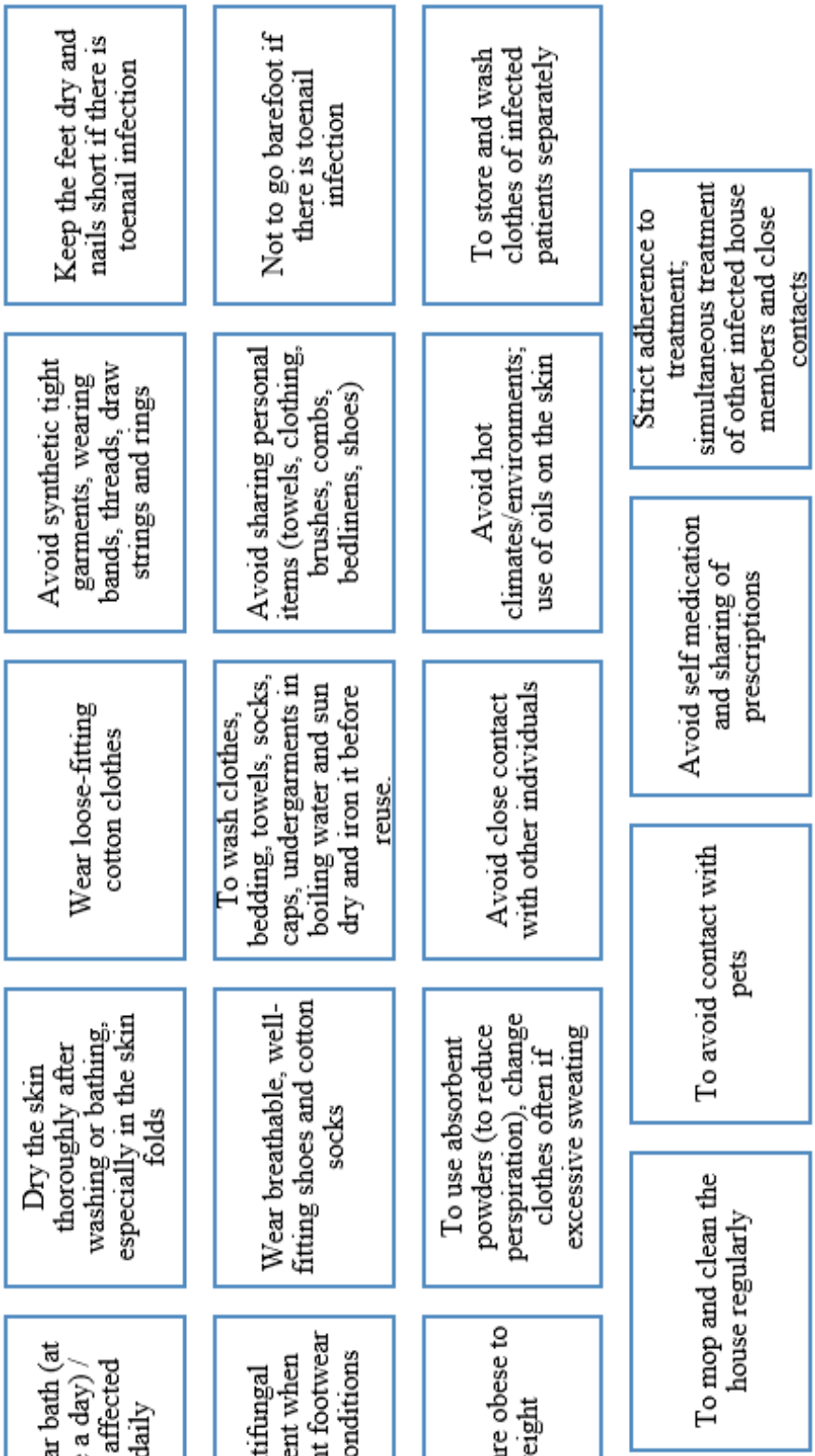


Fig. 6: Self care tips

Table 4: Managing skin fungal infections in primary care: use of topical application of clotrimazole[2,3,7,29,36,69–71]

