

# Current Perspectives on Onychomycosis: Etiological Insights, Diagnostic Modalities, and Preventive care

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## ABSTRACT

A serious and frequently underappreciated public health concern is onychomycosis, a fungal infection that affects the nail unit. Onychomycosis is a general term that encompasses infections caused by saprophytic moulds, yeasts, and dermatophytes. Its clinical manifestations include nail discoloration, subungual hyperkeratosis, onycholysis, and onychiauxis. The diagnosis is confirmed by microscopic, laboratory, and histopathologic examination. There are various treatment options for fungal nail infection, such as systemic therapies and oral and topical antifungal agents, with treatment selection determined by factors including age, gender, degree of infection, and peripheral vascular disease, among others. The prevalence rate of onychomycosis is specified by predisposing factors, age, social class, environmental conditions, and travel frequency. This investigation aims to provide a detailed, evidence-based understanding of onychomycosis. The aim is to compile the most recent peer-reviewed information on its etiology, pathophysiology, diagnosis, treatment, and epidemiology. The review provides insight into illness, comparative analyses of treatments, diagnostic approaches, and explanations of key issues and recent developments. By keeping in mind scientists and medical experts, this review is a valuable resource for them...

**Keywords:** Onychomycosis, Antifungal treatment, Epidemiology, Action pathway, Cellular mechanism.

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## INTRODUCTION

### 1.1. Background and Definition

Onychomycosis, or *tinea unguium*, is a fungal infection of the nail unit and represents a significant and often underrecognized public health issue. Onychomycosis is a broad term that encompasses infections caused by dermatophytes, yeasts, and saprophytic moulds. The term *tinea unguium* is used when the infection is attributable solely to dermatophytes. A nail exhibiting aberrant characteristics, not attributable to a fungal illness, is termed a dystrophic nail, highlighting the essential need for precise diagnosis. Onychomycosis can impact both fingernails and toenails, but the latter is far more common.

It is a common fungal condition that mostly affects the fingernails and toes and can be debilitating. Dermatophytes are keratinophilic fungi that are among the primary causes of this condition.<sup>1</sup> Onychomycosis frequency varies widely across the globe, based on factors such as climate, hygiene practices, and population demographics. The fact that it is estimated to affect between 2% and 18% of the population emphasises how important it is as a public health concern.<sup>2</sup> Onychomycosis can be brought on by several pathogenic fungi, including yeasts, dermatophytes, and non-

dermatophytic moulds. Many risk factors, such as obesity, psoriasis, diabetes mellitus, peripheral vascular disease, immunosuppression, and wearing occlusive synthetic footwear, have been associated with increased susceptibility to infection. Remarkably, onychomycosis is far more prevalent among the elderly, most likely due to age-related alterations in immune function and nail physiology.<sup>3</sup>

The most prevalent nail disease, Onychomycosis, which accounts for more than half of nail-related diseases, has a global prevalence of 5.5%.<sup>4</sup> The outcome of Onychomycosis significantly lowers the confidence of patients, majorly affects patients' lives, causing them pain, trauma, distress, and even embarrassment in working stations.<sup>5</sup> Onychomycosis can result in several symptoms, including nail thickness, dystrophy, discolouration, and infection of the nail unit and periungual tissues.<sup>6</sup> In addition to the physical effects of the illness, it often leads to a reduced quality of life. Comorbidities can further complicate diagnosis, treatment, and management, particularly in the cases of diabetes mellitus and peripheral vascular disease.<sup>7</sup> The most common rate of Onychomycosis is in adults, i.e. .6.4% and in children,

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0.14%. Apart from faster nail growth, thinner nail plates, reduced nail stress, improved peripheral circulation, and a lower prevalence of tinea pedis, these traits could all be explained by reduced childhood exposure to fungal infections.<sup>8,9</sup>

According to recent studies, the incidence of Onychomycosis is recurrent in immunocompromised individuals and children with Down syndrome. The predominant clinical manifestation of onychomycosis in children is distal Lateral subungual onychomycosis (DLSO). Despite dermatophytes being the primary etiologic agents in adults, yeasts, particularly *Candida* species, are increasingly recognised as significant pathogens in juvenile onychomycosis.<sup>10</sup> In addition to *Candida* species, other uncommon yeast pathogens have been found to cause onychomycosis, particularly in individuals with weakened immune systems. These include *Rhodotorula*, *Kodamaea*, *Geotrichum*, *Cryptococcus*, *Trichosporon*, and non-neoformans.<sup>11,12</sup>

*Kodamaeoheri*, formerly *Pichiaohmeri*, belongs to the class Ascomycetes and the Saccharomycetaceae family. Among immunocompromised patients, onychomycosis is related to endocarditis, peritonitis, urinary tract infections, otomycosis, and fungaemia. Environmental reservoirs such as sand, water, sea, freshwater, and fruits also contribute to its isolation.<sup>13,14,15</sup>

*Trichophyton rubrum* and *K. ohmeri* were identified in distal and lateral subungual onychomycosis, which accounted for 1.4% of cases among patients with type 2 diabetes mellitus.<sup>16</sup>

