Dermatophyte Infections

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Abbreviations

DLSO	Distal and lateral subungual onychomycosis
FDA	Food and Drug Administration
M.	*Microsporum*
OSI	Onychomycosis severity index
PDT	Photodynamic therapy
PSO	Proximal subungual onychomycosis
RCT	Randomized controlled trial
SO	Superficial onychomycosis
T.	*Trichophyton*
TDO	Totally dystrophic onychomycosis

Key Points

- Topical treatment with imidazoles is adequate for localized tinea corporis and tinea cruris.
- Widespread or follicular lesions of tinea corporis and tinea pedis require systemic treatment.
- Topical treatment with allylamines is indicated to treat most cases of tinea pedis.
- Systemic treatment with itraconazole, terbinafine, or fluconazole is necessary in cases of chronic tinea pedis, when topical therapy fails, or in "moccasin"-type tinea pedis.
- Controlling humidity and maceration is important in the prevention of recurrence of tinea pedis.
- Dermoscopy is a valuable tool in the diagnosis of tinea capitis.
- Tinea capitis usually requires systemic treatment.
- Tinea capitis caused by *Microsporum canis* is treated with griseofulvin, while terbinafine is used to treat tinea capitis caused by *Trichophyton* infections.
- The treatment of onychomycosis depends on the clinical type of infection.
- Superficial onychomycosis with patch infiltration and distal subungual onychomycosis with less than 50 % nail

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involvement can be effectively treated topically with nail lacquers.
- Distal subungual onychomycosis with greater than 50 % nail involvement, proximal subungual onychomycosis, and deeply infiltrating white superficial onychomycosis require systemic therapy, usually with terbinafine or itraconazole.
- Lateral nail plate involvement, dermatophytomas, and total dystrophic onychomycosis may require nail plate avulsion combined with topical or systemic treatment.

Tinea Corporis

Definition and Basic Concepts of Pathogenesis

Tinea corporis is an infective skin disease resulting from invasion and proliferation by the causal fungi in the stratum corneum. The fungi most commonly involved are *Microsporum* (*M.*) *canis*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes*. It most commonly involves exposed parts of the body, but can affect any site. Typical lesions are annular in shape, with a raised scaling erythematous edge. The presence of perifollicular granulomatous papules (Majocchi's granuloma) is a definite indication for systemic treatment.

General Principles of Treatment

Topical Treatment

In localized lesions of tinea corporis, topical treatment with imidazole derivatives, allylamines, phenylpropylmorpholine derivatives, tolnaftate, or cyclopiroxolamine is adequate. Treatment period varies between 2 and 4 weeks, except for allylamines that are effective after 1–2 weeks of therapy. Efficacy among the different classes is similar; however, butenafine may achieve faster mycological cure. Sertaconazole, a newer imidazole derivative, may be more effective at controlling symptoms of pruritus.

Systemic Treatment

Systemic treatment is required in widespread tinea corporis or when follicular lesions (Majocchi's granuloma) are present. Itraconazole (200 mg daily for 1 week), terbinafine (250 mg daily for 2 weeks), and fluconazole (150 mg weekly for up to 4–6 weeks) are currently preferred because time to treatment is usually shorter and they are better tolerated than griseofulvin.

Tinea Cruris

Definition and Basic Concepts of Pathogenesis

This infection mainly occurs in adult men and is usually caused *by Trichophyton rubrum* and *Epidermophyton floccosum*. Tinea cruris presents with an itchy scaling of the groin and insides of the thighs. The margin of the affected area typically presents with a raised erythematous border.

General Principles of Treatment

Topical Treatment

In localized lesions topical treatment, as for tinea corporis, may be sufficient.

Systemic Treatment

This is mandatory in long-standing lesions or when follicular granulomas are present. Itraconazole (200 mg daily for 1 week), terbinafine (250 mg daily for 2 weeks), and fluconazole (150 mg weekly for up to 4–6 weeks) are very effective.

Tinea Pedis

Definition and Basic Concepts of Pathogenesis

Tinea pedis is the most common dermatophyte infection and in most cases is caused by

Trichophyton (*T.*) *rubrum*, followed by *Trichophyton interdigitale*. *Trichophyton rubrum* usually produces noninflammatory lesions with different degrees of severity ranging from mild scaling to diffuse "moccasin-type" scaly rash. *Trichophyton interdigitale* usually causes interdigital or plantar inflammatory lesions that are often vesicular and pruritic.

