Chapter

Candida Onychomycosis: Mini Review

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Abstract

Onychomycosis is a common fungal infection affecting nails. 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. Furthermore, formation of biofilms and production of enzymes contribute as the virulence factors of the yeasts. Clinical manifestation of CO varies, from discoloration and marked thickening of the nail to dystrophic nails with fingernails more commonly affected. Paronychia is the most common type of CO and Candida granuloma is one of the severe types of CO which often occurs in chronic mucocutaneous candidiasis. Establishing the diagnosis of CO is crucial as well as the identification of each predisposing factors. Microscopic examination and fungal cultures are the gold standard examination for diagnosing onychomycosis, while for NDM, multiple confirmation and repeated examination is needed due to its as contaminants.

Keywords: candida onychomycosis, nail, fungal infection, diagnostic challenges, treatment

1. Introduction

Onychomycosis is a common nail infection caused by fungi, namely yeasts, dermatophytes, and non-dermatophyte molds (NDMs) [1]. The prevalence keeps increasing with age and it is commonly identified in elderly populations. Approximately 20% of adults in their second to fourth decades are affected by this disease. Yeasts contribute to 24–50% cases of onychomycosis with *Candida* species as the most common agent [2]. Various factors are associated with the event of onychomycosis, e.g. host's comorbidities (human immunodeficiency virus [HIV] infection, diabetes mellitus, peripheral circulation disturbances), repeated nail trauma, smoking, antibiotic therapy, immunosuppressive therapy, repeated exposure to fungi, humid climates, genetic predisposition, and occlusive footwear [2, 3]. Establishing the diagnosis of Candida onychomycosis (CO) is challenging. Albeit frequently identified in culture and direct microscopic examination, the presence of *Candida* species might only be colonization, not necessarily the cause of nail diseases. A careful interpretation of diagnostic tests' results and correlation with

results of clinical examination are necessary to establish the diagnosis of CO which will aid the clinicians in providing correct treatment for the patients [4].

2. Epidemiology

The prevalence of onychomycosis differs based on geographical location with worldwide prevalence of approximately 10% [5]. The incidence onychomycosis in North America ranges from 8.7–13.8% while the prevalence in Southeast Asia ranges from 2–6% [2, 3]. Higher prevalence is reported in countries with humid climates, such as Greece (27.99%) and Ethiopia (60,4%), [6, 7]. While there are three groups of fungi responsible for onychomycosis, dermatophytes are the most common cause of onychomycosis (60–70%) [3].

Yeasts, most commonly identified as *Candida* species in onychomycosis, contributes in approximately 40% of the onychomycosis cases in Southeast Asia. Other studies reported that the prevalence of CO varies between 24–50% of onychomycosis cases [2]. NDMs and yeasts onychomycosis is more common in subtropical and tropical climates while dermatophytes is more common in temperate climates [7]. *Candida albicans* is identified as the most common isolated species, followed by *C. parapsilosis, C. krusei, C. tropicalis,* and *C. glabrata* [2]. CO is more frequently to be identified in fingernails than toenails, especially in patients with hands continuously immersed in water [3].

3. Prognostic factors

In assessing the treatment outcome of CO patients, there are three types of cure to be considered, which area mycological cure, clinical cure, and complete cure. Clinical cure is described as a previously infected nail without signs and symptoms of onychomycosis. Mycological cure is described as negative results on both direct microscopic examination and culture. Complete cure is described as achieving both clinical and mycological cure [8]. Various prognostic factors have been identified for the treatment outcome of onychomycosis. In general, they can be divided into three groups, which are patient's characteristics, nail features, and the infectious agents (**Table 1**) [9].

Most studies reported that the onychomycosis is more commonly diagnosed in men. Male patients are associated with poor outcome because they are more likely to be exposed to repeated nail trauma and they usually do not seek health care until the disease becomes too advanced. Furthermore, they are more likely to have low compliance; hence, male patients become more resilient when it comes to treatment and have 2,6 times risk of not achieving clinical cure [8]. Increasing age is also known to be associated with poor prognosis in onychomycosis patients because elderly populations usually suffer from poor circulation system, poor immune status, decreased nail growth, and mixed fungal infections. Hence, their response to therapy might be lacking and they have 3,7 times risk of not achieving clinical cure [8, 9].

