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INFLUENCE OF ORAL CO-INFECTION ON THE COURSE OF SARS-COV-2

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Abstract

Subject. *Currently, the impact of coronavirus on the microbiomes of the mouth, lungs and intestines is not well understood. However, research has been done to alter the intestinal microbiota of pigs infected with the epidemic swine flu virus.*

The aim of the study is to identify the relationship between the influence of Co-infection of the oral cavity on the course of SARS-COV2.

Material and Methods. *Totally 201 patients aged 20 to 87 years, with a confirmed diagnosis on admission International classification of diseases (ICD-X: J18.9: coronavirus infection) took part in a clinical study at the Covid Hospital of the Bashkir State Medical University Clinic, Ufa (for 150 beds). The patients were divided into 2 groups: with the appearance of co-infection and with the disappearance of co-infection.*

Results. *The results of this study show that patients with co-infection had a severe course of the disease, more often it was necessary to transfer to non-invasive ventilation; the duration of hospitalization increased; required longer treatment and long-term rehabilitation, aimed at normalizing indicators and normalizing microflora. From this, it can be assumed that if there is an infection in the oral cavity, then the severity of the condition and the course of SARS-CoV-2. This means that the risk of co-infection, secondary infection should be taken into account.*

Conclusions. *In conclusion, it should be noted that the state of the immune system undoubtedly affects the degree of risk of SARS-CoV-2 disease, as well as the severity of the course of this disease.*

Keywords: *SARS-CoV-2, oral microbiome, co-infection, oral care*

Introduction

As of February 23, 2021, the WHO reported 111,938,012 total confirmed cases and 2,477,269,000 deaths from COVID-19 worldwide (WHO, 2021). SARS-CoV-2 has been designated a public health emergency of international concern. making it a serious public health threat . To date, there are 4189153 infected in the world. The mechanism associated with the proliferation of the virus and the interaction of the virus with other microorganisms in the lungs is unclear to this day. It is known that the axis of oral-pulmonary aspiration is a key factor leading to many infectious diseases [*Carvalho T.,2020; Mammen et al., 2020*].

The oral cavity is the second most contaminated, the largest microbiota in the human body. Includes bacteria, fungi, viruses, and archaea [*Dewhirst F et al., 2010*].

The main bacteria present in the normal oral cavity are Neisseria, Corynebacterium, Leptotrichia, Streptococcus, Prevotella, Veillonella, Fusobacterium, and Capnocytophaga [*Li et al., 2014*].

In healthy lungs, the main bacteria are Streptococci, Fusobacteria, Pseudomonas, Waylonella, Prevotella and Capnocytophaga [*Dickson RP, Hufnagle GB 2015; Venkataraman, A et al., 2015; Wypych TP et al., 2019*], they also colonize the oral cavity. Under these conditions, it is relevant to study the question of the interaction of oral microflora with SARS-CoV-2.

Information is provided on the SARS-CoV-2 infection caused by the SARS-COV2 coronavirus, which was temporarily called COVID-19 until February 11, 2020. On January 7, 2020, Chinese

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researchers identified the causative agent of the infection: the new coronavirus SARS-CoV-2, which had not been previously detected. The SARS-CoV-2 coronavirus is a type of virus from the Coronaviridae family that can be carried by both mammals and birds. The name came from the specific structure of the virus, the envelope of which is “crowned” with characteristic thorns, vaguely similar to the “crown”.

Microorganisms that migrated from the oral cavity are probably an important source of the normal lung microbiota [*Bassis C et al., 2015*]. Numerous studies have shown that the lung microbiota is more similar to the microbial picture of the oral cavity [*Segal L et al., 2013; Venkataraman A et al., 2015*].

