Primljen/ Received on 12.12.2013.
Revidiran/ Revised on 19.12.2013.
Prihvaćen/ Accepted on 26.12.2013.

INFORMATIVNI RAD
INFORMATIVE ARTICLE
doi: 10.5937/asn13683150

DIFERENCIJALNO-DIJAGNOSTIČKE I TERAPIJSKE KARAKTERISTIKE ORALNE KANDIDIJAZE

DIFFERENTIAL DIAGNOSIS AND THERAPEUTIC CHARACTERISTICS OF ORAL CANDIDIASIS

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Sažetak

Oralna kandidijaza je česta oportunistička infekcija u usnoj duplji izazvana prekomernim razmnožavanjem *Candida* specijes (najčešće *Candida albicans*). Kod 20-50% zdravih osoba *Candida albicans* je deo normalne flore usne duplje. Incidencija ovog oboljenja varira u zavisnosti od starosti pacijenta i predisponirajućih faktora (poremećaj funkcije pljuvačnih žlezdi – oralna suvoća, loša oralna higijena, nošenje zubnih proteza, dugotrajna upotreba lekova, ishrana zasnovana pretežno na ugljenim hidratima, pušenje, diabetes mellitus, Kušingov sindrom, maligna oboljenja, imunosupresivna stanja). Kod 2/3 bolesnika sa AIDS-om oralna kandidijaza predstavlja rani znak oboljenja.

Klinički se oralna kandidijaza manifestuje u obliku akutne (pseudomembranozna i atrofična kandidijaza) i hronične (atrofična, nodularna i mukokutanealna kandidijaza) forme.

Diferencijalno-dijagnostički kandidijaza se ubraja u bele lezije, pa je treba razlikovati od retikularne forme lihen planusa, leukoplakije, hemijskih oštećenja, mehaničkih oštećenja (kao što je grickanje oralne sluzokože), belog sunderastog nevusa, drugog stadijuma luesa, difterije i dr.

Nakon uzimanja istorije bolesti, identifikuju se i koriguju provokirajući faktori. Posle kliničkog pregleda i laboratorijske identifikacije izazivača oboljenja, primenjuju se adekvatni antifungalni lekovi: lokalno (rastvor Nistatina, Daktanol gel) ili sistemski (Flukonazol, Ketokonazol, Itrakonazol, Amfotericin B i dr.), dobra oralna higijena i sanacija zuba. Kod određenih rizičnih grupa pacijenata primenjuje se profilaksa antifungalnim lekovima koji smanjuju incidenciju i težinu oboljenja. U najvećem broju obolelih prognoza oboljenja je dobra.

Ključne reči: oralna kandidijaza, diferencijalna dijagnoza, terapija

Abstract

Oral candidiasis is a common opportunistic infection in the oral cavity and is caused by abnormal multiplication of *Candida* species (*Candida albicans*). In the 20 - 50% of healthy individuals, *Candida albicans* is a normal inhabitant of the oral cavity. The incidence of this disease varies depending on the patient's age and predisposing factors (salivary gland dysfunction - oral dryness, poor oral hygiene, wearing dentures, long-term use of drugs, diet based predominantly on carbohydrates, smoking, diabetes mellitus, Cushing's syndrome, cancer, immunosuppressive conditions). In 2/3 of patients with AIDS, oral candidiasis is an early sign of disease.

Oral candidiasis is clinically manifested as acute (pseudomembranous and atrophic candidiasis) and chronic forms (atrophic, nodular and mucocutaneous candidiasis).

Differentially, candidiasis is one of the white lesions, and should be distinguished from reticular form of lichen planus, leukoplakia, chemical damage, mechanical damage (such as biting the oral mucosa), white spongy nevus, the second stage of syphilis, diphtheria, and others.

After medical history is taken, provoking factors should be identified and corrected. Following clinical examination and laboratory identification of causative pathogens, appropriate antifungal drugs are applied: local (nystatin solution, Dactanol gel) or systemic (fluconazole, ketoconazole, itraconazole, amphotericin B, etc.), good oral hygiene and tooth repair. For certain high-risk patient groups, prophylactic antifungal drugs which reduce the incidence and severity of disease are applied. In the majority of patients, disease prognosis is good.