	Tinea corporis (Ringworm)[72–77]	**Tinea cruris/ inguinalis / glutealis** (Jock Itch)[15,61,74,75,78]	**Candidal yeast infection (Skin candidiasis)[79–84]**	**Tinea versicolor/ P. versicolor (yeasts)** (Beach fungus)[85–88]	**Tinea pedis** (Athlete's foot)[15,56,74,75,89–93]	**Onychomycosis** (Fungal nail infection)[94–97]
Common cause	*T. rubrum*	Trichophyton (most frequent) Epidermophyton Microsporum	*C. albicans*	*M. furfur*	*T. rubrum* (most common) *T. mentagrophytes E. floccosum*	*T. rubrum, T. mentagrophytes*
Commonly affects	Pre-pubertal children and immune compromised patients.	Adolescents and specifically young male adults.	All ages, may be exacerbated in immunocompromised individuals	Adolescents and young adults	Can affect all ages; most common in adult males	Affects all ages; common above 60 years
Common presentation	Red, scaly plaques on the body, typically on the trunk, neck, arms and legs.	Red, scaly, ring-shaped plaque usually found in the genital, pubic areas, perineum and perianal area.	Red, thin pustule or patches that can burn or itch; found in any area of the body but most commonly in the skin folds	Flaky, discoloured, round or oval patches (pink, brown or white) often on the upper trunk, upper arms, neck and face.	Itchy patches and peeling, red and blistering skin on feet and toes.	Yellow-brown discoloration and/or thickened, disformed or separating toe or fingers nail.
Spread	Easily between people and animals and also from one part of the body to another	Easily with skin-to-skin contact, particularly in warm, humid environments.	Does not typically spread between people but can be spread via bloodstream to other parts of the body.	Not contagious	Very contagious and can spread through contact with an infected person or contaminated surfaces; linked to the regular use of communal washing and changing rooms and swimming pools.	Is contagious and can spread through contact with an infected person or contaminated surfaces.
Diagnosis	Dermascopy Direct microscopy Fungal cultures Wood lamp	Direct microscopy Wood lamp Histopathology Fungal cultures	Direct microscopy Histopathology Fungal cultures	Direct microscopy Wood lamp Skin biopsy	Direct microscopy Histopathology Wood lamp Fungal cultures	Direct microscopy Fungal cultures Histopathology Polymerase chain reaction
Treatment - Refer to Figure 7 .[36,46,70,71]						

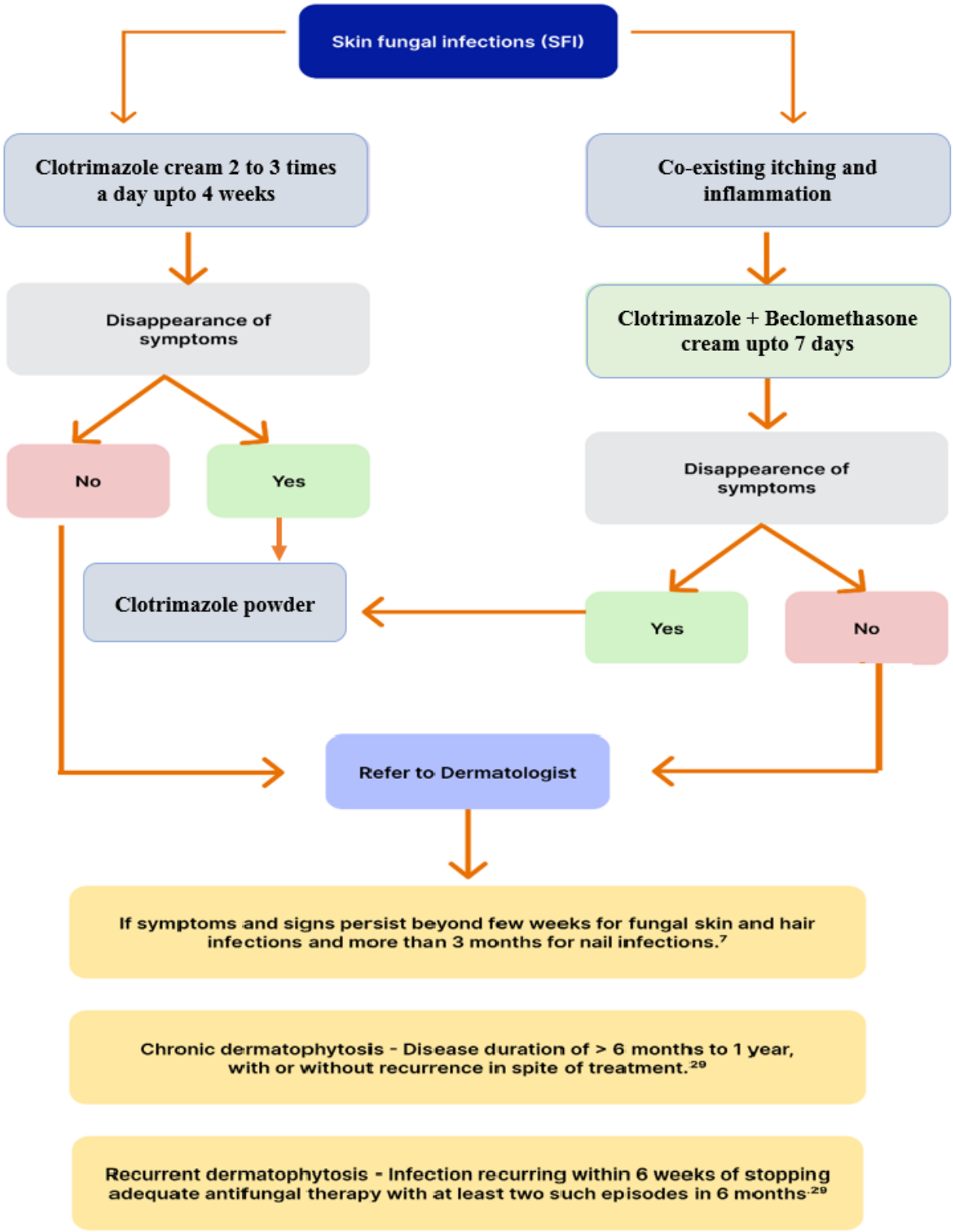


Fig. 7: Treatment algorithm[36,46,70,71]

