FROM THE LAB

Overlooked & Underdiagnosed: Onychomycosis

The Fungus Among Us

Fungal infection of the nails, known as onychomycosis, is the most common disorder affecting the nail unit. The prevalence of onychomycosis has been estimated to be as high as 5.5% in the general population,[1] 8.9% in hospitalized patients,[2] and 35% in elderly individuals over 65 years old.[3] Compromise of the nail due to either disease, injury, or environmental exposures may further increase the risk of developing this infection. Research has demonstrated an increased prevalence among patients with diabetes mellitus, peripheral artery disease, obesity, psoriasis, HIV, and other immunosuppressive disorders. An increased risk has also been shown to be associated with numerous common environmental factors, including tobacco use, occlusive footwear, local trauma, inadequate nail maintenance, athletics, and occupations that require frequent hand washing or exposure to moisture.[4]

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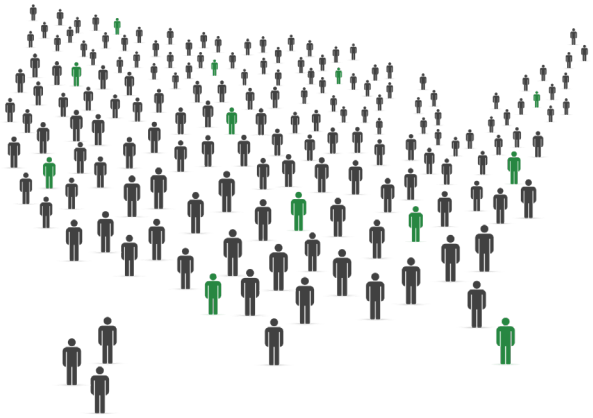


Onychomycosis may seem like a benign cosmetic concern, but it has been shown to have numerous implications beyond appearance. One systematic literature review found that onychomycosis can have profound psychological and social consequences that can negatively impact a patient's overall quality of life.[5] Moreover, severe forms of the infection can cause discomfort with activities as basic as putting on shoes. Finally, infected nails may also serve as a reservoir for both fungi and bacteria associated with skin infections, which can result in recurrent disease in immunocompromised patients.[6]

Pathogenesis and Microbiology

Fungal infections can involve various components of the nail apparatus, including the bed, plate, and matrix. Introduction of fungi most often occurs secondary to direct contact of a compromised nail with fungi in the environment or contiguous spread from local skin infections. After entering the nail unit, many fungi can form protective biofilms and produce enzymes that degrade keratin within the nail plate to further facilitate entry and growth.[7] Nails are particularly susceptible to this mechanism of localized fungal invasion due to a relative lack of protective cell-mediated immunity.[4]

Onychomycosis can be caused by a broad range of fungi spanning dermatophytes, non-dermatophytes, and yeast. Dermatophytes, particularly the *Trichophyton* species (e.g., *T. rubrum*, *T. mentagrophytes*), account for up to 70% of all onychomycosis cases. Non-dermatophytes, such as *Sarocladium* species, *Scytalidium* species., *Fusarium* species, *Alternaria* species, and *Aspergillus* species cause many of the remaining cases. Less commonly, yeast such as the *Candida* species can be the source of fungal nail infections.[1]

Clinical Classification of Onychomycosis

Onychomycosis occurs about ten times more often in toenails than fingernails, with the great toenail being the most commonly affected. Clinical manifestations of onychomycosis depend on the pattern and location of infection and can range from aesthetically displeasing discoloration to pain, paresthesia, and even ambulatory dysfunction.

Onychomycosis can be classified into five major clinical subtypes[8]:

1) Distal lateral subungual onychomycosis (DLSO) is the most common overall form of onychomycosis. Patients usually present with progressively worsening yellow-brown nail discoloration, subungual hyperkeratosis, and onycholysis. Discoloration usually begins at the nail corner before extending across the entire nail plate and advancing toward the cuticle. Most cases of DLSO are caused by Trichophyton rubrum.

2) White superficial onychomycosis (WSO) manifests as dull chalk-like patches or speckles and softening of the upper aspect of the nail plate. These infections tend to demonstrate outward progression from a central focus. WSO is most commonly caused by Trichophyton mentagrophytes but may also be due to alternative Trichophyton species, numerous non-dermatophyte species, or Candida.

3) Proximal subungual onychomycosis (PSO) is an uncommon subtype that predominantly affects immunocompromised individuals. Patients present with proximal leukonychia near the cuticle that progresses distally as the nail grows. PSO can be caused by a variety of fungi including Aspergillus species, Fusarium species, Trichophyton species, and Candida species.

