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## ALERGIJSKE MANIFESTACIJE U USNOJ DUPLJI

## ALLERGIC MANIFESTATIONS IN ORAL CAVITY

Ivan Minić<sup>1</sup>, Ana Pejčić<sup>2</sup>, Radmila Obradović<sup>2</sup>, Dimitrije Mirković<sup>3</sup>, Marija Bradić<sup>3</sup>

<sup>1</sup> UNIVERZITET U NIŠU, MEDICINSKI FAKULTET, KLINIKA ZA STOMATOLOGIJU, SLUŽBA ZA PARODONTOLOGIJU I ORALNU MEDICINU, STUDENT NA DOKTORSKIM STUDIJAMA, NIŠ, SRBIJA

<sup>2</sup> UNIVERZITET U NIŠU, MEDICINSKI FAKULTET, KLINIKA ZA STOMATOLOGIJU, SLUŽBA ZA PARODONTOLOGIJU I ORALNU MEDICINU,

<sup>3</sup> PRIVATNA STOMATOLOŠKA ORDINACIJA "SMILE – DENT", NIŠ, SRBIJA

<sup>1</sup> UNIVERSITY OF NIŠ, FACULTY OF MEDICINE, DEPARTMENT OF PERIODONTOLOGY AND ORAL MEDICINE, PHD STUDENT, NIŠ, SERBIA

<sup>2</sup> UNIVERSITY OF NIŠ, FACULTY OF MEDICINE, DEPARTMENT OF PERIODONTOLOGY AND ORAL MEDICINE,

<sup>3</sup> PRIVATE DENTAL PRACTICE "SMILE-DENT", NIŠ, SERBIA

### Sažetak

**Uvod:** Alergija je neuspešan odgovor organizma protiv stranih antigena. Ponovno uvođenje iste strane materije u organizam izaziva reakciju koja dovodi do uništavanja sopstvenog tkiva. Alergijske reakcije se mogu izraziti u različitim organima i u bilo kojoj starosnoj grupi.

**Materijal i metode:** U ovom radu učestvovalo je 84 pacijenta. Dijagnoza je zasnovana na pozitivnoj anamnezi preordiniranja leka, ugriza insekata, ranijih alergijskih reakcija, kao i tipične kliničke slike. Pratili su se varijante alergijskih promena, kao i najčešći uzroci njihove pojave. U potrazi za najčešćim alergenima, lekovi u stomatološkoj praksi takođe su smatrani potencijalnim pokretačima alergijskih događaja.

**Rezultati:** Najčešći oblik alergijske reakcije bio je Stomatitis allergica i Enanthema fixum, sa lokalizacijom na dorzalnoj površini jezika i sluzokožom obraza. Skoro polovina registrovanih pacijenata prijavila je promenu nakon uzimanja odgovarajućeg leka iz grupe sulfonamida i penicilina.

**Zaključak:** Ako je uzrok alergija poznat, prevencija kontrole alergijske reakcije je na prvom mestu. Visoka prevalenca alergijskih bolesti, poboljšane dijagnostičke procedure i tretmani imali su veliki uticaj na pružanje medicinske zaštite pacijentima sa alergijom. Ponekad možda neće biti moguće potpuno izbeći alergijsku reakciju, ali ovi koraci mogu pomoći u sprečavanju budućih alergijskih reakcija. Lekari treba da usvoje jasne nazive alergijskih poremećaja i pridržavaju se nomenklature u njihovoj profesionalnoj i javnoj komunikaciji.

**Ključne reči:** alergija, usna duplja, promene u ustima

### Corresponding author:

Ass. Prof. Ana Pejčić, DDS, MSc, PhD.  
Periodontology and Oral Medicine  
Faculty of Medicine, University of Niš  
Dr. Z. Djindjić 81 Blvd. 18000 Niš, Serbia  
+381642572178

### Abstract

**Introduction:** An allergy is the failed defensive effort of the organism against foreign antigens. Reintroduction of the same foreign substance into the organism causes a reaction that leads to the destruction of one's own tissue. Allergic reactions can express themselves in many different organs and in any age group.

**Material and methods:** In this paper, 84 patients were involved. The diagnosis was based on a positive history of pre-administration of a medicine, an insect bite, earlier allergic reactions, as well as a typical clinical picture. Variants of allergic changes, as well as the most common causes for their occurrence, were monitored. Looking for the most common allergens, dental practice drugs were also considered as potential drivers of allergic events.

**Results:** The most common form of allergic reaction was Stomatitis allergica and Enanthema fixum, with localization on the dorsal surface of the tongue and the mucous membrane of the cheeks. Almost half of the registered patients reported a change after taking the appropriate group of drugs: sulfonamides and penicillins.

**Conclusion:** If the cause of allergies is known, preventive control of an allergic reaction are in the first place. The high prevalence of allergic diseases and improved diagnostic procedures and treatments have had a great impact on the provision of medical care to allergic patients. Sometimes, it may not be possible to completely avoid allergic reaction, but these steps can help to prevent future allergic reactions. Physicians should adopt clear designations of the allergic disorders and adhere to this nomenclature in their professional and public communications.

**Key words:** allergy, oral cavity, oral changes

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za stomatologiju Niš. Sva prava zadržana.