With caries, Streptococcus remains dominant, but their number decreases (78%) and the species composition changes - the number of Str. Salivarius (45.4%), Str. Sanguis (38.2%), with Str. Mutans (18.2%), Str. Mitis (76.4%). The content of Lactobacillus sp. (63.6%) and Bifidombacterium sp. (67.3%), it is noteworthy that their number decreases as the carious process progresses. Also, from the resident flora, there is an increase in the colonization of Neisseria (16.4%) and fungi of the genus Candida (21.8%). Transient flora appears in the oral cavity of patients with caries -Enterobacteriaceae (E. Coli (7.3%), Klebsiella (3.6%), Enterobacter (5.4%), Citrobacter (1.8%), Peptostreptococcus (21). Thus, with caries, a change in the qualitative and quantitative composition of the microflora of the oral cavity is recorded [*Suvorova M, Medvedeva L, 2018*].

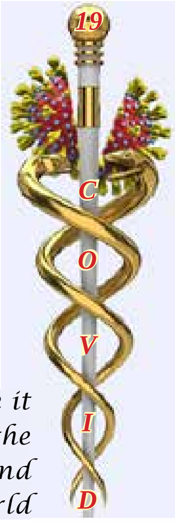
According to a number of authors, with periodontitis among the microflora associated with a healthy periodontium, the number of Veillonella decreases by 4-5 times. Treponema, Synergistaceae and Filifactor have been found to be most strongly associated with periodontitis, while well-known periodontopathogens such as Porphyromonas and Tannerella are partially associated with it. Moreover, the colonization of the periodontal by the genera P. intermedia and A. actinomycetemcomitans was in no way associated with inflammatory periodontal diseases, although they are often considered the most dangerous infectious pathogens directly responsible for the destruction of periodontal tissues. Perhaps this is due to the fact that only certain serotypes of A. actinomycetecomitans have periodontal pathogenicity, while other serotypes of these species, and especially other species of the genus Aggregatibacter, are not associated with chronic periodontitis [*Medvedeva L Suvorova M, 2018*].

Recently discovered candidates for periodontal pathogens include representatives of the genera Campylobacter, Abiotrophia, Gemella, Capnocytophaga and Neisseria. However, it is not yet clear how significant their role is in the development of periodontitis [*Medvedeva L Suvorova M, 2018*].

Currently, the impact of coronavirus on the microbiomes of the mouth, lungs and intestines is not well understood. However, a study was carried out to alter the intestinal microbiota of pigs infected with the epidemic swine flu virus (a member of the Coronaviridae family) [*Koh H et al., 2015*].

Interestingly, fusobacteria, usually the dominant taxa in the oral cavity, were found to be predominant in the infected group (approximately 32%, 0.1% in the normal group) [*Koh H et al., 2015*] According to the results obtained, Prevotella proteins, not viral proteins have been implicated in increasing the clinical severity of COVID-2019, that is, prevotella plays a role in the COVID-2019 outbreak, and attention should be paid to understanding disease mechanisms and improving treatment outcomes [*Khan A, Khan Z, 2020*].

Like SARS-CoV and MERS-CoV, SARS-CoV-2 can also induce excessive and aberrant ineffective host immune responses that are associated with severe lung disease and lead to death [*Hui D, Zumla A, 2019; Huang S et al., 2020*]. Most patients with SARS-CoV-2 suffer from a cytokine storm [*Xu H etal., 2020*] which is manifested by an increase in plasma concentrations of Interleukins (IL-2, IL-7, IL-10), Granulocyte colony stimulating factor), CXCL10, CCL2, CCL3, and tumor necrosis factor alpha (TNF-α) [*Hui D, 2019; Huang S et al., 2020; Ye G. et al., 2020*]. It was confirmed that cellular immunity and cytokine status are closely related to the state of the disease, with high levels of IL-6 and IL-10 in severe



*To overcome it
is possible, due to the
uniting the knowledge and
will of all doctors in the world*

patients [*Wan S et al., 2020*]. It is assumed that changes to cytokines to a certain extent reflect the state of the disease.

According to the Ministry of Health of the Republic of Bashkortostan, as of February 26, 2021, 28305 were infected (of which 9040 cases are in Ufa), 22,515 recovered, only 2506934 tests were performed, 5521 active patients, 5285 on outpatient treatment, 269 died for the entire period, revealed per day 178, discharged per day 190.

