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Topical Treatments for Onychomycosis

A Historical Perspective

Myron A. Bodman, DPM*
Lisa Feder, PhD†
Angela M. Nace, PharmD†

Topical treatment of onychomycosis, in contrast to systemic oral therapy, allows the patient to apply medication directly to the affected area, thereby decreasing the potential for adverse events and drug interactions. Historically, several topical antifungal agents have been used in the treatment of onychomycosis; however, the evidence for their effectiveness is based on very limited data or anecdotal reports. Recently, the development of new, effective topical agents has renewed interest in this form of therapy. As clinical experience with newer topical agents expands, they may be found to be an effective option for the treatment of onychomycosis. (J Am Podiatr Med Assoc 93(2): 136-141, 2003)

Onychomycosis is the most common disease of the nails,[1] accounting for approximately 30% of all nail infections.[2] It is estimated that this disease affects 2% to 13% of the general population,[3-7] with prevalence increasing with age. This fungal infection is caused by dermatophytes, nondermatophytic molds, or yeasts.[8-10] At least 80% of onychomycosis infections in temperate zones are caused by the dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes*.[9-11] Common nondermatophytic molds in North America include *Scopulariopsis brevicaulis*, *Aspergillus flavus*, and *Fusarium* species, which account for approximately 1.5% to 6.0% of fungal nail infections.[8, 12] Yeasts are responsible for 5% to 17% of all cases of onychomycosis, primarily affecting the fingernails, with *Candida albicans* isolated in more than 70% of patients.[9, 13]

*Cleveland Foot and Ankle Clinic, Ohio College of Podiatric Medicine, Cleveland.

†Scientific Connexions, Newtown, PA.

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Corresponding author: Myron A. Bodman, DPM, Cleveland Foot and Ankle Clinic, Ohio College of Podiatric Medicine, 10515 Carnegie Ave, Cleveland, OH 44106.

Diagnosis

Clinically, onychomycosis is evident from hyperkeratosis of the nail bed, yellow to brownish discoloration of the nails, and separation of the nail from the nail bed (onycholysis).[14] Diagnosis of onychomycosis is especially likely if tinea pedis caused by *T rubrum* is present. *Trichophyton rubrum* often invades the distal nail bed, resulting in the development of distal subungual onychomycosis.[15]

Accurate diagnosis by clinical presentation alone is possible in only 40% to 57% of cases.[14, 16] Direct microscopic examination, fungal culture, or both are required to confirm the diagnosis and to identify the infecting organism.[14, 17, 18] Direct microscopic examination for hyphal fragments is typically performed by preparing nail scrapings with potassium hydroxide (KOH).[14, 19] Although direct microscopy cannot identify the specific causative pathogen, it can determine whether the hyphae are characteristic of dermatophytes.[17] The most accurate test (85% sensitive) for the detection of mycotic nail infections is a routine histopathologic examination with periodic acid–Schiff stain.[20] Fungal culture is required to identify the specific infecting organism; however, because more than 90% of onychomycosis infections are caused by dermatophytes, treatment is often initiated on the basis of a positive

KOH result. Further research may determine whether sensitivity is enhanced by combining periodic acid–Schiff staining with fungal cultures.

Treatment Options: The Role of Topical Therapy

Treatments for onychomycosis range from minimal intervention or palliative care to systemic therapy or nail avulsion by surgical or chemical means. The choice of treatment modality may depend on several factors, including the presentation and severity of the disease, the medical condition and current patient medications, physician and patient preference, and the cost of therapy.[5] Because of the potential for drug interactions, use of systemic therapy may be inappropriate in patients receiving multiple medications, such as those with human immunodeficiency virus, patients with diabetes mellitus, and the elderly.[21-25] Topical therapy allows for direct application to the desired area and minimizes the chance of adverse systemic drug reactions that can be associated with use of oral antifungal agents.[9] This is also a good option for patients with mild-to-moderate disease and for those unwilling to take systemic medication.