## Uvod

Brzi, eksplozivni razvoj civilizacije i tehnologije, pored ogromnih prednosti za čovečanstvo, sa sobom nosi i niz neželjenih efekata. Ljudski organizam se sa razvojem tehnologije više nego ikada sreće sa nesa- gledivim ekološkim problemima i zagađenjem okoline. Hemijski, bakteriološki, fizičko- toksični, radioaktivni i dr. agensi predstavljaju opasnost sveopšteg opstanka na zemlji, ljudskog, životinjskog i biljnog sveta. Svaki živi organizam, s njim i čovek, u biti nosi poriv za održanjem vrste. Postoji period adaptacije više od 400 miliona godina<sup>1</sup> za ćelije, tkiva, organe i sam organizam. U tom evolutivnom periodu stvorili su se mehanizmi prepo- znavanja „svojeg od tuđeg“. Ta pojava prepoznavanja sreće se još kod najjedno- stavnijih životinjskih vrsta (sunderi, alge). U evolutivnom procesu postoje sve samo složenije i savršenije.

Zdrava individua se može zaštititi od mogućih štetnih mikroorganizama iz okoline efikasnim mehanizmima koje ima još od rođenja. To je tzv. urođeni nespecifični imunitet. Glavni činioci tog urođenog nespeci- fičnog imuniteta su genetski determinisani. Za razliku od urođenog, postoji i stečeni imunitet, koji zavisi od imunog odgovora na pojedini antigen, i on je specifičan samo za taj antigen<sup>2,3</sup>.

Najznačajnije komponente nespeci- fičnog imuniteta su: intaktna koža, sluzokoža sa lojnim i znojnim žlezdama i njihovim sekretima, kao i lizozimi. To je mehanička barijera za mnoge agense. Određenu ulogu u nespecifičnoj odbrani organizma ima i normalna telesna temperatura, fagociti (mikro i makrofage), serumski komplementi. Ipak, ukoliko agensi (mikroorganizmi) savladaju nespecifični urođeni imunitet, tzv. „prvu liniju odbrane“, organizam pokušava da se brani „drugom linijom odbrane“, odnosno stečenim imunitetom<sup>4</sup>.

Za razliku od urođenog, stečeni imunitet zavisi od imunog odgovora na pojedini antigen i specifičan je samo za taj antigen. Da bi do imunog odgovora došlo, potreban je predhodni kontakt organizma, odnosno ćelija imunog sistema (mikrofaga i limfocita) sa anti- genom<sup>5,6</sup>.

Brzi razvoj farmaceutske industrije omogućio je uvođenje brojnih novih sintetskih i prirodnih medikamenata. Ti medikamenti se koriste za lečenje bolesti, ublažavanje simptoma bolesti, kao i za skraćenje dužine trajanja bolesti.

## Introduction

The rapid, explosive development of civilization and technology, besides the enormous benefits for humankind, brings about a number of unwanted effects. With the technology development, the human organism, more than ever, encounters incomprehensible ecological problems and environmental pollution. Chemical, bacteriological, physical- toxic, radioactive, etc. agents pose a threat to the overall survival on the Earth, human, animal and plant life. Every living organism, and the man with it, essentially carries the urge to maintain the species. There is a period of adaptation of more than 400 million years<sup>1</sup> for cells, tissues, organs and the body itself. In this evolutionary period, mechanisms for distinguishing "own" and "someone else's" were created. This phenomenon of reco- gnition is found even in the simplest animal species (sponges, algae). In the evolutionary process, everything becomes more complex and more perfect.

A healthy individual can be protected from possible harmful microorganisms from the environment with effective mechanisms it develops since birth. This is the so-called innate non-specific immunity. The main factors of this innate non-specific immunity are genetically determined. Unlike innate, there is acquired immunity that depends on the immune response to an individual antigen, and it is specific only to that antigen<sup>2,3</sup>.

The most important components of non-specific immunity are intact skin, mucous membrane with sebaceous glands and sweat glands and their secretions, as well as lysozymes. This is a mechanical barrier to many agents. Certain role in the non-specific defence of the organism belongs to normal body temperature, phagocytes (micro and macrophages), serum complements. However, if the agents (microorganisms) overcome non- specific innate immunity, the so-called "first line of defence", the organism tries to defend itself using the "second line of defence" or acquired immunity<sup>4</sup>.

Unlike innate, acquired immunity depends on the immune response to an individual antigen and is specific to that antigen only. In order to obtain an immune response, a prior contact of the organism or the immune system cells (microphages and lymphocytes) with antigen<sup>5,6</sup> is required.

The rapid development of the pharma- ceutical industry has enabled the introduction of numerous new synthetic and natural medications.

Međutim, svaki od medikamenata može biti potencijalni alergen u smislu stvaranja senzibilizacije organizma<sup>7</sup>.

**Cilj rada** bio je da se iznese broj alergijskih manifestacija u ustima u periodu od tri godine (2014.-2016.) na Klinici za stomatologiju Medicinskog fakulteta u Nišu.

### ***Materijal i metode***

U ovom radu obrađeno je 84 pacijenta, koji su se javili Službi za oralnu medicinu i parodontologiju Klinike za stomatologiju Medicinskog fakulteta u Nišu zbog pojave različitih promena u usnoj duplji koje nisu prolazile. Uzimanje anamneze i klinički pregled obavljani su od strane jednog specijaliste oralne medicine i parodontologije korišćenjem stomatološkog ogledalceta pri veštačkom osvetljenju. Dijagnoza se zasnivala na pozitivnoj anamnezi o prethodnom uzimanju leka, ujedu nekog insekta, ranijim alergijskim reakcijama kao i tipičnoj kliničkoj slici.