cream should be used in highly inflammatory intertrigo-like lesions to avoid potential misuse of corticosteroid combination creams.

7. Self help Tips

A good personal hygiene is an important adjunct to antifungal therapy in managing patients with SFI of the skin.[19]

Things that one can do to help stop spreading of fungal infection to the surrounding skin and other body parts is mentioned in Figure 6[13,56,85–88]

8. Case Studies

8.1. Case 1: A typical but rare case of solitary tinea auricularis

A case of a healthy, 35-year-old female presented with a 2-week history of rash on her right ear. It was previously diagnosed as eczema and was given topical desonide cream with which there was no improvement. On examination, there was annular erythema with scaly borders centered around the external acoustic pore, there was no retro-auricular, scalp or face involvement. Direct microscopic examination of skin scrapings was positive and all fungal cultures grew colonies of *Trichophyton rubrum*. She was diagnosed to have tinea auricularis. After inquiry, she gave h/o suppurative otitis media a month back which was treated with levofloxacin and dexamethasone with endoscopic irrigation. She was given topical clotrimazole cream for 3 weeks after which her skin lesions resolved. There has been no recurrence of the rash post the completion of therapy.[101]

Local infection or external drug application can change the local skin immune situation and microbiota that can be one of the causes of fungal infection.[101]

8.2. Case 2: Unusual case of Tinea Nigra affecting both palms

A 14-year-old girl presented with bilateral slow-growing hyper pigmented macules on her palms for about 6 months. She gives history of frequent hand washing. The lesions were asymptomatic and her general health was good. She reported that the lesions were gradually blackening. There were multiple blackish patches with an irregular and well-demarcated border, size ranging from 0.2×0.2 cm to 1.0×1.0 cm resembling silver nitrate stain on the left and right palm in the volar region and the hypothenar eminence and extending up to the ulnar border of the wrist on examination. No scales, vesicles or other inflammatory changes. KOH mount showed light brownish short septate hyphae with scattered budding yeast-like cells. Culture on SDA at 25°C yielded moist shiny yeast-like colonies on 10^{th} day of incubation which were initially yellowish brown which later changed to shiny black by 3^{rd} week. The colonies produced abundant aerial hyphae, reverse of the colonies were black in colour. *Hortaea werneckii* was the organism identified, and the growth on SDA with 15% sodium chloride proved it to be halophillic and no growth at 37°C differentiated it from other species of the genus. Patient was treated with topical clotrimazole (1%) cream with which the lesions gradually disappeared over 2 weeks and there was no recurrence.

Patient had a complete cure with topical clotrimazole cream. Managing such cases is usually straight forward that often responds to topical therapy with azole antifungals and oral agents are unnecessary and often ineffective.[102]

8.3. Case 3: Tinea incognito due to Trichophyton rubrum

A case of a 72-year-old woman, who was unsuccessfully treated for skin lesions for 3 weeks with topical steroid cream by her family physician. On examination there were multiple nummular scaly papules and plaques over her arms and trunk. The lesions were circular, erythematous, sharply demarcated with raised scaly edge, some coalescing to form moderately infiltrated areas. Direct microscopy showed fungal hyphae and fungal culture was positive for *Trichophyton rubrum* on Sabouraud's agar. She was successfully treated with oral terbinafine 250 mg daily and 1% clotrimazole cream twice daily.

This case highlights the importance of considering a dermatophytosis when clinical presentation of dermatosis is atypical and disseminated scaly infiltrate lesions should be investigated for fungal infection in those who are treated with steroids previously, to avoid misdiagnosis and spread of infection.[103]

8.4. Case 4: Tinea atypica diagnosed as tuberculum mulgentium

A case of a 48-year-old male who presented with raised and erythematous lesions on the right hand. Culture on the SDA isolated *Trichophyton verrucosum*. He was initially treated with 2% fusidic acid cream that was not successful. He was then treated with oral fluconazole 50 mg for 20 days which was followed by 200 mg/week for additional period of 4 weeks and topical 1% clotrimazole cream that was effective.[104]

9. Conclusion

Fungal skin infections are common worldwide, but are more likely to develop in people living in tropical climates. Dermatophytes are the most common pathogens causing superficial fungal infections. Successful management of dermatophytosis is challenging due to the changing epidemiological factors and the emergence of drug resistant organisms. Appropriate dose and duration of drug in a compliant patient helps achieve successful clinical

and mycological cure. Topical antifungal medications particularly clotrimazole is frequently prescribed for localized superficial fungal infection. It is an effective, safe and well tolerated drug. In addition to pharmacological therapy, general measures and lifestyle changes also play a crucial role in preventing recurrences.

