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Topical and systemic antifungals in dermatology practice

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ABSTRACT
Introduction: Dermatophytosis is generally defined as an infection of the hair, nails, or glabrous skin. These infections are caused by the keratinophilic fungi Trichophyton spp., Microsporum spp., and Epidermophyton, which have been recovered from both symptomatic and asymptomatic individuals. Although dermatophytosis is generally not a life-threatening condition, these types of infections are among the most common infections worldwide, and their incidence has continued to increase consistently in recent years.

Area covered: This article provides an overview of the general characteristics of dermatophytes, including their taxonomy and epidemiology, as well as the different clinical forms and laboratory diagnostics of dermatophytosis. We further classify the topical and systemic antifungal compounds currently used to treat dermatophyte infections.

Expert commentary: Antifungal therapy is a central component of patient management for dermatophytosis, and depending on the strategy chosen, topical and/or systemic drugs can be used. However, for effective treatment, it is important to correctly determine the causal agents at the species level, which will enable administration of suitable therapeutics and initiation of appropriate management strategies.

1. Introduction

Dermatophyte fungi first emerged following World War II, not only in Europe but also all over the world [1,2]. An aging population, close human-to-human or animal-to-human contact, sport and tourism activities, sharing of objects (socks, shoes, slippers, combs, pillows, etc.), communal living, or inhabiting an endemic region are all considered potential risk factors for dermatophytic infection [3,4].

The anthropophilic species Trichophyton rubrum is the most common dermatophytic fungus worldwide, and its eradication has thus far posed an intractable challenge to society [5,6]. Such dermatophyte fungi, particularly anthropophiles (T. rubrum, Trichophyton tonsurans, Trichophyton violaceum, Epidermophyton floccosum, and Microsporum audouini), may also cause epidemics owing to close contact between infected individuals and society [7]. Although several dermatophyte species are endemic to certain countries (e.g. (i) Trichophyton concentricum is endemic in remote and humid tropical areas in the Southwest Pacific, Southeast Asia, Central and South America and (ii) Trichophyton megninii is endemic in Portugal, Corsica, and Sardinia) [8], human infection rates do not vary with respect to education status or ethnicity. Therefore, dermatophytes and dermatophytoses remain an important public health issue, and all strata of society should be educated as to how humans generally encounter these fungi and how to prevent infection [9].

Of note, a variety of oral and topical antifungal agents are available for the treatment of superficial fungal infections caused by dermatophytes [10,11]. However, for effective treatment, it is important to correctly determine the causal agents at the species level, which will enable administration of suitable therapeutics and initiation of appropriate management strategies [5,6].

In this paper, we present a brief overview of our current understanding of the classification of dermatophytosis based on clinical findings and patterns of dermatophytic infections, as well as contemporary methods of their management with conventional and novel antifungal compounds.

2. Taxonomy

Dermatophytes are ascomycetes with septate hyphae, and are most closely related to the pathogenic fungus Coccidioides immitis within the order Onygenales, whose members share the morphological feature of septate hyphae [3,4].

Dermatophytes are categorized into three asexual genera (anamorph: Trichophyton, Epidermophyton and Microsporum,
and an associated sexual state (teleomorphs), was previously classified in the genus *Arthroderma* [3,4]. There are at least 40 species of dermatophytes that are capable of infecting humans.

Dermatophytes can also be classified into three distinct groups according to their ecological characteristics: (i) anthropophilic (human-specific), (ii) zoophilic (animal-specific), and (iii) geophilic (soil-specific). Notably, all of these groups are able to infect humans, although anthropophilic dermatophytes (e.g. *T. rubrum*) are associated with long-term chronic, but limited disease and tissue destruction. In contrast, zoophilic species (*M. canis*) can cause acute and severe disease in humans. The effects of the geophilic species (e.g. *M. gypseum*) are intermediate between those of acute geophiles and chronic anthropophiles [2,12].

3. Epidemiology

It is generally considered that dermatophytic infections are the most common types of human fungal infections worldwide. Tinea pedis, commonly known as Athlete’s foot, is particularly common in the developed world [9], whereas tinea capitis is relatively more prevalent in developing countries [13]. It is estimated that dermatophytooses are responsible for at least half a billion dollars in healthcare costs [14]. Furthermore, the dermatophyte flora varies among countries or in among different regions within a country [1]. Thus, the flora of dermatophytes present in a given area can change over time, indicating the importance of close and continuous monitoring within a region [7].

4. Clinical manifestations

Dermatophytes are able to use keratin as a sole nutrient source [15,16]. They invade and grow on the hair, nails, and skin, but do not infect mucosal surfaces [12]. The transmission of dermatophytooses may occur by direct contact with an infected host or by contact with contaminated objects and environments.

Clinically, dermatophytic infections are designated as different forms of tinea (also known as ‘ringworm’) according to the body site involved: the scalp (tinea capitis), beard and mustache area (tinea barbae), face (tinea faciei), hand (tinea manuum), groin and skin folds (tinea cruris), other skin regions (tinea corporis), feet (tinea pedis), and nails (tinea unguium) [17]. In addition to these symptomatic infections, the carrier state or asymptomatic carriage of dermatophytes has been well-described in the literature, and these fungi have been widely recovered from a healthy appearing scalp, nails, and skin [18,19].