Pored broja obolelih, praćene su i varijante alergijskih promena, kao i najčešći uzročnici zaslužni za njihovo pojavljivanje. Tragajući za najčešćim alergenima, u obzir su uzeti i lekovi iz stomatološke prakse, kao moguća pokretača alergijskih zbivanja.

### ***Rezultati rada***

U periodu od tri godine, u Službi oralne medicine i parodontologije, registrovano je 84 pacijenta sa alergijskim reakcijama na sluzokoži usne duplje. Od 84 ispitanika, četrdeset i devet je bilo ženskog, a 35 osoba muškog pola, različite starosne dobi (tabela 1).

These medications are used to treat diseases, alleviate disease symptoms and shorten disease duration. However, each of the medicines can be a potential allergen in terms of creating organism sensitization<sup>7</sup>.

**The aim** of this paper was to present the number of allergic manifestations in the mouth of patients treated at the Clinic of Dentistry, Faculty of Medicine in Niš during a 3 year period (2014-2016).

### ***Material and methods***

In this paper, 84 patients with various lasting changes in the oral cavity who attended the Department of Oral Medicine and Periodontology were investigated.

Taking of a history and clinical examination was performed by a specialist in oral medicine and periodontology using a mouth mirror in artificial lighting. The diagnosis was based on a positive history of pre-administration of a drug, an insect bite, earlier allergic reactions, and a typical clinical picture.

In addition to the number of patients, variants of allergic changes, as well as the most common causes for their occurrence, were monitored. Looking for the most common allergens, dental practice drugs were also considered as potential drivers of allergic events.

### ***Results***

In the period of 3 years, 84 patients with allergic reactions on the oral cavity mucous membrane were registered in the Department of Oral Medicine and Periodontology. Out of 84 respondents, 49 were females, and 35 were males of different ages (Table 1).

**Tabela 1.** Starosna i polna struktura pacijenata  
**Table 1.** The age and gender structure of patients

<b>Ispitanici Respondents</b>	<b>Broj, procenat Number, percentage</b>
<b>Pol Gender</b>	
Muški-male	35 (41.20%)
Ženski-female	49 (58.80%)
<b>Godine Age</b>	
21-40	47 (55.95%)
41-60	26 (30.95%)
> 61	11 (13.10%)
<b>Ukupno Total</b>	84 (100%)

Od toga, 40 pacijenata bilo je sa dijagnozom *Stomatitis allergica*, 34 pacijenta sa dijagnozom *Enanthema fixum*, 6 pacijentata sa dijagnozom *Cheilitis allergica* i 4 pacijenta sa dijagnozom *Oedema Quincke* (tabela 2).

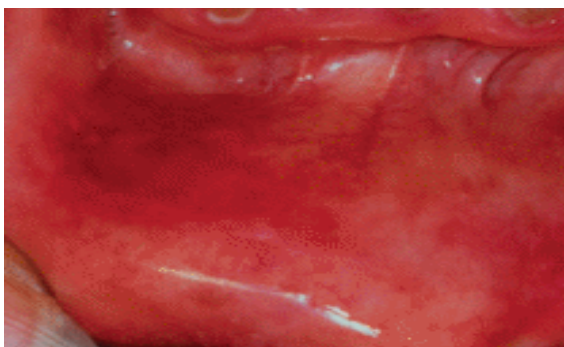
Of these, 40 patients were diagnosed with *Stomatitis allergica*, 34 patients were diagnosed with *Enanthema fixum*, 6 patients were diagnosed with *Cheilitis allergica* and 4 patients were diagnosed with *Oedem Quincke* (Table 2).

**Tabela 2.** Kliničke manifestacije alergijske reakcije na oralnoj sluzokoži  
**Table 2.** Clinical manifestations of allergic reactions on the oral mucous membrane

Oboljenje Disease	Muškarci Male	Žene Female	Broj, procenat (n,%) Number, percentage
<i>Stomatitis allergica</i>	18	22	40 (47.62%)
<i>Enethema fixum</i>	16	18	34 (40.47%)
<i>Cheilitis allergica</i>	-	6	6 (07.14%)
<i>Oedema Quincke</i>	1	3	4 (04.77%)
<b>Ukupno Total</b>	35	49	84 (100%)

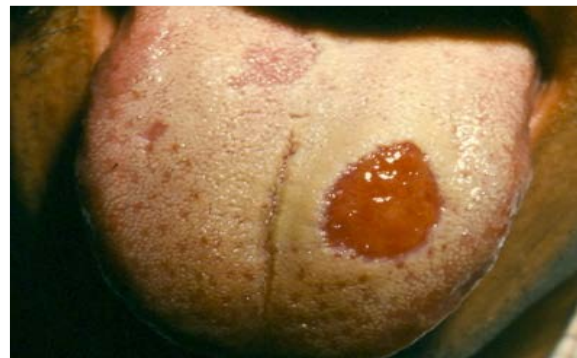
Kliničke manifestacije *Stomatitis allergica* karakteriše polimorfizam promena, što je uslovljeno stepenom senzibilizacije. Pacijenti dolaze sa enetomom i edemom čitave oralne sluzokože i pojavom erozija i ulceracija koje nastaju prskanjem vezikula i bula. Usled edema, na jeziku se vide impresije zuba, a jezik je manje pokretljiv. Promene su praćene subjektivnim tegobama u vidu bola, pečenja i žarenja, što je još više izraženo pri žvakanju i govoru. Kod pacijenata se oseća neprijatan zadah, jer je otežana oralna higijena ili je ona najčešće odsutna (sl.1).

