



# ASSESSMENT OF ALLERGIES TO FOOD AND ADDITIVES IN PATIENTS WITH ANGIOEDEMA, BURNING MOUTH SYNDROME, CHEILITIS, GINGIVOSTOMATITIS, ORAL LICHENOID REACTIONS, AND PERIORAL DERMATITIS

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**SUMMARY** – Oral cavity and perioral area are constantly exposed to a variety of antigens, including food and additives, which have a potential role in the development of different oral mucosal and perioral cutaneous diseases since they can cause hypersensitivity reactions. Oral and perioral diseases mainly include angioedema, burning mouth syndrome, cheilitis, gingivostomatitis, oral lichenoid reactions, and perioral dermatitis. Previous studies were focused on delayed-type oral allergies by performing patch testing but did not include tests for immediate-type allergic reactions. Therefore, the objective of this study was to determine common nutritive and additive allergens in the prevalent oral and perioral diseases by using skin prick tests. Our study evaluated 230 participants, i.e. 180 patients with oral/perioral diseases (angioedema, burning mouth syndrome, cheilitis, gingivostomatitis, oral lichenoid reactions, and perioral dermatitis), and 50 healthy control subjects. The results of skin prick tests showed that immediate-type allergic reactions to food and additives were mostly seen in patients with burning mouth syndrome (40%) and cheilitis (33.3%), whereas allergies were least frequently observed in perioral dermatitis (10%) and gingivostomatitis (20%). Fruits, mushrooms, and vegetables were the most frequent causes of nutritive allergies in oral and perioral diseases. The most commonly identified additive allergens were glutaraldehyde, citric acid, and sodium glutamate. Study results suggest the possible association with nutritive and additive allergies be considered in cases of persistent oral mucosal or perioral skin disease accompanied by respective medical history.

**Key words:** *Additives; Allergy; Food; Oral diseases; Perioral diseases; Skin prick test; Patch test; Skin; Angioedema*

## Introduction

Oral mucosa and perioral skin are constantly exposed to a variety of antigens, including food, additives, inhalants, dental materials, drugs, hygiene products, and cosmetics. It has been reported that these

allergens have a potential role in the development of oral and perioral diseases since they can cause both immediate- and delayed-type hypersensitivity reactions<sup>1,2</sup>. Clinically, allergic reactions in the oral and perioral area could often be persistent or recurrent conditions, with a wide spectrum of signs and symptoms, mostly presenting as angioedema, burning mouth syndrome, cheilitis, gingivostomatitis, oral lichenoid reactions, or perioral dermatitis<sup>1-3</sup>. Besides that, some patients have no clinically evident lesions of perioral skin or oral mucosa, but often experience un-

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comfortable sensations such as itching, swelling, burning or paresthesias due to oral allergy syndrome (also known as pollen-food allergy syndrome)<sup>1,4,5</sup>.

Food allergy occurs after consuming a certain food and it causes various symptoms. The most commonly described allergic reactions are urticaria, angioedema, and dermatitis. Food additives are natural or synthetic substances added to food, which can potentially cause an allergic, toxic, irritant or pharmacologic reaction. They are mainly classified as colorings, preservatives, antioxidants, thickeners, stabilizers, emulsifiers, and flavor enhancers<sup>6-9</sup>. Colorings (tartrazine) are added to change or enhance the color of a product. Preservatives (acetylsalicylic acid, citric acid, glutaraldehyde, potassium metabisulfite, sodium benzoate) and antioxidants (citric acid) are used to prolong the shelf life of food by inhibiting microbial growth<sup>6,7</sup>. Thickeners, stabilizers, and emulsifiers (gums) are added to enhance appearance and to give products desired consistency. Flavor enhancers (monosodium glutamate, citric acid) enhance existing flavors of food. Common adverse reactions to additives are erythema, pruritus, contact dermatitis, acute or inducible urticaria, angioedema, and rarely asthma<sup>6-9</sup>.

The key to getting an accurate diagnosis of allergy are skin patch and prick tests. Most of the previous studies were focused on delayed-type allergic reactions in oral diseases by performing patch testing but did not include tests for immediate-type reactions<sup>1-3,10-15</sup>. The objective of this study was to determine common nutritive and additive allergens in the prevalent oral and perioral diseases by using skin prick tests.

## Subjects and Methods

### Subjects

This prospective study was performed during the period of five consecutive years and included 230 participants<sup>1</sup>. All participants signed informed consent form before entering the study, which was approved by the Ethics Committee of the Sestre milosrdnice University Hospital Centre.

Patients included in the study were divided into six disease groups according to clinical presentation, as follows: angioedema, burning mouth syndrome (BMS), cheilitis, gingivostomatitis, oral lichenoid reactions (OLRs), and perioral dermatitis<sup>1</sup>. Each of the

six groups comprised of 30 patients<sup>1</sup>. We also included 50 healthy subjects as controls.

