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ONIHOMIKOZE KOD PACIJENATA OBOLELIH OD HRONIČNE VENSKE INSUFICIJENCIJE
ONYCHOMYCOSIS IN PATIENTS WITH CHRONIC VENOUS INSUFFICIENCY

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Sažetak

Onihomikoza je najčešća gljivična infekcija noktiju na svetu koja uzrokuje promenu boje i zadebljanje zahvaćenih noktiju. Češće se javlja kod pacijenata sa hroničnom venskom insuficijencijom ili perifernom vaskularnom bolešću zbog različitih faktora, uključujući starenje populacije. Razne vrste gljivica, posebno dermatofiti kao što su T. rubrum i T. mentagrophytes, glavni su uzročnici onihomikoze, koja može zahvatiti i nokte na rukama i nogama. Klinička prezentacija je različita, pri čemu je distalna lateralna subungvalna onihomikoza najčešći oblik. Dostupne su različite dijagnostičke metode za onihomikozu, pri čemu se direktna mikroskopija i kultivacija gljivica smatraju zlatnim standardom. Tačna i pravovremena dijagnoza mora biti potvrđena mikološkim ispitivanjem pre nego što se započne terapija, jer je reinfekcija česta, a teži slučajevi su manje podložni odgovoru na lečenje. Topička terapija se generalno preporučuje kao prvi izbor lečenja kod starijih pacijenata. Kada je sistemska terapija neophodna, terbinafin bi trebalo da bude lek prve linije zbog manjeg rizika od interakcija sa drugim lekovima. Nedavna istraživanja su istakla značajnu povezanost između hronične venske insuficijencije i onihomikoze, ali ograničen broj studija ukazuje na potrebu za daljim unapređenjem pridržavanja smernica za lečenje onihomikoze kod pacijenata sa hroničnom venskom insuficijencijom.
Ključne reči: *onihomikoza; venska insuficijencija; hronično oboljenje; nokti; periferno vaskularno oboljenje; mikoze; terapija*

Abstract

Onychomycosis is the most common fungal infection of the nails globally, characterized by discoloration and thickening of the affected nail plate. It is more frequently observed in patients with chronic venous insufficiency or peripheral vascular disease, due in-part to age-related changes and impaired circulation. A variety of fungi, predominantly dermatophytes such as *Ttichophyton rubrum* and *T. mentagrophytes*, are the primary causative agents, affecting both fingernails and toenails. The clinical presentation is polymorphic, with distal lateral subungual onychomycosis being the most prevalent subtype. Several diagnostic methods are available, with direct microscopy and fungal culture remaining the gold standard. Confirming the diagnosis through mycological examination is essential prior to initiating treatment, as reinfection is common and advanced cases often show poor therapeutic response. In elderly patients, topical therapy is generally preferred as the first-line treatment. When systemic therapy is indicated, terbinafine is the agent of choice due to its lower risk of drug interactions. Recent research has demonstrated a significant association between chronic venous insufficiency and onychomycosis; however, the limited number of studies emphasizes the need for improved guideline adherence in managing onychomycosis in this patient population.
Key words: Onychomycosis; Venous Insufficiency; Chronic Disease; Nails; Peripheral Vascular Diseases; Mycoses; Drug Therapy

Uvod

Hronična venska bolest (HVB) i onihomikoza noktiju na stopalima (OM) predstavljaju značajne zdravstvene probleme čija učestalost raste sa godinama, često negativno utičući NA kvalitet života pacijenata [1]. Brojne studije su potvrdile da se promene na noktima stopala često javljaju kod pacijenata sa HVB, pri čemu su takve promene zabeležene kod više od 83% obolelih, a onihomikoza je potvrđena u većini slučajeva [1–3]. Manifestacije hronične venske insuficijencije (HVI) na noktima često mogu imitirati promene karakteristične za onihomikozu, uključujući zadebljale nokte tamne boje sa prisutnom hiperplazijom ležišta nokta i čestom pojavom onihogrifoze. Pored toga, s obzirom na to da su i onihomikoza i venska insuficijencija češće u starijoj populaciji, nije retkost da se kod pacijenata sa HVI potvrdi prisustvo gljivične infekcije noktiju [2].

Onihomikoza je gljivična infekcija odgovorna za oko 50% svih bolesti noktiju [4, 5]. Globalna prevalencija iznosi 5,5%, dok se procenjuje da je u Sjedinjenim Američkim Državama između 2% i 14%, dok u Evropi varira od 0,5% do 24% [6, 7]. Infekcija može zahvatiti bilo koju komponentu nokatne jedinice, uključujući nokatnu ploču, matriks i posteljicu, kao i okolnu kožu [8, 9]. Ova bolest je hronična, ne prolazi spontano i karakteriše se zadebljanjem, lomljivošću, diskoloracijom i odvajanjem nokatne ploče [10–12]. Progresivne mikroangiopatske promene kapilara nokta usled HVI mogu doprineti razvoju onihomikoze [13].

Procena je da HVI pogađa oko 15% odrasle populacije, dok većina studija navodi raspon između 10% i 30%, pri čemu učestalost značajno raste kod starijih osoba [13]. Ova bolest obuhvata širok spektar kliničkih manifestacija, od varikoznih vena i hroničnog bola u donjim ekstremitetima do edema, kožnih promena i ulceracija [2]. Rizik od razvoja venskog ulkusa tokom života iznosi oko 1% kod opšte populacije, dok je prevalencija do tri puta veća kod osoba starije dobi [1]. U kliničkoj praksi je primećeno da ovi pacijenti često imaju promene na noktima koje ukazuju na prisustvo onihomikoze [14]. Lečenje onihomikoza stopala može biti izazovno zbog sporog rasta noktiju, što zahteva produženo lečenje, smanjene penetracije topikalnih preparata i visokog rizika od recidiva bolesti [10].

Introduction

Chronic venous disease (CVD) and toenail onychomycosis (OM) are prevalent and clinically significant conditions that increasingly affect the aging population, often compromising quality of life [1]. Numerous studies have reported a high frequency of toenail abnormalities among patients with CVD, with over 83% exhibiting such changes, and onychomycosis confirmed in the majority of cases [1–3]. The nail alterations associated with chronic venous insufficiency (CVI) may closely resemble those seen in onychomycosis, including thickened and darkened nails, hyperplastic nail bed, and onychogryphosis. Given that shared risk factors – particularly advanced age – coexistence of fungal infections in toenails of patients with CVI is not uncommon [2].

Onychomycosis accounts for approximately 50% of all nail disorders [4, 5], with a global prevalence of 5.5%. Prevalence rates vary widely, ranging from 2-14% in the United States and 0.5-24% in Europe [6, 7]. The infection may involve any component of the nail unit – nail plate, matrix, bed – as well as adjacent skin [8, 9]. Onychomycosis is a chronic, non-self-limiting condition, clinically characterized by thickening, brittleness, discoloration, and onycholysis (separation of the nail plate) [10–12]. In patients with CVI, progressive microangiopathic changes in the nail capillaries may further contribute to susceptibility to fungal nail infections [13].

CVI affects approximately 15% of the adult population, with reported prevalence ranging from 10-30% in most studies, and significantly increasing with age [13]. The clinical spectrum of CVI includes varicose veins, chronic leg pain, edema, skin changes, and venous ulcers [2]. The lifetime risk of venous ulceration is approximately 1% in the general population but can be up to three times higher among the elderly [1]. Clinical observations suggest that patients with CVI frequently present with nail changes suggestive of onychomycosis [14]. Treatment of toenail OM is often challenging due to slow nail growth, prolonged treatment duration, limited penetration of topical agents, and a high recurrence rate [10].