Clinical manifestations of *Stomatitis allergica* were characterized by the polymorphism of changes, which was conditioned by the degree of sensitization of patients coming with enanthema and edema of the entire oral mucosa and the occurrence of erosions and ulcers resulting from bursting of vesicles and bulla. Due to edema, teeth impressions were visible on the tongue, and the tongue was less mobile. The changes were accompanied by subjective problems in the form of pain and burning sensation, which were even more pronounced when chewing and speaking. Patients had unpleasant breath because oral hygiene maintenance was difficult or often absent (Fig. 1).



**Slika 1. / Figure 1.** *Stomatitis allergica*

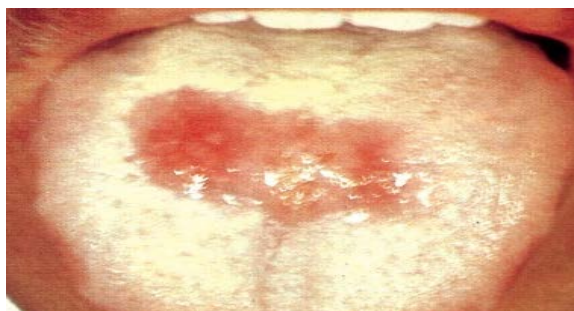
Kod ispitivanih pacijenata čest oblik alergijske reakcije je i *Enanthema fixum*. Promene su uglavnom bile lokalizovane na dorzalnoj strani jezika i sluzokoži nepca. Klinička slika ovih erupcija je takođe polimorfna.



**Slika 2. / Figure 2.** *Enanthema fixum*

In the examined patients, the frequent form of allergic reaction was *Enanthema fixum*. The changes were mostly localized on the dorsal side of the tongue and the palate mucous membranes.

Bolest može da se javi samo u vidu enanema pravilnog oblika, jasno ograničenog od okoline. Češće se na mestu erupcije javljaju bule ili vezikule, čijim prskanjem ostaju široko erodovane površine pokrivene krpama epitela i fibrinoznim eksudatom žućkasto sive boje. Subjektivne tegobe su u korelaciji sa veličinom i dubinom oštećene oralne sluzokože (sl.2).



**Slika 3. / Figure 3.** *Candida albicans*

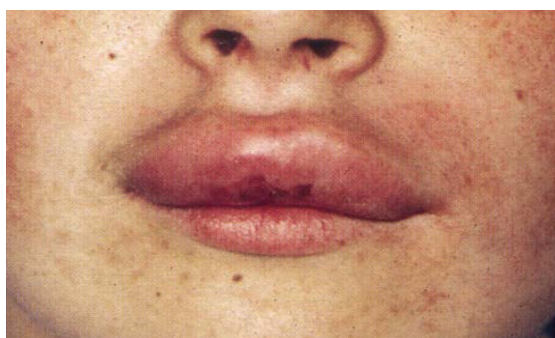
Moguće su disfagija i hipersalivacija. Usled otoka jezika javljaju se smetnje pri govoru. U hipertrofiji jezičnog pokrivača vidno učešće uzimaju gljivice tipa *Candida*. Dolazi do jasno uočljivog kontrasta između enetema, erozije i belih naslaga na jeziku (sl. 3). Kod 6 pacijenata ženskog pola alergijske reakcije su klinički opisane kao *Cheilitis allergica*. Kod svih je bio prisutan enanem i edem usana i to češće gornje usne. Promene su nastajale naglo sa izraženim subjektivnim tegobama zategnutosti usana, svraba i smanjene pokretljivosti usne (sl. 4).

The clinical picture of these eruptions was also polymorphic. The disease could only occur in the form of enanthema of the regular form clearly delineated from the environment. More often, at the site of the eruption, bullas or vesicles appeared whose bursting resulted in widely eroded surfaces covered with epithelial cloths and fibrinous exudates of yellowish-gray color. Substantial complaints were in correlation with the size and depth of damaged oral mucosa (Fig. 2).



**Slika 4. / Figure 4.** *Cheilitis allergica*

Dysphagia and hypersalivation were possible. Speech impediments occurred due to tongue swelling. *Candida* type fungi significantly participated in the hypertrophy of the tongue cover. There was a clearly visible contrast between enanthema, erosion and white deposits on the tongue (Figure 3). In 6 female patients, allergic reactions were clinically described as *Cheilitis allergica*. In all of them, there were lip enanthema and edema, involving more often the upper lip. Changes occurred suddenly with pronounced subjective problems in the form of tension, itching and decreased mobility of the lips (Figure 4).



**Slika 5. / Figure 5.** *Oedema Quincke*



Oralne manifestacije alergije javljaju se u sklopu angioneurotičnog edema (Oedema Quincke), što potvrđuje njegov nalaz kod četiri pacijenta. Kod njih je otok naglo nastajao i naglo nestajao. Kod jedne pacijentkinje, prema anamnestičkim podacima, otok je nastao posle uzimanja leka zbog migrenoznih bolova i to po drugi put, dok ostali nisu mogli da objasne njegovu pojavu. Otok je zahvatao usne, obraz i očne kapke (slika 5.). Rezultati pojedinih oblika alergijskih reakcija prema godinama ispitivanja (2014, 2015, 2016) prikazani su u tabeli 3.