Onychomycosis has traditionally been diagnosed by a combination of clinical assessment and laboratory procedures, including direct microscopic examination and fungal culture. The clinical heterogeneity and potential for misinterpretation of onychomycosis pose significant diagnostic challenges for healthcare professionals.<sup>17,18</sup>

Onychomycosis is currently treated with topical antifungal drugs, systemic medications, and, in some cases, surgery. However, despite advancements in treatment methods, relapse rates remain high and clinical outcomes remain uneven and sometimes suboptimal.<sup>19</sup>

## 1.2. Public Health Significance

Onychomycosis is not simply a cosmetic problem; it constitutes a widespread and escalating public health issue. Onychomycosis has an estimated global prevalence of 5.5%, affecting up to 10% of the U.S. population. Beyond psychological suffering, pain, and discomfort experienced by patients, it results in cellulitis, sepsis, and osteomyelitis in immunocompromised individuals.<sup>20,21</sup>

## 2. EPIDEMIOLOGY AND DISEASE BURDEN

### 2.1. Global and Regional Prevalence

The prevalence of onychomycosis is high and varies substantially across populations. According to global estimates, the point prevalence is 5.5%, and the lifetime prevalence is 20%. The United States has a minimum frequency of 12%, while other sources report a figure of approximately 10% of the population. The occurrence rate is increasing worldwide. Regional data on onychomycosis

indicate a broad distribution of the disease, with estimates of 23% in Europe, 14% in North Africa, and 0.5%- 5% prevalence in the general population. There is variation in the incidence of onychomycosis, with rates ranging from 1.2% to 45% in Delhi.<sup>21,22,23</sup> The older age groups in Japan show 10% prevalence and 16.6% incidence among patients visiting local clinics or medical facilities.<sup>24</sup>

### 2.2. Age-Related and Vulnerable Populations

The prevalence of onychomycosis is generally associated with age in older populations. Its symptoms are often unrecognized in children, with a prevalence of 0.5% to 2.6%. However, as age approaches adulthood, incidence rates are approximately 35% and 50% at ages 65 and 70, respectively. Cohort research indicates a mean patient age of 64.9 years, with a peak frequency at 50-59 years. This heightened vulnerability among the elderly is not a simple linear increase but rather the result of synergistic effects. It is a complex condition resulting from an interplay of biological factors, including reduced nail growth, impaired immune function, and poor peripheral circulation, all of which are common in older age. This is increased by a lifetime of cumulative exposure to pathogenic fungus. The confluence of these elements generates a "perfect storm" for the development of onychomycosis in the geriatric population.<sup>25,26,27</sup>

### 2.3. Demographic, Lifestyle, and Comorbidity Risk Factors

The risk of onychomycosis is influenced by multiple factors. Individuals may be predisposed to dermatophyte infections due to genetic susceptibility; some studies indicate that this predisposition is autosomal dominant. Males are more likely to have toenail onychomycosis, while females are more likely to have fingernail infections caused by yeast.

Environmental and lifestyle variables are important. Participating in sports or fitness activities, wearing occlusive footwear, and being in damp public spaces, such as locker rooms and swimming pools, are all associated with an increased risk. Frequent microtrauma to the nails, often from poorly fitting shoes, can weaken the hyponychial barrier and provide a point of entry for fungi.<sup>28</sup>

Moreover, underlying comorbidities are frequently associated with onychomycosis. Athlete's foot, or tinea pedis, is a particularly serious risk factor because infected skin can serve as a reservoir for infection. Obese patients are more vulnerable, a result that may be related to poor nail care and drug adherence issues in this demographic. The illness is also intimately linked to a number of immunosuppressive conditions, including HIV/AIDS, diabetes, psoriasis, and peripheral vascular disease (PVD).

A socio-epidemiological aspect of the illness is highlighted by the interdependence of various risk variables. Urbanisation and crowding are two examples of factors that may create conditions favourable for fungal spread. The aetiology of the infection may be influenced by environmental conditions and hygiene practices, as evidenced by the greater prevalence of non-dermatophyte moulds in data from a cohort of homeless people. Public health programs play a pivotal role in safeguarding public health. Dependence on a single treatment method that

targets the most prevalent pathogen may not yield promising results, as the most causative agent varies across environments and exposure settings. Table 1 presents the risk factors and their significance.<sup>29,30,31,32,33</sup>