Nail trauma can exert significant and irreversible damage which will predispose patients to onychomycosis. Patients who have abnormal nails with positive mycology examination had 5,4 times risk of developing onychomycosis [9]. Other poor prognostic factor is history of onychomycosis. Patients with prior infection have 2,3 times risk of not achieving clinical cure. These patients are more likely not to respond standard treatment course since they have been treated before. There might also be involvement of genetic susceptibility in the development of recurrent onychomycosis [8].

Poor Prognostic Factors	
Patient's characteristics	Male gender
	Increasing age
	History of nail trauma
	History of onychomycosis
	Poor immune status
	Poor peripheral circulation
	Uncontrolled diabetes mellitus
	Repeated exposure to water and detergents
	Repeated exposure to mud and soil
	Barefoot walking
Nail features	Subungual hyperkeratosis >2 mm
	Fingernail and toenail involvement
	More than 3 infected nails
	Matrix involvement
	Significant lateral disease
	Dermatophytoma
	Nail plate involvement >50%
	Slowly growing nails
	Hallux involvement
	Severe onycholysis
	Paronychia
	Melanonychia
	Total dystrophic onychomycosis
Infectious agents	Fungal and bacterial coinfections
	Yeasts
	Non-dermatophytes molds

Table 1.
Poor prognostic factors in onychomycosis [4, 8–10].

As most fungi are opportunistic agents, poor immune status can predispose patients to onychomycosis, especially in HIV patients with CD4 count <400/mm^3. The onychomycosis is more likely to involve fingernails and toenails also more severe [9]. Patients with hand and foot involvement have 1.1 times risk of not achieving complete cure and if the patients have more than 3 infected nails, they have 1.5 times risk of not achieving complete cure [4]. Furthermore, hallux involvement presents as poor prognostic sign because it is more likely to suffer repeated trauma lead to predisposition of continuous infection.

In addition, poor peripheral circulation caused by chronic venous disease is associated with poor prognosis. Chronic venous disease can cause nail dystrophy, hyperkeratosis, discoloration, hyperplastic nail bed, and onychogryphosis. Only 25% of patients treated with itraconazole are cured [9]. Poor peripheral circulation can also identified in patients with uncontrolled diabetes mellitus which associates with secondary infections and nonhealing ulcers. This population is also reported to have more severe onychomycosis, high recurrence rate and longer duration to achieve complete cure [9].

Repeated exposure to water and detergents will predispose patients to chronic paronychia and affect the drug delivery since the tissue is more edematous and inflamed. While repeated exposure to mud and soil, also barefoot walking will predispose the patients to repeated minor trauma. Most fungi are saprophytic; hence, they can invade nails easily in this condition. This often happened in tropical countries [10].

Subungual hyperkeratosis is host's reaction towards fungal infection by thickening the stratum corneum. The thick debris presents as a barrier to antifungal agents, both systemic and topical agents [9]. Furthermore, patients with matrix involvement have 2.1 times risk of not achieving complete cure [8]. Matrix is known to be the nail's origin [11]. Hence, matrix involvement in onychomycosis will affect the nail growth and drug delivery [8]. In addition, the slow nail growth is also a poor prognostic factor since the patients shed the infected portion of the nail more slowly. This association is also described in elderly populations. Slow nail growth is also seen in significant nail plate involvement. Greater surface involved is associated with greater fungi load; hence, lower cure rates [9].

Significant lateral disease affects the treatment outcome since there is poor attachment of the lateral edge to the nail groove. This can reduce the drug delivery about two thirds of normal nail. Similar cases are seen in severe onycholysis [9]. Patients with lateral disease have 3,5 times risk of not achieving complete cure [8]. Another poor prognostic factor is dermatophytoma, a dense thick-walled fungal elements presenting as white to yellow patch or longitudinal streak in nail plate. This dense mass is difficult to be penetrated by antifungal agents. Therefore, the patients with dermatophytoma have 2.9 times risk of not achieving clinical cure [8, 9].