Key words: oral candidiasis, differential diagnosis, therapy

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Uvod

Oralna kandidijaza je česta oportunistička infekcija u usnoj duplji izazvana preteranim razmnožavanjem *Candide* specijes. Za razvoj oralne kandidijaze najznačajnije su *Candida albicans* (najučestalija), *Candida tropicalis*, *Candida glabrata*, *Candida pseudotropicalis*, *Candida guillierimondii*, *Candida krusei*, *Candida lusitanae*, *Candida parapsilosis* i *Candida stellatoidea*¹⁻³. *Candida albicans*, *Candida glabrata* i *Candida tropicalis* čine više od 80% izolovanih u toku kliničkih infekcija⁴. Kod 20%-50% zdravih osoba *Candida albicans* je deo normalne flore usne duplje. Zastupljenost *Candide albicans* u usnoj duplji je 45% kod novorođenčadi, 45%-65% kod zdrave dece, 30%-45% kod zdravih odraslih osoba, 50%-65% kod osoba koje nose zubne proteze, 90% kod osoba sa akutnom leukemijom, koje primaju hemoterapiju, a 95% kod pacijenata sa HIV-om^{4,5}. Može se naći kao komensal i kao oportunistički patogen u usnoj duplji, a istraživanja otkrivaju nove faktore rizika koji provociraju njenu patogenost⁶. Oralna kandidijaza je često nedijagnosticovana kod starijih osoba, a pogotovo kod onih koji nose zubne proteze. Takođe, može biti znak postojanja sistemskog oboljenja, kao što je diabetes mellitus⁴. Učestalost oralne kandidijaze je u stalnom porastu zbog sve većeg broja imunokompromitovanih pacijenata⁷.

Faktori rizika

Faktori rizika za razvitak oralne kandidijaze su: poremećaj funkcije pljuvačnih žlezda – oralna suvoća, loša oralna higijena, nošenje zubnih proteza, dugotrajna upotreba lekova (antibiotika i kortikosteroida), ishrana zasnovana pretežno na ugljenim hidratima, pušenje, diabetes mellitus, Kušingov sindrom, maligna oboljenja, imunosupresivna stanja. Kod 2/3 bolesnika sa AIDS-om oralna kandidijaza je rani znak oboljenja^{4,5}. Granulociti i makrofage smatraju se glavnim efektornim ćelijama odgovornim za kontrolu infekcija izazvanih *Candidom albicans*, a ćelijski imunitet je osnovni mehanizam odbrane domaćina od oralne kandidijaze. Mehanizmi koji dovode do smanjenog imuniteta mukoze nisu dovoljno razjašnjeni i verovatno se zasnivaju na smanjenom nivou antimikrobnih proteina pljuvačke. Pušenje i

Introduction

Oral candidiasis is a common opportunistic infection in the oral cavity caused by abnormal multiplication of *Candida* species. For the development of oral candidosis, the important ones are *Candida albicans* (the commonest), *Candida tropicalis*, *Candida glabrata*, *Candida pseudotropicalis*, *Candida guillierimondii*, *Candida krusei*, *Candida lusitanae*, *Candida parapsilosis*, and *Candida stellatoidea*¹⁻³. *Candida albicans*, *Candida glabrata*, and *Candida tropicalis* represent more than 80% of isolates from clinical infection⁴. In the 20%-50% of healthy individuals, *Candida albicans* is a normal inhabitant of the oral cavity. The presence of *Candida albicans* in the oral cavity has been reported to be 45% in infants, 45%-65% in healthy children, 30% -45% of healthy adults, 50% -65% of people who wear removable dentures, 90% in patients with acute leukemia who received chemotherapy, and 95% in patients with HIV^{4,5}. In the oral cavity it can be found both as commensals and an opportunist pathogen and recent investigations have revealed many risk factors that provoke its pathogenicity⁶. It is common and underdiagnosed among the elderly, particularly in those who wear dental prostheses. It can also be a sign of underlying systemic diseases, such as diabetes mellitus⁴. The prevalence of candidiasis continues to escalate because of the increasing numbers of patients who are immunocompromised⁷.

