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Non-dermatophyte onychomycosis

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The prevalence of onychomycosis is increasing, and the number of organisms recognized as possible fungal pathogens is growing [1]. Dermatophytes, particularly *Trichophyton rubrum* and *Trichophyton mentagrophytes*, are the most common cutaneous fungal pathogens, accounting for approximately 90% of nail infections [2]. Non-dermatophyte pathogens are fungi with known habitats in soil, decaying plant debris, or plant disease. They have been traditionally regarded as uncommon or secondary pathogens of already diseased nails. The prevalence of non-dermatophyte molds as nail invaders ranges between 1.45% and 17.60% [3]. The variation in incidence might be because of geographic differences in mold distribution or diagnostic methods [3]. The proportion of individuals with pedal onychomycosis caused by non-dermatophyte molds is highest among older patients (> 60 years old) [4]. Non-dermatophyte molds such as *Scopulariopsis, Fusarium,* and *Aspergillus* might be primary pathogens that cause onychomycosis [5]. *Alternaria* and *Paecilomyces* species might also cause onychomycosis; however, this is rarely observed [6,7]. In addition, *Candida* species cause between 1% and 32% of toenail infections and 51% to 70% of fingernail infections, either as the primary pathogen or in combination with dermatophytes or molds [8].

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Although dermatophyte infections are more commonly discussed in the literature, non-dermatophyte organisms have become increasingly prevalent as etiologic agents of onychomycosis. Some non-dermatophyte molds that cause infections of the nail include species of *Scopulariopsis, Scytalidium, Fusarium*, *Aspergillus*, and *Onychocola canadensis*. *Candida* species, especially *C. albicans* and *C. parapsilosis*, are the major yeasts that cause onychomycosis.

Clinical presentations

Clinical patterns of onychomycosis include distal and lateral subungual onychomycosis (DLSO), superficial white onychomycosis (SWO), proximal subungual onychomycosis (PSO), and *Candida* onychomycosis [9]. Total dystrophic onychomycosis (TDO) results when any of the above clinical patterns progresses to involve the entire nail plate [10]. Endonyx onychomycosis has only been described recently in the literature [10,11].

DLSO is the most common pattern of infection. Dermatophytes, in particular *T. rubrum*, are the most frequently encountered causal agents. Non-dermatophyte molds such as *Scytalidium dimidiatum* can produce this clinical pattern of disease, but in these cases DLSO is often associated with onycholysis and (possibly) with paronychia in fingernails [12]. Other molds that can be responsible for DLSO include *Fusarium oxysporum, Scopulariopsis brevicaulis*, *Aspergillus* spp, and *Acremonium* spp [5,13].

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SWO is caused mostly by dermatophytes, with the most common organism being interdigital-type *T. mentagrophytes*. Non-dermatophyte molds such as *Aspergillus terreus, F. oxysporum,* and *Acremonium* spp [5,13], and yeasts (eg, *C. albicans*) can also result in this clinical pattern.

PSO is an uncommon pattern of onychomycosis caused predominantly by *Trichophyton* species. Non-dermatophytes that can also cause this clinical pattern of infection include *Fusarium* spp and *S. brevicaulis* [14,15]. A patient with chronic mucocutaneous candidiasis (CMCC) was recently reported to show transverse cloudy leukonychia that appeared beneath the normal cuticle of several fingernails; this pattern of infection is typical of PSO [16]. Proximal white superficial onychomycosis (PWSO) has been associated with immune disorders and might even be a clinical marker for an immunocompromised state, particularly among individuals who are HIV positive [13].

Endonyx onychomycosis (EO) begins at the distal edge of the nail plate and moves proximally [11,12]. Unlike in DLSO, however, the fungal elements directly invade and penetrate the nail plate, where they form milky white patches without subungual hyperkeratosis or onycholysis [12,17]. There is little or no involvement of the nail bed and no subungual debris. Endonyx onychomycosis has been associated with *Trichophyton soudanense* and *Trichophyton violaceum* [18].

Diagnosis

Identifying a type of nail infection normally caused by non-dermatophytes requires careful diagnostic attention [19]. Some organisms such as *Scytalidium* species produce infections that clinically mimic the signs and symptoms seen in dermatophyte infections. Correct identification becomes imperative because many non-dermatophyte molds respond poorly to therapy [1].