Dermatophytic infections can also lead to various complications, including immune dermal (id) reactions (see below), bacterial superinfection, Majocchi’s granulomas, tinea incognito, lymphangitis, and cellulitis, and can spread to other sites. Furthermore, dermatophytic infections may induce a T-helper type 2 response that can aggravate atopic dermatitis, chronic rhinitis, and asthma [9,20].

4.1. Tinea capitis

Tinea capitis is one of the most common causes of pediatric dermatophyte infections of the scalp, with a propensity for attacking the hair shafts and follicles. Tinea capitis predominantly affects preadolescent children, accounting for up to 92.5% of all cases of dermatophytosis in children younger than 10 years, but is infrequent in infants aged less than 1 year [21]. The disease is rare in adults, although it is occasionally found in elderly patients [22]. Because of its clinically atypical manifestations in adults, other inflammatory disorders are often initially considered in place of dermatophytosis, requiring anti-inflammatory topical corticosteroid therapy. Tinea capitis usually presents in six different clinical forms: (i) gray patch, (ii) moth-eaten, (iii) black-dot, (iv) diffuse scale, (v) pustular, (vi) kerion, and (vii) favus [17]. Currently, the most prevalent causes of tinea capitis, a fungal infection of the scalp, are *Trichophyton tonsurans* (in North America, northern Europe, and Japan) [23,24] and *Microsporum canis* (worldwide) [25,26].

4.2. Tinea corporis

Tinea corporis is a dermatophyte infection of the skin of the trunk and extremities, except for the feet, palms, scalp, and groin (Figure 1c). These infections may be transmitted directly from humans (including *T. rubrum*, *T. tonsurans*, *E. floccosum*, *T. concentricum*, anthropophilic *T. interdigitale*), animals (*M. canis*, zoophilic *T. interdigitale*, *T. mentagrophytes*, and *T. verrucosum*), soil (*M. gypseum*), or via autoinoculation from reservoirs such as tinea pedis, tinea cruris, or tinea capitis [17]. Overall, the anthropophilic species *T. rubrum*, the zoophilic species *M. canis* and *T. mentagrophytes*, and the geophilic species *M. gypseum* are most frequently reported as the causal agents of tinea corporis.

In patients with tinea capitis, infections may spread to the neck and upper trunk, whereas the buttocks and lower trunk are generally affected in patients with tinea cruris. Clinically, the classic presentation is single or multiple annular lesions with scales across the entire erythematous border. The lesions may be serpiginous or annular (ringworm-like), and can also be vesicular or pustular. Zoophilic or geophilic agents may cause follicular micropustules and show vellus hair involvement, which leads to resistance to topical antifungal treatment. Given that potassium hydroxide examination of the scales may be negative, vellus hair samples should also be taken for direct microscopic examination for an accurate differential diagnosis [27].

If tinea corporis is misdiagnosed and mistakenly treated with topical corticosteroids, inflammatory dermal nodules or plaques with follicular orifices oozing with pus may develop. These inflammatory lesions are similar to a kerion of the scalp or beard (tinea incognito). In particular, for patients with tinea pedis or tinea unguium, tinea incognito can be ruled out as a potential diagnosis in cases with resistant eczema-like patches. In addition, in patients with tinea corporis caused by zoophilic organisms, kerion-like inflammatory plaques or nodules may develop [20].

4.3. Tinea imbricata

Tinea imbricata is a chronic superficial mycosis caused by the anthropophilic dermatophyte *T. concentricum* [28]. Tinea imbricata is characterized by widespread, annular, erythema gyratum repens-like multiple concentric, polycyclic, scaly lesions with minimal inflammation [29], and is endemic to
three geographical areas: southwest Pacific, Southeast Asia, and Central and South America. Tinea imbricata in travelers returning from endemic areas is exceptionally rare. Tinea imbricate can be successfully treated with griseofulvin and terbinafine cream. Tinea imbricata-like concentric scaly rings may also develop due to T. interdigitale and T. tonsurans infections. The latter form is very rare and is known as tinea indecisiva.

4.4. Tinea faciei

Tinea faciei is a dermatophytic infection limited to the face, except for the mustache and beard areas of the adult male. Accordingly, some authors have also referred to tinea faciei as ‘tinea corporis located on the face and hand’. Tinea faciei may develop directly from an external source (e.g. due to infections of the T. mentagrophytes species complex via an infected pet mouse), or autoinoculation from reservoirs such as tinea pedis, tinea cruris, or tinea capitis (T. rubrum and T. concentricum). In close-contact sports such as wrestling, T. tonsurans has been reported to cause outbreaks of tinea faciei due to (i) human-to-human contact, (ii) auto-inoculation from an anatomical site, or (iii) from the mat. The clinical features of tinea faciei vary considerably. However, it is generally characterized by annular or circinate erythematous, centrifugally growing, discretely scaly patches or plaques. Simple papular lesions and erythematous patches of a few vesicles or pustules may also be found. The most common complaints of patients are itching, burning, and exacerbation after sun exposure. Dermatophytes can cause red face syndrome (Figure 1b). For this reason, tinea faciei may be confused with other causes of red face syndrome such as lupus erythematosus, psoriasis, rosacea, seborrheic dermatitis, and polymorphic light eruption.

