REVIEW ARTICLE

NCPD 2.0 Contact Hours | Rx 0.5 Pharmacology Contact Hour

Onychomycosis

A Comprehensive Overview

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ABSTRACT: Onychomycosis is a commonly encountered fungal infection of the nail that is increasing in prevalence worldwide. Diagnosis and treatment of onychomycosis is essential for any dermatologic practice, and the options available for both are numerous. The subtypes of this infection can help guide diagnostic techniques and determine the route and type of treatment that should be pursued. This article reviews the pathogenic organisms, epidemiology, clinical presentation and subtypes, and diagnostic and current treatment options available to treat this condition.

Key words: Dermatology, Nail Disease, Onychomycosis, Review

The term "onychomycosis" comes from the Greek word "*onyx*," which means nail, and "*mykes*," which means fungus (Thomas et al., 2019). Onychomycosis, therefore, is a fungal infection of the nail unit. This condition may present on both the toenails and fingernails, but the toenails are more commonly involved (Queller & Bhatia, 2015). It can present with nail pain, thickening, discoloration, and detachment of the nail plate (Hoy et al., 2012). It can affect any part of the entire nail unit, encompassing the nail matrix, bed, and plate (Queller & Bhatia, 2015).

PATHOGENIC ORGANISMS

Onychomycosis is caused by dermatophytes (*Trichophyton*, *Microsporum*, *Epidermophyton*), nondermatophyte molds (NDMs; *Scopulariopsis*, *Aspergillus*, *Fusarium*), and yeasts (*Candida*). Dermatophytes compromise most cases, making up more than 70% of infections. *Trichophyton rubrum* is the most common cause of dermatophyte onychomycosis, precipitating more than 50% of these infections. *Trichophyton mentagrophytes* consists of around 20% of these cases (Lipner & Scher, 2019a).

NDMs cause an estimated 20% of onychomycosis, and yeasts account for 10%–20% of cases (Svejgaard & Nilsson, 2004). Patients with an increased susceptibility to infection with the yeast organism include those with chronic mucocutaneous candidiasis and immunodeficiency. These patients tend to be particularly susceptible to infection in the fingernails (Leung et al., 2020). Onychomycosis can also be caused by multiple organisms; in addition, bacterial–fungal mixed infections are common (Gupta, Paquet, & Simpson, 2013).

EPIDEMIOLOGY

The overall prevalence of onychomycosis is 5.5%, thus making it the most common nail disease in the world (Gupta et al., 2020). The estimated prevalence of onychomycosis in North America ranges from 2% to 14% for adults and 0.44% for adolescents and children (Frazier et al., 2021). Onychomycosis occurs more frequently in older patients, and the prevalence increases with age (Gupta et al., 2020). The global prevalence is continuing to increase and is postulated to be because of the rising levels of obesity, increasing longevity, and the use of occlusive modern footwear (Thomas et al., 2010).

Fingernail onychomycosis caused by *Candida* is more common in women, and toenail onychomycosis is more common in men. Variations in climate also play a role in identifying the pathogenic organism, with humid and warm climates having a higher prevalence of *Candida* and fingernail onychomycosis, and more temperate climates possessing a higher prevalence of dermatophyte and toenail onychomycosis (Gupta et al., 2017).

CLINICAL PRESENTATION

When initially assessing a patient for nail disease, examination of all 20 nails should be performed, as well as a complete examination of the hands and feet. Onychomycosis commonly presents with toenail involvement,

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and the great toenail is the most frequently afflicted (Gupta & Stec, 2019b). Common clinical features of onychomycosis include discolored, hyperkeratotic, hypertrophic, or deformed nails; separation from the nail bed; thickening of the nail plate (onychauxis); subungual debris, brittle nails that break easily or crumble; and nails that are foul smelling (Figure 1; Frazier et al., 2021).

It is common for multiple toenails to be involved, and frequently, tinea pedis or hyperhidrosis is present. When multiple fingernails are infected, there is typically associated toenail involvement unless the patient has a history of recent trauma or is immunocompromised (Leung et al., 2020). Symptoms include pain, particularly when wearing footwear, and social embarrassment because of the physical manifestations.

