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MEDICINSKI ZNAČAJ PROTOZOA USNE DUPLJE U STOMATOLOŠKOJ PRAKSI

ORAL CAVITY PROTOZOA RELEVANT IN THE PRACTICE OF DENTISTRY

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Sažetak

Uvod: *Usna duplja čoveka je mesto za kolonizaciju najraznovrsnijih mikroorganizama u organizmu ljudi. Brojni faktori mogu uticati na homeostazu oralnog mikrobioma. Parodontalne bolesti nastaju usled poremećene homeostaze oralnog mikrobioma i odbrane domaćina, kada dolazi do inflamatorne reakcije, koja zahvata tkivo parodoncijuma. Uticaj parazita na patofiziologiju parodoncijuma još uvek nije dovoljno proučen, pa bi sadašnja i naredna naučna istraživanja trebalo da daju brojne odgovore.*
Cilj rada: *U svetlu sadašnjih saznanja vezanih za patogenezu, dijagnostiku i epidemiologiju infekcija oralne duplje uzrokovanih vrstama protozoa Entamoeba gingivalis i Trichomonas, cilj rada je da se kroz pregled literature ukaže na značaj protozoa u stomatološkoj praksi, kao i na moguće manifestacije parazitskih infekcija od značaja za javno zdravlje, koje se mogu ispoljiti i u usnoj duplji.*
Zaključak: *Stomatolozi imaju bitnu ulogu u dijagnozi oralnih oboljenja uzrokovanih protozoama usne duplje, kao i protozoa bitnih za javno zdravlje, koje daju sistemske infekcije, a patološke promene mogu se ispoljiti i u usnoj duplji. Njihovo dijagnostikovanje je svakako veliki izazov i zahteva multidisciplinarni pristup, u cilju što brže dijagnoze i adekvatnog lečenja.*

Ključne reči: *usna duplja, protozoe, parodontalne bolesti, lajšanijaza, toksoplazmoza*

Abstract

Introduction: *Oral cavity is the colonization site of most diverse microorganisms. The homeostasis of oral microbioma is affected by numerous factors. Periodontal diseases occur as a consequence of disturbed oral microbioma homeostasis, when an inflammatory reaction occurs in the periodontal tissue. The impact of parasites on periodontal pathophysiology has not been sufficiently studied, and present and future research should hopefully answer quite a few questions concerning the issue.*
Aim of the paper: *In the light of the present knowledge of the pathogenesis, diagnosis and epidemiology of oral cavity infections caused by Entamoeba gingivalis and Trichomonas tenax, the aim of the paper was review of literature which could to point to the importance of protozoa in the practice of dentistry and to possible oral cavity manifestations of parasitic infections relevant for public health.*
Conclusion: *Dentists have an essential role in the diagnosis of oral diseases caused by oral cavity protozoa, and protozoa relevant for public health that produce systemic infections, the pathological changes of which may manifest in the oral cavity. Their identification represents a challenge and requires multidisciplinary approach for a timely diagnosis and adequate management.*

Key words: *oral cavity, protozoa, periodontal diseases, leishmaniasis, toxoplasmosis*

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Uvod

Usna duplja čoveka je mesto za kolonizaciju najraznovrsnijih mikroorganizama u organizmu ljudi. Ova kolonizacija može uključivati različite endogene i egzogene vrste, koje formiraju oralni biofilm na površinama sluzokože usne duplje i zuba. Vrste su strukturno i funkcionalno organizovane u polimikrobne zajednice sa složenim međusobnim odnosima između određene oralne mikrobiote i organizma domaćina. Mnogi biotički i abiotički faktori mogu promeniti labilnu homeostazu oralnog mikrobioma[1,2,3]. Termin mikrobiom koristi se za označavanje ekološke zajednice komensalnih, simbiotskih i patogenih mikroorganizama. Oralni mikrobiom / oralna mikrobiota / oralna mikroflora predstavljaju mikroorganizme, koji se nalaze u ljudskoj usnoj duplji, koji čine bakterije, gljive, eukariote i virusi[4,5].

Parodontalne bolesti (gingivitis i parodontopatija) su rezultat poremećaja homeostaze oralnog mikrobioma i domaćina koje karakteriše inflamatorna reakcija koja zahvata tkivo parodoncijuma[6]. Nova klasifikacija parodontopatija obuhvata tri forme: (1) parodontitis, (2) nekrotizirajući parodontitis, (3) parodontitis kao direktna manifestacija sistemskih bolesti. Na osnovu opisa (lokalizovanog ili generalizovanog), težine i složenosti lečenja utvrđena su tri stadijuma: početni parodontitis (I stadijum), umereni parodontitis (II stadijum), teški parodontitis sa potencijalom za dodatni gubitak zuba (III stadijum) i uznapredovali parodontitis sa ekstenzivnim gubitkom zuba i potencijalom gubitka denticije (IV stadijum). Prema ovoj klasifikaciji, parodontitis može imati tri nivoa progresije (A - spora, B - umerena i C - brza) [7]. Višedimenzionalni sistem faza i stepena je osmišljen kako bi se opisale različite manifestacije parodontitisa u pojedinačnim slučajevima. Faze opisuju težinu i obim bolesti, stepeni opisuju verovatnu stopu progresije[7]. Kliničke karakteristike parodontalnih bolesti su: recesija desni, destrukcija alveolarne kosti, gubitak parodontalnih ligamenata povezanih sa pojavom parodontalnih džepova i naslagama zubnog kamenca[8]. Parodontalne bolesti promovišu uspostavljanje mikrookruženja koje omogućava rast anaerobnih mikroorganizama[9], migraciju mikroorganizama u tkiva, narušava imunski odgovor, izazivajući resorpciju parodoncijuma[10,11].

Introduction

Oral cavity is the colonization site of most diverse microbiomes in the human organism. Various endogenous and exogenous species may be involved, forming an oral biofilm on the mucosal surfaces of the oral cavity and teeth. The species are structurally and functionally organized in polymicrobial communities, with complex relationships existing between oral microbiota and the organism of the host. Many biotic and abiotic factors are capable of changing the unstable balance of oral microbiome[1,2,3]. The term microbiome is used to denote an ecological community of commensal, symbiotic and pathogenic microorganisms. Oral microbiome/oral microbiota/oral microflora consists of microorganisms that reside in the human oral cavity and comprises bacteria, fungi, eukaryotes and viruses[4,5].

Periodontal diseases (gingivitis and periodontitis) represent the result of disturbed host oral microbiome homeostasis, characterized by an inflammatory reaction involving the periodontal tissue[6]. The new classification of periodontitis includes the three following forms: (1) periodontitis, (2) necrotizing periodontitis, (3) periodontitis as a direct manifestation of systemic diseases. Based on the extent of the disease (localized or generalized), severity, and complexity of management,the three stadiumsare defined as follows: early periodontitis (I stadium); moderate periodontitis (II stadium); severe periodontitis, with the potential for added loss of teeth (III stadium); and advanced periodontitis, with extensive loss of teeth and potential loss of dentition (IV stadium). According to this classification, periodontitis is characterized by three levels of progression (A - slow, B - moderate and C - rapid)[7]. A multidimensional system of stages and grades has been devised to further describe the different manifestations of periodontitis in individual cases. Stages describe the severity and the extent of the disease, grades describe the likely rate of progression[7]. Clinical characteristics of periodontal diseases involve gingival recession, destruction of the alveolar bone, and loss of periodontal ligaments associated with the development of periodontal pockets and with dental plaque depositions[8]. Periodontal diseases favor the creation of an anaerobic microenvironment, which further enables the growth of anaerobic microorganisms[9], migration of microorganisms into tissues, and disrupts the immune response causing periodontal resorption[10,11].

Utvrđeni su i neki faktori rizika domaćina za nastanak parodontalnih bolesti, kao što su pušenje i *Diabetes mellitus*[12-14], ali i druge bolesti i stanja (dati u pregledu literature)[15-17].

Dok je patološka uloga nekih specifičnih bakterijskih sojeva tokom parodontalnih bolesti dobro dokumentovana, uticaj parazita na patofiziologiju parodoncijuma još uvek nema čvrste dokaze[18].

Parazit je patogeni organizam koji živi na račun domaćina i usled patogenog dejstva dovodi do razvoja bolesti kod domaćina. Patogenost je sposobnost parazita da prodre u organizam domaćina, održi se, razmnožava, oštećuje tkiva i remeti funkcije organizma i, u manjoj ili većoj meri aktivira imunski sistem domaćina. Proučavanjem medicinski značajnih protozoa, helminata i artropoda bavi se zooparazitologija (pripadnici carstva protisti i carstva animalia)[19]. Paraziti imaju složene životne cikluse, prolaze kroz nekoliko faza razvoja u životnom ciklusu i pri tom dolazi do morfoloških, strukturnih, biohemijskih i antigenskih promena samog parazita, što dovodi i do različitih kliničkih manifestacija i posledica po samog domaćina. U toku životnog ciklusa paraziti mogu imati i više domaćina, a mnoge parazitske infekcije prenose se sa životinja na ljude (zoonoze)[19]. Humane parazitske infekcije su brojne i mogu biti bez ikakvih kliničkih manifestacija, mogu biti blagog toka, čak bezazlene, ali isto tako mogu da dovedu i do fatalnog ishoda. Iako su najčešće prisutne u siromašnim sredinama, od parazitoza nisu pošteđeni ni ljudi u ekonomski razvijenim zemljama[19].

