



## COMMON ALLERGIES AND ALLERGENS IN ORAL AND PERIORAL DISEASES

Liborija Lugović-Mihić<sup>1,2</sup>, Ivana Ilić<sup>3</sup>, Jozo Budimir<sup>1</sup>, Nives Pondelj<sup>1</sup> and Marinka Mravak Stipetić<sup>4</sup>

<sup>1</sup>Department of Dermatovenereology, Sestre milosrdnice University Hospital Centre, Zagreb, Croatia;

<sup>2</sup>School of Dental Medicine, University of Zagreb, Zagreb, Croatia;

<sup>3</sup>Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia;

<sup>4</sup>Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia

**SUMMARY** – Allergic reactions sometimes participate in the development of perioral and oral diseases, indicating the need for appropriate allergen assessment. This review discusses current knowledge on the potential allergic reactions to different dental materials in patients with oral and perioral diseases. Aside from allergies to various dental materials, similar non-allergic, non-immune contact reactions (irritant or toxic) can occur. Among dental materials, the most frequent allergens are alloys, followed by rubber materials, polymers and acrylates. Allergic reactions to dental alloys that contain nickel, cobalt and amalgam are especially frequent since dentists use them for prosthetic and other restorations. There is a broad spectrum of clinical presentations of oral and perioral diseases possibly related to allergies, such as lichenoid reactions, cheilitis, perioral dermatitis, burning sensations, etc. Despite some limitations, patch test is crucial in the diagnosis and recognition of causative allergens because it reveals contact allergies, and is still superior in differentiating allergic and irritant contact reactions. It is important to examine patient medical histories (e.g., occurrence of symptoms after dental therapy or food consumption), and in consultation with their dentist, carry out allergy tests to specific dental allergens which are used or planned to be used in subsequent treatment.

**Key words:** *Allergy; Burning mouth syndrome; Cheilitis; Gingivostomatitis; Oral disease; Oral lichenoid reactions; Patch test*

### Introduction

Oral and perioral diseases are relatively frequent in the general population, and their symptoms can significantly affect the patient's quality of life. In cases of perioral and oral diseases, possible relations to various dental materials and procedures should always be taken into consideration when treating a patient<sup>1-3</sup>. Although there are many scientific papers on this issue, their results are ambiguous. Various substances can cause both immediate (type I) and delayed (type IV) allergic reactions, of which type IV allergic reactions are more common<sup>1,4,5</sup>.

On the other hand, some substances can provoke non-allergic, irritant or toxic reactions in which the immune mechanism is not involved<sup>6</sup>. Furthermore, patients often complain of unspecified sensations in perioral and oral soft tissues, which also makes it more difficult to evaluate the influence of allergies in perioral and oral diseases. Although there are no precise data on the incidence of side effects (unwanted reactions) from dental procedures and use of dental materials, it can be assumed that they are not very common<sup>7</sup>.

### Oral and Perioral Diseases Related to Allergic Reactions and Common Causative Allergens

There is a broad spectrum of clinical signs and symptoms of oral and perioral diseases that can be related to allergies, such as lichenoid reactions, cheilitis,

Correspondence to: Prof. Liborija Lugović-Mihić, MD, PhD, Department of Dermatovenereology, Sestre milosrdnice University Hospital Centre, Vinogradska c. 29, HR-10000 Zagreb, Croatia  
E-mail: liborija@gmail.com

Received June 27, 2019, accepted October 1, 2019

stomatitis, gingivitis, perioral dermatitis, burning sensations, swelling of the lips and face, etc.<sup>1,7-12</sup>.

Early allergic reactions (type I) with manifestations in oral and perioral regions mostly manifest with angioedema but sometimes may include oral paresthetic and burning sensations, pointing to oral allergy syndrome (OAS), a form of type I allergic reaction. Oral allergy syndrome usually occurs in patients who suffer from allergic rhinitis, mostly after taking fresh food (such as vegetables, fruits and various nuts), due to the cross-reaction between food and inhalants<sup>13</sup>.

On the other hand, various dental materials used in dental procedures may cause both allergic contact (delayed, type IV) and non-allergic contact reactions (irritant, toxic contact reactions). They appear when these materials have allergic or irritant effects on coming in contact with skin or oral mucosa. Unlike allergic reactions, in irritant contact reactions there is no allergic pathomechanism, no previous sensitizations to an allergen and no lesion spread<sup>14</sup>. The most common contact allergens that can cause allergic reactions in the oral cavity and perioral region are antiseptics, dental alloys, impression materials, local anesthetics, dental cement, latex gloves, acrylate, adhesives, mouth rinse liquids, various dental hygiene preparations, and others<sup>7</sup>.

Among dental materials, the most frequent allergens are dental alloys, followed by rubber materials, polymers and acrylates. (Notably, allergic reactions to local anesthetics are very uncommon). Metal salts in dental alloys, for example, have weak interactions with skin proteins and form complexes that make strong allergens that initiate hypersensitivity reactions<sup>14</sup>. Allergic reactions to dental alloys that contain nickel, cobalt and dental amalgam are especially frequent since dentists use them for prosthetic and dental restorations<sup>1,4,15</sup>.

Dental restorative materials include dental alloys, amalgams and tooth-colored fillings. Noble dental alloys, and semiprecious and nonprecious alloys as base metals are used in dental procedures<sup>10,11</sup>. (Noble alloys contain more than 40% gold, palladium and/or platinum, semiprecious alloys contain at least 25% noble metal, and nonprecious alloys often contain large percentages of nickel, cobalt, chromium or beryllium, stainless steel or titanium). Dental amalgam is produced by mixing liquid mercury with an alloy mixture consisting of silver, tin, zinc and copper, while tooth-colored fillings consist of composite resin, glass ionomer cement and porcelain<sup>10</sup>.