4.5. Tinea manuum

Tinea manuum is a dermatophyte infection of the hand. Although any species of dermatophyte may infect the skin of the hand, this is nonetheless a rare infection site for these fungi. The most common pathogen causing tinea manuum is T. rubrum. Unlike eczema and psoriasis, tinea manuum shows unilateral involvement in about half of all cases. However, unilateral tinea manuum may be accompanied by bilateral tinea pedis (see below). T. rubrum is usually the causal pathogen of this two-feet/one-hand syndrome, but occasionally T. interdigitale is involved. It is usually spread from lesions of tinea pedis or onychomycosis as a result of scratching. Possible predisposing factors are manual work, hyperhidrosis, existing inflammatory conditions, poor peripheral circulation, palmar keratoderma, and frequent use of alkaline soaps. Clinically, dermatophyte infections of the dorsal surface of the hand are similar to tinea corporis. Infection of the palmar skin may exhibit different clinical manifestations such as palmar hyperkeratosis, exfoliating, vesicular and erythematous patches, and follicular scaly papules. Palmar hyperkeratotic plaque is the most common form, and is unilateral in about half of all cases. Involvement of the flexural creases is a characteristic sign. Other clinical variants include crescentic exfoliating scales, circumscribed vesicular patches, and discrete red, papular, and follicular scaly patches. Vesicles may show an annular, segmental, or dyshidrosiform pattern. Furthermore, palmar bullous lesions have also been reported in patients with tinea manuum due to zoophilic T. verrucosum and T. rubrum infection. Tinea manuum can also mimic cellulitis and lymphangitis. If it is untreated, it spreads to the dorsal surface of the hand, and annular erythematous patches or plaques with scales may be seen.
4.6. Tinea cruris

Tinea cruris, also called as tinea inguinalis, is a superficial fungal infection of the groin and adjacent skin (Figure 1d). Although *T. rubrum* is a common causal pathogen, anthropophilic *T. interdigitale* and *E. floccosum* and rarely zoophilic *Microsporum canis* have been isolated from patients with tinea cruris [33]. Zoophilic dermatophytes, especially *T. mentagrophytes* and *T. verrucosum*, have also been reported in these cases.

Possible predisposing factors are having recently visited a tropical climate, wearing tight-fitting clothes, sharing clothing with others, sport activity, diabetes mellitus, and obesity. Men are more frequently affected than women, and tinea cruris usually develops between 18 and 60 years of age. However, children and babies may also be affected [39]. It is usually spread from tinea pedis or onychomycosis. In addition, dermatophytes can infect the skin via contaminated objects and from the floors of bathrooms, showers, saunas, gymnasiums, or hotel bedrooms. In the early stages, lesions begin as erythematous plaques with sharp margins on the inside of the proximal thigh, and then the lesions move from the groin down to the thighs. In men, the left side is more frequently affected since the skin on this side is usually in more intimate contact with the scrotum. When left untreated, the lesions may spread from the thigh to the scrotum, penis, gluteal folds, and mons pubis. Furthermore, tinea cruris may also spread to other folds, especially to the axillae, inframammary folds, and umbilicus. The inframammary folds and axillae may be the primary region of infection [17].

The severity of scaling observed is variable. If scaling is severe, it may mask the erythematous reaction. If inflammation is severe, it can mimic other inflammatory diseases such as eczema, psoriasis, seborrheic dermatitis, invers psoriasis, Hailey–Hailey diseases, and intertrigo [33]. For this reason, tinea cruris is often incorrectly treated with topical corticosteroid therapy, which leads to incognita [20]. Vesicles and bullae are very rare. Cases of tinea cruris due to *T. rubrum* are often associated with tinea pedis and generally manifest as chronic lesions. Dermal nodules are commonly found in these lesions, and extension of the infection from the groin to the lower back and the abdomen is common. When carefully examined, a few pustules may be determined. Satellite lesions may also be seen, which are sometimes fused with the primary lesion. The most important subjective symptom is mild or severe itching. Scratching may lead to lichenification and autoinoculation of new sites either near or distant from the primary lesions. The inflammatory lesions can cause difficulty in walking because of itching and burning. Secondary bacterial infections may develop in areas affected by tinea cruris, sometimes causing painful lymphadenopathy [17,33].

4.7. Tinea pedis

Tinea pedis is a common fungal infection of the foot and often serves as a reservoir for dermatophyte infections of other anatomical sites [40,41]. Its incidence is higher in hot and humid climates, and is associated with sporting activities and hyperhidrosis [42]. Tinea pedis usually presents in four different clinical forms: (i) interdigital, (ii) inflammatory (vesiculobullous), (iii) chronic hyperkeratotic (moccasin), and (iv) ulcerative tinea pedis.

In addition to these clinical forms, verrucous and pustular forms have also been reported [43,44]. Asymptomatic infections (occult tinea pedis) are also common, with a prevalence of 36–88%, particularly among athletes. *T. interdigitale* causes the majority of the occult cases of tinea pedis [45–47], and damp foot conditions may lead to aggravated symptoms due to coinfections with bacteria [48].

4.8. Tinea unguium

Dermatophytic onychomycosis, also known as tinea unguium, refers to a fungal infection of the fingernails and toenails, which is the most common nail disease in adults. It develops due to dermatophytes, yeasts, or molds, or a combination of two (or more) fungi from all three groups. Tinea unguium represents an onychomycosis that is specifically caused by dermatophytes, and is the most common form, with the majority of cases caused by *T. rubrum* (70%) and anthropophilic *T. interdigitale* (20%) [49]. The toenails tend to be affected more than the fingernails because of their slower growth, reduced blood supply, and frequent confinement in dark, moist environments. Predisposing factors are distorted nails, a history of trauma, genetic predisposition, hyperhidrosis, and psoriasis [50]. Onychomycosis usually presents in seven different clinical forms described below.

