Original Article

Updated Perspectives on The Diagnosis, Management And Novel Drug Delivery Strategies For The Treatment Of Onychomycosis

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Abstract

Onychomycosis is a common fungal infection of the nail unit worldwide which poses a therapeutic challenge for both practitioners & patients and can cause pain, difficulty with ambulation and psycho-social problems. The infection is frequently due to dermatophyte, while yeast and non-dermatophyte molds (NDMs) attributed especially in immunocompromised patients. NDMs and *Candida* species can be involved as primary or secondary pathogens. Candida onychomycosis (CO), most commonly caused by *C. albicans* and *C. parapsilosis*, is frequently associated with local or systemic immune disturbances. In the cases that the host immunity is severely affected, *Candida* acts as primary pathogen, while other diseases e.g., diabetes mellitus, malnutrition, and smoking serve as predisposing factors for candida to cause secondary infection. Approximately 90% of toenail and 75% of fingernail onychomycosis are caused by dermatophytes, notably *Trichophyton mentagrophytes* and *Trichophyton rubrum*. Clinical manifestations include discoloration of the nail, subungual hyperkeratosis, onycholysis, candida granuloma, paronychia and onychauxis. Microscopy and fungal culture are the gold standard techniques for onychomycosis diagnosis, but high false-negative rates have pushed for more accurate methods, such as histology and PCR. As NDMs are skin and laboratory contaminants, their presence as an infectious agent requires multiple confirmations and repeated sampling. The conventional treatment of onychomycosis involves oral and topical therapy. Oral terbinafine, itraconazole and griseofulvin and topical ciclopirox 8% nail lacquer, efinaconazole 10% solution and tavaborole 5% solution, amorolfine 5% nail lacquer are approved by the Food and Drug Administration for treatment of onychomycosis. The oral antifungal agents though quite effective, are hepatotoxic and cause drug-drug interactions. Topical therapy is more patient compliant being devoid of such adverse effects but it suffers from another setback of improper nail penetration. Since decades, efforts have been made to enhance topical delivery for efficiently treating onychomycosis. Mechanical, physical and chemical methods have been employed. Despite all the attempts made, the nail delivery issues are far from being solved. Recently, the focus has shifted to novel drug delivery systems like nanoparticles, microemulsions, polymeric films and nail lacquers for enhanced drug permeation and localized therapy. The research around the world is exploring their potential as effective treatment options. The study aimed to provide an update on the evaluation, diagnosis, and treatment and further explore the novel delivery strategies to treat a persistent fungal infection like onychomycosis. Recent patents related to the management of onychomycosis are also discussed.

Keywords: Candida onychomycosis, Nail discoloration, Fungal infection, Onychauxis Diagnostic challenges, Terbinafine.

INTRODUCTION

Onychomycosis is a fungal nail infection caused by dermatophytes (60-70%), non-dermatophyte molds (NDMs) (20%) and yeast (10-20%) [1-3]. It is the most common nail infection encountered in clinical practice [4], with a worldwide prevalence of 5.5% and an estimated prevalence of 2% to 14% in the United States (US) [5] and 0.5% to 24% in Europe [6-9]. It is a significant public health issue, as human to human transmission occurs via direct or indirect contact of surfaces contaminated with scales or keratin from infected patients, presenting with discoloration of the nail, onycholysis, and nail plate thickening [10, 11]. Any component of the nail unit, including the nail plate, nail matrix, and nail bed can be affected [12]. The term "onychomycosis" is derived from the Greek words "*onyx*" meaning nail and "*mykes*" meaning fungus [13]. Risk factors include prior dermatologic conditions, such as hyperhidrosis, tinea pedis, and psoriasis, as well as exogenous factors, including occlusive shoes, trauma, and poor nail grooming. Comorbidities, such as diabetes mellitus, immunosuppression, malignancy, venous insufficiency, peripheral arterial disease, obesity, and inflammatory bowel disease also increase risk [5]. Altered foot biomechanics due to biomechanical malignments, congenital deformities, or neurological deficits can result in repetitive microtrauma during walking and increase the risk of infection and recurrence [14, 15]. Genetics may predispose to developing infection [16, 17] and transmission risk increases when members of the same household are infected [18]. Onychomycosis may occur at any age, however prevalence increases with age [19, 20], affecting roughly 50% of patients greater than 70 years old [21], and is rather rare in the pediatric population, with increased risk seen in children with Down's syndrome or immunodeficiency [22].

Onychomycosis, especially with secondary bacterial infections, can result in local pain and paresthesia, which pose significant psychosocial consequences. Limited dexterity and ambulation and difficulty finding comfortable fitting footwear can lead to social embarrassment and decreased self-esteem, which can be largely distressing, even when the infection is not severe [5, 23]. Patients also report stigmatization and dissatisfaction with the aesthetic appearance of their nails, and thus may avoid social interactions [24]. Onychomycosis is important to diagnose as it is curable with antifungal agents such as oral terbinafine, itraconazole, albaconazole, posaconazole, and fluconazole [25, 26]. Topical antifungal solutions including ciclopirox 8%, amorolfine 5%, efinaconazole 10%, and tavaborole 5%, are used as adjuncts to oral agents in severe cases or as alternatives when oral agents are contraindicated or in mild cases [25]. Due to costs and long treatment course lasting at least 3 months, patients often find difficulty adhering to therapy [25, 27-29]. Ensuring that patients who do not have onychomycosis do not receive antifungal treatment is also important because oral antifungals have adverse systemic effects, including gastrointestinal disturbance and hepatotoxicity [26]. Laboratory confirmation of the clinical diagnosis of onychomycosis prior to initiating treatment is cost effective and is recommended [30]. In recent years, newer techniques enabling accurate and sensitive diagnosis of onychomycosis and novel treatments of this condition have emerged. The purpose of this communication is to provide readers with an update on current approaches to diagnosis and treatment of onychomycosis. Therefore, internet-based information about onychomycosis is lacking, highlighting the need for proper in-office patient education and counseling for this chronic and recurrent disease.

Pathogenic organisms

The majority of onychomycosis cases are due to dermatophytes (60-90%), most commonly *Trichophyton rubrum* and *T. mentagrophytes*. Less common dermatophytes include *T. verrucosum, T. violaceum, T. krajdenii, Epidermophyton floccosum*, and *Arthroderma* spp., with infection due to *Microsporum* spp. being very rare. Cases secondary to dermatophyte infections are specifically referred to as tinea unguium [5, 23]. Infection with NDMs account for about 10% of cases worldwide, with the most common organisms being, *Aspergillus* spp., *Fusarium* spp., *Acremonium* spp., *Scopulariopsis brevicaulis, Alternaria alternata*, and *Neoscytalidium* spp. Yeast infections account for up to 10-20% of cases, with the most common pathogen being *Candida* spp., including *C. albicans, C. krusei, C. parapsilosis, C. glabrata and C. tropicalis*. Yeast infections are more frequent in the fingernails, especially if the hands are routinely submerged in water. Onychomycosis due to the yeast *Kloeckera apiculata* is uncommon but has been isolated in select cases [31]. In children, infection with *T. tonsurans* may occur. Infections with two or more organisms can occur, and mixed dermatophyte-NDM infections account for estimated 3-11% of onychomycosis cases, which may potentially be more difficult to treat and more prone to recurrences [5, 23]. Importantly, prevalence and infecting pathogen can vary according to the population studied1 due to differences in geographic location, climates, and daily activities, including professions and personal habits. Specifically, prevalence in North America ranges from 8.7% to 13.8% and is predominately caused by dermatophytes due to immigration of dermatophytes from other parts of the world. Prevalence in Europe is broader at about 0.5-24%. In tropical and warmer climates, infection with NDM and yeasts are more common [31]. Additionally, instead of acting planktonically (in suspension, independent, and free-floating), Fungal organisms may group together to form biofilms in the nail rather than acting as independent spores and hyphae [32]. Biofilms are multicellular communities of fungi or bacteria that are attached to a surface. Most microbes are able to form biofilms, though fungi, when not deeply penetrating a substrate, alternate between free-floating planktonic forms and members of a surface biofilm [33, 34]. The characteristics of biofilms offer some advantages for growth and survival to the fungus as they are surrounded by extracellular matrix (ECM). The ECM protects them from the host's immune response, as well as antifungal drugs and physical and chemical removal strategies. It enables fungi to diffuse nutrients to the elements of the biofilm [34, 35]. Biofilm formation may be a reason for the treatment resistance observed in onychomycosis and for the inability to completely eradicate fungal spores in cases of chronic infection [36, 37].

Epidemiology

The overall worldwide prevalence of onychomycosis in the general population is approximately 5.5%, based on recently published epidemiological studies [5, 21, 38]. A 2013 systemic review of 11 population-based and 21 hospital based studies showed that the mean prevalence of onychomycosis in North America and Europe was 4.3% (95% confidence interval: 1.9 to 6.8) in the population-based studies and 8.9% (95% confidence interval: 4.3 to 13.6) in the hospital- based studies [39]. There is evidence that the prevalence is rising, possibly because of longer life expectancy, use of occlusive modern footwear, increased prevalence of obesity, and increased urbanisation [22, 40, 41]. The condition is much more common in adults than in children and the prevalence increases with age [1]. The prevalence in children in North America is approximately 0.4%, whereas the prevalence may be as high as 35% in the elderly (> 65 years of age) [42]. Toenail onychomycosis is more common in males whereas *Candida* fingernail onychomycosis is more common in females [43-45]. Other predisposing factors include fungal infection elsewhere on the body (in particular, tinea pedis), chronic paronychia, previous onychomycosis, wearing of occlusive and tight shoes, hyperhidrosis, participation in sports or fitness activities, nail trauma, poor nail grooming, use of commercial swimming pools, communal bathing, living with family members with fungal infection, poor health, genetic factors, immunodeficiency (in particular, acquired immune deficiency syndrome and transplant patients), diabetes mellitus, obesity, Down syndrome, psoriasis, smoking, peripheral vascular disease, venous insufficiency, hallux valgus, and asymmetric gait nail unit syndrome [44, 46].