Positive allergy skin patch tests to gold are usually associated with the amount of gold used in dental procedures, although definite correlation between contact allergic reactions to gold and oral lesions has not been proven<sup>1</sup>. While gold is not common allergen, it is especially important to take into consideration the percentage of other gold alloy ingredients such as silver, copper, and smaller amounts of platinum, palladium and zinc. Silver-palladium alloys (also contain zinc and copper, and occasionally palladium and silver), as well as many other metals such as cobalt, chromium, molybdenum, beryllium, gallium, rhodium, iridium and some others are also used in dental procedures. In their systematic review, Levi *et al.* point out that each type of metal exposure has a different rate of allergic reaction, which they explain by the extent of corrosion of the alloy, population exposure, and the biologic environment of each patient<sup>16</sup>.

One of the most commonly mentioned allergens is rubber, which can be found in latex gloves (worn by dentists and their assistants) and rubber dams (used to isolate the operative site from the rest of the mouth)<sup>17-19</sup>. Cases of adverse patient reactions to latex gloves worn by dental health care workers have been reported by Agrawal *et al.* Their study results showed that 16% of dental professionals reported allergy to latex gloves, with the prevalence significantly higher in those who had allergy to pollen grains, foodstuffs and rubber dam, asthma and eczema in their medical history<sup>17</sup>. Other allergic reactions may be caused by substances which contain acrylates (most commonly methyl methacrylate, triethylene glycol dimethacrylate and polymethyl methacrylate) used for the fabrication of dentures, as well as for complex restoration procedures and as binding materials<sup>20</sup>. Reactions to traces of benzoyl peroxide in dentures, hydroquinone and plasticizer dibutyl phthalate inhibitors, pigments, dyes, nylon fibers, titanium and zinc oxides are also possible.

The process of evaluating lesions and symptoms affecting the oral and perioral region is quite challenging due to their numerous possible manifestations. Some patients have burning symptoms and paresthesias without clinically evident oral lesions, whereas some patients have clear clinical signs such as lichenoid tissue changes or oral ulcerations<sup>12</sup>. In the diagnosis and recognition of causative allergens, patch test is crucial because it reveals and confirms contact allergies, including patients with orofacial changes (particularly



Fig. 1. Positive patch tests to nickel-sulfate and cobalt-chloride.



Fig. 3. Lip lesions in a patient with contact allergy to flavors and metals.



Fig. 2. Positive prick test results to inhaled allergens.



Fig. 4. Food-induced angioedema of upper lip.

prior to dental treatment) and dental workers with chronic dermatitis of the hands and face (Fig. 1). Patch test is still superior in differentiating contact allergic and contact irritant reactions; however, its usefulness has not yet been fully established because studies have yielded variable results<sup>14,21</sup>.

There are numerous studies that have confirmed metal allergies in patients with dental alloys in their orthodontic devices and considering that it is impor-

tant to emphasize which allergens are most common to cause diseases such as burning mouth syndrome (BMS), gingivostomatitis, cheilitis and oral lichen planus (OLP)<sup>22-25</sup>. According to Budimir *et al.*, some particular allergens increase the risk of certain oral diseases and symptoms<sup>22</sup>. This risk is several times higher in atopic patients and those with existing allergies even in the absence of statistically significant differences in the occurrence of allergic reactions between

Table 1. Causative allergens for each oral and perioral disease

Oral and perioral disease	Author (year)	Number of patients	Causative agent
Cheilitis	Budimir <i>et al.</i> , 2018	230 subjects (78.3% females, 21.7% males)	Cobalt chloride (10%), nickel sulfate (6.7%), mercury precipitate (6.7%)
	Khamaysi <i>et al.</i> , 2006	121 dental personnel with clinical presentation of oral and perioral disease were patch tested	Nickel sulfate (25.8%), gold sodium thiosulfate (22.6%), mercury (16.1%), palladium chloride (12.9%)
	Torgerson <i>et al.</i> , 2007	331 patients with BMS, LTR, cheilitis, stomatitis, gingivitis, orofacial granulomatosis, perioral dermatitis and recurrent aphthous stomatitis	Fragrance mix (13%), gold sodium thiosulfate (6.8%), dodecyl gallate (6.1%)
	Raap <i>et al.</i> , 2009	206 patients who underwent patch testing because of suspected contact allergy to dental materials	Amalgam (100%)
	Kim <i>et al.</i> , 2015	44 patients with oral disease from 2004 to 2011 (oral lichen planus, BMS, cheilitis)	Cobalt chloride hexahydrate (33.3%), nickel sulfate (16.6%), potassium dichromate (16.6%), mercury (16.6%)
(Gingivo)stomatitis	Budimir <i>et al.</i> , 2018	230 subjects (78.3% females, 21.7% males)	Nickel sulfate (10%), cobalt chloride (6.7%), mercury precipitate (3.3%)
	Torgerson <i>et al.</i> , 2007	331 patients with BMS, LTR, cheilitis, stomatitis, gingivitis, orofacial granulomatosis, perioral dermatitis and recurrent aphthous stomatitis	Mercury (14.3%), balsam of Peru (12.5%), gold sodium thiosulfate
	Raap <i>et al.</i> , 2009	206 patients who underwent patch testing because of suspected contact allergy to dental materials	Nickel sulfate (50%), palladium chloride (37.5%), gold sodium thiosulfate (37.5%)
	Rai <i>et al.</i> , 2014	20 patients who undergone dental procedures (13 patients with symptoms of oral lichen planus, oral stomatitis, burning mouth symptoms and recurrent aphthosis and 7 dental personnel)	Potassium chromate, nickel, palladium
Perioral dermatitis	Budimir <i>et al.</i> , 2018	230 subjects (78.3% females, 21.7% males)	Fragrance mix (6.7%), cobalt chloride (6.7%), nickel sulfate (3.3%)
	Khamaysi <i>et al.</i> , 2006	121 dental personnel with clinical presentation of oral and perioral disease were patch tested	Nickel sulfate (25.8%), gold sodium thiosulfate (22.6%), mercury (16.1%), palladium chloride (12.9%)
	Torgerson <i>et al.</i> , 2007	331 patients with BMS, LTR, cheilitis, stomatitis, gingivitis, orofacial granulomatosis, perioral dermatitis and recurrent aphthous stomatitis	Cobalt chloride (60%), gold sodium thiosulfate (25%), balsam of Peru (20%)