Parazitološka dijagnostika podrazumeva korišćenje konvencionalnih dijagnostičkih mikroskopskih metoda (nativni i trajno obojeni preparati), koje se zasnivaju na analizi morfoloških i morfometrijskih karakteristika parazita. Na osnovu ovih parametara teško je izvršiti preciznu dijagnostiku do nivoa vrste. Osetljivost trofozoita u spoljašnjoj sredini i neophodnost brzog dostavljanja uzorka, priprema preparata i brza identifikacija parazita često nisu u rutinskom radu ispoštovane pa je broj pozitivnih nalaza na protozoe iz usne duplje mali. Metode kultivacije ne koriste se u rutinskom radu i rezervisane su za referentne i naučnoistraživačke laboratorije. Novi alati molekularne biologije i genomske analize omogućile su detekciju i identifikaciju već poznatih, ali i „novih“ mikrobiota u mnogo većem broju, ali još uvek nisu deo rutinskog rada, već se koriste u naučno istrživačkom radu[19].

Host-related risk factors for periodontal diseases, such as *diabetes mellitus* and smoking[12–14] have also been established, along with other diseases and conditions included in the reference numbers[15–17].

While the pathological role of some specific bacterial species in periodontal diseases has been well documented, the impact of parasites on the pathophysiology of the periodontium has not been firmly established[18]. A parasite is a pathogenic organism living at the expense of its host and often produces a disease in the host organism. Pathogenicity is the parasite's ability to infest the host, and to survive, replicate, damage the tissues and disturb the functions in the host organism, activating to a lesser or greater extent the immune system of the host. Zooparasitology studies medically relevant protozoa, helminths and arthropods (members of the kingdom Protista and kingdom Animalia)[19]. Parasites have complex life cycles, with several different developmental stages;during the development,they undergomorphological, structural, biochemical and antigenic changes, which produces different clinical manifestations and consequences in their hosts. During their life cycle, parasites can infest different hosts, and many parasitic infections are transmitted from animals to human beings (zoonoses)[19]. Human parasitic infections are numerous. They may progress without any clinical manifestations, or they are associated with a mild clinical course, but they may produce a fatal outcome as well. Although they are present mostly in poor social environments, the people living in well developed countries are not spared either[19].

Parasitology diagnosis involves using conventional diagnostic microscopy methods (native and permanently stained preparations) based on the morphological and morphometric parasite characteristics. Based on these parameters it is difficult to precisely diagnose the parasite to the level of species. Trophozoite sensitivity in open air is often overlooked, and the necessity for rapid sample delivery, sample preparation and immediate parasite identification are not always well observed and performed in routine work; the number of positive findings of protozoa in the oral cavity is thus rather low. The methods of cultivation are not used in routine work - these are reserved for reference and research laboratories. The new tools of molecular biology and genomic analysis have made possible the detection and identification of even greater numbers of already known and „new“ microbiota, but are still not used routinely; they are used mostly in research work[19].

Cilj rada je da se kroz pregled literature ukaže na medicinski značaj protozoa, kao uzročnika infekcije oralne duplje u svetlu sadašnjih saznanja, vezanih za patogenezu, dijagnostiku i epidemiologiju vrsta *Entamoeba gingivalis* i *Trichomonas tenax,* kao i na moguće simptome i znake parazitskih infekcija uzrokovanih protozoama *Leishmania sp. i Toxoplasma gondii,* koje se mogu ispoljiti i u usnoj duplji i predstavljati veliku nepoznanicu i dijagnostičku dilemu u ordinaciji lekara stomatologa.

Entamoeba gingivalis

Entamoeba gingivalis (Gros, 1849; Brumpt, 1913.) je protozoa, komensal usne duplje ljudi, koja postoji samo u vegetativnoj formi (trofozoit – aktivni stadijum sposoban za metaboličke procese, deobu i kretanje). Trofozoiti *Entamoeba gingivalis (E. gingivalis)* ne preživljavaju izvan tela domaćina. Ova vrsta taksonomski pripada razredu Lobosea, familiji Entamoebidae, rodu Entamoeba gde pripada i patogena vrsta *E. haestolyticae* uzročnik amebijaze[19,20].

Trofozoit *E. gingivalis* je morfološki sličan trofozoitu *E. histolytica*, patogenoj protozoi digestivnog trakta. Neophodno je praviti razliku između njih, budući da se obe vrste mogu naći u uzorcima sputuma (*E. histolytica* ako je prisutna u plućnim apscesima u slučajevima invazivne, sistemske amebijaze). Veličina trofozoita kreće se od 5 μm do 30 μm, mada je uobičajena veličina od 10 μm do 20 μm. Trofozoit se diferencira na spoljašnju, providnu ektoplazmu i unutrašnju zrnastu endoplazmu. U periodu mirovanja, ektoplazma je jedva vidljiva, ali tokom perioda kretanja izgleda kao debeo sloj, koji čini oko polovine zapremine aktivno pokretne amebe[19]. Endoplazma je zrnasta, sadrži vakuole i obično je prepuna plutajućih čestica hrane. Vakuole sadrže zaobljena, tamno obojena tela, poreklom uglavnom iz jedara degenerisanih epitelnih ćelija, limfocita i povremeno leukocita, bakterija i bez prisustva eritrocita. *E. gingivalis* je „čistač" dezintegrisanih ćelija i bakterije nisu veliki izvor ishrane za njih. U endoplazmi se nalazi jedno malo, sferično jedro (nucleus), gotovo neupadljivo. Unutar jedra je prisutan centralni ili ekscentrični kariozom iz kojeg se fibrile zrakasto protežu do perifernog prstena. Umereno debela nuklearna membrana sadrži nepravilno raspoređen hromatin. Parazit se kreće formiranjem ektoplazmatskih pseudopodija i reprodukuje se binarnom fisijom[19].

The aim of the paper was to point out the medical significance of protozoa as the causes of oral cavity infections in the light of current knowledge of pathogenesis, diagnosis and epidemiology of the species *Entamoeba gingivalis* and *Trichomonas tenax*, as well as the possible symptoms and signs of parasitic infections caused by the protozoa *Leishmania sp.* and *Toxoplasma gondii* that may manifest in the oral cavity, presenting practising dentists with considerable diagnostic dilemmas.

Entamoeba gingivalis

Entamoeba gingivalis (Gros, 1849; Brumpt 1913) is a protozoan and a commensal in human oral cavity, existing only in its vegetative form (trophozoite is an active parasite stage, with metabolic processes, division and motility). *E. gingivalis* trophozoites cannot survive outside the host organism. Taxonomically, this species belongs to the class Lobosea, family Entamoebidae, genus Entamoeba, where also belongs the pathogenic species *E. haestolyticae*, the cause of amebiasis[19,20].

E. gingivalis trophozoite is morphologically similar to *E. haestolytica* trophozoite, a pathogenic protozoan of the digestive tract. It is necessary to differentiate between the two, since both species can be found in sputum specimens (*E. haestolytica* is encountered in the sputum if it is present in a pulmonary abscesses in the cases of invasive, systemic amebiasis). The size of trophozoites ranges from 5 μm to 30 μm, although it usually measures 10–20 μm. A trophozoite can be differentiated into outer, transparent cytoplasm, and inner, granular endoplasm. In the period of dormancy, the ectoplasm is barely visible, but in the period of motility it appears as a thick layer making up around half of the volume of an actively moving ameba[19]. The endoplasm is granular, contains vacuoles and is usually filled with floating food particles. The vacuoles contain round, dark stained bodies, originating mostly from the nuclei of degenerated epithelial cells, lymphocytes and at times leukocytes, bacteria, without the presence of erythrocytes. *E. gingivalis* is the „cleaner" of disintegrated cells and bacteria do not constitute a large food source for them. In the endoplasm, there is a small, spheric, almost completely inconspicuous nucleus. Within the nucleus, there is a central or eccentric karyosome, from which fibrils radiate towards the peripheral ring. Moderately thick nuclear membrane contains irregularly distributed chromatin. The parasite moves by forming ectoplasmic pseudopodia and replicates by binary fission[19].

E. gingivalis može biti faktor rizika povezan sa oralnim oboljenjima, ali se još uvek ne zna njena uloga u patogenezi ovih poremećaja[21]. Loša oralna higijena, gingivitis, parodontopatija i koegzistirajuće sistemske bolesti mogu dovesti do porasta populacije ove protozoe u usnoj duplji[12-17]. Najčešća lokacija su parodontalni džepovi (anaerobni uslovi pogoduju kolonizaciji), potom sluzokoža gingive, sluzokoža palatinskih krajnika i mekog nepca[22]. Dugotrajna ekstenzivna oralna upala može povećati rizik od kardio-vaskularnih bolesti[23,24], reumatoidnog artritisa[25] i oralnog karcinoma[26].

Ukupna prevalencija *E. gingivalis* procenjena je na 37% (95% CI 29–46%), a najveća prevalencija *E. gingivalis* utvrđena u Jordanu (87%) (95% CI 81–92%), dok je najniža u Portugaliji sa 3% (95% CI 0–10%)[17]. Istraživanje Eke i sar. je pružili su dokaze o visokoj prevalenciji parodontopatije kod odrasle populacije starije od 30 godina u SAD (42,2%, a 7,8% sa težim oblicima parodontopatije). Rezultati istraživanja su pokazali da je povećana prevalencija umerenog tipa parodontopatije zavisna od godina života (stariji muškarci), etičke i manjinske pripadnosti, ekonomskog statusa (siromašnija populacija) i oralne higijene[27]. Slična situacija je i zemljama zapadne Evrope[28]. U cilju smanjenja prevalencije parodontopatije među populacijom starosti 45-74 godine u USA je i zakonom obavezujući skrining oralnog zdravlja kod starijih osoba. U sklopu inicijative Zdravi ljudi 2020. oralno zdravlje je jedan od indikatora za praćenje zdravlja nacije[29].

