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Стаття надійшла до редакції  
24.12.2020



UDC 616.216.1-002-02:616.314]-07-095:612.017

<https://doi.org/10.26641/2307-0404.2021.3.242157>

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## MICROBIAL LANDSCAPE AND IMMUNE STATUS IN MAXILLARY SINUSITIS OF STOMATOGENIC ORIGIN

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**Цитування:** *Медичні перспективи*. 2021. Т. 26, № 3. С. 145-151

**Cited:** *Medicni perspektivi*. 2021;26(3):145-151

**Key words:** *stomatogenic maxillary sinusitis, microbiota, iatrogenic sinusitis, the etiopathogenesis of sinusitis, differential diagnostics*

**Ключові слова:** *стоматогенний верхньоощелепний синусит, мікробіота, ятрогенний синусит, диференціальна діагностика*

**Ключевые слова:** *стоматогенный верхнечелюстной синусит, микрофлора, ятрогенный синусит, дифференциальная диагностика*

**Abstract. Microbial landscape and immune status in maxillary sinusitis of stomatogenic origin. Kovach I.V., Varzhapetian S.D., Bunyatyan Kh.A., Reyzvikh O.E., Babenya A.A., Strogonova T.V.** Oroantral fistula (anastomosis) is an element preventing the restoration of homeostasis in the maxillary sinus due to the constant flow of microbes from the oral cavity. It also contributes to frequent exacerbations of maxillary sinusitis. Saprophytic gram-positive cocci and fungi of the oral cavity are dominating representatives of the microbial flora in the maxillary sinus. As the result of research, we found that in the case of maxillary sinusitis with oroantral fistula fungi made up 25.0% of microbiota, gram-positive bacteria – 41.7%, gram-negative bacteria – 33.3%. Gram-positive cocci from the *Staphylococcus* genus (*Staphylococcus aureus* and *Staphylococcus epidermidis*) and fungi (*Candida albicans*) comprised the biggest proportion of microbial flora that 33.3% and 16.7%, respectively. Slightly decreased levels of monocytes in venous blood was noted in 69.2% of patients. The average value of total serum IgE in group with oroantral fistula was 226.2 (70.4) IU/ml, the result exceeded normal limits almost in 2.26 times. Large circulating immune complexes (CICs) were normal in all patients in the group with iatrogenic maxillary sinusitis. The average levels of small size CICs was 170.2 (4.23) OU, which is in 1.06 times higher the upper limit of the norm (160 OU). Elevated levels of total Ig E in serum of patients with oroantral fistula indicates allergic sensitization. The detection of increased levels of CICs with small and medium sizes in serum may indicate a susceptibility of this category of patients to the development of immunopathological reactions.

**Реферат. Мікробний пейзаж та імунний статус при верхньощелепному синуситі стоматологічного походження. Ковач І.В., Варжапетян С.В., Бунятян Х.А., Рейзвих О.Е., Бабеня А.А., Строгонова Т.В.** Ороантральне співустя є елементом, який перешкоджає відновленню гомеостазу у верхньощелепному синусі через постійний потік мікробіоти з порожнини рота та спричиняє часте загострення синуситу. Проведене нами дослідження дозволило встановити, що сапрофітні коки та гриби з порожнини рота становлять більшу частину мікробіоти верхньощелепної пазухи в пацієнтів з ороантральним сполученням. При цьому гриби становлять 25,0%, грампозитивні бактерії – 41,7%, грамнегативні бактерії – 33,3%. Переважають грампозитивні коки роду *Staphylococcus* spp.: *Staphylococcus aureus* та *Staphylococcus epidermidis* (33,3%). Другими за поширеністю були гриби *C. albicans* (16,7%). Ми виявили помірне підвищення моноцитів у крові 69,2% пацієнтів, що може бути пов'язано з початком стадії гострого запалення. Наявність грибів свідчить про можливе порушення місцевого імунітету. Середній рівень загального IgE сироватки крові в досліджуваній групі становив 226,2 (70,4) МО/мл та перевищував норму майже в 2,26 рази. Рівні великих циркулюючих імунних комплексів (ЦІК) були нормальними у всіх пацієнтів у групі з ороантральною фістулою. Середнє значення малих ЦІК становило 170,2 (4,23) оптичних одиниць (ОО), що в 1,06 рази перевищувало верхню границю норми (160 ОО). Рівень загального сироваткового Ig E вказує на алергічну сенсibiliзацію організму. Виявлене підвищення рівня ЦІК малих та середніх розмірів у сироватці може свідчити про сприйнятливості цієї категорії хворих до розвитку імунопатологічних реакцій.