Table 1. Continued

Oral and perioral disease	Author (year)	Number of patients	Causative agent
Burning mouth syndrome	Budimir <i>et al.</i> , 2018	230 subjects (78.3% females, 21.7% males)	Cobalt chloride (13.3%), P-phenylenediamine colophony (3.3%)
	Khamaysi <i>et al.</i> , 2006	121 dental personnel with clinical presentation of oral and perioral disease were patch tested	Nickel sulfate (15.9%), mercury (15.8%), palladium chloride (10.5%), gold sodium sulfate (10.5%)
	Torgerson <i>et al.</i> , 2007	331 patients with BMS, LTR, cheilitis, stomatitis, gingivitis, orofacial granulomatosis, perioral dermatitis and recurrent aphthous stomatitis	Potassium dicyanoaurate (16.4%), nickel sulfate hexahydrate (12.3%), gold sodium thiosulfate (10.9%)
	Raap <i>et al.</i> , 2009	206 patients who underwent patch testing because of suspected contact allergy to dental materials	Gold sodium thiosulfate (66.6%), nickel sulfate (66.6%), palladium chloride (33.3%), cobalt chloride (33.3%)
	Rai <i>et al.</i> , 2014	20 patients who underwent dental procedures (13 patients with symptoms of oral lichen planus, oral stomatitis, burning mouth symptoms and recurrent aphthosis and 7 dental personnel)	Methylhydroquinone
	Kim <i>et al.</i> , 2015	44 patients with oral disease from 2004 to 2011 (oral lichen planus, BMS, cheilitis)	Cobalt chloride hexahydrate (25%)
Oral lichen planus (lichenoid tissue reaction)	Budimir <i>et al.</i> , 2018	230 subjects (78.3% females, 21.7% males)	Cobalt chloride (6.7%), gold (3.3%), thimerosal (3.3%)
	Khamaysi <i>et al.</i> , 2006	121 dental personnel with clinical presentation of oral and perioral disease were patch tested	Gold sodium thiosulfate (11.8%), nickel sulfate (5.8%), mercury (5.8%)
	Torgerson <i>et al.</i> , 2007	331 patients with BMS, LTR, cheilitis, stomatitis, gingivitis, orofacial granulomatosis, perioral dermatitis and recurrent aphthous stomatitis	Potassium dicyanoaurate (28%), fragrance mix (17.1%), gold sodium thiosulfate (15.1%)
	Raap <i>et al.</i> , 2009	206 patients who underwent patch testing because of suspected contact allergy to dental materials	Palladium chloride (44.4%), nickel sulfate (22.2%), gold sodium thiosulfate (22.2%)
	Rai <i>et al.</i> , 2014	20 patients who underwent dental procedures (13 patients with symptoms of oral lichen planus, oral stomatitis, burning mouth symptoms and recurrent aphthosis and 7 dental personnel)	Nickel, potassium chromate, copper sulfate, amalgam
	Kim <i>et al.</i> , 2015	44 patients with oral disease from 2004 to 2011 (oral lichen planus, BMS, cheilitis)	Gold sodium thiosulfate (33.3%), nickel sulfate (33.3%), potassium dichromate (33.3%), cobalt chloride hexahydrate (8.3%)

BMS = burning mouth syndrome; LTR = lichenoid tissue reaction

subjects with certain oral diseases and healthy controls<sup>22</sup>. This was shown to be true for BMS and its association to nutritive allergens and food additives, for oral lichen planus and inhalants, and for cheilitis and contact allergens such as cobalt-chloride and nickel-sulfate found in dental alloys. These findings contribute to the knowledge of the etiology of these diseases and the justification of using skin tests in these particular oral diseases.

According to Torgerson *et al.*, positive contact allergies were established in 44.7% of patients that underwent patch testing, as well as possible multiple positive reactions due to cross-reactions, which has also been noted in other studies<sup>12,22</sup>. The frequency of positive patch tests to dental materials was higher in some other studies, even reaching 70.5%<sup>10</sup>. Many studies show various frequencies of positive patch tests for allergens in certain oral and perioral diseases. Particularly common allergens established with patch testing are metals found in dental materials<sup>24</sup>. According to Khamaysi *et al.*, the most common contact allergens established with patch testing in their study were gold sodium thiosulfate (14.0%), nickel sulfate (13.2%), mercury (9.9%), palladium chloride (7.4%), cobalt chloride (5.0%) and 2-hydroxyethyl methacrylate (5.8%)<sup>9</sup>. In a study by Kim Tae-Wook *et al.*, the most common contact allergic reactions in oral and perioral diseases were established in oral lichen planus (75%), cheilitis (75%), BMS (25%), and other oral diseases (75%)<sup>10</sup>. [In the study by Khamaysi *et al.*, these were cheilitis (41.9%), perioral dermatitis (41.9%) and lichenoid reactions (35.3%)<sup>9</sup>. In addition to patch tests, immediate hypersensitivity tests such as prick tests and serum tests for determination of specific IgE can also be used sometimes (Fig. 2)<sup>7,11</sup>.

