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The Oral microbiome in post COVID-19: A Systematic review

Shilpa K [1] & Sangeetha R[2]

1. *Dayananda sagar college of dental sciences, Assistant professor Department of Microbiology, Kumaraswamy layout, Bengaluru-560078*
2. *Dayananda sagar college of dental sciences, Reader Department of Oral Pathology & Microbiology, Kumaraswamy layout, Bengaluru-560078*

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ABSTRACT

Background

The human microbiota is a group of microorganisms that live symbiotically with humans.

They play an important role in the host's immune response to respiratory viral infections. However, there is evidence of a relationship between the human microbiome and coronavirus disease (COVID-19).The purpose of this systematic literature review was to evaluate the existing evidence on the salivary microbiome in post-COVID cases.

Methods

Databases search includes PubMed, Embase, Cochrane Library, CINAHL, and Web of Science for articles in English by October 31, linking his COVID-19 with the human microbiome. systematically identified gender. A literature search was conducted in 2020.Results were qualitatively analyzed.

Results

Of the 543 articles identified by searchingdatabases, 16 were eligible for qualitative review in line with the research objectives. Abnormal and opportunistic pathogen rises were reported in 4,444 of the COVID-19 patients. Several studies, using lower respiratory tract specimens, have suggested dysbiosis in the lung microbiome of his COVID-19 patients, which is rich in opportunistic pathogens. The association between COVID-19 severity and an individual's microbiome remains unclear.

Conclusions

In summary, showed different microbiome composition and prevalence of antibiotic resistance genes in saliva. The salivary microbiome was much less affected and more resilient to antibiotic exposure, regardless of the antibiotic used. Levofloxacin showed significant and long-lasting effects on health-relevant microbial communities.

Keywords: Post COVID-19, Saliva, Oral Microbiome, Immunity, Mucormycosis, Antibiotics

I. INTRODUCTION:

Themicrobiota is widespread in the human body, and the human microbiota varies among individuals and ethnic groups. Despite the fact that the function of the human microbiota has not yet been fully elucidated, the human microbiome currently contains several diseases, including inflammatory bowel disease, type 2 diabetes, Parkinson's disease, and most colon cancers. believed to be associated with the disease of Among them, infectious diseases and respiratory diseases are directly or indirectly associated with specific species of microorganisms. For example, the human upper respiratory microbiome of influenza patients is disr upted by large numbers of Pseudomonas bacteria.

Coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and was declared an epidemic through the Arena Health Company. COVID-19 is a respiratory illness with a range of scientific manifestations, from asymptomatic or moderate illness with cough and fever to severe pneumonia with multiple organ failure and acute respiratory syndrome (ARDS) recurrence and dying amongst races, ethnicities, or countries stay uncertain at this second, for this reason, this systematic literature evaluate aimed to investigate existing evidence at the affiliation between the microbiome and COVID-19 in humans and summarize records on the microbiome in COVID-19 in the pandemic generation. moreover, in this assessment, the connection among the human microbiome and COVID-19 severity has been investigated.[1]

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Post COVID Mechanisms

Following trauma or a severe primary infectious disease like COVID-19, in which a systemic infammatory response syndrome or SIRS is predominant, an overwhelming and long-lasting counterbalancing compensatory antiinfammatory response syndrome (CARS) occurs that leads to postinfectious/posttraumatic immunosuppression. A mirror-image counterregulation of SIRS or systemic inflammatory response syndrome, the purpose of the CARS response is to attenuate the proinflammatory state, prevent maladaptive multi-organ failure, and lead to a return to immunological homeostasis or normalcy. That's it. Several simultaneously interacting and opposing factors come into play, creating a fine-tuned balance of pro- and anti-inflammatory responses. H. SIRS and CARS will coordinate what ultimately determines the outcome of COVID-19. An exaggerated inflammatory response is a function of viral exposure or inoculum, the presence or absence of comorbidities, and immunocompetence status, and is associated with proinflammatory cytokines such as interleukins 1, 6, 8, 17, and 1β, and monocytes. Characterized by excessive emission. Chemoattractant protein-1 and tissue necrosis factor alpha are collectively known as the 'cytokine storm'. This process is unabated and can lead to acute lung injury (ALI), acute respiratory distress syndrome (ARDS), coagulopathy, hypotension, hypoperfusion, and organ failure (also known as multiple organ failure (MOF) or multiple organ failure syndrome (MODS).known to occur, and death.[2]