The aim of this work is to study the effect of oral CO-infection on the course of SARS-COV2.

Materials and Methods

We examined 201 patients, with a confirmed diagnosis on admission International classification of diseases, (ICD-C: J18.9: coronavirus infection) their ages between 20 to 87 years. Observations were carried out on the basis of the Covid Hospital of the Bashkir State Medical University Clinic in Ufa (for 150 beds). Patients were divided into 2 groups: with the emergence of co-infection (70 people) and with the absence of co-infection (80 people). The exclusion criteria were: age up from 20 years old and to 87 years old.

Before the observation, the patients underwent a proper examination, which made it possible to obtain the initial information in a form convenient for further statistical processing. Dental status was formalized using a set of dental indices, and we used a dental formula recommended by the WHO to preserve information about the condition of teeth and periodontal tissues [*Petersen P, 2003*]. The examination of patients was carried out according to the plan, which included a standard set: interview, examination, palpation and occlusiogram. During the collection of the medical history, attention was focused on the features of the course of the disease, the presence or absence of bad habits, medicinal or other allergic reactions.

During the examination, the following was assessed: the depth of the vestibule of the oral cavity, the state of the mucous membrane of the oral cavity, the location of the frenum of the tongue and lips, the level of the height of the alveolar processes were noted according to the orthopantomogram data. Then the state of the surface of the tongue, hard and soft palate was described. All of the above, together with the condition of the teeth, was recorded in the individual patient records. To determine an objective assessment of the clinical state of the periodontal tissues, the Green-Vermilion hygienic index (HI), Simplified Oral Hygiene Index (OHI-S), simplified index of oral hygiene (IGR-U) [*Greene J, Vermillion J, 1964*], Russell periodontal index (PI) [*Russel A, 1956*], Papillary-marginal-alveolar index (PMA) index [*Schour I, Massler M, 1947*] were used Sputum culture and antibiotic sensitivity were determined. In parallel with the clinical dental examination, a microbiological study of dental plaque biofilm was carried out.

All results were statistically processed using the Statistica computer program from Statsoft. To analyze the dynamics of changes in indicators in the variational series, the arithmetic mean (M) and the standard error of the arithmetic mean (m) were calculated. Determination of the indicator of a significant difference between the two arithmetic means and their standard errors was performed using the unpaired Student’s t-test.

Sputum culture and antibiotic susceptibility testing in patients with SARS-CoV-2.

Collection of biomaterial

Sputum for sowing is collected in the morning before the first meal in a special sterile container with a tight-fitting lid. In order to prevent saliva and mucus impurities from entering the biomaterial, thorough cleaning of the oral cavity and nasopharynx is carried out before collecting a sample for research. Only fresh sputum released as a result of prolonged coughing is subject to analysis.

The analysis of sputum for sensitivity to antibiotics made it possible to accurately determine the causative agent of the disease and select an effective treatment [*Jorgensen J, Ferraro M, 2009; Bandara H, Samaranayake L, 2019*]. Microscopy used native and stained sputum preparations. To study the microbial flora (bacterioscopy), sputum smears are usually stained according to Romanovsky-Giemsa, Gram [*Jorgensen J, Ferraro M, 2009; Bandara H, Samaranayake L, 2019*].The test also included testing the bacteria’s response to drugs. Based on the analysis results, the patients received treatment recommendations [*Jorgensen J, Ferraro M, 2009; Bandara H, Samaranayake L, 2019*].