Patients with angioedema presented with recurrent or persistent swelling of the tongue, lips and perioral skin, with exclusion of hereditary angioedema and drug-induced angioedema<sup>1,4</sup>. The BMS group included patients with all clinical criteria for idiopathic BMS and patients having experienced burning sensations without visible oral mucosal lesions or diseases<sup>1,16,17</sup>. The cheilitis group comprised of patients with different forms of cheilitis (angular, contact, exfoliative, and granulomatous, and cheilitis simplex), so the diagnosis was made on the basis of clinical criteria<sup>1,18-20</sup>. Patients with gingivostomatitis had affected gingiva and oral mucosa, and were diagnosed with aphthous or ulcerative stomatitis and with exfoliative or plasma cell gingivitis<sup>1,21,22</sup>. OLRs were diagnosed based on the presence of solitary, unilateral oral lesions appearing after direct mucosal contact with offending agents, and on histopathologic findings<sup>1,23,24</sup>. Perioral dermatitis was diagnosed by the presence of multiple grouped erythematous papules or papulopustules of 1-2 millimeters in size on perioral skin not affecting vermilion border, commonly accompanied by itching and burning sensations<sup>1,20</sup>.

### Methods

After comprehensive diagnostic evaluation, skin prick tests (SPTs) were conducted with food and additives to determine the potential immediate-type allergic reactions.<sup>1</sup> The main nutritive allergens utilized for testing were eggs, milk, meat, vegetables, fruits, mushrooms, fish, flour, cocoa, coffee, and tea<sup>1,2</sup>. Additives used as test allergens were acetylsalicylic acid, citric acid, glutaraldehyde, potassium metabisulfite, sodium benzoate, sodium glutamate, and tartrazine<sup>1,6</sup>. SPTs were performed by application of allergen drops to forearm with both positive (1% histamine) and negative (saline solution) controls<sup>1</sup>. Skin test results were interpreted after 15 minutes by a dermatologist-allergist, and were considered positive if a wheal of at least 3 millimeters in diameter appeared<sup>1,2</sup>.

### Statistical analysis

In our study, statistical analysis considered the prevalence of nutritive and additive allergic reactions detected by SPTs as a dichotomous variable, and se-

Table 1. Age and gender distribution of patients with oral and perioral diseases, and controls

Disease	Mean age (decade)	Female		Male		Total N
		n	%	n	%	
Angioedema	55	19	63.3	11	36.7	30
Burning mouth syndrome	60	23	76.7	7	23.3	30
Cheilitis	50	23	76.7	7	2.33	30
Gingivostomatitis	50	28	93.3	2	6.7	30
Oral lichenoid reactions	50	22	73.3	8	26.7	30
Perioral dermatitis	30	23	76.7	7	23.3	30
Controls	40	42	84.0	8	16.0	50
Total	50	180	78.3	50	21.7	230

Table 2. Number and percentage of subjects with positive tests and frequent nutritive allergens in oral and perioral diseases

Disease	Subjects with positive tests		p	j	Nutritive allergens
	Number	Percentage			
Angioedema	1/30	3.3%	1.000	0.059	Mushrooms, milk, meat, vegetables
Burning mouth syndrome	5/30	16.7%	0.144	0.172	Mushrooms, fruits, vegetables, milk
Cheilitis	4/30	13.3%	0.416	0.126	Fruits, vegetables, milk
Gingivostomatitis	3/30	10%	0.667	0.074	Fruits, vegetables
Oral lichenoid reactions	2/30	6.7%	1.000	0.013	Fruits, vegetables
Perioral dermatitis	0/30	0%	0.288	0.153	/
Diseases in total	15/180	8.3%			Fruits, mushrooms, vegetables, milk, meat
Controls	3/50	6%			Fruits, vegetables, fish
Total	18/230	7.8%			

verity as the number of detected allergens<sup>1</sup>. The  $\chi^2$ -test was used to compare differences among the six disease groups, Fisher exact test compared each disease group with controls, and the j coefficient measured the effect size<sup>1</sup>. The research used SPSS Inc. Version 22.0 (Chicago, Illinois, USA) statistical software to analyze data, and results were considered statistically significant if the p-value was less than 0.05<sup>1</sup>.