**Table 1: Key Risk Factors and Associated Comorbidities for Onychomycosis.**

Category	Risk Factors	Specifics and Significance		
Demographic	Advanced Age	The prevalence rises sharply in people over 70, reaching 50%. connected to accumulated fungal exposure, slowed nail growth, and compromised circulation.		
	Genetic Predisposition	autosomal dominant inheritance pattern. indicates innate vulnerability in some people.		
	Male Sex	More prevalent in males, particularly for toenail onychomycosis.		
Comorbidities	Tinea Pedis	concurrent fungal infection of the foot, which serves as a holding ground for reinfection of the nails. One important preventive step is to treat <i>tinea pedis</i> .		
	Diabetes Mellitus	suppresses the immune system and promotes fungal		
			development. increases the risk of severe adverse effects like cellulitis and diabetic foot sores.	
			Obesity	Obesity is more frequently co-diagnosed in patients with onychomycosis. Poor nail cleanliness and noncompliance may be associated with decreased therapy efficacy.
			Immunosuppression	The prevalence of diseases like HIV/AIDS, which can be up to three times higher than in the general population, increases vulnerability. Certain clinical manifestations, such as WSO and PSO, could be indicators of the course of the illness.
	Lifestyle/Environment		Occlusive Footwear	Creates a dark, warm, moist environment conducive to fungal growth.
			Nail Trauma	Compromises the nail's natural barriers, allowing fungal penetration.

	Communal Exposure	Public places like swimming pools and locker rooms facilitate transmission.
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### 3. ETIOLOGY AND PATHOGENESIS

#### 3.1. The Causative Agents

The etiology of onychomycosis is dominated by a select group of fungal pathogens. Dermatophytes are the most frequent cause, responsible for 70% to 90% of onychomycosis cases. The most common dermatophyte is *Trichophyton rubrum*, which accounts for approximately 90% of cases of toenail onychomycosis. Other dermatophytes, such as *Trichophyton mentagrophytes* and *Epidermophyton floccosum* are also common culprits.<sup>34</sup>

While dermatophytes are the primary agents, yeasts and non-dermatophyte molds (NDMs) also contribute to the disease burden. Yeasts, most notably *Candida albicans*, account for about 2% of cases, particularly in fingernail infections. NDMs are increasingly recognized as the most prevalent pathogens, accounting for 10-15% of worldwide cases. Examples include *Aspergillus* spp., *Fusarium* spp., *Acremonium* spp., and *Scopulariopsis brevicaulis*. The isolation of NDMs is notably higher in certain vulnerable populations, such as homeless individuals, where they accounted for 48% of infectious agents in one study, compared to 28% in a housed control group.<sup>35</sup>

The environmental and host factors arising from etiological differences primarily affect treatment choices. The conventional protocols, which favour oral terbinafine -an agent effective against dermatophytes but have limitations among populations where NDMs are the main causative agent. This underscores a critical need for species-level diagnosis before initiating therapy to ensure that the chosen drug is effective against the specific causative agent.<sup>36</sup>

#### 3.2. Pathophysiology of Nail Invasion

Through the penetration of the protective nail plate, fungi infiltrate the nail. Fungal spores initially contact the nail edge or folds due to slight stress or disturbance (e.g., tight shoes, an accident, or athlete's foot). In order to enable hyphae to penetrate deeper into the nail bed and underside of the nail plate, dermatophytes generate keratinases and other enzymes that break down the keratin in the nail. Infection typically begins at the lateral nail folds or distal edge and moves proximally under the nail (against nail development). Due to its high keratin content and limited local immune surveillance, the nail unit is relatively immunoprecipitated, thereby promoting fungal survival. Because fungi thrive in the anaerobic, keratin-rich environment beneath the nail plate, infections are frequently chronic, indolent, and have minimal inflammation.<sup>37</sup>

Prevention focuses on keeping feet dry because dermatophytes thrive in the warm, humid environment of shoes or public spaces (locker rooms, showers). Moulds

and *Candida* frequently infect immunocompromised hosts or nails that have already been harmed by chronic paronychia. Although research is ongoing, it is believed that fungal hyphae biofilms on the nail surface contribute to treatment resistance.<sup>38</sup>

#### 4. Clinical Presentation and Diagnosis

4.1. Clinical Presentation and Subtypes: Clinically, onychomycosis results in thicker, brittle, and discoloured nails. Patients may observe subungual debris, yellow-white nail discoloration, and nail cracking or crumbling. Fingernails are less prevalent unless they are linked to a *Candida* infection or persistent hand eczema. Toenails, particularly the great toenail, are most frequently affected. Onychomycosis can cause mild or no pain and may lead to secondary bacterial infections or social or professional embarrassment.<sup>39</sup>

Dermatologists divide onychomycosis into several invasion patterns according to the location and mode of fungal entry into the nail:

Distal-lateral subungual onychomycosis (DLSO) – It is the most common type of infection. The infection begins at the distal or lateral nail edge and results in subungual debris, onycholysis, and thickening and yellow-white discoloration of the nail bed. The common pathogen is *Trichophyton rubrum*. Affected nails exhibit lifting of the nail plate, hyperkeratosis, and frequently spread to neighbouring nails.<sup>40</sup>

SWO/BWO, or superficial onychomycosis – It is an infection of the nail plate's upper surface. Chalky white spots or patches that are frequently scrapeable are the hallmark of white superficial onychomycosis. Toenails are typically the only affected area (often caused by *T. mentagrophytes*). Less common black superficial variants manifest as black dots.<sup>41</sup>