Kod 37 pacijenata (44.01%) alergijske reakcije pojavile su se kao reakcija na lekove. Iz anamneze su dobijeni podaci da su lekovi uzimani zbog upale grla, infekcije urinarnog trakata ili nekih bolova, jedan ili više dana. Kod nekoliko pacijenata postojao je i raniji kontakt sa istim lekom i sa sličnom kliničkom slikom. Kod ostalih, promene su se javile po prvi put.

Oral manifestations of the allergy occurred as part of angioneurotic edema (Oedema Quincke), which was confirmed by the findings in 4 patients. In them, the swelling suddenly emerged and suddenly disappeared. According to history data, in one patient, the swelling occurred after taking the migraine pain drug for the second time, while others could not explain its appearance. The swelling covered the lips, cheek and eyelids (Figure 5).

The results of individual forms of allergic reactions by the years of examination (2014, 2015, 2016) are shown in Table 3.

In 37 patients (44.01%) allergic reactions emerged as a reaction to drugs. The history data showed the administration of medicines for throat inflammation, urinary tract infections or some pain for one or more days. In several patients, there was an earlier contact with the same drug and a similar clinical picture. In others, changes were reported for the first time. Table 4 shows the drugs that most often cause allergic reactions on the oral mucous membrane.

**Tabela 3.** Učestalost alergijskih reakcija u toku ispitivanja  
**Table 3.** Frequency of allergic reactions during testing

Godina Year	Stomatitis allergica	Enanthema fixum	Cheilitis allergica	Oedema Quincke
2014	9	8	1	1
2015	16	15	3	1
2016	15	11	2	2
Ukupno Total	40	34	6	4

**Tabela 4.** Vrste lekova i oralne manifestacije alergija  
**Table 4.** Types of drugs and oral manifestations of allergies

Lek / promena Drug / change	Stomatitis allergica	Enanthema fixum	Cheilitis allergica	Oedema Quincke	Broj, procentat Number, percentage (n, %)
Bactrim	7	15	-	-	22 (27.29%)
Pentrexyl	2	-	-	2	4 (4.79%)
Cefachor	2	2	-	-	4 (4.79%)
Cliacil	1	2	-	-	3 (3.57%)
Brufen	2	-	-	1	3 (3.57%)
Chloramphenicol	-	-	1	-	1 (1.21%)
Ostali uzroci Other causes	27	11	5	3	46 (54.78%)
Ukupno Total	40	34	6	4	84 (100%)

U tabeli 4. prikazani su lekovi koji najčešće daju klinički manifestne alergijske reakcije na oralnoj sluzokoži.

U 22 slučaja promene su nastale perioralnom primenom kombinacije sulfametaksazol-trimetropina (Bactrim). U četiri slučaja, posle primene fenilaminoacetyl-amino-penicilinske kiseline (Pentrexyl) i u 4 slučaja primene cefahlora (Cefaklor), došlo je do pojave fiksnih erupcija, alergijskog stomatitisa i Quinckeovog edema. Fenoksimetilpenicilin-kalijum (Cliacil) je promene po tipu generalizovane oralne alergije i fiksne erupcije izazvao kod tri pacijenta, dok su nesteroidni antireumatici (Brufen) izazvali pojavu fiksne erupcije i Quinckeovog edema (tri pacijenta). Alergijski heilitis se javio kod jednog pacijenta koji je koristio hloramfenikol (Chloramphenicol). Kod preostalih 47 pacijenata pojavu alergijskih reakcija u usnoj duplji izazvali su drugi uzroci.

### *Diskusija*

Analiza rezultata pokazuje da je u periodu od 2014. do 2016. godine registrovano 84 pacijenta sa alergijskim reakcijama na oralnoj sluzokoži. Najčešće alergijske reakcije su oblika Stomatitis allergica i to kod 40 pacijenata (47,61%) i Enanthema fixum kod 34 pacijenta (40,47%). Verovatno je prisutan i veći broj pacijenata sa bilo kojim tipom alergijske reakcije oralne sluzokože koji nisu registrovani. S obzirom da se u svakodnevnoj praksi sa alergijom sreću i lekari opšte prakse, dermatovenerolozi, pedijatri i specijalisti drugih medicinskih disciplina, to je i razlog što taj broj nije mnogo veći.

Kod 37 pacijenata (44,01%) alergijske reakcije su bile posledica uzimanja lekova. Kod ostalih 47 pacijenata (55,9%) promene su bile rezultat drugih uzroka (hrana, ujed insketa, prašina itd.). Rezultati ovog istraživanja pokazali su najveću osetljivost oralne sluzokože nakon primene sulfonamida i antibiotika (penicilinskih preparata). Ove lekove neki pacijenti su više puta konzumirali i kod nekih je već bilo promena, a kod nekih su se prvi put javili.