Unlike tinea unguium, non-dermatophyte onychomycosis is often diagnosed inaccurately. In such cases, stringent criteria are required for the attribution of etiology to non-dermatophyte molds and yeasts. Direct microscopic examination (ie, potassium or sodium hydroxide, or, alternatively, histopathology) is mandatory. Non-dermatophyte mold infections should yield a corresponding positive microscopic result showing fungal filaments/hyphae consistent with the organism that is isolated (eg, dark if the organism is a melanized fungus) in the subungual keratin. Yeast infections should yield pseudohyphae in direct microscopy; these structures will ordinarily bear occasional budding outgrowths that can be used to confirm them as yeast elements [5,20,21]. To confirm that a non-dermatophyte mold is the sole etiologic agent, there should be repeated isolation of the suspected causal organism on two or more separate occasions (ie, from samples taken at different time points, not just from multiple sample pieces taken at one time point) in the absence of any growth of a dermatophyte. A repeated culture reduces the statistical probability that the non-dermatophyte is a contaminant; furthermore, it aids in the diagnosis of mixed infections (eg, a dermatophyte with a non-dermatophyte) [5].

English [20] suggested that at least five of 20 inocula (ie, separate pieces of nail material planted onto growth medium) must yield the same mold to establish the mold as a causative agent. Recent work has suggested that this ratio would generate more false-positive than true-positive results for non-dermatophyte mold infections, but that a count of 11 or more culture-positive inocula out of 15 planted (in combination with a positive KOH result) has a much stronger statistical correlation with the likelihood that the non-dermatophyte is the etiologic organism [5].

Histologic examination of the nail plate enables confirmation of invasive ungual infection; however, this technique does not identify the infecting organism.

The type of medium used to culture nail samples can affect the results and limit the identification of the causative organism. Historically, culture media have contained cycloheximide, which might prevent non-dermatophyte growth, thereby hindering detection of potential pathogens. Thus, it is imperative that nail samples are cultured on cycloheximide-free media as well as cycloheximide-supplemented media [21].

Clues that onychomycosis might be caused by non-dermatophyte molds include absence of tinea pedis, involvement of only one or two toenails, history of trauma preceding nail dystrophy, and a lack of response to systemic antifungal therapy (eg, fluconazole, itraconazole, and terbinafine) [22]. In onychomycosis caused by non-dermatophyte molds, there might also be inflammation/redness of the nail matrix [14,15,23].

Scopulariopsis species

Scopulariopsis is a common mold found in soil and dead organic matter. It grows especially well on protein-rich surfaces [24]. Some *Scopulariopsis* species (eg, *S. brevicaulis*, S. *brumptii, S. candida, S. carbonaria*, and *S. koningii*) are capable of digesting α-keratins [19,25]. Some of these organisms,

especially *S. brevicaulis*, have been associated with onychomycosis, occasionally as a primary invader but more often as a secondary pathogen following dermatophytosis or trauma [13,26].

Onychomycosis caused by *Scopulariopsis* affects mainly toenails, particularly the great toenail [13,27]. The infection generally begins at the free or lateral edge of the nail and less often at the proximal edge [13,28]. The nail might discolor to white, gray, or yellow, often with a yellow–orange ochre or occasionally with a green tinge [28]. Seven species have been reported as human pathogens: *S. brevicaulis, S. candida, S. brumptii, S. acremonium, S. fusca, S. asperula*, and *S. koningii* [29]. It should be noted, however, that not all published reports are reliable. In addition, some nail-infecting *Scopulariopsis* species forming a *Microascus* sexual state in culture have been reported under these teleomorph (sexual state) names, viz *Microascus cinereus* and *Microascus cirrosus* [30]. Onychomycosis caused by *S. brevicaulis* is diagnosed most often in elderly patients, with equal frequency in men and women [31].

Culture and microscopy

Scopulariopsis species grow rapidly and produce conidial structures within 7 days on Sabouraud dextrose agar at room temperature [13]. Initially, the colony surface is white, velvety, and rugose, but it soon becomes light tan or brown in *S. brevicaulis* and closely related species and dark gray in "black *Scopulariopsis*" species such as *S. brumptii* [13,24]. In direct examination in potassium hydroxide (KOH) mounts of scrapings or clippings, the hyphae are colorless or, rarely, light brown, branched, septate, and variable in width, with some elongated cells [32,33]. Conidiophores in culture are either branched in a penicillate, broom-like pattern or unbranched and short [32]. These conidia can occasionally be seen occurring in large masses in direct microscopy of heavily affected nails. Mature conidia are thick-walled, round with a flattened base, smooth to coarsely roughened, and hyaline to tan in mass, with a broad, truncate base [34].

