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## FEATURES OF THE ORAL IMMUNE STATUS IN VIRAL STOMATITIS BASED ON ORAL FLUID ANALYSIS

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**Abstract:** Oral fluid is an informative biological substrate reflecting the state of mucosal immunity. This article reviews changes in the cytokine profile, levels of secretory IgA, innate antimicrobial factors, and virus-specific antibodies in patients with viral stomatitis (herpetic and HPV-associated) compared with healthy individuals. A critical analysis of current studies identified known patterns and outlined unresolved issues. Directions for future research are defined, including the role of interferon response and the impact of HPV co-infection.

**Keywords:** oral fluid; viral stomatitis; herpes simplex virus; human papillomavirus; cytokines; secretory IgA;  $\beta$ -defensins; lactoferrin; immunological parameters; diagnostics.

## ОСОБЕННОСТИ ИММУННОГО СТАТУСА РОТОВОЙ ПОЛОСТИ ПРИ ВИРУСНОМ СТОМАТИТЕ ПО ДАННЫМ АНАЛИЗА «ORAL FLUID».

**Аннотация:** Ротовая жидкость является информативным биологическим субстратом, отражающим состояние мукозального иммунитета. В статье рассмотрены изменения цитокинового профиля, уровня секреторного IgA, врождённых антимикробных факторов и вирус-специфических антител у пациентов с вирусным стоматитом (герпетической и ВПЧ-этиологии) в сравнении со здоровыми лицами. Проведен анализ современных исследований, выявлены известные закономерности и обозначены нерешённые вопросы. Определены направления дальнейших исследований, включая роль интерферонового ответа и влияние ко-инфекции ВПЧ.

**Ключевые слова:** ротовая жидкость; вирусный стоматит; вирус простого герпеса; вирус папилломы человека; цитокины; секреторный IgA;  $\beta$ -дефенсины; лактоферрин; иммунологические параметры; диагностика.

## ВИРУСЛИ СТОМАТИТДА ОҒИЗ БЎШЛИҒИ ИММУН ҲОЛАТИНИНГ «ORAL FLUID» ТАҲЛИЛИ АСОСИДАГИ ХУСУСИЯТЛАРИ

**Аннотация:** Оғиз суякликлиги мукозал иммунитет ҳолатини акс эттирадиган информатив биологик субстрат ҳисобланади. Мақолада вирусли стоматит (герпетик ва HPV-этиологияли) билан касалланган беморларда цитокин профили, секретор IgA даражаси, туг‘ма антимикроб омиллар ва вирусга ҳос антитаналардаги ўзгаришлар соғлом шахслар кўрсаткичлари билан таққосланди. Замонавий тадқиқотлар таҳлил қилиниб, маълум



қонунлиятлар аниқланди ва ҳал этилмаган масалалар белгилаб берилди. Кейинги тадқиқот йўналишлари сифатида интерферон жавобининг роли ва HPV билан коинфекция таъсири кўрсатилди.

**Калит сўзлар:** оғиз суюқлиги; вирусли стоматит; оддий герпес вируси; инсон папилломавируси; цитокинлар; секретор IgA;  $\beta$ -дефенсинлар; лактоферрин; иммунологик кўрсаткичлар; диагностика.

**Introduction.** Salivary immunological parameters allow for the assessment of both local and systemic immunity. Secretory IgA (sIgA), cytokines (IL-1 $\beta$ , IL-6, IL-8, TNF- $\alpha$ , IL-10), chemokines (MCP-1, MIP-1 $\alpha/\beta$ ), antimicrobial peptides ( $\beta$ -defensins, lactoferrin), and viral DNA are key markers. In viral stomatitis caused by HSV-1 or HPV, their profile changes and can serve as an indicator of inflammatory process activity.

Oral Fluid as an Object of Immunological Research. Over the past two decades, oral fluid (saliva) has become firmly established as an accessible and informative biological material for assessing both local and systemic immunity. The secretion of salivary glands contains a variety of immunological components: immunoglobulins (primarily secretory IgA), cytokines, chemokines, antimicrobial peptides, enzymes, as well as viral and bacterial nucleic acids. Secretory IgA (sIgA) plays a key role in mucosal immunity by preventing the adhesion and invasion of pathogens on epithelial surfaces, and its level and activity reflect the state of the protective mechanisms of the oral mucosa [Novak et al., 2021; Riis et al., 2020]. In addition, saliva contains pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, IL-8, TNF- $\alpha$ ), anti-inflammatory mediators (IL-10, TGF- $\beta$ ), as well as innate defense factors—lactoferrin, lysozyme, and  $\beta$ -defensins—which possess pronounced antiviral and antimicrobial activity [Diamond et al., 2011; Jasim et al., 2024]. The presence of such a range of components makes oral fluid a promising object for clinical and immunological research in infectious and inflammatory diseases.