General Principles of Treatment

Topical Treatment

Topical antifungals are usually used to treat tinea pedis. They are also commonly utilized to prevent reinfections. Generally, allylamines have been shown to be more efficacious than azoles. Usually, topical therapy lasts 1–4 weeks. Naftifine and terbinafine are the commonly used allylamine in tinea pedis. A new drug that has completed phase III testing, terbinafine film-forming solution, has shown to be safe and efficacious in preventing tinea pedis with only one application (Chauvin et al. 2008). Among the azole treatment options are ketoconazole, econazole, oxiconazole, miconazole, and clotrimazole. A newer treatment option is sertaconazole. Compared to miconazole, sertaconazole has a statistically higher complete clinical cure rate. Sertaconazole also provided patients with greater relief from erythema and desquamation. Sertaconazole has the added benefit of being effective with once daily application. Luliconazole is a new drug currently undergoing phase 2 testing (Jarratt et al. 2013). Flutrimazole and bifonazole are available as powders that can be applied twice daily for 2–4 weeks and may be effective in curing tinea pedis.

Alternative treatment options, including *Ageratina pichinchensis* extract (active ingredient encecalin), Brazilian green propolis extracts, green tea polyphenols, and tea tree oil, have shown some effectivity. *Ageratina pichinchensis* demonstrated similar cure rates to ketoconazole. Use of Brazilian green propolis extracts showed improvement of clinical features over petroleum jelly. Green tea polyphenols have been shown in one randomized controlled trial (RCT) to improve tinea pedis; however, the study design only had one physician making assessments and thus lacked interobserver validity (Ikeda et al. 2013). Tea tree oil shows significant promise as an alternative treatment for tinea pedis. In an RCT, tea tree oil demonstrated statistically significant improvement in mycological as well as clinical cure rates compared to placebo after 4 weeks of twice daily application (Satchell et al. 2002).

Systemic Treatment

Systemic treatment is indicated, if topical therapy fails, in chronic conditions, or in cases of moccasin-type tinea pedis. Itraconazole, terbinafine, and fluconazole are effective in the treatment of tinea pedis. Common treatment regimens include itraconazole at 100 mg/day for 2–4 weeks, terbinafine at 250 mg/day for 2 weeks, or fluconazole at 150 mg weekly for up to 6 weeks. However, clinically, there is some variance in the regimens. Terbinafine may be the preferred agent as it may be more efficacious, has lower recurrence rates, and requires a shorter treatment duration.

Prevention of Recurrences

1. Reduction of maceration and humidity can be obtained by regular use of talcum powders.
2. The demonstration that dermatophytes occur in shoes (up to 17 % in one study), flooring, and carpets (Muslim community) indicates that any treatment directed solely at the feet is inadequate to control the disease. Effective control measures must also include simultaneous eradication of the organisms (such as disinfection of shoes with 1 % 8-hydroxycholine sulfate, formaldehyde) and/or the environment to prevent reinfection. However, there is limited data which shows a correlation of such measures and the prevention of athletes' foot. In such circumstances, evaluating the preventative efficacy of these measures against athletes' foot remains guesswork.

Tinea Capitis

Definition and Basic Concepts of Pathogenesis

In Europe, tinea capitis is predominantly caused by *Microsporum canis* and increasingly by *Trichophyton tonsurans*, with *Microsporum canis* being the most common agent of tinea capitis in Italy. Other dermatophytes responsible for tinea capitis include *T. soudanense*, *T. violaceum*, *M. gypseum*, *T. mentagrophytes*, and *T. schoenleinii*. The most common causative agents vary significantly by geographic region. The clinical manifestations of tinea capitis range from mild scalp scaling to severe inflammatory reactions. Cervical lymph nodes are often enlarged.

Dermoscopy is an important and underutilized tool in the diagnosis of tinea capitis. It can be especially useful in African-American patients where erythema may be subtle and difficult to appreciate. Characteristic signs such as comma hairs and corkscrew hairs may help in making the diagnosis. In tinea capitis favosa, there is no significant hair structure abnormality, but large amorphous yellow areas and wax-colored perifollicular areas can be observed. Black dots and broken dystrophic hairs are also seen in tinea capitis but are not specific to the disease.

General Principles of Treatment

Topical Treatment

Although tinea capitis always requires systemic treatment, the use of adjunctive topical therapy is important. Periodic hair shaving prevents diffusion of the infection. Antifungal shampoos such as ketoconazole 2 %, selenium sulfide shampoo 1 %, and ciclopirox shampoo 1 % should be given to the patient and family members in order to reduce transmission of infection. Family members and primary contacts should be screened for asymptomatic disease. Family pets of patients with *Microsporum canis* infection should be treated. Fomites, including toys, phones, clothing, furniture, and hair care items, may contribute to spread of the infection and can be sterilized using high temperature or microwaves.