10. Source of Funding

None.

11. Conflict of Interest

None.

12. Acknowledgement

Unrestricted educational grant supported by Bayer India. Manuscript and editorial support by Dr. Shoma Shetty, Manager – Medical Writing Services, Insignia Communication Pvt Ltd, Mumbai.

References

1. Gupta AK, Einarson TR, Summerbell RC, Shear NH. An overview of topical antifungal therapy in dermatomycoses. A North American perspective. *Drugs*. 1998;55(5):645–74.
2. Al-Khikani FH. Dermatophytosis a worldwide contiguous fungal infection: Growing challenge and few solutions. *Biomed Biotechnol Res J*. 2020;4(2):117–22.
3. Rajagopalan M, Inamadar A, Mittal A, Miskeen AK, Srinivas CR, Sardana K, et al. Expert consensus on the management of dermatophytosis in India (ECTODERM India). *BMC Dermatol*. 2018;18(1):6. doi:10.1186/s12895-018-0073-1.
4. Desomchoke R, Bunyaratavej S, Leeyaphan C, Prasertworonun N, Rujitharanawong C, Matthapan L, et al. Efficacy and Safety in 1% Clotrimazole Powder, Adjuvant Therapy in Patients with Superficial Fungal Cutaneous Infection in Intertriginous Areas. *J Med Assoc Thai*. 2016;99(12):1355–9.
5. Kaushik N, Pujalte GGA, Reese S. Superficial Fungal Infections. *Prim Care*. 2015;42(4):501–16.
6. Salmon N, Fuller C. Fungal skin infections: current approaches to management. *Prescriber*. 2013;24(8):31–7.
7. Moriarty B, Hay R, Jones RM. The diagnosis and management of tinea. *BMJ*. 2012;345:e4380. doi:10.1136/bmj.e4380.
8. Urban K, Chu S, Scheufele C, Giesey RL, Mehrmal RL, S. The global, regional and national burden of fungal diseases in 195 countries and territories: a cross sectional analysis from the Global Burden of Disease Study. *J Am Acad Dermatol* . 2017;2:22–7. doi:10.1016/j.jdin.2020.10.003.
9. Sahoo AK, Mahajan R. Management of tinea corporis, tinea cruris, and tinea pedis: A comprehensive review. *Indian Dermatol Online J*. 2016;7(2):77–86.
10. Ezomike NE, Ikefuna AN, Onyekonwu CL, Ubesie AC, Ojinmah UR, Ibe BC, et al. Epidemiology and pattern of superficial fungal infections among primary school children in Enugu, south-east Nigeria. *Malawi Med J*. 2021;33(1):21–7.
11. High WA. Chapter 19: Fungal Disease. [Internet]. Available from: https://dermatology.mhmedical.com/content.aspx?bookid=2932&sectionid=246136014.
12. Hay R. Superficial fungal infections. *Medicine*. 2017;45(11):707–10.
13. Rengasamy M, Shenoy MM, Dogra S, Asokan N, Khurana A, Poojary S, et al. Indian Association of Dermatologists, Venereologists and Leprologists (IADVL) Task Force against Recalcitrant Tinea (ITART) Consensus on the Management of Glabrous Tinea (INTACT). *Indian Dermatol Online J*. 2020;11(4):502–19.
14. Carrasco-Zuber JE, Navarrete-Dechent C, Bonifaz A, Fich F, Vial-Letelier V, Berroeta-Mauriziano D, et al. Cutaneous Involvement in the Deep Mycoses: A Literature Review. Part I-Subcutaneous Mycoses. *Actas Dermo-Sifiliográficas*. 2016;107(10):806–15.
15. Havlickova B, Friedrich M. The advantages of topical combination therapy in the treatment of inflammatory dermatomycoses. *Mycoses*. 2008;51(Suppl 4):16–26. doi:10.1111/j.1439-0507.2008.01615.x.