## Review of Oral and Perioral Diseases and Causative Allergens

*Cheilitis* (inflammation of the lips) includes many clinical types and is possibly related to many allergens (Table 1). Cheilitis can present alone or be associated with stomatitis or perioral eczema<sup>2,14,21,26</sup>. According to the latest classification of cheilitis, proposed by Lugović-Mihić *et al.*, it can be divided into three groups, as follows: mainly reversible (simplex, angular/infective, contact/eczematous, exfoliative, drug related); mainly irreversible (actinic, granulomatous, glan-

dular, plasma cell); and cheilitis connected to dermatoses and systemic diseases (lupus, lichen planus, pemphigus/pemphigoid group, angioedema, salivation disorder, etc.)<sup>26</sup>. Contact/eczematous cheilitis is the result of an irritating or allergic contact effect with various substances, such as medications, toothpaste ingredients (e.g., sodium lauryl sulfate), cleaning agents for dentures (potassium-persulfate), dental floss (colophony), nail polish, cosmetics (e.g., lipstick, lip gloss), food and flavors, musical wind instruments (nickel, wood), etc. (Fig. 3)<sup>1,27</sup>. Allergies and allergens can sometimes be difficult to establish in some patients. A study conducted in cheilitis patients established irritant contact dermatitis in 36% of patients having undergone patch testing, allergic contact dermatitis in 25%, atopic eczema in 19%, and unknown causes in 9%<sup>27</sup>. According to a recent study by Budimir *et al.*, patients with cheilitis showed a statistically significantly higher frequency of positive patch tests (26.7%) compared to healthy controls, and the common allergens were cobalt-chloride (10%), nickel-sulfate (6.7%) and mercury precipitate (6.7%)<sup>22</sup>. Torgerson *et al.* observed a similar frequency of positive patch tests in their patients (25.9%), whereas Kim *et al.* report an even higher frequency (75%), particularly when metals used in dental medicine were involved<sup>10,12</sup>.

*Angioedema* can be induced by various factors and allergens, such as drugs, foodstuffs, preservatives, cosmetics, etc. (Fig. 4). It predominantly appears as a hypersensitivity reaction type I, or sometimes type IV, and such reactions can occur after contact with latex, dental products, etc. during dental treatment (when dentist's glove comes in contact with the lip, or in contact with cinnamaldehyde, menthol or eugenol in toothpaste), etc.<sup>18,19</sup>. In dental practice, also possible are allergic reactions to formaldehyde (used for disinfection in root canals), immediate-type allergies to local anesthetics or delayed-type allergies from longer operative procedures (e.g., additives from the glove rubber or rubber dam)<sup>1,7</sup>. These reactions should be examined for both immediate and delayed hypersensitivity reactions, usually by skin allergy tests, which are conducted during remission of angioedema and when the patient is not under anti-allergic therapy. Also, food ingredients, e.g., benzoates, antioxidants or spices, can be the possible causes of angioedema. According to the results of the study by Budimir *et al.*, additive allergens were confirmed in 23.3% of angioedema

patients, and physicians were advised to monitor patient conditions after allergen elimination<sup>22</sup>. In addition, facial edema sometimes occurs due to metals in the oral cavity (e.g., crowns with palladium), and removal of such metals has proved beneficial. In a recent study by Budimir *et al.*, patch test was positive in 6.7% of angioedema patients, and the most frequent contact allergens were cobalt-chloride (3.3%) and nickel-sulfate (3.3%)<sup>22</sup>. In the study by Khamaysi *et al.*, the number of patients positive to gold and nickel was high (13.2%), but one half of the patients positive to nickel were also positive to palladium chloride and cobalt chloride, which most probably indicated cross reaction with nickel<sup>9</sup>. According to Budimir *et al.*, recent results on allergic reactions in the oral and perioral regions show that the risk of angioedema is 3-fold higher in subjects with established allergies and in men. Furthermore, the risk increases with age. It was also established that patients with angioedema exhibited reactions to more allergens than other patients<sup>22</sup>.

*Perioral dermatitis* is sometimes, although rarely, associated with allergic reactions and is possibly connected to many allergens (Table 1)<sup>22</sup>. The disease is benign and it is usually contact dermatitis caused by substances in toothpaste, gum, lipstick, or medications<sup>28</sup>. While some studies suggest that metals (e.g., nickel and chrome) in dental appliances can be the cause or aggravating factor for this disease, others did not record adverse reactions in patients allergic to nickel following application of dental crowns or bridges<sup>29,30</sup>. Torgerson *et al.* report positive patch tests in 80% of patients with perioral dermatitis, but positive patch tests were less frequent in the study by Budimir *et al.* (16.7%)<sup>12,22</sup>. Fragrances, cobalt-chloride and nickel-sulfate were the most common contact allergens in both these studies<sup>12</sup>. It is possible that perioral lesions are similar to allergic contact dermatitis and irritant contact dermatitis. Allergic contact dermatitis is a manifestation of type IV hypersensitivity reaction to agents that come in contact with the skin, and patients may present with inflammatory papules, vesicles, weeping or crusting, while distribution of lesions is dependent upon the specific sites of contact with the initiating agent. Unlike perioral dermatitis, intense pruritus is usually present, scaling is often prominent, and lesions fail to improve with antibiotic therapy. On the other hand, in irritant contact dermatitis, clinical findings vary based upon the nature of the external trigger

and site of involvement, and usually include papules, vesicles, scales, erythema or edema, and a burning rather than itching sensation, unlike allergic contact dermatitis but similar to perioral dermatitis. In irritant contact dermatitis, patient history is of value for identifying this diagnosis (as an example, irritant dermatitis related to chronic lip-licking behavior can resemble perioral dermatitis).