Proximal subungual onychomycosis (PSO) - Less prevalent, in which fungi infiltrate the matrix from the proximal nail fold. This results in yellow or white discoloration at the nail base near the cuticle. It could start proximally as a transverse band or white patch. Immunocompromised patients (such as those with HIV) frequently get PSO, and *T. rubrum* or *Candida* may be the culprit.<sup>42</sup>

Endonyx onychomycosis (EO) – It is rare for the infection to affect the nail bed; fungi infiltrate and demolish the interior of the nail plate. Clinically, the nail has milky-white discoloration and splits into thin layers (lamellar splitting), but the nail surface is mostly unharmed. *T. violaceum* or *T. soudanense* are frequently the cause.<sup>43</sup>

Total dystrophic onychomycosis (TDO) - The entire nail plate is swollen, damaged, and crooked. The nail can break or come loose. If treatment is not received, TDO may develop secondary to any of the other types. It is the last stage of onychomycosis.<sup>44</sup> Mixed or secondary patterns can occur in a single nail (e.g., DLSO with superficial spots) or onychomycosis can exacerbate another nail condition (e.g., psoriasis).

#### 4.3. Diagnosis

A range of techniques, from conventional to highly advanced, is available to confirm a diagnosis of onychomycosis.

**Direct microscopy (KOH prep):** After keratin is dissolved with potassium hydroxide, nail scrapings or clippings are inspected under a microscope. Yeasts, also known as fungal hyphae, are frequently observed. Although this test is quick and affordable, its sensitivity is only about 50–60%. In the appropriate clinical setting, a positive KOH test is typically sufficient to establish the diagnosis.<sup>45</sup>

**Fungal culture:** involves inoculating samples (debris or clippings) on fungal media. The organism (dermatophyte, mould, or yeast) can be identified by culture. However, culture takes weeks and exhibits variable sensitivity (typically 25–80%). To prevent false negatives, caution is required when sampling actively diseased areas (e.g., the proximal nail and hyponychium). It is possible to cultivate various fungi on a variety of media, with or without cycloheximide.<sup>46</sup>

**Histology (nail biopsy using PAS stain):** The nail clipping might be sent for histopathology if the KOH and culture results are negative, but the suspicion is still present. The most sensitive test is the Periodic-acid Schiff (PAS) stain on nail clippings, which reveals fungal components in about 80-90% of cases. This can rule out other problems and reveal fungal hyphae inside the nail.<sup>47</sup>

**Molecular techniques:** Fungal DNA can be quickly detected and identified using PCR assays and other molecular procedures. Although PCR can detect contaminants, it has excellent sensitivity (Approximately 93%) and very high specificity. Most often, these methods are employed in specialised laboratory or research settings.

**Dermoscopy** is a non-invasive procedure because onychomycosis has unique dermoscopic features, such as longitudinal striae and "spikes" close to the proximal onycholytic border. Dermoscopy can help differentiate between fungal and non-fungal nail changes, although it is not definitive.<sup>48</sup>

In brief, microscopy and culture are the gold standard. The empirical treatment, like oral drugs, has a negative effect, so to overcome them, a validated diagnosis is a must. Table 2 summarizes the key diagnostic modalities with their advantages and disadvantages.

**Table 2: Comparative Summary of Key Diagnostic Modalities.**

Modality	Key Characteristics	Advantages	Disadvantages
Potassium Hydroxide (KOH)	Direct microscopic examination of nail scrapings.	Rapid results, low cost.	Low sensitivity (53%-80%), does not identify species.
Fungal Culture	Culturing of nail clippings to grow and	Allows for species-level	Slow (weeks to get results), high false-

	identify the fungus.	identification.	negative rate.
Periodic Acid-Schiff (PAS) Stain	Histopathologic examination of a nail biopsy.	High sensitivity (92%), more reliable than KOH.	Invasive (requires biopsy), does not identify species.
Polymerase Chain Reaction (PCR)	Molecular detection and amplification of fungal DNA.	Highest sensitivity (100%), rapid results (hours), identifies species.	More expensive than conventional methods.

## 5. THERAPEUTIC STRATEGIES AND CLINICAL MANAGEMENT

### 5.1. Pharmacological Treatments

#### 5.1.1. Oral Antifungals

For moderate-to-severe cases (e.g. >50% of nail, matrix involvement, many nails), oral therapy is the primary line of treatment. During nail growth, oral medications are absorbed into the nail from the inside. The primary systemic therapies include:

**Terbinafine:** 250 mg of the allylamine terbinafine once daily (usually for fingernails, 6 weeks, and for toenails, 12 weeks). Terbinafine is the best treatment; it is licensed for dermatophyte nail infections and has a high mycologic cure rate (up to 70–80% in toes). Although pulse dosing is an option, a continuous regimen is the norm. Taste alterations and elevated liver enzymes are examples of side effects; interactions (e.g., with beta-blockers) may occur.<sup>49</sup>