Although onychomycosis is a benign and treatable condition, it can substantially affect

Iako je onihomikoza benigna i izlečiva bolest, može značajno uticati na svakodnevni život pacijenata. Pregledni članak studija o njenom uticaju na kvalitet života je pokazao da ova infekcija može uzrokovati fizičko oštećenje, ograničenu funkcionalnost, bol ili nelagodnost, kao i socijalnu stigmatizaciju, pri čemu su psihološki i psihosocijalni uticaj zabeleženi kod čak 92% kod obolelih pacijenata [17].

Etiopatogeneza i faktori rizika

Patogeni mikroorganizmi

Prema aktuelnim istraživanjima, mikološkim ispitivanjem je potvrđeno da približno 4% pacijenata, bez obzira na prisustvo karakterističnih kliničkih manifestacija, ima onihomikozu noktiju stopala uzrokovanu dermatofitima [10]. Uzročnici onihomikoze uključuju dermatofite, nedermatofitne plesni (NDP) i kvasnice. Većinu dermatofitnih infekcija noktiju (60–70%) izazivaju Trichophyton rubrum i Trichophyton mentagrophytes, dok nedermatofitne bući uključuju vrste kao što su Scopulariopsis brevicaulis, Acremonium spp., Aspergillus spp., Fusarium spp., Alternaria alternata i Neoscytalidium [9, 15, 16]. Onihomikoza izazvana kvasnicama je najčešće uzrokovana vrstama roda Candida [15]. NDP vrste nisu sposobne da razgrade keratin, te infekcija obično nastaje traumom, direktnim kontaktom sa zemljom i biljkama ili kao sekundarna infekcija [4].

Kod dermatofitne onihomikoze, tinea pedis se najčešće javlja kao predisponirajući faktor, a Zaias i saradnici su 1996. godine opisali porodični obrazac prenošenja infekcije, ističući genetsku predispoziciju za razvoj bolesti [17]. Nedermatofitne onihomikoze su oportunističke infekcije i tipično se karakterišu odsustvom interdigitalne infekcije. Izloženost NDB može dovesti do razvoja onihomikoze u prisustvu brojnih predisponirajućih faktora, kao što su visoke temperature i vlažna sredina, zatvorena obuća, hiperhidroza, deformiteti noktiju i povrede noktiju koje se klinički manifestuju kao asimetrični obrasci hoda koji utiču na nokatnu jedinicu [9, 18].

Faktori rizika

*Brojni faktori rizika doprinose razvoju onihomikoze **(Slika 1)**. Predisponirajući faktori se*

patients' quality of life. A systematic review assessing its impact found that it contributes to physical impairment, functional limitations, pain or discomfort, and social embarrassment, with psychological and psychosocial distress reported in up to 92% of patients [17].

Etiopathogenesis and risk factors

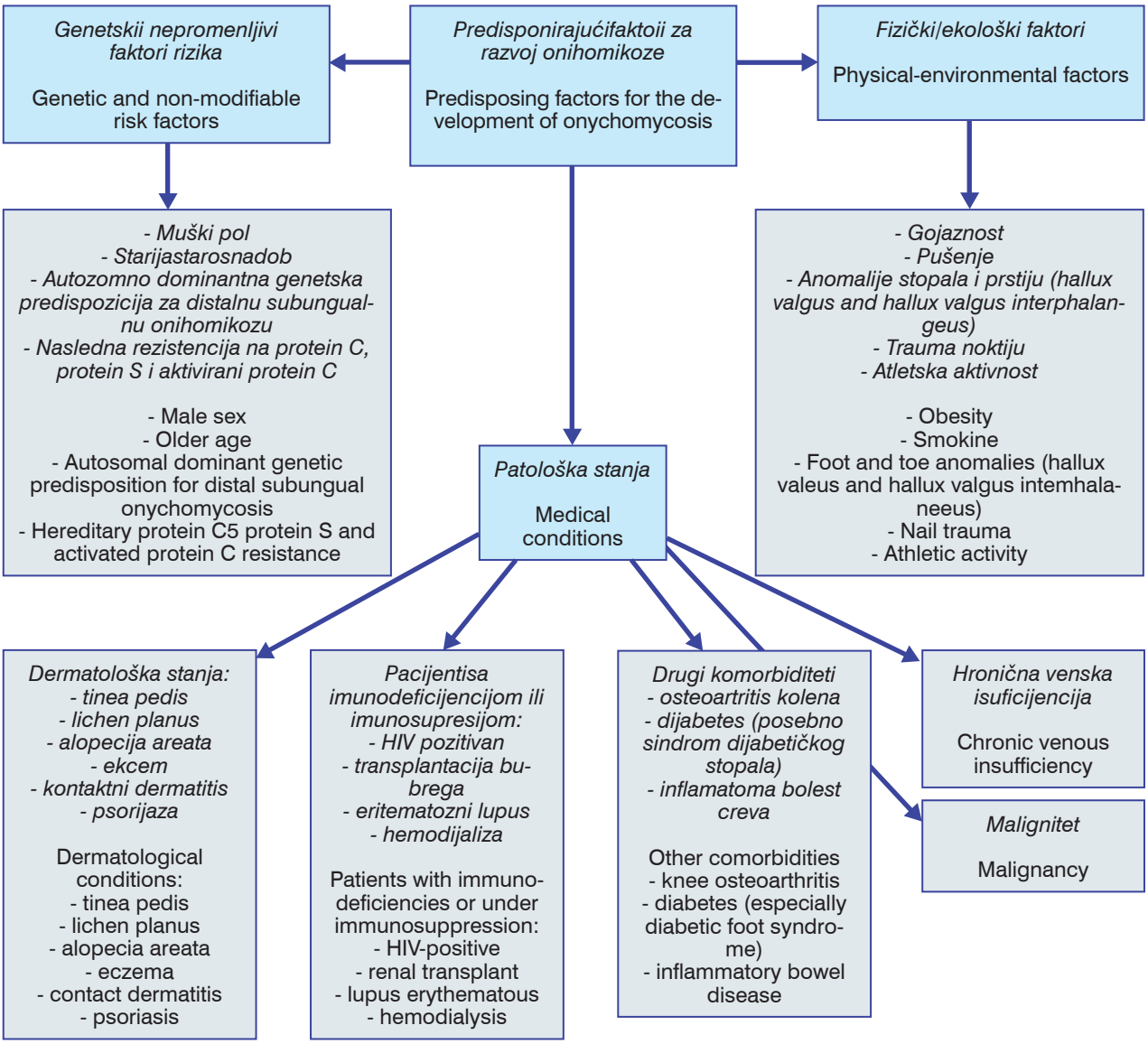
Pathogenic organisms

Current research indicates that approximately 4% of patients – whether or not they exhibit typical clinical signs – are confirmed to have toenail onychomycosis due to dermatophytes based on mycological testing [10]. The main causative agents of onychomycosis are dermatophytes, non-dermatophyte molds (NDM), and yeasts. Among dermatophytes, *Trichophyton rubrum* and *Trichophyton mentagrophytes* are responsible for 60–70% of infections. Other pathogens include NDMs such as *Scopulariopsis brevicaulis, Acremonium spp., Aspergillus spp., Fusarium spp. Alternaria alternate,* and *Neoscytalidium* [9, 15, 16]. Yeast-related onychomycosis is most commonly caused by *Candida spp*. [15]. NDMs are typically considered opportunistic pathogens, as they lack the ability to degrade keratin. Infections caused by NDMs are usually acquired via trauma, contact with soil or plants, or develop as secondary infections [4]. Unlike dermatophyte infections, NDM onychomycoses are rarely associated with concurrent interdigital tinea pedis. Risk of infection by NDMs increases with exposure to high temperatures, humidity, hyperhidrosis, occlusive footwear, and nail deformities – manifesting clinically as asymmetric gait nail unit signs [9, 18].