Hendersonula toruloidea and *Scytalidum* species

The pycnidial plant pathogenic fungus *Nattrassia mangiferae*, previously known as *Hendersonula toruloidea*, can infect human skin and nails [35]. The associated synanamorph seen in culture is *Scytalidium dimidiatum* [35]. *S. dimidiatum* is a keratinolytic organism that is widely distributed in tropical and subtropical parts of the world and Mediterranean-type climate areas of the western United States [36]. It might also be endemic to the southern part of the United States [37]. A closely related pathogenic species, *S. hyalinum*, occurs less commonly over a more limited range of tropical and subtropical areas. Like *T. rubrum* infections, *S. hyalinum* and *S. dimidiatum* tend to be chronic, suggesting that the immune response of the host is deficient or ineffective [13].

S. dimidiatum and *S. hyalinum* can produce tinea pedis, tinea manuum, and onychomycosis [38]. Infections caused by these organisms clinically mimic those caused by dermatophytes [38,39]. The clinical pattern of onychomycosis caused by *Scytalidium* species is generally DLSO. *S. dimidiatum*, as an invader of keratin, is able to infect normal nails [13]. Characteristics of onychomycosis caused by *S. dimidiatum* include onycholysis, paronychia, infection of a single nail, and transverse fracture of the proximal nail plate [40,79].

Culture and microscopy

S. dimidiatum and *S. hyalinum* grow well in standard fungal growth media, which provides a source of carbon and organic nitrogen (ie, Sabouraud dextrose). The colonies grow quickly or slowly according to the variant involved, and they produce deeply wooly aerial mycelium in fast-growing strains and compact and domed mycelium with a velvety or wire-wool textured surface in the slower-growing strains associated with the Indian subcontinent and its global diaspora [13,30]. In *S. dimidiatum*, the initially pale surface rapidly darkens to olivaceous gray, mouse gray, or fuscous black. In fast-growing variants, much of the aerial mycelium differentiates within 7 days into chains of cylindrical, oblong, or square-ish arthroconidia that can be one- or two-celled and that vary in size and degree of pigmentation. In slow-growing variants, similar arthroconidia form, but up to 5 weeks of cultivation might be required. Arthroconidia of *S. hyalinum* generally form within 14 days and are hyaline. *S. hyalinum* colonies are powdery white on the surface and pale yellow on the reverse [30].

In *Scytalidium* infections the hyphae have the following characteristics: irregularity in width, sinuous pattern, and a double-contoured appearance, which is brought about by formation of an unusually thick, glassy-looking cell wall [13,41]. Hyphae in *S. dimidiatum* infections are almost always hyaline and smooth but they might rarely be pigmented and sometimes also rough walled [13]. The hyphae in *S. hyalinum* infections are hyaline [13,35].