**Itraconazole:** Triazoles like itraconazole can be taken continuously or in pulses, such as 200 mg daily for 12 weeks or 400 mg daily for one week every month for three to four pulses. Candida, dermatophytes, and certain moulds are all covered by itraconazole. Compared with terbinafine, it has more medication interactions (cyclodextrin vehicle) and lower complete cure rates (Approximately 14–43%).<sup>50</sup>  
**Fluconazole:** Off-label use of fluconazole, a triazole, is common; weekly dosages range from 150 to 450 mg for 6 to 12 months. Treatment is lengthy, and cure rates are moderate (Approximately 21–48%). In general, fluconazole is regarded as third-line.<sup>51</sup>

The choice of treatment is determined by the causative organism and any contraindications. Terbinafine is the first-line treatment; however, itraconazole (or less frequently fluconazole) is used if the patient is unable to take it due to liver disease, drug interactions, or if the fungus is a yeast or mould.

**Adjunctive therapy:** Results can be enhanced by adjunctive therapies. The fungal load is decreased by mechanical debridement or nail avulsion, which involves removing the diseased nail. Cure rates may rise when oral and topical treatment are combined. CO<sub>2</sub> Laser and photodynamic treatment (PDT) are among the more recent methods. A solid-state laser containing active yttrium aluminium garnet (YAG laser). These techniques are still regarded as

experimental and are only FDA-approved for short-term improvements.<sup>50</sup>

Photodynamic therapy (PDT): Emerging therapeutic possibilities include a novel laser system and photosensitizers for photodynamic therapy (PDT). A photosensitising agent and a specific light source are used in photodynamic therapy (PDT), a non-invasive treatment, to generate reactive oxygen species (ROS) that destroy fungal infections within the nail unit. *Trichophyton rubrum* is among the many fungal species that PDT has shown to be effective against.<sup>52</sup>

In PDT, the most often used photosensitizers are as follows: Porphyrins, 5-aminolevulinic acid (ALA), methyl-amino levulinate (MAL), and phenothiazine dyes (such as methylene blue and toluidine blue).

Research indicates that improving photosensitiser penetration into the nail plate requires pretreatment with abrasion or chemical maceration (e.g., applying 20% urea ointment under occlusion).<sup>53</sup>

The need for numerous treatment sessions, typically three to twelve applications, is one of PDT's primary drawbacks. A higher prevalence of side effects, such as temporary pain and burning, is associated with increasing the irradiation dose, even though it may result in fewer sessions overall.

Lasers - With multiple laser types approved by the FDA, such as the carbon dioxide (CO<sub>2</sub>) laser, Nd: YAG laser, and diode lasers (870 nm and 930 nm wavelengths).<sup>54</sup> Laser therapy is an emerging alternative treatment option for onychomycosis. Due to its invasiveness and the availability of more sophisticated, non-invasive laser systems, the carbon dioxide laser, one of the first laser technologies used in dermatology, is now rarely employed. Clinical investigations have shown the Nd:YAG laser, especially the long-pulsed 1064 nm type, to be efficacious.<sup>55</sup> Mycological cure rates of up to 87.5% have been reported in small-scale investigations, with toenails showing significantly greater efficacy than fingernails.<sup>56</sup>

Treatment regimens are lengthy (often 6–12 months for toenails), regardless of the therapy used, and patient adherence is crucial. Side effects should be monitored in patients (e.g., liver tests for oral medications). Nails may remain dystrophic for months following treatment, until the infected nail is replaced by new growth.<sup>57,58</sup>

### 5.1.2. Topical Antifungals

For minor cases (such as superficial involvement or involvement of fewer than 50% of nails) or when systemic medications are not appropriate, topical treatment is indicated. Nail lacquer formulations that can penetrate the nail plate, such as ciclopirox 8% lacquer, amorolfine 5% lacquer, efinaconazole 10% solution, and tavaborole 5% solution, are the most widely used topical medications. However, topicals have comparatively low complete cure rates (e.g., ciclopirox, approximately 5–8%, amorolfine, approximately 15–18%, efinaconazole, approximately 15–26%). Topicals are more effective for superficial or distant infections and may require daily use for 6 to 12 months. Although the effectiveness of the more recent topical azoles (efinaconazole, tavaborole, and luliconazole) has improved, oral therapy generally remains superior. Additionally,

topicals can be used as maintenance following systemic therapy or in conjunction with oral medications. Table 3 summarizes the comparison of therapy efficacy.

Table 3: Antifungal Drug efficacy and safety profile.