Melanonychia is black pigmentation identified on the nail plate. This feature is associated with poor prognosis in onychomycosis. However, the association has not been elucidated yet. Total dystrophic onychomycosis (TDO) is the final destructive stage of onychomycosis, in which there is thickened nail bed, crumbling nail plate, and significant involvement of nail matrix. Patients with TDO have 1.1 times risk of not achieving complete cure [4, 9].

As for the infectious agents, CO and NDMs onychomycosis indicate poor prognosis. CO is associated with immunosuppression, especially in case of chronic mucocutaneous candidiasis (CMC) and HIV patients. While NDMs infections are difficult to be diagnosed and lack of data for treatment course. In addition, fungal and bacterial infections can complicate the treatment. Therefore, these factors can implicate in poor prognosis of onychomycosis patients [9].

In order to aid the clinicians in have better treatment outcome, several instruments have been developed to predict the prognosis in onychomycosis patients. The first developed instrument was Scoring Clinical Index for Onychomycosis (SCIO Index). This scoring assesses the nail's clinical component based on its clinical form, nail involvement, and subungual hyperkeratosis. In addition, it assesses the growth component based on the patient's age and location of onychomycosis. As the score increases, the onychomycosis might be more difficult to treat [12]. However, this scoring has not been validated and has other limitations, such as exclusion of important prognostic factors and complex calculation [9].

Another scoring was developed by Baran et al. (**Table 2**). The higher the score, the more likely the treatment failure will happen [13]. Albeit being the most comprehensive instrument, this index has not been validated and time-consuming [9].

The most commonly used instrument is Onychomycosis Severity Index (OSI). OSI is simpler by assessing three major components, which are area of involvement, proximity of disease to matrix, presence of dermatophytoma or subungual

	Descriptor	Subdivision	Score
1	Extent of involvement	Distal one-third of nail plate	1
		Distal two-thirds of nail plate	2
		Proximal nail plate involvement	3
2	Diffuse nail plate thickening	Mild or moderate	1
		Associate with onychogryphosis	3
3	Nail plate thickening associated with the appearance of linear streaks – includes the change confined to the lateral border	One streak only	2
		Two or more streaks	3
		If the streaks are black do not score but see 7	
4	Onycholysis	Affecting the distal two-thirds of nail plate	2
5	Location	Any one of:	
		Second to fifth toes or thumb	1
		Great toenail	2
6	Paronychia associated with nail plate disease	With diffuse melanonychia	3
		With melanonychia at the lateral edges of the nail	3
7	Melanonychia (without paronychia)	With one or more longitudinal streaks	3
		Diffuse pigmentation	4
8	Age of patient	Under 7 years	3
		7–25 years	1
		25–60 years	2
		Over 60 years	3
9	Presence of the following predisposing factors	Diabetes mellitus	1
		Known severe trauma to affected nail	2
		Immunosuppression (due to therapy, e.g., prednisolone, or disease, e.g., AIDS)	4
		Symptomatic peripheral vascular disease	2
10	Causative organism	*Scytalidium* spp.	4
		Other mold fungi	2
		Yeasts	1

Cited as is from Baran et al. [13].

Table 2.
Baran-Hay's severity index for onychomycosis [13].

hyperkeratosis >2 mm (**Table 3**). The score is multiplication of score for area of involvement with score for proximity of disease and addition of score for the presence of dermatophytoma or subungual hyperkeratosis >2 mm. Score 1–5 indicates mild onychomycosis; 6–15 indicates moderate onychomycosis; and 16–35 indicates severe onychomycosis [14]. This index has been validated with high reliability. However, this index only assesses one nail, does not correlate the severity of disease with treatment outcome, and excludes other important prognostic factor [9].

Predictor	Subdivision	Score
Area of involvement (%)	0	0
	1–10	1
	11–25	2
	26–50	3
	51–75	4
	76–100	5
Proximity of disease to matrix	<1/4	1
	1/4–1/2	2
	>1/2–3/4	3
	>3/4	4
	Matrix involvement	5
Presence of dermatophytoma or subungual hyperkeratosis >2 mm	No	0
	Yes	10

Cited as is from Carney et al. [14].

Table 3.
Onychomycosis severity index [14].