Table 1
Treatment of *Scopulariopsis* onychomycosis

Reference	Study type	No. of patients (evaluable)	Treatment and results
Tosti et al, 1996 [15]	Case report	3 (3)	ITR(P) (4 pulses)[a] 8 mo after discontinuation of therapy: MC: 1/3, CC: 1/3
Tosti et al, 1996 [15]	Case report	3 (3)	TER 250 mg/d for 4 mo 8 mo after discontinuation of therapy: MC: 0/3, CC: 0/3
Fischer, 1960 [24]	Case report	1 (1)	Information is not available
Fischer, 1960 [24]	Case report	1 (1)	Patient did not report for treatment
Fischer, 1960 [24]	Case report	1 (1)	GRIS 250 mg 4×/d Drug discontinued because *S. brevicaulis* is resistant to GRIS
Onsberg et al, 1980 [64]	Open	15 (7)	1% natamycin in 60% dimethylsulphoxide for 5 wk At follow-up (15 mo after completion of treatment), 2 patients reported permanent improvement and 3 a complete cure
Gupta et al, 2001 [65]	Open, prospective	4 (4)	ITR(P) (3 pulses)[a] At month 12: MC 4/4, clinical cure: 2/4
Gupta et al, 2001 [65]	Open, prospective	1 (1)	TER 250 mg/d for 12 wk At month 12: MC 0/1, clinical cure: 0/1
Ulbricht et al, 1994 [66]	Open, multicenter	51 (NS)	Ciclopirox nail lacquer 8% for 6 mo Data not provided for individual species
Nolting et al, 1994 [57]	Multicenter	7 (7)	TER 250 mg/d for 12 mo At end of treatment: MC: 3/7, CC: 3/7
De Doncker et al, 1997 [70]	Multicenter	21 (21)	ITR(P) (2–4 pulses)[a] At follow-up (12 mo after start of therapy): MC: 17/21, clinical cure: 17/21
De Doncker et al, 1997 [70]	Multicenter	2 (2)	ITR 200 mg/d for 6–12 wk At follow-up (12 mo after start of therapy): MC: 2/2, clinical cure: 2/2
Gupta et al, 2001 [47]	Prospective, comparative, parallel-group, SB, randomized	11 (11)	GRIS 600 mg bid for 12 mo At month 12: MC: 0/11, clinical cure: 3/11, CC: 0/11
Gupta et al, 2001 [47]	Prospective, comparative, parallel-group, SB, randomized	12 (12)	KETO 200 mg/d for 4 mo At month 12: MC: 8/12, clinical cure: 10/12, CC: 8/12
Gupta et al, 2001 [47]	Prospective, comparative, parallel-group, SB, randomized	12 (12)	ITR(P) (3 pulses)[a] At month 12: MC: 12/12, clinical cure: 12/12, CC: 12/12
Gupta et al, 2001 [47]	Prospective, comparative, parallel-group, SB, randomized	12 (12)	TER 250 mg/d for 12 wk At month 12: MC: 11/12, clinical cure: 12/12, CC: 11/12
Gupta et al, 2001 [47]	Prospective, comparative, parallel-group, SB, randomized	12 (12)	FLUC 150 mg/d for 12 wk At month 12: MC: 8/12, clinical cure: 8/12, CC: 8/12

Abbreviations: CC, complete cure; FLUC, fluconazole; GRIS, griseofulvin; KETO, ketoconazole; MC, mycological cure; NS, not stated; SB, single-bind; TER, terbinafine.

[a] Itraconazole Pulse [ITR(P)] given for 200 mg bid for 1 wk on followed by 3 wk off

Fusarium species

Fusarium species are widely distributed in soil and on subterranean and aerial plant parts, plant debris, and other organic substrates [42]. They are common in tropical and temperate regions and are known pathogens of plants, animals, and humans [22]. The genus includes more than 60 species, 10 of which are known human pathogens, with *F. oxysporum*, *F. verticillioides* (*F. moniliforme*), and *F. solani* being the most frequently isolated [29,43]. In humans, *Fusarium* species can cause disease that is localized, focally invasive, or disseminated [44].

Onychomycosis caused by *Fusarium* species—in particular *F. oxysporum*—features characteristic milky lesions [42,45]. The clinical patterns described include SWO, DLSO, and PSO [22]. Though PSO is uncommon, Baran et al [14] found that the combination of PSO with subacute or acute paronychia in an immunocompetent individual is a typical manifestation of *Fusarium* nail invasion. Leukonychia or periungual inflammation can also be associated with PSO [5]. The great toenails are almost always involved; fingernails only rarely manifest this combination of symptoms. *F. oxysporum* can penetrate and invade the keratinous part of the nail plate [42]. Onychomycosis caused by *Fusarium* species is generally a localized infection in immunocompetent individuals; however, in neutropenic individuals, it can act as a source of dissemination leading to a widespread, systemic *Fusarium* infection [22,42,44].

Culture and microscopy

Colonies of species causing human infection are fast growing and white to pale purple, pale tan, or (less commonly) orange on the surface, with colony reverse colors becoming vinaceous, purple, tea brown, chestnut red–brown, orange, or (rarely) carmine on potato dextrose agar [29]. Many isolates rapidly form typical canoe-shaped, multi-celled macroconidia with a distinctive foot cell within 7 to 14 days on potato dextrose or specialized *Fusarium* media [29]. Nearly all human pathogenic species also form copious single-celled, ellipsoidal, club- or sausage-shaped microconidia. Formation of structures on Sabouraud agar is often abnormal; this medium cannot be used in species identification.