Primenom tehnika molekularne biologije identifikovani su različiti subtipovi u usnoj duplji. Kod osoba sa zdravim parodoncijumom *E. gingivalis* subtip 1 (ST1) se javlja u 48,6%, a *E. gingivalis* ST2 - varijanta kamaktli (89% identična *E. gingivalis* ST1) u 29,5%. Prisustvo *E. gingivalis* ST1 prijavljeno je u 57,8% kod osoba sa parodontalnom bolešću, dok je *E. gingivalis* ST2 – kamaktli varijanta prisutna je u 50,0%[30]. Rezultati Garcia i sar. pokazuju ga je ST1 *E. gingivalis* utvrđen kod 47,5% pacijenata na ortodontskom lečenju, dok je 73,8% imalo *E. gingivalis* ST2 – varijanta kamaktli što ukazuje na njihove genetske razlike i razlike u patogenosti[31].

Takođe, nedavno objavljeni rezultati pokazuju da *E. gingivalis* napada upaljenu i oštećenu oralnu sluzokožu, inhibira proli-feraciju ćelija, bez mogućnosti regeneracije oštećenog tkiva. Aktivacijom interleukina 8 dolazi do povećane migracije neutrofila, monocita i T limfocita, oslobađanje histamina iz bazofila, što još više pojačava upalni process[32].

E. gingivalis can be a risk factor associated with oral diseases, but its exact role in the pathogenesis of these disorders is still unknown[21]. Poor oral hygiene, gingivitis, periodontitis and coexisting systemic diseases may induce the growth of this protozoan's population in the oral cavity[12–17]. The most common localization are periodontal pockets (this anaerobic environment favors colonization), then gingival mucosa, mucosa of the palatine tonsils and soft palate[22]. A long-lasting, extensive oral inflammation may increase the risk for cardiovascular diseases[23,24], rheumatoid arthritis[25], and oral cavity carcinoma[26].

The overall prevalence of *E. gingivalis* has been estimated at 37% (95% CI 29–46%), with the highest prevalence rate reported in Jordan (87%) (95% CI 81–92%) and the lowest in Portugal (3%) (95% CI 0–10%)[21]. The study by Eke et al. presented evidence for a high prevalence rate of periodontitis in adults aged above 30 years in the USA (42.2%, and 7.8% with more severe forms of periodontitis). The results of the study suggested that the increased prevalence of moderate-type periodontopathy was dependent on the age (older males), ethnicity and minority status, socioeconomic status (poor population groups) and oral hygiene[27]. The situation is similar in Western European countries[28]. Oral health screening has been even regulated by law in the USA for older population groups (from 45–74 years of age), in an attempt at reducing the prevalence of periodontitis in these individuals. In the Healthy People 2020 initiative, oral health is one of the indicants in overall national health surveillance[29].

Utilizing the techniques of molecular biology, different subtypes have been identified in the oral cavity. In individuals with a healthy periodontium, *E. gingivalis* subtype 1 (ST1) occurs in 48.6%, and *E. gingivalis* ST2 - Kamaktli variant (89% identical to E. gingivalis ST1) in 29.5%. *E. gingivalis* ST1 presence was reported in 57.8% of individuals with periodontal disease, while *E. gingivalis* ST2 -Kamaktli variant, was present in 50.0%.30 The results by Garcia et al. showed that *E. gingivalis* ST1 was established in 47.5% of patients on orthodontic treatment, while 73.8% had *E. gingivalis* ST2 - Kamaktli variant, which indicated their genetic and differences in pathogenicity[31].

Further, some recently published data indicate that *E. gingivalis* attacks inflamed and damaged oral mucosa and inhibits cell proliferation, without any possibility for the damaged tissue to regenerate.

Oštećeno tkivo pogoduje daljem razvoju protozoa u usnoj duplji. Parodontopatija dovodi do ireverzibilnog oštećenja epitela i gubitka koštanog tkiva alveolarnog nastavka, što rezultira gubitkom zuba ili totalnom bezubošću. U slučaju komplikacija parodontopatije (parodontalni apsces, nekroza tkiva parodonta) javljaju se intezivni bolovi i neprijatan zadah. Kliničkim pregledom uočava se krvarenje, otok gingive i povećana pokretljivost zuba[33,34].

Studija Bao[32] i autora pokazala je virulentni potencijal *E. gingivalis*. Navedeni autori smatraju da se ovaj kolonizator oralne sluzokože ne može smatrati oportunističkim mikroorganizmom. Umesto toga, *E. gingivalis* treba posmatrati kao moćnog mikrobnog pokretača destruktivnih oblika parodontopatije čija je uloga uglavnom bila potcenjena. Zato bi stomatolozi trebalo da se postaraju da parodontalni džepovi i tkivo budu očišćeni od ove protozoe[32].

E. gingivalis se prenosi direktnim, odnosno, oralnim putem (ljubljenjem, korišćenjem zajedničkog pribora za održavanje oralne higijene i pribora za jelo, ali i putem kontaminiralne vode i hrane (indirektnim putem). Prevencija uključuje izbegavanje direktnih i indirektnih puteva prenošenja: korišćenje sopstvenog pribora za ličnu higijenu i pribora za jelo predhodno dobro opranog, kao i izbegavanje ljubljenja ako postoji rizik da osoba može biti nosilac *E. gingivalis*[22].

Trichomonas tenax

Trichomonas tenax (T. tenax) pripada grupi kosmopolitskih, anaerobnih Protista – flagelata koji izazivaju oralnu trihomonijazu. *T. tenax*, kao i njegova srodna vrsta, *Trichomonas vaginalis* (uzročnik genitalne trihomonijaze), svrstan je u kolo Parabasalia, razred Zoomastigophora, porodicu Trichomonadidae, rod Trichomonas[35]. Javlja se u obliku trofozoita ovalnog ili okruglog oblika i nema formu ciste. Približne je dužine od oko 15μm, ima 4 slobodne flagele na prednjem širem kraju koje polaze iz blefaroplasta. Peta flagela je povezana sa površinom ćelije formirajući talasastu (undulentnu) membranu. Paralelno sa ovom membranom nalazi se hromatofilna nit *(costa)* i aksostil koji daje čvrstinu parazitu. Ima jedno jedro sa endozomom koje je raspoređeno u prednjoj zoni, blizu tačke umetanja flagela. Trofozoit je vegetativni oblik koji se hrani putem fagocitoze i pinocitoze od ostataka hrane i bakterijama iz usne duplje; razmnožava se i predstavlja infektivnu formu parazita (nema formu ciste). Reprodukcija je uzdužnom binarnom podelom, bez polne reprodukcije[35].

Increased neutrophil, monocyte and T lymphocyte migration and histamine release from basophils occur via interleukin-8 activation, which further intensifies the process of inflammation[32]. The presence of damaged tissue favors continued development of protozoa in the oral cavity. Periodontitis induces irreversible damage to the epithelium and bone tissue loss in the alveolar processus, which results in tooth loss or total edentulousness. In case of periodontal disease complications (periodontal abscess, periodontal tissue necrosis), strong pains and halitosis could occur as well. Clinical examination typically reveals bleeding, swollen gums and increased teeth movement[33,34].

The study by Boa et al. demonstrated the virulent potential of *E. gingivalis*. These authors believed that this oral mucosa colonizer could not be considered an opportunistic microorganism. Instead, *E. gingivalis* should be thought of as a potent microbial inducer of destructive periodontitis forms, the role of which was mostly underrated. Practising dentists should therefore take care that inflamed periodontal pockets and tissue should be made and stay clean of this protozoan[32].

E. gingivalisis transmitted by direct, i.e. oral route (by kissing, using the same toothbrush, eating tools and kitchenware), but also by contaminated water and food (indirect route). The prevention involves avoidance of direct and indirect transmission routes: using one's own personal hygiene tools and eating tools, well washed before use, and avoidance of kissing if there is a risk of *E. gingivalis* carrier status[22].

Trichomonas tenax

Trichomonastenax(T. tenax) belongs to the group of cosmopolitan, anaerobic flagellate protists which cause oral trichomoniasis. *T. tenax,* as well as its kin species *Trichomonas vaginalis* (the cause of genital trichomoniasis) is classified in the phylum Parabasalia, classis Zoomastigophora, family Trichomonadida, and genus Trichomonas[35]. It occurs in the trophozoite form of oval or round shape and does not have a cyst form. It measures about 15 μm in length. It has four free flagella on its anterior, wider end, originating in the blepharoplast. The fifth flagellum is connected to the cell surface, forming a wavy, undulant membrane. In parallel to this membrane, there is a chromatophilic thread (costa) and axostil, giving firmness to the parasite. There is one nucleus, with an endosome, situated in the anterior zone, close to the point of flagella insertion.

Prvobitno je identifikovan kao bezopasni komensal koji živi u ljudskoj usnoj duplji i distribuira se između zuba, desni, jezika i pljuvačke ljudi sa lošom oralnom higijenom[36,37], a zatim kao parazit nađen u parodontalnim džepovima[38].