Pathogenesis

Onychomycosis is acquired through direct contact of the nail with dermatophytes, non-dermatophyte molds, or yeasts. Because the nail unit does not have effective cell-mediated immunity, it is susceptible to fungal infection [5]. Fungal production of enzymes that have proteolytic, keratinolytic, and lipolytic activities help to degrade the keratin in the nail plate and facilitate fungal invasion of the nail [47, 48]. Factors that compromise barriers to fungal infection may increase the risk for fungal infection [47]. The site and pattern of fungal invasion account for the production of different clinical subtypes of onychomycosis [48]. The formation of fungal biofilms allows the fungi to evade current antifungal therapies and contribute to antifungal resistance [32].

Anatomical structure of the nail unit

The point of entry of the infectious agent with regard to the nail is the main characteristic utilized in classifying onychomycosis infections, and so it is worthwhile to review the anatomical composition of the nail unit before approaching classification. This review may also help to understand the role of the different risk factors involved. The nail unit is made up of the matrix, eponychium, cuticle, lunula, proximal and lateral folds (PNL, LNF), nail plate, nail bed and hyponychium Figure 1. Growth begins at the nail matrix, a concentration of cells located beneath the PNL, which generates the cells that keratinize and are pushed distally, becoming the nail plate. Under the PNF lies the eponychium, a band of cells which produce the cuticle. The cuticle is a keratinized layer of stratum corneum that stretches over the newly grown nail plate, creating a seal over the PNF, thus preventing water and yeast invasion. The lunula is the distal part of the matrix, visible as a lighter crescent shape. The nail plate is composed of layers of compacted keratin which confer strength and flexibility. It is avascular and non-innervated and depends on its strong attachment to the nail bed for nutrient supply. The shape and size is determined by the structure of the underlying distal phalanges, whereas the colour results from the capillaries present in the highly vascularized nail bed below. The nail bed extends distally, developing into the hyponychium as it reaches the free edge, where the keratinizing cells detach themselves. The seal formed by the attachment of the hyponychium to the underside of the nail plate is called the onychodermal band. The PNF and LNFs are cutaneous barriers which border the periphery of the nail plate, together known as the paronychium [49, 50].

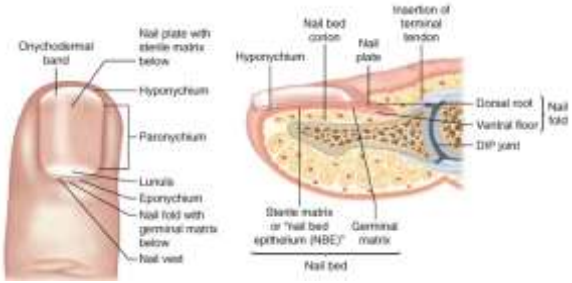

Figure 1: Anatomical structure of the nail unit

Clinical manifestations

Typically, onychomycosis presents as a white or yellow brown discoloration of the nail. Violaceous, green, and black discoloration of the nail plate have also been observed. Other clinical manifestations include subungual hyperkeratosis, detachment of the nail from the nail bed (onycholysis) and thickening of the nail plate (onychauxis). Dermatophytoma presenting as linear, single or multiple white, yellow, orange or brown bands on the nail plate is specific for onychomycosis (Figure 2). In general, toenails are affected seven to ten times more frequently than fingernails. The big toenails are most often affected. Generally, several toenails are affected and tinea pedis is often present (Figure 3). Also, it is unusual to have more than one fingernail involved without concomitant toenail involvement unless the patient is immunocompromised or there is a history of trauma [5, 21,46]. Based on the pattern of invasion, onychomycosis can be divided into the five clinical subtypes described below. It should be noted that patients may have a combination of these subtypes.

Figure 2: Dermatophytoma presenting as a linear, yellow, band on the nail plate of the right big toe in a patient with distal lateral subungual onychomycosis [46].

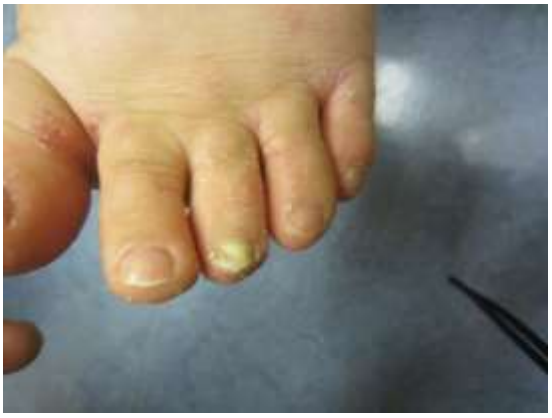

Figure 3: Onychomycosis in a patient with coexisting tinea pedis [46].

Distal and lateral subungual onychomycosis

Fungi reach the nail through the hyponychium and invade the undersurface of the nail unit plate spreading proximally. Distal and lateral subungual onychomycosis (DLSO) usually affects one or both of the great toenails and is also usually associated with tinea pedis [51]. The nail plate appears yellow-white, is detached due to onycholysis, with distal subungual hyperkeratosis (Figure 4). Less frequently, a brown, black or orange discoloration of the onycholytic nail can be seen (Figure 5). A possible presentation of DLSO due to dermatophytes is dermatophytoma, a subungual accumulation of hyphae and scales, scarcely reached by antifungals, which require excision of the area and systemic treatment. DLSO may be associated with black pigmentation of the nail (fungal melanonychia) (Figure 6), when the pathogen is the Melanoides variant of *Trichophyton rubrum* or other fungi that produce melanin, like *Neoscytalidium dimidiatum* or *Aspergillus niger* [52]. Onychomycosis due to non-dermatophytes is typically associated with a marked periungual inflammation (Figure 7). Differential diagnoses of DLSO include traumatic onycholysis (usually symmetrical and subungual hyperkeratosis is absent) and nail psoriasis (diffuse hyperkeratosis, several/all toenail involved, others skin and nail signs of psoriasis).

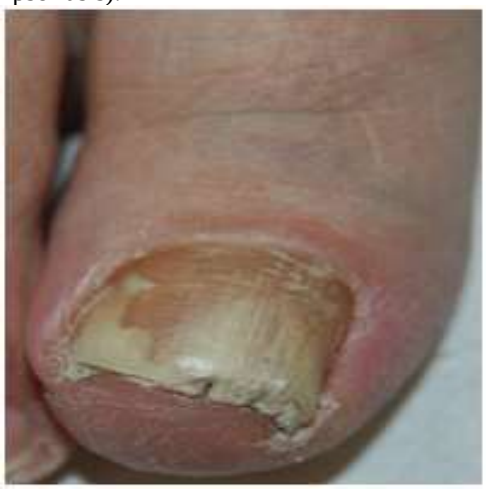

Figure 4 : Distal and lateral subungual onychomycosis (DLSO): whitish discoloration,onycholysis and subungual hyperkeratosis

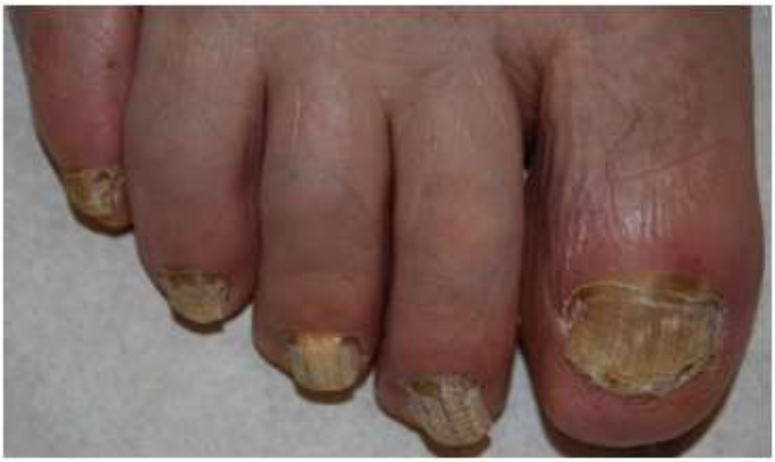

Figure 5: DLSO with prevalent yellow discoloration

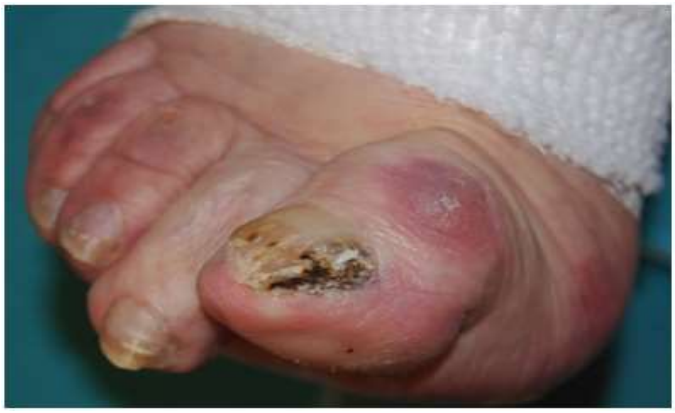

Figure 6: Pigmented DLSO

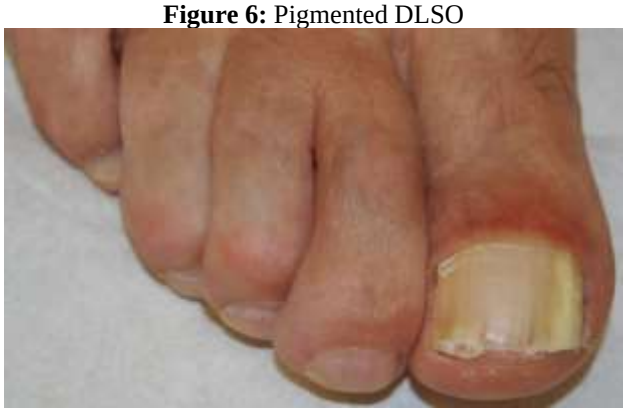

Figure 7: Onychomycosis due to molds, presenting the typical periungual inflammation

White superficial onychomycosis

Fungi invade the dorsal nail plate and form colonies that appear as white opaque formations, easily scraped away. The classical form is due to *Trichophyton interdigitale*, where dermatophytes colonize the most superficial layers of the nail plate without penetrating it (Figure 8), but *Fusarium* spp. and other molds may cause a white superficial onychomycosis (WSO) with a deeper nail invasion [53, 54]. Tinea pedis interdigitalis (athlete's foot) due to *T. interdigitale* is common [51] (Figure 9). Differential diagnosis includes superficial nail fragility due to prolonged wearing of nail polish and transverse toenail leukonychia due to trauma.

