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Review Article

Onychomycosis: A Comprehensive Review

Akanksha Patil*, Dr. Bharat Tekade

Department of Pharmaceutics, Kokan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Center, Karjat (India).

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ABSTRACT

Onychomycosis, a common fungal infection of the nail, is characterized by a range of clinical manifestations, including discoloration, thickening, and crumbling of the affected nails. This review aims to provide a comprehensive overview of onychomycosis, encompassing its etiology, pathophysiology, diagnostic methods, and treatment options. The condition is primarily caused by dermatophytes, yeasts, and molds, with Trichophyton rubrum being the most prevalent pathogen. Various diagnostic techniques, including clinical examination, mycological culture, and molecular methods, are employed to confirm the diagnosis. Treatment strategies are diverse, ranging from topical antifungals to systemic therapies, with the choice of treatment influenced by factors such as the severity of infection and patient comorbidities. Recent advancements in antifungal agents and delivery systems, along with the development of combination therapies, offer promising improvements in management outcomes. This review highlights current challenges in the treatment of onychomycosis and underscores the need for continued research to optimize therapeutic approaches and enhance patient outcomes.

INTRODUCTION

Onychomycosis (OM), also known as tinea unguium, is a fungal infection of the nail unit, encompassing the nail plate, nail bed, and surrounding tissues. The infection can affect both toenails and fingernails, although toenails are more commonly involved. Onychomycosis is predominantly caused by dermatophytes, but can also be due to non-dermatophyte molds and yeasts, particularly *Candida* species [1].

Onychomycosis is one of the most common nail disorders, affecting approximately 2-8% of the general population. The prevalence increases with age, with estimates suggesting that up to 20% of individuals over 60 years of age are affected. In specific populations, such as diabetics or

***Corresponding Author:** Akanksha Patil
Address: *Department of Pharmaceutics, Kokan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Center, Karjat (India)*
Email : akankshap841@gmail.com

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immunocompromised individuals, the prevalence can be significantly higher [2,3].

The risk of developing onychomycosis is influenced by several factors, including age, gender, diabetes, peripheral vascular disease, immunosuppression and environmental conditions such as high humidity and frequent exposure to moist environments. Genetic predisposition and nail trauma are also contributing factors [4].

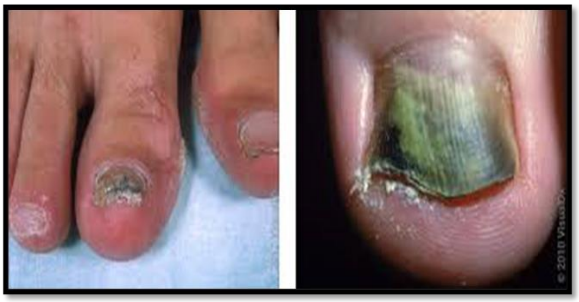

Figure 1: Onychomycosis

Pathogenesis

Onychomycosis begins with the exposure and entry of fungi, typically dermatophytes (*Trichophyton rubrum* and *Trichophyton mentagrophytes*), yeasts (*Candida species*) or molds (*Aspergillus species*) into the nail. These fungi often invade through minor trauma or breaks in the nail plate or surrounding skin with conditions like athlete's foot increasing susceptibility. Once the fungi adhere to the nail plate and nail bed, they utilize keratin, a protein found in the nail, to proliferate. This invasion leads to damage in the nail matrix, responsible for nail growth, resulting in thickening, discoloration, and deformation of the nail. The body's immune response, which includes activation of macrophages, neutrophils, and T lymphocytes, struggles to fully eradicate the infection, often leading to a chronic inflammatory response that exacerbates nail damage [5].

Clinical Manifestations

Onychomycosis presents with various clinical features depending on the causative organism and the stage of infection:

Total dystrophic onychomycosis (TDOM):

This kind manifests as the complete disintegration of the nail equipment, comprising the matrix, nail bed, and entire plate thickness. The affected nail thickens, deteriorates, and crumbles. It might be subsequent to any of the four earlier forms or primary, as in the case of chronic mucocutaneous candidiasis [6].

