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Review

The Dermatologist's Approach to Onychomycosis

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Abstract: Onychomycosis is a fungal infection of the toenails or fingernails that can involve any component of the nail unit, including the matrix, bed, and plate. It is a common disorder that may be a reservoir for infection resulting in significant medical problems. Moreover, onychomycosis can have a substantial influence on one's quality of life. An understanding of the disorder and updated management is important for all health care professionals. Aside from reducing quality of life, sequelae of the disease may include pain and disfigurement, possibly leading to more serious physical and occupational limitations. Dermatologists, Podiatrists, and other clinicians who treat onychomycosis are now entering a new era when considering treatment options—topical modalities are proving more effective than those of the past. The once sought after concept of viable, effective, well-tolerated, and still easy-to-use monotherapy alternatives to oral therapy treatments for onychomycosis is now within reach given recent study data. In addition, these therapies may also find a role in combination and maintenance therapy; in order to treat the entire disease the practitioner needs to optimize these topical agents as sustained therapy after initial clearance to reduce recurrence or re-infection given the nature of the disease.

Keywords: onychomycosis; onycholysis; subungual hyperkeratosis; recurrence; maintenance

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1. Introduction

The diagnosis and treatment of onychomycosis has entered a new era, which in some ways is trivial due to the ease of "detection" by way of the internet and media, patients can deduce the diagnosis before it has been clinically proven. Yet in the same breadth clinicians are encouraged since topical therapies which were once thought to be ineffective now have been proven more effective and safe in multiple clinical trials. As the mechanisms of therapy have become more elucidated, so has the success rate which encourages both practitioners and patients to adhere to therapy despite the time needed to achieve that once elusive clearance of disease. Moreover, as the mechanisms of therapy are better understood and consolidated into potential treatment regiments there will be more study data and clinical experience necessary to dictate the utility of combinations between topical therapies and systemic treatments, in addition to topical keratolytics, concomitant use of nail polish, and the optimization in patients with diabetes mellitus, peripheral vascular diseases, and other comorbities.

Unfortunately, as medicine continues during the era of patients making diagnoses from the internet and the photos driven by the media direct to consumer advertising, the perception of onychomycosis as a disease that requires objective proof of diagnosis and aggressive therapies continues to be an obstacle for successful treatment. The presence of any nail discoloration or change in the integrity leads to a presumptive diagnosis of onychomycosis to the untrained eye (Table 1).

Table 1. Mimickers of Onychomycosis.

Mimickers of Onychomycosis	Reference
Psoriasis	
Lichen Planus	
Bacterial Infections	
Onychogryphosis	
Traumatic onychodystrophies	
Yellow Nail Syndrome	[1]
Toenail Cellulitis	
Contact Dermatitis	
Nail-bed Tumors	
Onycholysis, nonspecific	
Pachyonychia Congenita	

2. Terminology

The appropriate diagnostic terminology is necessary when documenting the clinical findings of onychomycosis, not only to convey the objective assessment, but also as a marker of therapeutic milestones for improvement. Charting of the presentation is often difficult when there is a history of trauma to the nails, the chronicity of disease has obscured normal markers, and other nail disorders are present. The correct application of diagnostic terminology will convey an accurate presentation. Onychomycosis is a fungal infection of the nail unit [1]. Subungual thickening or hyperkeratosis can occur under the nail plate, resulting in onycholysis or lifting of the nail bed. Onycholysis, specifically is the loss of plate-bed adhesion. Onycholysis does not by itself signify onychomycosis. It can be seen in many other diseases

such as psoriasis and lichen planus [1]. There are numerous potential causes such as irritants or trauma, infections (*Candidiasis*, *Syphilis*), and drug-induced cases, which often affect multiple nails [1].