4. Pathogenesis and causative agent

The most common causative agent of yeast onychomycosis is candida species. Fingernails are the predilection site of CO, especially in patients who are regularly submerging their hands in water [3]. Candida species are a commensal part of the normal skin flora, which are present in nature. However, these species may exhibit opportunistic quality in an immunocompromised host. Candida species can be either primary or secondary causative agent in onychomycosis. Primary CO can be commonly encountered in a severe immunocompromised host, for example, in HIV patient. On the contrary, secondary CO is usually related to predisposing diseases or circumstances, for instance, diabetes mellitus, malnutrition, peripheral vascular disease, chronic nail trauma, smoking, and vulnerable age (elderly and children). Particular occupations such as housekeepers, fishers, and farmers are also at risk of CO due to the frequent trauma and excessive moisture on the nails, exposure to contaminants, and contact with chemicals [2].

Instead of appearing as individual spores and hyphae, fungal organisms tend to integrate, forming a biofilm which is a syntrophic group of fungi adhering to the host's surface. When not infiltrating a substrate, fungi may fluctuate between free-floating types and parts of a superficial biofilm. This particular feature provides benefits for fungi development while being surrounded by extracellular matrix (ECM). The surrounding ECM defends fungi from the host's immune response and antifungal treatments. ECM also supports fungi to distribute nutrients to the biofilm. Fungi biofilm contributes to the rationale of why onychomycosis is relatively refractory to antifungal treatment and challenging to eliminate the spores in chronic manifestation entirely [3].

The biofilm development by *C. albicans* is initially started with the adhesion and colonization of *C. albicans* cells on an appropriate substrate. Several features that influence the attachment process of *C. albicans* are non-specific factors (electrostatic forces and hydrophobic part of the cell membrane) and specific factors (adhesin on the extracellular layer of *C. albicans,* which connects the ligands on

the film). Besides attaching to their counterparts, *Candida* species can also occur secondary to bacteria that have previously colonized their host. When the attachment process followed by microcolonies formation has completed, *C. albicans* began to proliferate characterized by the budding yeasts, production of filamentous structure, and deposition of ECM materials, ultimately resulting in biofilm formation. The filamentous structure supports the biofilm scaffolding and protects the adhesion spots for the budding yeasts [15].

There are 3 definite stages of *C. albicans* observed through microscopic examination, including early stage (0–11 hours), intermediate stage (12–30 hours), and maturation stage (72 hours) [15, 16]. During the 3rd and 4th hour, budding yeasts' microcolonies can be observed, while pseudo-hyphae and true hyphae start to appear in the 4th hour and 8th hour, respectively. Throughout the intermediate stage, microcolonies are later bounded by hyphae, which eventually results a single coalescent layer formation. An opaque film overlaying the microcolonies can be observed at this stage, which is mainly composed of non-cellular material such as polysaccharides. The basal layer is composed of yeast cells, while the filamentous cells constitute the underlying structure. Eventually, the maturation stage is characterized by the multiplication of extracellular material in a time-dependent manner until the mature biofilm covering the entire fungi has been developed [15].

In addition to biofilm, yeast factors that contribute to the virulency of CO are synthetization of hydrolytic enzymes, including proteinase, hemolysin, and phospholipase, which are unique between each type of Candida species. Moreover, proteinase plays a part in the breakdown of protein and phospholipase contributes to the destruction of the host cell, allowing *Candida* species to invade the host [2]. The reported prevalence of CO is 5–10% of all onychomycosis cases. The most common causative species of CO are *C. albicans* and *C. parapsilosis* [17].

5. Clinical presentation in immunocompetent and immunocompromised patients

Most CO cases involve fingernails compared to toenails, with an estimated prevalence of up to 50% of onychomycosis cases in fingernails. Women at risk of developing CO are typically wet workers due to the recurrent moist in the hands, exposure to trauma, regular contact with washing liquids, and contamination to vaginal flora during cleansing, which ultimately provides a suitable niche for the development of Candida species [2].

Clinical presentations that are predictive for CO are nail plate dystrophy and off-white discoloration, commonly followed by pigmentation. Melanisation, one of the virulence factors for Candida, suggests an indication of progressive resistance to antifungal treatment. Classification of CO is established because of the complex etiopathogenesis and diverse clinical presentations. The first clinical classification of CO was suggested based on the clinical presentation, the affected location, and the infection route, which are Candida paronychia, Candida granuloma, and Candida onycholysis [2].