Risk factors

Risk factors for the development of oral candidiasis are: salivary gland dysfunction - oral dryness, poor oral hygiene, denture wearing, long-term use of drugs (antibiotics and steroids), diet based predominantly on carbohydrates, smoking, diabetes mellitus, Cushing's syndrome, cancer, immunosuppressive conditions. In 2/3 of patients with oral candidiasis, AIDS is an early sign of disease⁴. Granulocytes and macrophages are considered to be the main effector cells responsible for the controlling infection caused by *Candida albicans*, and cell-mediated immunity is the primary host defense mechanism against oral candidiasis. Mechanisms leading to impaired oral mucosal immunity in patients are poorly understood and may

upotreba psihotropnih lekova izazivaju povišen nivo kortizola, a povećana koncentracija steroida javlja se i u toku trudnoće. Višak egzogenih ili endogenih glikokortikoida izaziva umećenu hiperglikemiju, a koncentracija glukoze u pljuvački zavisi od nivoa glukoze u krvi i korelira sa kolonizacijom usne duplje *Candida albicans*. Drugi faktori u vezi sa oralnom kandidijazom su anemija izazvana nedostatkom gvožđa i vitamina B12⁴.

Klinička slika i diferencijalna dijagnoza

Candida albicans je normalno prisutna u usnoj duplji i ne predstavlja problem kod zdravih osoba. Preterano razmnožavanje *Candide* u toku kandidijaze, ipak, može izazvati neprijatnost u ustima, poremećaj ukusa, poremećaje u ishrani, u slučaju ezofagealne kandidijaze, spor oporavak pacijenta i produžen boravak u bolnici. Kod imunokompromitovanih pacijenata infekcija se može širiti krvotokom u gornji gastrointestinalni trakt, razvijajući se u tešku infekciju sa značajnim morbiditetom i mortalitetom. Step en smrtnosti u slučaju sistemske kandidijaze je 71% do 79%^{4,8}.

Oralna kandidijaza se klinički manifestuje u obliku: akutne (pseudomembranozna i atrofična) i hronične (atrofične, nodularne i mukokutalne) forme^{1,2,4,9}.

Akutna pseudomembranozna kandidijaza (*Candidosis acuta pseudomembranacea*) karakteriše se izraženim belo-žućkasto-sivim pseudomembranama, sačinjenim od deskvimiranih epitelnih ćelija, fibrina i gljivičnih hifa. Promene najčešće zahvataju labijalnu i bukalnu mukožu, meko i tvrdo nepce, jezik i orofarinks. Bolesnici se žale na bljutav ukus, suvoću i peckanje. Pseudomembrane se lako skidaju, pri čemu ispod njih ostaje eritematozna mukoza. Dijagnoza je jednostavna, jer se promene lako uočavaju, a ova forma je jedna od najčešćih oblika orofaringealne kandidijaze, čineći oko trećinu svih slučajeva^{4,9}. Dijagnoza se potvrđuje kultivisanjem brisa sa zahvaćene mukoze. Često se javlja kod dece, a predisponirajući faktori za njen razvitak su starost, diabetes mellitus, HIV/AIDS, leukemija, upotreba inhalatora na bazi kortikosteroida ili antibiotika širokog spektra, terminalni stadijum teških bolesti. Diferencijalno-dijagnostički, oboljenja u us-

involve reduced levels of some of the salivary antimicrobial proteins. Smoking and use of psychotropic drugs promote hypercortisolemia, and also increased saliva concentration of steroids is a feature of pregnancy. Excess of endogenous or exogenous glucocorticoids cause moderate hyperglycemia, and glucose concentrations in saliva depend on the level of glucose in the blood and correlates with oral *Candida albicans* colonization. Other factors implicated in the aetiology of this condition are iron deficiency anaemia and vitamin B12 deficiency⁴.

Clinical and differential diagnosis

Candida albicans is a normal commensal of the mouth and generally causes no problems in healthy people. Excessive growth of candida in the thrush, however, can cause local discomfort in the mouth, taste disorder, dysphagia in the case of esophageal candidiasis resulting in poor nutrition, slow recovery and prolonged hospital stay. In immunocompromised patients, infection can spread through the bloodstream or upper gastrointestinal tract leading to severe infection with significant morbidity and mortality. Systemic candidiasis carries a mortality rate of 71% to 79%^{4,8}.

Various clinical manifestations of oral candidiasis exist: acute forms (pseudomembranous and atrophic candidiasis) and chronic forms (atrophic, nodular and mucocutaneous candidiasis)^{1,2,4,9}.