Konvencionalna detekcija i identifikacija *T. tenax* se najčešće vrši metodom svetlosne mikroskopije i kultavacije[39,40], pa zavisno od korišćene metode (najčešće mikroskopija) i geografskog područja ispitivanja, prevalencija *T. tenax* je u rasponu od 0 do 94,1%[18]. Sem u usnoj duplji, *T. tenax* nađen je u pljuvačnim žlezdama, limfnim nodusima i u respiratornom traktu[41-45]. Trihomonada je otkrivena i u usnoj duplji pacijenata sa oslabljenim imunitetom usled urođenih sistemskih bolesti, kao i na hroničnoj imunosupresivnoj terapiji, što ne isključuje njena oportunistička svojstva[1,46]. Primenom molekularnih metoda dijagnostike, utvrđeno je da je *T. tenax* značajno zastupljeniji kod pacijenata sa Daunovim sindromom koji imaju parodontalne lezije, u poređenju sa kontrolnom grupom pacijenata, sa neznatnom razlikom u indeksu plaka između dve grupe[47].

Na patogeni potencijal *T. tenax* ukazala su istraživanja koja su utvrdila proteolitička, a posebno kolagenolitička svojstva ove flagelate kod ljudi sa patološkim promenama u usnoj duplji[48]. Rezultati studija objavljenih poslednjih šezdeset godina o etiopatogenezi T. tenax još uvek nisu dovoljni da potvrde ulogu ove flagelate u nastanku bolesti, iako je utvrđeno: 1) da se *T. tenax* češće otkriva u oralnom biofilmu sa mesta sa parodonto-patijom nego na zdravim mestima; 2) da je sposoban da proizvede različite enzime koji bi mogli da učestvuju u parodontalnoj razgradnji i da ima sposobnost da se prilepi na epitelne ćelije (njegov lizirani oblik bi mogao da izazove sintezu IL-8); 3) da detaljnije analize prisustva flagelate u usnoj duplji nisu sprovedene nakon nehirurškog lečenja parodontopatije[49].

Pacijenti sa dijagnozom infekcije koju izaziva *T. tenax* najčešće imaju suva usta, sindrom pečenja u ustima, spontani bol i bol tokom gutanja, a intraoralnim pregledom mogu se uočiti parodontalni džepovi, glositis i hronična parodontopatija[49].

Nedavni rezultati sistematskog pregleda literature i meta analize pokazali su globalnu objedinjenu prevalenciju od 17% (95% CI 14–22%) infekcije uzrokovane *T. tenax*. Najveća prevalencija je procenjena na 56% (42–69%) u Čileu, dok je najniža prevalencija u Keniji sa 3% (1–6%). Analiza je pokazala da je infekcija najčešća u starosnoj grupi od 46 do 55 godina sa 15% (0-100%).

The trophozoite is a vegetative form feeding by phagocytosis and pinocytosis on food debris and bacteria present in the oral cavity; it replicates and represents the infective parasite form (without any cyst form). The reproduction occurs by longitudinal binary division, without any sex reproduction[35].

The parasite has been originally identified as a harmless commensal living in the human oral cavity distributed between the teeth, on the gums, tongue and in the saliva of individuals with poor oral hygiene[36,37], and then has been found as a parasite in periodontal pockets[38].

Conventional detection and identification of *T. tenax* is most commonly performed using the method of light microscopy and cultivation[39,40]. Depending on the methodology used (usually microscopy) and geographic area, the prevalence of *T. tenax* ranges from 0% to 94.1%[18]. In addition to the oral cavity, *T. tenax* has been found in salivary glands, lymph nodes and respiratory tract[41-45]. The trichomonad has also been detected in the oral cavity of patients with a weak immunity due to congenital systemic diseases, as well as in those on chronic immunosuppressive therapy, which does not exclude its opportunistic characteristics[1,46]. Using the molecular diagnostic methods, it has been established that compared to controls, *T. tenax* is significantly more prevalent in patients with Down syndrome who have periodontal lesions, with a negligent difference in the plaque index between the groups[47].

The pathogenic potential of *T. tenax* has been stressed in the studies which have established proteolytic, and especially collagenolytic potentials of this flagellate in people with oral cavity pathologies[48]. The results of the studies of etiopathogenesis of *T. tenax* published in the last sixty years are still insufficient to confirm the role of this flagellate in the development of disease, although the following has been established: 1) *T. tenaxis* more frequently identified in the oral biofilm from the sites affected by periodontitis than from healthy localizations; 2) *T. tenax* has the ability to attach to epithelial cells (its lysed form could induce IL-8 synthesis); 3) more detailed analyses of the flagellate presence in the oral cavity have not been done after a non-surgical treatment of periodontitis[49].

Patients with the diagnosis of an infection caused by *T. tenax* usually have dry mouth, burning mouth syndrome, experience spontaneous pain and pain when swallowing, and an intraoral inspection may reveal the presence of periodontal pockets, glossitis and chronic periodontitis[50].

Ukupna prevalencija zavisno od primenjenih dijagnostičkih procedura identifikacije parazita (mikroskopija, kultivacija, molekularne metode) bila je 21% (12–32%), 19% (8–35%) i 17% (12–23%). Analiza podgrupa je pokazala prevalenciju *T. tenax* kod pacijenata sa kandidozom [22% (3–52%)], gingivitisom [21% (9–36%)] i parodontopatijom [27% (10–48%)[51].

Visoka heterogenost parodontalne prevalencije *T. tenax* može biti u korelaciji sa neusaglašenim skriningom populacije u pogledu uzrasta, pola, postojanja neke sistemske bolesti i metodama koje se koriste za parazitološku dijagnozu. Molekularne dijagnostičke tehnike za otkrivanje i identifikaciju vrsta roda Trichomonas, kao što su amplifikacija i sekvencioniranje genoma, pouzdan su alat za brzu i specifičnu karakterizaciju trihomonada[1]. Svakako, eksperimentalni modeli na životinjama, korišćenjem relevantnih fiziopatoloških modela parodontopatije, neophodni su da bi se ispitala sposobnost *T. tenax* da izazove i/ili pogorša bolest, kao i standardizovane eksperimentalno dizajnirane epidemiološke studije[18].

Kolonizacija usne duplje *T. tenax* se češće javlja kod starijih osoba i retko kod dece (kao i *E. gingivalis*). Put prenosa je pljuvačka i infekcija se može desiti direktno, poljupcem, ili indirektno, kontaktom preko pribora za jelo, ličnu higijenu sl., odnosno s bilo čim što može imati tragove zaražene pljuvačke[1]. *T. tenax* se lako prenosi između članova porodice[52], a novi podaci ukazuju na mogućnost međusobne razmene trihomonada između različitih vrsta domaćina[1]. Molekularnim tehnikama *T. tenax* je dijagnostikovana u usnoj duplji pasa, mačaka i u mandibularnoj žlezdi psa.1 Činjenica da je *T. tenax* pronađen kod životinja i njihovih vlasnika može ukazivati na porodični ili kućni karakter infekcije ovom vrstom i ukazuje na mogućnost prenošenja oralne trihomonijaze sa čoveka na domaće životinje i obrnuto; stoga se trihomonijaza usne duplje može smatrati antropozoonozom ili zooantroponozom[1].

Još jedan važan faktor koji utiče na infekciju oralne duplje je trajanje pranja zuba[53]. Pranje zuba kraće od 1 minuta, kao i suviše retko pranje, negativno utiču na stanje usne duplje i podstiču pojavu protozoa. S druge strane, negativno utiče i nepravilna upotreba dodatnih mehaničkih sredstava za oralnu higijenu, kao što su konac za zube ili čačkalice. Protisti se češće javljaju kod ljudi koji koriste mehanička sredstva. Ovo je verovatno zbog pogrešnog rukovanja ovim uređajima, koji mogu oštetiti tkivo desni i stoga izazvati upalu[53].

Recent results of a systematic literature review and meta-analysis have revealed global overall prevalence of 17% (95% CI 14–22%) of *T. tenax* infection. The highest prevalence rate was estimated to be 56% (42–69%) in Chile, while the lowest prevalence was reported in Kenya, with only 3% (1–6%). The analysis demonstrated that the infection was most common in those aged 46–55 years, with 15% (0–100%). The overall prevalence, depending on the applied diagnostic procedures for parasite identification (microscopy, cultivation, molecular methods), was 21% (12–32%), 19% (8–35%) and 17% (12–23%), respectively. The subgroup analysis dealt as well with the prevalence of *T. tenax* in patients with candidiasis [(22% (3–52%)], gingivitis [21% (9–36%)] and periodontitis [27% (10–48%)][51].

A high degree of heterogeneity of periodontal *T. tenax* prevalence could be related to unbalanced screening practices as to the factors of age, gender, presence of some systemic disease and methods utilized for parasitology diagnosis. Molecular diagnostic techniques devised to detect and identify the species of genus Trichomonas (such as genomic amplification and sequencing), represent a reliable tool for rapid and specific characterization of trichomonads[1]. Obviously, experimental animal models utilizing relevant physiopathologic models of periodontitis are necessary to assess the ability of *T. tenax* to cause and/or aggravate a disease, as well as standardized experimentally designed epidemiological studies[18].