Tinea pedis is often a precondition to dermatophyte onychomycosis. In 1966, Zaias et al. described a possible hereditary component, suggesting a genetic predisposition to fungal nail infection [17].

Risk factors

Numerous risk factors contribute to the development of onychomycosis **(Figure 1).** These can be broadly grouped into three categories: genetic and non-modifiable risk factors, physical and environmental factors, and medical conditions [19].



Slika 1. *Faktori rizika za razvoj onihomikoze*
Figure 1. Risk factors contributing to the development of onychomycosis

mogu svrstati u tri glavne kategorije: genetski i nepromenljivi faktori rizika, fizički i ekološki faktori, kao i razna patološka stanja [19].

Među faktorima rizika, vaskularna oboljenja kao što su hronična venska insuficijencija i periferna vaskularna bolest (PVB) smatraju se nezavisnim prediktorima onihomikoze (OM) [2, 13, 20]. Veruje se da progresivne mikroangiopatske promene u kapilarima nokta doprinose nastanku OM [20]. Rezultati novijih studija takođe potvrđuju povezanost između onihomikoze i razvoja ulkusa kože kod

Among these, vascular diseases, including chronic vascular insufficiency (CVI) and peripheral vascular disease (PVD), are considered independent and significant predictors of onychomycosis (OM) [2, 13, 20]. Progressive microangiopathic changes in nail capillaries due to vascular compromise are believed to promote fungal colonization and infection [20]. Recent studies have also demonstrated a strong association between onychomycosis and the development of skin ulcers in patients with CVI, identifying fungal nail infections as an

pacijenata sa HVI, ukazujući na njen značaj nezavisno od već dobro uspostavljenih faktora rizika poput vaskularnih bolesti, neuropatije i postojanja kožnih bolesti [21, 22]. Ipak, postoji mali broj radova u literaturi koji proučavaju učestalost onihopatije i onihomikoze kod ovih pacijenata. Saez de Ocariz i saradnici ispitujući onihomikozu i negljivične onihopatije pacijenata sa venskim ulkusima nogu, potvrdili su da je onihomikoza češće dokazana [3].

Etiopatogeneza onihomikoze kod pacijenata sa HVI

Etiopatogeneza kožnih i promena na noktima je kompleksna kod pacijenata sa HVI. Venska hipertenzija uzrokuje smanjenje protoka krvi kroz kapilare i smanjenje njihovog broja, što rezultira patološkim promenama u njihovim zidovima [1]. Hemodinamički poremećaji mogu nastati kao posledica valvularne insuficijencije ili venske opstrukcije [2]. Hipoperfuzija donjih ekstremiteta uzrokuje suboptimalnu oksigenaciju i oslabljenu razmenu hranljivih materija u stopalima [14]. Nedostatak hranljivih materija i ishemija verovatno su glavni uzroci povećane smrti ćelija i smanjene regeneracije tkiva [1]. Oslabljen dotok krvi i lokalna hipoperfuzija dovode do makroangiopatije, mikroangiopatije, neuropatije i ulceracija [10, 23]. Venska staza, edem i promene na koži koje prate CVI i periferne vaskularne bolesti takođe mogu narušiti prirodnu zaštitnu barijeru kože i noktiju, omogućavajući lakšu penetraciju gljivica. Smanjen protok krvi dodatno kompromituje lokalni imunski odgovor u pogođenim područjima, olakšavajući kolonizaciju i opstajanje gljivica u nokatnoj jedinici [24]. Gljivični enzimi sa proteolitičkom, keratinolitičkom i lipolitičkom aktivnošću pomažu u razgradnji keratina u nokatnoj ploči i pospešuju invaziju gljivica u nokat [8]. Ovi faktori povećavaju verovatnoću gljivične infekcije i smanjuju uspeh antimikotične terapije [23].

Sáez de Ocariz i saradnici su izvestili da je prevalencija onihomikoze nožnih noktiju kod pacijenata sa CVI iznosila 36,11%, što je više u odnosu na opštu populaciju [3]. Dokazana je značajna korelacija između venskih i perifernih vaskularnih bolesti i onihomikoze, što je u skladu sa prethodnim istraživanjima. U studiji preseka iz 2005. godine koja je uključivala

important contributing factor – independent of other well-established risks such as vascular disease, neuropathy, and existing skin disease [21, 22]. However, the literature remains limited regarding the frequency and distribution of both onychopathy and onychomycosis in this population. In a study by Saez de Ocariz et al., which investigated fungal and non-fungal nail changes in patients with venous leg ulcers, onychomycosis was confirmed in over a half of the evaluated cases [3].

Etiopathogenesis of onychomycosis in patients with CVI

The development of skin and toenail abnormalities in CVD is complex. Venous hypertension reducs blood flow through the capillaries and decreases capillary density, ultimately causing pathological changes in vessel walls [1]. These hemodynamic disruptions may arise from valvular insufficiency or venous obstruction [2]. Impaired perfusion of the lower limbs leads to suboptimal oxygenation and diminished nutrient exchange, particularly in the feet [16]. Nutrient deficiency and ischemia likely contribute to increased cellular apoptosis and impaired tissue regeneration [1]. This compromised blood supply and regional hypoperfusion can result in macroangiopathy, microangiopathy, neuropathy, and ulceration [10, 20]. In addition to circulatory impairment, venous stasis, edema, and skin barrier damage – all characteristic of CVI and PVD – disrupt the skin and nails' natural defenses, facilitating fungal invasion. The reduction in local blood supply also compromises immune surveillance, enabling fungi to persist within the nail bed [29]. Fungi contribute to this process through the secretion of proteolytic, keratinolytic, and lipolytic enzymes, which degrade the nail plate's keratin structure and promote deep invasion [30, 31]. These pathophysiological mechanisms not only increase susceptibility to fungal infections but also reduce the effectiveness of antifungal treatments [20].

In a study by Saez de Ocariz et al., toenail onychomycosis was diagnosed in 36.11% of patients with CVI, a prevalence notably higher than that observed in the general population [3]. A significant association between venous and peripheral vascular disease and onychomycosis has been consistently report-

42 ambulantna pacijenta sa onihomikozom i 39 kontrolnih ispitanika, venska insuficijencija je bila češća u grupi pacijenata sa onihomikozom nego u kontrolnoj grupi [13]. Takođe prospektivna epidemiološka studija iz 2000. godine sprovedena na 254 pacijenta u vaskularnoj ambulanti pokazala je značajnu povezanost između onihomikoze i periferne vaskularne bolesti [25].

