Treatment of Onychomycosis in Diabetic Patients

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In 2005, the estimated number of Americans with diabetes was 20.8 million people, with an additional 1.5 million cases diagnosed that year in those ≥ 20 years of age.[1] Onychomycosis is a fungal infection of the nail that is estimated to cause up to 50% of all nail problems[2] and 30% of all cutaneous fungal infections.[3] Approximately one in three people with diabetes are afflicted with onychomycosis.[4] Many studies have been undertaken to assess whether diabetic individuals suffer from a higher incidence of onychomycosis than those without diabetes,[4–10] and most have concluded that they do. One study observed an increased risk among all three major groups of organisms that can cause onychomycosis: dermatophytes, yeasts, and nondermatophyte molds.[5]

Onychomycosis in people with diabetes is more than a cosmetic nuisance; it increases the risk for other foot disorders and limb amputation.[4,10–22] The outcome from not treating onychomycosis in diabetic patients can be worse than in those without diabetes. Thus, effective treatment in these patients is of paramount importance.[13] Because onychomycosis in diabetic patients can lead to many complications, most insurance companies cover treatment in documented cases. Thickened, dystrophic nails can be very painful and make walking difficult. Injury to adjacent skin from mycotic nails may occur without patients' awareness and can lead to secondary infections, both fungal and bacterial, including paronychia and cellulitis.[3,4,9,14,15] Thickened nails can cause erosions of the nail bed and hyponychium because of pressure, just as tight shoes can cause friction blisters in these patients. When combined with peripheral neuropathy, blisters and erosions may progress to cellulitis or osteomyelitis of the underlying bone.[3,4,14,15] Extension of the fungal infection to surrounding skin causes tinea pedis, which may lead to fissures in the plantar and interdigital skin. These may also provide a route for the entry of bacteria.[15]

Patients with diabetes-related comorbidities are at especially increased risk for morbidity in onychomycosis. Diabetic patients suffering from decreased foot sensation are more prone to trauma, which damages the nail and nail matrix, opening portals of entry for the fungus to infect the nail.[13,15] Some diabetic patients can be obese, which may make the act of bending over to examine their feet difficult.[15] Diabetic patients with cataracts[16] or retinopathy[15] may be unable to properly examine their feet regularly. Retinopathy has been found to be an independent risk factor for onychomycosis in diabetes.[9] Other risk factors include peripheral neuropathy,[3,9,15] impaired peripheral circulation,[4,9] age,[4,9] family history,[4] and intake of immunosuppressant drugs.[4] In addition, duration of diabetes is correlated with severity of onychomycosis when present.[4] Male diabetic patients have a three times higher risk of onychomycosis than female diabetic patients.[4]

IN BRIEF

Onychomycosis is more common in diabetic than nondiabetic patients. It is more than a cosmetic problem, and diabetic patients have a greater risk of serious complications from the disease, including limb amputations. This article reviews the various diagnostic and therapeutic options available for onychomycosis with an emphasis on their roles in diabetic patients.

The presence of fungal infection in the nails increases the risk of other infections of the foot and leg. In one study, diabetic patients with onychomycosis had a 15% rate of secondary infections compared with a 6% rate of secondary infections in diabetic patients without onychomycosis. Additionally, diabetic patients with onychomycosis had an approximately three times greater risk of gangrene or foot ulcer compared with diabetic patients without it.[10]

The total annual costs for toe, leg, and foot amputations in the United States in 2003 was almost $2 billion.[17] These costs covered 112,551 total amputations, with an average cost of $16,826 for each procedure.[17] In 2001, the total cost of amputations in diabetic patients was > $1.6 billion.[18] The majority of lower limb amputations occur in diabetic patients.[19] Because the risk of amputation increases with onychomycosis, it is imperative for clinicians to examine diabetic patients' feet and, when suspicious, obtain a sample for diagnosis.