Aspergillus species

Aspergillus species, when implicated in colonization of dystrophic nails, are usually considered to be opportunists invading keratins that were altered previously by other diseases [23]; however, studies have often documented *Aspergillus* species as the primary cause of onychomycosis, with SWO being the clinical pattern that is most often seen [23]. Onychomycosis caused by members of the *Aspergillus versicolor* complex is predominantly seen in elderly individuals (>60 years old) and features chronic involvement of the great toenail [46]. When

Table 2
Treatment of *Scytalidium* onychomycosis

Reference	Study type	No. of patients (evaluable)	Treatment and results
Elewski, 1996 [36]	Case report	1 (1)	FLUC 300 mg/wk for 6 wk; increased to FLUC 400 mg/wk then discontinued when organism was identified
Rollman et al, 1987 [67]	Case report	1 (1)	Affected nails partially avulsed using 40% urea ointment prior to application of 1% ciclopiroxolamine cream for 2–4 mo (re-treated if necessary) At follow-up (12 mo after cessation of treatment) all 4 fingernails were MC and clinically cured
Downs et al, 1999 [68]	Case report	1 (1)	Topical 5% amorolfine bid At 8 wk nails markedly improved
Hay et al, 1985 [69]	Open	3 (3)	Tioconazole 28% solution for up to 12 mo At follow-up (3 mo after therapy) 1 patient in clinical and mycological remission
Ulbricht et al, 1994 [66]	Open, multicenter	1 (NS)	Ciclopirox nail lacquer 8% for 6 mo Data not provided for individual species

Abbreviations: FLUC, fluconazole; mc, mycological cure.

proximal subungual onychomycosis is associated with periungual inflammation and black pigmentation of the proximal nail fold, the possibility of onychomycosis caused by *Aspergillus niger* should be considered [23]. The color of the proximal nail fold might result from *A. niger* black conidia within the nail keratin. When similar features are present and associated with greenish discoloration of the nail plate, the possibility of onychomycosis caused by *A. nidulans* and *A. glaucus* should be considered [23]. Purulent discharge from the proximal nail fold might also be present.

Culture and microscopy

In direct microscopy, *Aspergillus* infections show hyaline hyphae that are generally somewhat wider than dermatophyte hyphae. They also tend to bear irregular swellings and vesicles that are distinct from the regular chains of substrate arthroconidia produced in tissue by

Table 3
Treatment of *Fusarium* onychomycosis

Reference	Study type	No. of patients (evaluable)	Treatment and results
Fusarium spp			
Tseng et al, 2000 [22]	Case report	1 (1)	TER cream bid for 4 wk, on follow-up visit patient given cephalexin for 1 wk. Treatment changed to FLUC 100 mg/d then to FLUC 300 mg/wk and increased to FLUC 300 mg bid with periodic nail debridement Significant improvement seen with resolution of paronychia and slow regrowth of normal nail
De Doncker et al, 1997 [70]	Multicenter	1 (1)	ITR 200 mg/d for 6–12 wk At follow-up (12 mo after start of therapy): MC: 1/1, clinical cure: 1/1
De Doncker et al, 1997 [70]	Multicenter	2 (2)	ITR(P) (2–4 pulses)[a] At follow-up (12 mo after start of therapy): MC: 2/2, clinical cure: 0/1
Gupta et al, 2001 [65]	Open, prospective	1 (1)	ITR(P) (3 pulses)[a]. At month 12: MC 1/1, clinical cure: 1/1
Gupta et al, 2001 [65]	Open, prospective	1 (1)	TER 250 mg/day for 12 weeks. At month 12: MC 0/1, clinical cure: 0/1
F. oxysporum			
Romano et al, 1998 [7]	Case report	NS (4)	ITRA(P) (4 pulses)[a] At follow-up (1 y): 3 patients achieved MC and clinical cure
Romano et al, 1998 [7]	Case report	NS (2)	Ciclopirox nail lacquer for 6–8 mo 1 patient completely recovered
Baran et al, 1997 [14]	Case report	1 (1)	Ciclopirox ointment and bifonazole ointment MC and clinical cure achieved
Baran et al, 1997 [14]	Case report	1 (1)	Partial nail avulsion and 8% ciclopirox nail lacquer Complete clearing of the nail lesions
Baran et al, 1997 [14]	Case report	1 (1)	No therapy
DiSalvo et al, 1980 [71]	Case report	1 (1)	Surgically excised Toe appeared to be healed and asymptomatic
Gianni et al, 1997 [72]	Case report	2 (2)	TER 250 mg/d for 3 mo Complete recovery achieved
Gianni et al, 1997 [72]	Case report	2 (2)	ITR 200 mg/d for 3 mo Nail resolved
De Doncker et al, 1997 [70]	Multicenter	1 (1)	ITR(P) (2–4 pulses)[a] At follow-up (12 mo after start of therapy): MC: 1/1, clinical cure: 1/1