Klinička slika

Hronična ponavljana mikrotrauma nokta dovodi do subungualne hiperkeratoze, oniholize, paronihije, Beauovih linija, onihomadeze i onihomikoze [23, 26]. Progresivne mikroangiopatske promene u kapilarama nokta izazvane HVI, koje dovode do zadebljanja i zamućenja noktiju, mogu doprineti razvoju onihomikoze [27]. Uobičajeni klinički znaci OM uključuju promenu boje nokta (žuta, bela, gde je gljivica gusta, braon ili mešavina svih boja), odvajanje nokta od nokatne ploče (oniholiza), lomljivost, zadebljanje nokta i subungvalno nakupljanje keratinskog materijala [9, 10, 18]. Infekcije izazvane NDP i kvasnicama izgledaju kao žutobela promena boje praćena upalom i gnojnim iscetkom, dok bakterijske pseudomonas infekcije mogu izazvati zelenu prebojenost nokta [28]. Inficirani nokti, posebno u slučaju sekundarnih bakterijskih infekcija, mogu izazvati lokalni bol i paresteziju, što može imati značajne psihosocijalne posledice [7].

Klinička klasifikacija

Na osnovu obrasca zahvaćenosti nokatne jedinice, onihomikoza se može klasifikovati u pet podtipova: distalna lateralna subungvalna onihomikoza (DLSO), superficijalna bela/crna onihomikoza (SO), proksimalna subungvalna onihomikoza (PSO), endoniks onihomikoza (EO) i totalna distrofija noktiju (TD) [16, 19]. Pored toga, pacijenti mogu imati mešovite oblike onihomikoze, najčešće sa DLSO i SO, kao i sekundarnu onihomikozu [4, 16, 29]. Najčešći oblik onihomikoze je distalna subungvalna forma, koja se češće javlja na noktima nožnih prstiju. Ukoliko se ne leče, svi ovi oblici mogu dovesti do totalne distrofije nokta [30]. Primeri različitih tipova onihomikoza su prikazani na ***Slici 1a–c****.*

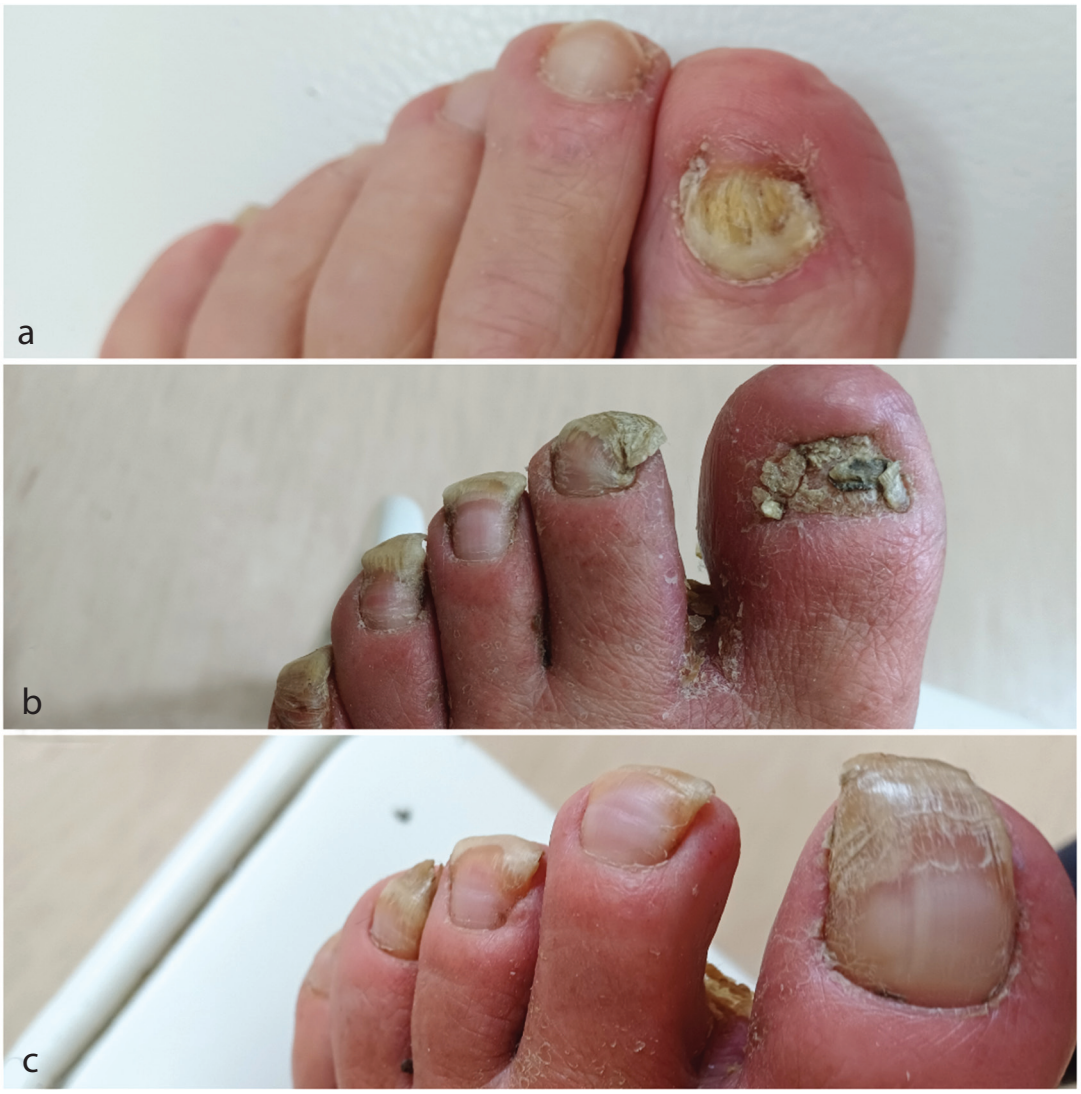
ed in previous studies. In a 2005 cross-sectional study of 42 outpatients with onychomycosis and 39 control subjects, venous insufficiency was significantly more frequent in the affected group [13]. Similarly, a 2000 prospective epidemiological study of 254 patients assessed in a vascular clinic confirmed a strong correlation between onychomycosis and PVD [32].

Clinical presentation

Chronic and repetitive microtrauma to the nail can result in a variety of nail changes, including subungual hyperkeratosis, onycholysis, paronychia, Beau's lines, onychomadesis, and ultimately onychomycosis [23, 26]. Progressive microangiopathic alterations in nail capillaries due to CVI contribute to nail thickening, increased opacity, and may facilitate fungal infection [27]. The typical clinical features of OM include nail discoloration (ranging from yellow, white, and brown to mixed shades, depending on the fungal load), onycholysis (separation of the nail plate from the nail bed), brittleness, thickening of the nail plate, and subungual scaling and debris accumulation [9, 10, 18]. Infections caused by NDM and yeast often manifest as yellow-white nail discoloration, accompanied by inflammatory changes and sometimes purulent discharge. In contrast, bacterial infections – most notably by Pseudomonas aeruginosa – can give the nail a greenish hue [28]. In cases complicated by secondary bacterial infections, patients may experience pain, paresthesia, and notable psychosocial impacts [7].