Acute pseudomembranous candidiasis (thrush) (*Candidosis acuta pseudomembranacea*) is characterised by extensive white-yellowish-gray pseudomembranes consisting of desquamated epithelial cells, fibrin, and fungal hyphae. These white patches occur on the surface of the labial and buccal mucosa, hard and soft palate, tongue, and oropharynx. Patients complain about the bland taste, dryness and burning. Pseudomembranes can easily be removed with a swab and below them remains erythematous mucosa. The diagnosis is usually simple because the changes can easily be noticed, and this form is one of the most common ones accounting for almost a third of all cases^{4,9}. Diagnosis can be confirmed microbiologically by culturing a smear from the affected mucosa. It often occurs in children and predisposing factors include extremes of age, diabetes mellitus, patients who have HIV/AIDS or leukaemia, those using steroid aerosol inhalers, broad spectrum antibiotics, and pa-

noj duplji koja se manifestuju sličnim belim promenama su: retikularni lihen planus, karcinom skvamoznih ćelija, lihenoidne reakcije, leukoplakija, hemijska oštećenja, mehanička oštećenja (grickanje oralne sluzokože), linea alba, beli sunderasti nevus, drugi stadijum lusa, difterija^{1,2,4,9}.

Akutna atrofična kandidijaza (*Candidosis acuta atrophica*) obično se povezuje sa osećajem pečenja celih ustiju ili jezika⁴. Jezik je depapiliran, svetlo crven, a ovakvo stanje se naziva „gladak antibiotski jezik“. Pored promena na jeziku, često su prisutni difuzni enantemi na tvrdom nepcu. Bolesnik se žali na peckanje u ustima, suvoću i teško formiranje zalogaja, smetaju mu začinjena hrana i gazirana pića. Ova forma oralne kandidijaze je često udružena sa oralnom suvoćom⁹. Diferencijalno-dijagnostički, treba uzeti u obzir simptom peckanja u ustima, pogotovo kod starijih pacijenata koji nose proteze ili su pod antibiotskom, citostatskom ili inhalacionom kortikosteroidnom terapijom. Značajnu pomoć u dijagnozi pruža bris zahvaćene mukoze⁴.

Hronična atrofična kandidijaza (*Candidosis chronica atrophica*) je poznata pod nazivom „stomatitis protetica“ i vidi se kao lokalizovani hronični eritem sluzokože ispod protezne ploče. Lezije su obično lokalizovane na tvrdom nepcu i alveolarnom nastavku gornje vilice, ali mogu biti prisutne i na mandibuli. Bolesnici se žale na simptome peckanja pri nošenju proteze. Pravilna dijagnoza zahteva skidanje proteza, pažljivu inspekciju i uzimanje brisa. U 65% slučajeva proteznog stomatitisa dokazano je prisustvo oralne kandidijaze^{1,2,4,10}.

Hronična nodularna (hiperplastična) kandidijaza (*Candidosis chronica hyperplastica*) obično se javlja na bukalnoj mukozi i lateralnim ivicama jezika kao prskane ili homogene bele naslage okružene enantomom koje se ne mogu skinuti^{1,2}. Ova vrsta kandidijaze povezuje se sa pušenjem i potpuno izlečenje zavisi od njegovog prestanka. Stanje se naziva i „kandida leukoplakia“ i može progredirati u izražene displastične promene i maligno alterisati. Ipak, *Candida* specijes nije uvek izolovana iz oralne leukoplakije, tako da se njeno prisustvo smatra komplikacijom prisutnog stanja, a ne njegovim izazivačem⁴. Ovo stanje se može u dijagnozi zameniti sa lihen planusom, pemfigoidom, pemfigusom i karcinomom skvamoznih ćelija^{4,9}. Slične promene, poznate kao

tients who are terminally ill. Other conditions that can give rise to white patches in the mouth are lichen planus reticularis, squamous cell carcinoma, lichenoid reaction, leukoplakia, chemical damages, mechanical damages (biting of oral mucosa), linea alba, white sponge nevus, the second stage of syphilis, diphtheria^{1,2,4,9}.