Distal lateral subungual onychomycosis (DLSOM):

First, the hyponychium's keratin is contaminated. Subsequently, the infection spreads to the nail plate and nail bed [6]. Through the nail plate, the infectious agent migrates proximally. Mild inflammation is accompanied by onycholysis, subungual hyperkeratosis, localized parakeratosis, and thickening or deformation of the nail plate. Dermatophytes particularly T. rubrum [7] are typically responsible for this kind, while T. mentagrophytes, T. tonsurans, and E. floccosum are also occasionally involved. Compared to fingernails, toenails are more frequently impacted. Tenea pedis frequently coexists with toenail involvement, but tinea mannum nearly invariably involves fingernail involvement.

Endonyx Onychomycosis (EOM):

This variation involves the fungus developing between the nail plate lamellae, causing a primary and exclusive attack on the nail plate. T. soudanense exhibits a unique invasion pattern that might be related to its strong affinities for hard keratins. Clinically, EOM is characterized by a diffuse, milky white discoloration of the afflicted nail that forms uneven, broad waves with pits and lamellar breaks; onycholysis or nail bed hyperkeratosis are absent. Both the thickness and the surface of the nail plates are normal. There are numerous visible fungal hyphae on the nail plate, however there are no fungal components in the nail bed or hyponychium [8,9].

Superficial white onychomycosis (SWOM):

In this uncommon variation, the fungus develops small, superficial white patches on the dorsal side

of the nail plate, which may eventually combine to cover the entire nail plate. It primarily affects the toenails and is somewhat uncommon. T. mentagrophytes is the isolated organism in most of the instances [10]. There have been isolated reports of non-dermatophyte molds such Aspergillus terreus, Fusarium oxysporum, and Acremonium spp. SWO is typically brought on by T. rubrum and has also been reported in fingernails in HIV patients [11].

Proximal White Subungal Onychomycosis (PWSOM):

The most frequent cause is T. rubrum [12]. PWSOM manifests clinically as leukonychia, proximal onycholysis, subungual hyperkeratosis, and proximal nail plate disintegration. Moreover, it could manifest as a single digit-specific pattern of proximal to distal longitudinal leukonychia, a single transverse band, or several transverse bands divided by regions of normal nail. It has been reported that both finger and toenail patterns follow this pattern. The organism enters the proximal nail fold's stratum corneum first, then moves on to the matrix and the nail plate's underside [13]. But new information has shown that PWSOM can also manifest as a fast-moving illness that affects multiple nails in a matter of days, particularly when HIV-related immunosuppression is present. Rather with any fresh external infection being picked up through the proximal nail fold, a likely role of lymphatic dissemination, endogenous reactivation, or auto reinfection from a deeper site seems more likely [14].

Impact on Quality of Life

Onychomycosis can have a significant impact on an individual's quality of life, affecting both physical and psychological well-being:

Physical Discomfort: Symptoms such as pain, itching and discomfort can impair daily activities. In severe cases, the infection can lead to nail deformity and loss.

Aesthetic Concerns: Discoloured and deformed nails can cause embarrassment and affect personal and professional interactions, leading to reduced self-esteem and social withdrawal.

Functional Limitations: The condition may interfere with activities requiring fine motor skills or manual labor, impacting occupational performance and daily living activities.

Emotional and Psychological Impact: Chronic infections and visible nail changes can lead to anxiety, depression, and diminished overall life satisfaction. The combination of these factors underscores the importance of effective treatment options for onychomycosis to alleviate symptoms, improve nail appearance and enhance the overall quality of life for affected individuals [15-17].

Diagnosis

Polymerase chain reaction (PCR) Testing

Fungal DNA can be identified more precisely using PCR. In order to identify pathogenic fungi from nail samples as well as from fungal colonies, they can offer a quick, reliable, and accurate substitute. The techniques utilized for samples from cultivated colonies include PCR restriction fragment length polymorphism (RFLP), double round PCR, real-time PCR, randomly primed PCR, and PCR direct sequencing [18]. PCR demonstrated a sensitivity of 37% in a research analyzing 550 impacted nail samples, compared to 54% for PAS, 40% for KOH, and 22% for culture [19]. Excellent specificity is achieved using PCR, but contamination is more likely. Furthermore, pathogenic and nonpathogenic fungi cannot be distinguished by PCR. Li et al. devised and assessed the triplex PCR procedure's effectiveness in directly identifying pathogenic fungus from OM specimens. The results showed that the specificities of PCR, microscopy, and culture were 100%, 86.4%, and 100%, respectively; the sensitivity was 93.3%, 100%, and 64.4%, and the positive predictive values were 100%, 84.9%, and 100%, and the negative predictive values were

95.2%, 100%, and 78.7%, respectively. This eight-hour molecular diagnostic procedure could differentiate between the three categories of pathogens associated with onychomycosis: dermatophyte, yeast and mold [20].