Topical Antifungal Agents

Historically, several classes of topical antifungal medications have been used to treat onychomycosis, including polyenes (eg, nystatin); imidazoles (eg, clotrimazole, tioconazole, econazole, ketoconazole, miconazole, sulconazole, and oxiconazole), which have fungistatic properties *in vitro;* and allylamines/benzylamines (eg, naftifine, terbinafine, and butenafine), which have fungistatic and fungicidal properties *in vitro*.[26] Few well-designed clinical studies have evaluated the efficacy of these agents for the treatment of onychomycosis; therefore, most of the available data supporting their use are derived from small and poorly controlled studies.

In an effort to improve outcomes, topical agents have been combined with 20% to 40% urea ointment to soften the onycholytic nail plate, thereby facilitating debridement and antifungal penetration.[27-31] One of the most widely used antifungal–urea combinations evaluated in several small-scale trials is 1% bifonazole in combination with 40% urea ointment.[27, 30-33] In one trial,[27] 28 patients with onychomycosis were treated with 40% urea–1% bifonazole cream once daily for 6 months. A "cure" was defined as normal nail growth throughout the 6- to 12-month follow-up period and negative culture findings. Cure rates of 81% for fingernails and 69% for toenails were achieved. In a study[30] evaluating the efficacy of bifonazole–urea application in 25 children (aged 1.8 to 15.0 years) with onychomycosis, bifonazole–urea use resulted in a 68% (17/25) therapeutic success rate (clinical cure and negative KOH and culture results), a 24% (6/25) improvement rate (important clinical changes, positive or negative KOH results, and negative culture results), and an 8% (2/25) failure rate (no clinical or mycologic [KOH/culture] changes or exacerbation of the process and positive KOH and culture results). In another study[31] evaluating 50 patients with onychomycosis, application of bifonazole–urea cream resulted in a 90% cure rate (negative culture results and negative clinical evaluation) 1 month after treatment. This response was maintained for 4 months after treatment. In a similar small-scale study[32] evaluating daily use of 40% urea–1% bifonazole paste in 22 patients with toenail onychomycosis, 63% of the nails were mycologically negative after 12 weeks of treatment, and 46% remained negative 24 weeks after initiating treatment. Adverse events observed in these trials included nail pain and dermatitis.[27, 30, 31] A 40% urea–1% bifonazole cream is commercially available in several countries outside of the United States.[34, 35]

To date, two topical therapies have been approved for the treatment of onychomycosis in Europe: ciclopirox nail lacquer and amorolfine. Of these, only ciclopirox is approved for use in the United States. Ciclopirox nail lacquer 8% solution (Penlac, Dermik Laboratories, Berwyn, Pennsylvania) is a hydroxypyridone derivative that differs chemically and mechanistically from other marketed antifungal agents (including imidazoles and allylamines).[5] The mechanism of action of ciclopirox is thought to be related to the chelation of polyvalent cations (Fe^{+3} or Al^{+3}). It is a broad-spectrum antifungal agent with activity against dermatophytes such as *T rubrum* and *T mentagrophytes*, *Candida* species, and some nondermatophyte molds. Ciclopirox was introduced in 1975 and was first approved approximately 10 years ago in France for the treatment of onychomycosis.[5]

After repeated applications to the nail surface, ciclopirox has been detected in all layers of the nail plate and the skin below.[36, 37] Figure 1 illustrates the penetration of C^{14}-labeled ciclopirox in excised, mycotically involved toenails. As expected, the concentration of the topical agent was highest in the upper layers of the nail plate,[37] and at a depth of 0.4 mm, ciclopirox exceeded the minimum inhibitory concentrations for the most common fungal species associated with onychomycosis (Table 1).[38, 39] Drug penetration of the nail varies, with more pronounced penetration observed in the damaged, friable areas of mycotic nails.[37]

