

Etiology, Clinical Spectrum, Epidemiology, New Developments in Diagnosis and Therapeutic Management of Onychomycosis: An Update

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Abstract Fungal infections are recognized as an important cause of morbidity as well as mortality, especially in the immune-suppressed subjects worldwide. Onychomycosis is a sporadic fungal infection that can affect any part of the nail unit, including the matrix, bed, and plate. It is caused by a wide variety of fungi that include dermatophytes, yeasts, and non-dermatophyte moulds. Dermatophytes are the most common cause of onychomycosis among the numerous fungi. The disease is mainly sporadic and has been recorded in sexes, all age groups, in rural and urban settings, and developing and developed countries. Onychomycosis affects more than 5% of the world's population today. Distal lateral subungual onychomycosis (DLSO), white superficial onychomycosis (WSO), proximal subungual onychomycosis (PSO), endonyx onychomycosis (EO), and candidal onychomycosis are the five primary subtypes of onychomycosis. The condition can manifest itself in a variety of clinical forms, all of which impact the nails on the fingers and legs. Generalized infections involving both hands have been found on occasion. The infection in immunocompromised patient may cause a serious health problem. A plethora of factors, such as nail trauma, occlusive foot wear, and humidity may predispose to fungal nail infections. Clinical diagnosis should be supported with laboratory findings. Direct microscopic demonstration of the fungal agent in the afflicted nail using the potassium hydroxide procedure and isolation of fungi in pure culture on mycological media, such as Sabouraud dextrose agar, dermatophyte test medium, and Pal sunflower seed agar helps to confirm the diagnosis of onychomycosis. The precise morphology of fungal cultures taken from the clinical specimens of patients can be easily investigated in staining solutions, such a PHOL and Narayan. Direct microscopy in potassium hydroxide is still considered the simplest, quickest, and cheapest way to detect fungal agents in nail scrapings. Onychomycosis medications can be applied locally (amorolfine, ciclopirox, efinaconazole, tavaborole) or taken orally (fluconazole, itraconazole, terbinafine). The cure rate is increased when topical and systemic treatments are used together. Depending on the extent of nail involvement, therapy might last from 3 to 6 months or even longer. It is imperative to manage the risk factors. Hygiene is considered the best prevention strategy of onychomycosis.

Keywords: antifungal drugs, dermatophytes, nails, non-dermatophytic fungi, onychomycosis, yeasts

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1. Introduction

Onychomycosis is a fungal infection of the nail that accounts for around half of all nail disease cases and is the

most frequent nail problem according to clinical statistics [1]. Onychomycosis is most common in adults, but it can also affect children. Nail discolouration, subungual hyperkeratosis, onycholysis, nail plate splitting, and nail plate destruction are all common clinical symptoms [2]. Its prevalence has continuously risen in tandem with the

rise in the number of elderly and immunocompromised people [3].

Distolateral subungual (DLSOM), superficial white, proximal subungual, endonyx, and total dystrophic (TDOM) onychomycosis are among the kinds of onychomycosis that have been identified [4]. Dermatophytes are pathogenic fungi that can infect the skin, hair, and/or nails. They are thought to be responsible for 90% of toenail cases, and 50% of fingernail cases of onychomycosis [5]. Yeasts (especially *Candida albicans*) and non-dermatophyte moulds, especially in previously wounded nails, may also be involved [6,7].

The clinical symptoms of onychomycosis might be mistaken for a variety of other nail conditions. As a result, before starting a treatment plan, a laboratory diagnosis of onychomycosis must be established. Direct microscopy is unable to detect the fungal pathogen that causes onychomycosis. To identify the organism's species, a fungal culture must be employed [8]. Fungal nail infections are tough to treat and rarely go away without antifungal medications. Prescription antifungal medications taken by oral are usually the best treatment for a fungal nail infection [9]. The objective of this communication is to delineate the etiology, clinical spectrum, epidemiology, current diagnostic and therapeutic approaches of onychomycosis.