4.8.1. Distal lateral subungual onychomycosis (DLSO)

Fungal nail infections begin at the lateral or distal undersurface of the nail plate and then spread to the nail plate and bed. The main clinical features are distal and lateral subungual hyperkeratosis, onycholysis, and discoloration. Onycholysis is occasionally the only clinical symptoms [51]. Discoloration is usually white or yellowish, but brown to black longitudinal melanonychia is more common in tinea unguium caused by dermatophytes such as the nongranular pigment-producing species *T. rubrum* var. *nigricans*. When untreated, infection can progress proximally, causing linear channels or ‘spikes’ [52].

4.8.2. Proximal subungual onychomycosis (PSO)

In PSO, the pathogens are spread from the proximal nail folds. PSO is quite rare and occurs more frequently in immunosuppressed patients, especially those with HIV/AIDS [53].

4.8.3. Superficial onychomycosis

This form may present as a range of dyschromias, and is mostly caused by *T. rubrum*, followed by *T. interdigitale*. According to the pathogen involved, the discoloration may be white, black, or brown [51,52].

4.8.4. Endonyx onychomycosis

In this variant of onychomycosis, the nails show white discoloration. Characteristically, there is no inflammation of the nail bed or subungual hyperkeratosis. This form of onychomycosis is usually caused by *T. soudanense*. However, other organisms such as *T. violaceum* have also been isolated in these cases [54].
4.8.5. Mixed-pattern onychomycosis
Combinations of two or more patterns of onychomycosis may be found. The most common combinations are PSO and SO or DLSO and SO [55].

4.8.6. Total dystrophic onychomycosis
In total dystrophic onychomycosis, the dermatophytes cause prominent acanthosis and hyperkeratosis in the nail bed epithelium [52]. Clinically, it is observed as subungual hyperkeratosis. The most characteristic sign of this onychomycosis is yellow streaks medially or laterally that frequently reach the nail matrix (Figure 1f) [17].

4.8.7. Secondary onychomycosis
Tinea unguium may develop in a nail affected with another nail condition such as traumatic nail dystrophy or psoriasis. Appearance of the nail varies depending on the type of primary disease [52].

4.9. Majocchi’s granuloma
Long-standing tinea corporis can progressively disseminate into the subcutaneous tissues and cause a perifollicular granulomatous reaction called Majocchi’s granuloma, which is due to a complication of the long-term use of potent topical corticosteroids or chemotherapeutic agents, or systemic immunosuppression [56,57]. Clinically, Majocchi’s granuloma is characterized by inflammatory nodular, papular, or pustular lesions that generally develop on the limbs. The discrete or grouped papules and nodules can typically be found on the more active borders of the erythematous plaques or alone; additionally, in some rare cases, they can be keloidal or verrucous in nature. Unlike kerions, Majocchi’s granuloma lesions do not suppurate until late in their course, unless secondary impetigo occurs. Pustules and crust are observed on the erythematous plaques. Red-purple, or occasionally brown, papular and nodular lesions may resolve spontaneously without cutaneous scarring; however, lesions may result in eventual atrophic and hypertrophic scar formation [56–58]. Features of cellulitis such as indurated plaques without papules, nodules, or pustules have been observed in 5.4% of all cases. Although subjective complaints are usually not reported, pruritus (10.9%) and slight tenderness following the application of pressure (9.5%) have been observed. Vulvar swelling was reported in one case [59]. Majocchi’s granuloma may have a variable clinical presentation such as abscess formation, especially if occurring in an immunodeficient host [60,61]. Inflammatory subcutaneous masses with grains (mycetoma) have also been reported, although very rarely [62].

4.10. Immune dermal (id) reaction
An id reaction refers to a distant skin reaction caused by circulating antibodies or activated T lymphocytes directed against microbial antigens [62,63], which may complicate allergies and asthma and contribute to refractory atopic disease [64]. As a rule, diagnosis of an id reaction relies on negative testing for fungal pathogens in direct smears or histopathologic preparations, and secondary reactions should resolve spontaneously after treatment of the primary dermatophyte infection. Patients with an id reaction tend to show a positive skin reaction to Trichophyton or Epidermophyton [65].

The incidences of dermatophyte id reactions (dermatophytid) with tinea capitis, tinea corporis, and tinea pedis have been reported to be 0.2%, 5%, and 17%, respectively [66,67]. The incidence of id reactions is generally similar in adults and children (4.6% and 4.2%, respectively), and varies according to the fungal pathogen species involved. The frequencies of dermatophytid due to members of the T. mentagrophytes complex, T. rubrum, and E. floccosum have been determined to be 34.6%, 5.5%, and 16.7% of cases with dermatophyte infections, respectively [67].

Id reactions have been reported in different forms such as vesicular, morbilliform, and scarlatiniform, and present as a lichenoid rash, urticaria, anaphylaxis, erythema multiforme, erythema nodosum, and erythema annulare centrifugum [68]. Rarely, systemic symptoms such as high fever, anorexia, generalized lymphadenopathy, splenomegaly, and hematologic alterations (leukocytosis and lymphocytosis) may develop [69].

