Onychomycosis and the Role of Topical Antifungals

Warren Joseph, DPM, FIDSA (chair), Richard Pollak, DPM, FACFAS, Tracey Vlahovic, DPM, Bryan Caldwell, DPM, Maureen Jennings, DPM, Scott Ashton, DPM, FACFAS, Bryan Markinson, DPM, FASPD, Alex Reyzelman, DPM, FACFAS, Jay Lifshen, DPM, FACFAS, Harry Goldsmith, DPM

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Panelists

Warren Joseph, DPM, FIDSA (Chair)
Dr. Joseph is a consultant in lower extremity infectious diseases and is a Fellow of the Infectious Diseases Society of America. He is affiliated with Roxborough Memorial Hospital in Philadelphia.

Richard Pollak, DPM, FACFAS
Dr. Pollak is a Diplomate of the American Board of Podiatric Surgery and Fellow of the American College of Foot and Ankle Surgeons. He is in private practice in San Antonio.

Tracey Vlahovic, DPM
Dr. Vlahovic is an Associate Professor and J. Stanley and Pearl Landau Faculty Fellow at the Temple University School of Podiatric Medicine. She is a Diplomate of the American Board of Podiatric Surgery.

Bryan Caldwell, DPM
Dr. Caldwell is the Assistant Dean and Professor of Clinical Education and Clinic Operations at the College of Podiatric Medicine at Kent State University. He is a Diplomate of the American Board of Podiatric Medicine.

Maureen Jennings, DPM
Dr. Jennings is the President of the Jennings Institute for Clinical Research in Brick, NJ She is an Adjunct Professor at Georgian Court University in Lakewood Township, NJ, and previously completed an NIH fellowship in clinical pharmacology at the Cornell University Medical Center.

Scott Ashton, DPM, FACFAS
Dr. Ashton is board certified by the American Board of Podiatric Surgery and the American Board of Quality Assurance and Utilization Review Physicians. He is a Fellow of the American College of Foot and Ankle Surgeons. Dr. Ashton is in private practice at multiple office locations in Texas.

Bryan Markinson, DPM, FASPD
Dr. Markinson is the Chief of Podiatric Medicine and Surgery in the Leni and Peter W. May Department of Orthopedic Surgery at the Mount Sinai School of Medicine in New York City. He is board certified by the American Board of Podiatric Medicine.

Alexander Reyzelman, DPM, FACFAS
Dr. Reyzelman is the Co-Director of the UCSF Center for Limb Preservation in San Francisco, and is an Associate Professor at the California School of Podiatric Medicine at Samuel Merritt College. He is board certified in foot surgery by the American Board of Podiatric Surgery.

Jay Lifshen, DPM, FACFAS
Dr. Lifshen is certified by the American Board of Podiatric Surgery. He is the founder and president of Podiatric Medical Partners of Texas, PA and is the podiatric consultant to the Dallas Mavericks of the NBA. He practices in Irving, Tx.

Harry Goldsmith, DPM, CSFAC
Dr. Goldsmith is the CEO of Codingline. He is board-certified (administrative) by the American Board of Podiatric Surgery and is a certified surgical foot and ankle coder.

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Onychomycosis: An Infectious Disease

Warren Joseph, DPM, FIDSA

Onychomycosis is an infectious disease that should be treated with anti-infectives. Relatively rare 100 years ago, onychomycosis has become more common because of changes in lifestyle (in particular urbanization, communal bathing areas, use of occlusive footwear, and increasing incidence of diabetes and HIV infection). The correlation between diabetes, tinea pedis and onychomycosis is well known. Also, people are involved in occupations and activities today that carry an increased risk, such as miners, soldiers and runners.[1]

As an infection, onychomycosis has a genetic predisposition; an autosomal dominant trait with an inability to mount a cell mediatied response to *T. rubrum*. Left untreated onychomycosis is a progressive disease, spreading within the toenail to the rest of the toenails, and to other parts of the body. It can also spread from one person to the other. As a result, patients will often ask, "Is this contagious?" It can cause an immunologic response, affect quality of life (QoL), and as with any infection lead to recurrence or re-infection. This relapse can be a major issue because whenever a new product comes out for onychomycosis, people will ask, "Why should I treat it? It is just going to come back." We are not curing the disease. We are putting it into remission, and this leads to the important question about how we manage onychomycosis long-term.