Acute atrophic candidiasis (*Candidosis acuta atrophica*) is usually associated with a burning sensation in the mouth or on the tongue⁴. The tongue may be without papillae, and this situation is called „smooth antibiotic tongue“. In addition to tongue localisation, often are present diffuse enantema on the hard palate. The patient complains of symptoms of burning in the mouth and dryness, difficulty chewing and has problems with spicy food and fizzy drinks. This form of oral candidiasis is often associated with oral dryness⁹. In the differential diagnosis, a sore tongue should be considered especially in an older patient with dentures who has received antibiotic or cytostatic therapy or who is on inhaled steroids. A smear from the affected mucosa may help diagnosis⁴.

Chronic atrophic candidiasis (*Candidosis chronica atrophica*) also known as „denture stomatitis“ is characterised by localized chronic erythema of tissues covered by dentures. Lesions are usually localized to the hard palate and maxillary alveolar process, but can also be present on alveolar process of the mandible. Patients complain of burning symptoms when wearing dentures. Proper diagnosis requires removal of dentures, careful inspection and swab taking. The presence of oral candidiasis is confirmed in 65% of denture stomatitis^{1,2,4,10}.

Chronic nodular (hyperplastic) candidiasis (*Candidosis chronica hyperplastica*) characteristically occurs on the buccal mucosa or lateral border of the tongue as speckled or homogeneous white plaques surrounded by enanthema that cannot be wiped away^{1,2}. This type of candidiasis is associated with smoking, and complete resolution depends upon cessation of smoking. The condition is also called „Candidal leukoplakia“ and can progress to severe dysplasia and malignancy. However, species of *Candida* are not always isolated from oral leukoplakia lesions so its presence is considered a complication of the present situation rather than a causative factor⁴. This condition may be confused with lichen planus, pemphigoid, pemphigus, and squamous cell carcinoma^{4,9}. Similar changes, known as the Hyperplasia palati duri papillaris are seen in patients who have a high palate, and do not wear dentures. Clinically,

Hyperplasia palati durii papilaris vide se kod pacijenata koji imaju visoko nepce, a ne nose proteze. Klinički se vide brojni mali sferični nodulusi, koji su obično crvene boje⁹.

Hronična mukokutana kandidijaza je heterogena grupa kliničkih simptoma koju karakterišu promene na koži, noktima i sluzokožama. Bolest počinje u detinjstvu i obično je udružena sa brojnim imunološkim abnormalnostima u sklopu ćelijskog imuniteta. Oralne lezije su slične onima u pseudomembranoznoj formi, a kasnije mogu biti nodularne. Lezije su generalizovane, ali postoje i predilekciona mesta, kao što komisura usana, bukalna sluzokoža, jezik, nepce i usne, sa tendencijom širenja ka orofarinksu i ezofagusu. Kožne i nokatne lezije mogu biti udružene sa oralnim promenama i klinički se različito manifestuju⁹.

Medijalni romboidni glosit je hronična promena na dorzalnoj površini jezika ispred opšanih papila na kojoj su atrofirale filiformne papile. U više od 85% slučajeva biopsijom ovog područja izoluje se *Candida* specijes. Smatra se da je u vezi sa pušenjem i inhalacijom kortikosteroida^{1,2,4,9}.

Angularni heilit se vidi kao crvena fisura na jednom ili oba ugla usana. Obično je povezan sa intraoralnom kandidijazom, ali i drugi mikroorganizmi mogu biti izazivači, kao što su stafilokoke i streptokoke. Kod starijih osoba, usled produbljivanja bora u uglovima usana i duž nazolabijalnog nabora, dolazi do stalnog vlaženja i lakšeg razvitka promena. Promene su teže kod osoba koje duži niz godina nose zubne proteze usled resorpcije alveolarnog grebena i sniženja vertikalne dimenzije lica^{1-3,9}.

Dijagnoza

Dijagnoza kandidijaze postavlja se kliničkim pregledom, direktnim mikroskopskim pregledom uzoraka sa lezija ili kulturom na specijalnim podlogama. Hronične forme zahtevaju patohistološko ispitivanje¹¹.

Terapija

Za pravilnu terapiju bitno je uzimanje adekvatne istorije bolesti, identifikacija i korekcija provocirajućih faktora. Nakon kliničke i laboratorijske identifikacije izazivača, primenjuju se

numerous small spherical nodules can be seen, usually red in color⁹.