Systemic Treatment

Microorganism identification may be useful in the treatment of tinea capitis as the different species show varying susceptibilities. In tinea capitis due to *Microsporum canis*, griseofulvin is commonly prescribed. The drug should be administered at 10–25 mg/kg per day for 2–3 months. The azole antifungals fluconazole and itraconazole are effective in the treatment of *Microsporum canis* infection of the hair, with fluconazole being the only one available in a pleasant-tasting liquid formulation. The suggested regimen for fluconazole is 4–6 mg/kg per day for 8–12 weeks and may be administered on a weekly basis as well. Itraconazole can be administered at 5 mg/kg per day or as pulse therapy and is available in both capsule and oral solution. The length of treatment varies by organism, with *M. canis* requiring treatment for 6 weeks. Terbinafine is less effective in tinea capitis due to *M. canis* but may be more efficacious compared to griseofulvin in treating infection by the *Trichophyton* species. Dosages used in this setting are 3.125–6.25 mg/kg per day for terbinafine, 3–5 mg/kg per day for itraconazole, and 4–6 mg/kg once a week for fluconazole. Duration of treatment ranges from 2 to 6 weeks. Oral or topical steroids can be given in association with systemic antifungals to reduce pain, swelling, and inflammation.

Onychomycosis

Definition and Basic Concepts of Pathogenesis

Dermatophytes account for more than 90 % of onychomycosis, with T. rubrum being the most common pathogen. They may produce several different clinical types of onychomycosis, depending on the modality of nail invasion by the fungus.

Distal and Lateral Subungual Onychomycosis (DLSO)

DLSO (Fig. 21.1) is the most common of the clinical entities and involves invasion from the lateral or distal part of the nail plate. The affected

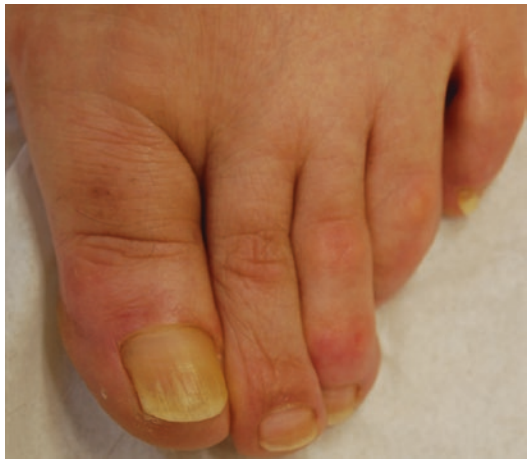

Fig. 21.1 Distal subungual onychomycosis due to *T. interdigitale* involving the distal 1/3 of the nail

nails usually show subungual hyperkeratosis, onycholysis, and white or yellow discoloration. Infrequently, brown, black, or orange discoloration may also be seen. In certain cases, longitudinal streaking of the nail, called dermatophytoma, can be seen. These infections are difficult to treat and may require excision of the area and systemic treatment rather than topical therapy. Since the skin of the palms and soles is the primary site of infection, DLSO is usually associated with tinea manuum or tinea pedis. This form of infection is seen with a variety of causative agents including dermatophytes.

Superficial Onychomycosis (SO)

SO can present with superficial patches or transverse striae and may arise from the superficial nail plate or emerge from the proximal nail fold. These bear clinical implications on treatment. In the classic form, previously known as white superficial onychomycosis, dermatophytes colonize the most superficial layers of the nail plate without penetrating it. The affected nail presents multiple friable white opaque spots in a patchy distribution that can be easily scraped away. This form is amenable to topical treatment. In contrast, in the striate form when the infection emerges from the proximal nail fold and with deep penetration of the nail plate, oral therapy is indicated.

Endonyx Onychomycosis

Endonyx onychomycosis is characterized by massive nail plate parasitization in the absence of nail bed inflammatory changes. Clinically, the affected nail may show lamellar splitting and a milky white discoloration. The nail plate is firmly attached to the nail bed and there is no nail bed hyperkeratosis or onycholysis. This type of infection is commonly seen with *T. soudanense* but can also be seen with *T. violaceum*.

Proximal Subungual Onychomycosis (PSO)

PSO is characterized by a primitive invasion of the nail matrix keratogenous zone through the proximal nail fold horny layer. Fungal elements are typically located in the ventral nail plate with minimal inflammatory reaction. The affected nail shows proximal leukonychia that progresses distally with nail growth. PSO can be divided into either patchy, striate, or secondary to paronychia. Among the dermatophytes, these infections are usually caused by T rubrum. PSO is difficult to treat and requires oral therapy.