Onychomycosis is progressive, recurring and requires treatment.[2,3] There can be psychological issues if it impacts QoL, and it can be symptomatic causing pain on ambulation.[4] There are risks for further complications especially in our diabetic patients, those with peripheral vascular disease (PVD) and the immunocompromised patient.[5] Onychomycosis is a reservoir for infection, spreading to other nails and anatomical sites[4] and other individuals.[5] There can also be systemic or multi-system involvement. For example, it may be a trigger for asthma attacks in rare cases,[6] and be a source of cellulitis.[5]

Onychomycosis is a common nail disease with over 35 million people having it in the United States. It causes 11.2 million office visits and the number of patients diagnosed with onychomycosis is about 6.3 million.[7] There are a significant number of patients who have onychomycosis, but have never been to a physician to be diagnosed. There is an increase in incidence with age. In those patients who are diagnosed, 59% are aged 55 and over, and only 20.5% of the diagnosed population are between ages 30 and 45.[7] In addition, podiatrists tend to see an older population than dermatologists.

Onychomycosis accounts for approximately 50% of all nail disease.[8] In discussing the epidemiology of onychomycosis it is important to consider the host, the environment and the pathogen (**Figure 1**). There is little that can be done about the host (age, genetic make up, co-existing diseases), and the key pathogens, *T. rubrum* or *Trichophyton mentagrophytes* are ubiquitous organisms that you can find in most places.

Onychomycosis can be caused by dermatophytes, molds or yeast. While the most common are *T. rubrum* and *T. mentagrophytes*, variation exists worldwide.[9] The role of molds as a pathogen is still not clear. Although they do not have the capability of digesting keratin, so it is unclear physiologically how they would cause infection. There appear to be 2-3 molds that can be pathogens and significant criteria do need to be met for diagnosis of a mold infection.

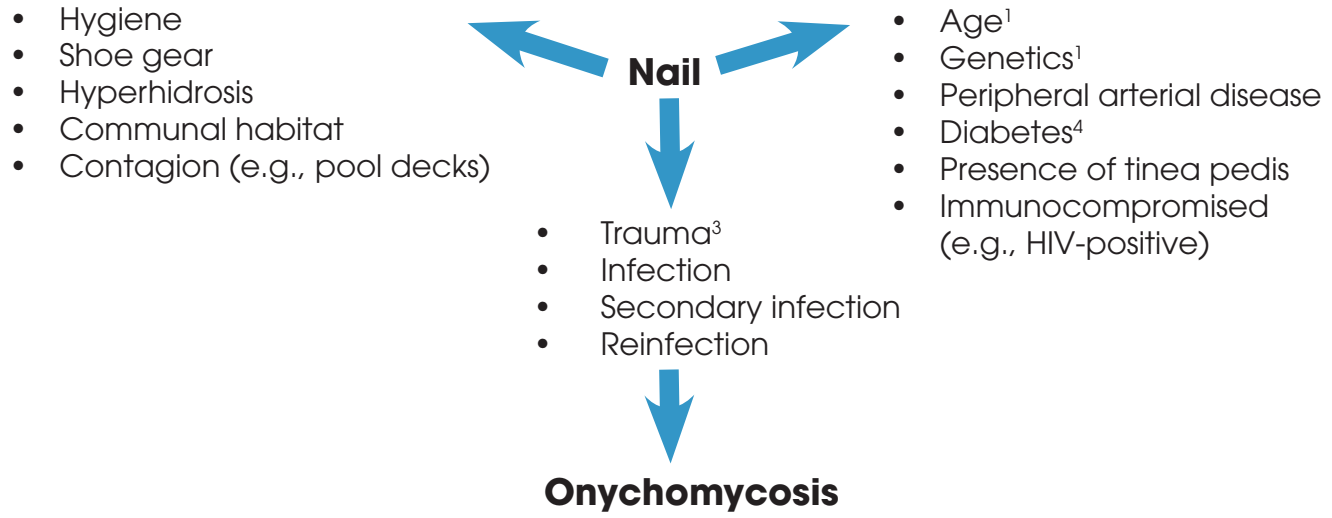
In diagnosing onychomycosis, most studies suggest that periodic acid-Schiff (PAS) staining of nail clippings is probably the most sensitive and predictive test,[10,11] but it is not specific to the individual organism unlike mycological fungal culturing. Fungal culture is the only test that can confirm a specific pathogen, mode of infection and vitality of fungi.[10,11] However, there are limitations. For example, it may take up to a month for cultures to grow, and the vitality of the cultures may be adversely affected by transport to a remote laboratory.[12] There is a wide variability in KOH sensitivity and this test is prone to false positive/false negative results.[10] Molecular means of diagnosis is probably the future (especially polymerase chain reaction [PCR] and molecular sequencing). What are the best ways to make a diagnosis in your everyday practice, and what will the payors accept to confirm a diagnosis of onychomycosis are two important practical questions we face every day.