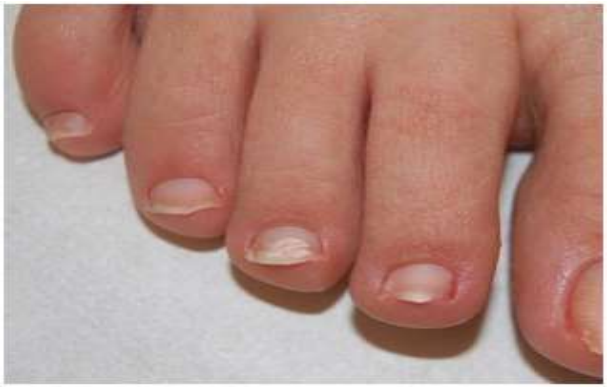

Figure 8: White superficial onychomycosis (WSO): white opaque friable patches of the nail plate

Figure 9: Tinea pedis interdigitalis, often associated with WSO

Proximal subungual onychomycosis

Fungal elements are typically located in the ventral nail plate, producing a proximal leukonychia. Proximal subungual onychomycosis (PSO) due to dermatophytes is very rare, and in the past, the form due to *T. rubrum* was considered as a sign of HIV infection. It presents as a white area under the proximal nail plate, in the lunula area (Figure 10). PSO is a common presentation of non-dermatophyte mold infection, especially due to *Aspergillus* sp. and *Fusarium* sp., and acute periungual inflammation is often associated. Differential diagnosis includes acute bacterial paronychia and pustular psoriasis of the nail [55].

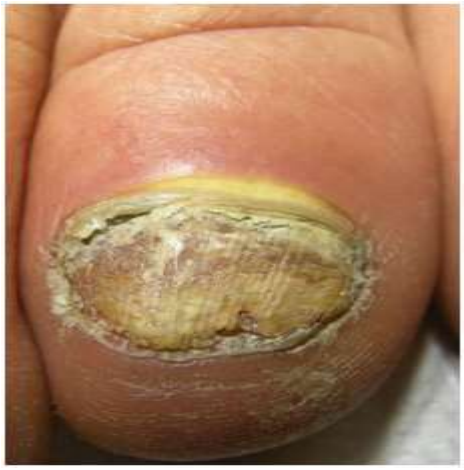

Figure 10: Proximal subungual onychomycosis (PSO): white discoloration of the proximal nail plate

Endonyx onychomycosis

Endonyx onychomycosis is characterized by massive nail plate invasion in the absence of nail bed involvement. Clinically, the affected nail may show lamellar splitting and a milky white discoloration. The nail plate is firmly attached to the nail bed, and there is no nail bed hyperkeratosis or onycholysis [56] (Figure 11). This type of infection is very rare and caused by *T. soudanense* or *T. violaceum.*

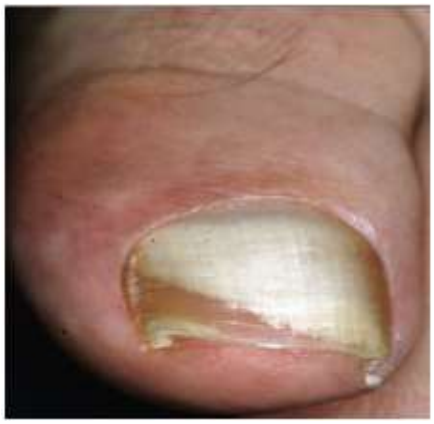

Figure 11: Endonyx onychomycosis: white discoloration of the nail plate that is firmly attachedto the nail bed

Total dystrophic onychomycosis

Total dystrophic onychomycosis (TDO) is the most severe stage of onychomycosis, and it can result from a long-standing DLSO or PSO. The nail plate is diffusely thickened, friable and yellowish (Figure 12) [55].

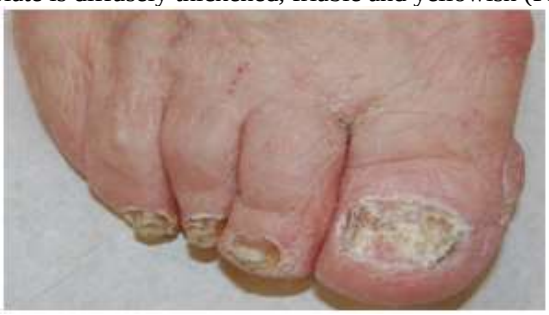

Figure 12: Total onychomycosis: the nail plate is completely invaded by fungi and friable

Diagnosis and diagnostic studies

Although the clinical appearance of the nail can offer some clues towards the most likely agent involved, these associations are not definitive, and the same organism can produce various presentations. Most clinical nail signs have

multiple aetiologies and therefore mycological analysis is fundamental in avoiding inefficient treatments and incorrect diagnosis [38, 57, 58]. Fungal identification is also beneficial with regard to choosing therapeutic management, as particular drugs or preparations may be indicated against certain organisms or subtypes. Despite this reasoning, empiric treatment continues to be highly implemented [59].

Diagnostic methods include: direct microscopy, culture, histopathology and molecular biology. To ensure clinically significant results, systemic antifungal treatment should be suspended three months prior to specimen collection, and topical treatment 2 to 4 weeks prior, as the presence of remaining antifungals can inhibit culture growth. Similarly, proper specimen collection is essential; samples should be carried out with sterile clippers and/or curette blades, and avoid collecting external contaminants present distally. Preparation should involve cleansing with alcohol and removal of hyperkeratotic matter to partially expose the affected nail bed.56 The clinical sub-type of onychomycosis determines the preferred site of sample collection and the type of sample required [48, 60].

Table 1: Preferred location of sample collection by clinical subtype

	Preferred area of sample collection
Distal and lateral subungual onychomycosis	Removal of the affect distal/ lateral nail plate and hyperkeratosis. Sample collection from the most proximal point of involvement.
Proximal subungual onychomycosis	Debride the affected proximal upper nail plate to expose nail bed. Collect hyperkeratotic debris at sample site at nail bed near the lunula.
Superficial white onychomycosis	Scraping of friable areas on the superficial nail plate. Sample taken from deeper areas.
Endonyx onychomycosis	Nail clipping for histopathology and microscopy should show internal fungal growth.
Total dystrophic onychomycosis	Debride and remove distal aspects of the destroyed nail. Nail clipping of proximal nail to avoid contaminants.

Dermoscopy

Nail plate dermoscopy is a non-invasive technique capable of differentiating between onychomycosis, traumatic onycholysis and melanonychia. A positive onychomycosis diagnosis is suggested by jagged proximal edges and polychromatic longitudinal striae in the area of onycholysis, resembling the aurora borealis. Regions of hyperkeratosis manifest with a "ruined" appearance, and melanin producing fungi present a homogenous brown pigmentation, in the absence of melanin granules [61, 62]. Dermoscopy can be used prior to direct microscopy to help select adequate regions for sampling [63, 64].

Direct microscopy

Direct microscopy utilizes potassium hydroxide (KOH 10-20%) and an optical microscope. The KOH dissolves the keratin structure of the nail plate, leaving behind fungal hyphae if these are present [65].This method is one of the most efficient as it can be carried out in-office in minutes, however, it has low sensibility. The reliability of the interpretation depends on the experience of the technician and on the quality of the sample collected. Furthermore, optic microscopy is unable to identify the species responsible, or yet establish the viability of the fungi. Chicago blue sky added to the preparation can improve visibility of hyphae and spores, increasing sensibility and pushing specificity above 90%, without compromising on speed [66, 67]. Alternative colorations with higher specificity include counterstaining with chlorazol black, which marks fungal hyphae, or fluorescent microscopy with calcofluor white, which stains the chitin contained within the fungal cell wall. However, these are less available in office as they require more specialized microscopes [38, 68, 69].

Fungal culture

Fungal culture remains the only technique capable of identifying any organism responsible and verifying its viability, thus it is considered the gold-standard diagnostic method. Samples should be sent for culture irrespective of the results of direct microscopy, as lack of visual observation does not fully exclude the diagnosis. Different culture mediums are required to provide for the various species of fungi. Unfortunately, culturing is a lengthy process, with NDMs taking 1 week and dermatophytes requiring at least 2; a standard time-frame of 4 weeks is usually implemented, with a false-negative rate of 20-35% [69, 70]. Cultures are considered pathogenic upfront if dermatophytes are identified; yeasts and other NDM cultures however, demand identification of hyphae, spores, or yeast-like cells on previous direct microscopy to be considered significant. Conclusive confirmation of NDMs requires 3 consecutive isolations of the agent within 1-2 week intervals, without simultaneous growth of dermatophytes. It is important to note that cases of co-infection are increasingly being reported and pose a unique diagnostic and therapeutic challenge, often requiring repeat sampling techniques, as one agent can mask the growth of the other [70, 71].

Histopathology

Histopathological analysis utilizes nail plate clippings which are embedded in paraffin wax, sectioned into thin slices, and stained with Periodic Acid Schiff (PAS), before being microscopically analysed; this stain is able to identify

glycogen and mucoproteins in the fungal cell wall and is more sensitive than KOH preparation and culture alone. Hence, histopathology is often referred to in patients with previously negative diagnostic exams- despite a high level of suspicion - and has a role in eliminating differential diagnoses. Similar to direct microscopy, it is unable to identify the species or viability of the organisms encountered [72, 73].

Polymerase chain reaction assay

Lastly, Polymerase Chain Reaction (PCR) amplification of fungal DNA fragments is a speedy method of diagnosis offering a high level of specificity, for an equally high price point, which unfortunately renders it unsuitable for everyday practice. At the moment, PCR assay is only capable of identifying *T. rubrum*, and is unable to assess viability [60, 74].

Artificial intelligence

More recently, artificial intelligence (AI) algorithms have been developed for onychomycosis, with studies showing competitive diagnostic accuracy when compared with dermoscopy and observation by experienced dermatologists [75].71 These tools could potentially serve as gate-keeping methods to more costly lab-based techniques, aiding primary care physicians in their clinical decision-making. AI also has a role in improving literacy in healthcare, offering patients a valid diagnostic tool for their own use, before resorting to healthcare services [75, 76].