Od sulfonamidskih preparata, Bactrim je najčešći uzročnik pojava alergijskih reakcija u organizmu<sup>8</sup>. U ovom ispitivanju, kao uzročnik pojave alergije javio se kod 22 pacijenta. S obzirom da se Bactrim najčešće primenjuje u lečenju urinarnih infekcija, verovatno je i najviše registrovanih alergijskih reakcija izazvanih ovim lekom. Većina autora iznosi reakcije na ovaj lek po tipu fiksne erupcije<sup>9-11</sup>,

In 22 cases, changes were caused by perioral application of the sulfamethaxazol-trimethopine combination (Bactrim). In 4 cases, after the application of phenylaminoacetyl-amino-penicillanic acid (Pentrexyl) and in 4 cases after the application of cefahlor (Cefachlor), fixed eruptions, allergic stomatitis and Quincke's edema appeared. Phenoxymethylpenicillin-potassium (Cliacil) caused changes in the form of generalized oral allergy and fixed eruption in 3 patients, while non-steroidal antirheumatics (Brufen) caused the occurrence of fixed eruption and Quincke's edema (3 patients). Allergic heilitis occurred in one patient using Chloramphenicol. For the remaining 47 patients, allergic reactions in the oral cavity were caused by other causes.

### *Discussion*

The analysis of the results shows that in the period 2014-2016, 84 patients with allergic reactions in oral mucous membranes were registered. The most common allergic reactions are Stomatitis allergica in 40 patients (47.61%) and Enanthema fixum in 34 patients (40.47%).

There is probably a higher number of patients with any type of oral mucous membrane allergic reactions that were not registered. Given that also general practitioners, dermatovenerologists, paediatricians and specialists in other medical disciplines encounter allergies in their everyday practice, this is the reason why this number is not much higher.

In 37 patients (44.01%) allergic reactions were the result of taking medications. In the remaining 47 patients (55.9%) the changes were the result of other causes (food, insect bite, dust, etc.). The results of this study showed the highest sensitivity of oral mucosa after the administration of sulphonamide antibiotics (penicillin preparations). Some of the patients took these medications repeatedly and some of them already faced changes, while in some they appeared for the first time.

Of sulphonamide preparations, Bactrim is the most common cause of allergic reactions in the body<sup>8</sup>. In this study, it emerged as a cause of allergy in 22 patients. Since Bactrim is most commonly used in the treatment of urinary infections, probably, the most commonly reported allergic reactions are caused by this medicine. Most authors report reactions to this medicine by the type of fixed eruption<sup>9-11</sup>, which is confirmed by the results of this study.

što potvrđuju i rezultati ovog ispitivanja. Pored promena na oralnoj sluzokoži, promene se mogu javiti i na genitalnoj sluzokoži i koži<sup>12,13</sup>. Kožne promene manifestuju se kao makule, eritem ili Erythema exudativum multiforme, koje se javljaju kao reakcije III i IV tipa<sup>14,15</sup>.

Analiza rezultata učestalosti alergija prema godinama u ovom ispitivanju nije dala statistički znatne razlike u pojavi alergije u ispitivanom periodu.

Antibiotici su druga grupa lekova koja je dala alergijske reakcije kod pacijenata koji su se javili u Službu oralne medicine i parodontologije. To je još jedna potvrda najčešće opisivanih medikamentoznih alergija na antibiotike, tj. penicilinske preparate<sup>16-18</sup>. Smatra se da je 10% osoba alergično na penicilin<sup>19</sup>.

Penicilin može izazvati alergijsku reakciju po bilo kom tipu hipersenzibilnosti. Najteža je anafilaktička reakcija koja se javlja kod oko 20% osoba koje su primile penicilin<sup>20</sup>. Relativno često se javlja urtikarija sa angioedemom<sup>21</sup>. Najčešće su kožne promene po tipu makulopapulozne ospe praćene svrabom, kao i alergijski kontaktni dermatitis<sup>22,23</sup>, posledica primene penicilina lokalno u vidu masti, solucije ili praha. Kod 4 osobe alergičnih na penicilin postoji rizik od alergija na cefalosporine. Kliničke manifestacije medikamentozne alergije mogu biti različite. Jedan lek kod različitih osoba može dati različite alergijske manifestacije, odnosno različiti lekovi mogu dati istu alergijsku reakciju kod iste osobe. Reakcija se može javiti i posle duže upotrebe leka ili posle uzimanja više puta istog leka, jer se za to vreme razvio imuni odgovor. Ispoljavanje alergijske reakcije pri prvom kontaktu organizma sa lekom objašnjava se tzv. mehanizmom ukrštene reakcije sa nekim drugim lekom ili sličnim antigenom<sup>24-26</sup>. Kad se jednom ispolji alergijska reakcija, svaka sledeće primena tog leka ili sličnog, u minimalnim količinama, daje iste promene.

Dijagnoza medikamentozne alergije zasniva se na dobroj anamnezi i kliničkom nalazu. Najčešće su pacijenti davali pozitivnu anamnezu o prethodnom uzimanju leka i ranijim alergijskim reakcijama na sluzokoži ili koži. Puno puta je teško doći do definitivne dijagnoze. Treba posumnjati na lek koji pacijent uzima ukoliko se promene jave u toku njegove primene ili registrovati lek ukoliko se pri njegovom prekidu promene povuku. Pojava istih simptoma po ponovnom unošenju istog leka olakšava dijagnozu, što se saznaje iz pozitivne anamneze. Dijagnoza se potvrđuje laboratorijskim testovima.

In addition to changes in oral mucous membranes, changes can occur on genital mucous membrane and skin<sup>12,13</sup>. Skin changes are manifested as macula, erythema or erythema exudativum multiforme, which occur as reactions of III and IV types<sup>14,15</sup>.

The analysis of the results of the allergy frequency by age in this study did not give statistically significant differences in the occurrence of allergy in the studied period.

