REVIEW

DOI: 10.4274/jtad.galenos.2023.78942
J Turk Acad Dermatol 2023;17(4):83-86

# Current Approaches in the Treatment of Superficial Fungal Infections

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## ABSTRACT

Fungal infections are divided into two groups according to location: superficial and deep fungal infections. Superficial fungal infections (SFI) of the skin are mainly caused by dermatophytes from the genera "Microsporum, Trichophyton and Epidermophyton". Dermatophytoses are common skin diseases and affect 25% of the global population. The type of treatment firstly depends on the severity of the infection. The location of the disease also influences the type of treatment. Topical treatment is mostly enough for tinea corporis, pedis and inguinalis. Especially in immunocompromised patients and in the presence of tinea capitis, tinea unguium, oral treatment should be started. Besides, if the infestation is extensive and/or topical treatment is unsuccessful, oral treatment should again be considered. Oral terbinafine seems as the first step in the treatment of SFI because it has lower potential drug interactions, provides more mycological cure, and has fewer side effects compared to itraconazole treatment.

Keywords: Superficial fungal infections, Treatment, Antifungal

## Introduction

Fungal infections are divided into two groups according to location: superficial and deep fungal infections. Superficial fungal infections (SFI) of the skin are mainly caused by dermatophytes [1]. Dermatophytes have evolved over time to live on the keratin protein, which is resistant to many other microorganisms. For this reason, they cause diseases in structures such as skin, hair and nails, where keratin is the major protein. Dermatophytoses are common skin diseases and affect 25% of the global population [2]. It is also a fact that increased mobility of people around the world has been changing the epidemiological trends [3]. Therefore, recognizing diseases in this group is especially important for preventive medicine.

### Clinical Features

The naming is done by adding the word "tinea" placed at the beginning and the Latin word indicating "anatomical infection site". The main superficial dermatophyte infections of the skin are examined in detail below:

### Tinea Capitis

This is an infection of scalp and hair invaded by dematophytes and especially seen in children [4]. The most common agents are Microsporum and Trichophyton species. Clinical appearance in tinea capitis varies depending on the agent, hair involvement type, and the degree of the host's inflammatory response according to his/her immune status. Clinically, scaly alopecic patches, alopecic patches where the hair broken off from the skin level (are observed

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Received: 07.11.2023 Accepted: 09.11.2023

as black dots in the follicular opening), or seborrheic dermatitis-like lesions accompanied by dandruff on the scalp are observed. The severe form of tinea capitis, characterized by pustules and nodules, is called "kerion" [5]. If it is not treated early, it may cause cicatricial alopecia.

### Tinea Barba

It is a dermatophyte infection observed in the beard and mustache area in men. Generally, zoophilic dermatophytes are the causative agent. It can be transmitted from animals through direct contact with the diseased area or indirect contact with materials that have come into contact with the diseased area [6]. The use of contaminated shaving materials may cause human-to-human transmission. It can have three different clinical presentations; tinea corporis-like lesions, folliculitis-like form and kerion-like form.

### Tinea Corporis

Tinea corporis is the dermatophyte infection of integument other than feet, groin, hands and face. Tinea corporis observed in the hairless areas of the face is called "tinea facialis". It is transmitted directly by contact with the diseased lesion or indirectly through clothing that comes into contact with the diseased area. The lesion begins as an erythematous papule, and over time, its center fades and turns into a ring-shaped plaque. Squams, pustules or vesicles may be present on active edges [7].

### Tinea Inguinalis (Tinea Cruris)

It is a dermatophyte infection of the inguinal region and also known as "jock itch" and is more common in adult men. Typical lesion is in the form of an erythematous ring in the inguinal region, with a skin-colored center and edge activation. It can spread to the pubic area, perineal and perianal areas. Itching is a common symptom [7]. Infection to this area often occurs from the foot area, so patients should also be evaluated for the infection of feet.