Oral cavity colonization with *T. tenax* is more common in older individuals and is rare in children (similar to *E. gingivalis*). The transmission route is saliva and infections occur directly, by kissing, or indirectly, by a contact with eating tools, personal hygiene items, and similar, i.e. with anything that has come into contact with infected saliva[1]. *T. tenax* is easily transmitted between family members[52], and some recent data suggest the possibility of exchange of trichomonads between different host species1. Using molecular techniques, *T. tenax* has been diagnosed in the oral cavity of dogs and cats, and in the mandibular gland in dogs1. The fact that *T. tenax* has been identified in animals and their owners may indicate the possibility of a familial or household character of the infection with this species and suggests the possibility of transmission of oral trichomoniasis from humans to domestic animals and vice versa; oral trichomoniasis can therefore be considered an anthropozoonosis or zooanthroponosis[1].

Ostale protozoa: *Leishmania spp., Toxoplasma gondii*

Leishmania spp.

Vrste roda Leishmania su obligatni intracelularni paraziti tkiva sisara koje pripadaju potkraljevstvu Protozoa, kolu Sarcomastigophora, razredu Zoomastigophora (kao i rod Trichomonas, odnosno vrsta *T. tenax*). Uzročnici su oboljenja lajšmanioza koje je rasprostranjeno širom sveta, sem u Australiji i na Antarktiku. Lajšmanijaza je endemska parazitoza u mnogim zemljama, a najviše u zemljama u razvoju. Svetska zdravstvena organizacija je uvrstila lajšmanijazu na listu zanemarenih tropskih bolesti koje treba eliminisati do 2030[54].

Transmisija vrsta ovoga roda je najčešće zoonotska. Lajšmanije prenose ženke hematofagnih insekata (kolokvijalno peščane muve, eng. *Sand flies*) iz roda Phlebotomus i/ili Lutzomyia (vrste rasprostranjene u Americi) sa domaćih i divljih životinja (rezervoari parazita). Za vreme krvnog obroka insekta dolazi do ingestije amastigota (infektivni oblik za insekta) iz zaraženih domaćina. U crevima insekta (prelazni domaćin - vektor) amastigoti prelaze u promastigotni oblik koji je pokretan. Promastigoti se umnožavaju prostom binarnom fisijom u digestivnom traktu insekta i potom prelaze u metaciklične promastigote (infektivni oblici za čoveka) kada vrše invaziju bukalne šupljine insekta. Krvnim obrokom, ubodom preko kože, insekt unosi žrtvi (sisaru) infektivni oblik parazita koji vrši invaziju citoplazme mononuklearnih fagocita i prelazi u formu amastigota (Lajšman Donovan telo, eng. *Leishman Donovan body*) efikasno izbegavajući imunski odgovor nosioca. Nakon niza deoba i stvaranja velikog broja amastigota dolazi do pucanja zaražene ćelije. Osobođeni paraziti (amastigoti) vrše najezdu novih fagocita preko kojih se, zavisno od vrste parazita i imunskog statusa domaćina, infekcija širi (jetra, slezina, kostna srž, limfni nodusi, koža, creva i td.). Amastigoti koji se nađu u krvotoku nakon liziranja napadnute ćelije, ali i prepune parazitirane ćelije, budu ingestirani od strane insekta prilikom novog uboda[19].

Humana lajšmanioza je u prvom redu zoonoza, ali se može sa obolelog čoveka preneti na drugog čoveka (interhumani prenos) transfuzijom krvi, korišćenjem zajedničkih igala, sporadično seksualnim putem i transplancentarnim putem (kongenitalna lajšmanioza)[19].

Vrste roda Leishmania su morfološki istovetne, što ponekad pravi zabune u taksonomiji.

Another important factor of impact on oral cavity infection is the duration of teeth brushing[53]. Teeth brushing shorter than a minute, as well as very rare teeth brushing, has an unfavorable impact on the oral cavity health and may favor protozoan colonization. On the other hand, improper use of additional mechanical devices for oral hygiene, such as dental flosses or toothpicks, may also have a negative impact. Protists more commonly occur in people who tend to use these mechanical devices. This is probably the consequence of improper use of the devices, which may inflict damage to the gums and thus induce inflammation[53].

Other protozoans: *Leishmania spp., Toxoplasma gondii*

***Leishmania** spp.*

The species of the genus Leishmania are obligate intracellular parasites of mammalian tissues that belong to the subregnum Protozoa, phylum Sarcomastigophora, classis Zoomastigophora (as well as the genus Trichomonas, i.e. *T. tenax* species). They cause leismaniosis, a globally present disease (with the exception of Australia and Antarctica). Leishmaniasis is an endemic parasitosis in many countries, mostly affecting the developing countries. The World Health Organization classified leishmaniasis among the neglected tropical diseases that should be eliminated until 2030[54].

Transmission of the species of this genus is usually zoonotic. Leishmanias are transmitted by the bite of female hematophagous insects (colloquially called *sand flies*) from the genu s Phlebotomus and/or Lutzomyia (the species living in America) from domestic or wild animals (parasite reservoirs). During their blood meal, insects ingest amastigotes (an infective form for insects) from infected hosts. In the insect bowel (an intermediary host–vector) amastigotes transform to promastigotes (a mobile stage). Promastigotes replicate by simple binary fission in the insect digestive tract and then transform into metacyclicpromastigotes (a form infective to humans), when they invade the insect buccal cavity. By a blood meal, i.e. via a bite on the skin, the insect introduces the infectious parasite form into the victim (a mammal), which futher invades the cytoplasm of mononuclear phagocytes and transforms into the amastigote form (Leishman-Donovan body), efficiently evading the host immune response. After a sequence of divisions and creation of a large number of amastigotes, the

Poslednjih nekoliko godina zahvaljujući primeni metoda molekularne biologije izvršena je nova klasifikacija. Tako, subgenus Leishmania čine pet kompleksa u kojima se nalaze brojne vrste. Leishmania donovani kompleks obuhvata vrste: *L. donovani, L. infantum, L. chagasi, L. archibaldi*. Iste vrste lajšmanija mogu usloviti različite kliničke oblike lajšmanijaze, i obrnuto. Izdvojena su četiri klinička entiteta lajšmanijaze.1) visceralna lajšmanijaza (VL), 2) kožna lajšmanijaza (KL), 3) kožno-sluzokožna lajšmanijaza (KSL), 4) difuzna kožna lajšmanioza (DKL)[19].

Visceralna lajšmanijaza (kala-azar, Dum-dum groznica) je sistemsko oboljenje koje se karakteriše visokom temperaturom, hepatosplenomegalijom, limfoadenopatijom, anemijom, leukopenijom, trombocitopenijom, značajnim gubitkom telesne težine i slabljenjem organizma. U nelečenih osoba, stopa smrtnosti je gotovo 100% u periodu od dve godine. Infekciju izazivaju vrste *L. donovani* kompleksa, i to: *L. donovani* je uzročnik indijske VL; *L. infantum* je uzročnik mediteranske VL; *L. chagasi* je uzročnik južnoameričke VL i *L. archibaldi* je uzročnik sudanske VL[19].

Kod mediteranskog tipa kala-azara (Mediteran, Jugoistočna Evropa, ali i Kina, Srednja Azija, Centralna i Južna Amerika), glavni rezervoar infekcije je pas. Lanac infekcije je na relaciji pas-insekt-pas, ali i na relaciji pas-insekt-čovek. Najčešće oboljevaju deca (otuda i naziv), ali nisu pošteđeni ni odrasli. Prvi autohtoni slučajevi VL u Srbiji su zabeleženi 1945. godine u Nišu i Dobričkom okrugu. U naredne tri godine na teritoriji južne, istočne i zapadne Srbije registrovano je preko 350 slučajeva lajšmanijaze, a tokom 1949. godine nekoliko obolelih u neposrednoj okolini Beograda (Srbija). U navedenom periodu, kala–azar je bio endemičan u svim republikama nekadašnje Jugoslavije, sem na teritoriji nekadašnje Hrvatske i nekadašnje Slovenije[55]. Glavni rezervoar parazita, prema sprovedenim istraživanjima, je pas, a vektori flebotomusi[56]. U prvoj dekadi ovog veka zabeležena su 22 slučaja VL u Srbiji i 1 slučaj koinfekcije HIV/lajšmanijaza koji je zabeležen u jugoistočnoj Srbiji (grad Niš)[57,58]. Jedna od glavnih pretnji u kontroli VL je interakcija s HIV infekcijom. Naime, VL se pojavila kao važna oportunistička infekcija (posle toksoplazmoze i kriptosporidioze) povezana sa HIV-om. U endemskim područjima visceralne lajšmanioze mnogi ljudi imaju asimptomatsku infekciju i istovremenu infekciju HIV-om (koinfekcija) što povećava rizik za razvoj aktivne VL između 100 i 2320 puta!

infected cell bursts. The released parasites (amastigotes) infect new phagocytes through which, depending on the parasite species and immune status of the host, the infection spreads further (to the liver, spleen, bone marrow, lymph nodes, skin, intestines, etc.). Amastigotes present in the bloodstream after the lysis of an infected cell (or a parasite-filled infested cell), are ingested by an insect during a new bite[19].

Human leishmaniasis is primarily a zoonosis, but can be transmitted from an infected individual to others (interhuman transmission) by blood transfusion, by sharing needles, sporadically even by sexual route and transplacentally (congenital leishmaniasis)[19].