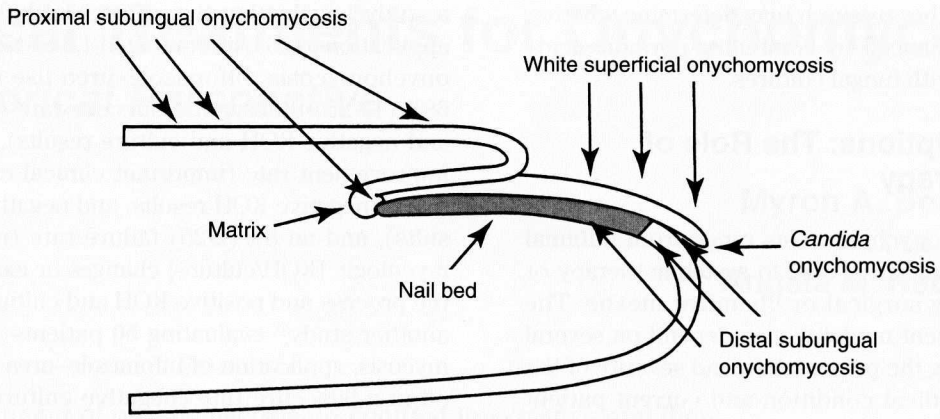

Figure 1. Penetration of C^{14}-labeled ciclopirox in excised, mycotically involved toenails after a single application of ciclopirox nail lacquer 8% solution. (Reprinted with permission from Del Rosso.[15])

The efficacy of ciclopirox in the treatment of onychomycosis of dermatophytic origin was recently demonstrated in two double-blind, vehicle-controlled US trials.[40] These studies of 460 patients with mild-to-moderate onychomycosis included 231 individuals receiving ciclopirox and 229 receiving vehicle only. Ciclopirox or vehicle control was applied to all toenails and affected fingernails (including approximately 5 mm of the surrounding skin) once daily for 48 weeks. Efficacy was determined on the basis of the results of fungal cultures and KOH microscopy of nail specimens, an investigator-assessed global evaluation score, and planimetric measurement of the involved area. The primary efficacy variable in the studies was treatment success, defined as simultaneous negative KOH and culture results and 10% or less area involvement of the target nail plate as determined by planimetry. The most common causative organism was *T rubrum* (96%). Treatment success was achieved in 6.5% (study 1) and 12% (study 2) of patients treated with ciclopirox, compared with less than 1% for those in the vehicle groups ($P < .05$ for both studies). Significantly more patients treated with ciclopirox nail lacquer had negative culture results (84% for both studies) compared with patients receiving vehicle (37% and 44%, respectively; $P < .001$).

Table 1. Antifungal Efficacy of Ciclopirox

Organism	Minimum Inhibitory Concentration (μg/mL)						
	0.49	0.98	1.95	3.92	7.8	15.6	31.2
Trichophyton rubrum (n = 37)	1	14	20	2	–	–	–
Trichophyton mentagrophytes (n = 29)	10	17	2	–	–	–	–
Epidermophyton floccosum (n = 5)	2	3	–	–	–	–	–
Microsporum canis (n = 20)	1	2	13	4	–	–	–
Candida albicans (n = 37)	–	21	11	5	–	–	–
Candida tropicalis (n = 12)	–	6	6	–	–	–	–
Candida pseudotropicalis (n = 9)	–	–	5	4	–	–	–
Candida krusei (n = 11)	–	2	8	1	–	–	–
Candida parapsilosis (n = 10)	–	–	5	5	–	–	–
Other *Candida* species (n = 6)	–	1	2	3	–	–	–
Scopulariopsis brevicaulis (n = 1)	–	–	1	–	–	–	–
Aspergillus species (n = 28)	–	1	9	10	3	5	–
Scytalidinium hyalinum (n = 1)	–	1	–	–	–	–	–
Fusarium solani (n = 1)	–	–	–	–	–	–	1

Source: Data from Refs. 38 and 39.
Note: Data are given as number of patients.

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