5. Laboratory diagnosis
The information reviewed above clearly demonstrates the wide variety of the clinical manifestations of dermatophyte infections. In addition, misdiagnosis is possible with only a clinical examination, given that these manifestations can mimic those of various other infectious or inflammatory diseases [38]. For this reason, a fungal culture, microscopic examination of skin scrapings (Figure 2), or culture-independent molecular techniques should be conducted to obtain a definitive diagnosis of dermatophytic infections [70,71]. Conditions of sampling, transporting, storage, and handling of specimens are very important for obtaining a correct diagnosis [72].

6. Treatment of dermatophyte infections
In general, the most important considerations in the treatment of dermatophyte infections, including asymptomatic dermatophyte infections such as tinea pedis or onychomycosis, are to eliminate any aggravating factors; improve hygiene of the skin, hair, and nails; and avoid prolonged humid environments. Specifically, patients with tinea corporis and tinea capitis should be closely examined for possible infections or as carriers of an animal source such as those found on pets, in order to ensure that the optimal therapeutic measures are taken [73]. Importantly, topical and systemic antifungal therapy remains a central component of patient management for dermatophytosis.

6.1. Systemic antifungals
Systemic antifungal agents can be grouped into four classes based on their site of action in pathogenic fungi, and include the polyenes, azoles, echinocandins, and nucleoside analogs.
6.1. Polyenes
Polyenes constitute the oldest class of systemic antifungal drugs. More than 200 polyene macrolides have antifungal activity, and most are produced by the soil actinomycete *Streptomyces*. Polyenes bind to ergosterol, the main component of fungal membrane sterols, and form large pores that disrupt cell function [74,75]. This interaction results in the formation of transmembrane pores that disrupt cell permeability, resulting in rapid cellular damage or death [76]. The polyenes currently available for the treatment of systemic fungal infections are amphotericin B and nystatin.

6.1.2. Azoles
Azoles are cyclic organic molecules characterized by a core 5-member azole ring, which can be divided into two groups based on the number of nitrogen atoms on the azole ring: the imidazoles and triazoles with two and three nitrogen atoms within the azole ring, respectively [77]. The azoles inhibit the synthesis of ergosterol from lanosterol in the fungal cell membrane by the binding of the free nitrogen atom of the azole ring to the iron atom of the heme group of a fungal enzyme [78,79]. Their target enzyme is the cytochrome P450 (CYP)-dependent 14-α-demethylase (CYP51 or Erg11p), which catalyzes the targeted synthetic reaction. The inhibition depletes ergosterol, and methylated sterols accumulate in the cell membrane and either inhibit the growth or induce the death of fungal cells, depending on the species and antifungal compound involved.

Overall, the azoles are the most widely used class of antifungal drugs [80]. One imidazole (ketoconazole) [77], and five triazole compounds (fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole) have been clinically approved and are currently widely used for the prevention and treatment of several life-threatening fungal diseases [81,82]. The triazoles have different affinities for the CYP-dependent 14-α-demethylase, which in turn results in variability of the susceptibilities to fungal infection, side effects, and drug–drug interactions [83].

6.1.3. Echinocandins
The echinocandins are the only class of antifungal agents that directly target the fungal cell wall [84,85]. They are semisynthetic amphiphilic lipopeptides formed during the fermentation of some fungi such as *Zalerion arboricola* or *Aspergillus nidulans* var. *echinulatus* [86]. The echinocandins inhibit β-1,3-D-glucan synthase, which catalyzes the biosynthesis of glucan, a key component of the fungal cell wall [87]. Of note, mammalian cells do not contain this polysaccharide target (1, 3-β-D-glucan), and therefore direct human cell toxicity is minimal [88]. The echinocandins that are currently approved for clinical use include caspofungin, micafungin, and anidulafungin.

6.1.4. Nucleoside analogs
Flucytosine (5-fluorocytosine or 5-FC) is the only systemic antifungal agent belonging to the class of nucleoside analogs. It was the first agent used for the treatment of invasive mycoses in 1968 [89]. Flucytosine is the fluorinated analog of cytosine and was discovered in 1957 as an analog of the cytostatic chemotherapeutic agent 5-fluorouracil (5-FU), which is used for antitumor therapy [90]. After it penetrates the cell wall, which is controlled by the enzyme cytosine permease, 5-FC is converted to 5-FU by the enzyme cytosine deaminase and then is further converted to 5-fluorouridine [91]. After three phosphorylation steps, it is incorporated into RNA instead of uracil, which results in the blockade of protein synthesis. This pathway leads to reduced DNA synthesis because of a reduction in the available nucleotide pool [92].
6.2. Recommended systemic antifungals for treating dermatophytosis

Systemic antifungal agents currently recommended for the treatment of dermatophytosis are classified in Table 1.

6.2.1. Griseofulvin

Griseofulvin is a metabolite of Penicillium griseofulvum and Penicillium janczewski that inhibits cell wall synthesis. It binds to tubulin and disrupts both the alpha and beta subunits by inducing conformational changes via impaired processing of newly synthesized cell wall constituents at the growing tips of hyphae [93]. Griseofulvin mainly concentrates in keratinocytes; therefore, it is only used for noninvasive dermatophyte infections [94].

Overall, all of the dermatophytes (Microsporum spp., Trichophyton spp., and Epidermophyton) are susceptible to griseofulvin. Since the late 1950s, griseofulvin has been the gold standard for the systemic therapy of tinea capitis [95]. However, the advent of newer antifungals that exhibit more favorable pharmacokinetic and toxicity profiles has largely relegated griseofulvin to a second-line agent against dermatophytes. The main disadvantage of griseofulvin is the long duration of treatment required (6–12 weeks or longer), which may lead to reduced compliance [96]. Another challenge is the high expense of griseofulvin because of the large quantity of drug required for a cure. Moreover, the efficacy of griseofulvin has decreased in recent years owing to the decreased susceptibility of the infective fungi due to changes in epidemiology and genetic mutations [97], and now requires larger doses and longer treatment durations.