Abbreviations: CC, complete cure; FLUC, fluconazole; KETO, ketoconazole; MC, mycological cure; NS, not stated; TER, terbinafine.

[a] Itraconazole Pulse [ITR(P)] given for 200 mg bid for 1 wk on followed by 3 wk off

dermatophytes. In some cases, conidiophores and conidia might be produced in nail fissures. In culture, *Aspergillus* species feature thick-walled, upright conidiophores, each ending in a swollen vesicle that is coated with fertile, conidiogenous cells or short branches bearing tufts of such cells. These cells give rise to rough- or smooth-walled, more or less rounded conidia in long chains. Colonies might commonly be blue, green, tan, white, or black, and they are usually deeply powdery from massive conidial formation.

Onychocola canadensis

Onychocola canadensis is an uncommon organism whose natural habitat is unknown [13,47]. This organism has been identified in Canada, New Zealand, and (more recently) in France and Britain [48,49]. Sigler et al [50] first described this nondermatophyte in three cases of chronic infection of the great toenail. *O. canadensis* frequently affects individuals who are gardeners or farmers, which

Table 4
Treatment of *Aspergillus* onychomycosis

Reference	Study type	No. of patients (evaluable)	Treatment and results
Aspergillus spp			
Gupta et al, 2001 [65]	Open, prospective	6 (6)	ITR(P) (3 pulses)[a] At month 12: MC 5/6, clinical cure: 3/6
De Doncker et al, 1997 [70]	Multicenter	1 (1)	ITR(P) (2–4 pulses)[a] At follow-up (12 months after start of therapy): MC: 1/1, clinical cure: 1/1
Lebwohl et al, 2001 [73]	DB, randomized, placebo-controlled, multicenter	2 (2)	TER 250 mg/d for 12 wk At month 6: MC: 2/2, CC: 1/2
Lebwohl et al, 2001 [73]	DB, randomized, placebo-controlled, multicenter	5 (5)	TER 250 mg/d for 24 wk At month 6: MC: 3/5, CC: 2/5
A. flavus			
Scher et al, 1990 [74]	Case report	1 (1)	Whitfield's ointment bid for several months followed by ITR(C) 100 mg/d for 5 mo At 4 mo almost all of nail plate was normal
De Doncker et al, 1997 [70]	Multicenter	1 (1)	ITR 100 mg/d for less than 20 wk At follow-up (12 mo after start of therapy): MC: 1/2, clinical cure: 1/1
De Doncker et al, 1997 [70]	Multicenter	1 (1)	ITR 200 mg/d for 6–12 wk At follow-up (12 mo after start of therapy): MC: 1/2, clinical cure: 1/1
A. niger			
Tosti, 1998 [23]	Case report	2 (2)	TER 250 mg/d for 3 mo Patients clinically and mycologically cured 6 mo after therapy
Ulbricht et al, 1994 [66]	Open, multicenter	6 (NS)	Ciclopirox nail lacquer 8% for 6 mo Data not provided for individual species
De Doncker et al, 1997 [70]	Multicenter	3 (3)	ITR 200 mg/d for 6–12 wk At follow-up (12 mo after start of therapy): MC: 2/3, clinical cure: 2/3.
A. fumigatus			
Rosenthal et al, 1968 [75]	Case report	1 (1)	Whitfield's ointment for 6 mo Nail appeared normal at month 6
Ulbricht et al 1994 [66]	Open, multicenter	2 (NS)	Ciclopirox nail lacquer 8% for 6 mo Data not provided for individual species

Abbreviations: CC, complete cure; DB, double-blind; MC, mycological cure; NS, not stated; TER, terbinafine.
[a] Itraconazole Pulse [ITR(P)] given for 200 mg bid for 1 wk on followed by 3 wk off

suggests that it might originate in soil [4]. Patients have more often been females than males, and the majority are older individuals [48,49,51].