Differential diagnosis

Differential diagnosis includes nail changes in psoriasis, lichen planus, alopecia areata, chronic dermatitis, onychogryphosis, chronic paronychia, pityriasis rubra pilaris, pachyonychia congenita, trachyonychia, onychogryphosis, median nail dystrophy, melanonychia striata, subungual melanoma, pemphigus vulgaris, pemphigoid, epidermolysis bullosa acquisita, bullous epidermolysis, subungual wart, subungual exostosis, subungual keratoacanthoma, rheumatoid arthritis, scleroderma, lupus erythematosus, scabies, tungiasis, twenty nail dystrophy, yellow nail syndrome, traumatic onychodystrophy, onychomatricoma, idiopathic onycholysis, porphyria, amyloidosis, myxoid cyst, fibroma, glomus tumor, Bowen disease, and squamous cell carcinoma [46].

Complications

Onychomycosis may serve as a reservoir for cutaneous fungal infections such as tinea pedis, tinea corporis, and tinea cruris. The fungus may also disseminate to other nails. There is an increased risk for bacterial infections such as cellulitis and paronychia, especially in immunocompromised individuals including diabetics. Severe onychomycosis may interfere with standing, walking, nail function, and daily activities. The condition, if left untreated, may cause discomfort, pain, paresthesia, nail deformities such as transverse over-curvature, difficulties in trimming thick nail plates, difficulties in fitting shoes, and low self-esteem. In addition, onychomycosis can be unsightly and socially embarrassing (especially for females) and may have an adverse affect on quality of life [46].

Conventional treatment therapy

Laboratory confirmation of onychomycosis before beginning a treatment regimen is cost-effective and should be considered to avoid misdiagnosis. A misdiagnosis might result in unnecessary treatment and expose the patient to inherent risks of the side effects of the medications, potential negative drug-to-drug interactions associated with systemic antifungal medications, and therapeutic failure. It might also impose a financial burden to the patient. However, empiric treatment of onychomycosis is still performed by many physicians. Onychomycosis is notoriously difficult to treat because of the deep-seated nature of the fungus within the nail plate, the prolonged treatment required for resolution, poor patient compliance, and frequent recurrences. Treatment options include oral antifungal therapy, topical antifungal therapy, laser therapy, photodynamic therapy, and surgical avulsion (e.g. very thick and chronic fungal nail) [46].

Oral therapies

Systemic medications administered orally are used to treat onychomycosis because of accessibility, relatively low cost, and efficacy. Terbinafine and itraconazole are the most commonly prescribed oral antifungals due to their high cure rates, and are approved to treat onychomycosis in Europe, USA, Canada, Japan, and Australia, among other countries [77-79]. Treatment courses are typically 12 weeks. Fluconazole is also prescribed off-label in North America for onychomycosis, but is approved in Europe and China [80, 81].

Terbinafine is an allylamine that inhibits the enzyme squalene epoxidase, thus inhibiting functional fungal cell membrane development (Figure 13) [82]. It is effective in eradicating dermatophytes and shows some activity against NDMs. It is not as effective as azoles against Candida onychomycosis [83]. Treatment regimen is 250 mg daily for 6 or 12 weeks, for fingernail and toenail infections, respectively. It can be detected in the distal nail within a week of starting therapy [84-86]. The mycological cure rate for toenails is 70% and the complete cure rate is 38% [87]. There are side effects associated with the medication, predominantly gastrointestinal symptoms, hepatotoxicity, headaches, and rashes, but these are generally not considered serious enough to discontinue treatment. Patients may uncommonly experience loss or change of taste [88, 89]. Terbinafine bioavailability is similar when the drug is taken with or without food [90]. Terbinafine is considered an FDA category B drug and is excreted in breast milk [87]. Thus, women should avoid its use during pregnancy and not initiate any treatment until breastfeeding is complete. Itraconazole is a triazole that

inhibits the enzyme 14α-demethylase, which disrupts fungal cell membrane biosynthesis (Figure 13). Its antifungal activity is broader than that of terbinafine, and it is effective against dermatophytes, NDMs, and Candida spp. [91]. The dose for itraconazole is 200 mg daily for 12 weeks to treat infected toenails. Pulsed regimen of itraconazole is also effective in treating onychomycosis. A single pulse consists of 400 mg daily for 1 week, followed by 3 weeks of no drug. 2 and 3 pulses are recommended for treating fingernail and toenail onychomycosis, respectively. The mycological cure rate for toenails is 54% and the complete cure rate is 14%. The most common side effects of itraconazole are similar to those of terbinafine-gastrointestinal distress, headaches, and upper respiratory tract infections. More serious side effects include hypertriglyceridemia, elevated transaminase and a form of hepatic injury in which 0.5%-1% of patients develop hepatitis [92-94]. Itraconazole is a category C drug and should be avoided during pregnancy. Contraception should be used for 2 months following the end of treatment. It is also excreted into breast milk, thus the use of itraconazole should be delayed until breastfeeding is completed.

Fluconazole is another triazole that works similarly to itraconazole and targets dermatophytes, some NDMs, and Candida spp. Although it is approved in Europe and China, it is used only as an off-label onychomycosis treatment in the United States. Advantages of fluconazole are that its absorption is not dependent on gastric pH (unlike itraconazole), and it is rarely associated with liver injury or failure as side effects [95,96]. In a double-blind study with 362 patients, fluconazole treatment groups (150 mg, 300 mg, or 450 mg once weekly for 12 months) showed high mycological cure rates 47% - 62% and clinical cure rates 28%- 36% compared to placebo [97]. Similar to itraconazole, the most common adverse side effects of fluconazole are drug interactions, which include hypoglycemic agents and warfarin. Finally, it is an inhibitor of CYP2C9 and CYP3A4, so it may not be used with certain medications [98]. Fluconazole is an FDA category D drug and there have been case reports of fetal anomalies in humans [99,100]. As it is excreted into human milk, its use should be delayed until after pregnancy and breastfeeding. Terbinafine can be used intermittently (pulsed) to treat onychomycosis. This strategy is not FDA-approved, but has been used in clinical trials and is thus an off-label treatment [101]. Pulse terbinafine regimens have been shown to have similar effectiveness as continuous regimens in achieving complete cure. A pulsed regimen of two cycles of 250 mg terbinafine per day, for 4 weeks on and 4 weeks off, had the highest efficacy of all terbinafine pulse regimens. The mycological and complete cure rates were comparable to that of continuous terbinafine for 12 weeks at 250 mg per day. However, further studies need to be done on these pulsed regimens to analyze their cost efficacy, compliance, safety, AE profile and supremacy over continuous terbinafine regimen. [102]. Terbinafine and itraconazole can be used as a booster or supplemental therapy after the original antifungal course is completed. This strategy is thought to be effective in patients with slow growing nails, thick nail plates of >2mm, lateral involvement of the disease, over 75% nail plate involvement, and immunosuppression [103,104]. An additional 4 weeks of terbinafine given continuously or an additional pulse of itraconazole is administered 6-9 months after initiation of the antifungal therapy, providing a “boost” of antifungal drug. [105,106]. Posaconazole has been examined as an alternative treatment for onychomycosis due to its efficacy and promising safety profile. Posaconazole is a potential consideration for infections that are refractory to terbinafine, itraconazole, and fluconazole, patients intolerant to terbinafine, itraconazole, and fluconazole, or for NDM infections [107]. In a phase 2B study, onychomycosis patients received one of several posaconazole regimens (oral suspension 100, 200, or 400 mg once daily for 24 weeks; 400 mg once daily for 12 weeks), terbinafine 250 mg tablets once daily for 12 weeks, or placebo for 24 weeks. All the posaconazole treatment arms had significantly greater proportions of patients achieving complete cure at 48 weeks ($P \leq 0.012$) compared to placebo at week 48. Proportions of patients with complete cure were higher for posaconazole 200 mg for 24 weeks (54.1%) and 400 mg for 24 weeks (45.5%), but lower for 400 mg for 12 weeks (20%) compared to terbinafine (37%; all were not significantly different). Mycological cure at week 48 for posaconazole 200 mg and 400 mg for 24 weeks was similar to terbinafine (70.3%, 78.8%, and 71.4%, respectively), whereas cure rates were numerically lower for posaconazole 100 mg for 24 weeks (37.1%) and 400 mg for 12 weeks (42.9%). Posaconazole was well tolerated, with 7 patients (n=182 receiving posaconazole) dropping out due to asymptomatic elevated liver enzymes [107]. Similarly, a phase 2 randomized studies of 584 patients examined the efficacy and safety of albaconazole, a novel triazole, as a once-weekly treatment for DSLO [108]. Patients received 100 or 200 mg of albaconazole for 36 weeks, or 400 mg albaconazole and placebo for 24 and 12 weeks, respectively. Mycological cure was assessed at week 52. All the treatment groups achieved greater mycological cure rates (71% for 400 mg for 36 weeks; 54% for 400 mg for 24 weeks; 43% for 200 mg for 36 weeks; 34% for 100 mg for 36 weeks) compared to placebo (6%, $P<0.001$ for all groups). Complete cure was only achieved by albaconazole groups, was dose dependent (33%, 26%, 21%, and 12%, respectively) and statistically different from placebo (0%, $P<0.001$). Additionally, no serious hepatic or cardiac adverse events were observed [108]. A phase 3 randomized studies assessed the efficacy of a novel 200 mg formulation of itraconazole versus two 100 mg capsules of the currently available formulation. The novel 200 mg tablet was formulated with Meltrex technology delivery system [109,110]. The technique employed is popularly known as melt extrusion or hot melt extrusion and has been used in the plastic industry for many years, only recently being adapted to the pharmaceutical industry. Heat and pressure are applied to bind an active drug with a polymer, which acts as a carrier for delivery of the drug. The polymer is melted and forced through a die along with the active drug to form a homogenized solid dispersion. This ‘solid solution’ formulation of itraconazole delivers the same dosage as two 100 mg tablets in a single tablet, aids in sustained drug release, and may improve bioavailability of the drug. Both these dosages had similar efficacy and comparable cure rates. The advantage of using the novel itraconazole 200 mg formulation in treating onychomycosis is improvement in patient compliance as this is a simpler dosing regimen with the same efficacy [109]. A prodrug of ravuconazole, fosravuconazole L-lysine ethanolate