6.2.2. Terbinafine

Terbinafine is an allylamine antifungal agent that has largely replaced the use of griseofulvin for the treatment of dermatophytic infections and onychomycosis [98]. Its antifungal activity is mediated via the noncompetitive inhibition of squalene epoxidase (SE), an enzyme that acts on its substrate squalene, an early intermediate in the fungal ergosterol biosynthesis pathway [99,100]. Notably, terbinafine inhibits the enzymatic activity of fungal SE at a very low concentration (noncompetitive inhibition) than that required to inhibit the mammalian counterpart (4000-fold higher concentration needed; competitive inhibition) [101].

This drug is well absorbed from the gastrointestinal tract and then rapidly diffuses from the bloodstream into several skin tissue compartments, including the dermis and epidermis. In addition, terbinafine can remain in the stratum corneum and nails for several months after stopping the medication, even after very short-term therapy [102]. Moreover, terbinafine is highly lipophilic, and is highly (>99%) plasma protein-bound in humans, which impairs its distribution to the brain and cerebrospinal fluid, and leads to its high concentration in the hair follicles, skin, nail plate, and adipose tissue [102].

Several studies have reported the excellent activity of terbinafine against dermatophytes in vitro, including infections of T. rubrum, T. mentagrophytes, and E. floccosum, and ringworm infections, including tinea pedis, tinea cruris, tinea corporis, and tinea unguium [99]. Terbinafine has been widely reported to elicit a strong clinical response against Trichophyton species, with the cure rate reaching >80% [103,104].

Terbinafine has demonstrated a good toxicity profile at the recommended dosage. Most of the reported side effects are generally limited to gastrointestinal upset and, rarely, hepatotoxicity [105,106].

6.2.3. Fluconazole

Fluconazole is a first-generation triazole drug that exhibits antifungal activity against most of the common clinical isolates of Candida and Cryptococcus spp. and the endemic molds Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum, and Paracoccidioides brasiliensis. However, fluconazole lacks efficacy against molds such as Aspergillus spp. [107] It is a water-soluble compound with 10% protein binding, which distributes well throughout the body, leading to better efficacy in vivo [108]. Fluconazole has been recommended for treating tinea capitis. Previous studies have shown that high doses of fluconazole (4–8 mg/kg per week) applied for long durations (12–16 weeks) are required regardless of the fungus type [95].

6.2.4. Itraconazole

Itraconazole is another first-generation drug that is structurally similar to ketoconazole. It is a high-molecular weight, highly hydrophobic, highly protein-bound (>99%), and water-insoluble compound, which exhibits a broader range of antifungal activity than fluconazole. Itraconazole remains the preferred azole for use in human patients to treat non-life-threatening systemic mycoses that do not involve the central nervous system [80]. Itraconazole is effective against both Microsporum and Trichophyton species and offers an alternative to griseofulvin for the treatment of kerion and noninflammatory tinea capitis [109].

6.2.5. Other systemic antifungals as effective treatment alternatives

To date, no clinical study has been conducted using polyenes, posaconazole, voriconazole, isavuconazole, and/or echinocandins for the treatment of tinea infections. However, several in vitro studies reported the susceptibility profiles of clinical dermatophytes isolated from tinea infections over a wide geographical range to newer antifungals. Overall, for all tested strains, posaconazole, terbinafine, voriconazole, amphotericin B, itraconazole, and caspofungin showed low minimum inhibitory concentrations, whereas flucytosine did not exert notable inhibitory effects [103,104,110–115].

6.3. Topical antifungals

A wide variety of topical agents belonging to different classes of antifungals are available as creams, ointments, gels, lotions, powders, shampoos, and other formulations. Table 2 provides a list of the currently available topical antymycotic substances used in routine clinical practice that are highly effective against dermatophytes. Of note,
Table 1. Recommended indications of systemic antifungal drugs against dermatophyte infections.