Causes of Onychomycosis

Three classes of fungi can cause nail infections in humans: dermatophytes (especially *Trichophyton* species), yeasts (e.g., *Candida albicans*), and nondermatophyte molds.[2,20] Dermatophytes constitute the vast majority of infectious

etiologies.[21] In one epidemiological survey, dermatophytes were found in 82% of isolates and *Candida albicans* in ~ 7%.[22]

Diagnosis of Onychomycosis

Clinical diagnosis

Infected nails appear thick, brittle, and discolored, often with a yellow hue. The nail plate may separate from the nail bed (onycholysis), and there may be inflammation of the skin near the nail edge (paronychial inflammation).[20]

Onychomycosis has four classic clinical presentations in nails. Distal and lateral subungual infection is the most common type. In this pattern, the infection spreads proximally from the distal or lateral aspects of the nail, eventually raising the free edge of the nail plate and causing onycholysis and nail-plate thickening with subungual hyperkeratosis. The infection spreads proximally, causing yellow-brown discolorations.[23] The most common organism is *Trichophyton rubrum*, followed by *Trichophyton mentagrophytes*. *Candida* species also cause this pattern of infection, as can molds such as the *Aspergillis* and *Fusarium* species. When complicated by infection with pigmented molds or bacteria such as *Pseudomonas aeruginosa*, the nails may appear dark green to black.[23]

Proximal subungual infection is rare but more common in AIDS and immunosuppressed patients. In this pattern, the organisms invade via the proximal nail fold and spread to the nail matrix and then the deep surface of the nail plate.[23]

White superficial onychomycosis is normally limited to the toenails. It presents with small well-defined superficial white patches on the nail that can merge to cover the entire nail.[16,23] The diseased nails are brittle and may crumble. The vast majority of the cases are caused by the fungus *Trichophyton interdigitale*.

Total dystrophic onychomycosis is the most severe clinical manifestation of onychomycosis. In this form, the entire nail except for small fragments is destroyed, leaving a thickened nail bed.[23]

Differential diagnosis

Only 57% of diabetic patients with abnormal-appearing toenails are confirmed to have onychomycosis.[4] Many common disorders, including psoriasis, lichen planus, onychogryphosis, trauma, and idiopathic dystrophic nails are included in the differential diagnosis.

Psoriasis is the most common disorder that mimics onychomycosis[24] and can show subungual hyperkeratosis, onycholysis, and onychodystrophy of the entire nail.[23] Although psoriasis usually also has classic manifestations on other skin areas, it can be limited to the nails. Pitting and "oil drop" spots are far more common in psoriasis than in onychomycosis.[23,24] Often in psoriasis a "salmon patch," an irregular yellow or pink area under the nail plate, will be present. This does not occur in onychomycosis.[25]

Patients with lichen planus can have nail manifestations of the disease.[24] Clinicians should carefully examine patients' extremities and mucous membranes for the pathognomic violaceous papules.[26] Lichen planus can affect both fingernails and toenails, causing them to become brittle and ridged. Subungual hyperkeratosis and distal onycholysis may also occur.[27]

Onychogryphosis is a severe deformation of the nail, most often affecting the great toes. The nail becomes very thick and discolored, resembling a ram's horn. The nail bed can become hypertrophied. Onychogryphosis is most commonly caused by infrequent nail cutting and impaired peripheral circulation but may also be caused by trauma.[28]

Repeated trauma to the nails, which can increase the risk of onychomycosis,[5] can cause distal onycholysis with subsequent microbial colonization and altered pigmentation.[24] In addition, a subungual hematoma from trauma may cause discolorations that can be confused with onychomycosis.[25]

Normal nails can have morphological variation, especially as an individual ages. White spots and lines in the nails, leukonychia punctata, and transverse striate leukonychia are benign and may result from minor trauma to the nail matrix.[27] Onycholoysis can be idiopathic or caused by trauma.[28] Dermatophytes can be found in idiopathic onycholysis but are considered to be commensal.[29]