2. Etiology

Table 1. Fungi implicated in the etiology of onychomycosis

Major groups of fungi	Fungal species isolated from affected nails
Dermatophytic fungi	<i>Epidermophyton floccosum</i> <i>Trichophyton mentagrophytes</i> <i>T. rubrum</i> , <i>T. tonsurans</i> , <i>T. verrucosum</i> , <i>T. violaceum</i>
Non-dermatophyte moulds	<i>Aspergillus candidus</i> , <i>A. flavus</i> , <i>A. melleus</i> , <i>A. niger</i> , <i>A. nomenis</i> , <i>A. sydowii</i> , <i>A. tamarii</i> , <i>A. terreus</i> , <i>A. versicolor</i> <i>Botrydiodiplodia theobromae</i> <i>Chaetomium globosum</i> <i>Cladosporium carrionii</i> , <i>Exophiala jeanselmei</i> , <i>Fusarium oxysporum</i> , <i>F. proliferatum</i> , <i>F. solani</i> <i>Geotrichum candidum</i> <i>Hendersonula toruloides</i> <i>Neoscytalidium dimidiatum</i> <i>Onychochola Canadensis</i> <i>Penicillium marneffeii</i> <i>Pyrenochaeta unguis-hominis</i> <i>Scopulariopsis brevicaulis</i> <i>Scytalidium dimidiatum</i> <i>Scytalidium hyalimum</i> <i>Syncephalostrum racemosum</i> <i>Ulocladium botrytis</i>
Yeasts	<i>Candida albicans</i> , <i>C. glabrata</i> , <i>C. guilliermondii</i> , <i>C. krusei</i> , <i>C. parapsilosis</i> , <i>C. tropicalis</i> <i>Trichosporon beigelli</i>

Onychomycosis is a fungal infection of the nail caused by pathogenic dermatophytes viz: *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*. It can also be caused by yeasts namely *Candida albicans*, *C. parapsilosis* and *Candida guilliermondii*, and by non-dermatophyte molds, such as *Acremonium* species, *Alternaria* species, *Aspergillus*

species, *Cephalosporim* species, *Chaetomium globosum*, *Cladosporium* species, *Fusarium* species, *Hendersoluna* species, *Neoscytalidium dimidiatum*, *Onychochola canadensis*, *Scopulariopsis brevicaulis*, *Scytalidium dimidiatum*, *Syncephalostrum species* [10-22]. Dermatophytes are the most common, accounting for 60 to 70% of all infections. Non-dermatophyte molds and yeasts infections may account for 30 to 40% of fungal nail infections, and 10 to 20% of fungal nail infections, respectively [2]. *Trichophyton rubrum*, a dermatophyte, is the most prevalent fungus that causes distal lateral subungual onychomycosis (DLSO) and proximal subungual onychomycosis (PSO). White superficial onychomycosis (WSO) is mainly caused by the dermatophyte *Trichophyton mentagrophytes*, but it can also be caused by non-dermatophyte molds [23]. A wide variety of fungi are attributed as the cause of onychomycosis (Table 1).

3. Epidemiology

Onychomycosis is the most frequently encountered nail disorder in the human clinical practice throughout the world. It is the most common nail condition in adults, accounting for 50% of all nail disorders. Toenails are much more likely than fingernails to become infected. Onychomycosis affects 30% of people who have a cutaneous fungal infection [25]. It is reported that onychomycosis affects 5.5 percent of the world's population [1]. Onychomycosis is estimated to affect 3% of the adult population in the United Kingdom [26], and 4.3 percent of the entire population in the United States and Europe. Furthermore, researches with a hospital-based population showed a prevalence rate of 8.9% [27]. The prevalence rates for onychomycosis in children are as varied as they are in adults: a review of studies on the subject in numerous nations outside of North America found prevalence rates ranging from 0% (United States, Wales, and Finland) to 2.6 percent (United Kingdom, Wales, and Finland) (Guatemala) [28].

Aging, diabetes, tinea pedis, psoriasis, immunodeficiency, and living with family member who has onychomycosis, are all considered the risk factors for fungal nail infections [2]. Contact with the source of the infection constitutes a risk factor; for example, *Trichophyton verrucosum* commonly infects the faces of farmers who lean against their cows while milking them [3]. There is no doubt that onychomycosis has become more common as a result of various variables peculiar to modern life. These include the wearing of shoes, particularly fashionably tight, high-heeled shoes; the increased use of damp spaces such as locker rooms and gymnasiums by large groups of people; the aging American population's declining health; and the rise in the number of immunocompromised patients due to disease (e.g., HIV infection) or therapeutic agents (e.g., immunosuppressive therapies associated with cancer or post-transplantation care, and the extensive use of broad-spectrum antibiotics). Direct trauma to the nail is another factor that raises the incidence of onychomycosis [29]. Fungal infection of the nail can also occur while walking barefoot in a warm, humid, and moist area [14].

4. Clinical Spectrum

Onychomycosis normally has no symptoms unless the nail thickens to the point where it hurts to wear shoes. People with onychomycosis frequently visit the doctor for cosmetic reasons rather than for physical pain or other onychomycosis-related issues. Onychomycosis can make standing, walking, and exercising difficult as the nail swells. Pain, discomfort, and a lack of agility (dexterity) may occur as a result of paresthesia (a sensation of pricking, tingling, or creeping on the skin with no objective cause and frequently linked with nerve injury or irritation). Self-esteem issues, embarrassment, and social issues can all arise. *Candida* infections that are severe enough can disfigure the fingertips and nails [24]. One or more swollen, discolored toenails are common symptoms of pedal onychomycosis. One or both great toenails are usually damaged [5].