16. Panda S, Verma S. The menace of dermatophytosis in India: the evidence that we need. *Indian J Dermatol Venereol Leprol*. 2017;83(3):281–4.
17. Uhrla S, Verma SB, Graser Y, Rezaei-Matehkolaei A, Hatami M, Schaller M, et al. Trichophyton indotineae-An emerging pathogen causing recalcitrant dermatophytoses in India and Worldwide-A multidimensional perspective. *J Fungi*. 2022;8(7):757. doi:10.3390/jof8070757.
18. Shen JJ, Arendrup MC, Verma SS, and DLS. The Emerging Terbinafine-Resistant Trichophyton Epidemic: What Is the Role of Antifungal Susceptibility Testing? *Dermatology*. 2022;238(1):60–79. doi:10.1159/000515290.
19. Rezabek GH, Friedman AD. Superficial fungal infections of the skin. Diagnosis and current treatment recommendations. *Drugs*. 1992;43(5):674–82.
20. Dogra S, Narang T. Emerging Atypical and Unusual Presentations of Dermatophytosis in India. *Clin Dermatol Rev*. 2017;1(1):12–8.
21. Verma SB, Panda S, Nenoff P, Singal A, Rudramurthy SM, Uhrlass S, et al. The unprecedented epidemic-like scenario of dermatophytosis in India: I. Epidemiology, risk factors and clinical features. *Indian J Dermatol Venereol Leprol*. 2021;87(2):154–75. doi:10.25259/IJDVL_301_20.
22. Singh S, Shukla P. End of the road of terbinafine? Results of a pragmatic prospective cohort of 500 patients. *Indian J Dermatol Venereol Leprol*. 2018;84(5):554–7. doi:10.4103/ijdvl.IJDVL_526_17.
23. Verma S, Madhu R. The Great Indian Epidemic of Superficial Dermatophytosis: An Appraisal. *Indian J Dermatol*. 2017;62(3):227–36.
24. Shenoy MM, Jayaraman J. Epidemic of difficult‑to‑treat tinea in India: Current scenario, culprits, and curbing strategies. *Arch Med Health Sci*. 2019;7(1):112–7.
25. Dabas R, Janney MS, Subramaniyan R, Arora S, Lal SV, Donaparthi N, et al. Use of over-the-counter topical medications in dermatophytosis: A cross-sectional, single-center, pilot study from a tertiary care hospital. *Indian J Drugs Dermatol*. 2018;4(1):13–7. doi:10.4103/ijdd.ijdd_5_18.
26. Inamadar A, Rengasamy M, Charugulla SN. Treatment approach for superficial dermatophytosis infections and factors contributing for noncompliance to antifungal therapy in India: An epidemiological survey. *Clin Dermatol Rev*. 2022;6:15–21. doi:10.4103/cdr.cdr_122_20.
27. Bongomin F, Gago S, Oladele RO, Denning DW. Global and Multi-National Prevalence of Fungal Diseases-Estimate Precision. *J Fungi*. 2017;3(4):57. doi:10.3390/jof3040057.
28. Benedict K, Whitham HK, Jackson BR. Economic Burden of Fungal Diseases in the United States. *Open Forum Infect Dis*. 2022;9(4):ofac097. doi:10.1093/ofid/ofac097.
29. Patro N, Panda M, Jena AK. The menace of superficial dermatophytosis on the quality of life of patients attending referral hospital in Eastern India: A cross-sectional observational study. *Indian Dermatol Online J*. 2019;10(3):262–6. doi:10.4103/idoj.IDOJ_342_18.
30. Bicer S, Ulas Y, Atasoy M, Ozyurt K, Ulas S, Ertas R, et al. Impact of pruritus on quality of life I patients with tinea. *Int Phys Med Rehabil J*. 2018;3(6):534–8. doi:10.15406/ipmrj.2018.03.00160.
31. Hay R. Therapy of Skin, Hair and Nail Fungal Infections. *J Fungi (Basel)*. 2018;4(3):99. doi:10.3390/jof4030099.