As we have already discussed, onychomycosis can have a significant impact on QoL. A total of 258 patients with confirmed onychomycosis were surveyed by telephone at three centers using a validated questionnaire.[13] Pain was found in 48% of patients, embarrassment 7%, nail pressure 40%, shoe discomfort 38% and physician visits averaged 3.8/year.[13] This research is important for two reasons – the incidence of pain and the number of physician visits. Any condition in which pain exists in almost 50% of our patients cannot be considered a cosmetic condition, and four physician visits a year has significant economic consequences.

It is known that there is a genetic pre-disposition to *T. rubrum* in some families,[14,15] with every affected child having at least one affected parent.[15] In families

Figure 1: Epidemiology of Onychomycosis

Onychomycosis is the most common nail disease, accounting for approximately 50% of all nail problems[1]



[1]Faergemann J, Baran R. Epidemiology, clinical presentation and diagnosis of onychomycosis. *Br J Dermatol.* 2003;149(suppl 65):1-4. [2]Rogers P, Bassler M. Treating onychomycosis. *Am Fam Physician.* 2001;63(4):663-672,677-678. [3]Scher RK, Daniel CR, eds. *Nails: Therapy-Diagnosis-Surgery.* 2nd ed. Philadelphia, PA: W.B. Saunders Co; 1997. [4]Gupta AK, Konnikov N, MacDonald P, et al. Prevalence and epidemiology of toenail onychomycosis in diabetic subjects: a multicentre survey. *Br J Dermatol.* 1998;139(4):665-671.

the most common primary *T. rubrum* infections present as tinea pedis with distal subungual onychomycosis (DSO) as a secondary infection.[14] Patients predisposed to onychomycosis are also going to be predisposed to having fungal infections in other parts of their body, such as tinea corporis, tinea cruris and tinea pedis.

Tinea pedis is inexorably linked to onychomycosis. Onychomycosis starts in almost every case as tinea pedis. The fungus infects the skin, minor trauma breaks the hyponychial seal and the fungus migrates beneath the nail. Maybe the patient doesn't even recognize it is happening. Essentially, all patients with onychomycosis have or have had tinea pedis at one point, and you really need to treat both. If you treat patients with an oral antifungal for their onychomycosis it will treat their tinea pedis as well. But with a topical you have to treat the tinea pedis in addition, otherwise it will just act as a reservoir for re-infection of the tinea. Likewise if you only treat the tinea pedis the onychomycosis can re-infect the skin.

Onychomycosis is very common in patients with diabetes, where the prevalence is 2.8 times greater than in patients without diabetes.[16] Thickened fungal nails can develop serious bacterial infections and foot ulcerations.[17] Patients with diabetic neuropathy tend to wear shoes that are too small, because they can't feel that the shoe doesn't fit well, leading to ulceration. Foot ulceration has been reported in about 19% of diabetics, and in those with ulceration the prevalence of amputation ranges from 6%–43% depending on the severity of the ulceration.[18,19] In patients who have had a unilateral amputation the 5-year mortality rate is between 39% and 68%.[20] There is also a correlation between secondary gangrene infections in diabetics with onychomycosis.[21]

DISCUSSION POINTS: Prevalence

Jay Lifshen, DPM: Onychomycosis is very prevalent in our practice; being in Texas with the Southern climate we see a lot more of these types of problems. From an economic perspective, our group has created our own lab to capture the technical component of the lab expense. In probably 15%–20% of all the patients we see, onychomycosis is their primary presenting complaint. Our practice has a lot of diabetic patients and many return for repeat foot care secondary to their diabetes; many are considered high-risk patients in light of PAD and/or neuropathy.

Bryan Caldwell, DPM: I have practiced in both Florida and Ohio, so I can concur about the prevalence of onychomycosis in Southern climates. In Ohio, we have 2 very different demographics, having a clinic in the suburbs and one in the city. The city clinic sees a predominantly African-American population. We see more onychomycosis patients here than in the suburbs. Indeed, almost every other patient we see has onychomycosis or at least a chronic tinea pedis leading to onychomycosis. I really believe that there is a genetic susceptibility for the development of chronic tinea pedis

and onychomycosis, but also an increase in prevalence in the Southern states, so we have to consider environment and genetics. Does someone who is genetically predisposed to onychomycosis assume a greater risk if he or she moves to a Southern climate? Diabetes is increasing for a variety of reasons, so it is no surprise that onychomycosis rates are increasing as well, given that there is a 3:1 susceptibility issue.