Onychomycosis is classified into subgroups that can be distinguished by the location of the infection in relation to the nail structure. In distal lateral subungual onychomycosis (DLSO) the nail plate is thick and foggy (opaque), the nail bed underneath the nail thickens and hardens (nail bed hyperkeratosis), and the nail separates from the bed underneath (onycholysis). The nail plate displays a milky white staining in endonyx onychomycosis (EO), however, unlike DLSO, the nail does not detach from the bed (no onycholysis). WSO (white superficial onychomycosis) is a fungal infection that affects the toenails. On the surface of the nail plate, small white speckled or powdery-looking areas form. The nail gets tough and readily crumbles. In proximal subungual onychomycosis (PSO) white spotting, streaking, or staining (leukonychia) develops around the nail fold and may extend to deeper layers of the nail. While yeast infection (*Candida albicans*) affects the nail, it can also cause other symptoms. *Candida* infection can affect toenails and fingernails, but it can also affect the tissue around the nail. The nail fold becomes erythematous (inflamed) or the nail plate separates from its bed (onycholysis) [24]. A severe form of candidal onychomycosis affecting all the fingers of both hands is shown in Figure 1.



Figure 1. Clinical lesions of onychomycosis in a patient affecting all the finger nails of both hands (Source: [14])

5. Diagnosis

The diagnosis of onychomycosis can be confirmed by several techniques, such as direct microscopy in potassium hydroxide, fungal culture, histopathology, PCR and flow cytometry [14,15,30]. The clinical presentation of dystrophic nails should alert the clinician to the possibility of onychomycosis; however, because fungi cause only about half of all nail dystrophies, accurate diagnosis is required [31]. The infection of nail can be identified through visual inspection, questioning the patient about their symptoms, or a fungal culture on mycological media [9]. The diagnosis of fungal infection of the nail can be established by direct microscopic inspection with potassium hydroxide, fungal culture of desquamated subungual material, or fungal stain of nail clipping preserved in formalin, according to the AAP's Red Book [32].

Direct microscopy of the affected nail clippings in a 20% potassium hydroxide (KOH) solution in dimethyl sulfoxide (DMSO) is a good screening test to rule out fungus [14]. The nails must be cut and cleaned with an alcohol swab to remove bacteria and debris before taking a sample for mycological diagnosis. Curettage should be used to acquire a specimen from the nail bed in cases of distal lateral subungual onychomycosis. The overlaying nail plate must be peeled and a sample of the ventral nail plate collected in proximal subungual onychomycosis. The specimens from the afflicted nail bed closest to the proximal and lateral edges should be obtained if candidal onychomycosis is suspected [33]. Direct microscopy is unable to detect the fungal agents that cause onychomycosis. To determine the organism's species, a fungal culture must be utilized. To isolate yeasts and non-dermatophyte molds, two types of growing media should be used: one containing cycloheximide (dermatophyte test medium, mycosel, or mycobiotic) to select for dermatophytes and one without cycloheximide (Sabouraud glucose agar, Littman oxgall medium, or inhibitory mold agar) [34]. Pal sunflower seed medium that was originally developed for the rapid isolation and presumptive identification of *Cryptococcus neoformans* [35] can be successfully employed for the isolation of several other fungi including *Candida albicans*, *Candida tropicalis*, *Rhotorula glutinis*, *Trichosporon beigeli*, *Geotrichum candidum*, *Aspergillus flavus*, *A. fumigatus*, *A.niger*, *A.terreus*, *Alternaria* spp. *Penicillium* spp. and *Fusarium* spp. from a wide variety of clinical specimens [14,36].

Recently, Dave and Pal developed a new medium called "APRM" (Anubha, Pratibha, Raj and Mahendra) for the isolation of non-dermatophytic fungi from clinical and environmental samples. Several species of fungi including *Aspergillus* species, *Exophiala* species, *Fusarium* species, *Penicillium* species and others were isolated from nail clippings on APRM agar [20]. It is pertinent to mention that isolation of dermatophytes from the affected nail must be considered as pathogen. The inoculated specimens on mycological media should be incubated at 25 to 30 centigrade. The detailed microscopic morphology of the fungi isolated from the affected nails can be studied in staining solutions like lactophenol cotton blue [14], PHOL (Pal, Hasegawa, Ono, Lee) satin [37], and Narayan stain [38]. It is suggested Pal sunflower seed

medium and APRM agar can be routinely used in the microbiology laboratories for the isolation of yeasts and non-dermatophytic fungi. The histopathological examination of nail biopsy by Grocott methanamine silver stain, and periodic acid-Schiff (PAS) technique is also useful to demonstrate fungal elements [14].