32. Kyle AA, Dahl MV. Topical therapy for fungal infections. *Am J Clin Dermatol*. 2004;5(6):443–51.
33. Mijaljica D, Spada F, Harrison IP. Emerging Trends in the Use of Topical Antifungal-Corticosteroid Combinations. *J Fungi (Basel)*. 2022;8(8):812. doi:10.3390/jof8080812.
34. Kumar S, Khan R, Sharma B. Clotrimazole: A review of its structure, therapeutic class and pharmaceutical properties, pharmaceutical dosage forms and administration and analytical study. *World J Pharm Pharm Sci*. 2021;10(10):325–38.
35. Dias MFG, Bernardes-Filho F, Quaresma-Santos MVP, Amorim ADF, Schechtman RC, Azulay DR, et al. Treatment of superficial mycoses: review - part II. *An Bras Dermatol*. 2013;88(6):937–44.
36. Crowley PD, Gallagher HC. Clotrimazole as a pharmaceutical: past, present and future. *J Appl Microbiol*. 2014;117(3):611–7. doi:10.1111/jam.12554.
37. NIH. Clotrimazole. Compound Summary. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/clotrimazole.
38. Tushir R, Chauhan A, Bansal R, Dalal A, Kumar P. A descriptive review on pharmacokinetics and pharmacodynamics profile of an antifungal agent. *Clotrimazole EJPMR*. 2022;9(4):204–16.
39. Sheehan DJ, Hitchcock CA, Sibley CM. Current and Emerging Azole Antifungal Agents. *Clin Microbiol Rev*. 1999;12(1):40–79.
40. Sawyer PR, Brogden RN, Pinder RM, Speight TM, Avery. Clotrimazole: a review of its antifungal activity and therapeutic efficacy. *Drugs*. 1975;9(6):424–47. doi:10.2165/00003495-197509060-00003.
41. Khatter NJ, Khan MAB. Clotrimazole. vol. 2022. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560643.
42. Weinstein A, Berman B. Topical Treatment of Common Superficial Tinea Infections. *Am Fam Physician*. 2002;65(10):2095–102.
43. NIH. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Clotrimazole. [Updated 2019 Apr 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548320/.
44. Electronic Medicines Compendium. Clotrimazole Cream 1% - Summary of Product Characteristics. [Internet] . Available from: https://www.medicines.org.uk/emc/product/2598/smpc#gref.
45. Walsky RL, Gaman EA, Obach RS. Examination of 209 drugs for inhibition of cytochrome P450 2C8. *J Clin Pharmacol*. 2005;45(1):68–78.
46. NHS. How and when to use clotrimazole cream, spray and solution. Available from: https://www.nhs.uk/medicines/clotrimazole/how-and-when-to-use-clotrimazole-cream-spray-and-solution/.
47. Mayo clinic Clotrimazole (Topical Route) Proper Use. Available from: https://www.mayoclinic.org/drugs-supplements/clotrimazole-topical-route/proper-use/drg-20063212.
48. Antifungal agents for common paediatric infections. *Can J Infect Dis Med Microbiol*. 2008;19(1):15–8.
49. Drugs.com. Betamethasone and clotrimazole (Topical). Available from: https://www.drugs.com/cons/betamethasone-and-clotrimazole-topical.html.
50. De Bersaques J, Bjerke JR, Borelli S, Brown AC, Cottenot F, Daniel F, et al. Comparison of oral fluconazole and topical clotrimazole in the treatment of fungal infections of the skin: European and American experience. *Int J Dermatol*. 1992;31(2):21–6.
51. Lucker PW, Beubler E, Kukovetz WR, Ritter W. Retention time and concentration in human skin of bifonazole and clotrimazole. *Dermatologica*. 1984;169(1):51–5.
52. El-Gohary M, Van Zuuren EJ, Fedorowicz Z, Burgess H, Doney L, Stuart B, et al. Topical antifungal treatments for tinea cruris and tinea corporis. *Cochrane Database Syst Rev*. 2014;(8):CD009992. doi:10.1002/14651858.CD009992.
53. Zhao D, Chen B, Wang YT, Jiao CH. Topical clotrimazole cream for the treatment of tinea cruris. A retrospective study. *Medicine*. 2020;99(47):e23189. doi:10.1097/MD.0000000000023189.
54. Ongsri P, Bunyaratavej S, Leeyaphan C, Pattanaprichakul P, Ongmahutmongkol P, Ariyatanasuporn N, et al. Efficacy of antifungal cream versus powder in the treatment of fungal foot skin infection and unpleasant foot odor at medical department of Thai Naval Rating School. *Southeast Asian J Trop Med Public Health*. 2018;49(2):297–303.
