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Onychomycosis: Epidemiology, Diagnosis, and Treatment in a Changing Landscape

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ABSTRACT

Onychomycosis is an often overlooked and/or undertreated disease. This may be in part due to an under appreciation among both physicians and patients of its impact on quality of life and the potential for significant complications, from tinea corporis and cruris, to bacterial superinfection. Some health care providers are unaware of the effective low-risk treatments currently available. Changing demographic characteristics such as the relative aging of the population; the increasing prevalence of diabetes and peripheral vascular disease, and widespread iatrogenic immunosuppression; and changes in lifestyle practices such as earlier and greater participation in sports, are likely to lead to an increased prevalence of onychomycosis in both adults and children. Two topical onychomycosis treatments, efinaconazole 10% solution, and tavaborole 5% solution were recently approved by the FDA. This article reviews the state of knowledge and describes, briefly, these new treatment options.

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INTRODUCTION

Nearly half (48%) of nail abnormalities result from documented onychomycosis,[1] with toenails affected most often (toenail-fingernail ratio: 10.6).[2] In addition to its cosmetic impact, onychomycosis can be painful and thereby significantly affect patients' quality of life (QoL).[3,4] These effects increase with disease duration and extent and/or number of toenails affected. The average number of toenails involved is 5, with approximately 15% of patients having all 10 affected.[4] Spontaneous resolution is rare and disease duration is often >5 years.[3,4]

Treatment paradigms will likely shift due to the introduction of new topical agents and the increasing recognition that all ages are at risk for fungal nail infections. This paper will review the epidemiology, diagnosis, and management of onychomycosis in the context of these new developments.

Epidemiology

Disease prevalence estimates vary widely across studies; however, a recent meta-analysis calculated a rate of approximately 4% in North America/Europe.[2] Between-study variation may be due to differences in study location (prevalence varies with geography/cultural practices), study methodology, and population medical office visits, or unselected/general population). Prevalence is clearly higher in males and increases with age.[1,5,6]

Risk factors for onychomycosis include tinea pedis,[6,7] nail trauma,[8] diabetes,[8-11] peripheral vascular disease (PVD),[5,8,12,13] and personal/family history of onychomycosis.[7,8] Significant associations also exist for psoriasis.[7,14] These conditions may contribute to onychomycosis susceptibility via slower/poor nail growth (due to age or poor circulation), immune suppression, and/or nail trauma (diabetic neuropathy, psoriatic nail changes). Vasoconstriction and/or hypoxemia due to nicotine exposure or PVD may further increase the risk of onychomycosis.[12]

The incidence of onychomycosis will likely rise due to projected increases in important risk factors such as age, diabetes, and PVD.

Diabetes

Approximately half (46-50%) of patients with diabetes have toenail abnormalities,[9,15] of which 57-65% are due to onychomycosis[9,11] (13-30% prevalence[9,15,16]). Similar to the general population, older age,[9,16] male gender,[9] PVD,[9] and family history of onychomycosis[9,15] are all significant risk factors among

neuropathy,[15] duration of hyperglycemia,[15] and severity of diabetic nail changes.[16]

Inappropriately managed onychomycosis has the potential to lead to serious complications in diabetic patients, including cellulitis[17] and foot ulcers.[18] The latter conditions may result in additional morbidity including the need for amputation.

Peripheral Vascular Disease

Chronic venous insufficiency is associated with nail abnormalities in 61-84% of patients, and of these, 59-75% are onychomycosis[19,20] (36% prevalence[19]). The relationship between onychomycosis and peripheral arterial disease is less clear.[12,13]

Psoriasis

The majority (78-82%) of psoriasis patients have some nail abnormalities,[21,22] of which 19-31% are related to onychomycosis.[23,24] The prevalence of toenail onychomycosis is 5-13% among US/European psoriasis patients.[23] Male gender,[14,21] older age,[14] and use of certain psoriasis therapies[25] are significant onychomycosis risk factors, although the duration of psoriasis is not.[14]