O. canadensis causes onychomycosis, and it has been suspected—but not demonstrated—to cause lesions of the palms or the toewebs [13]. The clinical pattern of onychomycosis most commonly seen is DLSO. The nail becomes white or yellow in color and is often hyperkeratotic and friable [47]. *O. canadensis* can also cause SWO, which suggests that it has the ability to degrade keratin [47].

Culture and microscopy

O. canadensis is slow growing in culture. The surface texture is velvety, and the colony is typically yellow to pale sandy brown with a deep brown–gray reverse [30,47,51]. Arthroconidia are formed after 14 to 21 days and are broad ellipsoidal to nearly spherical, smooth, usually single-celled (but occasionally two-celled), and they are often found in long, more or less upright chains that do not readily fragment into separate conidia [47]. Old cultures might form distinctive broad, brown, thick-walled, nodose hyphae resembling peridial appendages of the *Arachnomyces* sexual state [51].

Candida species

Candida onychomycosis affects fingernails more often than toenails. Primary *Candida* infection is seen in patients with CMCC or in individuals who are immunocompromised, such as patients who are HIV positive. In these patients, DLSO might be present initially and might progress to total dystrophic dis-

Table 5
Treatment of *Onychocola canadensis* onychomycosis

Reference	Study type	No. of patients (evaluable)	Treatment and results
Sigler et al, 1990 [50]	Case report	1 (1)	Debridement, thymol 4% in chloroform bid for 2 mo Marked clinical improvement, but direct microscopy still positive for fungal filament 9 mo after therapy
Sigler et al, 1990 [50]	Case report	1 (1)	Refused treatment
Sigler et al, 1990 [50]	Case report	1 (1)	Surgical excision; lost to follow-up
Sigler et al, 1994 [51]	Case report	1 (1)	Griseofulvin 6 mo Treatment discontinued because of gastrointestinal distress
Sigler et al, 1994 [51]	Case report	3 (3)	No data
Sigler et al, 1994 [51]	Case report	1 (1)	Oral ketoconazole for 10 d; topical nystatin KETO discontinued because of hepatotoxicity
Sigler et al, 1994 [51]	Case report	1 (1)	Betnovate for psoriasis; no other treatment
Sigler et al, 1994 [51]	Case report	1 (1)	Surgical excision New growth beginning
Gupta et al, 1998 [47]	Case report	7 (7)	No therapy
Gupta et al, 1998 [47]	Case report	1 (1)	TER 250 mg/d for 12 wk then 16 wk; ITR(C) for 4 pulses No data
Gupta et al, 1998 [47]	Case report	1 (1)	ITR(P) (5 pulses)[a] Clinical response; MC
Gupta et al, 1998 [47]	Case report	1 (1)	*T. rubrum* responded to therapy
Koenig et al, 1997 [49]	Case report	3 (3)	Refused treatment
Campbell et al, 1997 [76]	Case report	4 (4)	No data
Contet-Audonneau et al, 1997 [48]	Case report	1 (1)	Econazole powder and TER 250 mg/d No data
Contet-Audonneau et al, 1997 [48]	Case report	3 (3)	Amorolfine nail lacquer No data
Contet-Audonneau et al, 1997 [48]	Case report	1 (1)	Ciclopirox nail lacquer No data
Gupta et al, 2001 [65]	Open, prospective	1 (1)	ITR(P) (3 pulses)[a] At month 12: MC 1/1, clinical cure: 1/1

Abbreviations: KETO, ketoconazole; MC, mycological cure; TER, terbinafine.

[a] Itraconazole Pulse [ITR(P)] given for 200 mg bid for 1 wk on followed by 3 wk off

ease, which involves the entire nail plate. In CMCC, the nail unit and surrounding soft tissues might also be involved [10]. In otherwise healthy individuals, *Candida* can merely cause onycholysis of constantly wetted or damaged nails; in this case the clinical presentation might be distal or lateral onycholysis with or without paronychia [52–54].