Direct microsopy

This method of diagnosis confirmation in a clinical context is quick, easy and affordable. The gathered material is cultivated in a 10% potassium hydroxide solution (KOH) to break down keratin and expose the fungal hyphae. Faster clearance is achieved with higher KOH percentages. Exhibits with nails clear more slowly than those with skin. Specimen can be inspected in 10 minutes with 10 15% KOH if there is only subungual debris or extremely small fragments. Nevertheless, it takes a lot longer to remove thicker nail plate portions [21]. The samples must first be divided into smaller pieces, incubated for one minute at 370 ^{0}C, and then analyzed. Ordinary bright field microscopy may clearly show fungal components at ×400 magnification. This method has been improved by the addition of phase contrast microscopy, which allows for the differentiation of distinct hyphae or arthroconidia, dark field microscopy, and the use of calcofluor white or other unique stains to aid in process refinement. The use of Chicago sky blue (CSB) stain to increase the sensitivity and specificity of direct microscopy investigation of suspected cases of onychomycosis has been described by Lim and Lim recently [22]. Direct microscopy can identify a potential fungal group but is not able to distinguish between various species.

Fungal Culture

As the only regularly available test that can identify the fungus in question, culture was once thought to be the gold standard of diagnosis. Cultural sensitivity has been shown to range from 25 to 80% [23]. When the sample is little, taken from far areas, or isn't crushed before inoculation, up to 30% of instances may have falsely negative results [23, 24]. Specimens ought to be plated on two distinct media: a basic medium, such as Sabouraud's dextrose agar, that promotes the development of all fungi, including yeasts and NDM, and a selective medium that includes components such cycloheximide that inhibit the growth of saprophytes [21]. Weekly examinations are performed after the cultures have been cultured for three to four weeks. Growth patterns, color, microscopic creation of macro and micro, and other characteristic growth traits are used to evaluate fungal colonies. The infective agent is most likely a dermatophyte if growth is observed on both types of media; if growth is only observed on the cycloheximide-free medium, the infective agent may be an NDM. To conclusively distinguish between dermatophyte species, additional specialized culture media, such as potato glucose agar or urea agar, would be required. In [25]. It takes multiple laboratory analyses to diagnose NDM because fungal growth is inconsistent. According to English *et al.*, criteria, a dermatophyte is deemed to be the pathogen if it is isolated. Molds and yeasts, however, are only considered noteworthy if mycelia, arthrospores, or yeast cells are discovered during the KOH test. In addition, for the NDM to be classified as a pathogen, at least five colonies of the same mold must be isolated (out of 20 nail pieces plated per individual) and dermatophytes must be absent [26]. But these requirements are strict, hard to meet, and lead to a lot of misleading negative outcomes.

Histopathology

It is possible to examine mycelia threads and spore morphology in detail through histopathological analysis, which is also helpful in differentiating between dermatophytes, yeast, and NDM [27, 28]. The gold standard currently in use for diagnosing OM is surgical pathology testing using PAS (periodic acid Schiff stain). Rather big nail clippings are obtained for histological analysis,

fixed for 4–8 hours in formalin, and then softened with things like mercuric chloride-containing chitin softening solution, 10% Tween 40, 5% trichloroacetic acid, or potassium hydroxide (KOH). After being dehydrated and embedded, softened tissue samples are fixed for 24 hours in 10% buffered phosphate formalin. It takes roughly 24 to 48 hours to complete the process of obtaining semi-thin sections (5 microns) using a microtome and staining them with periodic acid Schiff (PAS) [28]. Prior to processing, nail clippings for histopathology can be pre-treated with 20% NaOH, as explained by Nazarian et al. According to the study, doing this results in sections of much greater quality for both PAS- and Hematoxylin and Eosin (H and E)-stained sections. It also makes cutting the tissue easier and promotes better tissue adherence to glass slides.