Mixed Pattern Onychomycosis

Oftentimes, different patterns of infection may be seen in the same patient. DLSO may occur with superimposed SO or PSO and SO may occur with superimposed DLSO or PSO. The most common of these are PSO with SO or DLSO with SO. Mixed pattern onychomycosis often requires oral treatment.

Totally Dystrophic Onychomycosis (TDO)

TDO is the end stage of onychomycosis and can result from DLSO as well as PSO. The nail plate, in these cases, crumbles and the underlying nail bed is thickened.

Secondary Onychomycosis

In some cases of nail pathologies such as psoriasis or traumatic nail dystrophy, a secondary fungal infection can occur.

General Principles of Treatment

The treatment choice depends on the clinical type of the onychomycosis, the number of affected nails, and the severity of nail involvement.

The onychomycosis severity index (OSI) was developed in 2011 and provides a fast and effective way to evaluate the extent of onychomycosis and may provide an objective measurement on which to base treatment (Carney et al. 2011). Furthermore, the OSI scoring system demonstrates excellent interobserver reliability. The categories assessed when calculating the OSI are area of involvement, proximity of disease to matrix, and the presence of dermatophytoma or subungual hyperkeratosis greater than 2 mm. First, the area of involvement is determined as the percentage of the nail that is onychomycotic. Involvement is categorized as 1–10 %, 11–25 %, 26–50 %, 51–75 %, or 76 % or greater with scores ranging from 0 to 5, respectively. Next the proximity of disease to matrix is assessed by visualizing the leading edge of disease proximally. The nail is divided transversely into quarters. Scores of 1 through 4 are assigned, with 1 for only distal quarter involvement and 4 for proximal quarter involvement. If the proximal edge extends into the nail fold or if the lunula is involved, a score of 5 is given. The third step is to assess the presence of dermatophytoma, defined as the presence of a patch or a longitudinal streak, or subungual hyperkeratosis greater than 2 mm. If either of these is present, a score of 10 is given. The OSI is calculated by multiplying the score for the area of involvement by the score for proximity of disease to the matrix and adding 10 if necessary from the third step. Scores range from 0 to 35 with higher numbers correlating with increased severity. Scores of 1–5 indicate mild onychomycosis, scores of 6–15 indicate moderate onychomycosis, and scores of 16–35 indicate severe onychomycosis. A score of zero indicates a cured state.

Topical Treatment

Penetration of a topical antifungal through the nail plate requires a vehicle that is specifically formulated for transungual delivery. The two most commonly used agents are amorolfine 5 % nail lacquer and ciclopirox 8 % nail lacquer. However, agents such as miconazole, tioconazole, ketoconazole, tolnaftate, naftifine, and tea tree oil have been tested with varying success rates in the past. Amorolfine nail lacquer is applied once a week, whereas ciclopirox nail lacquer is applied daily.

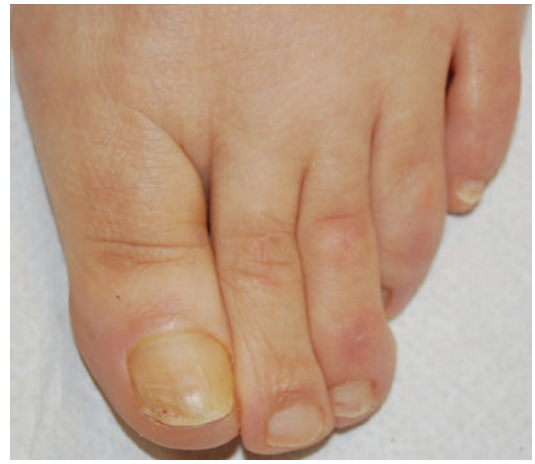

Fig. 21.2 Complete cure of the onychomycosis after 6 months of topical application of a nail lacquer containing ciclopirox with hydroxypropyl chitosan as vehicle

Nail lacquers are effective as monotherapy in the treatment of superficial onychomycosis, with patch infiltration, and of distal subungual onychomycosis, limited to less than 50 % of the distal nail (Hay and Baran 2011). Treatment duration should be 6–12 months (Fig. 21.2). Nail lacquers are also utilized in combination with systemic antifungals or nail avulsion in severe onychomycosis to reduce duration of treatment and increase cure rate.

Application of amorolfine nail lacquer once every 2 weeks after completion of treatment may be effective prophylaxis to prevent the recurrence of onychomycosis.