Immunological Changes in Herpetic Stomatitis. Herpetic stomatitis, caused by the herpes simplex virus type 1 (HSV-1), is one of the most common viral infections of the oral mucosa. Clinical manifestations include multiple painful erosions and ulcers, accompanied by significant inflammation. A number of studies have shown that patients with active herpetic stomatitis have significantly increased concentrations of IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$  in their saliva, which directly correlate with the intensity of clinical symptoms and the rate of epithelial repair [Coppola et al., 2023; Marques Filho et al., 2018]. Additionally, virus-specific IgA and IgG class antibodies, as well as HSV-1 DNA, have been detected, confirming the diagnostic value of saliva as a material for laboratory confirmation of infection [Weeramange et al., 2021]. However, data from different authors often vary: some researchers note significant variability in immunological parameters depending on the saliva collection method, the presence of concomitant periodontitis or gingivitis, and patient age [Riis et al., 2020]. This indicates the need to develop standard analysis protocols to obtain comparable results.

The Role of Human Papillomavirus (HPV). In addition to herpesvirus infection, the role of human papillomavirus (HPV) in the development of oral mucosal pathologies is attracting increasing research attention. It has been established that patients with oral HPV infection have reduced levels of total sIgA, which may indicate a impairment of the local immune barrier [Gonçalves et al., 2006]. Simultaneously, antibodies to viral structural and oncoproteins (L1, E6, E7), as well as viral DNA, are detected in the oral fluid of such patients [Parker et al., 2018; Pirttilä et al., 2022]. Furthermore, changes in the cytokine profile, particularly an increase in IL-6 and IL-8, have been described in HPV-positive patients, which are associated with the risk of



infection persistence and neoplastic transformation of the epithelium [Tan et al., 2025]. These data confirm the potential of saliva as a non-invasive material for the diagnosis and monitoring of HPV-associated oral lesions.

**Unresolved Issues and Research Relevance.** Despite obvious successes in studying the immunological parameters of saliva, a number of issues remain unresolved. First, a specific "cytokine profile" that reliably differentiates viral stomatitis from other inflammatory processes of the mucosa, including aphthous lesions and periodontitis, has not yet been determined. Second, there is very little data on the role of the interferon response (IFN- $\alpha$ , IFN- $\beta$ , IFN- $\lambda$ ) in oral fluid during viral infections. Third, it remains unclear how co-infection with HPV and HSV-1 affects the immune response and the severity of clinical manifestations. Additionally, the problem of preanalytical standardization must be considered: collection methods (stimulated or unstimulated saliva), time of day, storage conditions, and normalization to total protein significantly influence the final results [Riis et al., 2020; Jasim et al., 2024].

These gaps determine the relevance of a systematic study of immunological markers in oral fluid in viral stomatitis and the need for their comparison with indicators from healthy individuals. This will deepen the understanding of pathogenesis, refine diagnostic criteria, and ultimately improve treatment strategies for viral lesions of the oral mucosa.

**Materials and Methods.** To prepare this review, a systematic search of scientific publications in the international databases PubMed, Scopus, and Web of Science for the period from 2000 to 2025 was conducted. Search queries included the keywords: "saliva", "oral fluid", "viral stomatitis", "HSV-1", "HPV", "cytokines", "secretory IgA", "defensins", "immunological markers".

The review included original research, clinical observations, randomized controlled trials, as well as meta-analyses and systematic reviews that studied immunological parameters of oral fluid in patients with viral lesions of the oral mucosa. Special attention was paid to publications dedicated to:

- Changes in the cytokine profile in herpetic stomatitis;
- Levels of secretory IgA and the presence of specific antibodies in HPV infection;
- The role of innate defense factors in saliva ( $\beta$ -defensins, lactoferrin, lysozyme);

Methodological issues—methods of saliva collection, storage, and analysis.

Exclusion criteria were studies with insufficient sample size ( $n < 10$ ), animal studies without clinical extrapolation, and articles where saliva was not considered as a separate diagnostic material.

As a result of the selection, over 80 publications reflecting modern concepts of the diagnostic potential of oral fluid in viral mucosal lesions were included in the analysis. The most significant and frequently cited works were used to build the conceptual basis of this review.

**Literature Review Results. Cytokine Profile.** Patients with viral stomatitis have significantly elevated levels of IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$  in their saliva compared to healthy individuals. In herpetic infection, cytokine levels correlate with the severity of pain and the time to epithelialization. HPV-positive patients have been described to have elevated IL-6 and IL-8, associated with the risk of infection persistence. **Immunoglobulins.** Patients with HPV infection have reduced levels of total sIgA compared to healthy individuals, which may contribute to viral persistence. Virus-specific antibodies to HSV and HPV (IgA, IgG) are also detected in saliva. **Innate Factors.**  $\beta$ -defensins (hBD-2/3), lactoferrin, and lysozyme possess antiviral activity. Their concentrations in saliva increase during mucosal inflammation. **Viral Load.** Detection of HSV



and HPV DNA in saliva is possible, making it a convenient non-invasive biomaterial for diagnosis.