Laboratory diagnosis

The standard of care in diagnosing onychomycosis is clinical impression with one confirmatory laboratory finding, such as KOH-prepared direct microscopy, fungal culture, or histopathology with periodic acid Schiff (PAS) staining.[30–32] It is important to verify clinical suspicion with laboratory investigations. One study compared the costs of empirically treating all patients with onychodystrophy with antifungals versus PAS staining all nails and treating only those with a positive histology. The study found that it was cost-effective to first diagnose and then treat empirically.[33]

Samples for microscopy, culture, or histopathology can be collected from the nail plate or subungual debris. When collecting a sample, care should be taken with diabetic patients to avoid injuring the nail bed, which may increase the risk of secondary bacterial infection.[15]

Histological examination. Most clinicians find it easiest to send nail clippings for histopathological evaluation with a PAS stain. Clippings are sent to the pathology laboratory in formalin, are embedded in paraffin, and are stained with haematoxylin, eosin, PAS, and toluidine blue.[23] This method, also called "PATHPAS," has been shown to be the most sensitive test.[30,32,34] One study evaluated 105 patients with suspected onychomycosis using KOH preparation, culture, biopsy with PAS stain, and biopsy with calcoflur white stain. Biopsy with calcoflur white stain was considered the gold standard. The study found that the KOH preparation was 80% sensitive and 72% specific,

biopsy with PAS stain was 92% sensitive and 72% specific, and culture was 59% sensitive and 82% specific.[34]

Direct examination. Collected pieces are placed on a slide and treated with 10–30% KOH solution. The slide may be warmed over a flame to quicken the clearing of the nail and highlight the fungal features. Some recommend a combination of KOH and dimethylsulfoxide for clearer and faster results.[23] Onychomycosis caused by dermatophytes can be diagnosed based on the appearance of long, regularly-shaped hyphae. If yeasts are the etiological agent, the appearance of budding spores can often be seen.[21] Although the appearance of the nail may provide clues to the etiological agent, it cannot be used to diagnose the agent.[23]

Culture. Culture alone without clinical manifestations should not be used to diagnose onychomycosis.[21] Cultures may be positive without a truly invasive infection because of contamination with comorbid onychodystrophy.[5] For culture, samples from the nail plate and subungual keratosis should be placed in Sabouraud's agar and incubated at 26º C for 7–14 days.[20,23] Antibiotics in the agar prevent the growth of coexisting bacteria. If possible, samples should be placed on agar both with and without cycloheximide because cycloheximide inhibits the growth of most nondermatophytes.[23] Unfortunately, culture is less sensitive than direct microscopy, especially when a patient has already been given treatment. However, culture is the only method available for identification of the specific pathogen, which may be helpful in the choice of therapy, particularly if the nails do not respond to therapy with oral terbinafine (discussed below).[20]

Treatment of Onychomycosis in Diabetes

The treatment of onychomycosis in diabetic patients is the same as in patients without diabetes.[13] Toenails grow at one-third to one-half the rate of fingernails and thus need to be treated longer.[23] Elderly diabetic patients' nails may grow even slower and require a longer duration to treat.[15] Several modalities can be used for the treatment of onychomycosis in diabetic patients: topical therapy, systemic therapy, combination therapy, and nail removal.[15,23] Patients > 55 years of age may have a higher rate of relapse. In addition, patient education is vital to reduce the risk of recurrence. Many studies have compared the mycological cure rates, recurrence rates, and cost-effectiveness of the various treatment options. Although it has been shown that diabetic patients with onychomycosis have a higher rate of complications and infections than diabetic patients without onychomycosis,[10] to our knowledge, no study has compared treatment options with outcomes such as diabetic complications or secondary infections.

Topical therapy

There are three classes of topical antifungal creams: polyenes (e.g., nystatin), imidazoles (e.g., clotrimazole), and allylamines-benzylamines (e.g., terbinafine). All three are active against *Candida*, but only imidazoles and allylamines-benzylamines are active against dermatophytes.[20] In general, topical therapy is not adequate for clearing nail infections, probably because of inadequate penetration of the medication into the affected tissues and nail bed.[23] The exception to this is superficial white onychomycosis, which is easily treated with a topical agent because the organism grows on the upper nail plate rather than in the nail bed.