Subtypes

The most frequently encountered subtype is distal lateral subungual onychomycosis. It presents as whitish, brownish, or yellowish discoloration of the distal corner of a nail (Leung et al., 2020). This subtype is most commonly caused by *T. rubrum* (Shemer, 2012). A nail sample should be taken by first clipping the distal onycholytic nail plate and then retrieving the sample from the closest area of involvement and most active area of infection (Gupta et al., 2020).

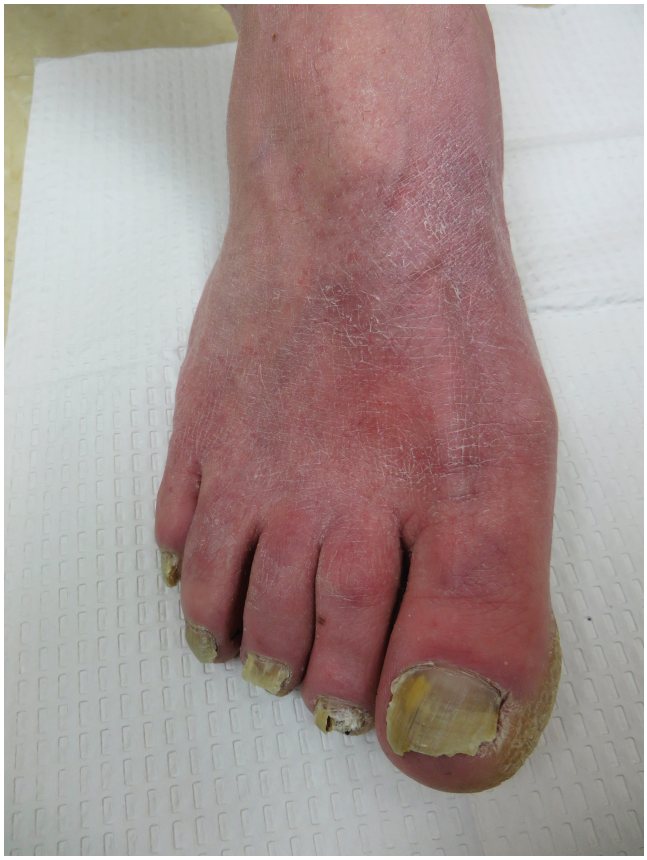

FIGURE 1. Onychomycosis of the toenails.

Superficial onychomycosis is a fungal infection of the upper surface of the nail plate. Common clinical features include black or white superficial patches on the nail plate that can be easily scraped off (Frazier et al., 2021). The nail can appear to have "powder-like patches of transverse striae on the surface" (Westerberg & Voyack, 2013, p. 763). The most common organism is *T. mentagrophytes* (Shemer, 2012). A nail sample is easily acquired by using a Number 15 blade to scrape the involved superficial nail plate (Gupta et al., 2020).

Proximal subungual onychomycosis arises when a fungus invades beneath the nail fold near the cuticle and then extends distally. It typically presents as leukonychia in the proximal nail plate and moves simultaneously as the nail grows (Leung et al., 2020). This subtype is especially common in immunocompromised patients (Westerberg & Voyack, 2013). The most frequently encountered organisms are *T. rubrum* and *Fusarium* spp (Shemer, 2012). A nail sample should be taken by first debriding or paring the upper nail plate of the proximal nail and then collecting the underlying nail debris with a curette (Leung et al., 2020).

Endonyx onychomycosis is an isolated infection of fungi involving only the nail plate, with no involvement of the nail bed. It is typically described as diffuse white discoloration with an absence of onycholysis or keratosis (Frazier et al., 2021). The nail plate remains tightly attached, and there is no subungual hyperkeratosis. Commonly encountered organisms include *Trichophyton soudanense* and *Trichophyton violaceum* (Shemer, 2012).

Total dystrophic onychomycosis is described as obliteration of the complete nail apparatus and can be the sequalae of any subtype. It presents as a thick and extremely dystrophic nail plate (Elewski, 1998).

DIAGNOSIS

Onychomycosis is a great mimicker, with multiple nail conditions causing discoloration and a change in nail structure and integrity. The differential diagnosis of onychomycosis is broad and includes psoriasis, onychogryphosis, lichen planus, toenail cellulitis, contact dermatitis, nonspecific onycholysis, nail bed tumors, and traumatic onychodystrophies (Queller & Bhatia, 2015). Diagnosis can only be confirmed with the acquisition of a nail specimen.