Pediatrics

Nail abnormalities are present in 0.4-1.8% of pediatric patients,[26-28] representing approximately 5% of all nail abnormalities regardless of age.[29,30] Among children with nail abnormalities, 10-49% are confirmed to be onychomycosis.[26-29,31] A recent retrospective review of all pediatric patients presenting to a large academic dermatology practice noted an incidence of approximately 3%; however, referral bias has likely inflated this number somewhat.[32] Like the adult population, the prevalence of onychomycosis increases with age[26,28-31,33] and is at least as common in boys as girls.[26-29,31,33] The prevalence of, or at least awareness of, onychomycosis appears to be rising in the pediatric population.[33,34] This may be due to greater surveillance, 'perfect progeny' attitudes among parents, earlier and increased participation in sports (leading to greater exposure to fomites and/or more toenail trauma), and/or commonplace use of occlusive shoes.

"Dermatophytes are the primary causative agent in the majority of patients (65% worldwide, 82% in North America) with *T. rubrum* being the most common species."

Diagnosis

Many health care providers frequently diagnose onychomycosis based solely on clinical examination; however, this can be misleading due to overlapping clinical signs and extensive dif-

TABLE 1.

Differential Diagnosis of Onychomycosis

Nail Trauma
Psoriasis
Lichen Planus
Paronychia
Bacterial Infection
Pachyonychia Congenita
Yellow Nail Syndrome
Phlebitis
Twenty Nail Dystrophy
Alopecia Areata
Nail Bed Tumors and Verrucae
Contact/Atopic Dermatitis
Idiopathic Onycholysis
Nail Changes Associated with Systemic Disease or Nail Cosmetics

Presence of unilateral dystrophy involving ≥2 toenails and dystrophy of both the first and fifth toenails on the same foot are predictive of onychomycosis.[6] When onychomycosis is suspected based on clinical examination, the presence of plantar desquamation is also predictive of fungal infection.[35] Dystrophy of a single toenail or of all 10 toenails were neither supportive nor contraindicative of onychomycosis.[6]

Distal lateral subungual onychomycosis (DLSO; 86%) is the most commonly observed subtype, followed by superficial onychomycosis (SO; 14%) and proximal subungual onychomycosis (PSO; 0.23%).[1] Total dystrophic onychomycosis (TDO) and endonyx onychomycosis (EO) are uncommon. In some cases, a mixture of infective patterns is observed, so called mixed pattern onychomycosis (MPO).

Dermatophytes are the primary causative agent in the majority of patients (65% worldwide, 82% in North America) with *T. rubrum* being the most common species (45% worldwide, approximately 59% in North America).[2]

Special Populations

The pattern of causative agents in patients with diabetes[10,11,16] or PVD[19] is similar to the general population. In patients with psoriasis, the pattern is also similar,[23] although the proportion of nondermatophyte molds and yeasts may be greater in patients with psoriasis, most likely due to the increased likelihood of fingernail infections where nondermatophyte mold and yeast infections are more common.[21,36]

Similar to adults, dermatophytes are the most common patho-

overall, toenails are the most common site of infection[27-29,31]; however, the fingernail-toenail ratio and causative agent profile shifts over pediatric age groups. Thus, yeast infections of the fingernails are most prevalent in infants and pre-school–aged children but in patients older than 6 years, dermatophyte toenail infections are most common.[29,33]

Diagnostic Tests

Since onychomycosis is caused by different genera of fungus, it is important to confirm clinical diagnoses utilizing a combination of mycologic culture and microscopy (KOH staining) or histomycology (PAS staining). However, newer PCR techniques have several advantages over these more traditional methods – results are available quickly (days instead of weeks with culture); it is less susceptible to contamination, sampling technique, fungal viability, and morphologic/phenotypic differences; and it is better adapted to identifying mixed infections.[37]

Treatment

Until recently, onychomycosis treatments have been disappointing in terms of efficacy and tolerability. Topical treatments have been largely ineffective due to poor nail bed penetration, and dependent on lacquer-based vehicles and debridement. Systemic treatments have been more effective but potential drug-drug interactions and other adverse effects limit their use.

The efficacy of an antifungal therapy can be assessed by several measures. Mycological cure is usually defined as negative microscopy (KOH) and negative culture results. Complete cure, defined as a completely clear/normal nail (0% nail involvement) and mycological cure, is the FDA's preferred endpoint for the evaluation of antifungal efficacy, although a completely normal nail may be unattainable due to matrix damage. Endpoints like 'almost complete cure' (≤5% nail involvement and mycological cure) and 'clinical cure' (≤10% nail involvement and mycological cure) may be more practical and most patients and physicians find this degree of resolution satisfactory.