Dental maxillary sinusitis accompanied by communication of the maxillary sinus with the oral cavity differs from others by pathophysiology, microbiology, and clinical symptoms [15]. One of the local factors that form the clinical course of the traumatic iatrogenic sinusitis is oroantral fistula. The inflammatory exudate exit from the sinus at the site of the connection of the maxillary sinus with the oral cavity, so a more favourable course of inflammation in the sinus becomes possible: the symptoms of the acute phase of the disease are less pronounced and the general condition of the patients suffers relatively less. On the other hand, infectious agents from the oral cavity constantly enter the sinus with sufficient size of the oroantral fistula.

Studies show that the incidence of stomatologic sinusitis reaches up to 30-40% of all cases of chronic maxillary sinusitis. Inflammation in the sinus with the iatrogenic origin and spreading from periapical foci of untreated teeth (odontogenic) are the most common causes of maxillary sinusitis [13]. Symptoms in both odontogenic and non-odontogenic sinusitis are similar, but there are clear clinical

differences. It is important to distinguish maxillary sinusitis by its aetiology because the causative factor contributes significantly to the pathogenesis and distinctive characteristics of the disease. Usually, the standard treatment is symptomatic and temporary. In turn, the establishment of the fistula prevents the restoration of balance in the maxillary cavity due to the constant flow of infects from the oral cavity with frequent exacerbations of sinusitis [10]. The condition of continuous infection of the maxillary sinus may lead to the impairment of other vital systems of the organism, such as cardiovascular and renal systems [13].

It is well known, that tooth extraction is often performed when the treatment of a periapical infection is unsuccessful. Aerobic and anaerobic gram-negative bacteria and optional streptococci have been found to be present in the primary foci of canals infections and periodontal tissues of teeth [6]. Oral saprophytic bacterial flora comprises mainly gram-positives that penetrate the sinus during the treatment through the oroantral fistula or the root canal [14]. Perhaps the circumstances listed above can explain the mixed microbial landscape in the

maxillary sinuses of patients with iatrogenic sinusitis. In their early works, Brook I (2017) defined that normal healthy sinus is colonized by aerobic and anaerobic bacteria, including *Staphylococcus aureus* [5]. However, it is not known, whether the paranasal sinuses involve representatives of the normal microbiome which may play a role in the pathogenesis of sinusitis. The studies show the large predominance of sterile maxillary sinus cavities in asymptomatic adults with endoscopically normal mucosa [15].

In case when the maxillary sinusitis develops against the background of surgical dental procedures on the upper jaw and on teeth are included in the group of the traumatic iatrogenic maxillary sinusitis with stomatological origin [1].

Information about the composition of the microbial flora of the maxillary sinus during inflammation is required to understand the driving forces of the disease, the proper conduct of treatment and ways of its prevention.

The purpose of the research was to assess the composition of microbial landscape and measure the indicators of either cellular or humoral immunity in patients with maxillary sinusitis which developed after extraction of molars of the upper jaw resulting in the oroantral fistula.

#### MATERIALS AND METHODS OF RESEARCH

The study involved 36 (100%) patients (aged 43.8 (14.0) years old) with stomatogenic maxillary sinusitis treated in the maxillofacial hospital on the clinical base of Zaporizhzhia Medical Academy of Postgraduate Education (Ukraine) at the Department of surgical and therapeutic dentistry. According to anamnesis, participants were assigned into two groups. The group I comprised 23 (63.9%) patients who developed clinical symptoms of maxillary sinusitis after the extraction of large molars of the upper jaw and the formation of a connection between the oral cavity and maxillary sinus, i.e. oroantral fistula. In group II 13 (36.1%) participants who had sinusitis developed after previously untreated teeth were enrolled.

Samples for bacteriological assay were taken from ten (43.5%) patients of group I and 13 (100%) participants of group II. Immune indicators were evaluated in venous blood samples of 13 patients (56.5%) of group I and seven participants (53.8%) of group II.

One of the important conditions of the microbiological study was a collection of clinical samples directly from the maxillary cavity. Another condition was the absence of pus in the taken material. The material was taken from the walls of the maxillary sinuses during «maxillary sinusotomy» surgery using sterile swabs and standard tubes with Ames' media [9].