Optical Coherence Tomography (OCT)

By detecting the backscattering of inhomogeneities within the sample near infrared light, it enables non-invasive and non-contact cross-sectional imaging of biological tissue. In OM, the transverse and longitudinal tomograms reveal a thickening of the nail plate with spots of low scattering areas encircling signal-intense structures. When hyphae are grouped together and have a high chitin content, they reflect light, which causes them to appear with a higher signal intensity when histologically linked. The surrounding hyperkeratotic nail plate lacunae are represented by the low scattering areas. OCT has proven to be more accurate than KOH preparations and cultures, yielding results that are comparable to those of specimens stained with PAS. With false negative KOH preparation and culture, OCT is therefore a dependable, user-friendly, non-invasive, and non-destructive technique for seeing fungal components in vivo. It also provides a means of screening multiple nail plate locations, which can help identify any fungal elements that may still be present following local or systemic therapy [30].

Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry (MALDI-TOF MS)

This method is predicated on identifying biochemical traits that arise from the action of diseases other than infectious ones, such as mycological infections. Proteolytic breakdown products of natural nail proteins serve as a representation for these. Small amounts of peptides obtained from tryptic digests of collected samples are used in the process to analyze the protein patterns of nail samples. Through comparison with known peptide spectra from nail disorders kept in an already-existing database, the peptide patterns of the affected samples are discovered. No living or non-living fungal material is needed for the procedure to confirm or rule out OM. Additionally, it can distinguish between nonfungal nail diseases and OM, which is a clear benefit over traditional procedures like KOH and culture that either confirm or deny the presence of fungi. Compared to other more recent approaches, observer skill is less significant because software-assisted analysis is used to determine the outcomes. The nail material may be prepared easily. The process is quick as well; findings are available in a day [31].

Phase contrast hard X-ray microscopy

This method makes use of synchrotron radiation-powered phase contrast microscopes. Because of its brightness and great spatial resolution (up to 70 nm), synchrotron radiation may produce an accurate image of an incredibly small item. As such, it is able to visualize the interior anatomy of dermatology specimens with accuracy. This makes it easier to see little structures without the need for stains or fixatives [32]. There is also a significant improvement in resolution. Similar to histology, the primary benefit of this microscopy approach is that it offers concrete proof of fungal invasion of

the nail plate, demonstrating the pathogenicity of the fungi [33].

Treatment

Effective management of onychomycosis involves a combination of proper diagnosis, suitable treatment, and preventive measures to avoid recurrence.

Oral Antifungal Agents

Because of its shorter treatment durations and higher cure rates when compared to topical antifungal medication, it is regarded as the gold standard for onychomycosis in both adults and children. Children are less likely to experience side effects from oral antifungal medications. Terbinafine (Lamisil), itraconazole (Sporanox, Sporaz, Orungal), and fluconazole (Diflucan, Celozole) are examples of oral antifungal medications used to treat onychomycosis [34].

Fungicidal among the allylamine group's antifungal agents is terbinafine. In contrast, terbinafine is not fungistatic, while itraconazole and fluconazole have a higher possibility for adverse effects and medication interactions [35]. Terbinafine produces superior clinical and mycological cure rates than other treatments for toenail onychomycosis, according to a 2017 Cochrane meta-analysis of 48 randomized controlled trials (n = 10, 200) evaluating the effects of oral antifungal medicines for the treatment of the condition [36]. At the moment, the recommended medication for onychomycosis treatment is oral terbinafine (< 25 kg, 125 mg once day; 25 to 35 kg, 187.5 mg once daily; > 35 mg, 250 mg once daily) [37, 38]. For toenail onychomycosis, continuous terbinafine treatment is generally equally effective as pulsed terbinafine treatment; nevertheless, certain trials have demonstrated the advantage of continuous over pulsed terbinafine treatment [39]. For patients whose onychomycosis is caused by non-dermatophyte molds or yeasts, or whose condition is intolerable or unresponsive to oral terbinafine, oral itraconazole (children: < 20 kg, 5 mg/kg daily; 20 to 40 kg, 100 mg daily; > 40 kg, 200 mg daily for one week per month; adults: 200 mg daily for one week per month for 3 to 6 months) should be considered [40]. In the US, Canada, and Australia, off-label treatment for onychomycosis involves the use of oral fluconazole (children: 3 to 6 mg/kg once per week; adults: 150 mg once per week). In individuals who cannot tolerate itraconazole or terbinafine, the medicine may be taken into consideration [41]. All forms of OM should be treated with oral antifungal medications, particularly if more than 50% of the nail is impacted, several nails are infected, the nail matrix is compromised, or dermatophytoma is seen. When topical and oral antifungals are administered together, the pace of cure is accelerated. Combination therapy can be applied concurrently or sequentially. Each patient should receive a treatment plan that is specific to them. It could be necessary to undergo repeated treatment sessions, particularly for chronic onychomycosis [35, 41].