Drug	Dosage & Regimen	Treatment Duration	Effectiveness (Mycological Cure)	Notes / Special Indications	Safety Profile	References
Fluconazole	150–300 mg weekly	>6 months	>90% fingernail, Approximatley 80% toenail infections (general efficacy); less effective for dermatophyte onychomycosis	Used when other agents unsuitable; may require prolonged therapy	Good	[59]
Itracozole	400 mg/day (pulse therapy) for 1 week per month	2 months (fingernails), 3 months (toenails)	>90% fingernail, Approximatley 80% toenail infections	Effective in diabetics; can be combined with avulsion in dystrophic/lateral nail disease	Good	[60]
Terbinafine	Continuous: 250 mg/day for 12 weeks Pulse: 500 mg/day (4 weeks on, 4	Approximately 12 weeks (continuous)	>90% fingernail, approximately 80% toenail infections	Effective and safe in diabetics; may be combined with avulsion for resista	Good	[61]

	weeks off)			nt forms		
Posaconazole	Investigational / new therapy	—	Data limited	Potential alternative therapy	Good (based on early data)	[62]
Albiconazole	Investigational / new therapy	—	Data limited	Potential alternative therapy	Good (based on early data)	[63]
Combination / Adjunctive Therapy	Surgical or chemical avulsion with topical/systemic itraconazole or terbinafine	As needed	Improves outcomes in dystrophic or dermatophyte cases	Used for resistant or lateral nail involvement	—	[54]

downstream ergosterol synthesis, resulting in a significant deficiency of this vital membrane component. Second, and perhaps more importantly for its fungicidal capacity, the blockade causes toxic accumulation of the substrate, squalene, at high intracellular concentrations. This accumulation significantly disrupts fungal membrane function and cell wall synthesis, resulting in cell death. The combination of squalene toxicity and ergosterol depletion confers a primary fungicidal action against dermatophytes.<sup>64,65</sup>

**Class II: Mid-to-Late Pathway Blockade (Azoles and Morpholines)**

**Azoles (Fluconazole, Itraconazole, Efinaconazole):** Azoles act by inhibiting the key P450 enzyme in the ergosterol pathway: lanosterol 14-alpha-demethylase (CYP51). This enzyme catalyses the crucial transformation of lanosterol into ergosterol precursors. Inhibition of CYP51 leads to two cellular abnormalities. First, the fungal cell membrane is depleted of ergosterol, impairing its structural integrity and activity. Second, the inhibition promotes the accumulation of toxic precursor sterols upstream of the block, particularly 4,4-dimethylsterols and 4-alpha-methylsterols (14-DM substrates), which further destabilize the membrane. These activities are typically fungistatic and can be fungicidal at high doses.<sup>66,67</sup>

**Morpholines (Amorolfine):** It is primarily applied as a topical nail lacquer. Amorolfine acts later in the ergosterol pathway than both allylamines and azoles. It functions by inhibiting two distinct enzymes: Delta 14-reductase and Delta 7,8-isomerase. This dual blockage reduces ergosterol and increases non-typical spherical sterols, notably ergosterol, in the fungal cytoplasmic membrane. The resulting changes in cell membrane structure confer broad-spectrum antifungal activity against dermatophytes (*Trichophyton* species), yeasts (*Candida* species), and other fungi.<sup>68</sup>

**Class III: Non-Ergosterol Pathway Inhibitors**

**Hydroxypyridones (Ciclopirox):** Ciclopirox, a topical medicated nail polish, utilises a novel, multi-target method involving the chelation of important polyvalent metal cations, notably ferric iron and aluminium. By sequestering these cofactors, Ciclopirox causes extensive suppression of various metal-dependent enzymes important for fungal life, including cytochromes, catalase, and peroxidase. Disruption of mitochondrial electron transport processes. Which causes Interference with energy generation. Blockage of nutrient absorption across the cell membrane. Ciclopirox also produces secondary effects, including alterations and disruptions of the fungal plasma membrane. This pleiotropic, multi-target approach targeting critical metal cofactors necessary for detoxification, respiration, and nutrition transport yields a broad-spectrum antifungal activity, coupled with established antibacterial and anti-inflammatory activities. Pharmacologically, targeting a pervasive cellular cofactor like ferric ions makes the establishment of specialised resistance pathways difficult, as several unrelated cellular processes are affected simultaneously (Figure 1).<sup>69,70</sup>

**5.1.3 Mechanistic approach to the antifungal treatment**

**5.1.3.1 Ergosterol Biosynthesis Inhibitors:** Ergosterol is crucial for preserving membrane fluidity, integrity, and the functionality of membrane-bound enzymes in fungal cells. Disrupting its synthetic pathway is a highly effective approach to antifungal therapy. The review focuses on the agents used in antifungal therapy for onychomycosis rather than all agents used.

**Class I: Early Pathway Blockade (Allylamines)**

**Terbinafine:** Acts through specific, potent, and non-competitive inhibition of the enzyme squalene epoxidase (SQE), also referred to as squalene monooxygenase. SQE facilitates the transformation of squalene into squalene epoxide, which is a preliminary step prior to the formation of lanosterol in the ergosterol pathway. Inhibition of SQE results in dual pharmacological effects that underlie the drug's high efficacy. Disruption of the pathway inhibits

**Boron-Containing Agents (Tavaborole):** Tavaborole’s mechanism is entirely non-sterol-based. It selectively inhibits the cytosolic enzyme leucyl-transfer RNA synthetase (LeuRS). LeuRS is an essential enzyme required for the accurate synthesis of fungal proteins. Inhibition of LeuRS prevents the correct charging of tRNA with leucine, effectively terminating essential protein synthesis. The rapid shutdown of protein production inhibits fungal cell growth and ultimately leads to cell death, thereby classifying tavaborole as a fungicidal agent.<sup>71</sup>