The most frequent type of CO is paronychia. Humidity plays an essential role in the development of Candida paronychia. Clinical manifestation of Candida paronychia comprises erythema and swelling in the nail folds followed by gradual dystrophy in the nail plate accompanied by paronychia and Beau lines, which is depicted by an oblique dent in the nail plate suggesting parasite infestation on the nail matrix. The most severe type of CO is granuloma, which is frequently observed in patients with chronic mucocutaneous candidosis. Clinical

manifestation of Candida granuloma displays brittle nails and a deformity resembling drumstick which is also referred to as pseudoclubbing. The last type of CO is onycholysis. Clinical manifestation of Candida onycholysis is characterized by subungual distal hyperkeratosis, which further develops into a group of keratosis separating the nail plate from the bed. Moreover, a recent classification was proposed, including four clinical groups of CO, which are chronic paronychia with secondary nail dystrophy, distal onychomycosis, chronic mucocutaneous candidosis, and secondary candidosis [17].

Chronic paronychia initially emerges from the proximal nail fold, although lateral nail folds are occasionally affected in the beginning. Swelling of the periungual skin and a noticeable gap between the fold and nail plate is observed, followed by the nail plate involvement. Marks with a white, green, or black color can be detected at the lateral and distal parts, respectively. The longitudinal ridges and opaqueness appear on the nail that develops into a brittle and easily detached nail. Pressure and movement on the nail can be painful in contrast to dermatophyte infections. A superimposed infection caused by bacteria into the subcuticular space usually occurs, leading to a vicious cycle. Chronic paronychia usually appears in adults whose occupations regularly contact water and children because of the thumb sucking habit [17].

Distal candida nail infection manifests as subungual hyperkeratosis along with onycholysis. Differentiating the clinical manifestation with dermatophytosis can be challenging, however the candida results in less extent damage to the nail compared to dermatophyte. In addition, the predilection of CO usually affects the fingernails, while most dermatophytes invade the toenails. The prevalence of distal candida nail infection is infrequent and most of the cases are related to vascular problems, such as Raynaud's phenomenon [17].

Total dystrophic onychomycosis occurs in patients with chronic mucocutaneous candidosis. The organism invasion on the nail plate results in hyperkeratotic and gross thickening of the nail. Chronic mucocutaneous candidosis has multifaceted etiology which results in the weakened cell-mediated immunity. The variety of clinical appearance depends on the severity of immunosuppression; however, thickening of the nails can be observed in advanced cases due to the Candida granuloma. In addition, the involvement of the mucous membrane is nearly presented in most cases [17].

Secondary candida onychomycosis results because of other diseases involving the nail apparatus, most commonly psoriasis [17].

6. Diagnostic tests

Common tests utilized in the diagnosis of onychomycosis are potassium hydroxide (KOH) preparation, fungal culture, histopathology, polymerase chain reaction (PCR), and flow cytometry (**Table 4**). The combination tests are usually performed; however, the gold standard of diagnostic tests are microscopy and culture [3].

Onychoscopy can also be used for initial diagnosis of onychomycosis. The most common findings in onychomycosis are jagged edge with spikes of the proximal part of the onycholysis, parallel bands of various color resembling aurora borealis pattern, and ruin appearance at the subungual part [3].

KOH microscopy and fungal culture are presently the gold standards to establish the diagnosis of onychomycosis. However, it remains questionable because KOH microscopy demonstrates a false-negative rate between 5% to 15% and false-positive for evaluating the medication, given that KOH microscopy visualizes both

Test	Procedure	Pros	Cons	Fungal viability	Fungal identify
Potassium hydroxide (KOH)	Dissolved large keratinocytes result in the flattening of nail segment and decreasing reflection from cell borders. Examined with microscopy	Quick, on-the-spot	Low sensitivity	No	No
Fungal culture	Cleaned and clipped subungual debris of the nail are scraped into the gauze. Culture developed in the agar with or without cycloheximide. Examined with microscopy	Precise	Results obtained in ≥3 weeks, high false-negative rate	Yes	Yes
Histopathology	Stained by hematoxylin and eosin to depict the elements of the fungi. Periodic acid-Schiff or Grocott's methenamine-silver can be utilized to enhance the appearance of hyphae	Validate the presence of fungus	Involves specific laboratory equipment	No	No
PCR	Employ a target gene part of ribosomal DNA or chitin synthase genes	Quick, 48 hours	Costly	Yes (real-time PCR)	Yes
Flow cytometry	Employ granulosity, cell volume, DNA, and protein markers to produce definite profiles for fungi	Very specific	Involves great sample size, costly	No	Yes

Cited as is from Gupta et al. [3].