Topical Antifungal Agents

In addition to topical antifungal medications, nail lacquers and solutions are used [42, 43]. Topical antifungal medications prepared in aqueous carriers tend to penetrate the nail more readily. The topical antifungal agent is applied to the dorsal portion of the nail as part of the transungual route of drug delivery. Concurrent use of nail polish does not reduce the effectiveness of topical antifungal medications (e.g., efinaconazole); but, over time, concurrent use of nail paint may result in undesired cosmetic alterations to the polish's quality [44,45]. Therefore, using nail polish concurrently should be avoided. Topical antifungal agents that are frequently used are amorolfine (Curanail, Loceryl, Locetar, Odenil), terbinafine (Lamisil) (10% nail solution), ciclopirox (Ciclodan, Penlac, Loprox) (8% nail lacquer or hydrolacquer), and efinaconazole (Jublia, Clenafin) (10% nail solution) [46, 47].

Topical antifungal medications are generally well tolerated; side effects are rare and include burning at the application site and periungual erythema [48]. However, because topical therapy penetrates the nail plate insufficiently, it may be less successful than oral therapy and requires longer treatment periods (typically 48 weeks or longer). The keratin network's extremely stable disulfide bonds and hydrogen bonds are responsible for the nail's impermeability [42]. According to a 2019 meta-analysis of 26 randomized controlled trials (n = 8, 136) evaluating the effectiveness of monotherapy for toenail onychomycosis, oral terbinafine or itraconazole continuous treatment considerably increases the probabilities of a mycological cure compared to topical antifungal therapies [49]. When less than 50% of the nail is damaged without matrix involvement and only a few (<3) nails are infected, topical monotherapy may be used for mild to moderate onychomycosis [35]. Because the infection is superficial, topical antifungal therapy is frequently adequate for treating white superficial onychomycosis. When oral antifungal medications are not appropriate or are not tolerated, topical antifungal therapy is a viable treatment option. Because of the medications' synergistic antifungal effect, topical antifungals can also be used as an adjuvant therapy in conjunction with oral antifungal therapy to boost the cure rate [45]. Children are more likely than adults to respond better to topical antifungal medication because of their faster rate of nail growth and thinner nail plate [50].

Lasers

The majority of lasers operate on the selective photothermolysis concept, in which the fungal mycelia selectively absorb laser energy, which causes a sudden rise in temperature and subsequent fungal cell death [51]. The risk for systemic adverse outcomes is eliminated because the treatment is focused and does not harm the surrounding tissue. Lasers must have a wavelength of between 750 and 1300 nm in order to pass through the nail; additionally, their pulse duration must be less than the fungus's "thermal relaxation time"; and finally, their beam must be spatially uniform in order to prevent "hot spots" [44]. Long pulsed neodymium-doped yttrium aluminium garnet (Nd:YAG) laser, fractional carbon dioxide (CO2) laser, and diode laser have all been utilized to treat onychomycosis [52]. Research has indicated that laser treatments can help achieve some cosmetic goals in onychomycosis, but they cannot match or surpass the effectiveness of the available topical and oral antifungal treatments in terms of reaching medical goals. In order to potentially improve the likelihood of a successful fungal clearance, individuals for whom systemic antifungal medications are contraindicated or those undergoing combination therapy may be candidates for laser therapies, which are costly but safe [53].