## Results

Of the 230 participants enrolled in our study, there were 180 (78.3%) patients with oral and perioral diseases (angioedema, BMS, cheilitis, gingivostomatitis, OLRs, and perioral dermatitis) and 50 (21.7%) healthy control subjects. Each of the six disease groups com-

prised of 30 patients. The average age of the participants was 50 years, ranging from 18 to 90 years. The BMS patients were oldest and those in the perioral dermatitis group youngest (60 *vs.* 30 years). Most of the subjects were aged 50 (cheilitis, gingivostomatitis, and OLRs groups) or 55 (angioedema group), while the median age of control subjects was 40 years. According to gender, females predominated (78.3%) over males (21.7%). Therefore, women predominated in all six disease groups (with a minimum of 63.3% in angioedema group, 73.3% in OLRs group, 76.7% in BMS, cheilitis, and perioral dermatitis group each, and maximum of 93.3% in gingivostomatitis group), as well as in the group of healthy controls (84.0%). The age and gender distribution of all study participants is shown in Table 1.

Table 3. Number and percentage of subjects with positive tests and common additive allergens in oral and perioral diseases

Disease	Subjects with positive tests		p	j	Additive allergens
	Number	Percentage			
Angioedema	7/30	23.3%	0.120	0.188	Glutaraldehyde, sodium glutamate, citric acid
Burning mouth syndrome	7/30	23.3%	0.120	0.181	Glutaraldehyde, citric acid, sodium glutamate, potassium metabisulfite
Cheilitis	6/30	20%	0.315	0.141	Glutaraldehyde, sodium glutamate, citric acid, potassium metabisulfite
Gingivostomatitis	3/30	10%	1.000	0.000	Glutaraldehyde, citric acid, sodium glutamate
Oral lichenoid reactions	6/30	20%	0.315	0.141	Citric acid, sodium glutamate, glutaraldehyde, sodium benzoate
Perioral dermatitis	3/30	10%	1.000	0.000	Glutaraldehyde, sodium glutamate
Diseases in total	32/180	17.8%			Glutaraldehyde, citric acid, sodium glutamate, potassium metabisulfite, sodium benzoate
Controls	5/50	10%			Glutaraldehyde, citric acid, potassium metabisulfite
Total	37/230	16.1%			

Positive SPTs to nutritive allergens were identified in 15 of 180 patients (8.3%). Nutritive allergic reactions were most common in the groups of patients with BMS (16.7%) and cheilitis (13.3%), mainly caused by fruits, mushrooms, and vegetables, followed by milk, meat, and fish. Less often, allergens were found in gingivostomatitis (10%), OLRs (6.7%), and angioedema (3.3%) groups. No allergic reaction was observed in patients with perioral dermatitis. Fruits, vegetables, and fish caused positive skin tests in 6% of control subjects. Table 2 shows the number and percentage of subjects with positive SPTs and the most frequently identified nutritive allergens in specific oral and perioral diseases.

Additive allergies were identified in 32 of 180 patients (17.8%), according to positive SPTs. Allergic reactions were mostly found in patients with angioedema and BMS (23.3%), both in cheilitis and OLRs groups (20%), but somewhat less in patients with gingivostomatitis and perioral dermatitis (10%). The most common additive allergens were glutaraldehyde, citric acid, and sodium glutamate, followed by potassium metabisulfite and sodium benzoate, to which 10% of healthy controls also reacted. The number and percentage of subjects with positive SPTs and the most com-

monly identified additive allergens in specific oral and perioral diseases are shown in Table 3.

## Discussion

Most similar studies were focused on delayed hypersensitivity reactions in oral mucosal diseases by conducting patch tests<sup>2,3,11-15</sup>, rather than by performing skin prick tests to detect immediate-type allergic reactions. What is more, previous research mainly investigated the role of contact allergens and inhalants in oral diseases, usually not determining common nutritive or additive allergens in oral and perioral diseases using skin prick tests<sup>1-3</sup>. Skin prick tests are regularly used to prove and confirm early-type hypersensitivity, but in cases of allergies to food and additives, hypersensitivity reactions are considered to appear due to a contact allergic reaction to an allergen. Therefore, allergy skin tests for delayed-type hypersensitivity are mainly applied, not pointing to the potential role of nutritive and additive allergens in the pathogenesis of oral and perioral diseases.

Our results of skin prick tests demonstrated that immediate-type allergic reactions to foods and additives were mostly seen in patients with BMS (40%)

and cheilitis (33.3%), moderately present in angioedema (26.6%) and oral lichenoid reactions (26.7%), while allergies were least frequently observed in gingivostomatitis (20%) and perioral dermatitis (10%). Out of 180 patients with oral and perioral diseases, positive results of skin prick tests were recorded in 26% of patients, compared to 16% of controls. Many significant differences were found between patients and healthy controls. The most commonly identified additive allergens were glutaraldehyde, citric acid, sodium glutamate, potassium metabisulfite, and sodium benzoate. Fruits, mushrooms, and vegetables were the most frequent causes of nutritive allergic reactions in oral and perioral diseases.