Table 4.
Diagnostic tests for onychomycosis [3].

live and dead hyphae which are identical through microscope. Furthermore, fungal culture has a wide-ranging sensitivity from 30% to 57% and requires incubation for weeks. Latest studies comparing a variety of diagnostic tests indicate that histopathology staining has higher sensitivity than KOH microscopy or culture, although another study suggests PCR for a quicker and precise alternative for fungal culture, particularly in NDM onychomycosis. Therefore, the combination of diagnostic tests is recommended to diagnosis onychomycosis accurately. A feasible option can be a KOH microscopy and PCR (or culture in a resource-limited setting) if the KOH shows positive results [3].

In the case of CO, obtaining sample for KOH microscopy and culture can be performed from the proximal and lateral parts of the nail. Nevertheless, sample can be obtained from the distal part in the case of onycholysis. Culture result may reveal creamy-whitish colonies on Sabouraud dextrose agar media or primary isolation can also be attained using chromogenic media, for instance CHROMagar Candida®. Anti-fungal susceptibility should be performed following the identification of the isolated strains to achieve the most effective therapy. Histopathological results of

CO usually display hyphae and pseudomycelia on the nail through Schiff's periodic acid stains or Grocott's methenamine silver stains. PCR can also be utilized for further identification [2].

7. Treatment algorithm

Defining the resolution of onychomycosis can be achieved through clinical, mycological, and complete cure. Clinical cure is described as 100% improvement depicted by clear nail, while mycological cure is described as negative KOH microscopy and negative fungal culture, respectively. Ultimately, complete cure comprises 100% clear nail and mycological cure. The goal of treating onychomycosis for physicians and affected stakeholders are achieving the complete cure. However, it is difficult for an infected nail to return into an utterly normal appearance, particularly in advanced stage although mycological cure has been attained [3].

The treatment choices (**Figure 1**) available for managing onychomycosis are oral medication, topical therapy, and devices. Oral antifungals (**Table 5**) are the first-line therapy because they result in high success rates. Nevertheless, oral antifungals are contraindicated in patients with chronic or active liver disease, congestive heart failure, and kidney failure. Besides, oral antifungals may interact with other pharmacological agents, which can trigger a severe adverse reaction. These setbacks urged the request for the safer option which leads to the awareness of topical therapy. Topical treatments (**Table 6**) are indicated in mild–moderate cases and patients with contraindication for oral antifungals. However, they also have limitations which are smaller cure rate, prolonged therapy and difficulty applying for patients with mobility problems. Ultimately, lasers are FDA-approved device therapy for short-term clearance and/or nail enhancement. However, laser therapy is lacking conclusive guidance and its efficacy demonstrates notable disparities among all treatment modalities. Topical antifungals eradicate the fungus from the outward penetrating the dorsal part of the nail, whereas oral antifungals eliminate from the inward infiltrating the ventral part of the nail [3].

Another proposed treatment algorithm is based on the severity of onychomycosis assessed with SCIO (**Table 7**) [12].