Clinical classification

Onychomycosis is clinically classified into five main subtypes based on the pattern of nail unit involvement: distal lateral subungual onychomycosis (DLSO) – the most common type, especially on toenails, superficial white/black onychomycosis (SO), proximal subungual onychomycosis (PSO), endonyx onychomycosis (EO), and total dystrophic onychomycosis (TDO) [16, 19]. In addition, patients may present with mixed patterns of onychomycosis (MPO), most frequently combining DLSO and SO, or with secondary onychomycosis [4, 16, 29]. If left untreated, all subtypes may progress to total nail dystrophy



Slika 1. *Klinička prezentacija onihomikoze (a. Distalna lateralna subungualna onihomikoza, b. Totalna distrofija noktiju, c. Distalna onihomikoza)*
Figure 1. Clinical presentation of onychomycosis (a. Distal lateral subungual onychomycosis, b. Total dystrophic onychomycosis, c. Distal onychomycosis)

Dijagnoza i diferencijalna dijagnoza

Dijagnoza onihomikoze se može postaviti na osnovu medicinske i socijalne anamneze pacijenta, faktora rizika, kliničkog pregleda i dermoskopije, ali ovi podaci sami nisu dovoljni za konačnu dijagnozu [7, 16]. Dijagnostički postupak uključuje mikološke testove uzoraka koristeći konvencionalne metode poput mikroskopije i kulture, kao i molekularne tehnike [30]. Istraživanja pokazuju da prevalencija onihomikoze može varirati u zavisnosti od korišćene dijagnostičke metode [10]. Antifungalni lekovi

[30]. Examples of various clinical forms of onychomycosis are shown in **Figure 1a-c**.

Diagnosis and differential diagnosis

Diagnosing onychomycosis requires a comprehensive approach that includes patient medical history, risk factor assessment, clinical examination, and dermoscopy. However, these methods alone are insufficient for a definitive diagnosis [7, 16]. Confirmation relies on mycological testing using convention-

se mogu zadržati u subungvalnim ostacima i nokatnoj ploči, potencijalno prelazeći u kultivacioni medijum, što može inhibirati rast gljivica i uticati na druge dijagnostičke testove [4, 7].

Mikroskopija kalijum-hidroksidom

Gljivice se mogu uočiti mikroskopskim ispitivanjem strugotina nokta tretiranih 5–40% kalijum-hidroksidom (KOH) [7, 31]. KOH rastvara keratin i ostatke, čineći gljivične strukture poput hifa vidljivijim [7, 8]. Iako ova metoda potvrđuje dijagnozu, ne pravi razliku između gljivica niti identifikuje specifični patogen [16]. Ovaj test niskog troška daje odmah rezultate, sa senzitivnošću 48–60% i specifičnošću između 38% i 78% [8, 31].

Kultura na gljivice

Mikološka kultura je jedina metoda koja identifikuje mikroorganizam i potvrđuje njegovu vitalnost. Sabouraudov dektrozni agar, sa cikloheksimidima ili bez njih, koristi se u laboratoriji za rast dermatofita i NDP [7]. Glavni nedostaci su duže vreme kultivacije i sporiji proces identifikacije patogena [30]. Kulture gljivica imaju do 40% lažno negativnih rezultata, posebno kada su delimično primenjeni antifungalni tretmani [9, 31]. Iako su kulture vrlo specifične (83–100%), njihova osetljivost je niska (60–65%), skupe su, a rezultati se čekaju 2–4 nedelje [8, 31, 32].

Histopatologija

Iako se mikroskopija i mikološka kultura smatraju zlatnim standardom za dijagnostiku onihomikoze, njihov visok procenat lažno negativnih rezultata doveo je do primene preciznijih metoda poput histologije i PCR [9]. Histopatologija može otkriti kvasnice, spore, hife i pseudohife, ali ne može identifikovati organizam niti odrediti njegovu vitalnost. PAS bojenje (Periodic acid schiff) ili bojenje Grokotovim metenamin-srebrom zlatni su standardi za detekciju gljivičnih elemenata, dok PCR i kultura gljivica identifikuju gljivicu [7, 16]. Osetljivost se kreće 82–88%, ali kombinovanjem PAS boje i kulture osetljivost raste na 96% [8].

PCR test

PCR testiranje omogućava brzo i specifično amplifikovanje fragmenta gljivične DNK

al methods, such as microscopy and fungal culture, in addition to more advanced molecular techniques [30]. The diagnostic yield can vary significantly depending on the method employed [10]. Importantly, prior antifungal therapy may cause drug residue to accumulate in the subungual debris and nail plate, potentially interfering with culture growth and other diagnostic tests [4, 7].

Potassium hydroxide (KOH) microscopy

KOH microscopy is a widely used initial diagnostic tool. Nail scrapings are treated with 5–40% potassium hydroxide (KOH), which dissolves keratin and debris, enhancing the visibility of fungal structures such as hyphae under the microscope [7, 8, 31]. While this method confirms the diagnosis, it cannot distinguish between types of fungi or identify the specific pathogen [16]. This low-cost screening test provides immediate results, with reported sensitivity ranging from 48–60%, and specificity between 38–78% [8, 31].

Fungal Culture

Fungal culture is the only method that can identify the specific organism and confirm its viability. Sabouraud dextrose agar is used for dermatophytes, while media without cycloheximide are preferred to isolating non-dermatophyte molds (NDM) [7]. The drawbacks include long cultivation period (results may take 2 to 4 weeks) [30]. Fungal cultures have up to 40% false-negative rates, especially when antifungal treatments have been partially used [9, 31]. While cultures are highly specific (83–100%), their sensitivity is low (60–65%), and they cost more than KOH microscopy [8, 31, 32].

Histopathology

Although fungal culture and microscopy are considered the diagnostic gold standard, their false-negative rates justify the use of histology and PCR [9]. Histology enables the detection of yeast, spores, hyphae, and pseudohyphae, although it cannot assess organism viability or determine the exact species. While the Periodic acid-Schiff (PAS) or Grocott methenamine-silver (GMS) staining are the gold standards for detecting fungal elements, PCR and

[8]. Molekularna dijagnostika nudi veću osetljivost i brže rezultate u poređenju sa tradicionalnim kulturama gljivica [32]. Međutim, rezultati zasnovani na PCR-u se mogu razlikovati u zavisnosti od tipa testa, kao što su konvencionalni PCR ili real-time PCR (qPCR) [10]. Zbog visokih troškova i ograničene dostupnosti, ove tehnike se ne koriste široko u opštoj praksi [8, 30].

Dermoskopija nokta

Dermoskopija noktiju je brza, neinvazivna i efikasna metoda za razlikovanje onihomikoze od drugih bolesti noktiju [8, 33]. Najčešći dermoskopski obrazac je nazubljeni proksimalni rub sa šiljcima u području oniholize [6, 8]. Takođe, može pomoći u identifikaciji optimalnog mesta za uzimanje uzorka tokom mikološkog ispitivanja [8].

Diferencijalna dijagnoza

Onihomikoza može da imitira druge benigne promene, uključujući promene na noktima u sledećim stanjima: Onychodystrophia traumatica, Psoriasis, Lichen planus, Paronychia chronica, Pityriasis rubra pilaris, Pachyonychia congenita, Trachyonychia, Onychogryphosis, Onycholysis idiopathica, Onychodystrophia medialis, Melanonychia striata, Exostosis subungualis, Verruca, Onychomatricoma, Scleroderma, Lupus erythematosus, Pruritus, Tungiasis, Infectiones bacteriales. Diferencijalna dijagnoza takođe uključuje maligna stanja kao što su karcinom skvamoznih ćelija, kao i subungualni i amelanotični melanom [7, 8]. U ovim slučajevima, empirijska antifungalna terapija povećava rizik od nepotrebnih neželjenih efekata, ne dolazi do poboljšanja, može ga čak pogoršati i povećati morbiditet i mortalitet [7].