Recent studies on lipid diffusion enhancers and water-soluble biopolymers have shown promise (Baran et al. 2009; Hafeez et al. 2013). Terbinafine nail solution and a terbinafine spray using lipid-based vesicles currently under development, labeled TDT 067, may be viable treatment alternatives in the future (Elewski et al. 2013;

Table 21.1 New topical antifungal treatment options for onychomycosis

Drug	Nail involvement	Mycological cure	Clinical cure	Complete cure	Author
Efinaconazole	<50 %	53.4*–55.2 %*	–	15.2*–17.8 %*	Elewski et al. (2013)
Tavaborole 5 % and 7.5 %	20–60 %	Culture: 97 %, 94 % KOH: 63 %, 60 %	–	–	Beutner et al. (2009)
Urea, propylene glycol, and lactic acid (K101)	<50 %	27.2 %*	–	–	Emtestam et al. (2012)
Bifonazole after ablation with 40 % urea	<50 %	64.5 %*	86.6 %*	54.8 %*	Tietz et al. (2013)
Terbinafine nail solution	25–75 %	12.7–18.8 %*	2.3–3.5 %	1.2–2.2 %	Elewski et al. (2013)
Terbinafine spray (TDT 067)	–	90.1 %	–	–	Dominicus et al. (2012)
Terbinafine HCL with iontophoretic patch	25–75 %	84 %*	–	–	Amichai et al. (2010)

*Indicates statistically significant difference

Dominicus et al. 2012). Other formulations with terbinafine that are undergoing phase II trials include MOB-015 and TMI-358. Luliconazole has completed phase I and IIa testing for treatment of moderate to severe distal subungual onychomycosis with positive results (Jones and Tavakkol 2013). Refer to Table 21.1 for a comprehensive list of new topical antifungal treatment options for onychomycosis.

Treatments with photodynamic therapy (PDT) using photosensitizers may also prove to be effective treatment options in the future. Laser therapy is also currently being researched and may be effective in the treatment of onychomycosis. Food and Drug Administration (FDA)-approved lasers for onychomycosis include carbon dioxide laser, Nd:YAG laser, and the diode 870 nm, 930 nm laser. The carbon dioxide laser is the oldest laser and is infrequently used today. With the Nd:YAG laser, small clinical trials have demonstrated mycological cure rates as high as 87.5 % (Zhang et al. 2012). Similarly, the diode laser has shown some efficacy in small trials, with mycological cure rates as high as 38 % reported at 9-month follow-up (Landsman and Robbins 2012). Large randomized control trials need to be conducted to validate the efficacy of these lasers and PDT in the treatment of onychomycosis.

Systemic Treatment

Distal subungual onychomycosis that involves greater than 50 % of the nail, proximal subungual onychomycosis, and deeply infiltrating white superficial onychomycosis require systemic therapy. Systemic treatment with terbinafine or itraconazole produces mycological cure in more than 90 % of fingernail infections and in about 80 % of toenail infections. These success rates can be increased by associating a topical treatment with a nail lacquer to the systemic treatment. However, compared to itraconazole, terbinafine has a higher mycological and clinical cure rate and a lower rate of recurrence. Terbinafine can be administered as a continuous therapy at 250 mg per day for 12 weeks or an intermittent regimen of two pulses of 250 mg/day for 4 weeks on and 4 weeks off. Itraconazole is administered as pulse therapy at the dosage of 200 mg twice a day for 1 week a month. The treatment duration is 2 months for fingernails and 3 months for toenails.

Fluconazole is also used in onychomycosis but is less effective. The recommended dosage is 150 mg weekly for more than 6 months, especially for toenails. Posaconazole and albaconazole are newer drugs that could be alternative therapy options.

In cases of lateral nail plate involvement or dermatophytomas, surgical or chemical avulsion of the nail plate combined with topical or systemic treatment is indicated. Total dystrophic onychomycosis is an extremely recalcitrant entity. Surgical nail avulsion followed by topical therapy may not be enough to provide a cure in this situation; however, chemical avulsion with urea nail lacquer may be a viable treatment option. Sequential treatment with itraconazole and terbinafine has been utilized to increase cure rates: the suggested regimen is two pulses of itraconazole 400 mg/day for 1 week a month followed by one or two pulses of terbinafine 500 mg/day for 1 week a month.

Mycological cure can be evaluated at the end of treatment. Evaluation of clinical response, on the other hand, requires several months due to the slow growth rate of the nail. Recurrences and reinfection are not uncommon and vary with type of treatment (rates of 35.7 % reported with itraconazole). These may be prevented by the regular application of nail lacquers on the previously affected nails and topical antifungals on soles and toe webs.

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