Ipsium Diagnostics developed a multi-component test that uses PCR and other histology testing methods to quickly identify the disease-causing agent in an onychomycosis infection, providing same-day results and evidence-based treatment options for both bacterial and fungal species [39]. SSI Diagnostica has created a commercial Dermatophyte Real Time PCR kit that can be used to diagnose dermatophytes in nail samples, notably *T. rubrum* [40]. A fungus (mycology) culture test developed by LabCorp analyzes a nail sample for an onychomycosis infection and provides results in 24-42 days [41]. A comparable nucleic acid test is available from Ability Diagnostics, which detects 11 different fungus species that are thought to cause fungal infections [42].

6. Treatment

The clinical type of onychomycosis, the number of afflicted nails, and the severity of nail involvement all influence onychomycosis treatment [43]. Antifungal medicines, such as tavaborole and efinaconazole, and laser therapy are now used to treat onychomycosis; additional treatments under development include iontophoresis and photodynamic therapy [1]. Fluconazole, terbinafine, or itraconazole can be used to treat dermatophytes, but fluconazole works better for *Candida* spp. infections [27]. Torres-Rodrigues and co-workers [44] tried a non-traumatic topical treatment of onychomycosis by using a combination of 1% bifonazole and 40% urea in a cream base, and the results were encouraging. Topical medication with cyclopiroxolamine was attempted in two cases of nail infections due to dermatophytes [14]. Topical antifungal therapies, on the other hand, are considered less efficient due to difficulties entering the nail, but have little side effects than systematic drugs [45]. Topical antifungals can be used in conjunction with laser treatment [34]. A recent study conducted to assess the efficacy of fractional carbon dioxide laser with 1% terbinafine cream versus oral itraconazole in the management of onychomycosis reported that more encouraging results were obtained with fractional carbon dioxide laser along with 1% terbinafine [46]. Itraconazole, an orally active azole shows antifungal activity against non-dermatophytic fungi, *Candida* spp. and dermatophytes. In some patients, minor side effects, such as nausea, headache, fatigue and diarrhea are observed [14]. This drug is contraindicated in patients who are suffering from congestive cardiac failure [47]. If the nail matrix is affected, which can be seen as yellow streaks on the nail, both a systemic and topical antimycotic treatment is indicated [27]. Treatments may take months or years before showing signs of improvement; also, a toenail onychomycosis infection is apparently more difficult to treat than a fingernail infection, with a recurrence rate of 5-50 percent [5]. The cure rate is increased when systemic and topical treatments are used together [43]. It is suggested that

in-vitro susceptibility to the antifungal drugs should be conducted to institute the specific chemotherapy [14].

7. Prevention and Control

Although it may be impossible to prevent everyone from contracting onychomycosis, there are measures to lessen a person's chances of contracting the disease. Some of the strategies for preventing nail infections are as follows: Maintain a clean and dry environment for your hands and feet. Keep your fingernails and toenails short and tidy by clipping them. In places like locker rooms and public showers, don't walk barefoot. Do not share your nail clippers with others. Choose a nail salon that is clean and licensed by your state's cosmetology board when you go. Ensure that the salon's instruments (nail clippers, scissors, etc.) are properly sterilized after each use, or bring your own [9]. Antifungal power can be sprayed inside the shoes two times a week. One should avoid going barefoot in the public places [15]. It is important to mention that treatment of the underlying condition and immediate attention to mechanical injury of the nail plate is very imperative [14].

8. Conclusion

Onychomycosis is the most frequent nail problem observed in the human clinical practice, and it is caused by a wide variety of fungi that include dermatophytes, non-dermatophytes moulds, and yeasts. It is a significant issue because it can cause local pain, paresthesias, difficulty performing daily activities, and social interactions. Toe nails are more frequently affected than fingernails. Different treatment modalities that include topical, systemic and surgical have been applied. Onychomycosis is a curable nail disorder that can be treated with both oral and topical medicines. The clinical type of onychomycosis, the number of affected nails, and the severity of nail involvement all influence onychomycosis treatment. Because the rate of recurrence is still high, even with newer agents, the decision to treat should be based on a thorough assessment of the costs and hazards, as well as the risk of recurrence. It is advised that one should avoid trauma to the nail; and the person with a minor traumatic injury should not work in outdoor activities, which involve handling of the soil. The management of the underlying disorders is highly imperative. As Pal sunflower seed medium and APRM agar are very cheap than the other mycological media, the wider application of both the media for the isolation of yeasts and no-dermatophytic fungi in the public health and microbiology laboratories are emphasized. Further research to elucidate the role of other fungi in the etiology of onychomycosis and development of safe, cheaper, and most effective chemotherapeutic agents for the better management of disease will be rewarding.

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Contribution of Authors

All the authors contributed equally. They read the final manuscript and approved for final submission for publishing.

Conflict of Interest

There was conflict of interest among the authors.

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