Maureen Jennings, DPM: My podiatric practice is predominantly a medical practice in New Jersey, where patients are >55-years-old, have a high incidence of diabetes and I probably see 65%-70% of the practice having onychomycosis, either primary or secondary. For a lot of my patients, it is embarrassment—they don't like the way it looks. Pain relief is a definite consideration with the hope of improving nail appearance.

Scott Ashton, DPM: As the presenting or at least secondary complaint, it is probably 30%-40% of the patients that I see. A lot choose not to have their onychomycosis treated; some don't have the where withal to treat it properly. But there are a lot of fastidious folks in North Dallas who want their toenails to be immaculate. It is a problem in populations that spend most of their time in sandals with their toenails visually exposed. I don't see pain as the presenting complaint—dystrophy is the main issue, appearance and the fear of it spreading to other nails.

Alex Reyzelman, DPM: I agree we see a lot of onychomycosis in these communities. It may be an interesting area to explore. They are likely to have more diabetes and alcohol-induced neuropathies. I also think we have to look at the different age groups. Embarrassment is a key psychological issue. Onychomycosis is certainly more recognized following promotion to patients.

Richard Pollak, DPM: I used to think that onychomycosis was a "by the way disease" and not necessarily the primary reason patients were coming in to see us in the office. The Doyle data ties in with the public health issue and bears out our experience.[21] The incidence of onychomycosis is clearly higher in the diabetic patient population, or the underserved patient population. I can't think of one patient I didn't amputate on (other than trauma) that didn't have onychomycosis, or tinea pedis, meaning that these people have bad disease state. This is an underserved patient population, they are not being treated and they are just not taking care of themselves.

Tracey Vlahovic, DPM: I am seeing patients with the absence of tinea pedis, but with the presence of nail disease due to pedicures. We are typically seeing this because they have been inoculated with a dirty unsterilized instrument. I do a lot of education on appropriate pedicures and looking for places that autoclave. Another concern I get in my practice is nail discoloration. They might have already been treated by another physician and been given oral terbinafine, but what they have is not fungal. I see a lot of misdiagnosis. I am telling patients that it is more likely they don't have fungal disease than they do. It is my job to determine if it is really onychomycosis or not.

Harry Goldsmith, DPM: Total annual Medicare reimbursement for routine foot care (eg, debridement and trimming of nails) is $350-375 million. Compared to overall Medicare expenditures, that's a relatively small amount, but for podiatry, it is significant. CPT 11721 (debridement of nails 6 through 10) is the #1 billed code to Medicare by podiatrists in just about every state. CPT 11720 (debridement of nails 1-5) consistently is listed in the top 10 codes billed by podiatrists. Debridement of nail codes are the #1 audited codes for podiatrists. Prior to billing these codes, Medicare does not require laboratory proof that onychomycosis is present; it only needs the doctor to document clinical findings consistent with onychomycosis. Some Medicare contractor policies will also allow the billing of these debridement codes because the nails are thick, dystrophic or misshaped. One should keep in mind that the performance of nail debridement, while reducing the "fungal load" in the nails, in and of itself does not mean that the nail has been or is actively being treated, unless you consider debridement a primary treatment. Typical qualifying conditions for billing either CPT 11720 or CPT 11721 are either associated with "at risk" routine foot care or symptoms (ie, pain) associated with nails. Regardless, payers have been increasingly aware that in addition to the debridement of nails, the identification and treatment of the nail fungus is critical to the prevention of fungal spread to other nails and surrounding skin. The public as a result of years of direct marketing—pharmaceutical companies, laser manufacturers and podiatrists—are increasingly aware that a nail infected with fungus can be treated and that it wasn't just an ugly nail anymore. Awareness is driven by market activity and market activity is driven by public awareness.

Dr. Joseph: Dermatologists say that 50% of nail dystrophies are not onychomycosis. In a podiatric practice more likely 75% of the nails we see are onychomycotic toenails.

DISCUSSION POINTS: Diagnosis

Dr. Pollak: I will often do a PAS stain to confirm the diagnosis of fungus. I occasionally will do a PAS stain to prove the negative. Often times, fungus may be misdiagnosed. Many patients would like treat-

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