Determination of the characteristics of the biofilm composition in patients with SARS-CoV-2. A microbiological study of supragingival dental plaque was carried out [*Greene J, Vermillion J, 1964; Jorgensen J, Ferraro M, 2009*]. This index is used when assessing the amount of soft and hard plaque. The examination includes 6 teeth: 1.6,1.1, 2.6, 3.1 - vestibular surfaces 3.6, 4.6 - oral surfaces. Visually and using a coloring solution such as Schiller-Pisarev solution, assess plaque. Samples for culture were taken from each patient from the area of maximum accumulation of supragingival dental plaque. The material was taken in the morning, on an empty stomach, before brushing your teeth. The transport system was used, which included a sterile swab probe and a tube with Amies medium with activated charcoal, closed with a stopper. After sampling the material, the test tube with the medium was transferred to a microbiological laboratory for inoculation and determination of the qualitative and quantitative composition of the biofilm. Washes of periodontal pockets (soft plaque) were removed from the periodontal pocket (in the case of pathology) or from the gingival groove (in the case of normal) using sterile paper endodontic points. In the case of parallel sampling of soft and hard plaque, a soft plaque was first taken from each of the teeth selected for the study, then hygienic treatment of the oral cavity as a whole was carried out and the gingival groove (pocket) of the test tooth was cleaned separately with a cotton swab. When performing serial analysis of soft plaque, the sampling was carried out in two different points of the periodontium of each patient.

Prior to the DNA extraction procedure, the pins were preserved in 1.5 *ml* Eppendorf tubes containing 0.5 ml of a solution for homogenization of samples from the Proba-Rapid kit (NPO DNA-Tekhnologiya, Russia). The samples were cooled and in this form were delivered to the laboratory for the isolation of DNA from biological material. The samples were stored at a temperature of -20˚C for no more than 2 weeks.

Clinical results.

To study the features of the microbial composition of dental plaque, a bacteriological study of dental plaque was carried out [*Medvedeva L Suvorova M, 2018*]. For comparison, material was taken from each patient from the enamel surface in the cervical region in the zone of normal position of the teeth in the dentition. The study was conducted only in patients with a confirmed diagnosis of SARS-CoV-2. Table 1 shows data on the pathogenic flora of the periodontium in patients with a confirmed diagnosis of SARS-CoV-2.

The composition of microbial plaque taken

TABLE1.

Features of the microbial composition of dental plaque in patients with a confirmed diagnosis of SARS-CoV-2

Types of microorganisms	Detection rate			
	Signs of co-infection		Signs of lack of co-infection	
	N	%	N	%
Red Complex				
Porphyromonasgingivalis	9	15	1	1.7
Tannerellaforsythia (B. forsytus)	7	11	2	3.3
Treponemadenticola	5	8.3	1	1.7
Orange complex				
Fusobacteriumnucleatum	48	80	9	15
Prevotellaintermedia	32	53.3	5	8.3
Prevotellanigrescens	28	46.7	4	6.7
Peptostreptococcusmicros	46	76.7	3	5
Streptococcusconstellatus	25	41.7	2	3.3
Eubacteriumnodatum	24	40	3	5
Campylobactershowae	31	51.7	4	6.7
Campylobactergracilis	29	48.3	4	6.7
Campylobacterrectus	22	36.7	3	5
Yellow complex				
Streptococcussanguis	60	100	60	100
Streptococcusoralis	59	98.3	58	96.7
Streptococcusmitis	57	95	58	96.7
Streptococcusgordonii	54	90	53	88.3
Streptococcusintermedius	51	85	51	85
Green Complex				
Eikenellacorrodens	30	50	22	36.7
Capnocytophagasputigena	35	58.3	30	50
Aggregatibacter Actinomycetemcomitans	12	20	10	16.7
Purple and bluecomplexes				
Actinomicesnaeslundii	60	100	60	100
Veilonellaparvula	52	86.7	52	86.7
Actinomicesodontolyticus	40	66.7	38	63.3

from the surface of the teeth of patients with a confirmed diagnosis of Sars-CoV-2 and the presence of co-infection has fundamental features - periodontal pathogenic microorganisms of the red, orange and green Socransky complexes, sow more often [*Socransky S. et al., 1998*]. Microorganisms of the red complex are detected on average 5 times more often than among cadets without signs of psycho emotional stress, and bacteria of the orange complex are detected 6.5 times more often. At the same time, microorganisms of the yellow and purple complexes were detected with the same frequency both in patients with and without co-infection. Microorganisms of the red-orange complex are considered the main cause of the development of inflammatory periodontal diseases; more often they are found in mature, highly organized dental plaque. In the presence of a confirmed diagnosis of Sars-CoV-2 and the presence of co-infection, the quality of individual oral hygiene is much worse, mature dental plaque is more often formed in this zone and, accordingly, periodontal pathogenic microorganisms are more often detected.