The species of the Leishmania genus are morphologically identical, which sometimes creates confusion in their taxonomy. In recent years, owing to the molecular biology methods, a new classification has been made. The subgenus Leishmaniais thus composed of five complexes with numerous species. The Leishmaniadonovani complex involves the following species: *L. donovani*, *L. infantum*, *L. chagasi*, and *L. archibaldi*. The same leishmania species can cause different clinical forms of leishmaniasis, and vice versa. Four clinical entities of leishmaniasis are recognized: 1) visceral leishmaniasis (VL); 2) cutaneous leishmaniasis (CL); 3) mucocutaneous leishmaniasis (MCL); and 4) diffuse cutaneous leishmaniasis (DCL)[19].

Visceral leishmaniasis (kala-azar, Dum-dum fever) is a systemic disease characterized by high temperature, hepatosplenomegaly, lymphadenopathy, anemia, leukopenia, thrombocytopenia, and significant loss of body weight. In untreated individuals, the mortality rate is almost 100% in the period of two years. The infection is caused by the following species from the Leishmaniadonovani complex: *L. donovani*, as the cause of Indian VL; *L. infantum*, as the cause of Mediterranean VL; *L. chagasi*, as the cause of South American VL; and *L. archibaldi*, as the cause of Sudan VL[19].

In the Mediterranean type of kala-azar (Mediterranean region, South Eastern Europe, but also China, Middle Asia, Central and South America) the principal infection reservoir is the dog. The infection chain is dog-insect-dog, but also dog-insect-human. Children are most commonly affected, but adults are not spared either. The first autochthonous (native) cases of VL in Serbia were recorded in 1945 in Niš and in Dobrič County. In the next three years there were over 350 reported cases of leishmaniasis in the territories of South, Eastern and Western Serbia, and in 1949, there were several infections in the vicinity of Belgrade as well.

U Južnoj i Jugoistočnoj Evropi oko 70% slučajeva VL kod odraslih je povezano sa HIV infekcijom[19,59]. Pored HIV infekcije, na povećanu učestalost lajšmanijaze kao oportunističke bolesti uticao je povećani broj ljudi sa imunokompromitovanim imunitetom usled hroničnih bolesti, neoplazmi, imunosupresivnih tretmana, transplantacije[60]. Post kalaazarne kožne lezije (PKKL) mogu se javiti nakon izlečenja VL, naročito u endemskim područjima lajšmanioze uzrokovane *L. donovani*. Fizikalnim pregledom uočava se makulopapulozni nodularni osip koji je uglavnom lokalizovan oko usta i nešto manje na grudnom košu i nadlakticama. Međutim, može se javiti i generalizovani osip, čirevi i kraste, kao i heilitis i lezije na mekom i tvrdom nepcu. Bolest je hroničnog toka, može trajati godinama iako paraziti ne vrše invaziju unutrašnjih organa[19].

Kožna lajšmanijaza se karakteriše pojavom papula na koži na otkrivenim delovima tela (lice, ruke, noge) koje su praćene regionalnom limfoadenopatijom. Papule se javljaju nakon 1-2 meseca od uboda insekta, potom ulcerišu kada nastaju krateri na koži. Ivice lezija su jasno ograničene i eritematozne, a potom nastaje granulaciono tkivo. Promene su bezbolne i spontano zaceljuju kod nekomplikovanih formi KL. Međutim, patološke promene lokalizovane na vidljivim, izloženim delovima tela, sa mogućnošću destrukcije tkiva i stvaranja ožiljaka, zahtevaju medikamentoznu terapiju. Uzročnici KL su morfološki identični sa vrstama koje uzrokuju VL. U zemljama Starog sveta to vrste *L. tropica, L. major i L. aethiopica*, mada u Južnoj Evropi i zemljama mediteranskog basena uročnik KL može biti vrsta *L. infantum*. KL Novog sveta izazivaju vrste L. mexicana complex i L. braziliensis complex[19].

Kožno-sluzokožna lajšmanijaza se karakteriše lezijama na koži i sluzokoži koje delimično ili potpuno vrše destrukciju tkiva što dovodi do estetskih promena sa psihičkim poremećajima, kao i do ozbiljnih, po život opasnih, funkcionalnih promena na organima. Uzročnici KSL su *L. major, L. tropica, L. aethiopica, L. mexicana, L. brasiliensis* (Centralna Amerika, ređe Istočna Afrika). Nakon 1-4 nedelje od uboda insekta, lezija može spontano da se zaleči. Karakteristično je da se primarna lezija progresivno povećava u periodu od nekoliko nedelja i/ili godina. Bolne, destruktivne, metastatske lezije u usnoj i nosnoj duplji javljaju se u 2-50% slučajeva[19].

In this period, kala-azarwas endemic in all ex-Yugoslav republics, with the exception of Croatia and Slovenia[55]. The main infection reservoir, according to the studies, was the dog, and vectors were phlebotomi[56]. In the first decade of this century, there were 22 recorded cases of VL in Serbia and one case of HIV/leishmaniosis-coinfection in Southeastern Serbia (the city of Niš)[57,58]. One of the major threats in the control of VL is its interaction with HIV infection. In particular, VL appeared to be an important opportunistic infection (after toxoplasmosis and cryptosporidiosis) associated with HIV. In the regions endemic for VL, many people have an asymptomatic infection and concomitant infection with HIV (coinfection), which increases the risk of developing active VL one hundred to 2,320 times!

In Southern and South-Eastern Europe around 70% of cases of VL in adults are associated with HIV infection[19,59]. In addition to HIV infection, increased prevalence of leishmaniasis as an opportunistic infection is influenced by increased numbers of individuals immunocompromised due to chronic diseases, neoplasms, immunosuppressive treatments, transplantations[60]. Post-kala-azar skin lesions (PKSL) can appear after VL has been cured, especially in endemic regions for leishmaniosis caused by *L. donovani*. On physical examination, maculopapular rash is seen, primarily around the mouth and slightly less on the chest and upper arms. However, generalized rash may also occur along with boils and crusts, cheilitis and soft and hard palate lesions. The disease follows a chronic course and can last for years, although the parasites are not invading the internal organs[19].

Cutaneous leishmaniasis (CL) is characterized by the appearance of papules in the skin on the exposed parts of the body (face, arms, legs), accompanied by regional lymphadenopathy. Papules tend to occur 1–2 months after the insect bite, and after that ulcerate, producing crater-like lesions. The edges of the lesions are clearly delineated and erythematous; after that, granulation tissue is created. The changes are painless and heal spontaneously in uncomplicated forms of CL. Nevertheless, pathological changes situated in the exposed, visible parts of the body, which may destruct tissue and create scars, require medicamentous therapy. The causative agents of CL are morphologically identical to the species that cause VL. In the Old World countries these

Nekoliko godina od zalečene primarne lezije mogu se javiti metastatske lezije. Moguća su razaranja nosne pregrade, tvrdog nepca i grkljana. Takođe su opisane i deformacije usana i obraza[60-63]. Zahvatanje samo oralne duplje je veoma retko, mada su dokumentovani i takvi primeri[60,64]. Kod obolelih može se javiti: groznica, gubitak težine, anemija i sekundarna bakterijska infekcija. Anamneza i prepoznavanje kliničke slike KSL su presudne u dijagnozi bolesti. U odmakloj fazi bolesti je lečenje znatno oteženo, a takođe su mogući i relapsi. Paraziti se retko nalaze u uzorcima sa ivice primarnog ulkusa i/ili sa lezija na sluzokoži obolelog. Bolesnici su seropozitivni, a takođe je pozitivan i intradermalni test. Ozdraveli pacijenti su otporni na reinfekciju[19].

Difuzna kožna lajšmanioza se karakteriše lezijama na koži koje nalikuju lepromatoznim promenama; hroničnog je toka i teška za lečenje. Najpre se javljaju papule, potom lokalizovane lezije koje se vremenom šire na čitavu površinu tela u vidu plakova i čvorova koji su čvrsti i glatki, a kasniji i hrapavi. Promene ne ulcerišu i ne zahvataju sluzokože i unutrašnje organe[19].

Mere prevencije lajšmanijaze su različite i zavise od brojnih faktora: geografskog područja, staništa sisara domaćina i vektora. Neophodno je sistematsko otkrivanje obolelih i njihovo lečenje; periodično zaprašivanje insekticidima sa rezidualnim dejstvom, korišćenje repelenata i zaštitnih mreža oko prostora za spavanje; dispozicija đubrišta; uništavanje malih glodara i zaraženih pasa. Dijagnostikovanje oralne lajšmanijaze predstavlja izazov u medicinskoj praksi. Rana dijagnoza je neophodna da bi se obezbedio brzi tretman i da bi se izbegli recidivi[19].

Toxoplasma gondii

Rod Toxoplasma pripada kolu Apicomplex, razredu Sporozoa. Protozoa *Toxoplasma gondii* (*T. gondii*) je ubikvitarni parazit rasprostranjen po čitavom svetu. Prema podacima Centra za kontrolu i prevenciju bolesti (eng. *Centers for Disease Control and Prevencion,* CDC) prevalencija toksoplazmoze u različitim delovima sveta je više od 60% i varira u zavisnosti od geografskog područja, klimatskih prilika, načina života (ishrana, higijena)[65]. U urbanim sredinama najčešći put infekcije je konzumiranje termički nedovoljno obrađenog mesa, dok je u ruralnim sredinama češće putem prljavih ruku ili udisanjem oocista.

are *L. tropica, L. major and L. aethiopica*, although in southern Europe and the Mediterranean basin the cause of CL can be *L. infantum*. In the New World, CL is caused by *L. mexicana complex and L. braziliensis complex*[19].