Terapija onihomikoze

Onihomikoze je teško lečiti zbog ograničene dostupnosti antifungalnih lekova, potrebe za dugotrajnom terapijom i lošeg poverenja pacijenata [34]. Među svim dermatomikozama, ona je najteža za lečenje, uglavnom zbog anatomije nokta i teškoće prodora lekova u zaraženo područje [23]. Obavezna je preporuka potvrde dijagnoze pre početka lečenja, posebno sistemskom terapijom [35–37]. Empirijski oralni antifungalni lekovi

fungal culture can identify the fungus [7, 16]. Sensitivity ranges from 82–88% when used alone, but combining PAS stain and fungal culture can raise sensitivity to 96% [8].

PCR

PCR enables the rapid and specific amplification of fungal DNA fragments [8]. Compared to traditional fungal cultures, molecular diagnostics provide higher sensitivity and faster turnaround times [32]. However, PCR results may vary depending on the specific method used, such as conventional PCR or real-time PCR (qPCR) [10]. Despite their advantages, high costs and limited accessibility restrict their use in routine clinical practice [8, 30].

Nail Dermoscopy

Nail dermoscopy is a noninvasive, quick, and effective technique for differentiating onychomycosis from other nail disorders [8, 33]. The most characteristic dermoscopic finding is a jagged proximal edge with spikes extending in the onycholytic area [6, 8]. Dermoscopy also facilitates precise sample collection by identifying optimal areas for mycological sampling [8].

Differential diagnosis

Onychomycosis can mimic other benign conditions, including nail changes in traumatic onychodystrophy, psoriasis, lichen planus, chronic paronychia, pityriasis rubra pilaris, pachyonychia congenita, trachyonychia, onychogryphosis, idiopathic onycholysis, median nail dystrophy, melanonychia striata, subungual exostosis, verruca, onychomatricoma, scleroderma, lupus erythematosus, scabies, tungiasis, and bacterial infections. Differential diagnosis also includes malignant conditions such as squamous cell carcinoma, and subungual and amelanotic melanoma [7, 8]. Empirical antifungal treatment in such cases may not only be ineffective but also delay proper diagnosis and management, potentially increasing morbidity and mortality [7].

Treatment approach for onychomycosis

Onychomycosis remains one of the most difficult dermatomycoses to treat, primarily

su pokazali otpornost kod nekih pacijenata [16, 38]. Najčešći ishodi u studijama o onihomikozi su kliničko i mikološko izlečenje. Kliničko izlečenje odnosi se na normalan nokat bez znakova gljivične infekcije, što je najvažnije za pacijente. Izlečenje podrazumeva negativnu kulturu i negativnu direktnu mikroskopiju. Potpuno izlečenje obuhvata oba, a lekari ga često uopotrebljavaju za procenu uspešnosti lečenja [16].

Topikalna antimikotična terapija

Topikalna antifungalna terapija uključuje lakove za nokte, rastvore i druge topikalne preparate [39]. Nokti su generalno prodorniji za antifungalne lekove u vodenim formulacijama, a lak za nokte ne ometa značajno prodor, što omogućava pacijentima da sakriju onihomikozu tokom lečenja. Topikalni tretmani nude nisku sistemsku izloženost i minimalne nuspojave, ali obično imaju nisku efikasnost, bilo da se koriste samostalno ili kao adjuvantna terapija [8, 16]. Koncentracija leka u tkivu zavisi u velikoj meri od propustljivosti topičkog sredstva, zbog čega je poboljšanje transungualnog isporučivanja ključno za razvoj novih tretmana [17]. Pridržavanje terapije može biti problem zbog dugog trajanja lečenja (48 nedelja) i čestih aplikacija [40]. Nuspojave su minimalne i obično se svode na lokalne reakcije poput crvenila ili peckanja [31].

Broj FDA odobrenih topikalnih antifungalnih lekova je bio ograničen zbog poteškoća u penetraciji kroz nokatnu ploču. Do 2014. godine, ciklopiroks 8% lak je bio jedini odobren topički tretman za OM [16]. Godine 2014. FDA je odobrila efinakonazol 10% i tavaborol 5% rastvore, koji su pokazali bolji prodor u nokat nego ciklopiroks. Metaanaliza je pokazala da je efinakonazol imao najveću verovatnoću izlečenja, u poređenju sa oralnim itrakonazolom [16].

Sistemska antimikotična terapija

Sistemska terapija se često koristi za lečenje onihomikoze zbog njihove dostupnosti, visoke efikasnosti i relativno niske cene [9, 19]. Međutim, koncentracija leka koja dospeva do inficiranog mesta je ograničena zbog loše cirkulacije krvi do nokatnog ležišta [41]. Oralne terapije se smatraju zlatnim standardom za umerenu do tešku onihomikozu, jer pružaju

due to limited drug penetration through the nail plate, slow nail growth, which prolongs treatment duration, and poor patient adherence to long-term therapy protocols [23, 34]. Given these challenges, confirming the diagnosis before initiating therapy, especially systemic treatment, is strongly recommended [35–37]. Empirical use of oral antifungals can lead to resistance with some patients [16, 38]. The primary goals of treatment are clinical and mycological cures. Clinical cure refers to restoration of normal-appearing nail with no visible signs of fungal infection, which is often the most relevant outcome for patients. Mycological cure implies negative findings on both culture and direct microscopy. Complete cure is a combination of both clinical and mycological cure, typically used as the endpoint in clinical trials and to assess overall treatment success [16].

Topical antifungal treatment options

Topical antifungal therapies include nail lacquers, solutions, and other external agents designed to act locally on the infected nail unit [39]. Water-based formulations are generally more effective due to better nail permeability, and the use of cosmetic nail polish does not significantly impede antifungal penetration, allowing for aesthetic concealment during therapy. Topical treatments are associated with low systemic absorption and minimal side effects, but their efficacy is limited whether used alone or as an adjuvant [8, 16]. Drug concentration in the tissue depends heavily on the permeability of the topical agent, making improved transungual delivery a key focus for developing new treatments [17]. One major drawback is the lengthy treatment duration – typically 48 weeks – and the need for frequent applications, which can negatively affect patient adherence [40]. Side effects are usually mild and localized, such as erythema or burning sensations [31].

Until 2014, ciclopirox 8% nail lacquer was the only FDA-approved topical treatment for OM [16]. Subsequently, efinaconazole 10% solution and tavaborole 5% solution were approved, offering superior nail penetration and improved efficacy. A recent meta-analysis found efinaconazole to have the highest cure probability among topical agents, with efficacy comparable to oral itraconazole [16].

najefikasniji tretman. Tri osnovna oralna leka su terbinafin, itrakonazol i flukonazol. Često je potrebno produženo korišćenje zbog njihove ograničene bioraspoloživosti i izazova u održavanju adekvatnih koncentracija leka u nokatnom krevetu [31].