*Oral lichenoid reactions* (OLR) are often associated with contact allergies and positive patch tests (Table 1). In patients with oral lichenoid lesions, determination of metal sensitivity is quite important<sup>12,31-33</sup>. There are many studies that confirm the effect of metal allergies in oral lichenoid lesions, especially in dental restorations and orthodontic devices. Laine *et al.* established allergies to metals in 67.7% of OLR patients using the patch test, particularly to mercury (66.1%), gold (9.3%), cobalt (3.3%), and others (tin, silver, palladium and chrome)<sup>31</sup>. Studies often point out allergic reactions to mercury, although their percentages vary<sup>33,34</sup>. Irritant contact reactions to mercury are possible in cases when patch test is negative; thus, removal of an adjacent amalgam can initiate improvement due to the fact that amalgam releases mercury<sup>7,32,33</sup>. Dunsche *et al.* report that 27.7% of 134 patients with oral lichenoid lesions showed positive patch test results to inorganic mercury or amalgam. Amalgam removal led to improvement in 97.1% of patients<sup>33</sup>. However, two studies (performed by Budimir *et al.* and Kim *et al.*) observed no positive reactions to mercury, which may be connected to the use of amalgam as restorative material, as shown previously by Choi *et al.*<sup>10,22,35</sup>. Scalf *et al.* report that 49% of 51 patients with lichenoid lesions in different regions and tissues (oral, genital, cutaneous) had positive patch test with at least one mercurial allergen<sup>36</sup>. In the same study, positive patch test reactions were detected to chromate, gold and thimerosal exposure, and interestingly, 100% of patients declared improvement after metal replacement. Torgerson *et al.* established positive patch tests in 55.9% of OLR patients, whereas Budimir *et al.* found positive patch test (10%) less frequently, and the commonest contact allergens were cobalt-chloride (6.7%), gold sodium thio-sulfate (3.3%) and thimerosal (3.3%)<sup>12,22</sup>. In OLR, a connection with other metals (particularly gold, chrome and cobalt) is also sometimes observed<sup>22</sup>. Gold can cause various oral difficulties (including OLR, facial dermatitis and oral burning symptoms); in such

cases, removal of gold can result in improvement<sup>37</sup>. This leads to a conclusion that contact allergy to different metals is more common among people having lichenoid tissue changes. Taking all the above into consideration, performing patch tests before dental procedures or implanting orthodontic materials is quite important. In addition, for instance, after consumption of sour or spicy food or drinks, people with OLR can react to other substances in various ways, ranging from pricking sensation to severe pain. Because these patients often complain of oral sensitivity and an unpleasant burning sensation in the mouth, the immediate hypersensitivity test is also useful<sup>7,38</sup>. By using prick tests in different oral diseases, recently we established that allergic reactions were most common in lichen (53.3%), and also more frequently occurred in atopic patients, thus appropriate diagnostics should be carried out to establish possible OAS<sup>22</sup>.

*Gingivostomatitis* is a disease of oral cavity that can also be associated with contact allergies after exposure to dental materials (e.g., metals or plastics in dentures), as it has been shown that stomatitis is associated with partial dentures and some dental metals (e.g., palladium, gold or manganese) (Table 1)<sup>7,39,40</sup>. Gingivostomatitis as a reaction to acrylates is also possible (e.g., due to allergy to 2-hydroxyethyl methacrylate, HEMA, used in dentures). In this case, a patient can have tingling sensation or feel jaw pain, but symptoms gradually disappear after acrylate has been removed<sup>41</sup>. As for the etiology in cases of gingivostomatitis, reactions to food additives (e.g., benzoic acid) and flavors (e.g., cinnamaldehyde) are also possible, which can cause inflammation of oral mucosa. Avoiding these additives and flavors is the only therapy. According to the results reported by Budimir *et al.*, patch test was positive to at least one contact allergen in 16.7% of patients with gingivostomatitis, while Torgerson *et al.* established statistically more frequent contact allergies in patients with stomatitis and gingivitis (30.8% and 64% of tested patients, respectively)<sup>12,22</sup>. The most common contact allergens in our recent study of patients with gingivostomatitis were nickel-sulfate, cobalt-chloride and mercury precipitate, although with no statistical significance in comparison to healthy controls<sup>22</sup>.