Chronic mucocutaneous candidiasis is a heterogeneous group of clinical symptoms, characterized by lesions on the skin, nails and oral mucosa. The disease begins in childhood and is usually associated with a number of immunological abnormalities in the cellular immunity. Oral lesions are similar to those in pseudomembranous candidiasis, but later may be nodular. The lesions are generalized, but there are some predilection sites like lip commissure, buccal mucosa, tongue, palate and lips with a tendency to spread to the oropharynx and esophagus. Skin and nail lesions may be associated with oral changes and may be clinically manifested differently⁹.

Median rhomboid glossitis is a chronic symmetrical area on the dorsal surface of the tongue in the front of circumvallate papillae. In more than 85% of the area biopsy, *Candida* species are confirmed. It is believed to be associated with smoking and the use of inhaled steroids^{1,2,4,9}.

Angular cheilitis is a red fissuring on one or both corners of the mouth. It is usually associated with interoral candidiasis, and other microorganisms can be the cause, such as staphylococci and streptococci. In the elderly people due to the facial wrinkling at the corners of the mouth and along the nasolabial folds a constantly moisturized environment is created, which further favors the infection. The changes are more severe in long term denture wearers because there is resorption of bone on which the dentures rest leading to a reduction in vertical dimension of face^{1-3,9}.

Diagnosis

Diagnosis of candidiasis is done with clinical examination, direct microscopic examination of samples of lesions or cultivation on special media. Chronic forms require histopathological examination¹¹.

Treatment

For the proper treatment taking adequate history, identification and correction of provoking factors are necessary. After clinical and laboratory identification of causative pathogens good oral hygiene, tooth repair, appropriate an-

dobra oralna higijena, sanacija zuba, adekvatni antifungalni lekovi (lokalni ili sistemski) i dezinfekcija zubnih proteza¹²⁻¹⁷.

Održavanje adekvatne oralne higijene i lokalna primena antifungalnih lekova u najvećem broju slučajeva dovoljni su za terapiju nekomplikovane oralne kandidijaze. Održavanje oralne higijene obuhvata svakodnevno čišćenje zuba, obrazne sluzokože, jezika i zubnih proteza. Zubne proteze treba skidati noću ili minimum 6 sati u toku dana. Protezu treba potopiti u rastvor za održavanje zubnih proteza, kao što je hlorheksidin^{3,18-20}. Na ovaj način se eliminiše više *Candida* sa proteze nego samo četkanjem, jer je protezna površina neravna i porozna, pa *Candida* lako adherira i samo četkanjem se ne može ukloniti. Zatim, proteze treba isprati običnom vodom, jer ih hlorheksidin može prebojiti, a zatim osušiti na vazduhu, čime se dodatno uništava na njima adherirana *Candida*^{15,16}. Pre ispiranja usta antifungalnim rastvorom, neophodno je skinuti zubne proteze kako bi lek delovao i na nepčanu sluzokožu. Lek treba podržati u ustima nekoliko minuta. Rastvor nistatina i hlorheksidina ne bi trebalo koristiti zajedno, jer se međusobno inaktiviraju. Za vreme dok se usta ispiraju antifungalnim rastvorom proteze treba potopiti u rastvor hlorheksidina^{4,15,16}.

Lokalna antifungalna terapija se uvek preporučuje kao prva terapija u slučaju nekomplikovane oralne kandidijaze. Lokalnom aplikacijom leka izbegavaju se sistemski sporedni efekti i interakcija sa drugim lekovima. U slučaju da je neophodno primeniti i sistemsku terapiju, lokalna aplikacija se nastavlja, jer se na ovaj način smanjuje doza i vreme sistemske aplikacije leka. Ranijih godina dvadesetog veka lek izbora bila je gencijana violet, ali zbog sporednih efekata (kao što je prebojavanje oralne mukoze) zamenjena je nistatinom i amfotericinom B. Oni se ne resorbuju iz gastrointestinalnog trakta i lokalno deluju u usnoj duplji. Nistatin je načešće lokalno korišćen lek u terapiji oralne kandidijaze³. Nalazimo ga u obliku lingvaleta i rastvora. Kao rastvor koristi se četiri puta dnevno u trajanju od dve nedelje ili duže. Od sporednih efekata može izazvati mučninu, povraćanje i proliv. Rastvor sadrži saharozu, pa je pogodan kod bezubih pacijenata i pacijenata sa oralnom suvoćom kao što su pacijenti na zračnoj terapiji ili sa HIV-om³.

antifungal drugs (local or systemic) and disinfection of removable intraoral dental prostheses should be applied¹²⁻¹⁶.