**Table 1.**  
**Immunological Parameters in Saliva in Viral Stomatitis and in Healthy Individuals**

| №. | Parameter                                | Healthy Individuals | Viral Stomatitis (HSV, HPV)       | Clinical Significance               |
|----|------------------------------------------|---------------------|-----------------------------------|-------------------------------------|
| 1. | IL-1 $\beta$ , IL-6, IL-8, TNF- $\alpha$ | Low baseline values | Significant increase              | Indicators of inflammation activity |
| 2. | IL-10, TGF- $\beta$                      | Normal levels       | Decrease or variability           | Regulation of inflammation          |
| 3. | Total sIgA                               | High stable level   | Decreased in HPV, variable in HSV | Marker of mucosal immunity          |
| 4. | Anti-HSV, anti-HPV antibodies            | Absent or minimal   | Detected depending on infection   | Diagnosis and monitoring            |
| 5. | $\beta$ -defensins (hBD-2/3)             | Low background      | Increased in mucosal inflammation | Innate defense                      |
| 6. | Viral DNA                                | Absent              | HSV/HPV detected by PCR           |                                     |

Most authors confirm the high diagnostic value of oral fluid as a non-invasive biomaterial for assessing the condition of the oral mucosa in viral stomatitis. The studies included in the review showed that the cytokine profile, the level of secretory IgA, innate defense factors, and the presence of viral DNA in saliva allow for judgment on the activity of the inflammatory process and also predict its course. The increase in IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$  in herpetic stomatitis and the enhancement of IL-6/IL-8 in HPV-associated lesions reflect the universality of the mucosal pro-inflammatory response; however, the question of their specificity remains open.

Despite the accumulated data, the literature lacks a validated cytokine "signature" that could unambiguously differentiate viral stomatitis from other inflammatory processes of the mucosa (aphthous lesions, bacterial gingivitis, or periodontitis). This is due to both the high variability of the cytokine response and methodological differences—varying methods of saliva collection (stimulated or unstimulated), storage conditions, and the analytical methods used. Thus, multicenter studies with unified protocols are necessary to standardize the obtained data.

Of particular interest is the role of the interferon response (IFN- $\alpha$ , IFN- $\beta$ , IFN- $\lambda$ ), which is a central component of antiviral defense. However, most available studies report unstable or very low levels of interferons in saliva, likely due to the limited sensitivity of the methods used. Incorporating ultra-sensitive immunoassays and molecular markers of interferon-stimulated gene (ISG) activity in future research will clarify the significance of this system in the pathogenesis of viral stomatitis. The influence of HPV and HSV-1 co-infection deserves special attention. Data have now been accumulated indicating that HPV shifts the cytokine balance towards IL-6/IL-8-



mediated inflammation and reduces the level of secretory IgA; however, there is practically no information on how these changes affect the clinical presentation and course of herpetic stomatitis. Investigating the interaction of the two viruses in the oral mucosa may reveal new mechanisms of infection persistence and chronicity of the inflammatory process.

Finally, the problem of preanalytical standardization remains unresolved. Even in studies confirming the informativeness of saliva, it is noted that results can vary significantly depending on the conditions of sample collection, time of day, prior food or liquid intake, and the method of data normalization (to total protein or saliva volume). Without unified rules, the results from different research groups are difficult to compare, which limits the possibilities for meta-analysis and clinical implementation. Thus, the accumulated body of data confirms the potential of oral fluid for the immunological diagnosis of viral stomatitis. However, further research should focus on standardizing methodology, clarifying the role of the interferon response, and studying the interaction of HSV-1 and HPV, which will allow for the development of precise and reproducible biomarkers of the disease.

**Conclusions.** The conducted review showed that oral fluid has high diagnostic potential in viral stomatitis associated with both herpes simplex virus (HSV-1) and human papillomavirus (HPV). The most reproducible changes include increased levels of pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, IL-8, TNF- $\alpha$ ), a decrease or variability in anti-inflammatory factors (IL-10, TGF- $\beta$ ), a decreased total level of secretory IgA in HPV infection, the appearance of virus-specific antibodies, and the detection of viral DNA in saliva by PCR. These parameters confirm the possibility of using oral fluid as a "liquid biopsy" for the diagnosis and monitoring of viral lesions of the oral mucosa.

At the same time, unresolved issues persist: there is no specific cytokine "signature" for viral stomatitis, the role of the interferon response is insufficiently studied, there is little data on the interaction between HPV and HSV-1, and difficulties with standardizing saliva collection and analysis methods remain. All this limits the practical implementation of the obtained knowledge into clinical dentistry.

Thus, further research should be aimed at developing unified analysis protocols, incorporating ultra-sensitive methods for interferon detection, and studying the impact of co-infections. Solving these tasks will improve diagnostic accuracy, optimize treatment strategies, and expand the possibilities for non-invasive monitoring of viral diseases of the oral mucosa.

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