All patients were hospitalized under exacerbation of maxillary sinusitis and they were receiving antibacterial and anti-inflammatory therapy. Antibiotics were cancelled 24 hours before the operation. The «swab-loop» inoculation method was used to obtain information on the quantitative and qualitative composition of microbes in the sampled material. A standard set of culture mediums included agar with 5% sheep blood, chocolate agar, Endo agar, Chistovich's and Sabouraud's medium with chloramphenicol. Cultivation was performed in incubator at 37°C under aerobic conditions during 24-48 hours for bacterial isolates and 72-120 hours for fungal growth. Identification of isolates performed by «Vitek 2-compact» («bioMérieux», France) [8].

The venous blood sampling was carried out following the guidelines of the Zaporizhzhia Synevo (Belgium) laboratory. Alcohol, smoking, eating, physical activity and medications were excluded 12 hours before the sampling. The important condition for ensuring the quality of laboratory blood testing was taking the material on an empty stomach in the morning (before 12 a.m.). All patients in the study were hospitalized in an urgent manner that is in the acute phase of inflammation in the sinus. The biological material was collected within two days after the time of admission. The immunity indices were determined by enzyme-linked immunosorbent assay (ELISA) and flow cytometry [3].

Statistical processing of the obtained data was performed using the application package STATISTICA (StatSoft Inc. USA, version 6.0).

We used the Student-Fisher' exact two-tailed method to estimate the level of reliability of differences in the results obtained; a confidence level of at least 95 is generally accepted for biological and medical research ( $p < 0.05$ ). With small numbers of sample objects ( $n$ ) and a significant confidence probability ( $p$ ) close to 0 or 1, the Clopper-Pearson Exact method was used to calculate the confidence intervals. The arithmetic mean with standard deviation was used [2].

The research was approved by the Commission on Bioethics of the State Establishment «ZMAPE MH of Ukraine» dated 11.19.2018. All studies were conducted following the requirements of the Helsinki Patient Rights.

#### RESULTS AND DISCUSSION

A positive culture was obtained in 80.0% ( $n=8$ ) of samples of group I (those after large molars extraction). A wide spectrum of microbes was cultured. We had 12 isolates represented seven bacterial and two fungal species. Bacteria from genus *Staphylococcus*, *Streptococcus*, *Klebsiella*, *Escherichia*, *Pseudomonas* and fungi *Candida spp.*

and *Cryptococcus spp.* were found. The fungi composed 25.0% of the microbiota. Gram-positive microbiota like *S. aureus*, *Staphylococcus epidermidis* and *Streptococcus pyogenes* occupied 41.7%.

Gram-negatives like *E. coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* made up 33.3% (Table 1).

Table 1

**Representatives of maxillary microbial landscape in odontogenic sinusitis**

Obtained isolates	group I Me (Q1; Q3), %	group II Me (Q1; Q3), %
<i>Staphylococcus aureus</i>	25.4 (2.1; 48.4)	20 (17.3; 64.3)
<i>Staphylococcus epidermidis</i>	16.7 (2.1; 48.4)	20 (17.3; 64.3)
<i>Staphylococcus haemolyticus</i>	-	10 (1.8; 40.4)
<i>Streptococcus pyogenes</i>	8.3 (2.1; 38.5)	-
<i>Klebsiella pneumoniae</i>	8.3 (2.1; 38.5)	-
<i>Escherichia coli</i>	8.3 (2.1; 38.5)	-
<i>Pseudomonas aeruginosa</i>	8.3 (2.1; 38.5)	10 (1.8; 40.4)
<i>Acinetobacter baumannii</i>	-	40 (16.8; 68.7)
<i>Candida albicans</i>	16.7 (2.1; 48.4)	-

The microbial growth was revealed in 61.5% of the samples from group II. A total of ten isolates represented five bacterial species (*Staphylococcus spp.*, *Acinetobacter spp.*, *Pseudomonas spp.*) were plated in the group. Gram-positive cocci *S. aureus* and *S. epidermidis* dominated in microbial flora and made up 33.3%. Fungi *C. albicans* was plated from 16.7% of samples and ranked second in shared proportion. Remained representatives occupied only 8.3%.

It worth mentioning, the growth of monoculture was revealed in 75.0% (n=6) of samples. This comprised 60.0% of all patients with traumatic iatrogenic sinusitis and 50.0% with microbiota.

The microbial associations included the following combinations: 1) *S. aureus* (10<sup>3</sup> CFU/ml) and *C. albicans* (10<sup>3</sup> CFU/ml); 2) *E. coli* (10<sup>7</sup> CFU/ml) and *K. oxytoca* (10<sup>7</sup> CFU/ml), *C. albicans* (10<sup>7</sup> CFU/ml) and *Cryptococcus laurentii* (10<sup>7</sup> CFU/ml).