Mucocutaneous leishmaniasis (MCL) is characterized by lesions in the skin and mucosa which partially or completely destruct tissue, leading to esthetic changes with resultant psychological problems, as well as to serious, life-threatening functional organ changes. The causes of MCL are *L. major, L. tropica, L. aethiopica, L. mexicana, L. braziliensis* (Central America, less commonly East Africa). One to four weeks after the insect bite, the lesion may heal spontaneously. It is characteristic that the primary lesion progressively increases in the period of several weeks and/or years. Painful, destructive, metastatic lesions in the oral and nasal cavity occur in 2–50% of cases[19]. Several years after the primary lesion has healed, metastatic lesions may appear. Destruction of the nasal septum, hard palate and larynx is possible. Deformations of the lips and cheeks have also been described[60–63]. Oral cavity involvement is rare alone, although such instances have been reported as well[60,64]. In the affected the following may occur: fever, loss of weight, anemia and secondary bacterial infections. Patient history and recognition of the MCL clinical picture are essential in the diagnosis. In more advanced disease stages the treatment is difficult, and relapses tend to occur as well. The parasites are rarely present in the samples taken from the primary ulcer edges and/or from the mucosal lesions. The patients are seropositive, and the intradermal test is also positive. The healed patients are resistant to reinfection[19].

Diffuse cutaneous leishmaniosis is characterized by lesions in the skin similar to leprous changes; it is a chronic disease, difficult to treat. Papules tend to occur first, followed by localized lesions which spread to involve the whole body surface in the form of plaques and nodules which are firm and smooth and become rough later. The changes do not ulcerate, nor they involve mucosa or internal organs[19]. The measures to prevent leishmaniosis differ and depend on a number of factors: geographical area, habitat of the mammalian host and vectors. Systematic detection of the affected and their treatment are essential; periodical dusting with residual insecticides; use of repellents and protective nets over the sleeping spaces; waste disposal; elimination of small rodents and infected dogs.

Do infekcije može doći i korišćenjem u ishrani svežih jaja domaće živine, mleka, ali i putem krvi, pljuvačke i urina zaraženih životinja (trofozoit ili pseudocista). Moguć prenos je i nesterilnim iglama, preko posteljice (transplacentarni prenos), nakon transfuzije krvi ili transplantacije organa inficiranog davaoca. Interhumani prenos je redak, a zabeležene su izolacije *T. gondii* iz pljuvačke i sa tonzila[19].

Toxoplasma gondii ima složeni životni ciklus koji se sastoji od seksualne i aseksualne faze. Brojne vrste mačaka (Felide), uključujući i domaću mačku (Felis domestica) su jedini domaćini kod kojih se odvija seksualna i aseksualna faza životnog ciklusa parazita. Mačke se, najčešće, inficiraju oocistama dospelim iz spoljne sredine (hrana), ali i putem hrane u kojoj se nalaze aseksualni oblici parazita (inficirani prelazni domaćin, obično miš). Aseksualna faza životnog ciklusa može se odvijati u različitim tkivima velikog broja domaćina uključujući i čoveka[19].

Nakon *per os* unosa pravih cisti u digestivnom traktu mačke se razgrađuje zid ciste i osobađaju se bradizoiti koji ulaze u epitelne ćelije u kojima se odvija aseksualna faza razvoja, tj. šizogonija. Formiraju se šizonti i merozoiti koji nakon oslobađanja iz dezintegrisane ćelije inficiraju nove epitelne ćelije. Nakon više aseksualnih ciklusa, pojedini merozoiti prelaze u fazu gametogonije kada nastaje zigot (nesporulisana oocista) koja fecesom mačke dospeva u spoljnu sredinu. Oociste se u fecesu mačke mogu naći nakon 1-3 nedelje od infekcije, a u spoljnoj sredini u periodu od 2 - 4 dana sazrevaju (sporulišu), odnosno postaju infektivne. Oociste su otporne u spoljnoj sredini, glavni rezervoar je zemljište, ali može biti i voda. Kada ove zrele, infektivne oociste dospeju u digestivni trakt mačke, oslobađaju se sporozoiti koji prodiru u epitelne ćelije intestinuma, transformišući se u tahizote koji se brzo razmnožavaju što dovodi do pucanja ćelije domaćina. Tahizoiti mogu inficirati susedne ćelije intestinuma, ali se mogu hematogenim i limfnim putem diseminovati po čitavom organizmu mačke. Aseksualna faza životnog ciklusa može se odvijati u ćelijama: intestinuma, CNS-a, mišićima, ćelijama retikuloendo-telijalnog sistema (RES) i dr. ćelijama stalnih, ali i prelaznih domaćina. Kod mačke se aseksualni stadijum razvoja (sem u intestinumu) odvija i u centralnom nervnom sistemu (CNS), mišićima i drugim tkivima, tzv. endodiogenija (mačke su nosioci i tkivnih stadijuma parazita), odnosno može se razviti generalizovana parazitemija.

The diagnosis of oral leishmaniosis presents a challenge in medical practice. Early diagnosis is necessary so that a timely treatment could be provided and relapses avoided[19].

Toxoplasma gondii

The genus Toxoplasma belongs to the phylum Apicomplexa, class Sporozoa. The protozoan *Toxoplasma gondii (T. gondii)* is a ubiquitous parasite present worldwide. According to the data from the Centers for Disease Control and Prevention (CDCs), the prevalence of toxoplasmosis in various parts of the world is over 60% and varies depending on the geographical area, climate, way of life (nutrition, hygiene)[65].

In urban surroundings, the infection route is most commonly by mouth through the intake of insufficiently cooked meat, while in rural areas the infection is usually contracted via dirty hands and inhalation of oocysts. The infection may also arise by using fresh eggs of domestic poultry or by milk, but also via blood, saliva and urine of infected animals (trophozoites or pseudocysts). Transmission by infected needles is also possible, as well as through the placenta (transplacental transmission) and after blood transfusions or organ transplantation from infected donors. Interhuman transmission is nevertheless rare, and T. gondiihas been isolated from the saliva and from the tonsils[19].

Toxoplasma gondii has a complex life cycle that consists of the sexual and asexual phases. Numerous cat species (Felide), including the domestic cat (Felisdomestica), are the only hosts in which sexual and asexual phases of the parasite's life cycle occur. Cats are usually infected by oocysts present in the environment (via food), but also via the food in which asexual parasite forms are present (infected intermediary hosts, usually mice). The asexual phase may take place in different tissues of a large number of hosts, including humans[19].

After a per os intake of proper cysts, the cyst wall is decomposed by the cat digestive tract, releasing the bradyzoites which enter the epithelial cells within which the asexual developmental phase takes place, i.e the schizogony. Schizonts and merozoites are formed, capable of infecting new epithelial cells after being released from the disintegrated cell.

Prelazni domaćini (čovek i drugi kičmenjaci) zaraze se unosom sporulisanih oocista iz spoljne sredine i/ili unosom pseudocisti, ali i pravih cisti koje se nalaze kod drugih prelaznih domaćina (npr. meso zaražene životinje). Oslobođeni paraziti, fagocitovani od strane makrofaga, dospevaju u ekstraintestinalne strukture prelaznog domaćina. U akutnoj fazi su zahvaćeni mezenterični limfni nodusi i jetra, dok su u hroničnoj fazi zahvaćeni CNS, srce i skeletni mišići[19].

Tahizoiti su pseudociste (ćelijski zid potiće od ćelije domaćina) ispunjene trofozoitima koji imaju intezivan metabolizam i ubrzanu deobu (endodiogenija) tokom aseksualne faze životnog ciklusa. Ekstracelularno se mogu naći u momentu prskanja ćelije domaćina kada atakuju na nove ćelije (pravi intracelularni paraziti). Mogu se javiti u akutnoj ili subakutnoj fazi toksoplazmoze. Potom, paraziti prelaze u drugi aseksualni stadijum tzv. stadijum prave ciste ispunjene bradizoitima ili cistozoitima koji takođe nastaju endodiogenijom. Bradizioti su uspavane forme parazita usporenog metabolizma koje ostaju incistirane dok su aktivni mehanizmi odbrane domaćina. Sekretuju sopstveni zid ciste formirajući pravu cistu (najbrojnije na mozgu, očima, skeletnim mišićima) koja sadrži brojne parazite (čak na hiljade) koji godinama mogu ostati vitalni. Pritom, njihov domaćin tokom života nema simptome i znake infekcije parazitom *T. gondii* bez obzira na lokalizaciju cisti (najčešće lokacije su abdominalni organi, skeletni mišići, mozak, oči, embrionalno tkivo), tzv. hronična infekcija. Međutim, zid ciste može da prsne kada se paraziti oslobađaju i pritom može doći do recidiva kliničkih manifestacija tokoplazmoze. To se obično dešava kod imunokompromitovanih domaćina kada toksoplazmoza ima akutni ili subaktni tok bolesti. Ciste nakon dužeg perioda mirovanja mogu da kalcifikuju. Ako prave ciste dospeju u spoljašnu sredinu brzo propadaju. Infektivne su ako se per os unesu zajedno sa organom u kome se nalaze[19].

Toksoplazmoza ljudi nastaje unosom oocisti *T. gondii* preko prljavih ruku, unosom hrane i vode kontaminirane fecesom mačaka tzv. horizontalna trasmisija. Moguća je i horizontalna trasmisija putem tkivnih cisti, ali i vertikalna transmisija tahizoitima. Na težinu bolesti kod infekcije parazitom *T. gondii,* pored virulencije soja, utiču i osetljivost, imunski status i starost domaćina.