Onychomycosis more commonly involves the toenails [1]. It is caused by a variety of fungi including dermatophytes, non-dermatophyte molds, and *Candida* [2,3]. More specifically, there are five subtypes related to the method of fungal invasion of the nail unit, the most common being distal lateral subungual onychomycosis (DLSO) (Table 2) [4,5]. In DLSO, the fungus enters the distal lateral part of the nail bed, the region of the hyponychium, often as an extension of tinea pedis. Hyperkeratosis occurs under the nail plate, resulting in onycholysis, with subungual thickening. White superficial onychomycosis is less common than DLSO, accounting for about 10% of onychomycosis cases [6]. The superficial nail plate is usually involved initially; most commonly caused by *Trichophyton mentagrophytes* and several non-dermatophyte molds (such as *Fusarium*, *Aspergillus*, and *Acremonium* spp.) [7]. To the patient the nail feels coarse but may become soft and crumbly where the fungus has initiated the infection [8], and it can be scraped off easily with a scalpel [7]. Proximal subungual onychomycosis (PSO), a relatively uncommon subtype, occurs when the fungus invades under the cuticle or nail plate, and advances from the proximal to distal part of the nail [5]. Endonyx onychomycosis differs from DLSO because of the absence of nail-bed hyperkeratosis and onycholysis, and is usually caused by *Trichophyton soudanense* [7] (not found in the United States). *Candida* onychomycosis only affects immunosuppressed patients and the presentation involves the entire nail plate, often with paronychia [7].

Table 2. Subtypes of Onychomycosis.

Subtypes of Onychomycosis	Reference
Distal lateral subungual onychomycosis (DLSO)	
White superficial onychomycosis (WSO)	
Proximal subungual onychomycosis (PSO)	[1]
Endonyx onychomycosis (EO)	
Candidal onychomycosis	

3. Prevalence and Risk Factors

The prevalence of onychomycosis is increasing; according to studies over the last 20 years, it has increased from 2% to 14% [7], especially with a rise in men and the elderly [9,10], but is relatively uncommon in children [11]. Psoriasis is also a risk factor, particularly in dermatophyte onychomycosis [12]. A 27% prevalence of onychomycosis was reported in psoriatic patients when the toenail was clinically abnormal, and 13% onychomycosis was found in psoriatic patients overall [13].

4. Diagnosis

A definitive diagnosis of onychomycosis is made by the presence or absence of fungal elements using potassium hydroxide (KOH) preparation or a periodic acid-Schiff (PAS) stain, and identification of the fungi with a culture. Most experts perform a KOH and do a fungal culture. Many dermatologists use a PAS stain because it is less subjective to errors than fungal cultures; however it may be more expensive. Only about 50% of dystrophic nails are attributed to fungi, the rest are a feature of something else such as trauma, psoriasis, or onychogryphosis [7]. There are varying techniques when sampling the different

subtypes of onychomycosis. In DLSO, the specimen should be obtained from the nail bed by curettage to maximize the yield for study. Removing the onycholytic nail plate will yield a more useful sample at a site most proximal to the cuticle, since that is where the highest concentration of hyphae are located. In PSO, clinicians should pare down the overlying nail plate before sampling the ventral plate to obtain the optimal exposure. In WSO, a 15 blade is often used to effectively remove a specimen from the nail surface. In Candidal onychomycosis, specimens should be sampled from the most proximal and lateral edges.

5. Determining Severity and Outcomes

In 2011, Carney *et al.* proposed a classification system for grading the severity of onychomycosis [14]. The authors' goals were to establish an objective method for defining mild, moderate and severe onychomycosis using a numerical scoring system. This scoring classification accounts for the area of involvement (range, 0–5), which is then multiplied by the score for the proximity of disease to the nail matrix (range,1–5), and 10 points are added if the presence of a longitudinal streak or patch is seen or if there is greater than 2 mm of subungual hyperkeratosis. Mild nail involvement with onychomycosis is classified as a score of 5 or less; moderate, 6 through 15; and severe, 16 through 35. A baseline or clinically cured nail is classified as a score of 0. This index provides a standardized method for evaluating onychomycosis that can be utilized throughout a patient's treatment course. This is a promising tool, however, further research is necessary in order to properly correlate nail disease severity with prognostic outcomes.