### Tinea Pedis

Tinea pedis is a very common infection in society. The prevalence is higher in older population [8]. Wearing closed shoes for a long time, hyperhidrosis, working in a wet environment and common areas are predisposing factors for tinea pedis [9]. It has four clinical forms. The intertriginous subtype manifests itself with maceration, cracking and some scaling between the toes [10]. Hyperkeratotic tinea pedis is a chronic type and manifests itself with dense plantar scaling and erythema. It also involves the lateral surfaces of feet. There is usually no involvement on the dorsal surfaces. It is usually bilateral and can infect the hands [11]. The prevalence of vesiculobullous form of tinea pedis is relatively low and the similarity to dyshidrotic eczema makes them difficult to differentiate clinically. Acute ulcerative type is the rarest form of tinea pedis. The cause of the recurrences of tinea pedis may be the nail fungal infections which did not treated sufficiently. Therefore one should be careful to examine the nails also if the patient has tinea pedis.

### Tinea Unguium

Tinea unguium is also known as onychomycosis and it is the name given to dermatophytic fungal infection of the nails. Its prevalence is close to 50% in people over the age of 70 [12]. Approximately 80% of patients with tinea unguium also have dermatophyte infection in other body parts (often tinea pedis) [10]. The risk of developing tinea unguium increases in people with any underlying nail disease. Distal lateral subungual onychomycosis is the most seen fungal infection of the nails and in the clinical appearance there are yellowish or brownish discolorations, subungual hyperkeratosis and onycholysis [13]. In white superficial onychomycosis subtype, there are some white spots appearances on the surface of the nails. The least common form is proximal subungual onychomycosis [13]. It is frequently seen in immunocompromised cases. It is observed as whitish or white-brown areas on the proximal part of the nail. Onychomycosis has many imitations, so it is required that one should reach a mycological diagnosis before starting antifungal treatment to avoid unnecessary treatments.

### Tinea Incognito

Tinea incognito is named for a tinea infection that has been treated with a topical corticosteroid or some other immunosuppressive agents mistakenly [1]. The typical clinical appearance of superficial fungal infection disappear and diagnosis becomes difficult. Dermatophytic invasion of the dermis or subcutaneous tissue may cause deep-seated folliculitis (Majocchi granuloma) [7].

### Treatment Modalities

The severity and location of the infection determine the type of the treatment [1]. Topical treatment is mostly enough for tinea corporis, pedis and inguinalis. Especially in immunocompromised patients and in the presence of tinea capitis, tinea unguium, oral treatment should be started. Besides, if the infestation is extensive and/or topical treatment is unsuccessful, oral treatment should again be considered.

### Topical Treatment

The most effective and widely used topical antifungals are mainly allylamines, azoles and tolnaftate. Terbinafine 1% cream is recommended in the first step, because it is more effective. In resistant or unusable cases, other groups can be tried. It is recommended to use it one time a day for 2 weeks. But sometimes it should be used 2 times a day for until 4 weeks. Duration varies depending on the area of involvement. While up to 4 weeks may be required in areas with thick skin, such as hand or foot involvement,

2 weeks may be sufficient in other parts of the body with thinner skin [14,15].

### Combined Topical Treatments

SFIs affect 20-25% of the population and can present in many different ways. Therefore, treatment approaches should be planned specifically for each patient. Especially in cases with an inflammatory component, the patient's complaints are more pronounced and may need to be taken under control more quickly.

Keratin degradation during SFI creates the initial immune response, causing the release of proinflammatory cytokines. This causes typical inflammation symptoms such as itching, erythema, swelling, and burning at the infection site. These symptoms are not only cause discomfort to the patient and impair compliance with treatment, but may also disrupt the integrity of the skin, causing the infection to spread and making the environment suitable for bacterial contamination.

Topical steroids, which are used in many skin diseases due to their anti-inflammatory, immunosuppressive, antimitotic and vasoconstrictive effects, constitute a good treatment option when used in combination with antifungals in SFIs with an inflammatory component. The combined use of corticosteroids (hydrocortisone, diflucortolone valerate, mometasone furoate) and antifungals (terbinafine, isoconazole nitrate) is increasingly recommended in international guidelines. In this way, rapid relief can be achieved in inflamed lesions.

Combination treatments are usually used in the first 1-2 weeks of treatment and then treatment is continued with a topical antifungal. In follow-up treatment, it is recommended to choose the antifungal in combination to prevent the development of resistance.

In summary, the addition of a topical steroid to a topical antifungal agent reduces inflammatory symptoms and the risk of bacterial superinfection, increases patient compliance with treatment, and increases the effect of the antifungal agent [16,17,18,19].