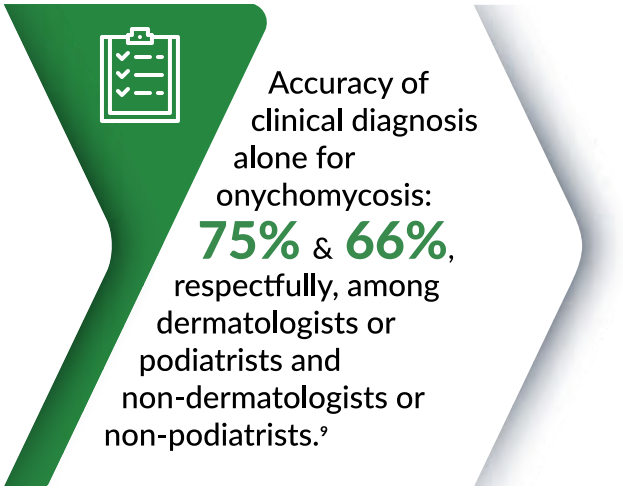
4) Endonyx onychomycosis (EO) manifests as white discoloration and lamellar splitting of the interior nail plate that spares the nailbed and lacks subungual hyperkeratosis. EO is caused most often by Trichophyton species (e.g., T. soudanense, T. violaceum).

5) Total dystrophic onychomycosis (TDO) is characterized by complete nail unit destruction secondary to longstanding and untreated onychomycosis. Nails in TDO appear disfigured, yellow-brown, universally thick, and friable.

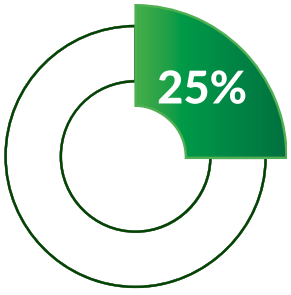
Patients may also present with a combination of these clinical phenotypes.

Diagnostic Challenge of Onychomycosis

The variable presentation of onychomycosis can make it difficult to make a strictly clinical diagnosis in patients presenting with onychomycosis. One study reported that the accuracy of clinical diagnosis alone for onychomycosis among dermatologists or podiatrists and non-dermatologists or non-podiatrist providers was 75% and 66%, respectively.[9] While these numbers may be surprising, they reflect the challenge added by oftentimes vague patient history and the use of cosmetic nail products.



Conventional diagnostic tests for onychomycosis each have their strengths and weaknesses. Potassium hydroxide (KOH) preparations can function as a low-cost screening tool, as they are able to identify the presence of fungal components such as spores and hyphae. However, the sensitivity and specificity of KOH testing have been reported to be as low as 48% and 38%, respectively.[1] Histopathologic examination with a periodic-acid Schiff (PAS) stain can offer a higher sensitivity but is more expensive and laborious. Regardless, both options are unable to identify specific species of fungi or confirm the viability of fungal elements.[10] Fungal cultures are able to identify specific fungal species and offer higher specificity, but can take up to a month to result, and exhibit sensitivity as low as 60%.[5]



of dermatophytes causing onychomycosis were detected by PCR only.[12]

Molecular techniques, such as real-time polymerase chain reaction (PCR) testing, can significantly enhance traditional diagnostic methods.[11] Real-time PCR can identify the presence of fungal DNA and specifically pinpoint the causative fungal species through highly sensitive fungal DNA fragment amplification. One study comparing real-time PCR and fungal cultures reported that 25% of dermatophytes causing onychomycosis were detected by PCR only.[12] Furthermore, in contrast to fungal cultures, **real-time PCR can rapidly provide results that are accessible in 24-48 hours rather than weeks**. PCR also offers the option to simultaneously identify the presence of non-fungal co-infections that may further confound onychomycosis and its treatment. For example, coinfections with Pseudomonas aeruginosa and Staphylococcal species have been reported to complicate the diagnosis of onychomycosis in the

literature.[13] Ultimately, **quick and accurate identification of fungal and non-fungal pathogens with PCR can facilitate confidence in making an onychomycosis diagnosis, as well as guide the best choice of therapy for each patient**.

Assurance Scientific Laboratories Panels

Assurance Scientific Laboratories offers a real-time PCR-based fungal infection panel (view Fungal Panel) tailored for identifying the dermatophytes, non-dermatophytes, and yeast responsible for causing the vast majority of onychomycosis. In addition, we offer a bacterial add-on to detect the presence of Pseudomonas aeruginosa and an antibiotic resistance add-on to detect the mecA gene responsible for methicillin-resistance in MRSA. Together, these options facilitate rapid and specific diagnosis to help guide management and treatment in patients with onychomycosis. Learn more at assurancescientificlabs.com.

General Guidelines

Laboratory test results should always be considered in the context of clinical observations and epidemiological data (such as local prevalence rates and current outbreak/epicenter locations) in making a final diagnosis and patient management decisions. With any test, the possibility of false-positive and false-negative results should always be considered, and the impact on patient management decisions and clinical outcomes should be carefully weighed.

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