Oral hygiene and topical antifungals are usually adequate for uncomplicated oral candidiasis. Oral hygiene involves cleaning the teeth, buccal cavity, tongue, and dentures, if present, daily. Dentures should be left out overnight or for at least six hours daily. The dentures should be soaked in a denture cleaning solution such as chlorhexidine^{3,18-20}. This is more effective in eliminating candida than brushing because dentures have irregular and porous surfaces to which candida easily adheres and brushing alone cannot remove them. Afterwards, dentures should be rinsed with water because Chlorhexidine can discolour them, and afterwards dentures should be allowed to air dry as this also kills adherent candida on dentures^{15,16}. When rinsing the mouth with the topical antifungal, dentures should be removed to allow contact between the mucosa and the antifungal. The patient should held antifungal in the mouth for a few minutes. Combining nystatin with chlorhexidine solution inactivates both drugs. Therefore, this combination should not be used. The dentures should be removed each time the mouth is rinsed with the oral antifungal preparation and the dentures should be soaked in chlorhexidine solution^{4,15,16}.

Topical antifungal therapy is the recommended first line treatment for uncomplicated oral candidiasis. The systemic adverse effects and drug interactions that occur with the systemic agents do not occur with topical agents. Where systemic treatment is needed, topical therapy should continue as this reduces the dose and duration of systemic treatment required. In the early 20th century, the treatment of choice was gentian violet, however, due to resistance development and side effects (such as staining of the oral mucosa), it was replaced by nystatin and amphotericin B. They are not absorbed from the gastrointestinal tract and are locally applied in the mouth. Nystatin is the most widely used topical agent for the treatment of oral candidiasis. It is available as an oral pastille and suspension³. It should be used as a rinse four times a day for two weeks or longer. It can cause nausea, vomiting, and diarrhoea. The oral rinse contains sucrose and is useful in edentulous patients and those with oral dryness such as patients receiving radiotherapy and those with HIV infection³.

Systemic antifungal therapy in oral candidiasis is appropriate in patients intolerant of or refractory to topical treatment and those at

Sistemska terapija oralne kandidijaze primenjuje se kod pacijenata koji su netolerantni ili ne reaguju na lokalnu terapiju i kod pacijenata koji su pod povećanim rizikom za razvitak sistemske kandidijaze. Rastvor nistatina i tablete klotrimazola sadrže visok nivo sahara i u slučaju povećanog rizika od karijesa, postojanja diabetes mellitusa, upotrebe kortikosteroida, primenjuju se triazoli jednom dnevno (flukonazol, itakonazol). Kod imunokompromitovanih pacijenata koji imaju kandidijazu koja je rezistentna na flukonazol, primenjuje se itakonazol zbog svog šireg spektra dejstva. Ketokonazol je takođe efikasan kao i flukonazol, ali se njegova primena ne preporučuje kod starijih osoba zbog interakcija sa drugim lekovima i sporednih efekata kao što je hepatotoksičnost^{3,17}.

Antifungalni lekovi novije generacije koji se koriste u terapiji oralne kandidijaze i invazivnih gljivičnih infekcija su posakonazol, ravukanazol i ehinokandins kao što su Caspofungin, Micafungin i Anidulafungin²¹. Oni predstavljaju manje toksične alternative u odnosu na amfotericin B. Posakonazol je 2006. godine odobren za upotrebu kod invazivnih infekcija kao što su aspergiloza i kandidijaza. Ravukanazol je visokoefikasan kod mnogobrojnih gljivičnih infekcija, uključujući kandidijazu i primenjuje se u terapiji ezofagalne kandidijaze kod pacijenata sa HIV-om. Caspofungin ima inhibitoran efekat na Aspergillus i Candida specijes. Micafungin je visokoefikasan u terapiji ezofagalne kandidijaze i pokazao je manje sporednih efekata u odnosu na Caspofungin. Anidulafungin je najnoviji ehinokandin i in vitro je pokazao visoku efikasnost protiv Candide specijesa^{3,22,23}.

Novija istraživanja u oblasti terapije oralne kandidijaze sugerišu upotrebu probiotskih bakterija, za koje je već poznato da smanjuju rast patogenih mikroba^{3,24}. Takođe, uočeno je smanjenje rasta Candide upotrebom amin fluorida u vodicama za ispiranje u kombinaciji sa pastama za zube^{3,25}.