Antibiotics are another group of drugs that have caused allergic reactions in patients who reported to the Department of Oral Medicine and Periodontology. This is another confirmation of the most commonly described medicinal allergies to antibiotics, i.e., penicillin preparations<sup>16-18</sup>. It is thought that 10% of people are allergic to penicillin<sup>19</sup>.

Penicillin can cause an allergic reaction of any type of hypersensitivity. The most severe is the anaphylactic reaction that occurs in about 20% of people who have received penicillin<sup>20</sup>. Relatively frequent is urticaria with angioedema<sup>21</sup>. The most common are skin changes of the type of maculopapular rash accompanied by itching, as well as allergic contact dermatitis<sup>22,23</sup> that occur as a consequence of using penicillins locally in the form of ointment, solution or powder. In people who are allergic to penicillin, there is a risk of allergy to cephalosporins in 25% of people. Clinical manifestations of medicinal allergy can be different. One drug can cause different allergic manifestations in different individuals and different drugs can cause the same allergic reaction in the same person. The reaction can occur after prolonged use of the drug or after repeatedly taking the same drug because an immune response has developed during this time. The manifestation of an allergic reaction at the first contact of the organism with a medicine is explained by the so-called cross-reaction mechanism with another drug or a similar antigen<sup>24-26</sup>. Once an allergic reaction is manifested, any subsequent administration of this drug or similar in minimum amounts yields the same changes.

The diagnosis of allergy to a medicine is based on a good history and clinical findings. Most commonly, patients gave a positive history of the previous taking of the drug and previous allergic reactions on the mucous membrane or skin. It is often difficult to reach a definitive diagnosis. There is a need to suspect a medicine the patient takes if changes occur during the course of its use or register a medication if changes disappear after discontinuation of its use.



Međutim, testovi nisu pokazali očekivane rezultate u potvrđivanju alergije na lekove. Oni su često negativni, jer se lekovi biotransformišu u degradacione produkte, pa se u većini slučajeva ne zna aktivna supstanca. Ako se ispitivanja vrše u toku alergijske reakcije mogu se dobiti nespecifično pozitivni rezultati, odnosno negativni, ako su se privremeno utrošili imunoglobulini ili specifični imuni limfociti<sup>3,5</sup>.

Visok procenat alergije je posledica istovremene upotrebe različitih lekova, dostupnosti mnogih lekova u slobodnoj prodaji i neznanja o međusobnoj interakciji različitih vrsta lekova.

Znatan broj radova pokazuje na čestu pojavu alergija na lekove<sup>16,17,19,24</sup>. Zabeleženo je nekoliko stotina lekova koji mogu dovesti do neke reakcije preosetljivosti. Lekovi mogu izazvati alergiju na jedan od bilo koja četiri tipa hipersenzibilnosti<sup>2</sup>. Pritom mogu biti odgovorni imunološki mehanizmi humoralnog celularnog imuniteta<sup>4</sup>. Postoji i genetska osnova preosetljivosti na lekove. Poznata je alergijska diateza na lekove kod mnogih osoba kao i članova čitave porodice<sup>27,28</sup>.

Većina lekova deluje kao haptent koji se kovalentno vezuje za proteinski omotač, najčešće za albumin seruma (antibiotici, sulfonamidi, lokalni anestetici, salicilati). Manji broj lekova ima svojstvo kompletnog alergena (vakcine, serum, enzimi)<sup>29,30</sup>. Kao alergeni mogu delovati i metaboliti pojedinih lekova<sup>27</sup>.

Smatra se da alergijske reakcije nisu toliko zavisne od njegovih farmakoloških svojstava koliko od brzine kovalentnog vezivanja leka ili njegovih produkata za proteinske omotače<sup>4</sup>.

Opisane su i alergijske reakcije na više lekova i materijala koji se koriste u zbrinjavanju zuba i usta<sup>31</sup>. Pored preparata formaldehida, joda, žive, bakra, zlata, najčešće se opisuje alergija na akrilat<sup>32,33</sup>. Akrilat je po hemijskom sastavu metilni estar metakrilne kiseline dobijen na bazi polimerizacije kao polimetilmetakrilat. Smatra se da je mogući senzibilizirajući agens rezidualni monomer pri nedovoljnoj polimerizaciji. Ne isključuje se da i ostale komponente akrilata imaju antigeni potencijal. Promene usled alergije na akrilat klinički se manifestuju u vidu enanema i edema. Klinička iskustva pokazuju da te promene, koje se često javljaju i proglašavaju alergijom na akrilat, mogu biti i reakcije sluzokože na učestale mehaničke, infektivne, toplotne ili hemijske iritacije.

The occurrence of the same symptoms after re-administration of the same drug facilitates the diagnosis which is learned from a positive history. Diagnosis is confirmed by laboratory tests. However, the tests did not show the expected results in confirming the allergy to a medicine.

They are often negative because the drugs are biotransformed into degradation products, so in most cases, the active substance is not known. If tests are carried out during an allergic reaction, non-specific positive or negative results may be obtained if immunoglobulins or specific immune lymphocytes are temporarily depleted<sup>3,5</sup>.

A high percentage of allergies to a medication are a consequence of the simultaneous use of various drugs, the availability of many medicines in the free sale to patients themselves and the ignorance of the interaction of different types of drugs.

A significant number of works show a frequent allergy to medication<sup>16,17,19,24</sup>. There are several hundreds of drugs that can lead to a certain hypersensitivity reaction. Drugs can cause allergy to any of the 4 types of hypersensitivity<sup>2</sup>.