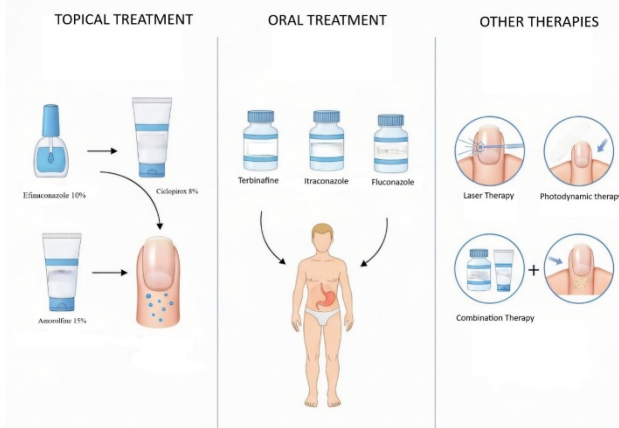
**Benzofurans (Griseofulvin):** Griseofulvin exerts its antifungal activity by binding particularly to the protein tubulin. Tubulin polymerizes to generate microtubules, which are key components of the cytoskeleton and crucial for the mitotic spindle structure required for chromosomal separation during fungal cell division. By blocking microtubule polymerization, Griseofulvin destroys the mitotic spindle, preventing fungal cell division and halting the development of the infection (Table 4).<sup>72,73</sup>

**Table 4: Molecular Mechanisms of Major Antifungal Agents Used in Onychomycosis.**

Antifungal Class	Drug Examples	Molecular Target (Enzyme)	Specific MOA Detail	Primary Pharmacological Effect
Allylamine	Terbinafine	Squalene Epoxidase (SQE)	Non-competitive inhibition, blocking squalene-to-squalene epoxide conversion.	Fungicidal (Squalene accumulation, Ergosterol deficiency)
Azole (Triazole)	Itraconazole, Fluconazole, Efinacozazole	Lanosterol 14 $\alpha$ -Demethylase (CYP51)	Nitrogen coordinates with heme Fe <sup>3+</sup> , blocking sterol demethylation.	Fungistatic/Fungicidal (Precursor sterol accumulation, Ergosterol deficiency)
Hydroxypyridone	Ciclopirox	Polyvalent Metal Cations Fe <sup>3+</sup> , Al <sup>3+</sup>	Chelation of cations, disrupting metal-depend	Fungicidal/Fungistatic (Broad cellular disruption)

			ent enzymes (cytochromes, catalase) and mitochondrial function.	
Boron-Containing	Tavaborole	Cytosolic Leucyl-tRNA Synthetase (LeuRS)	Inhibition of LeuRS, leading to termination of essential fungal protein synthesis.	Fungicidal
Morpholine	Amorolfine	$\Delta^{14}$ -Reductase, $\Delta^7$ - $\Delta^8$ Isomerase	Blocks two key late-stage enzymes in ergosterol synthesis.	Fungistatic (Irgosterol accumulation, Ergosterol deficiency)
Benzofuran	Griseofulvin	Tubulin	Binds to fungal tubulin, inhibiting microtubule polymerization and mitotic cell division.	Fungistatic

## ONYCHOMYCOSIS TREATMENT OPTIONS



**Figure 1: Treatment options for Onychomycosis.**

### 6. PREVENTION

Onychomycosis can be prevented by lowering risk factors and exposure. Since fungi prefer warm, humid conditions, it is advisable to keep hands and feet clean and dry, wear breathable shoes, and refrain from going barefoot in public places such as locker rooms and showers. If you are experiencing perspiration, use antifungal powders /sprays and allow your shoes to dry. The treatment of athlete's foot (tenia pedis) should be done immediately. Avoid sharing shoes, socks, and nail clippers. Daily examination of the feet and nails of infected patients and those suffering from diabetes. Maintain proper hygiene to reduce the risk of fungal infection and its prevalence.<sup>74,75,76,77</sup>

7. Prognosis: The relapse rate of onychomycosis is 20% to 25% within two years of successful therapy. The reason for relapse is older age (>70), nail history trauma, and disease conditions like diabetes.<sup>78</sup>

### 8. MANAGEMENT IN SPECIAL POPULATIONS

#### 8.1. Onychomycosis in Diabetic Patients

Diabetes patients with onychomycosis need to be managed with a customised and detailed strategy. The prevalence of persistent hyperglycaemia affects treatment outcomes by decreasing immune response and extending therapeutic timelines, even when the causative organisms are essentially the same as in the general population. Due to pressure from the thicker nail plate, diabetic foot ulcers and cellulitis are among the major problems that diabetic individuals with onychomycosis are more likely to experience. Beyond medication, a comprehensive management strategy must incorporate joint decision-making, patient education on good hygiene, and careful foot-care optimisation.<sup>79</sup>

Since research has traditionally excluded patients with serious comorbidities such as peripheral vascular disease, diabetic neuropathy, and poorly managed diabetes, there are currently few studies on the effectiveness and safety of antifungal medications in this population. The evidence-based foundation for treating individuals most at risk of severe infection-related consequences is seriously lacking.<sup>80</sup>

#### 8.2. Onychomycosis in Immunocompromised Patients

Immunocompromised patients, including those with HIV/AIDS, have a prevalence of onychomycosis that is up to three times higher than in the general population. The clinical presentation in this group can be distinctive, with a higher prevalence of white superficial onychomycosis (WSO) and proximal subungual onychomycosis (PSO), which may serve as indicators of disease progression in HIV patients.