*Burning mouth syndrome* is a disease of unknown etiology and is possibly related to some allergens (Table 1). Some authors differentiate BMS into primary

and secondary type, primary being idiopathic and secondary determined by local, systemic or psychological factors<sup>2</sup>. There is a controversy of connecting BMS with contact allergy although sometimes, various substances like foodstuffs (instant coffee, peanuts, chestnuts), additives (benzoic acid, sodium metabisulfite) metals (cadmium, mercury, nickel, cobalt-chloride), plastics (epoxy resins, benzoyl peroxide, bisphenol A), etc. are mentioned as potential causes<sup>7,21</sup>. It is therefore necessary to rule out all possible etiologic factors, including allergy. A few studies have indicated that patients with BMS exhibit clinically relevant contact allergies to gold and nickel, even small quantities of them in dental materials can cause these allergies<sup>25</sup>. While Torgerson *et al.* report positive patch test in 42.1% of BMS subjects, according to Budimir *et al.* positive test was less frequent (20% of patients)<sup>12,22</sup>. The most frequent contact allergens were cobalt-chloride, Ursol<sup>TM</sup> and colophony<sup>12</sup>. Some studies also indicated that in part of BMS patients, immediate-type allergies to nutritive allergens were established in the same patients<sup>12</sup>. Based on the results of the study conducted by Budimir *et al.*, the risk of BMS was higher in atopic patients, although with no statistical significance<sup>22</sup>. However, it is possible that an established allergy may not be related to oral symptoms, so positive allergy tests should be taken with caution and additional diagnostic workup should be considered.

### Importance of Examination for Allergy and Patch Test Usefulness

Given the different results of individual studies on the usefulness of performing allergy tests in diagnosing oral and perioral diseases with non-specific sensations, it is justified in the cases of unknown etiology to carry out allergy tests in order to establish possible allergies (mostly using patch tests and prick tests). Skin patch testing is a simpler procedure and preferred to mucosal testing. Other reasons for choosing skin test before mucosal are the higher specificity and sensitivity of the skin patch test and the requirement of a significantly higher concentration of allergens for mucosal testing, which often results in many adverse reactions<sup>42</sup>. Taking into account the fact that burning symptoms in the oral cavity can be caused by allergic cross-reactions between food and inhalants (OAS), it is also justified to examine the possible immediate al-

lergic hypersensitivity, usually by prick testing<sup>13</sup>. The choice of the allergens to be tested is also important; it varies by studies, countries and number of allergens. Allergy unit prepares testing samples according to patient history and in consultation with dentists.

One should also keep in mind that patch tests have a few limitations and pitfalls when it comes to the significance for oral diseases<sup>2</sup>. This is due to different allergen concentrations and standard preparations for patch testing, as well as due to different pH of the skin and oral mucosa, which may result in either false-positive/negative reactions or non-specific irritant reactions<sup>2</sup>. When carrying out patch test and establishing reactions, it is important to consider that standard reading may be insufficient and subsequent test (in 10 days or more) should be read in case of false-positive results (e.g., up to one-third of patients allergic to mercury)<sup>1</sup>. When establishing reactions, other potential factors should be considered, as well as the possibility that oral difficulties are in no way connected with the suspected dental materials or that the same substances can cause different reactions in one patient (either allergic or irritant). In such cases, it is possible that, regardless of a negative patch test, such a substance induces an irritant (non-allergic) reaction. Here it is crucial to emphasize that occasionally, some patients may have negative results to patch to metals on standard reading and positive results on delayed reading after 10 days (this often refers to allergy to mercury)<sup>14</sup>.

Clinical relevance of positive results to haptens in patch test is also difficult to evaluate because of the high number of products and their contents that are in contact with patient oral cavity and mucosa every day, which makes it difficult to prove one particular hapten blameworthy by avoiding method<sup>2</sup>. However, patch tests with dental screening series are worth considering for oral diseases, especially for oral lichen planus<sup>10</sup>. In a study by Holmstrup, the author suggests indications for patch testing, including OLRs and mucositis resistant to treatment, objective and evident relation between allergen and lesions, and absence of symmetry in lesions, in order to prevent adverse effects and sensitization in these patients<sup>43</sup>. There are some other diagnostic tools that could be helpful in the future for determination of allergies in the oral and perioral area, such as persistent manifestations. Some studies suggest that histology would be useful in case of revealing whether the specific T cells for certain allergen are

present at the lesion site, or that the flow cytometry technique could demonstrate increase in the concentration of T cells in blood after exposure to allergen, which would improve both diagnostic and treatment aspects of oral and perioral manifestations/diseases<sup>15,44</sup>. There also are some other new methods for detecting type IV hypersensitivity to metals, which are promising but not yet widely available, such as memory lymphocyte immunostimulation assay or MELISA<sup>14</sup>.

## Conclusion

In conclusion, we would like to point out that in the cases of non-specific oral difficulties, it is important to examine patient medical histories (e.g., occurrence of symptoms after dental therapy or food consumption) and in consultation with their dentist, carry out allergy tests to the specific dental allergens that are used or planned to be used in subsequent treatment. One should always keep in mind that the same substances can cause undesirable (either allergic or irritant) and different reactions in patients. Therefore, it is important to follow up patients and determine whether elimination of certain substances will contribute to the elimination of ailments.

## References

1. Bakula A, Lugović-Mihić L, Šitum M, Turčin J, Šinković A. Contact allergy in the mouth: diversity of clinical presentations and diagnosis of common allergens relevant to dental practice. *Acta Clin Croat.* 2011;50:553-61.
2. Minciullo PL, Galati P, Isola S, Lombardo G, Gangemi S, Di Leo E, Nettis E, Mallamace A, Vacca A. The role of dental series patch tests in oral mucosal diseases. *Dermatitis.* 2010; 21:123-4.
3. Rai R, Dinakar D, Kurian SS, Bindoo YA. Investigation of contact allergy to dental materials by patch testing. *Indian Dermatol Online J.* 2014;5:282-6. doi: 10.4103/2229-5178.137778.
4. Linauskienė K, Malinauskienė L, Blažienė A. Metals are important contact sensitizers: an experience from Lithuania. *Biomed Res Int.* 2017;2017:3964045. doi: 10.1155/2017/3964045.
5. Rochford C, Milles M. A review of the pathophysiology, diagnosis, and management of allergic reactions in the dental office. *Quintessence Int.* 2011;42:149-56.
6. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC. Revised nomenclature for allergy for global use: Report of the Nomen-