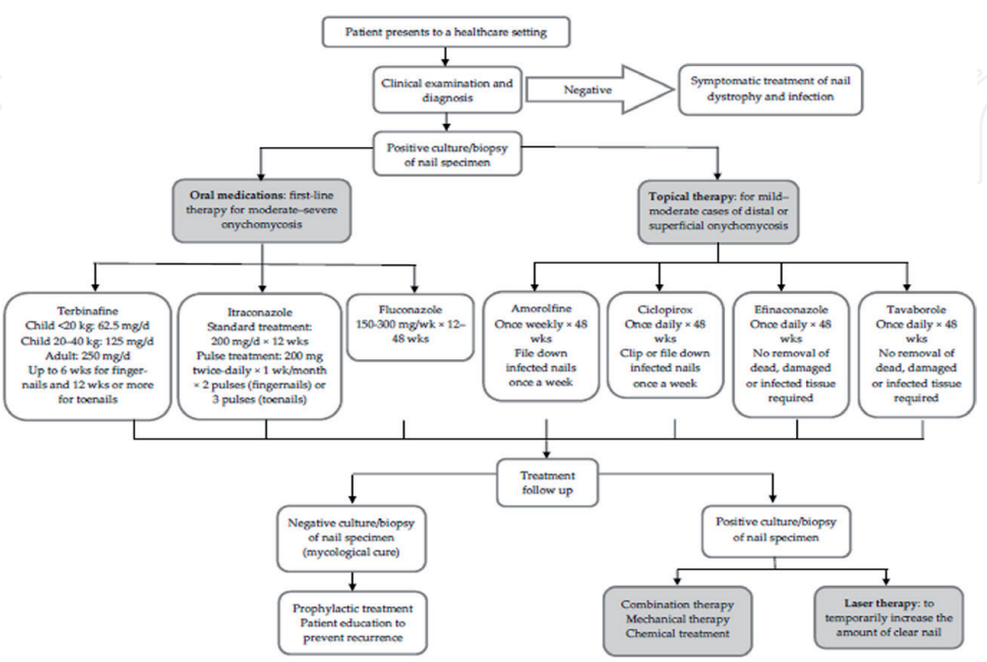

Figure 1.
Treatment algorithm of onychomycosis [16]. Cited as is from Christenson et al. [16].

Drug name		Terbinafine	Itraconazole	Fluconazole
Trade name		Lamisil	Sporanox	Diflucan
Chemical structure		Allylamine	Triazole	Triazole
Molecular formula		$C_{21}H_{25}N•HCl$	$C_{35}H_{38}Cl_2N_8O_4$	$C_{13}H_{12}F_2N_6O$
Mass (g/mol)		291.3	705.64	306.27
Mechanism of action		Squalene epoxidase inhibitor	Lanosterol 14α-demethylase inhibitor	Lanosterol 14α-demethylase inhibitor
CYP[+] inhibition		CYP2D6	CYP3A4	CYP2C9, CYP2C19, CYP3A4
Spectrum of action		Dermatophytes, some activity against NDMs	Dermatophytes, NDMs, and *Candida* spp.	Dermatophytes, some NDMs, and *Candida* spp.
Efficacy	MC	70%	54%	47–62%
	CC	38%	14%	28–36%[*]
Approval		US–1996	US–1995	US–1990†
		EU–1991	EU–1989	EU (UK)–1988
		Canada–1993	Canada–1993	EU (Finland)–1993
				China–1993
				Canada–1990[*]
FDA pregnancy class		B	C	D

CYP, cytochrome P450; NDM, non-dermatophyte molds; MC, mycological cure; CC, complete cure.
[*]Data provided are clinical cure rates.
[†]Fluconazole was FDA-approved for use in humans in 1990, but is not yet approved for treatment of onychomycosis in the US or Canada.
Cited as is from Gupta et al. [3].

Table 5.
Summary of available oral antifungal [3].

Drug name	Efinaconazole	Tavaborole	Ciclopirox	Amorolfine
Trade name	Jublia	Kerydin	Penlac	Loceryl
Chemical structure	Triazole	Oxaborole	Hydroxypyridone	Morpholine
Molecular formula	$C_{18}H_{22}F_2N_4O$	$C_7H_6BFO_2$	$C_{14}H_{24}N_2O_3$	$C_{21}H_{35}NO$
Mass (g/mol)	348.39	151.93	207.27	317.51
Mechanism of action	Lanosterol 14α-demethylase inhibitor	Aminoacyl †RNA synthetase inhibitor	Chelation of polyvalent heavy metal ions	Δ^{14}-sterol reductase and cholestenol
				Δ-isomerase inhibitor
Spectrum of action	Dermatophytes, NDMs, and *Candida* spp.	Dermatophytes, NDMs, and yeasts	Dermatophytes, *Candida* spp., and some NDMs, gram-positive and negative bacteria	Dermatophytes, NDMs, and yeasts