Terbinafin

Terbinafin se dozira u količini od 250 mg dnevno za šest nedelja u slučaju infekcija na rukama i 12 nedelja za infekcije na stopalima [16, 19]. Stope potpunog izlečenja su 59% i 38%, a stope mikološkog izlečenja su 79% i 70% [9]. Potencijalne nuspojave su blage i uključuju glavobolje, osipe, gastrointestinalne simptome, a retko i hepatotoksičnost [19, 42]. Terbinafin se može primeniti kao pulsna terapija kao off-label opcija za lečenje onihomikoze, što može biti isplativo i poboljšati pacijentovu usklađenost sa terapijom [7, 43]. Kontinuirana terapija terbinafinom ima sličnu efikasnost kao i pulsna terapija, iako su neka istraživanja pokazala superiornost kontinuirane terapije u odnosu na pulsnu za onihomikozu noktiju na stopalima [8].

Pregledni članak iz 2020. godine koji je analizirao 30 studija upoređujući kontinuirane i pulsne režime terbinafina, nije pronašao značajne razlike u stopi mikološkog izlečenja [44]. Takođe, Cochrane metaanaliza iz 2017. godine kojom je obuhvaćeno 48 randomizovanih kontrolisanih ispitivanja sa 10.200 učesnika zaključila je da terbinafin dovodi do viših stopa kliničkog i mikološkog izlečenja u poređenju sa drugim terapijskim opcijama za onihomikozu stopala [8].

Itrakonazol

Itrakonazol se obično dozira u pulsnom režimu (jedna nedelja sa 400 mg dnevno, nakon čega sledi tri nedelje pauze), osam nedelja za onihomikozu noktiju na rukama i 12 nedelja za onihomikozu na stopalima [25]. Itrakonazol se može primeniti i u kontinuiranom režimu od 200 mg dnevno tokom 12 nedelja. Studije koje su ocenjivale oralnu primenu itrakonazola pokazale su stopu izlečenja 46–69% [16]. Potencijalne nuspojave uključuju glavobolju, infekcije gornjih respiratornih puteva, gastrointestinalne simptome, hipertrigliceridemiju, povišene transaminaze, a retko i perifernu neuropatiju i hepatitis [9, 19].

Oral antifungal treatment options

Systemic antifungal agents remain the gold standard for treating moderate to severe onychomycosis due to their availability, superior efficacy, and affordability [9, 19]. However, the drug concentration that reaches the infected site is limited by poor vascularization of the nail bed [41]. The three most commonly used oral antifungals are terbinafine, itraconazole, and fluconazole. Because bioavailability is limited, long treatment courses are often required to achieve adequate drug concentrations in the nail bed [31].

Terbinafine

Terbinafine is typically administered at 250 mg daily for 6 weeks (fingernails) and 12 weeks (toenails) [16, 19]. The complete cure rates are 59% for fingernails and 38% for toenails, and the mycologic cure rates are 79% for fingernails and 70% for toenails [9]. Potential side effects are generally mild and include headache, rash, gastrointestinal disturbances, and rare hepatotoxicity [19, 42]. Pulse therapy with terbinafine, though off-label, is sometimes used to reduce cost and improve compliance [7, 43]. While some studies suggest continuous regimens may be more effective, particularly for toenail infections, overall outcomes are similar [8].

A 2020 systematic review of 30 studies found no significant differences in mycological cure rates between continuous and pulsed terbinafine regimens [44]. Likewise, a 2017 Cochrane meta-analysis involving 48 randomized controlled trials and 10,200 participants concluded that terbinafine yielded higher clinical and mycological cure rates than other oral antifungals for toenail onychomycosis [8].

Itraconazole

Itraconazole is administered either as pulse therapy (400 mg/day for 1 week, followed by 3 weeks off, repeated for 8 weeks for fingernails and 12 weeks for toenails),or as continuous therapy (200 mg/day for 12 weeks) [25]. Clinical studies have reported mycological cure rates between 46% and 69% [16]. Itraconazole is generally well tolerated, although potential side effects include headache, upper respiratory tract infections, gas-

Metaanaliza iz 2019. godine koja je obuhvatila 26 randomizovanih kontrolisanih ispitivanja (n = 8.136) pokazala je da kontinuirana primena oralnog terbinafina ili itrakonazola imaju značajno višu stopu mikološkog izlečenja u poređenju sa topikalnim preparatima [45]. U randomizovanoj studiji sa jednom slepom probom koja je obuhvatila 101 pacijenta starijeg od 60 godina, kontinuirani terbinafin kao i pulsni itrakonazol postigli su više od 60% izlečenja i kliničke efikasnosti nakon 18 meseci, bez značajnih razlika između grupa [7]. Ostale metaanalize ukazuju da terbinafin (250 mg dnevno) i pulsni itrakonazol (400 mg) nadmašuju oralni flukonazol i druge lokalne terapije, pri čemu je oralni terbinafin najefikasniji [16, 45].

Flukonazol

Flukonazol je odobren za lečenje onihomikoze u Evropi i Kini, dok se u SAD koristi off-label [9, 19]. Doza je 150 mg nedeljno tokom 6–9 meseci, odnosno 12–18 meseci. Zbog kratkotrajne koncentracije leka u noktima, neophodna je duža primena terapije [7].

Terapija laserom

Većina lasera koristi princip selektivne fototermolize [8]. Od 2012. godine FDA je odobrila četiri sistema lasera (1064 nm Nd:YAG laseri, kako kratkopulsni tako i Q-switched laseri, ugljen-dioksidni laseri i diodni laseri 870, 930 nm) i koriste se zbog kratkog vremena tretmana i manji broj tretmana koji je potreban [9, 16]. Međutim, kliničke studije nisu pokazale značajno bolje rezultate od trenutnih lokalnih i sistemskih antifungalnih terapija u potpunom izlečenju onihomikoze [16]. Laser terapije su sigurne, ali skupe, i mogu se razmotriti kod pacijenata kod kojih su sistemski antifungalni lekovi kontraindikovani ili kao deo kombinovane terapije [46].

Proceduralni tretmani

Procedure poput debridmana, skraćivanja inficiranih noktiju, avulzije ili matriksektomije mogu se razmotriti kod pacijenata sa recidivom onihomikoze [16]. Keratolitički agensi kao što su urea, salicilna kiselina, mlečna kiselina i papain mogu poboljšati unos topikalnih antifungalnih agensa u nokte [8]. Studije koje su

trointestinal disturbances, hypertriglyceridemia, elevated transaminases, and rarely, peripheral neuropathy and hepatitis [9, 19].

A 2019 meta-analysis of 26 randomized controlled trials (n = 8,136) concluded that oral terbinafine and oral itraconazole result in significantly higher mycological cure rates than topical therapies [45]. Additionally, a single-blind, randomized trial of 101 elderly patients (≥60 years) showed that both continuous terbinafine and pulse itraconazole achieved >60% mycological cure and clinical efficacy at 18 months, with no statistically significant differences between groups [7]. Other meta-analyses confirm that terbinafine (250 mg daily) and pulsed itraconazole (400 mg/day) outperform oral fluconazole and topical therapies, with terbinafine considered the most effective oral agent overall [16, 45].

Fluconazole

Fluconazole is approved for treating onychomycosis in Europe and China, while it is used off-label in the US [9, 19]. The typical regimen is 150 mg weekly for 6–9 months (fingernails) and 12–18 months (toenails). Due to its short residual concentration in the nail, prolonged treatment durations are required to achieve therapeutic efficacy [7].