<table>
<thead>
<tr>
<th>Class of antifungals</th>
<th>Name</th>
<th>Year approved by the US FDA</th>
<th>Brand name</th>
<th>Route of administration</th>
<th>Dosage formulation</th>
<th>Indication</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyens</td>
<td>Amphotericin B</td>
<td>1957</td>
<td>Fungizone</td>
<td>IV, PO</td>
<td>IV formulation (50 mg vial), suspension (100-mg)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B-lipid complex</td>
<td>1995</td>
<td>ABLC</td>
<td>IV</td>
<td>IV formulation (100 mg vial)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B colloidal dispersion</td>
<td>1996</td>
<td>ABCD, Amphotil, Amphotec</td>
<td>IV</td>
<td>IV formulation (50 mg vial)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Liposomal amphotericin B</td>
<td>1997</td>
<td>AmBisome</td>
<td>IV</td>
<td>IV formulation (50 mg vial)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Azoles</td>
<td>Nystatin</td>
<td>1976</td>
<td>Fungicidin</td>
<td>PO</td>
<td>Tablet, 200 mg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
<td>1981</td>
<td>Nizoral</td>
<td>PO</td>
<td>Suspension, 100,000 units/ml</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
<td>1990</td>
<td>Difucan</td>
<td>PO</td>
<td>Suspension, 350 or 1400 mg: tablet, 50, 100, 150, or 200 mg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Itraconazole</td>
<td>1992</td>
<td>Sporanox</td>
<td>PO, IV</td>
<td>Capsule, 100 mg; solution, 10 mg/ml; injection ampule, 10 mg/ml</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td>2002</td>
<td>Vfend</td>
<td>PO, IV</td>
<td>Tablet 50 and 200 mg: suspension, 200 mg/5 ml; injection, 200 mg/vial</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Posaconazole</td>
<td>2006</td>
<td>Noxfil</td>
<td>PO, IV</td>
<td>Suspension 40 mg/ml; tablet delayed release 100 mg; injection 300 mg/16.7 ml (18 mg/ml)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Isavuconazole</td>
<td>2015</td>
<td>Cresemba</td>
<td>PO, IV</td>
<td>Capsule 186 mg: injection 372 mg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>Caspofungin</td>
<td>2001</td>
<td>Cancidas</td>
<td>IV</td>
<td>Lyophilized powder for injection (50 and 70 mg/vials)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Anidulafungin</td>
<td>2006</td>
<td>Eraxis (in U.S. and Russia), Ecalta (in Europe)</td>
<td>IV</td>
<td>Lyophilized powder for injection (50 and 100 mg/vials)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Micafungin</td>
<td>2005</td>
<td>Mycamine</td>
<td>IV</td>
<td>Lyophilized powder for injection (50 and 100 mg/vials)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nucleoside analogs</td>
<td>Flucytosine</td>
<td>1971</td>
<td>ANCOBON</td>
<td>Oral</td>
<td>Capsule, 250 or 500 mg</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Class of antifungals</th>
<th>Name</th>
<th>Year approved by the US FDA</th>
<th>Brand name</th>
<th>Route of administration</th>
<th>Dosage formulation</th>
<th>Indication</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolite</td>
<td>Griseofulvin</td>
<td>1971</td>
<td>GRIFULVIN V, GRIS-PEG, GRISACTIN, ULTRAGRIS</td>
<td>Oral</td>
<td>Suspension 125 mg/5 ml; tablet 250 or 500 mg</td>
<td>Tinea capitis, tinea corporis, tinea pedis, tinea cruris, tinea barbae, and tinea unguium (onychomycosis)</td>
<td>Children weighing 35–60 pounds – 125–187.5 mg daily. Pediatric patients weighing over 60 pounds – 187.5–375 mg daily. Children and infants 2 years of age and younger – dosage has not been established. Adults: daily administration of 375–750 mg (as a single dose or in divided doses). Note for treatment duration: tinea capitis, 4–6 weeks; tinea corporis, 2–4 weeks; tinea pedis, 4–8 weeks; tinea unguium – depending on rate of growth – fingernails, at least 4 months; toenails, at least 6 months.</td>
</tr>
<tr>
<td>Allylamines</td>
<td>Terbinafine</td>
<td>1992</td>
<td>Lamisil</td>
<td>Oral</td>
<td>Tablet 250 mg</td>
<td>Tinea capitis</td>
<td>Children &lt;25 kg: 125 mg/day for 4–6 weeks. Adults: 250 mg/day for 4–6 weeks. One 250 mg tablet, once daily for 6 weeks. One 250 mg tablet, once daily for 12 weeks.</td>
</tr>
</tbody>
</table>

IV: intravenous; ABLC: AmB-lipid complex; ABCD: AmB colloidal dispersion.
Topical antifungal compounds alone can reduce the transmission of spores [108].

Topical antifungals can be applied to the skin, nails, or mucous membranes, or can be applied vaginally to kill or inactivate fungi. Regardless of the actual mechanism of action of the drug, or the viscosity, hydrophobicity, and acidity of the formulation, the drug’s ability to penetrate or permeate deeper skin layers is an important property impacting the therapeutic efficacy of topical antifungals [116–118].

Topical terbinafine and butenafine creams are usually effective for the treatment of tinea glabrosa within 2 weeks [119]. In cases of tinea cruris, topical tolnaftate, terbinafine, and the imidazoles for 2–4 weeks is recommended [73]. In the topical treatment of tinea pedis, imidazoles (e.g. bifonazole, clotrimazole, econazole, miconazole, and sertaconazole), ciclopirox olamine (hydroxypyridone), allylamine (terbinafine), amorolfine (morpholine), and tolnaftate (thiocarbamate) may be used. Topical antifungals are usually applied twice daily for 4 weeks. However, bifonazole and terbinafine may be used once a day [115]. Butenafine may be used once daily for 4 weeks or twice daily for 1 week [120]. In addition, luliconazole (1% cream) showed clinical improvement even when used only once daily for 1 week [121].

In onychomycosis, topical antifungal agents such as 28% tolnaftate, 8% ciclopyroxolamine, efinaconazole, 5% tavaborol solution, and amorolfine nail paint should be limited for the treatment of superficial onychomycosis (except in transverse or striate infections) cases involving <80% of the distal nail plate or when systemic antifungals are contraindicated.