Antifungal nail lacquers are available for treating onychomycosis and penetrate the nail better than creams and gels. One lacquer contains the active ingredient amorolfine, which is in a new class of antifungals, the morpholines. Another lacquer contains ciclopirox, which has a broader spectrum of activity.[23] Nail lacquers are applied daily for 48 weeks, and once-weekly removal with nail polish remover is required. Mycological cure rates (negative results on microscopy and fungal culture) in U.S. studies have been as high as 36%.[35]

Topical antifungals alone do have a place for the reduction of relapses and reinfection once the initial infection has been fully treated.[14] One author recommends using a miconazole nitrate 2% powder every 3 days to the web spaces to prevent relapses once the initial infection has been completely treated.[14]

Oral therapy

Many studies have evaluated systemic treatments for onychomycosis in the general population. However, diabetic patients with onychomycosis pose a special problem because they frequently take other medicines and have other health problems.[36]

Oral agents (summarized in Table 1) are absorbed via the circulation through the nail bed and take ~ 7 days to reach minimal inhibitory concentration (MIC). Once administration of the drug is discontinued, it can remain active in the nail for up to 90 days, and the nail does not need to be completely clear before the medication is stopped.[14]

Griseofulvin was the standard oral therapy for onychomycosis for > 30 years. However, it has a narrow therapeutic window and significant adverse reactions. It also has several interactions with other drugs and is active only against dermatophytes, with a cure rate of < 40%. For these reasons, it is rarely used today to treat onychomycosis.[23]

The imidazole class of medications is active against most of the organisms that cause onychomycosis. However, they are not approved for the treatment of onychomycosis in the United States. Ketoconazole is slightly more efficacious than griseofulvin but also has many adverse effects and drug interactions.[20] It is rarely used to treat onychomycosis today.[23] Fluconazole, 300 mg once a week for 6 months, is more efficacious and has been shown to be safe.[37]

Itraconazole, a triazole antifungal, binds more specifically to fungal cytochrome P-450 than other azoles, reducing the incidence of side effects. It is active against dermatophytes *Candida*

Table 1. Oral Medications for Onychomycosis

Drug	Organisms	Dosage	Length of Treatment	Common Side Effects	Common Drug Interactions	Monitoring/Other
Griseofulvin	Dermatophytes	500–1,000 mg daily	Until infection clears	Rash Uritcaria Nausea Vomiting Diarrhea Headache	Warfarin Barbiturates Oral contraceptive pills	Liver function tests Renal function tests Complete blood count every 6–8 weeks
Fluconazole	Dermatophytes, some nondermatophyte molds, *Candida spp.*	150–300 mg weekly	Fingernails: 6–9 months Toenails: 12–18 months	Nausea Headache Rash Vomiting Diarrhea	Cimetidine Hydrochlorothiazide Tolbutamide Glipizide Glyburide Phenytoin Theophylline	Pretreatment liver function test in patients with known hepatic abnormality Not FDA-approved for onychomycosis
Itraconazole	Dermatophytes, some nondermatophyte molds, *Candida spp.*	Pulse: 200 mg twice daily for 1 week each month	Fingernails: 6 weeks Toenails: 12 weeks	Headache Diarrhea Dyspepsia Flatulence Abdominal pain Dizziness Rash	Statins Benzodiazepines Terfenadine Carbamazepine Anticonvulsants Antacids H_2-blockers Proton pump inhibitors Erythromycin Clarithromycin Digoxin Verapamil Oral hypoglycemics Buspirone Methylprednisolone Warfarin	Pretreatment liver function test in patients with known hepatic abnormality
Terbinafine	Dermatophytes, some nondermatophyte molds, **NOT** *Candida spp.*	250 mg daily	Fingernails: 6 weeks Toenails: 12 weeks	Gastrointestinal disturbance Rash Nausea Diarrhea Taste disturbance	Caffeine Theophylline Warfarin β-Blockers Cimetidine	Pretreatment liver function test Complete blood count in immune-suppressed patients