Physical Modalities

Laser treatments and photodynamic therapy (PDT) are only FDA-approved for temporarily improving the appearance of affected nails and there is limited published peer-reviewed clinical data on which to base their use.[38] Consequently, most experts feel it is premature to recommend it.

In combination with topical therapy, debridement may reduce symptoms, improve appearance, and lead to better patient satisfaction[39,40]; however, debridement alone has not been shown to impact mycological cure.[41]

Systemic Treatments

Currently available systemic treatments that are widely used the latter is not FDA-approved for onychomycosis. A study comparing all three agents for dermatophyte infections demonstrated clinical (>75% reduction in onycholysis, subungual hyperkeratosis, and percentage of nail involvement) and mycological (KOH and culture negative) cure rates at the end of 9 months (3 months treatment, 6 months follow-up) that were 81% and 75% with terbinafine (250 mg QD), 78% and 61% with itraconazole (200 mg BID, first week each month), and 38% and 31% with fluconazole (150 mg once weekly), respectively, with terbinafine and itraconazole being statistically better than fluconazole.[42] The use of these systemic treatments is often limited by safety concerns such as liver toxicity with terbinafine and fluconazole[43,44] or ventricular disfunction with itraconazole.[45] Potential drug-drug interactions also limit their use (Table 2).

TABLE 2.

Potential Drug-Drug Interactions With Systemic Antifungals

Terbinafine	Itraconazole	Fluconazole
Beta-blockers	Antiarrhythmics	Antiarrhythmics
Antiarrhythmics	Statins	Antipsychotics
Tricyclic Antidepressants	Antihypertensives	Antihistamines
Selective Serotonin Reuptake Inhibitors (SSRIs)	Benzodiazepines Opioids	
Monoamine Oxidase Inhibitors (MAOIs)	Antipsychotics Vasoconstrictors (ie, migraine treatments)	

Following recent regulatory actions related to liver and adrenal toxicity,[46] ketoconazole should not be used to treat superficial fungal infections, including onychomycosis, under any circumstances.