In our study, the fungi *C. albicans* had the second (16.7%) shared position in the microbiota of the maxillary sinus. Presumably, fungi cannot penetrate the epithelial layer when the patient's immune system is functioning normally [7].

In the case of the odontogenic maxillary sinusitis with untreated teeth (II group), the microbial landscape of the inflamed sinuses counted equal proportions of gram-positive cocci (50.0%) and gram-negative rods (50.0%). However, non-fermenter *A. baumannii* was the most common. It occupied

40.0% of the cultured flora in odontogenic sinusitis. The mixed culture was plated from 15.3% of patients; quantitatively the maximum contamination of the sinus reached 10<sup>7</sup> CFU/ml. There were no fungi in such samples. Monoculture was found in 46.1% (n=6) patients. In all remained cases mixed culture was represented by a combination of *S. aureus* and *A. baumannii*.

A study of immunity indicators in peripheral blood samples was performed in both groups of patients either after extraction of large molars or untreated teeth.

There were increased rates of T-lymphocytes (CD3+, CD19-) in 15.4% (n=2) of patients with iatrogenic maxillary sinusitis accompanied with oroantral fistula. The indicator unreliably exceeded the proportion of low values (p<sub>1</sub>=0.14) in the group and was significantly lower than in proportion with normal value (p<sub>2</sub>=0.0012). But, on average, the value of this index in the group was within the limit of normal (54-83%).

An important factor for the manifestation of the pathogenic properties of the circulating immune complexes (CICs) is their size. Low molecular weight complexes are worse than the large complexes that activate complement [7]. The detected increased levels of serum CICs with small and medium sizes may indicate a susceptibility to the development of immunopathological reactions.

*T*-helpers/inductors (*CD4+*, *CD8-*) were increased to 62.1% (upper normal limit of 58.0%) in 7.7% of patients with iatrogenic maxillary sinusitis ( $p_1=0.348$ ,  $p_2=0.000...$ ).

*T*-suppressors/cytotoxic cells (*CD4-*, *CD8+*) were outside the normal range (normal is 21-35%) in 38.5% of patients with iatrogenic maxillary sinusitis ( $p_2=0.24$ ). Specifically, in 80.0% of cases (in 30.8% of patients) this indicator was low. A high value of *CD4-*, *CD8+* cells (in 20.0% of cases) was found in 7.7% of patients ( $p_1=0.13$ ).

There were 53.9% of patients with impairment of the immunoregulatory index (*CD4+*, *CD8/CD4-*, *CD8+*),  $p_2=0.69$ : 15.4% of patients had a low value up to 0.8% (the norm is 1.2-2.2%), 38.5% of patients had high value (2.7 to 3.5%),  $p_1=0.18$ .

*Cytotoxic cells* (*CD3+*, *CD56+*) in patients with traumatic iatrogenic sinusitis did not meet the norm in 23.1% of cases ( $p_2=0.0061$ ): low value of 1.7% (normal 3-8%) was observed in 7.7% of patients, while high value (8.5 and 14.2%) – in 15.4% of patients ( $p_1=0.54$ ).

The values of *NK-cells* (*CD3-*, *CD56+*) did not meet the norm (the norm is 5-15%) in 38.5% of

patients ( $p_2=0.24$ ): the low value of index (2.3%) was noted in 7.7% of cases, the high value (from 17.4% to 24.8%) – in 30.8% of cases ( $p_1=0.13$ ). The value of *B-lymphocytes* (*CD3-*, *CD19+*) reached 19% (the norm is 5-14%) in 7.7% of cases ( $p_1=0.31$ ;  $p_2=0.000...$ ). A slightly low index of monocytes in the blood can be an indicator of the initial period of the acute inflammatory period. Low content of *monocytes* in the blood (from 3.1 to 6.0%) was found in 62.9% of patients, which made up 100.0% of cases of disturbance of value of this index in the group ( $p_2=0.050$ ).

The increase in total serum Ig E in patients with traumatic iatrogenic sinusitis indicates the fact of allergic sensitization of the organism [11]. We identified patients with impaired total serum Ig A, M and G levels. Values of Ig A, M, G were elevated in 7.7% of cases ( $p_1=0.31$ ;  $p_2=0.000$ ). IgG was low (5.62 and 6.87 g/l) in 15.4% of patients ( $p_1=0.54$ ;  $p_2=0.005$ ). The content of IgE was too high (from 114 to 597.2 IU/ml) in 61.5% of patients ( $p_2=0.24$ ).

The average values of indicators of humoral immunity are shown in table 2.