With the diagnosis of SARS-CoV-2, the quality of individual oral hygiene deteriorates significantly, mature plaque is more often formed in this zone, and, accordingly, periodontal pathogenic microorganisms are more often detected.

When examining the dental status, patients diagnosed with Sars-Cov-2 showed poor hygiene. In all patients, in 100% of cases, the PMA index was 61%, which indicates a severe degree of inflammatory diseases of the periodontal tissues. Plaque index Green-Vermillion, OHI-S (IGR-U) in 100% of cases was 2.7. The level of oral hygiene according to the total value of the hygiene index is poor.

According to the study, Co-infection and secondary infection with a bacterial infection in COVID-19 in general occurs in no more than 18% of patients. Gram-negative flora accounted for 56% of nosocomial pneumonia pathogens and 23.6% of community-acquired pneumonia [*Bartlett JG,2011; Patel J, Sampson V. 2020; Wan S et al., 2020*]. Sputum was a good clinical specimen with a high positive rate (74.4 ~ 88.9%), followed by nasal swabs (53.6 ~ 73.3%) and throat swabs (50 ~ 61.3%).

Discussion.

Mixed infections are much more common than diagnosed. In conditions of altered reactivity, tissue barriers are violated, as a result, microorganisms may enter organs and environments, where they can cause pathological processes. In addition, many have asymptomatic clinical infections - for example, in the nasopharynx. These are some kind of periodic bronchitis, constant coughing. The causes of these chronic diseases are in most cases unknown. But in the later stages, they can sharply lead to a serious condition.

As a result of the study, the following results were obtained. Patients with + Co-infection had a severe course of the disease, more often a transfer to non-invasive ventilation was required; the duration of hospitalization increased; required longer treatment and long-term rehabilitation, aimed at normalizing indicators and normalizing microflora. From this, it can be assumed that if there is an infection in the oral cavity, then the severity of the condition and the course of SARS-CoV-2. This means that the risk of co-infection, secondary infection should be taken into account.

And finally, knowledge of the mechanisms of interaction between viruses, fungi and bacteria gives hope for the creation of drugs that will effectively resist even such combined attacks.

Conclusion

In conclusion, it should be noted that the state of the immune system undoubtedly affects the degree of risk of SARS-CoV-2 disease, as well as the severity of the course of this disease.

The oral cavity, as a point of entry into the body, may play a crucial role in the pathogenesis of SARS-CoV-2 infection, which caused the global outbreak of coronavirus disease 2019 (COVID-19). The available data indicate that the oral cavity can be an active focus of infection and an important reservoir of Acute respiratory viral infections (ARVI). Given that the oral surface is colonized by a diverse microbial community, it is likely that viruses interact with the host microbiota. Patients infected with SARS-CoV-2 may have changes in the oral and gut microbiota, while oral species have been found in the lungs of COVID-19 patients. In addition, interactions between the oral, lung, and gut microbiomes appear to occur dynamically, with the result that the dysbiotic microbial community in the oral cavity can influence respiratory and gastrointestinal diseases. However, it is unclear whether SARS-CoV-2 infection can alter the local homeostasis of the resident microbiota, actively cause dysbiosis, or affect interorganismic interactions. Here we propose a conceptual framework for the potential impact of SARS-CoV-2 oral infection on local and distant microbiomes via the respiratory and gastrointestinal tracts ('oral-tract axes'), which remains largely unexplored. Would further clarify the pathogenic mechanism of SARS-CoV-2 and the course of infection, as well as the clinical symptoms of COVID-19 in various parts of the human body.

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