- clature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol.* 2004;113:832-6.
7. Gawkrödger DJ. Investigation of reactions to dental materials. *Br J Dermatol.* 2005;153:479-85.
  8. Ahlgren C, Isaksson M, Möller H, Axéll T, Liedholm R, Bruze M. The necessity of a test reading after 1 week to detect late positive patch test reactions in patients with oral lichen lesions. *Clin Oral Investig.* 2014;18:1525-31. doi: 10.1007/s00784-013-1122-0.
  9. Khamaysi Z, Bergman R, Weltfriend S. Positive patch test reactions to allergens of the dental series and the relation to the clinical presentations. *Contact Dermatitis.* 2006;55:216-8.
  10. Kim TW, Kim WI, Mun JH, Song M, Kim HS, Kim BS, Kim MB, Ko HC. Patch testing with dental screening series in oral disease. *Ann Dermatol.* 2015;27:389-93. doi: 10.5021/ad.2015.27.4.389.
  11. Syed M, Chopra R, Sachdev V. Allergic reactions to dental materials – a systematic review. *J Clin Diagn Res.* 2015;9:ZE04-9. doi: 10.7860/JCDR/2015/15640.6589.
  12. Torgerson RR, Davis MD, Bruce AJ, Farmer SA, Rogers RS 3<sup>rd</sup>. Contact allergy in oral disease. *J Am Acad Dermatol.* 2007;57:315-21.
  13. Kelava N, Lugović-Mihić L, Duvančić T, Romić R, Šitum M. Oral allergy syndrome – the need of a multidisciplinary approach. *Acta Clin Croat.* 2014;53:210-9.
  14. Lugović-Mihić L, Šitum M, *et al.*, editors. *Skin Diseases with Facial and Oral Lesions.* Zagreb: Medicinska naklada, 2019; p. 16-27.
  15. Di Tola M, Marino M, Amodeo R, Tabacco F, Casale R, Portaro L, Borghini R, Cristaudo A, Manna F, Rossi A, De Pità O, Cardelli P, Picarelli A. Immunological characterization of the allergic contact mucositis related to the ingestion of nickel-rich foods. *Immunobiology.* 2014;219:522-30. doi: 10.1016/j.imbio.2014.03.010.
  16. Levi L, Barak S, Katz J. Allergic reactions associated with metal alloys in porcelain-fused-to-metal fixed prosthodontic devices – a systematic review. *Quintessence Int.* 2012;43:871-7.
  17. Agrawal A, Bhatt N, Kk S, Singh K, Chaudhary H, Asawa K. Prevalence of allergy to latex gloves among dental professionals in Udaipur, Rajasthan, India. *Oral Health Prev Dent.* 2010; 8:345-50.
  18. Japundžić I, Lugović-Mihić L. Skin reactions to latex in dental professionals – first Croatian data. *Int J Occup Saf Ergon.* 2017;14:1-6. doi:10.1080/10803548.2017.1388026.
  19. Japundžić I, Vodanović M, Lugović-Mihić L. An analysis of skin prick tests to latex and patch tests to rubber additives and other causative factors among dental professionals and students with contact dermatoses. *Int Arch Allergy Immunol.* 2018; 177:238-44. doi: 10.1159/000490181.
  20. Aalto-Korte K, Henriks-Eckerman ML, Kuuliala O, Jolanki R. Occupational methacrylate and acrylate allergy – cross-reactions and possible screening allergens. *Contact Dermatitis.* 2010;63:301-12. doi: 10.1111/j.1600-0536.2010.01760.x.
  21. Eisen D, Eisenberg E. Oral lichen planus and the burning mouth syndrome. Is there a role for patch testing? *Am J Contact Dermatitis.* 2000;11:111-4.
  22. Budimir J, Mravak-Stipetić M, Bulat V, Ferček I, Japundžić I, Lugović-Mihić L. Allergic reactions in oral and perioral diseases – what do allergy skin test results show? *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2019;127:40-8. doi: 10.1016/j.oooo.2018.08.001.
  23. Chakravarthi S, Padmanabhan S, Chitharanjan AB. Allergy and orthodontics. *J Orthodont Sci.* 2012;1:83-7. doi: 10.4103/2278-0203.105871.
  24. Mittermüller P, Hiller KA, Schmalz G, Buchalla W. Five hundred patients reporting on adverse effects from dental materials: frequencies, complaints, symptoms, allergies. *Dent Mater.* 2018;34:1756-68. doi: 10.1016/j.dental.2018.09.012.
  25. Pigatto PD, Brambilla L, Guzzi G, Spadari F. Burning lips syndrome. *Contact Dermatitis.* 2007;57:344-6.
  26. Lugović-Mihić L, Pilipović K, Crnarić I, Šitum M, Duvančić T. Differential diagnosis of cheilitis – how to classify cheilitis? *Acta Clin Croat.* 2018;57:342-51. doi: 10.20471/acc.2018.57.02.16.
  27. Freeman S, Stephens R. Cheilitis: analysis of 75 cases referred to a Contact Dermatitis Clinic. *Am J Contact Dermatitis.* 1999;10:198-200.
  28. Lopez CM, Mendez MD. Food allergies. In: *StatPearls [Internet].* Treasure Island (FL): StatPearls Publishing; 2018. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK482187/>
  29. de Silva BD, Docherty V. Nickel allergy from orthodontic appliances. *Contact Dermatitis.* 2000;42:102-3.
  30. Spiechowicz E, Glantz PO, Axell T, Grochowski P. A long-term follow-up of allergy to nickel among fixed prostheses wearers. *Eur Prosthodont Restor Dent.* 1999;7:41-4.
  31. Laine J, Kalimo K, Happonen RP. Contact allergy to dental restorative materials in patients with oral lichenoid lesions. *Contact Dermatitis.* 1997;36:141-6.
  32. Thanyavuthi A, Boonchai W, Kasemsarn P. Amalgam contact allergy in oral lichenoid lesions. *Dermatitis.* 2016;27:215-21. doi: 10.1097/DER.0000000000000204.
  33. Dunsche A, Kästel I, Terheyden H, Springer IN, Christophers E, Brasch J. Oral lichenoid reactions associated with amalgam: improvement after amalgam removal. *Br J Dermatol.* 2003; 148:70-6.
  34. Wong L, Freeman S. Oral lichenoid lesions (OLL) and mercury in amalgam fillings. *Contact Dermatitis.* 2003;48:74-9.
  35. Choi EJ, Jung TR, Kim CC, Kim YJ. The changes in practice pattern and patient distribution for the last 5 years (2000-2005) in the Department of Pediatric Dentistry at Seoul National University Dental Hospital. *J Korean Acad Pediatr Dent.* 2006;33:673-7.
  36. Scalf LA, Fowler JF Jr, Morgan KW, Looney SW. Dental metal allergy in patients with oral, cutaneous and genital lichenoid reactions. *Am J Contact Dermatitis.* 2001;12:146-50.