(F-RVCZ) exerts broad, potent antifungal activity. The pharmacokinetics, safety, and efficacy of ravuconazole were studied in a randomized, double-blind phase I/II study. Four dosing regimens of fosravuconazole (12 week treatment period) were assessed (200 mg/day, 400 mg/week, 100 mg/week, and placebo). The effective cure rate at week 48 (mycological and clinical cure (nail improvement > 30%)) was observed in 56% and mycological cure in 59% of the patients in the 200 mg/day dosing regimen and was the highest among all the groups. It was concluded that 200 mg/day fosravuconazole for 12 weeks was a safe treatment option for onychomycosis [111]. The efficacy and safety of fosravuconazole were also compared to placebo in a phase 3 randomized studies in Japan [112]. Patients received either F-RVCZ (100 mg) or placebo once daily for 12 weeks and complete cure was evaluated at week 48. Complete cure rates were significantly higher at week 48 with F-RVCZ (59.4%) than placebo (5.8%) in the full analysis set ($P<0.001$). Mycological cure rates were also higher with F-RVCZ (82%) than placebo (20.0%, $P<0.001$). Adverse drug reactions were observed in 23.8% of patients, but none were serious. Thus, fosravuconazole is a promising treatment option.
The RENOVATE trials examined the safety and efficacy of VT-1161, a novel tetrazole inhibitor of CYP51 (Figure 13). In the phase 2B study, patients received 300 or 600 mg VT-1161 or matching placebo, once weekly, for 10 or 22 weeks following a 14-day loading dose. At week 48, complete cure rates were 32%- 40% and mycological cure rates were 61% -72% for VT-1161 [113]. Additionally, VT-1161 showed favorable pharmacokinetics and safety profile. There is no FDA-approved systemic treatment of onychomycosis in children. However, terbinafine, itraconazole, and fluconazole are all used off-label for this purpose [114-117]. The British Association of Dermatologists suggests terbinafine or itraconazole as a first-line treatment in children [118].

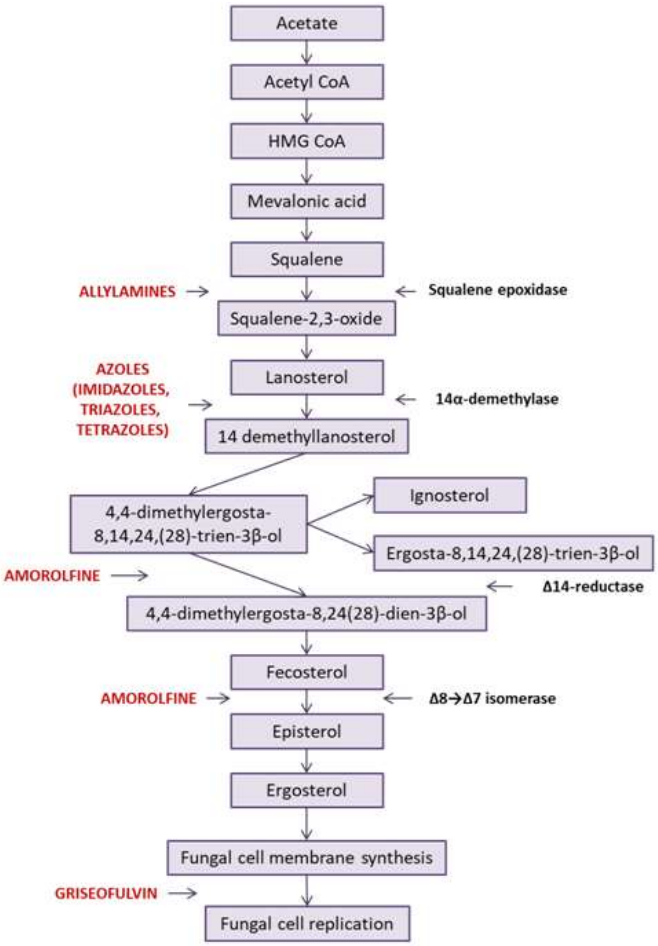

Figure 13: Fungal cell replication process and sites of action of antifungal drugs [23]

Topical treatments

Due to the potential systemic side effects of oral antifungals, there has been an increased demand for topical options with minimal side effects and no drug-drug interactions. Formulations are designed to penetrate the nail plate and to deliver the drug transungually to the nail bed in which the fungus resides. However, compliance is problematic, as treatments must be applied for at least 48 weeks (for the toenails), and may be difficult to use for those with limited mobility and dexterity. Topical antifungals include efinaconazole, tavaborole, ciclopirox and amorolfine [119-124]. Their side effects are generally limited to exfoliation, erythema, and dermatitis at the application site [119,120]. When using topical agents to treat onychomycosis it is important to look for and treat associated fungal skin infections, which may appear interdigitally (typically between the fourth and fifth toes, i.e. fourth toe web space) or on the bottom of the foot (i.e. plantar tinea pedis), as this integrated treatment increases cure rates [125].
Efinaconazole is a triazole that inhibits lanosterol 14α-demethylase and disrupts ergosterol synthesis in the fungal cell membrane. It is effective for dermatophytes, NDMs, and Candida spp. and is formulated as a 10% solution with a brush

applicator. Patients are instructed to apply the product to affected toenails once daily for 48 weeks, ensuring that the folds and undersurface of the nail plate (ventral surface) are coated as well. Efinaconazole demonstrates low keratin affinity, permitting increased availability of free drug to the site of infection in the nail. In two studies from phase 3 trials of this drug, patients with 20%-50% nail involvement were treated for 48 weeks and evaluated at 52 weeks. Mycological cure rates from these studies were 55.2% and 53.4%, whereas complete cure rates were 17.8% and 15.2% [126]. There were subgroups of patients who exhibited elevated cure rates after a shorter period of time than that needed for the main cohort; they included female subjects, persons with onychomycosis of the great toenail only, those with a relatively short duration of disease, and those lacking tinea pedis [126,127-131].

Preliminary data suggest that efinaconazole can be applied safely beyond one year and the efficacy rates after 18 to 24 months of application are higher than those seen after 12 months of usage [132]. The pharmacokinetics, efficacy and safety of efinaconazole 10% were assessed in a phase 4, open-label study for the treatment of pediatric onychomycosis. The pediatric patients in this study were 6 to 16 years of age and diagnosed with DLSO. Efinaconazole demonstrated high cure rates in the pediatric population compared to the adult population. Mycological cure was 65% and complete cure was 40% at week 52 following a 48 week daily application [133]. Efinaconazole is a pregnancy category C drug – there is no human embryotoxicity data, and it is not yet known if the drug is secreted into breast milk.

Tavaborole is an updated formulation of oxaborole, a boron-based drug that inhibits fungal protein synthesis at the point of cytosolic leucyl-transfer RNA synthetase [134]. It has broad-spectrum activity against dermatophytes, NDMs, and yeasts. It penetrates the nail well due to its small size and hydrophilicity. The mycological cure rates from two trials were 31.1% and 35.9%, and clinical cure rates were 6.5% and 9.1% [135]. The safety, efficacy, and pharmacokinetics of tavaborole 5% were assessed in a phase 4, open-label study for the treatment of pediatric onychomycosis. Pediatric patients aged 6 to 17 years were included. The clinical type was moderate to severe distal subungual toenail onychomycosis (≥20% affected nail) and the treatment regimen followed was daily topical application of tavaborole 5% solution for 48 weeks. The primary outcome was complete cure (which included both mycological cure and complete, clear nail) and the secondary outcome was complete/almost complete cure (mycological cure and complete, clear/almost clear nail with ≤5% affected nail). The complete cure at week 52 was 8.5% and complete/almost complete cure at week 52 was 14.9%. All of the side effects were mild to moderate. The systemic absorption and plasma concentrations were comparable to that of an adult population; thus, tavaborole was deemed safe to treat pediatric onychomycosis [136]. Tavaborole is classified as a category C drug. Ciclopirox 8% nail lacquer may be used to treat dermatophytes, Candida spp., and some NDMs. Ciclopirox is a hydroxypyridone, a molecule that chelates trivalent cations and thus inhibits metal-dependent enzymes [137,138]. Ciclopirox interferes with the active membrane transport of macromolecular precursors, disrupting the cell membrane integrity and inhibiting enzymes required for cellular respiration [139]. This drug also targets some gram-positive and gram–negative bacteria. While using ciclopirox, patients are advised to clip their nails weekly and receive monthly office debridement to increase efficacy. The mycological cure rates for toenails range from 29%- 36%, whereas the complete cure rate ranges from 5.5%- 8.5% [121,140]. It is still unknown if the drug is excreted into breast milk, so treatment should be delayed in pregnant and breastfeeding women as it is a category C pregnancy drug [121]. Amorolfine is a morpholine drug that inhibits the fungal enzymes Δ14 reductase and Δ7-Δ8 isomerase, thus interfering with fungal sterol synthesis pathways (Figure 13). This drug is approved in Europe for the treatment of onychomycosis and is used off-label in the United States [141], and is effective against dermatophytes, some yeasts, and molds [122,142]. Amorolfine achieved complete cure rates of 54.2% and 46.0%, depending on whether patients applied the lacquer twice or once weekly, respectively. Similarly, the mycological cure rates were 76.1% for twice-weekly application and 70.6% for once-weekly application [143]. Another study on daily 5% amorolfine application showed mycological and complete cure rates of 60% and 38%, respectively [123]. There is insufficient research to determine whether the product is safe in pregnant women, so it should be avoided during pregnancy and breastfeeding.

In Europe, a novel technology based on hydroxypropyl chitosan (HPCH) is being used to deliver ciclopirox 8% into the nail as a hydrolacquer [144]. The HPCH forms an invisible film on the surface of the nail, stopping fungal invasion and facilitating ciclopirox penetration into the nail [145,146]. A randomized, evaluator-blinded, controlled, parallel-group clinical trial demonstrated that the hydrolacquer is superior to amorolfine after a 48 week treatment. Complete cure, based on negative KOH, culture, and no clinical involvement of the nail, was 35% for the hydrolacquer and 11.7% for amorolfine ($p<0.001$). Mycological cure rates were 100% and 81.7%, respectively ($p<0.001$). Ciclopirox 8% hydrolacquer is not approved for the treatment of onychomycosis in the USA, but is approved and marketed in more than 40 countries [147]. There are several novel formulations of topical terbinafine that are in various stages of development across the globe. Similar to ciclopirox 8% nail hydrolacquer that uses HPCH technology (P-3051), terbinafine has a topical formulation that employs the same technology. P-3058 is a topical terbinafine drug which has 10% terbinafine hydrochloride as the active compound. A randomized, phase 3 trial is ongoing to study the safety and efficacy of P-3058 in treating toenail DLSO when administered once weekly for 48 weeks [148]. Another topical formulation of terbinafine is MOB-015 that recently met the treatment endpoints in a randomized, phase 3 trial with a mycological cure of 70% and complete cure of 4.5% at week 52 [149]. TDT-067 is a topical formulation of terbinafine (liquid spray) in a transfersome (lipid based vehicle) at 15 mg/ml. It is applied on infected nails, nail grooves, and surrounding skin. It is a potential treatment option for toenail onychomycosis which is still under trial for safety and efficacy [150,151]. ME1111 acts by inhibiting succinate dehydrogenase, an enzyme in the electron transport chain,

which in turn affects ATP production in fungal cells. It has a small molecular size and has higher penetration capacity in the nail plate than ciclopirox [152,153].