FDA, U.S. Food and Drug Administration

and *Aspergillus* but not *Scytalidium*, a mold.[23] Because it is lipid-soluble, it remains in the nail plate long after the drug is discontinued. It has been detected 6 months after discontinuation after a 3-month course. Using 200 mg daily for 3 months achieved a mycological cure rate of 79% 6 months after therapy.[38] Because of the high cost of itraconazole, a pulse regiment has been formulated and tested. Pulse treatment involves using 200 mg twice daily for 1 week during each of 2 months in fingernails and 3 months in toenails. Pulse therapy has been reported to be just as effective as continuous therapy with fewer adverse events and half the cost.[39]

Azole antifungals, including itraconazole and fluconazole, have been shown to elevate levels of oral hypoglycemic drugs.[15] Nevertheless, systemic therapy with itraconazole has been found to be safe and effective for use in diabetic patients at a dose of 200 mg twice daily.[40,41] No statistically significant changes in hemoglobin A_{1c} levels have been noted in diabetic patients receiving pulse itraconazole for 3 months.[40]

Terbinafine, an allylamine antifungal drug, is the first-line agent for treating onychomycosis. Unlike itraconazole's wide spectrum of activity, terbinafine is only active in vivo against dermatophytes and does not treat *Candida* or mold species.[23] Terbinafine, 250 mg once daily for 3 months, has been shown to achieve a mycological cure rate of 82% in toenail onychomycosis and 71% in fingernail onychomycosis.[42] In one multicenter trial, 89 patients with diabetes (both insulin dependent and non–insulin dependent) and onychomycosis were treated with continuous oral terbinafine, 250 mg for 12 weeks, and were followed for 36 weeks posttreatment. After 48 weeks, a mycological cure rate of 73% was achieved. There were no reported episodes of hypoglycemia.[36] Another study of 81 diabetic patients with onychomycosis found equal efficacy of terbinafine in individuals with and without diabetes.[43] Pulse therapy with terbinafine has not been shown to be as efficacious as continuous therapy.[44,45]

Terbinafine does not have any significant interactions with oral hypoglycemic drugs.[46] One study examining the safety and efficacy of terbinafine found that although 9.1% of diabetic subjects had serious adverse events while on terbinafine, no causal relationship between the drug and the events could be found. It was concluded that terbinafine is relatively safe in diabetic patients and is acceptable for the long-term maintenance of healthy nails in diabetic patients.[47]

Studies comparing continuous terbinafine and continuous itraconazole have shown mixed results. One study found a 73% mycological cure rate for continuous terbinafine compared with 45.8% in continuous itraconazole for 12 weeks. Both drugs were well tolerated.[48] Another study comparing continuous terbinafine and pulse itraconazole in elderly patients for 12 weeks plus an additional 4 weeks, if needed, after 6 months found a mycological cure rate for continuous terbinafine of 64% compared with 62.7% for pulse itraconazole.[49] A second study of 496 patients with onychomycosis comparing continuous terbinafine with pulse itraconazole found that after 72 weeks in groups who were treated for 12 weeks, 75.7% of the terbinafine group achieved a mycological cure compared with 38.3% in the itraconazole group. In groups who were treated for 16 weeks, 80.8% of the terbinafine group achieved a mycological cure compared with 49.1% in the itraconazole group.[50] A third study looked at long-term cure and relapse rates in continuous terbinafine compared with pulse itraconazole for 12 and 16 weeks. After 5 years, 47% of the terbinafine group compared with 13% of the itraconazole group still had negative mycology.[51]