Photodynamic Therapy

Using light at particular wavelengths to photoactivate a photosensitizer is known as photodynamic treatment. The photosensitizer's energetic level is raised by the photoactivation. As a result, reactive oxygen species and harmful free radicals are created when the energy produced combines with the dissolved oxygen in the treated tissue [54]. When the photosensitizer is absorbed by the fungus, it becomes more vulnerable to apoptosis or necrosis than the surrounding healthy tissue [41]. Methyl Aminolevulinate (MAL), 5-Aminolevulinic Acid (5-ALA), porphyrins, aluminium-phthalocyanine chloride, methylene blue, toluidine blue, and rose bengal are examples of photosensitizers that have been utilized [54, 55]. Photodynamic therapy may be helpful in the treatment of onychomycosis, according to a 2016 comprehensive review of five in vitro and twelve in vivo studies [55]. Photodynamic therapy has proven to be a successful treatment for onychomycosis, as demonstrated by two recent

studies [54] that each involved twenty patients with the disease. Formal recommendations about the use of photodynamic therapy for the treatment of onychomycosis cannot be made until well-designed, large-scale, randomized studies have confirmed the treatment's effectiveness.

Miscellaneous

If required, nail abrasion, trimming, avulsion, and debridement can be carried out to improve antifungal medication topical penetration and lower fungus load. Treatment options for white superficial OM include mechanical removal (such as scraping) of the affected region and topical antifungal medication. Nail avulsion surgery is uncomfortable and might result in deformity [42].

The use of a unique nail drill technology that allows for controlled micro-penetration of the nail without entering the nail bed beneath was described by Bristow et al. The device was successfully used, according to the authors, to administer a topical antifungal medication directly and quickly to the location of fungal infection while preserving the integrity of the nail and causing the fewest possible adverse events [56].

Chiu et al. created micropores on the nail surface using a dermaroller (Infinitive Beauty, Birmingham, UK). The FDA has approved PathFormer (Path Scientific, Carlisle, USA) as a device for this microporation method. Topical antifungal medications may be more effectively delivered to the nails when combined with keratolytic agents such papain, urea, salicylic acid, and lactic acid. Urea, fumaric acid, 1, 3-buthylene glycol, a gel-forming polymer, a cross-linking agent, and 45–60% by weight of water makes up the innovation. The preparation can be used to treat onychomycosis because it possesses keratolytic and moisture-retention properties [57].

Topical urea (40% ointment or cream) may be used for people with thick, dystrophic nails that are challenging to clip. Prior to therapy, applying urea topically to the affected area may soften the nail and improve treatment effectiveness [54, 55].

In a topical formulation, urea, propylene glycol, and lactic acid are combined to create K101 nail solution (Emtrix, Nalox, Naloc). A retrospective study (n=91) revealed that oral terbinafine or itraconazole alone does not always lead to the same rate of onychomycosis clearance as combination therapy using topical K101 nail solution [58]. The permeability of the nail to topical ketoconazole was demonstrated to be improved by Repka et al.'s topical application of phosphoric acid gel to the nail plate; the treated nail exhibited six times more ketoconazole permeation than the nonetched nail [59].

Iontophoresis may improve the distribution of topical antifungal medications to the nail plate and other nail apparatus components, according to preliminary research. The current application may provide a tingling feeling [60, 61]. To ascertain the effectiveness and safety of iontophoresis in the management of onychomycosis, more research is required.

CONCLUSION

Onychomycosis remains a prevalent and challenging condition that impacts individuals' quality of life and can lead to significant morbidity if left untreated. Despite advances in understanding the diseases etiology and pathophysiology, effective management continues to be complicated by factors such as diagnostic difficulties, variability in treatment responses and the emergence of antifungal resistance. Current treatment options, including both topical and systemic antifungal agents, offer varying degrees of efficacy, with combination therapies and novel formulations showing promise in enhancing outcomes. Future research should focus on developing more effective and patient-friendly treatments, improving diagnostic accuracy, and addressing the issues of drug resistance and adherence. A multidisciplinary approach,

incorporating dermatological, pharmacological, and patient-centered strategies, is essential for optimizing the management of onychomycosis and improving overall patient care.

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