Lasers

In January 2012, the FDA approved four laser systems for "temporarily increasing clear nail in onychomycosis", based on substantial equivalence to already approved devices with similar technical specifications and applications [154]. Lasers offer some advantages over drug-based options, such as shorter and fewer treatments, and no systemic side effects. The FDA-approved lasers are all 1064 nm Nd:YAG lasers, both short-pulsed and Q-switched lasers, other lasers in development include carbon dioxide lasers, and the diode 870 nm, 930 nm laser. Some lasers have also been approved for onychomycosis treatment by health regulatory bodies in Canada, Europe, Australia, Korea, South America, and Japan [155-157]. There is limited evidence that lasers eradicate pathogenic fungi because reporting is incomplete and there is a lack of randomized clinical trials [158, 159]. Clinical studies have demonstrated the safety and effectiveness of the lasers, but clinical trial data released for lasers is incomplete- it does not include the types of infections, details of treatment protocols, mycological or complete cure rates, or relapse rates with follow up at 12 months post-treatment. In one review, a temporary improvement in nail appearance was seen in 78% of patients during treatment and follow-up. A decrease in nail involvement of ≥50% was seen in 46% of patients, while 17% of patients had <10% nail involvement at the last clinical assessment. Only 9% (2 of 23 patients) achieved clinical cure [160]. In another review, overall mycological and clinical cures were 11% and 13%, respectively [161]. The inclusion criteria and definitions of efficacy outcomes between drugs and medical devices differ, which makes it difficult to compare the treatments [162]. A similar off-label therapy to laser treatments is photodynamic therapy (PDT). PDT works by irradiating specific wavelength of light onto topically-applied photosensitizers such as 5-aminolevulinic acid, methyl aminolevulinate, or methylene blue. When activated by certain wavelengths of light, these sensitizers get excited and produce highly reactive oxygen species which cause apoptosis in fungal cells. Not many studies have been reported using PDT for the treatment of onychomycosis [163].

Permeation enhancing methods

Topical therapy for onychomycosis requires longer treatment periods and has lower success rates than oral therapies, partly due to the impenetrable nature of the nail plate. Therefore, mechanical, physical, and chemical permeation enhancers are continuously being studied as adjuvants to topical treatments. Mechanical abrasion of the dorsal nail plate can increase the surface area of topical application by creating micro holes and valleys in the surface of the nail. Physical permeation enhancing methods includes etching, lasers, electropulsation, ultrasound, microneedling, hydration, and iontophoresis, which increase the surface area of application, introduce holes for deeper penetration, or separate the keratin strands of the nail plate allowing larger molecules to penetrate [164]. An example of etching or microneedling is illustrated by a recent US patent that describes a nail treatment kit that etches 1 mm sized holes in the nail while dispensing antifungal treatment [165]. Iontophoresis, on the other hand, employs a small amount of electric current to enhance the delivery of the topical drug to the infected site. An ex vivo study used iontophoresis and terbinafine cream to successfully eradicate fungal infections from the nail plate [166]. Chemical permeation enhancers include solvents, enzymes, etchants, and keratolytic agents, which either hydrate the nail and/or break the bonds between the nail keratin strands, both resulting in larger pores or spaces for topical treatment to pass through [164]. Two recently-patented topical formulations employ vastly different penetration enhancing and antifungal characteristics. The WO2019088055A1 patent describes a formulation containing a classic antifungal drug, such as efinaconazole or luliconazole, alongside the penetration enhancer ethyl lactate, among other volatile and non-volatile chemicals. In vitro and mammalian in vivo tests suggest this formula has improved permeation and fungicidal properties [167]. The CN109303815A patent proposes a unique plant extraction formula including turpentine, petrolatum, belladonna extract, azone, and salicylic acid, among other chemicals, and is suggested to have good antifungal and permeation properties [168].

Surgical and mechanical treatments

Surgical or chemical avulsion of the affected nail can be helpful in cases known to be resistant to topical and systemic treatment, e.g. those featuring severe onycholysis, dermatophytoma, longitudinal yellow streaks, or involvement of the lateral nail sulcus. Chemicaavulsion with 40% urea applied onto the plate and occluded for 1 week is an easy and non-painful option. Surgical avulsion requires local anesthesia and allows partial or total removal of the nail plate [169, 170].

Novel drug delivery strategies

The chances of relapse in the onychomycosis cases are very high. Current oral therapy poses the risk of hepatotoxicity and drug-drug interactions whereas topical therapy suffers from extremely longer duration of treatment. Both of these situations are inconvenient to patients as well as ineffective due to frequent relapses [171]. This calls for better and effective therapies leading to extensive research in this area. Various novel drug delivery systems like nanoparticles, microemulsions, hydrogels *etc*. have been tried in research across the field. The same will be discussed following in the review.

Nanoparticles

Nanoparticles in topical/ transungual drug delivery have gained a lot of attention in recent years. Nanoparticles in the form of a topical medication can be easily applied on nail and also dodge the adverse effects associated with oral drugs. The inclusion of nanoparticles improves drug targeting and also enhances the drug profile and permeation [172]**.** Below are some of the nanoparticles which have been tried for treating onychomycosis.

Nanocapsules

Nanocapsules are nanosized drug delivery carriers that have a core comprising a solid or liquid bound by a polymeric shell on the outside. The core is usually a lipophilic solvent like oil which is employed for enclosing lipophilic/ hydrophobic drugs. Synthetic polymers like poly [lactic acid] [PLA] and poly [lactide-co-glycolide] [PLGA] are usually involved in the preparation of nanocapsules. Encapsulating antifungal drugs in nanocapsules ensures sustained release, antifungal efficacy and enhanced permeation. Some research studies showing the use of nanocapsules delivering antifungal drugs for onychomycosis are discussed below [173].

Flores *et al.* [2013], developed and evaluated nanocapsules and nanoemulsions containing *Melaleuca alternifolia* essential oil [tea tree oil] in an onychomycosis model. The *in vitro* antifungal activities were evaluated against *Trichophyton rubrum* species by two onychomycosis models. The diameter of the fungal colony was measured in both the cases. It was found that the nanocapsules containing tea tree essential oil performed better in reducing the growth of *T. rubrum.* It was also found to facilitate better permeation into the fungal cells [174]. In another study, Flores *et al.* [2016] developed Tioconazole-loaded nanocapsule suspensions with a coating of a cationic polymer for transungual drug delivery. It presented a size of 155 nm for uncoated nanoparticles and 162 nm for those with the cationic coating. The formulations demonstrated good *in vitro* antifungal activity against C. albicans. Pullulan nanobased nail formulation demonstrated good viscosity which is essential for nail application. The nanocapsule suspensions and Pullulan nanobased nail formulation also demonstrated lesser irritancy than free drugs and commercial formulations. Pullulan nano-based nail formulation was found promising for the treatment of onychomycosis [175]. This work has been further extended to the addition of *in vitro* release tests [IVRT] and *in vitro* permeation tests [IVPT]. The effect of nail poration on penetration was also studied. Series of experiments with Nile Red and confocal microscopy utilizing fluorescent marker into the nail plate was employed to observe the pathway and depth of nail penetration. The tioconazole loaded-nanocapsule formulation was found to provide sustained and greater drug release. With the Nile red experiments a penetration depth of 90-160μm was found to attain after 7 days. Moreover, the nail poration aided in better nail permeation of the nanocapsules formulations [176].

Polymeric nanoparticles

Since last few years, polymeric nanoparticles have been exploited for novel drug delivery to target various diseases. The reasons behind its success have been biocompatibility, flexible designing, stability and longer duration of action. Polymeric nanoparticles have also found use in treating onychomycosis [177]. For example, Chiu *et al.* [2015], formulated polymeric nanoparticles of poly-[ε-caprolactone] loaded with Nile Red for visualization after topical application. The nails were pretreated with microneedle poration so as to open up pores to facilitate fluorescent probe-loaded polymeric nanoparticles penetration. Laser scanning confocal microscopy was employed to visualize the pathway. Afterwards, two-photon fluorescence and stimulated Raman scattering microscopies were used in combination to further track the Nile Red loaded polymeric nanoparticles and observe their fate. Sustained release of polymeric nanoparticles was clearly observed and the techniques were successful in monitoring the release. Microneedle poration facilitated fluoroscent probe delivery into deeper regions of the nail. The results support the potential of polymeric nanoparticles acting as drug reservoirs in the deeper regions of nail and microneedle poration facilitating drug delivery and deeper nail penetration [178].

A recent research work carried out by Wang *et al.* [2018], demonstrated the potential of ketoconazole-encapsulated crosslinked fluorescent supramolecular nanoparticles as controlled release formulation for treating onychomycosis. The preparation of such novel nanoparticles required a two stage approach. The nanoparticle delivery was done intradermally *via* tattoo. Nanoparticle characterization revealed good encapsulation efficiency and sustained release of ketoconazole. *In vivo* studies using tattoo were carried out on a mouse model. The results support the use of ketoconazole encapsulated crosslinked fluorescent supramolecular nanoparticles as an intradermal controlled release solution for treating onychomycosis [179].

Nanoemulsion

Nanoemulsion consists of droplets of a mixture of lipids and surfactants lying within the size range of 10-500nm. It possesses all the characteristics essential for antifungal therapy like stability, improving solubilization issues, enhanced permeation effect and targeted action. They are better alternatives to less stable liposomes [173]. Much research work has been carried out exploiting nanoemulsions for onychomycosis therapy. Many times the nanoemulsion is delivered in the form of gel which has been termed as nanoemulgel. Some studies are delineated below.