And here the immune mechanisms of humoral cellular immunity may be responsible<sup>4</sup>. There is also a genetic basis for hypersensitivity to drugs. An allergic diathesis to medicines is known in many people as well as members of the entire family<sup>27,28</sup>.

Most drugs work like a haptent that covalently binds to a protein coat, most commonly to serum albumin (antibiotics, sulphonamides, local anaesthetics, salicylates). A smaller number of drugs have the property of a complete allergen (vaccines, serum, enzymes)<sup>29,30</sup>. Metabolites of certain drugs can also act as allergens<sup>27</sup>.

It is considered that allergic reactions are not as dependent on its pharmacological properties as on the rate of covalent binding of the drug or its products to protein coats<sup>4</sup>.

Allergic reactions to several drugs have been reported for materials used in teeth and mouth care<sup>31</sup>. Apart from allergy to preparations of formaldehyde, iodine, mercury, copper, gold, allergy to acrylate is most often described<sup>32,33</sup>. Acrylate is chemically a methyl ester of methacrylic acid obtained on the basis of polymerization as a polymethylmethacrylate. It is believed that a residual monomer in insufficient polymerization is a possible sensitizing agent.

It is not excluded that other acrylate components have antigenic potential. Changes

Alergijske reakcije u usnoj duplji mogu biti praćene i promjenama na koži i drugim sluzokožama. Često se javljaju i hematogene promene: anemija, eozinofilija, limfocitoza, trombocitopenija, smanjen procenat hemoglobina i ubrzana sedimentacija<sup>3,5,15</sup>.

Morfološke promene koje prate alergijske reakcije na oralnoj sluzokoži su često modifikovane, što je rezultat traumatskog oštećenja pri mastikaciji, delovanja pljuvačke, mehaničkog dejstva protetskih nadoknada i oralne infekcije *Candidom*.

Što se tiče terapije, kod većine pacijenata alergičnih na lekove prekida se sa primenom sumnjivog leka. Uz primenu antiseptičnih sredstava promene se za kratko vreme regresiraju. Kod težih promena davani su antihistaminici per os ili parenteralno 2-3 dana. Ređe, kod teških oblika davani su i kortikopreparati.

### **Zaključak**

Posle detaljnog pregleda rezultata i sveopšte analize podataka, može se zaključiti da je za period od tri godine (ispitivani period) registrovan znatan broj pacijenata sa pojavom alergijskih reakcija na sluzokoži usne duplje. Najčešća forma alergijske reakcije bila je *Stomatitis allergica* i *Enanthema fixum*, sa lokalizacijom na dorzalnoj površini jezika i sluzokoži obraza. Skoro polovina od registrovanih pacijenata javila se zbog promena nakon uzimanja odgovarajućeg leka i to sulfonamida i penicilina.

Ako se zna uzrok alergija, preventivno sprečavanje alergijske reakcije je na prvom mestu. Ove reakcije se mogu sprečiti izbegavanjem alergena koji utiču na pojavu alergije. Međutim, simptomi se mogu vratiti ako se ponovo dođe u kontakt sa alergenom. Tada se javlja mogućnost pojave burne alergijske reakcije koja može dovesti i do smrti.

Kada se dijagnostikuje uzrok alergije, može se izbegavati izlaganje alergenima, tražiti medicinska nega i ordinirati antihistaminike. Možda se neće moći izbeći alergijska reakcija u potpunosti ali ovi koraci mogu pomoći da se spreče buduće alergijske reakcije

due to acrylic allergy are clinically manifested in the form of enanths and edema. Clinical experience shows that these changes, which often occur and are declared an allergy to acrylate, can also be the reaction of mucous membrane to frequent mechanical, infectious, thermal or chemical irritations.

Allergic reactions in the oral cavity can be accompanied by changes in the skin and other mucous membranes. Hematogenic changes of anaemia, eosinophilia, lymphocytosis, thrombocytopenia, decreased haemoglobin and accelerated sedimentation<sup>3,5,15</sup> often occur.

Morphological changes that accompany allergic reactions on the oral mucous membrane are often modified as a result of traumatic damage during mastication, saliva action, and mechanical effect of prosthetic compensations and oral *Candida* infections.

As for therapy, in most patients with an allergy to the medication, the use of a suspected drug was discontinued. With the use of antiseptic agents, changes regressed in a short time. In severe changes, antihistamines were administered per os or parenterally for 2-3 days. Rarely, corticosteroids were also given in severe forms.

### **Conclusion**

After a detailed review of the results and the overall data analysis, it can be concluded that a significant number of patients with allergic reactions on the oral cavity mucous membrane was registered for a period of three years (examined period). The most common form of allergic reaction was *Stomatitis allergica* and *Enanthema fixum*, with localization on the dorsal surface of the tongue and the mucous membrane of the cheeks. Almost half of the registered patients reported changes after taking the appropriate drug: sulfonamides and penicillins. If the cause of allergies is known, preventive control of an allergic reaction is in the first place. These reactions can be prevented by avoiding allergens that affect the allergy. However, symptoms may return if the patient again comes into contact with the allergen. Then, there is the possibility of a severe allergic reaction that can even be fatal.

When the cause of allergy is diagnosed, exposure to an allergen can be avoided. The patient can look for medical care and carry antihistamines. It may not be possible to completely avoid allergic reaction, but these steps can help to prevent future allergic reactions.

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All involved patients gave their consent forms

**Ethics approval**

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