Table 2

### Indices of humoral immunity in case of stomatogenic maxillary sinusitis with iatrogenic (group I) and odontogenic origin (group II)

Total immunity indices in serum	Normal values, g/l	group I (n=13)	group II (n=7)	p
		Me (Q1;Q3)	Me (Q1;Q3)	
IgA	0.7-4.0	2.2 (1.99; 2.42)	2.33 (2.02; 2.96)	>0.05
IgM	0.7-2.3	1.4 (1.24; 1.94)	1.19 (1.08;1.84)	>0.05
IgG	7.0-16.0	10.4 (9.77; 11.16)	9.61 (9.19;10.69)	>0.05
IgE	>100.0*	121 (13.04;279.1)	71.49 (23.20;147.7)	<0.05
C3 component of complement	0.9-1.8	1.07 (1.06; 1.17)	1.18 (1.08;1.35)	>0.05
C 4-2 component of complement	0.1-0.4	0.31 (0.24; 0.38)	0.26 (0.25; 0.32)	>0.05

Note. \* IU/ml.

The average value of IgE in group I was 226.2 (70.4) IU/ml, which exceeded the normal almost in 2.26 times. The average index of total serum IgE was elevated up to 136.95. The most common change in the cellular immunity level was expressed in the anomaly of the immunoregulatory index in 57.1% of patients from group II.

*Large size CICs* were normal in all patients with traumatic iatrogenic sinusitis. Values of the *mean*

*size CICs* were high (from 90 to 111 OU) in 46.1% of cases and low in 7.7% ( $p_1=0.027$ ;  $p_2=0.698$ ). The discrepancy between the *mean size CICs* and the laboratory norm was noted in 53.8% of cases. Changes in the indices of *small size CICs* manifested in the increase of their value (from 160 to 188 OE) in 92.3% of cases,  $p_{1,2}=0.000$ , (Table 3).

**Circulating immune complexes in serum during iatrogenic (group I) and odontogenic (group II) maxillary sinusitis**

Immunity indices understudy	Norm, OU	group I (n=13)	group II (n=7)	p
		Me (Q1;Q3)	Me (Q1;Q3)	> 0.05
Large size CICs	> 20,0	6.0 (4.0; 9.0)	7.0 (4.0; 10.0)	> 0.05
Medium size CICs	60,0-90	93.0 (82.0; 94.0)	94.0 (88.0; 98.0)	> 0.05
Small size CICs	130,0-160	173.0 (168; 179)	177.0 (171; 183)	> 0.05

The average value of the *medium size CICs* within the group of patients with iatrogenic stomatogenic sinusitis was within the normal range. The average value of *small size CICs* was 173.0 (168; 179) OU, which is 1.06 times above the limit of the norm (160 OU). Possibly oroantral connection and the removal of the causative tooth might contribute to such immune peculiarities.

It should be noted that the results presented in this manuscript were obtained without considering the timing of oroantral fistula occurrence, age and sex of patients, demographic, and health-related factors such as time of admission, antibiotics consumption, concurrent viral infections and lifestyle-related habits such as smoking and alcohol intake. These circumstances affect the microbiota and immune status of the human body [4]. In the future, we plan to investigate differences in the composition of the microflora of the maxillary sinus and the immune status of patients with traumatic iatrogenic sinusitis with stomatogenic origin considering the factors listed above. This study enables the creation of a general presentation of the pathogenesis of the traumatic iatrogenic sinusitis with stomatogenic genesis.

### CONCLUSIONS

1. Microbial landscape in maxillary sinus was changed either in case of iatrogenic or odontogenic sinusitis. Oroantral fistula facilitates the penetration of oral microbiota into the maxillary sinus. Our data indicates the dominance in the maxillary sinus commensals of the oral cavity, *S. aureus* and *S. epidermidis* (33.3%); also the presence of *Candida* fungi occurred after tooth extraction in the microbiota of maxillary sinusitis accompanied with oroantral communication. In the maxillary sinuses with odontogenic origin the main microbial player was gram-negative bacteria *A. baumannii* (40%); any fungi were found.

2. Immune indexes were similar in both odontogenic and iatrogenic maxillary sinusitis. In the case of oroantral communication after tooth extraction increased levels of total serum IgE (121 (13.04; 279.1) IU/ml) indicated more pronounced allergic sensitization. Impaired levels of CICs with medium and small size reflected the active inflammatory process and may indicate the risk of immunopathological reactions.

Conflict of interests. The authors declare no conflict of interest.

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Стаття надійшла до редакції  
08.07.2020