Drug name		Efinaconazole	Tavaborole	Ciclopirox	Amorolfine
Efficacy	MC	53.4–55.3%	31.1–35.9%	29–36%	60%[125]
	CC	15.2–18.8[122]	6.5–9.1%[121]	5.5–8.5%[123]	
Approval		US–2014	US–2014	US–1999	EU–1991
		Canada–2013		Canada–2004	Australia–1996
		Japan–2014			
FDA pregnancy class		C	C	B	Poor systemic absorption, safe in animals, no studies in pregnant women†

CC, complete cure; MC, mycological cure; NDM, non-dermatophyte molds.
†Not approved by FDA, thus no pregnancy classification.
Cited as is from Gupta et al. [3].

Table 6.
Summary of available topical antifungal [3].

SCIO	Treatment approach
1–3	Topical treatment: remove (cut or scrape off) affected marginal parts of the nail
	Use topical antifungals until healthy nail regrows
3–6	Topical treatment with lower success, which often depends on growth rate
	Systemic therapy recommended in slower-growing nails or proximal onychomycosis type
6–9	Systemic therapy. Use scheme proposed for fingernails (e.g., itraconazole: 2 pulses of 200 mg bid)
9–12	Systemic therapy. Use scheme proposed for toenails (e.g., itraconazole: 3 pulses of 200 mg bid)
12–16	Systemic therapy. Use scheme proposed for fingernails with any antifungal (e.g., 4–5 pulses of itraconazole, 200 mg bid)
16–20	Combination therapy (systemic antifungal + topical measures)
	Adequate keratolytic treatment recommended
20–30	Consider nail avulsion (e.g., with urea paste), continue with systemic therapy

Cited as is from Sergeev et al. [12].

Table 7.
Proposed treatment approach based on scoring clinical index of onychomycosis (SCIO) [12].

8. Prevention and education

As CO commonly recurs with overall onychomycosis recurrence rate of 10–53%, additional measures should be implemented to prevent this recurrence. For the clinicians, it is imperative to confirm the diagnosis and identify the infectious agent before providing treatment. Assessing and treating the comorbidities is also crucial since some comorbidities are risk factors for onychomycosis, also portend as poor prognostic factors. Tinea pedis should be treated properly as the infected skin can play a role as reservoir for the pathogens [3].

When the patients are diagnosed, the clinicians should provide them with optimal onychomycosis therapy, provide counseling on the expectations and adherence to treatment. The patients should also be provided with information to maintain hand and foot hygiene, avoid occlusive shoes, trim the nails regularly, use broad toed shoes with absorbent materials, and avoid barefoot walking in locations with

abundant fungal density (e.g., swimming pool, communal showers, gymnasium floors). Good sanitization measures should be taken for previous infected socks and shoes. Socks should be washed with hot water (60 °C) for 45 minutes and shoes should be exposed to ultraviolet rays or ozone or can be sprayed with antifungal sprays. The close contacts or family members of the patients should be examined and treated if they suffer from onychomycosis or tinea pedis [3, 18].

Prophylaxis can be considered for patients with high probability to suffer from recurrence. Topical antifungal agent in the form of solution or lacquer can be applied once daily for a month then twice weekly for at least two years after the cure have been achieved [3].

9. Conclusions

CO is a common nail infection affecting people worldwide. Establishing the diagnosis of CO becomes a challenge for the clinicians since *Candida* spp. is a well-known normal flora inhabiting human's skin, nails and mucosa. In addition to confirming the diagnosis, the clinicians should pay attention to patient's characteristics, nail features, and the infectious agent as it can portend as poor prognostic factors. A proper treatment course along with additional measures will aid the patient to achieve complete cure and prevent recurrence.

Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclatures

CMC	Chronic Mucocutaneous Candidiasis
CO	Candida Onychomycosis
HIV	Human Immunodeficiency Virus
KOH	potassium hydroxide
NDMs	Non-Dermatophyte Molds
PCR	Polymerase Chain Reaction
SCIO	Scoring Clinical Index of Onychomycosis
TDO	Total Dystrophic Onychomycosis

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