After several asexual cycles, individual merozoites enter the phase of gametogony, when a zygote (non-sporulatedoocyst) is produced, which is excreted via cat feces in the environment. Oocysts can be identified in the cat feces 1–3 weeks after the infection; in the environment, they maturate (sporulate) in the period of 2–4 days, becoming infective. Oocysts are resilient in the environment; their main reservoir is soil, although it can be water as well. When these mature, infective oocysts enter the cat digestive tract, sporozoites are released, which enter intestinal epithelial cells transforming into tachyzoites which rapidly replicate, causing the host cell to burst. Tachyzoites may infect adjacent intestinal cells, or be disseminated via bloodstream or lymph throughout the cat body. The asexual phase of the life cycle can take place in the cells of the intestinum, CNS, muscles, reticuloendothelial system (RES) and other cells in the organism of definitive and intermediary hosts. In cats, the asexual phase of development (in addition to the intestines) takes place in the central nervous system (CNS), muscles and other tissues (the so called endodyogeny) – cats host the tissue stages of the parasite as well, i.e. generalized parasitemia may develop. Intermediary hosts (humans and other vertebrates) are infected by the intake of sporulatedoocysts from the environment and/or by the intake of pseudocysts or proper cysts present in other intermediary hosts (i.e. by the meat of infected animals). The released parasites, phagocytised by macrophages, reach the extraintestinal structures of the intermediary host. In the acute phase, mesenteric lymph nodes and the liver are involved, while in the chronic phase the CNS is also involved, as well as the heart and skeletal muscles[19].

Tachyzoites are in fact pseudocysts (with the cell wall originating from the host) packed with trophozoites with an intense metabolism and rapid rate of division (endodyogeny) during the asexual phase of the life cycle. Extracellularly, they can be identified in the moment of cellular burst, when they attack new cells (proper intracellular parasites). They can occur in the acute or subacute phase of toxoplasmosis. Afterwards, the parasites enter the second asexual stage, the so called proper cyst stage, with the cyst filled with bradyzoites or cystozoites, which are also produced by endodyogeny.

Mnogi ljudi inficirani parazitom *T. gondii* nemaju znake i simptome infekcije tokom stečene (akvirirana) toksoplazmoze. Ponekad, kod imunokompetentnih osoba, uključujući i zdrave trudnice, simptomi i znaci infekcije mogu biti blagi, i nalikuju gripu i/ili infektivnoj mononukleozi (temperatura, bolovi u mišićima i zglobovima, malaksalost, glavobolja, retko bol u grlu i farinksu). Često dolazi do lokalizovane limfadenopatije u predelu glave i vrata (limfni nodusi su čvrsti, bezbolni i pokretni na palpaciju)[19,66,67]. Sa razvojem imunskog odgovora dolazi do smanjenja parazitemije, a ciste toksoplazme ostaju u tkivima i sadrže žive parazite. Ciste mogu da se aktiviraju ako dođe do imunosupresije.

Kod imunokompromitovanih pacijenata *T. gondii* opisane kliničke manifestacije su većeg intenziteta, uključujući limfo-adenopatiju, a kod generalizovane infekcije može biti zahvaćen CNS. Tokso-plazmoza kod imunokompromitovanih osoba je posledica reaktivacije hronične infekcije, a znatno ređe primoinfekcije. Reaktivacija može biti lokalizovana, na mestu prskanja cisti, ili se razvija generalizovana toksoplazmoza sa teškom kliničkom slikom (toksoplazmatski encefalitis, najčešća oportunistička infekcija CNS-a kod obolelih od AIDS-a; intersticijski pneumonitis; gastrična toksoplazmoza; miokarditis) i mogućim smrtnim ishodom[19,66,67].

Iako kod tokoplazmoze u kliničkoj slici obolelih nema primarnih simptoma i znakova infekcije *T. gondii* u usnoj duplji, zbog uvećanih limfnih nodusa u predelu glave i vrata pacijenti dolaze u ordinaciju stomatologa. U ovim slučajevima, potrebno je pacijenta uputiti najpre na neinvazivne dijagnostičke procedure, u prvom redu na serodijagnostiku specifičnih antitela klase IgA, IgM i IgG prema *T. gondii*. U slučaju negativnih seroloških rezultata predložiti biopsiju suspektnih limfnih nodusa u cilju potvrde infekcije *T. gondii*[19,66,67].

Bradyzoites are dormant parasite forms, with a slow metabolism, which remain incysted while the host active defense mechanisms are active. They secrete their own cyst wall, forming a proper cyst (most numerous in the brain, eyes, skeletal muscles), that contains numerous parasites (even thousands of them) which may remain vital for years. At the same time, the host experience no symptoms and signs of infection with *T. gondii* regardless of the cysts' localization (most common sites are abdominal organs, skeletal muscles, brain, eyes, embryonal tissue) – this is a chronic infection. However, the cyst wall may burst open when parasites are released and on that occasion the clinical manifestations of toxoplasmosis may recur. This usually happens with immunocompromised hosts when toxoplasmosis have an acute or subacute disease course. After a long period of dormancy, the cysts may undergo calcification. In the environment, proper cysts tend to perish rapidly. They are infective if ingested by mouth together with the organ they are infesting[19].

Human toxoplasmosis occurs after the intake of *T. gondii* oocysts via dirty hands, with foods or water contaminated by cat feces (the so called horizontal transmission). Horizontal transmission by tissue cysts is also possible, as well as vertical transmission by tachyzoites. The severity of the disease caused by *T. gondiii* nfection is influenced by the strain virulence and sensitivity, immune status and age of the host. Many individuals infected with *T. gondii* do not have any signs and symptoms of infection during the acquired (activated) toxoplasmosis. At times, in immunocompetent individuals, including healthy pregnant women, the symptoms and signs of infection can be rather mild and resemble a flu and/or infectious mononucleosis (with symptoms such as fever, muscle and joint pain, fatigue, headache, and rarely pain in the larynx and pharynx). Localized lymphadenopathy is also common in the region of head and neck (lymph nodes are firm, painless and movable on palpation)[19,66,67]. With the development of immune response, parasitemia usually subsides, while the cysts remain in the tissues containing living parasites. If immuno-suppression develops, the cysts can undergo activation. In immunocompromised patients with *T. gondii* infection, the described clinical manifestations are more severe, including lymphadenopathy, and in cases with a generalized infection the CNS can be involved as well. Toxoplasmosis in immuno-compromised individuals represents the consequence of reactivation of a chronic infection, and rarely a primary infection.

Zaključak

Oralni mikrobiom je odraz oralnog, ali i opšteg zdravstvenog stanja organizma. Mikrobiološki stanovnici su koevoluirali zajedno sa čovekom milionima godina, tako da oralni mikrobiomi nisu nasumično kolonizovani. Razvojem tehnologije za detekciju, identifikaciju i analizu oralnih mikrobioma, danas postoje detaljnije informacije o njihovom postojanju, sastavu i specifičnim ulogama. Naredne studije trebale bi da razreše dilemu da li promene u oralnom mikrobiomu prethode kliničkim znacima bolesti ili obrnuto. U prvom slučaju, oralni mikrobiom bi omogućio utvrđivanje mogućih rizika od bolesti. Stomatolozi igraju važnu ulogu u dijagnozi oralnih oboljenja uzrokovanih protozoama usne duplje, ali i protozoa koje dovode do oboljenja koja imaju uticaja na usnu duplju. Njihovo dijagnostikovanje je svakako veliki izazov i zahteva multidisciplinarni pristup. Rana dijagnoza je neophodna da bi se obezbedilo brzo i adekvatno lečenje.

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Zahvalnice: Nema

Such a reactivation can be localized, at the cyst rupture site, or generalized toxoplasmosis may develop, with a rather serious clinical picture (toxoplasmatic encephalitis, the most common opportunistic infection of the CNS in patients with AIDS; interstitial pneumonitis; gastric toxoplasmosis; myocarditis) and possible fatal outcome[19,66,67].

Although with toxoplasmosis the typical clinical picture does not contain primary signs and symptoms of *T. gondii* infection of the oral cavity, enlarged lymph nodes in the head and neck region prompt patients to visit their dentists. In these cases it is necessary to refer the patient first for non-invasive diagnostic procedures, primarily the serodiagnosis of class IgA, IgM and IgG specific antibodies to *T. gondii*. In case that serology results are negative, the biopsy of the suspect lymph nodes should be recommended in order to confirm the infection with *T. gondii*[19,66,67].

Conclusion

Oral microbiome reflects oral and overall health status of the organism. Microbiological inhabitants of the oral cavity have evolved together with humans for millions of years, so that oral microbiomes are not colonized randomly. With the development of technology used for detection, identification and analysis of oral microbiomes, nowadays there is more detailed information about their existence, composition and specific roles they play. Further studies should resolve the dilemma whether the changes in oral microbiome precede clinical signs of disease or vice versa is the case. In the first case, oral microbiome would help in establishing possible risks for certain diseases. Dentists play an important role in the diagnosis of oral diseases caused by oral cavity protozoans, and also the protozoans which can produce systemic diseases with an impact on oral cavity. Their diagnosis represents a challenge of a kind and certainly require a multidisciplinary approach. Early diagnosis is essential in order that a rapid and adequate treatment could be initiated.

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