Before obtaining the specimen, the nail plate and tissue around the area should be disinfected with ethyl or 70% isopropyl alcohol (Welsh et al., 2010). A sterile nail clipper should be utilized to clip back the nail plate, and subungual debris should then be secured by using a sterile blade or curette (Bertanha & Chiacchio, 2016). The subtype of onychomycosis is important in determining where on the nail a sample must be obtained, as explained above. To ensure diagnostic accuracy, antifungals should not be used within 90–180 days of obtaining the nail specimen.

Mycological laboratory testing and confirmation are ideal ways to obtain an accurate diagnosis and can enhance cost savings in comparison with treating empirically

with antifungal medications. The gold standard for the diagnosis of onychomycosis is microscopy and fungal culture; however, multiple modalities can be utilized. These include histopathologic examination using periodic acid–Schiff (PAS) stain, potassium hydroxide (KOH), and polymerase chain reaction (PCR; Gupta et al., 2020).

Dermoscopy

Dermoscopy is an expedient and practical method that can assist in differentiating onychomycosis from other nail disorders (Bet et al., 2015). Findings commonly include a jagged edge with spikes and longitudinal striae. Other potential findings include subungual hemorrhages that appear as blackish globules, pigmentation produced in parallel bands known as aurora, and a ruin appearance describing subungual debris on the underside of the nail plate. Another common manifestation is a dermatophytoma, which manifests as uniform, yellow–orange discoloration (Vlahovic et al., 2021).

Microscopy

KOH is commonly used as a confirmatory test in the United States. Parker's blue–black ink and fluorescent staining are less frequently utilized but also viable microscopic preparations (Gupta et al., 2017). KOH microscopy is performed by obtaining a nail specimen and placing it onto a glass slide with the addition of a drop of 10%–20% KOH. This specimen is then inspected utilizing light microscopy, and a positive test will show spores, yeast, and fungal hyphae.

A drawback to microscopy is that it will not provide details related to the causative organism and therefore lacks sensitivity. This technique is also dependent on the experience of the clinician performing the test, which can impede accuracy. However, performing sequential KOH microscopy up to 3 times has been shown to increase sensitivity (Meireles et al., 2008). Overall, KOH preparation should be utilized as a screening test to rule out onychomycosis because it yields rapid results at minimal cost.

Histopathologic Examination

Histopathologic examination utilizes a PAS stain of the affected nail and provides an image of yeasts, spores, pseudohyphae, and hyphae. PAS stain is an expedient diagnostic modality, allowing for results within a day. Unfortunately, like KOH, PAS staining does not allow identification of the causative organism (Weinberg et al., 2003) Histopathologic examination with PAS stain is the more sensitive technique when compared with fungal culture or KOH; however, PAS stain also tends to be more expensive than KOH preparation (Leung et al., 2020). An alternative but less frequently utilized stain includes Grocott methenamine silver.

Fungal Cultures

The gold standard for diagnosing onychomycosis is the fungal culture. This technique allows for the identification of specific fungal organisms. Fungal cultures are extremely specific but are not overly sensitive (Gupta et al., 2018). Factors contributing to false negatives include differences in methodology used, incomplete treatment of the organism, interference because of antifungal drugs, and acetone or alcohol utilized before the culture. Another limitation includes the time it takes to receive results, which can be as long as several weeks (Gupta et al., 2017).

Fungal culture should begin by disinfecting the nail unit with 70% isopropyl alcohol, soap, and water. The nail plate should then be clipped, ensuring subungual debris is obtained and sent to the laboratory (Watanabe & Ishida, 2017) There is a potential for nail clippings to contain contaminants; therefore, subungual debris is necessary (Lipner & Scher, 2015).

Polymerase Chain Reaction

PCR is expedient, is specific, and works by amplifying copies of fungal DNA (Watanabe & Ishida, 2017). PCR is also able to identify the causative organism and can do so rapidly, typically within days. When compared with fungal culture, PCR has been shown to be 3–4 times less likely to result in a false negative (Gupta & Nakrieko, 2017). The use of more than two restriction enzymes can distinguish between dermatophytes, yeasts, and molds. PCR assays are costly; however, "in-house" PCR kits are becoming more readily available. These tend to be cost effective and allow for sensitive, accurate, and rapid diagnosis of dermatophytes (Gräser et al., 2012).