### Table 2. Topical antifungal drugs currently used in clinical practice.

<table>
<thead>
<tr>
<th>Class of antifungals</th>
<th>Name</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polyens</strong></td>
<td>Amphotericin B</td>
<td>Nystatin</td>
</tr>
<tr>
<td><strong>Azoles</strong></td>
<td>Ketoconazole</td>
<td>Clotrimazole</td>
</tr>
<tr>
<td></td>
<td>Miconazole</td>
<td>Sertaconazole</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
<td>Clotrimazole</td>
</tr>
<tr>
<td></td>
<td>Miconazole</td>
<td>Sertaconazole</td>
</tr>
<tr>
<td></td>
<td>Terbinafine</td>
<td>Tioconazole</td>
</tr>
<tr>
<td></td>
<td>Tioconazole</td>
<td>Tioconazole</td>
</tr>
<tr>
<td></td>
<td>Terbinafine</td>
<td>Tioconazole</td>
</tr>
<tr>
<td></td>
<td>Naftifine</td>
<td>Tioconazole</td>
</tr>
<tr>
<td></td>
<td>Butenafine</td>
<td>Tioconazole</td>
</tr>
<tr>
<td></td>
<td>Amorolphone HCL</td>
<td>Ciclopirox olamine</td>
</tr>
<tr>
<td><strong>Morpholone derivatives</strong></td>
<td>Tolnaftate</td>
<td>Tavaborole</td>
</tr>
<tr>
<td><strong>Piridone derivatives</strong></td>
<td>Tolnaftate</td>
<td>Tolnaftate</td>
</tr>
<tr>
<td><strong>Thiocarbamate</strong></td>
<td>Tolnaftate</td>
<td>Tolnaftate</td>
</tr>
<tr>
<td><strong>Oxaborole</strong></td>
<td>Tolnaftate</td>
<td>Tolnaftate</td>
</tr>
</tbody>
</table>

### 7. Conclusion

Overall, the treatment of dermatophyte infections is based on the clinical picture and mycological identification of the etiologic agent down to species level [73]. Depending on the strategy chosen, topical and/or systemic drugs can be used. The newer antifungal drugs such as terbinafine and novel triazoles such as posaconazole and voriconazole have the main advantage of shorter treatment duration than required with fluconazole, itraconazole, and griseofulvin, and may remain present in fungicidal concentrations for several weeks after the course of treatment has been completed. These characteristics allow for a short treatment duration and prevention of reinfection, thus popularizing their use in the treatment of dermatophytosis in clinical practice.

### 8. Expert commentary

Dermatophytosis is not a life-threatening infection; however, it is one of the most common dermatophytic infections in the world. Of note, the incidence of dermatophytosis has continued to increase continuously in recent years. Antifungal therapy is a central component of patient management for dermatophytosis. However, for effective treatment, it is important to correctly determine the causal agents at the species level to prescribe suitable therapeutics and initiate appropriate management strategies.

### 9. Five-year view

Several in vitro and in vivo studies suggest that the newer generation of antifungals, including voriconazole, posaconazole, and echinocandins, might be considered as effective alternatives to the currently recommended antifungals for the treatment of dermatophytoses. In addition, efforts are underway to develop newer antifungals for the treatment of dermatophytosis, including: luliconazole (33525), VT-1161, LAS41003, and ME-1111.

### Key issues

- Dermatophytes are keratinophilic fungi, classified into three genera: *Trichophyton*, *Epidermophyton*, and *Microsporum*.
- There are at least 40 species of dermatophytes that are capable of infecting humans.
- Dermatophytic infections are considered the most common types of human fungal infections worldwide.
- The transmission of dermatophytoses may occur by direct contact with an infected host or by contact with contaminated objects and the environment.
- Dermatophytic infections are designated as different forms of tinea (also known as ‘ringworm’) according to the body site involved: the scalp (tinea capitis), beard and moustache area (tinea barbae), face (tinea faciei), hand (tinea manuum), groin and skin folds (tinea cruris), other skin regions (tinea corporis), feet (tinea pedis), and nails (tinea unguium).
Treatment of dermatophyte infections relies on the clinical picture and mycological identification of the etiologic agent down to the species level.

Topical and systemic antifungal therapy remains a central component of patient management for dermatophytosis.

Griseofulvin, terbinafine, fluconazole, and itraconazole are currently recommended systemic antifungal agents for the treatment of dermatophytosis.

A wide variety of topical antifungal agents belonging to different classes of antifungals are available for the treatment of dermatophytosis in the form of creams, ointments, gels, lotions, powders, shampoos, and other formulations.

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Declaration of interest
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References
Papers of special note have been highlighted as of interest (•) to readers.
   • First paper addressing that molecular biology has contributed to our knowledge of the taxonomy and phylogenetic relationships of dermatophytes.
   • This article highlights the antifungal susceptibility profile of novel triazoles and echinocandins against dermatophytes.
   • An overview of global epidemiology of tinea pedis.
   • An overview of new antifungal agents against dermatophytes.
   • This study highlights the impact of using different species concepts on the nomenclature of dermatophytes, which significantly may affect the quality of communications with care providers.
• An overview of key pharmacological aspects of systemic antifungal agents as well as evolving strategies.
105. Jaiswal A, Sharma RP, Garg AP. An open randomized comparative study to test the efficacy and safety of oral terbinafine pulse as a monotherapy and in combination with topical ciclopirox olamine 8% or topical amorolfine hydrochloride 5% in the treatment of onychomycosis. Indian J Dermatol Venereol Leprol. 2007;73(6):393–396.
• This paper reports the susceptibility profile of terbinafine against dermatophyte isolates obtained from patients with tinea capitis worldwide.