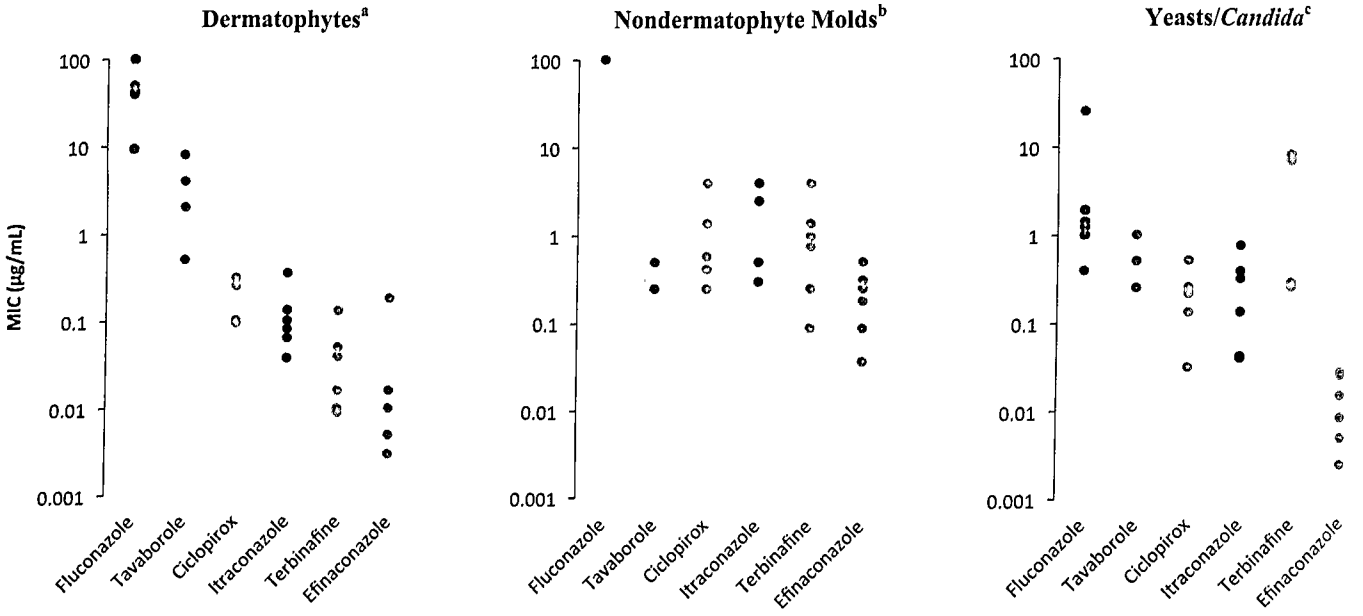
Topical Therapies

With the recent approval of two new agents, available FDA-approved topical treatment options now include ciclopirox 8% nail lacquer, efinaconazole 10% solution, and tavaborole 5% solution. The rates of mycological cure, clinical cure, and complete cure observed in pivotal Phase 3 studies with these topical agents are summarized in Table 3.[47-49] Note that these products were studied in different trials and conclusions regarding comparative differences is not possible.

Considerations for Treatment Choice

Treatment choice may be based on causative agent, particularly differentiating between dermatophytes, yeasts, and molds, though in practice some patients begin treatment without mycologic disease confirmation. In vitro antifungal activities, as measured by minimally inhibitory concentration (MIC),[50-53] are predictive (but not definitive) of clinical success (low MIC val-

FIGURE 1. MIC Values for Fluconazole,[50] Tavaborole,[51,52] Ciclopirox,[52,53] Itraconazole,[53] Terbinafine,[53] and Efinaconazole.[53]



[a] *T. rubrum, T. mentagrophytes, E. floccosum, T. tonsurans, M. gypseum, M. canis*
[b] *A. fumigatus, F. solani, A. potronii, A. sclerotigenum, A. sydowii, S. brevicaulis*
[c] *C. albicans, C. neoformans, C. parapsilosis, C. tropicalis, C. krusei, C. glabrata*

TABLE 3.

Topical Treatment Efficacy[a]

	Ciclopirox vs Vehicle	Tavaborole vs Vehicle	Efinaconazole vs Vehicle
Mycological Cure			
(negative microscopy [KOH] and negative culture)	29-36% vs 9-11%	31-36 vs 7-12%	56% vs 17%
Clinical Cure			
(some nail involvement and mycological cure, not defined consistently)	7-12% vs 1%[b]	26-28% vs 9-15%[b]	28% vs 8%[c]
Complete Cure			
(0% nail involvement and mycological cure)	6-9% vs 0-1%	7-9% vs 1-2%	19% vs 5%

[a] due to differences in study design, direct comparison between agents is not possible
[b] 'almost complete cure' (≤10% nail involvement and mycologic cure)
[c] 'almost complete cure' (<5% nail involvement and mycologic cure)

Overall, the evidence to date supports the use of topical treatment for patients with mild-to-moderate onychomycosis. There is interest in considering topical therapy for maintenance/preventative[54] or booster therapy,[55] though this has yet to be formally studied.

In pediatric patients, topical therapy may be particularly effective due to faster nail growth and thinner nails,[56] and parents certainly may appreciate that topical therapy does not require laboratory monitoring. In addition, early topical treatment, instituted when the disease is still mild, may alleviate the necessity for systemic therapy, and may also prevent permanent nail plate alterations.

For patients with severe onychomycosis and/or poor prognosis factors,[7] oral treatment or combination oral-topical treatment

ticular challenge. Little clinical data are available about the prevalence or treatment of these infections, but both terbinafine[62] and itraconazole[63] have proven effective in treating mixed nondermatophyte-dermatophyte infections.

Whether the newer topical agents can treat severe onychomycosis as monotherapy has not been determined.

CONCLUSION

Our understanding of the epidemiology and optimal treatment of onychomycosis continues to evolve. As the population ages and other high-risk groups expand (diabetes, PVD), the prevalence of onychomycosis is expected to increase. Current research suggests that prevalence may also be increasing

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