Profilaksa

Profilaksa antifungalnim lekovima kod pacijenata koji se leče od malignih oboljenja smanjuje incidenciju oralne kandidijaze. Uočeno je da je u ovim slučajevima flukonazol efikasniji od lokalne primene antifungalnih lekova.

high risk of developing systemic infections. Both nystatin oral rinses and clotrimazole troches have a high sucrose content and if tooth decay is a concern, oral candidiasis complicated by diabetes, steroid use or an immunocompromised state, triazoles (fluconazole, itraconazole) once per day have been found to be effective in these cases. Itraconazole has a wider spectrum of activity than fluconazole and is therefore valuable in salvage treatment of the immunocompromised patients with fluconazole resistant candidosis. Ketoconazole is also as effective as fluconazole and itraconazole but its use in elderly patients is not recommended due to drug interactions and side effects, which include hepatotoxicity^{3,17}.

Antifungal drugs of new generation used in the treatment of oral candidiasis and invasive fungal infections are Posaconazole, Ravucanazole, and Echinocandins such as Caspofungin, Micafungin, and Anidulafungin²¹. They are less toxic alternatives to Amphotericin B. Posaconazole was approved in 2006 for the treatment of invasive Aspergillosis and Candida infections. Ravucanazole is highly effective against many fungal infections, including candidiasis and has been used in the treatment of esophagus candidiasis in HIV (human immunodeficiency virus) patients. Caspofungin has inhibitory effects against various Aspergillus and Candida species. Micafungin is highly effective in the treatment of esophageal thrush and showed fewer side effects compared to Caspofungin. Anidulafungin is the newest echinocandin and appears to be very effective against Candida species in vitro^{3,22,23}.

Recent research in the field of treatment of oral candidiasis advise the use of probiotic bacteria which are known to reduce the growth of pathogenic microbes^{3,24}. The reduction of Candida overgrowth with the use of an amine fluoride in mouth rinse and toothpaste combination was noticed^{3,25}.

Prophylaxis

Prophylaxis with antifungal agents reduces the incidence of oral candidiasis in patients with cancer undergoing treatment and fluconazole has been found to be more effective than topical polyenes. Also, prophylaxis with antifungals reduces the incidence of oral candidiasis in patients with HIV. The use of a chlorhexidine rinse only in bone marrow transplant patients as prophylaxis was found to be very effective.

Takođe, profilaksa antifungalnim lekovima smanjuje incidenciju oralne kandidijaze kod pacijenata sa HIV-om. Profilaksa rastvorom hlorheksidina pokazala se efikasnom jedino kod pacijenata sa transplantacijom kostne srži.

Prognoza

Uz adekvatnu terapiju, prognoza oralne kandidijaze je veoma dobra kod imunokompetentnih pacijenata. Recidiv oboljenja je najčešće posledica slabe saradnje pacijenta, neadekvatnog čišćenja proteza i njihovog stalnog nošenja ili usled nemogućnosti eliminisanja predisponirajućih faktora rizika.

Zaključak

Oralna kandidijaza je oportunistička infekcija u usnoj duplji, često nedijagnostikovana kod starijih osoba, a pogotovo kod osoba koje nose zubne proteze. Može biti znak postojanja sistemskog oboljenja, a njena učestalost je u stalnom porastu zbog sve većeg broja imunokompromitovanih pacijenata, pa je od velikog značaja njeno blagovremeno otkrivanje i adekvatno lečenje, koje smanjuje mogućnost nastanka komplikacija i progresije oboljenja, a značajno unapređuje kvalitet života pacijenata.

Prognosis

With adequate treatment the prognosis is good for oral candidiasis in immunocompetent patients. Relapse is most commonly the consequence of poor compliance with therapy, failure to remove and clean dentures appropriately, or inability to resolve the predisposing factors to the infection.

Conclusions

Oral candidiasis is an opportunistic infection in the mouth often undiagnosed in the elderly, especially in people who wear dentures. It can be a sign of underlying systemic disease, and its incidence is increasing due to the growing number of immunocompromised patients. Of great importance is the timely diagnosis and treatment which reduce the possibility of complications, disease progression and significantly improve the quality of life of patients.

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