Mahtab *et al.* [2016] prepared Ketoconazole nanoemulgel with the incorporation of permeation enhancer for transungual drug delivery and checked its efficacy in inhibiting the growth of dermatophytes *in vitro*. *In vitro* cumulative drug released at the end of 24 h from formulations NE3, NEG1 and drug suspension were found to be 98.87±1.29, 84.42±2.78% and 54.86±2.19%, respectively. *Ex vivo* transungual permeation studies were performed. The

antifungal effect of NEG1 on *Trichophyton rubrum* and *Candida albicans* showed a significant zone of inhibition as compared to drug solution. The results demonstrated enhanced permeation with ketoconazole nanoemulgel [180].
In yet another study done by Kumar *et al.* [2012], nano-emulsion-gel of ciclopirox olamine was developed, evaluated and optimized for treating subungual onychomycosis. The formulation was developed by aqueous phase titration method and was evaluated *in-vitro*. Pseudoternary phase diagrams were constructed and Box Benkhem model [RSM] was employed for optimization. Size and zeta potential were taken as dependent variables and formulation components were taken as independent variables. Series of nanoformulations were developed. Fluorescence microscopy was employed to observe the longer retention capability of the nanoemulsion-gel formulation. So, the study successfully formulated a thermodynamically stable antifungal nanoemulsion gel carrying ciclopirox olamine with prolonged retention capability [181].

Nanovesicles

Vesicular systems have always been fair option while promoting skin penetration. Although vesicles like liposomes, ethosomes, and transferosomes have shown their capability as drug delivery systems, yet another new class of vesicles called penetration enhancing vesicles have also shown promise [182]. These nanovesicles have been employed for transungual delivery for nail fungal infections as well. The studies conducted are discussed below.
Bseiso *et al.* [2015], developed and characterized nanovesicles loaded with sertaconazole for transungual delivery. The nano- penetration enhancing vesicles [nPEVs] were prepared using different nail penetration enhancers and characterized. The selected nPEVs formula and the marketed Dermofix creams were compared. N-acetyl-Lcysteine was found to be the optimum nail penetration enhancer for incorporation within vesicles. nPEVs showed high encapsulation efficiency of sertaconazole ranging from 77 to 95%, a size ranging from 38-538nm. Compared to the conventional marketed cream, the selected nPEVs formula showed 1.4-folds higher hydration and drug uptake enhancement into nail clippings and higher zone of inhibition too [183].
Elsherif *et al.* [2016] formulated terbinafine hydrochloride in a spanlastic nano-vesicular carrier that enables and enhances transungual drug delivery. A full factorial design was implemented to study the effect of different formulation and process variables. An optimized formulation with high entrapment efficiency [62.35±8.91%], average particle size of 438.45 ±70.5 nm, and 29.57±0.93 was obtained. The release of drug was 59.53±1.73% after 2 and 8 h, respectively. An *ex vivo* study was also conducted in a human cadaver nail plate. The results confirmed that nanovesicular spanlastics exhibit promising results for the transungual delivery of Terbinafine for onychomycosis [184].

Liposomes

Liposomes are phospholipid bilayered vesicles which consist of an aqueous core and phospholipid outer membrane. The structure is similar to that of natural membrane thereby imparting a unique characteristic for drug delivery. Liposomes have been found suitable for both hydrophilic and hydrophobic drug delivery. Liposomes have been widely employed in topical drug delivery applications due to their advantageous features like biocompatibility, better skin penetration, stability, less toxicity and sustained release. For better stability and controlled release, usually cholesterol is added in liposomes. Moreover, if ethanol is added in lipid vesicles, it becomes ethosomes consisting of phospholipid, ethanol and water. It is believed that liposomes and ethosomes are capable of taking advantage of some lipophilic pathways in the nail which makes them a promising option for nail drug delivery. Several antifungal drugs have already been incorporated in liposomes and ethosomes for topical antifungal therapy [173, 185].
Tanrıverdi and Ozer [2012] conducted a research in which they developed terbinafine loaded liposome and ethosome formulations with their gel forms. Evaluation tests along with *in vitro* and *ex vivo* release studies were also carried out. Nail characterization studies showed changes in the nail surface after application of all the formulations with gel formulations inducing more changes than others. It was found that all the formulations had the potential for efficiently delivering terbinafine to the nail. Moreover, the accumulation studies showed that liposome poloxamer gel formulation was the best regarding better accumulation and easier application to the nail [185]. Tanrıverdi and Ozer continued the research work with others in liposomal formulations for nail delivery by doing another study in 2015. They developed and evaluated a new film formulation of terbinafine hydrochloride loaded liposome. The efficacy of the terbinafine loaded liposome film was compared with terbinafine-loaded liposome, ethosome, liposome poloxamer gel and ethosome chitosan gel formulations. Characterization studies involved drug content estimation, bioadhesive and tensile strength. *In vitro* and *ex vivo* permeation studies were also carried out to identify an optimum film formulation which demonstrated better antifungal activity than the rest. This was done to validate the use of such a novel formulation for treating onychomycosis. It was found that terbinafine- loaded liposome film formulation had better antifungal activity on fungal nails than all other formulations [186].

Microemulsion

Microemulsion is a thermodynamically stable carrier having low surface tension and droplet size in the range of 10-100nm. It possesses superior qualities like enhanced bioavailability, absorption and permeation. It enhances bioavailability of all kinds of drugs including hydrophilic as well as lipophilic [187]. Undoubtedly, microemulsions have garnered a place for themselves in novel drug delivery systems due to their versatility and ease of preparation. Microemulsions include oil, surfactant, cosurfactant, and water in defined ratios. They have become popular means of delivery for topical and transdermal formulations due to their capacity to hold large amounts of drug and enhancing diffusion across dermal membranes [188].
Barot *et al.* [2011], developed a microemulsion based gel of terbinafine for onychomycosis therapy. D-optimal design was applied in order to optimize the amount of oil, mixture of surfactant and cosurfactant and water in the

microemulsion. The prepared formulations were evaluated for droplet size and drug solubility. The formulation was adapted into gel form with 0.75% w/w carbopol 934P. The optimized gel demonstrated better penetration and retention as compared to commercial formulation. It also showed better antifungal activity against strains of *Candida albicans* and *Trichophyton rubrum*. The optimized microemulsion based gel showed promising results as potential therapy for onychomycosis [188].

Yet another microemulsion based gels were developed by Kansagra and Mallick [2015] for solubilizationand better nail penetration of novel antifungal drug, Luliconazole. The microemulsion was optimized with its components of Olive oil as oil, Capmul MCM as a surfactant and iso propyl alcohol as a cosurfactant. Evaluation tests like particle size analysis, droplet size, spreadability, stability, *in vitro* release studies were conducted. The globule size of the optimized batch was 32.59 nm. The microemulsion based gel demonstrated antifungal activity against *Candida albicans* indicating its efficacy as a formulation in onychomycosis [189].

Hydrogels/ *In situ* gels

Hydrogels are hydrophilic polymeric networks which possess the ability to absorb huge amounts of water or physiological fluids. Hydrogels can be synthesized from both natural and synthetic polymers. They have demonstrated good viscosity and bioadhesion without causing any irritation or sensitization. They can be easily washed out and adhere well. Self- assembling type hydrogels are formed in response to some external stimuli like temperature or pH or even concentration. Such systems are called *in situ* gelling systems [190]. The hydrogel solution turns to gel and then to sol [solgel transition] due to self- assembly because of hydrophobic interactions. The most common examples of such polymers are Pluronics R or poloxamers which undergo transition due to temperature changes. Such systems offer many advantages like ease of administration, better local availability, simple manufacturing and patient compliance [191]. Hydrogels have been employed in topical drug delivery a lot. The good reputation is due to swelling character, adhesiveness and biocompatibility. Most importantly, incorporation of a drug in hydrogel improves the release kinetics and solubility profile of the drug [192]. Some of the research work targeted at onychomycosis is described below.

Nogueiras-Nieto *et al.* [2013] explored the use of *in situ* gelling hydrogels based on polypseudorotaxanes of Pluronic F- 127 and partially methylated β-cyclodextrin as aqueous nail lacquers. Nacetylcysteine and urea were incorporated as penetration enhancers. The transungual drug delivery of the formulation across human nail was found to be better than a marketed organic lacquer which supports the growing hypothesis that aqueous based nail lacquers are better drug delivery strategy in nail topical delivery [193]. El-sherif *et al.* [2017] developed two drug delivery dosage forms; the *in-situ* gel and the nail lacquer and evaluated them for their ability to deliver terbinafine hydrochloride [TBH] encapsulated in spanlastic carriers to the nail plate. The optimized *in-situ* gel formulation, showed higher amounts of retained TBH in the nails [2.05±0.008 mg/cm2] compared to the marketed product Lamisil cream 1% [1.36±0.03 mg/cm2] indicating successful transungual delivery of TBH from the prepared *in-situ* gels [191]. Celebi *et al.* [2014], developed hydrogels and microemulsion -based gel both enclosing terbinafine hydrochloride and assessed their antifungal efficacy. Three different hydrogel formulations were prepared using chitosan, Carbopol 974 and Natrosol 250 polymers [192]. The microemulsion based gel was prepared using Carbopol 974. Comparative release studies were conducted between the formulated gels and the marketed product. The *in vitro* release studies demonstrated that the Natrosol gel exhibited highest drug release, followed by Carbopol gel, chitosan gel, commercial product, and then the microemulsion-based gel. Consequently, Natrosol based hydrogel loaded with terbinafine exhibited highest potential as a topical formulation against fungal infections like onychomycosis.

Other novel strategies

There are many other research studies conducted for developing novel treatment for onychomycosis. Some of these are currently undergoing clinical trials and have shown immense potential in antifungal activity against onychomycosis. These are discussed as follows.

PB-3058

P-3058 is another novel terbinafine transungual solution. Dose finding investigation studies were conducted in patients suffering from mild to moderate onychomycosis with P-3058. P-3058 5% o.d., 10% o.d. and 10% o.w. gave superior results as compared to P-3058 2% after 24 weeks. A phase IIb still needs to be conducted at a larger scale to determine its efficacy as a formulation [194]. A Multicenter, Randomized, Double-blind, Parallel, Vehicle-controlled Study to Evaluate the Efficacy and Safety of P-3058 10% Nail Solution [NCT02549001] in the treatment of onychomycosis is still being conducted and was expected to complete by October 2018. The study was in Phase III [195].