Candida albicans is the most common cause of candidal onychomycosis; it accounts for approximately 80% of such infections [53]. More recently, *Candida parapsilosis* is being recognized as a major cause of onychomycosis [55]. For instance, the most frequent *Candida* species stated to cause onychomycosis in Israel is *C. parapsilosis* (39.5% in toenails, 36.7% in fingernails) [56]. In a multicenter study, *C. albicans* and *C. parapsilosis* were implicated in an almost equal number of cases [57]. Other *Candida* species, such as *C. tropicalis, C. krusei,* and *C. guilliermondii* have also less commonly been implicated as causative agents of dermatological infections [52]. In addition, *C. ciferrii* has been associated with onychomycosis in elderly patients with trophic disorders of the legs [58].

Treatment

Studies have reported success in treating non-dermatophyte molds and *Candida* species using terbinafine, itraconazole, and fluconazole. These oral therapies have higher cure rates, higher compliance, and lower relapse rates than the older agents (eg, griseofulvin), and they cause fewer adverse events while requiring shorter treatment durations [59]. Griseofulvin would not be expected to be effective against onychomycosis caused by *Candida* species or non-dermatophyte molds [60]. Compared to dermatophytes, non-dermatophytes might require treatment

Table 6
Treatment of *Candida* onychomycosis

Reference	Study type	No. of patients (evaluable)	Treatment and results
Candida spp			
Segal et al, 1996 [8]	Open	28 (20)	TER 250 mg/d for 16 wk At wk 48: MC: 2/20, CC: 12/20
Lestringant GG et al, 1996 [77]	Open	32 (32)	Amorolfine 5% applied twice weekly for up to 67 wk 90% of nails were cured or showed only minor residual dystrophy
Rashid et al, [80]	Open, noncomparative	13 (13)	ITR(P) (3 pulses)[a] At wk 12: CC: 13/13
Gupta et al, 2000 [78]	Open, multicenter	44 (32)	ITR(P) (2–3 pulses)[a] MC: 29/32, CC: 24/32
Lebwohl et al, 2001 [73]	DB, randomized, placebo-controlled, multicenter	12 (12)	TER 250 mg/d for 12 wk At mo 6: MC: 10/12, CC: 4/12
Lebwohl et al, 2001 [73]	DB, randomized, placebo-controlled, multicenter	11 (11)	TER 250 mg/day for 24 weeks. At mo 6: MC: 11/11, CC: 6/11
C. albicans			
Nolting et al, 1994 [57]	Multicenter	NS (26)	TER 250 mg/d for 12 mo At mo 6: MC: 18/26, CC: 14/26
C. parapsilosis			
Nolting et al, 1994 [57]	Multicenter	NS (32)	TER 250 mg/day for 12 months. At mo 6: MC: 27/32, CC: 20/32
C. albicans and *C. parapsilosis*			
Nolting et al, 1994 [57]	Multicenter	NS (2)	TER 250 mg/day for 12 months. At mo 6: MC: 2/2, CC: 0/2

Abbreviations: CC, complete cure; DB, double-blind; MC, mycological cure; NS, not stated; TER, terbinafine.
[a] Itraconazole Pulse [ITR(P)] given for 200 mg bid for 1 wk on followed by 3 wk off

for a longer period of time [57,61]. Non-dermatophytes have been successfully treated with ciclopirox nail lacquer topical solution 8%. This agent has a broad spectrum of action with activity against dermatophytes and non-dermatophytes (molds and *Candida* species) [61,62]. Tables 1–6 summarize the therapies used to treat onychomycosis caused by non-dermatophytes. It is important to note that not all of the studies present adequate mycological or clinical details, nor are complete cure rates always documented, which suggests a need for improved reporting of results.

S. dimidiatum and *O. canadensis* might be poorly responsive or unresponsive to systemic treatments [61]. *C. parapsilosis* responds better to terbinafine treatment than does *C. albicans* because terbinafine is fungicidal towards *C. parapsilosis* but is only fungistatic towards *C. albicans* [8,57,63].

Summary

Non-dermatophyte organisms are becoming increasingly prevalent in onychomycosis. This apparent emergence might be an artifact of improved diagnostic techniques and increased awareness that these fungi are potential etiologic agents. It is important to bear in mind that all isolated organisms should be evaluated as potential pathogens when diagnosing fungal infections, especially given the increasing use of immunosuppressive drugs and the increasing numbers of chronically immunocompromised individuals. While many patients with non-dermatophyte mold onychomycosis will respond to oral or topical antifungal therapy, poor or incomplete response might still be expected in some patients.

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