Overall Diagnosis

Onychomycosis can be diagnosed by one or more techniques, and the method chosen should consider rapidity of diagnosis, patient characteristics, clinician experience, specificity, sensitivity, and cost. Multiple diagnostic modalities should be utilized. The most frequently used combination in clinical practice is KOH and fungal culture, which are considered the current standard for diagnosis (Gupta et al., 2017).

KOH with direct microscopy has a low cost and is expedient and, thus, is recommended as the initial diagnostic test. PCR or fungal culture should then be performed if KOH is positive as they allow for identification of the causative organism. KOH can be repeated if the initial test was negative. PCR or PAS could also be performed to increase the sensitivity, followed by a fungal culture if positive. If *Candida* or NDM is present, or if results are indeterminate, these tests should be duplicated using fresh samples. If the culture is negative but the stain was positive, it is recommended that another culture be obtained because of the high false-negative rate of fungal cultures.

TREATMENT

Onychomycosis therapy possesses a dual goal, elimination of the causative organism and reversion back to normal nail growth. When evaluating "cures" for onychomycosis, there are multiple different end points used. These include complete, mycologic, and clinical cures. A complete cure is a clinically normal nail as well as a negative KOH microscopy and culture. A mycologic cure is a negative KOH microscopy and culture, whereas a clinical cure is a clinically normal nail (Lipner & Scher, 2016). A clinical cure is not always possible, and failure to reach this end point can be seen with severe damage to the nail bed, secondary nail disease, trauma, immunocompromised status, and severe onychomycosis.

Treatment modalities include drugs such as topical or oral antifungals, debridement, surgeries to remove the nail plate, and laser therapy (Gupta et al., 2018). Unfortunately, complete, clinical, and mycological cures are not always possible, and patients with onychomycosis will commonly experience relapse or reinfection. Typically, this is because of a failure to completely treat the existing pathogen or can be caused by an additional infection with a different strain (Gupta et al., 2021). Several other factors can also play a role in the increased incidence of reinfection and relapse. These include genetic predisposition, infection with NDMs, mixed infections, active tinea pedis, medical comorbidities, and antifungal resistance (Gupta et al., 2021).

The clinical subtype of onychomycosis also helps guide treatment. The superficial white subtype has the highest response rate to therapy, whereas the total dystrophic subtype has the lowest response rate. Topical antifungal therapy is typically effective when less than two nails are involved or when treating superficial onychomycosis (Gupta, Paquet, & Simpson, 2013). However, oral antifungal agents are first line because of their efficacy and low cost.

Oral Antifungals

Terbinafine and itraconazole are the two predominantly used antifungals for onychomycosis, both holding FDA approval for this indication. Fluconazole can also be used but is only available as an off-label option within the United States. These drugs are effective but possess a wide range of interactions and side effects (Gupta & Stec, 2019a). Patient compliance tends to be higher with oral therapy because of the shorter duration of use when compared with topical therapies (Gupta et al., 2018).

As stated above, oral antifungals are generally considered to be more efficacious than topicals in nearly all cases. However, specific indications for oral therapy include a lack of response to a 6-month duration of topical therapy and proximal subungual onychomycosis, specifically, when more than 50% of the nail matrix or nail plate is involved or if there are numerous nails infected (Gupta, Paquet, & Simpson, 2013).

Terbinafine

Terbinafine disrupts the synthesis of sterols by inhibiting the enzyme squalene monooxygenase. Terbinafine has minimal activity against NDMs and yeast but possesses broad-spectrum activity against dermatophytes. The recommended dosage for onychomycosis is 250 mg once a day for 12 weeks for toenails and 6 weeks for fingernails (Gupta, Paquet, Simpson, & Tavakkol, 2013). Clinical cure rates for toenail onychomycosis are reported to be 74% after a 12-week period (Drake et al., 1997).