37. Möller H. Contact allergy to gold as a model for clinical-experimental research. *Contact Dermatitis*. 2010;62:193-200. doi: 10.1111/j.1600-0536.2010.01671.x.
38. Thongprasom K, Carrozzo M, Furness S, Lodi G. Interventions for treating oral lichen planus. *Cochrane Database Syst Rev*. 2011;CD001168. doi: 10.1002/14651858.CD001168.pub2.
39. Pardo J, Rodriguez-Serna M, de la Cuadra J, Fortea JM. Allergic contact stomatitis due to manganese in a dental prosthesis. *Contact Dermatitis*. 2004;50:41.
40. Yoshimura FC, Cunha Vdo E, Hahnstadt RL, Pires MC. Evaluation of dental material series from patients with dental prostheses and suspicion of delayed-type hypersensitivity. *An Bras Dermatol*. 2016;91:141-8. doi: 10.1590/abd1806-4841.20164116.
41. Martin N, Bell HK, Longman LP, King CM. Orofacial reaction to methacrylates in dental materials: a clinical report. *J Prosthet Dent*. 2003;90:225-7.
42. McParland H, Warnakulasuriya S. Oral lichenoid contact lesions to mercury and dental amalgam – a review. *J Biomed Biotechnol*. 2012;2012:589569. doi: 10.1155/2012/589569.
43. Holmstrup P. Oral mucosa and skin reactions related to amalgam. *Adv Dent Res*. 1992;6:120-4.
44. Shigematsu H, Kumagai K, Kobayashi H, Eguchi T, Kitaura K, Suzuki S, Horikawa T, Matsutani T, Ogasawara K, Hamada Y, Suzuki R. Accumulation of metal-specific T cells in inflamed skin in a novel murine model of chromium-induced allergic contact dermatitis. *PLoS One*. 2014;9:e85983. doi: 10.1371/journal.pone.0085983.

#### Sažetak

### UČESTALE ALERGIJE I ALERGENI U ETIOLOGIJI ORALNE I PERIORALNE SLUZNICE I KOŽE

*L. Lugović-Mihic, I. Ilić, J. Budimir, N. Pondeljak i M. Mravak Stipetić*

Alergijske reakcije ponekad sudjeluju u razvoju perioralnih i oralnih bolesti, što ukazuje na potrebu određivanja potencijalnih alergena. Ovaj pregledni članak govori o trenutnim saznanjima o potencijalnim alergijskim reakcijama na različite dentalne materijale u bolesnika s oralnim i perioralnim bolestima. Uz alergije na razne dentalne materijale mogu se pojaviti slične nealergijske, neimunske kontaktne reakcije (nadražujuće ili toksične). Među zubnim materijalima zubne legure najčešći su alergeni, a slijede ih gumeni materijali, polimeri i akrilati. Alergijske reakcije na zubne legure koje sadrže nikal, kobalt i amalgam osobito su česte, jer ih stomatolozi koriste za protetičke i druge restauracije. Postoji širok spektar oralnih i perioralnih bolesti koje su vjerojatno povezane s alergijama, poput lichenoidnih reakcija, heilitisa, perioralnog dermatitisa, osjećaja pečenja itd. Unatoč određenim ograničenjima epikutani test je presudan u dijagnozi i prepoznavanju uzročnih alergena, jer otkriva kontaktne alergije i još je superiorniji u razlikovanju alergijskih i iritativnih kontaktnih reakcija. Važno je uzeti detaljnu anamenu bolesnika (npr. pojavu simptoma nakon stomatološke terapije ili konzumiranja hrane) i uz savjetovanje sa stomatologom provesti alergološko testiranje na specifične stomatološke alergene koji se koriste ili se planiraju koristiti u sljedećem liječenju.

**Ključne riječi:** *Alergija; Sindrom pečenja usta; Heilitis; Gingivostomatitis; Bolesti usne šupljine; Oralne lichenoidne reakcije; Epikutani test*