The newer antifungal agents, including terbinafine and itraconazole, rarely cause serious adverse reactions.[52] Common adverse reactions occurring while patients took terbinafine included headache (12.9%), diarrhea (5.6%), rash (5.6%), and dyspepsia (4.3%). Liver enzyme abnormalities occurred in 3.3%.[53] Common adverse reactions occurring while patients took itraconazole to treat onychomycosis of the toenails included headache (10%), rhinitis (9%), upper respiratory tract infection (8%), and sinusitis (7%). Liver enzyme elevations caused discontinuation of therapy in 4%.[54] With both agents, the frequency of adverse events is comparable to placebo.[52] The manufacturer of terbinafine recommends obtaining pretreatment liver function tests in all patients and monitoring a complete blood count in immunosuppressed patients receiving terbinafine for > 6 weeks.[53] The manufacturer of itraconazole recommends obtaining liver function tests only in patients who have preexisting liver function abnormalities or who have had liver abnormalities while on other medications.[54]

Another consideration in choosing medications is cost, especially considering the long course of treatment for onychomycosis. One study examined the total cost of therapy for continuous terbinafine compared with continuous itraconazole. This study included the costs for the initial physician visit, follow-up visits, mycology, various recommended laboratory investigations while patients are on the medications, and the costs for treating the various adverse reactions that could be expected for each of the medications. The final cost to treat onychomycosis with continuous terbinafine was $697.55–$699.11 compared with $1,216.40–$1,218.80 for continuous itraconazole.[55] However, the costs are comparable if pulse itraconazole is compared with continuous terbinafine.

Combination therapy

Combining oral and topical antifungals is a newly developed treatment option that increases the likelihood of a cure. One study showed improved efficacy of terbinafine when combined with topical amorolfine.[56] Another showed improved efficacy of continuous itraconazole

when combined with topical amorolfine.[57] Yet another compared three groups of patients: those who received terbinafine (4 weeks on, 4 weeks off) and 48 weeks of topical ciclopirox; those who received continuous terbinafine for 12 weeks and 48 weeks of ciclopirox; and those who received only 12 weeks of continuous terbinafine without topical antifungal medicine. Mycological cure was seen in 66.7, 70.4, and 56.0%, respectively.[58] Another study found a mycological cure rate of 88.2 versus 64.7% when continuous terbinafine for 16 weeks was combined with topical ciclopirox for 9 months.[59]

Nail removal, avulsion

Removal of diseased nails can be used as an adjunctive therapy but not as the sole therapy for onychomycosis.[23] Surgical nail avulsion is rarely used to treat onychomycosis in diabetic patients because of their increased risk for secondary infections, gangrene, and poor wound healing.[60] However, in severe or refractory cases, nail removal may be used.[20] It may also be used when oral therapy is contraindicated or ineffective.[3,61]

Education

High-risk diabetic patients, especially those with peripheral neuropathy or peripheral vascular disease, need to be educated about proper foot and leg examinations.[14] In patients with a history of onychomycosis, it is especially important to examine the web spaces, heels, and perionychium for any breaks in the skin.[14] It is important to stress that patients cannot rely solely on discomfort or pain because of decreased sensation.[14]

Conclusion

Onychomycosis is an important cause of morbidity in diabetic patients, increasing their risks for limb amputation and local and systemic secondary bacterial infections. Because onychomycosis is more common in diabetic patients and can complicate the disease, clinicians must be vigilant in its diagnosis and complete in its treatment.

The most sensitive method for diagnosis is pathology with PAS staining. Culture is also important to guide the choice of therapy. Currently, the most effective therapy is 250 mg of oral terbinafine daily for 12 weeks, possibly with concomitant topical therapy with a nail lacquer, such as amorolfine or ciclopirox. Patients should be treated until mycological cure is achieved, and they must be followed closely for recurrent infection. If the causative organism is a yeast or mold, pulse itraconazole should be used instead. After treatment, suppressive topical therapy may be used, such as miconazole nitrate 2% powder every 3 days. In addition, patient education, including proper foot and toe examinations, is essential to prevent relapses and complications.

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