According to the allergy skin test results in previous similar studies in patients with oral/perioral diseases, different data were obtained. According to Torgerson *et al.*, who wanted to determine the prevalence of contact allergy to dental acrylates, flavorings, medications, metals, and preservatives in patients with oral disease, flavorings and preservatives had the highest relevance, comprising 11 of 18 most relevant allergens<sup>2</sup>. Dodecyl gallate was the preservative with the highest percentage of positive reactions (4.2%), while the second most reactive preservative was benzoic acid (3.2%)<sup>2</sup>. Their results emphasize the importance of including allergens other than metals for a comprehensive allergen series when evaluating patients with oral disease<sup>2</sup>. One of the allergens we used in our study, i.e. citric acid, was also used by Torgerson *et al.*<sup>2</sup> in 289 of their patients, but with no positive or relevant reactions.

Wray *et al.*<sup>3</sup> conducted a study to assess the prevalence of positive results to cutaneous patch testing and the relevance of exclusion of identified allergens in oral mucosal diseases; all participants were tested with food additives, chocolate, flavorings, and perfumes<sup>3</sup>. Patients with recurrent aphthous stomatitis and orofacial granulomatosis were significantly more likely to have reactions to food additives, especially benzoic acid<sup>3</sup>. Salicylic acid and tartrazine as food additives were used by Wray *et al.*<sup>3</sup>, as well as in our study.

Although some literature data indicate a connection between reactions to food or additives and immediate-type allergic reactions, there are only few studies investigating it, especially regarding immediate-type reactions in oral and perioral diseases. According to an earlier study conducted in patients with atopic derma-

titis and chronic urticaria, positive results of skin prick tests were more often observed in patients with atopic dermatitis (64.3%) and those with chronic urticaria (25%) as compared to controls (10%). In the same study, the most frequent nutritive allergens were vegetables. As for additive allergens, acetylsalicylic acid, potassium metabisulfite, sodium benzoate, and tartrazine caused positive reaction to an allergy test most frequently<sup>9</sup>.

## Conclusion

Our results indicate that a possible association with nutritive and additive allergies should be considered in cases of a persistent oral mucosal or perioral skin disease and respective medical history. After examining the results of allergy skin tests, it is important to advise on allergen avoidance, thus obtaining crucial data on pathogenic association.

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### Sažetak

## PROCJENA ALERGIJA NA HRANU I ADITIVE U BOLESNIKA S ANGIOEDEMOM, SINDROMOM PEKUĆIH USTA, HEILITISOM, GINGIVOSTOMATITISOM, ORALNIM LIHENOIDNIM REAKCIJAMA I PERORALNIM DERMATITISOM

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Usna šupljina i perioralna regija izložene su različitim antigenima, osobito hrani i aditivima, koji imaju potencijalnu ulogu u razvoju različitih bolesti oralne sluznice i perioralne kože s obzirom na to da mogu potaknuti reakcije preosjetljivosti. Oralne i perioralne bolesti najčešće se manifestiraju kao angioedem, sindrom pekućih usta, heilitis, gingivostomatitis, oralne lihenoidne reakcije ili perioralni dermatitis. Dosadašnje studije usmjerile su se na istraživanje kasne alergijske preosjetljivosti kod bolesti oralne sluznice koristeći samo epikutane (*patch*) testove. Stoga je cilj našeg istraživanja bio odrediti najčešće nutritivne i aditivne alergene u oralnim i perioralnim bolestima primjenom kožnog ubodnog (*prick*) testa. U istraživanje je bilo uključeno ukupno 230 ispitanika, tj. 180 bolesnika s oralnim/perioralnim bolestima (angioedem, sindrom pekućih usta, heilitis, gingivostomatitis, oralne lihenoidne reakcije i perioralni dermatitis) i 50 zdravih ispitanika. Rezultati kožnih ubodnih testova pokazali su da su alergijske reakcije rane preosjetljivosti na hranu i aditive najčešće uočene u bolesnika sa sindromom pekućih usta (40%) i heilitisom (33,3%), dok su najrjeđe opažene u bolesnika s gingivostomatitisom (20%) i perioralnim dermatitisom (10%). Najučestaliji uzrok nutritivnih alergijskih reakcija u oralnim i perioralnim bolestima bilo je različito voće, gljive i povrće, a najčešće identificirani aditivni alergeni bili su glutaraldehid, limunska kiselina i natrijev glutamat. Rezultati našeg istraživanja upućuju na to da kod ustrajnih bolesti oralne sluznice ili perioralne kože te značajnih povezanih anamnestičkih podataka treba razmotriti moguću povezanost s nutritivnim i aditivnim alergijama.

**Ključne riječi:** *Aditivi; Alergija; Hrana; Oralne bolesti; Perioralne bolesti; Ubodni kožni test; Epikutani test; Koža; Angioedem*