TDT- 067

TDT-067 is the novel formulation of terbinafine in a transferosome particle. It has completed Phase II clinical trials [196]. Transferosome promotes more drug absorption because of its hydrophilic surface. The formulation is potent against Trichophyton rubrum, T. mentagrophytes, and Epidermophyton floccosum with a minimum inhibitory concentration in the range of 0.03 to 15ng/ml. Phase II clinical studies involved administration of TDT-067 twice daily for about 12 weeks. Only 23.5% of patients reported mild adverse effects [196]. TDT-067 demonstrated more potent antifungal activity against dermatophyte species than conventional terbinafine formulations [197].

NB-002

Pannu *et al.* [2009], designed NB-002 which is a novel formulation of terbinafine in the form of nanoemulsion. It demonstrated better antifungal activity against major dermatophytes involved in onychomycosis and Candida albicans too. NB-002 includes a penetration enhancer called cetylpyridinium chloride. In a randomized, double blind, vehicle-controlled trial, sponsored by NanoBio Corporation, participants were administered NB-002 at 0.25% twice daily, 0.5% once daily, 0.5% twice daily or vehicle once or twice daily for 42 weeks. Only mild dermal side effects were noticed. It has completed Phase II clinical trials but the data is not available [198].

Novel techniques

Novel techniques like device based therapies are gaining a lot of appreciation lately because they circumvent some of the issues associated with oral and topical therapy. These therapies can be used or in combination with antifungal drugs to improve efficacy. The major disadvantage of such techniques is the requirement of a medical assistant throughout the treatment process [199]. Some techniques which have been recently developed are:

*Mesoscissioning technology:*This technique involves the creation of micro-conduits of 300- 500 microns through the nails. They serve as transporting pathways for drugs across the nail plate.

Nanopatchnail fungus: This involves the application of AC/DC current to facilitate delivery of drugs though nail cuticle. This treatment can be used to target fungus at its source of growth [200].

The recent work done in the field of novel delivery systems for onychomycosis [201-204] is discussed in Table 2

Table 2: Most recent research work done on novel drug delivery strategies for treating onychomycosis

Category	Year	Novel Formulation	Main Techniques/ Studies	Key Findings	Advantages
Nanoparticles	2018	Ketoconazole encapsulated crosslinked fluorescent supramolecular nanoparticles	Radiometric mixing, *in vivo* fluorescent imaging, high performance liquid chromatography, matrix-assisted laser desorption/ ionization mass spectrometry imaging, histology, mouse model, tattoo based delivery.	The nanoparticles showed high encapsulation efficiency, appropriate fluorescence, sustained release and intra dermal retention.	Less invasive, localized and controlled release, Dodges systemic side effects, can be applied to other diseases as well.
Nanoparticles	2018	Tioconazole loaded polymeric nanocapsules	Ultrafiltration centrifugation, *in vitro* release and *in vitro* permeation tests, nail poration, laser scanning confocal microscopy, photon fluorescence, Raman scattering imaging, confocal microscopy.	3 formulations- lacquer, nanocapsule and film were prepared and characterized, almost 100% encapsulation efficiency, were stable, consistent release profile, nail poration provided no leverage, localized therapy observed through Nile Red.	Prolonged release, Efficient delivery, greater drug payload, greater penetration.
Nanoparticles	2017	Voriconazole loaded nanostructured lipid carriers (NLC)	HPLC, hydration studies, nanoparticles characterization, stability studies, *in vitro* studies with porcine hooves, statistical analysis.	Maximum penetration was obtained with Urea as enhancer, drug release was 78- 86%, formulations were stable, the release kinetics fitted Higuchi model.	Deeper nail penetration, controlled release.
Nanoparticles	2017	Tioconazole Pullulan nano-based nail formulation	Nanocapsule characterization, morphological analysis, Ultrafiltration-centrifugation, *in vitro* release studies, bio adhesion assays, antifungal study, irritant potential through Hen's Egg Test – Chorio allantoic Membrane method.	Homogenous nanoparticles, Newtonian properties, release was bi- exponential, better antifungal activity against *C.albicans*, less irritant potential.	A hydrating formulation so increases ermeation easily, better efficacy and deeper nail permeation.
Nanoparticles	2016	Terbinafine loaded nano-based spanlastic vesicular carriers (nanovesicles)	Ethanol injection method, *in vitro* release studies, 24 full factorial design, Differential Scanning Calorimetry, X-ray Diffractometry, *ex vivo* permeation, nail pulverization.	Entrapment efficiency was 8 to 80%, sonication reduce particle size, amorphous, particles were unilamellar and spherical, better drug retention, more drug distribution and deeper nail penetration.	Better drug release and nail penetration.
Nanoparticles	2016	Ketoconazole loaded nanoemulgel with penetration enhancer	Ultra-performance liquid chromatography (UPLC), Aqueous titration, high pressure homogenization (HPH), Stress-Stability Studies, Nanoparticle characterization, nanoemulgel evaluation studies, *in vitro* release, tranungual permeation, antifungal activity and histo- pathological studies.	Optimized mean droplet size range: 63-126nm, No phase separation or flocculation occurred, non-Newtonian, pseudo-plastic nature, maximum drug release was 98%, better antifungal activity than drug solution.	Less toxicity and irritant potential, kinetically stable, safe and effective.
Spanlastic	2017	Terbinafine loaded spanlastics delivered through novel dosage forms*in situ* gels and nail lacquer	Ethanol injection method, characterization studies, *in vitro* drug release, 23 full factorial experimental design, *ex vivo* nail permeation studies.	Drug permeation was obtained in the order: *In situ* gel> nail lacquer> marketed product.	Greater efficacy, patient compliance, more coverage, no irritation.
Nail lacquer	2017	Terbinafine delivery *via* liposome loaded Nail lacquer	Thin film hydration technique, quality by design (QbD) technique, liposomes characterization, *In Vitro* Drug Release, Lyophilization, characterization of liposome loaded nail lacquer, *In Vitro* drug permeation, antifungal activity.	Drug permeation was more with liposome loaded nail lacquer than with simple nail lacquer, same antifungal activity as of drug solution, formulations passed all evaluation tests.	Enhanced permeation And more therapeutics efficacy.
Nail lacquer	2017	Ciclopirox-based Eudragit RLPO Nail Lacquer	Penetration enhancers screening, 33 full factorial design, Physicochemical characterization, *in vitro* release study, *ex vivo* nail permeation, Confocal Laser Scanning Microscopy.	Endopeptidase enzyme was selected as penetration enhancer, better permeation than marketed lacquer, better drug diffusion.	Enhanced permeation, noninvasive, localized therapy.
Nail lacquer	2017	Terbinafine in polyurethane nail lacquer	Quasi-pre-polymerization method, Fourier Transform Infrared Spectroscopy (FTIR), *In vitro* cytotoxicity assay, Determination of wettability, *In vitro* adhesion test, *in vitro* release study, *in vitro* antifungal activity, positron annihilation lifetime (PAL) measurement.	Contact angle< 90°, no cytotoxicity, better adhesion, lower MIC value, better *in vitro* drug release.	Biocompatible lacquers, Better drug diffusion, hydrophilic nature, nail adhesion.
Polymeric films	2016	Polymeric films as novel dosage form for onychomycosis	Carboxy methyl cellulose sodium salt (Sod CMC), Chitosan, 2-Hydroxy ethyl cellulose (HEC), (Hydroxy propyl)methyl cellulose (HPMC), Polyvinyl pyrrolidone (PVP), Propylene glycol (PPG) were the polymers used for making films, film characterization, irritation studies, microscopic studies, adhesive studies.	Dry and non-sticky films, no irritation, HEC and HPMC showed swelling, the polymeric films showed stability, flexibility, water resistance and adhesiveness.	Non- invasive, suitable for nail application.

Prevention

Because fungi thrive best in moist warm environments, patients should be advised to wear non-occlusive shoes, keep feet dry and cold, use absorbent socks, and clip nails short. Tinea pedis, if present, should be treated [205]. Also, family members with tinea pedis and onychomycosis should be appropriately treated [206]. To prevent recurrence, some authors suggest the use of topical antifungal therapy once weekly or twice monthly in high-risk patients for up to two years after completion of treatment [207, 208]. An ultraviolet C-based treatment device for footwear can be considered, as well as washing of running shoes (nonleather) in hot water.

Prognosis

Generally, the prognosis is good with appropriate treatment. Yellow streaks along the lateral margin of the nail, the presence of dermatophytoma, and onychomycosis caused by non-dermatophyte molds (in particular, *Fusarium* species) are associated with a poor response to therapy. Other factors associated with a poor response include noncompliance, old age, advanced disease, nail matrix involvement, subungual hyperkeratosis greater than 2 mm, two feet-one hand syndrome, and immunodeficiency. Poor response to therapy may also result from poor permeation of topical antifungal drugs across the nail plate and the deep-seated and recalcitrant nature of fungal infection. Recurrences are not uncommon, with reported rates ranging from 10 to 53% [46, 209]. Typically, recurrences occur within 3 years of completing therapy. Recurrence may be caused by relapse or reinfection.

Conclusion

Onychomycosis is the most common nail disorder with a significant burden. The condition is most commonly caused by dermatophytes followed by non-dermatophyte molds and yeasts. Although the diagnosis can be strongly suspected based on clinical grounds, laboratory confirmation is necessary prior to treatment. Relapses still happen even after years of therapy and the more technical treatment options come with high cost and requirement of assistance. Moreover, patients are not still comfortable being subjected to iontophoresis or laser therapy no matter how efficient these techniques are. Longer therapies frustrate patients and they have to switch over to the last resort of surgical nail removal. In such a scenario, novel options like nanoparticles, liposomes or transferosomes, seem promising. With negligible side effects, better and deeper drug release and drug retention, these systems have a lot to offer to the antifungal therapy. Coupled with a novel dosage form which can act as an excellent delivery vehicle, novel delivery systems have the potential to replace the conventional therapy in coming years. More attention is being focused on eradicating the long-standing issues associated with onychomycosis and it will not be surprising to assume the solution may well be on its way.

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