6. To Treat or Not to Treat?

Onychomycosis is notoriously difficult to treat. The main goals of onychomycosis treatment include eradication of pathogens, restoration of healthy nails, and prevention of relapse or recurrence. It is an infectious disease that deserves prompt and appropriate care [4]. Successful management of onychomycosis can be challenging due to the limited availability of effective treatments, patient adherence, and recurrence or reinfection [15]. The disease is often associated with substantial distress, which can affect the patient's quality of life. Aside from reducing quality of life, the disease sequelae can include pain and disfigurement, in addition to serious physical and occupational limitations resulting in disabilities [16,17]. There is also a high potential for dissemination to other nails and local skin. Complications do arise in immunocompromised patients, as well as those with Diabetes Mellitus. In general, most clinicians feel that onychomycosis is an important problem that should be properly diagnosed and treated, especially if it is symptomatic or bothersome. Patients often present to the dermatologist with a long history of onychomycosis; substantial nail involvement, and therefore usually require oral therapy. The addition of an effective topical antifungal to the physician's therapeutic armamentarium would address an important unmet medical need. In the past, when encountering a patient with onychomycosis who was not a candidate for oral antifungals, most clinicians were left with no adequate treatment modalities. However, multiple clinical trials now have demonstrated that there are viable topical treatments. As of today, treatment options include systemic agents, topical agents, and laser procedures.

7. Systemic Therapies

Two systemic treatments, terbinafine and itraconazole, are approved by the US Food and Drug Administration (FDA) for onychomycosis, taken orally for three months, with lab monitoring every six weeks [18]. Pulsed itraconazole is only approved for the treatment of fingernail onychomycosis, and fluconazole is not FDA-approved at all for this indication [19].

When deciding between systemic or topical therapies, several factors must be considered. One should take into account if there is lunular or matrix involvement, the overall severity (number of nail involvement), the patient's risk factors, (hepatic, cardiac, *etc.*), concomitant medications and potential for CYP450 drug interactions, lifestyle choices with alcohol intake, patient reliability for laboratory, follow-up and monitoring, and of course patient preference, concerns, and fears. Additionally, assessment of one's risk of resistance to antifungal therapy should be considered, as *Fusarium* spp. and other non-dermatophyte filamentous fungi are especially difficult to eradicate using standard treatment with terbinafine and itraconazole [20] PCR fungal identification can aid in demonstrating the presence of molds in order to use an alternative treatment [20].

8. New Topical Therapies

The development of topical antifungals focusing on new formulations of existing antifungals and formulating new agents entirely has been ongoing in the recent years since there is an obvious need for an effective topical modality. The use of topical ciclopirox 8% lacquer was disappointing both in clinical trials and in practice given the low complete clearance percentages [21,22]. Poor nail penetration limited its effectiveness, and as a result topical ciclopirox has been reserved for mild cases of the disease [23]. The reported mycological cure rates for ciclopirox topical lacquer are 29%–54.3% [21,24]; and complete cure rates by proof of a negative culture and negative KOH combined with investigator assessments are 5.5%–8.5% [21].

The new topical formulations seem to be very promising, thanks to new technology in the vehicles as well as optimal application of the active antifungal ingredients. The route of entry into the nail plate and the nail bed plays a vital role in determining the efficacy of a drug. Oral agents reach the nail bed by achieving antifungal levels in the blood stream that are in excess of the minimum inhibitory concentration. The primary route of drug delivery for topical lacquers is transungual, with the agent applied to the dorsal aspect of the nail plate and it then penetrates to the underlying nail bed. The new topical agents approved in the US for the treatment of onychomycosis are solutions with increased nail penetration characteristics and low surface tension; therefore, these agents penetrate via the transungual route, and through the space between the nail plate and the nail bed [25]. This low surface tension is believed to enhance penetration and achieve clinical success by providing a dual mode of delivery in accessing the nail bed [26]. This route is an essential means for its drug delivery by circumventing the thickness of the nail plate.

Efinaconazole's primary mechanism of action is blockage of ergosterol biosynthesis, through sterol 14 α-demethylase inhibition [27,28]. Efinaconazole has a broad spectrum of activity against dermatophytes, non-dermatophytes, and yeasts. It works against the most common pathogens including, *T. rubrum* and

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