Common side effects can include gastric upset, altered taste, elevated liver function tests, headache, and rash (Bhatia et al., 2019). It is also important to keep in mind that terbinafine clearance is decreased with renal or hepatic dysfunction (Shear et al., 1991). Terbinafine is considered one of the safest oral antifungals for use in pregnancy but should still be used with caution (Andersson et al., 2020). Drug interactions are possible in patients taking beta-blockers, tricyclic antidepressants, monoamine oxidase inhibitors, Class 1C antiarrhythmics, and selective serotonin reuptake inhibitors, because of its inhibition of the CYP2D6 isozyme (Gupta, Paquet, & Simpson, 2013).

Advantages of terbinafine include its increased efficacy compared with the other antifungals when treating dermatophyte onychomycosis. When compared with pulse dosing or continuous itraconazole, utilizing continuous terbinafine results in the lowest recurrence rate (Yin et al., 2012). Oral terbinafine is considered first-line therapy for the treatment of onychomycosis because of its superior cost-effectiveness ratio when compared with other oral antifungals (Darkes et al., 2003).

Itraconazole

Itraconazole inhibits ergosterol synthesis by inhibiting lanosterol 14α-demethylase. It is effective at treating *Candida*, dermatophytes, and NDMs (Elewski, 1993). The suggested dose is a pulse regimen utilizing 400 mg of itraconazole daily for 1 week, followed by 3 weeks off and continued for three to four total pulses. Mycologic and clinical cure rates with this regimen are 63% and 70%, respectively (Gupta et al., 2004).

Common side effects include dyspepsia, flatulence, diarrhea, abdominal pain, fatigue, dizziness, pruritus, and elevated transaminases (Gupta et al., 1998). It is recommended that itraconazole be avoided during pregnancy, especially during the first trimester (Pilmis et al., 2015). Itraconazole possesses drug–drug interactions with astemizole, carbamazepine, cisapride, cyclosporine, didanosine, digoxin, H2 receptor blockers, isoniazid, lovastatin, midazolam, phenytoin, oral contraceptives, quinidine, rifampin, tacrolimus, vincristine, and warfarin because of its CYP3A4 inhibition (Leyden, 1998).

Overall, itraconazole can be used for onychomycosis because of mixed infections, NDMs, and *Candida spp*. However, when treating onychomycosis caused by dermatophytes,

the most common cause, terbinafine has consistently been shown to be more effective (Trivedi & Shah, 2010).

Griseofulvin

Griseofulvin inhibits the assembly of microtubules and disrupts the formation of the mitotic spindle, inhibiting mitosis in dermatophytes. It is effective against *Epidermophyton*, *Microsporum*, and *Trichophyton* but is ineffective against *Candida*. The suggested dosing for onychomycosis is 1000 mg daily for 4 months in toenails and 6 months in fingernails (Olson & Troxell, 2022).

This medication has almost completely been replaced by more efficacious antifungal agents such as terbinafine and itraconazole. Therefore, it should rarely be utilized for treating onychomycosis. Adverse reactions range from diarrhea, vomiting, and nausea to photosensitivity and urticaria. Other side effects include a disulfiram-like reaction, and thus, alcohol should be avoided when taking this medication (Olson & Troxell, 2022).

Off-Label

Fluconazole

Fluconazole, a triazole, interacts with 14α-demethylase, an enzyme responsible for catalyzing the conversion of lanosterol to ergosterol (Govindarajan et al., 2022). It is only available as an off-label option in the United States but is approved in Europe to treat onychomycosis. Treatment is normally continued until the fingernail or toenail is completely grown, which can be as long as 9 and 18 months, respectively. Clinical and mycological cure rates for toenail onychomycosis utilizing a weekly dose of 150 mg are 39% and 57%, respectively (Gupta, Drummond-Main, & Paquet, 2013).

The most common side effects include elevation of transaminases, abdominal pain, headache, nausea, and rash (Muńoz et al., 1991). It is also rarely associated with hepatotoxicity, which occurs more often in immunosuppressed individuals. It should be avoided in pregnancy, particularly the first trimester, because of its association with spontaneous abortions and heart malformations (Zhang et al., 2019). Fluconazole is an inhibitor of fungal cytochrome P450 and thus possesses numerous drug interactions (Kowalsky, 1990).

Overall, fluconazole should be utilized when the use of first-line antifungals is contraindicated or when a patient struggles with compliance or desires an oral medication with less frequent dosing.