Laser therapy

Most lasers use the principle of selective photothermolysis [8]. Since 2012, the four FDA-approved laser systems (1064 nm Nd:YAG lasers (short-pulsed and Q-switched), carbon dioxide lasers, and diode lasers (870 and 930 nm) have been utilized due to short treatment sessions and fewer total treatments [9, 16]. However, clinical studies have not demonstrated superior efficacy compared to conventional topical or oral antifungal therapies for complete resolution of onychomycosis [16]. Laser therapy is considered safe but expensive, and may be suitable for patients cannot tolerate systemic antifungal agents or as part of combination therapy [46].

Procedural treatments

Procedural interventions such as nail debridement, trimming of infected nail plates, partial or total avulsion, and matrixectomy can

upoređivale terbinafin kao monoterapiju vs. prethodni debridman, pokazale su bolje rezultate sa debridmanom noktiju na stopalima [7]. Studija koja je istraživala efekte debridmana u poređenju sa debridmanom uz topičku antifungalnu terapiju, pokazala je da kombinovana terapija dovodi do značajnog mikološkog izlečenja od 76,7%, dok nije bilo mikološkog izlečenja samo sa debridmanom [16].

Specifičnosti terapije kod starijih odraslih

Hronična venska insuficijencija koja je povezana sa onihomikozom, često se javlja u starijim populacijama, a njena učestalost raste sa godinama [18]. Postoji mali broj navoda u literaturi koji procenjuju efikasnost i sigurnost antifungalnih lekova kod starijih pacijenata [8, 34]. Sistematska terapija ima ograničenu efikasnost kod ovih pacijenata, a komorbiditeti zahtevaju razmatranje alternativnih tretmana poput keratolitika. Itrakonazol je pokazao stopu izlečenja od svega 25%, u poređenju sa uobičajenih 60–70%, što je verovatno rezultat deformacija noktiju koje otežavaju penetraciju leka. Stoga, pre nego što se započne antimikotična terapija onihomikoze kod pacijenata sa HVI, posebno kod starijih osoba, važno je priznati mogućnost suboptimalnih rezultata [2]. Ovi pacijenti imaju specifične faktore rizika koji ih predodređuju za loš odgovor na antifungalnu terapiju, uključujući spor rast noktiju, rekurentnu onihodistrofiju i povećanu prevalenciju PVB [7]. Zbog toga, topikalni i sistemski antifungalni lekovi treba da se koriste u opštoj populaciji, ali terapija treba da traje duže. Lokalna terapija se preporučuje kao prva linija lečenja za starije pacijente sa ograničenim zahvatanjem noktiju. Za pacijente kojima je potrebna sistemska terapija, terbinafin je lek izbora zbog nižeg potencijala za interakcije sa lekovima, dok se itrakonazol može primeniti za kandidijalnu onihomikozu, uzimajući u obzir moguće interakcije. U određenim situacijama, hemijska avulzija nokta ili mehanički debridman mogu biti prikladniji [34].

Zaključak

Onihomikoza je gljivična infekcija nokta koja uzrokuje promenu boje i zadebljanje zahvaćenih noktiju. Studije pokazuju povezanost između površinske venske insuficijencije i onihomikoze. Ona je češća kod pacijenata sa HVI ili PVB zbog nekoliko faktora koji doprinose

be effective adjuncts, especially in cases of onychomycosis recurrence [16]. The use of keratolytic agents, including urea, salicylic acid, lactic acid, and papain, has been shown to enhance topical antifungal penetration into the nails [8]. Studies comparing terbinafine monotherapy to terbinafine proceeded by debridement have shown improved therapeutic outcomes with the addition of debridement [7]. Furthermore, one clinical trial demonstrated that combined debridement and topical antifungal therapy achieved 76.7% mycological cure, whereas debridement alone yielded no significant mycological cure [16].

Therapeutic considerations in elderly patients

Chronic venous insufficiency (CV), a condition increasingly prevalent in aging populations, is frequently associated with onychomycosis [18]. However, limited data are available regarding the efficacy and safety of antifungal therapy in the elderly [8, 34]. Systemic antifungal treatment in this population is often complicated by comorbidities, necessitating consideration of alternative treatments such as keratolytics. Itraconazole showed only 25% cure rate in elderly patients, compared to the typical 60–70% observed in younger populations, likely due to nail deformities impeding drug penetration. Therefore, it is essential to acknowledge the potential for suboptimal outcomes before initiating antifungal treatment for onychomycosis in patients with CVI, particularly older individuals [2]. These patients have specific risk factors predisposing them to poor response to antifungal therapy, including slow nail growth, recurrent nail dystrophy, and increased prevalence of PVD [7]. Therefore, topical and systemic antifungals should be used in the general population, but therapy should be extended. Topical therapy is preferred as the first line treatment in older adults with limited nail involvement. When systemic therapy is required, terbinafine is favored over azoles due to its lower risk of drug-drug interactions. Itraconazole may still be considered for candida-associated infections, though careful monitoring is essential. In selected cases, chemical nail avulsion or mechanical debridement may be more suitable [34].

nastanku bolesti. Dermatofiti su najčešći gljivični uzročnici onihomikoze. Mikroskopija i mikološke kulture se smatraju zlatnim standardom u dijagnostici onihomikoze, iako visoki nivoi lažno negativnih rezultata zahtevaju upotrebu precizнijih metoda. Uprkos hroničnom i benignom kliničkom toku, onihomikoze karakterišu visoke stope reinfekcija i recidiva čak i nakon dugotrajnog lečenja. Značajan broj starijih pacijenata koristi višestruke terapije lekovima zbog različitih komorbiditeta. Zbog toga je topička terapija obično preferisana opcija lečenja za ovu specifičnu grupu. Kada je sistemsko lečenje neophodno, oralni terbinafin treba da bude izbor prvog reda, jer nosi manji rizik od interakcije sa drugim lekovima u poređenju sa azolima.

Dostupne preporuke za lečenje onihomikoze kod pacijenata sa HVI nude vrlo ograničen uvid u ovakve specijalne slučajeve. Nedostaju dobro kontrolisane studije koje bi pomogle u donošenju odluka o lečenju u ovakvim grupama, pa je potrebno dalje istraživanje kako bi se procenila povezanost između onihomikoze noktiju i HVI. Buduća istraživanja trebalo bi da se fokusiraju na uspostavljanje robustno dizajniranih kliničkih ispitivanja u različitim populacijama pacijenata, kako bi se dalje istražile nove terapije i utvrdile optimalne i standardizovane smernice za kombinovanu terapiju.

Conclusion

Onychomycosis is a common fungal nail infection characterized by discoloration and thickening of the affected nail plate. Studies indicate a correlation between superficial venous insufficiency and onychomycosis. It is more frequently observed in patients with CVI or PVD due to multiple contributing factors. Dermatophytes remain the predominant causative agents. While microscopy and fungal culture are still the gold standard for diagnosis, their limitations in sensitivity have encouraged the adoption of more advanced diagnostic modalities. Despite its benign appearance, onychomycosis is associated with high reinfection and recurrence rates even after prolonged treatment. Due to frequent comorbidities and polypharmacy, topical therapy is generally the first-line option in this specific group. Oral terbinafine should be considered when systemic treatment is necessary, as it poses a lower risk of drug-drug interactions compared to azoles.

Current treatment recommendations specific to OM in CVI patients are limited. The lack of large, well-controlled clinical trials prevents definitive guidance for managing this subgroup. Future research should prioritize robust clinical studies in diverse populations, with the aim of identifying effective combination therapies and establishing evidence-based, standardized treatment protocols.

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