55. Mayo clinic Betamethasone And Clotrimazole (Topical Route). Available from: https://www.mayoclinic.org/drugs-supplements/betamethasone-and-clotrimazole-topical-route/precautions/drg-20061704.
56. Nigam PK, Saleh D. Tinea Pedis. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. [Updated 2022 Jul 3]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470421/.
57. Drugs.Com. What does micronized mean? . Available from: https://www.drugs.com/medical-answers/micronized-mean-3570285/#:~:text=Drug%20particles%20can%20dissolve%20more.
58. Adib ZM, Ghanbarzadeh S, Kouhsoltani M, Khosroshahi AY, Hamishehkar H. The effect of particle size on the deposition of solid lipid nanoparticles in different skin layers: A histological study. *Adv Pharm Bull*. 2016;6(1):31–6.
59. Kadnur M, Jartarkar SR, Narayanaswamy G, Kumar AS, Arora M, S. A clinico-mycological study of dermatophytoses and their in-vitro sensitivity to antifungal drugs. *Indian J Dermatopathol Diagn Dermatol*. 2022;9(2):54–8. doi:10.4103/ijdpdd.ijdpdd_41_21.
60. Spiekermann PH, Young MD. Clinical evaluation of clotrimazole. *Arch Dermatol*. 1976;112(3):350–2.
61. Singal A, Pandhi D, Agrawal S, Das S. Comparative efficacy of topical 1% butenafine and 1% clotrimazole in tinea cruris and tinea corporis: A randomized, double-blind trial. *J Dermatolog Treatment*. 2005;16(5-6):33–5. doi:10.1080/09546630500375783.
62. Bannerjee M, Ghosh AK, Basak S, Das KD, Gangopadhyay DN. Comparative evaluation of effectivity and safety of topical amorolfine and clotrimazole in the treatment of tinea corporis. *Indian J Dermatol*. 2011;56(6):657–62. doi:10.4103/0019-5154.91823.
63. Crevits B, Picoto A, Staberg B, Silny W, Urbanowski S. Comparison of efficacy and safety of oral Fluconazole and topical Clotrimazole in the treatment of Tinea corporis, Tinea cruris, Tinea pedis and cutaneous Candidiasis. *Curr Ther Res*. 1998;59(7):503–10.
64. Clayton YM, Connor BL. Comparison of clotrimazole cream, Whitfield's ointment and nystatin ointment for the topical treatment of ringworm infections, pityriasis versicolor, erythrasma and candidiasis. *Br J Dermatol*. 1973;89(3):297–303.
65. Clayton YM, Knight AG. A clinical double-blind trial of topical miconazole* and clotrimazole+ against superficial fungal infections and erythrasma. *Clin Exp Dermatol*. 1976;1(3):225–32.
66. Lalosevic J, Rojas R, Estorga E, Gip L. Bifonazole cream in the treatment of superficial candidosis. *Dermatologica*. 1984;169(1):99–106.
67. Palacio AD, Ortiz FJ, Peârez A, Pazos C, Garau M, Font E, et al. A double-blind randomized comparative trial: eberconazole 1% cream versus clotrimazole 1% cream twice daily in Candida and dermatophyte skin infections. *Mycoses*. 2001;44(5):173–80. doi:10.1046/j.1439-0507.2001.00632.x.
68. Gumaa SA. Pityriasis versicolor in the Sudan: comparative topical treatment with clotrimazole and benzoic-salicylic acid ointment. *Trans Roy Soc Tropical Med Hygiene*. 1976;70:145–8.
69. Chou L. Identifying and managing fungal skin infections . Available from: https://www.pharmacytimes.com/view/identifying-and-managing-fungal-skin-infections.
70. Noble SL, Forbes RC, Stamm PL. Diagnosis and Management of Common Tinea Infections. *Am Fam Physician*. 1998;58(1):163–74.
71. NHS. Guidelines for the prescribing of topical antifungal agents.
72. Yee G, Aboud AA. Tinea Corporis. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. [Updated 2022 Aug 8]. . Available from: https://www.ncbi.nlm.nih.gov/books/NBK544360/.
73. Leung AKC, Lam JM, Leong KF, Hon KL. Tinea corporis: an updated review. *Drugs in Context*. 2020;9:5–6. doi:10.7573/dic.2020-5-6.
74. Ely JW, Rosenfeld S, Stome MS. Diagnosis and management of tinea infections. *Am Fam Phys*. 2014;90(10):702–10.