Topical Therapy

Indications for topical therapy include an absence of nail matrix involvement and patients not amenable or unable to take oral medications (Lecha et al., 2005). They may also be used in conjunction with oral antifungals or debridement in severe cases of onychomycosis. Topical agents can be used without concern for drug interactions or contraindications. Topical antifungal use as monotherapy is constrained by its penetration of the nail plate, thus making it difficult to maintain high concentrations to treat the infection (Gupta, Paquet, & Simpson, 2013). Thus, the route of entry is essential in ensuring maximum efficacy. Transungual entry, where the topical medication is applied to the dorsal nail plate, allows it to penetrate the underlying nail bed. Approaches to enhance transungual delivery include mechanical methods, such as nail avulsion and abrasion; chemical methods, such as urea and ethanol; and physical methods, including etching and microneedling (Akhtar et al., 2016).

Ciclopirox

Ciclopirox 8% nail lacquer is a synthetic hydroxypyridine antifungal (Westerberg & Voyack, 2013). It has a broad spectrum of activity against some yeast, dermatophytes, and some NDMs (Grover & Khurana, 2012). Ciclopirox 8% hydroxypropyl chitosan is the recommended lacquer of choice, and once-a-day application for 48 and 60 weeks for toenail onychomycosis results in complete cure rates of 5.7% and 12.7%, respectively. This should be used in combination with once-a-week nail filing and clipping for optimal penetration (Piraccini et al., 2020). Adverse effects include stinging, burning, and itching at the site of application (Gupta et al., 2000).

Efinaconazole

Efinaconazole is an inhibitor of fungal lanosterol 14α-demethylase. It can be used to treat yeast, dermatophytes, and NDMs. It is a 10% solution and should be applied once a day for 48 weeks (Gupta et al., 2018). Mycologic cure rates are 53.4%–55.2%, and complete cure rates are 15.2%–17.8% (Gupta & Cooper, 2021). Adverse effects include local dermatitis, burning, and vesicles (Poulakos et al., 2017).

Tavaborole

Tavaborole 5% solution is an oxaborole and halts fungal protein synthesis by inhibiting leucyl-tRNA synthetase, a fungal enzyme required for protein synthesis. It can be used to treat yeast, dermatophytes, and NDMs and is able penetrate the nail plate because of its low molecular weight (Rock et al., 2007). Mycologic cure rates for toenail onychomycosis are 31.1%–35.9% and complete cure rates are 6.5%–9.1% when tavaborole 5% is applied daily for 48 weeks (Elewski et al., 2015). Side effects are typically local and include irritation, erythema, and dermatitis (Poulakos et al., 2017).

Laser Therapy

As an adjunct to typical onychomycosis treatment, laser and photodynamic therapies offer a new "treatment" alternative. The FDA has approved multiple Nd:YAG laser therapies for the "temporary increase of clear nail in onychomycosis" (Gupta & Simpson, 2012a). This indication is a cosmetic outcome that is different from the medical approval given to oral and topical medications.

In an effort to standardize and compare traditional oral and topical therapy to laser therapy, one review evaluated laser-induced treatment to oral and topical treatments for onychomycosis. This review showed that laser treatment provided mycologic cure rates of only 11%, compared with therapies approved by the FDA, which ranged from 29% to 61% (Gupta & Versteeg, 2017).

The number of sessions required and the extended length of treatment are disadvantages to utilizing laser therapy. Multiple treatments are typically performed, and the length of treatment can be as long as 19 months (Lipner & Scher, 2019b). Side effects include mild-to-moderate discomfort during the procedure (Gupta & Versteeg, 2017). Minimal clinical data on laser therapies exist; however, it is clear that cure rates utilizing laser-based treatment options are inferior to topical and oral therapy and therefore should not be utilized as first-line therapy.

HELPFUL TIPS

Nail trimming and debridement can be performed in combination with any other treatment modality and can offer benefits when used in conjunction with standard therapy. One study has indicated oral terbinafine in combination with nail debridement had increased clinical cure rates compared with those who received only oral terbinafine (Jennings et al., 2006).

There are also other lifestyle measures patients can undertake to improve treatment outcomes and decrease the rate of recurrence. These include disinfecting socks and shoes regularly, avoiding going barefoot in public spaces, and keeping the feet dry and cool (Gupta & Stec, 2019a). ■

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