Standard oral antifungal therapies may be unsuitable for these patients due to the risk of significant drug-drug interactions with their other medications. In fact, the introduction of combined antiretroviral therapy (cART) has been observed to improve onychomycosis by restoring immune function, sometimes without the need for additional antifungal therapy. This highlights the complex interplay between systemic health and the localized infection. The management of onychomycosis in this population requires careful consideration of the entire patient profile and a preference for local antifungal administration or alternative delivery methods to avoid systemic adverse effects.<sup>81</sup>

### 7. CHALLENGES AND FUTURE DIRECTIONS

#### 7.1. The Escalating Threat of Antifungal Resistance

One of the most urgent issues in the treatment of onychomycosis is the worldwide spread of antifungal resistance. The emergence of terbinafine-resistant strains, such as the South Asian strain *Trichophyton indotineae*, has led to outbreaks of nearly epidemic proportions and threatens the effectiveness of current first-line treatment. The fungicidal action of terbinafine targets the squalene epoxidase gene, and mutations in this gene cause this resistance.<sup>82</sup>

This issue has been directly exacerbated by the pervasive use of empirical treatment in the absence of conclusive, species-level diagnosis. Clinicians may prescribe a medication ineffective against a resistant strain or a non-dermatophyte organism without verifying the causative agent, thereby encouraging the spread of resistance. There has never been a greater pressing need for sophisticated diagnostics, such as PCR-based assays, to find resistant bacteria and direct treatment.<sup>83</sup>

#### 7.2. High Recurrence and Prevention

The high rate of reinfection and recurrence, which can reach 20%-25% following effective treatment, is a significant obstacle. A vicious circle of treatment failure is probably the cause of this high relapse rate. Patient noncompliance may result from a high fungal load being maintained for an extended period due to the nail's slow growth rate, and full recovery may not be evident for up to 18 months. Reinfection is also made possible by insufficient post-treatment prophylaxis and neglecting to treat coexisting *Tinea pedis*, which preserves an infectious reservoir.<sup>84</sup>

A comprehensive approach that goes beyond a single treatment plan is necessary for effective long-term management. Preventive measures should include wearing clean shoes and socks, maintaining foot hygiene, and treating comorbid tinea pedis. It has also been demonstrated

that the preventive application of topical antifungals substantially reduces recurrence rates.<sup>85</sup>

**7.3. Research Gaps and the Outlook for Novel Treatments**  
Substantial research gaps remain despite recent advancements. The literature on the effectiveness and safety of onychomycosis treatments in individuals with numerous, serious comorbidities is noticeably lacking. Because this high-risk group is frequently left out of current therapeutic studies, a sizable section of the patient population does not have an evidence-based foundation for their care.<sup>86</sup>

Furthermore, it is challenging to assess the genuine therapeutic value of novel and emerging therapies such as laser therapy and PDT, and to compare results across studies, due to the absence of standardised metrics. Consistent treatment techniques and endpoints across modalities must be the primary focus of future research.

The area of interest is the invention of novel formulations with enhanced nail penetration and decreased affinity for keratin. The discovery of new delivery methods, such as transferosomes and nanoemulsions, overcomes the nail plate's physical barrier and yields enhanced therapeutic outcomes. Lastly, growing research on non-invasive diagnostic techniques such as AI-driven systems and novel optical methods shows promising results in providing reliable and cost-effective diagnostic solutions for clinical management.<sup>87, 88, 89, 90</sup>

## 8. CONCLUSION

Onychomycosis remains a frequent and complex condition with a rising frequency, particularly in at-risk groups. The available evidence underscores the critical importance of moving beyond a presumptive diagnosis to a definitive, species-level confirmation before initiating therapy. Oral terbinafine is the most effective first-line treatment, but its dominance is threatened by the global spread of resistant strains, a problem compounded by the underutilization of new diagnostic technologies. Effective management is not a one-time event but a long-term, multi-pronged strategy that must address both the existing infection and the risk factors for recurrence. The future of onychomycosis management will likely involve a personalised, integrated, and holistic strategy. This technique precisely utilises diagnostic tools to inform treatment, combining pharmacology and adjuvant therapies to elucidate the biology, structure, and function of the nail, and to address patient education and preventive measures to break the cycle of recurrence. By addressing existing research gaps and adopting emerging treatment techniques, the trajectory of patient outcomes can be significantly improved

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