### Oral Treatment

The first-line treatment agent for adults is terbinafine, and the treatment dose is 250 mg terbinafine once daily. Terbinafine works by inhibiting fungal ergosterol synthesis via squalene epoxidase [20]. Food and Drug Administration (FDA) approved terbinafine as the alternative to griseofulvin, which is not available in Turkey, for tinea capitis infection, which is very common in children [6]. 62.5 mg/day is used for children under 20 kg, and 125 mg/day is used for children between 20-40 kg [6]. Terbinafine is generally a safe drug and there is usually no need any blood monitoring [21]. The FDA removed its recommendation for monitoring liver function tests (LFT) from terbinafine, following long-term safety data [22]. Pregnancy category is B1. The location of the dermatophyte infection determines the duration of oral treatment: four weeks for the scalp, six weeks for fingernails and 12 weeks for toenails (especially in the elderly, longer treatment is required due to reduced blood flow in the area). A Cochrane review by Kreijkamp-Kaspers et al. [23] in 2017 determined that in the clinical and mycological treatment of tinea unguium, terbinafine was superior to both itraconazole and fluconazole. Terbinafine is metabolized by cytochrome P450 enzymes. By inhibiting CYP2D6, the cytochrome P450 enzyme responsible for the metabolism of tricyclic antidepressants, beta-blockers and SSRIs, it may increase blood levels of these drugs [24]. Adverse effects reported with oral terbinafine include the central nervous system (e.g., headache, difficulty concentrating), the gastrointestinal tract (e.g., diarrhea, dyspepsia, nausea) and effects on the cutaneous system (e.g., erythema, pruritus) [20].

In adults, itraconazole and fluconazole are recommended as second-line treatments. Itraconazole inhibits C-14a-demethylation of lanosterol and prevents fungal ergosterol synthesis by disrupting fungal cell membranes [20]. Both intermittent and continuous treatments with itraconazole have similar efficacy. Intermittent itraconazole treatment means 200 mg twice a day for one week a month. This type of treatment should be used for two months for the fingernails and three months for the toenails. Continuous itraconazole treatment requires continuous use of 200 mg daily. The duration of this type of treatment is six weeks for fingernails and 12 weeks for toenails [6,21,22,23,24,25]. Regular LFT monitoring every four to six weeks (depends on the patient's background) are recommended when initiating oral itraconazole therapy. Pregnancy category is C. Itraconazole undergoes hepatic metabolism mainly by CYP3A4, forming more than 30 metabolites, including hydroxy-itraconazole with antifungal activity. All resulting metabolites are CYP3A4 inhibitors with a higher affinity for CYP3A4 than the parent drug. Increased itraconazole exposure may cause cardiac toxicity through decreased CYP3A4 activity [26]. Contraindicated in patients with congestive heart failure due to increased risk of negative inotropic effects [27]. Coadministration of cisapride, pimozide, and quinidine is contraindicated due to the risk of prolonging the QT interval and increasing the risk of arrhythmia [24]. Also there are some side effects on central nervous system (e.g., headache, dizziness), gastrointestinal system (e.g., diarrhea, dyspepsia, abdominal pain) and skin system [20].

Fluconazole acts by inhibiting C-14a-demethylation of lanosterol and has the potential to inhibit human host cytochromes (e.g., CYP2C9 and CYP2C19) [20]. Fluconazole, in 150-300 mg per week, must be used for longer durations compared to terbinafin and itraconazole for the treatment of onycomycosis. It is for 12-24 weeks for fingernails and for 24-52 weeks for toenails [6,21,22,23,24,25]. LFT and full blood tests are required before starting fluconazole treatment. Fluconazole inhibits both CYP3A4 and CYP2C9 and

requires close monitoring when prescribed with drugs metabolized by these enzymes. Concomitant use of fluconazole with terfenadine or cisapridine is contraindicated [28,29]. Pregnancy category is D. Fluconazole may have similar side effects to terbinafine and itraconazole, including headache, nausea, and skin rash [20].

## Conclusion

Oral terbinafine is the first step in the treatment of SFI because it has lower potential drug interactions, provides more mycological cure, and has fewer side effects compared to itraconazole treatment. In cases where it cannot be used, other agents may be preferred.

### Ethics

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Concept: B.D., N.D.A., Z.K., Data Collection or Processing: B.D., N.D.A., Z.K., Analysis or Interpretation: B.D., N.D.A., Literature Search: B.D., N.D.A., Z.K., Writing: B.D., N.D.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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