75. Hainer BL. Dermatophyte infections. *Am Fam Phys*. 2003;67(1):101–8.
76. 2021. Available from: https://www.cdc.gov/fungal/diseases/ringworm/treatment.html.
77. Shukla S, Khachemoune A. CDC. Ringworm information for healthcare professionals; 2021. Available from: https://emedicine.medscape.com/article/1091473-treatment#d8.
78. Pippin MM, Madden ML, Das M. Tinea Cruris. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. [Updated 2023 Jan 23]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554602/.
79. Flowers RH. Cutaneous candidiasis. Medscape ; 2020. Available from: https://emedicine.medscape.com/article/1090632-overview.
80. NICE. Clinical Knowledge Summaries. Candida – skin; 2017. Available from: https://cks.nice.org.uk/topics/candida-skin/.
81. Taudorf EH, Jemec GBE, Hay RJ, Saunte DML. Cutaneous candidiasis - an evidence-based review of topical and systemic treatment to inform clinical practice. *J Eur Acad Dermatol Venereol*. 2019;33(10):1863–73. doi:10.1111/jdv.15782.
82. Richardson JP, Naglik JR. Special Issues: Mucosal fungal infections. *J Fungi*. 2018;4(2):43. doi:10.3390/jof4020043.
83. Kalra MG, Higgins KE, Kinney BS. Intertrigo and secondary skin infections. *Am Fam Physician*. 2014;89(7):569–73.
84. Aaron DA. Candidiasis (mucocutaneous). Dermatologic Disorders – MSD Manual; 2020. Available from: https://www.msdmanuals.com/en-gb/professional/dermatologic-disorders/fungal-skininfections/candidiasis-mucocutaneous.Accessed.
85. Gupta AK, Bluhm R, Summerbell R. Pityriasis versicolor: a review of pharmacological treatment options. *J Eur Acad Dermatol Venereol*. 2002;16(1):19–33. doi:10.1046/j.1468-3083.2002.00378.x.
86. Gupta AK, Kogan N, Batra R. Pityriasis versicolor: a review of pharmacological treatment options. *Exp Opin Pharmacother*. 2005;6(2):165–78. doi:10.1517/14656566.6.2.165.
87. Hu SW, Bigby M. Pityriasis versicolor: a systematic review of interventions. *Arch Dermatol*. 2010;146(10):1132–40. doi:10.1001/archdermatol.2010.259.
88. NICE. Pityriasis versicolor. NICE Clinical Knowledge Summary. NICE; 2022. [Accessed January 2022]. Available from: https://cks.nice.org.uk/topics/pityriasis-versicolor/.
89. Hasan MA, Fitzgerald SM, Saoudian M, and GK. Dermatology for the practicing allergist: tinea pedis and its complications. *Clin Molecular Allergy*. 2004;2(1):5. doi:10.1186/1476-7961-2-5.
90. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. *Cochrane Database Syst Rev*. 1434;(3):CD001434. doi:10.1002/14651858.CD001434.pub2.
91. Drake LA, Farmer ER, Goltz RW, Graham GF, Hordinsky MK, Lewis CW, et al. Guidelines of care for superficial mycotic infections of the skin: tinea corporis, tinea cruris, tinea faciei, tinea manuum, and tinea pedis. *J Am Acad Dermatol*. 1996;34(2 Pt 1):282–6. doi:10.1016/s0190-9622(96)80135-6.
92. Crawford F. Athlete's foot. *Clin Evidence*. 2009;p. 1712.
93. Canavan TN, Elewski BE. Identifying sings of tinea pedis: a key to understanding clinical variables. *J Drugs Dermatol*. 2015;14(10):42–7.
94. Thomas J, Jacobson GA, Narkowicz CK, Peterson GM, Burnet H, Sharpe C, et al. Toenail onychomycosis: an important global disease burden. *J Clin Pharm Ther*. 2010;35(5):497–519. doi:10.1111/j.1365-2710.2009.01107.x.
95. Westerberg DP, Voyack MJ. Onychomycosis: current trends in diagnosis and treatment. *Am Fam Phys*. 2013;88(11):762–70.
96. Gupta AK, Mays RR, Versteeg SG, Piraccini BM, Takwale A, Shemer A, et al. Global perspectives for the management of onychomycosis. *Int J Dermatol*. 2019;58(10):1118–29. doi:10.1111/ijd.14346.
97. Daggett C, Brodell RT, Daniel R, Jackson J. Onychomycosis in athletes. *Am J Clin Dermatol*. 2019;20(5):691–8. doi:10.1007/s40257-019-00448-4.
98. Erbagci Z. Topical Therapy for Dermatophytoses. *Am J Clin Dermatol*. 2004;5(6):375–84.
99. Schaller M, Friedrich M, Papini M, Pujol RM, Veraldi S. Topical antifungal-corticosteroid combination therapy for the treatment of superficial mycoses: conclusions of an expert panel meeting. *Mycoses*. 2016;59(6):365–73.
100. Wadhwa SL, Thomas J, Ainapure SS, Desai A. Candid-B cream in the treatment of candidiasis with inflammatory dermatoses–National Study Group. *J Indian Med Assoc*. 2000;98(9):580–2.
101. Hu W, Xia X, Ma Y, Xu AE. A Typical but Rare Case of Solitary Tinea Auricularis. *Infect Drug Resist*. 2023;16:239–41. doi:10.2147/IDR.S392159.
102. Sarangi G, Dash D, Chayani N, Patjoshi SK, Jena S. Bilateral Tinea Nigra of palm: A rare case report from Eastern India. *Indian J Med Microbiol*. 2014;32(1):86–8. doi:10.4103/0255-0857.124336.
103. Kastelan M, Massari LP, Brajac I. Tinea incognito due to Trichophyton rubrum–a case report. *Coll Antropol*. 2009;33(2):665–7.
104. Zisova LG, Dobrev HP, Tchernev G, Semkova K, Aliman AA, Chorlevae KI, et al. Tinea atypica: report of nine cases. *Wiener Medizinische Wochenschrift*. 2013;163(23-24):549–55.

Author biography

Shashank Bhargava, Assistant Professor

Siddhartha Chakrabarty, Consultant Physician and Skin Specialist

Rajan T Damodaran, Dermatologist

Prasanna Kumar Saikia, Senior Dermatologist

Manjunath Shenoy, Professor and HOD

Nikhil Bangale, Head Medical Affiars

Poonam Shah, Manager- Medical and Regulatory Affairs

Cite this article: Bhargava S, Chakrabarty S, Damodaran RT, Saikia PK, Shenoy M, Bangale N, Shah P. Rising burden of superficial fungal infections in India and the role of Clotrimazole for optimal management. *IP Indian J Clin Exp Dermatol* 2023;9(1):1-16.