Human Saliva and COVID-19

Human saliva, which contains 94-99% water produced by the salivary glands, is important for food digestion, lubrication of the oral mucosa, and cleaning and maintenance of the oral cavity. It also contains food particles, oral microbes and their metabolites, serum components, white blood cells, and exfoliated epithelial cells. More than 700 microbial species have been detected in saliva, which prevents the overgrowth of certain pathogens and acts as a gatekeeper (first layer of defense) that protects the respiratory and gastrointestinal tracts. prevent it from spreading. It is also important to prevent viral infections. SARS-CoV-2 can enter human saliva via droplet nuclei of the lower and upper respiratory tract. It can enter the mouth through blood from periodontal fluid and salivary ducts from infectedsalivary glands. Previous studies on SARS-Cov confirmed infection of salivary gland epithelial cells through increased expression of angiotensin-converting enzyme 2 (ACE2). Furthermore, ACE-2 expression was found to be higher in minor salivary glands than in lungs. SARS-CoV RNA is detected in saliva samples before lung lesions appear. Live virus can be cultured in saliva samples.Thus, salivary glands are important viral reservoirs. This suggests that SARS-CoV-2 spreads through contaminated saliva in asymptomatic infections.

Oral Microbiota

Like other pandemics, significant numbers of viral, bacterial, and fungal co-infections have been observed in COVID-19, which originates in the oral cavity. Oral pathogens such as Veillonella and Capnocytophaga have been identified by NGS in bronchoalveolar lavage fluid of COVID-19 cases A higher nasal viral load in the pharynx has been reported. The oral cavity is home to her second largest microflora in the human body, including bacteria, viruses, fungi, and archaea. Important genera of bacteria in the human oral cavity are Neisseria, Prevotella, Streptococcus, Corynebacterium, Fusobacterium, Leptotorichia, Veiroella, and Capnocytophaga. Many such pathogens can asymptomatically colonize the respiratory tract of healthy individuals. The oral microbiome thus modulates mucosal immunity and influences virulence.[3]

Saliva of Asymptomatic Individuals Contain Infectious Virus

Our results indicated two potential sources of SARS-CoV-2 in saliva. A cell-free fraction from infected glands producing de novo virus and a cellular fraction from shed infected oral mucosa. To test the infectivity of both acellular and cellular saliva fractions of, high viral load saliva samples from COVID-19 patients were incubated with Vero cells to detect the viral cytopathic effect (CPE). After confirming SARS-CoV-2 RNA in the saliva ofcompletely asymptomatic individuals, samples were processed to separate cell-free salivary fluid from epithelial cells (Methods). Acellular saliva induced CPE typical of coronavirus infection starting at A cell fraction induced CPE. To confirm replication, supernatants from monolayers with and without evidence of CPE were collected and used to confirm infection in new Vero monolayers. These cultures followed the same timeline as their parent culture. These

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results demonstrate the infectivity of saliva from asymptomatic/presymptomatic individuals with COVID-19. In particular, these results suggest that exhaled oral droplets containing infectious virus and infected cells may be responsible for airborne transmission of SARS-CoV-2.

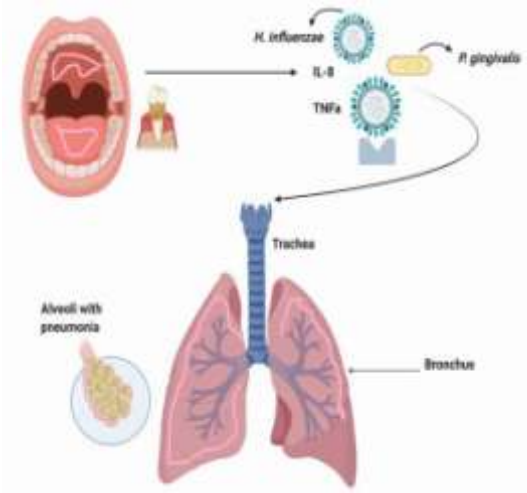
SARS-CoV-2 levels in saliva correlate with altered taste

To investigate SARS-CoV-2 dynamics in asymptomatic and symptomatic individuals with COVID-19, this study assessed SARS-CoV-2 RNA levels in saliva and NP swabs and viral antigens in saliva. Presence of antibodies assessed againstVirus was rapidly cleared from secretions, although not in all truly asymptomatic individuals, based on time since first positive NP swab test. Of her 39 participants in the study, 22% reported no symptoms at all, with virus clearance ranging from 0.5 weeks for him to 3.5 weeks for him. The mean clearance rate in this cohort was lower for her week than for symptomatic individuals, suggesting that some asymptomatic individuals may harbor SARS-CoV-2 in their nasopharynx and saliva for long periods of time. suggests. Of the 8 asymptomatic participants, 5 tested positive only in her NP swabs, 2 of whom became positive for viral load midway through the surveillance period.[4]

Oral Microbial Characterization

Nucleic acid testing byRT-PCR is considered the gold standard for COVID-19. However, the high false-negative rate is due to several factors, such as low viral titers and sampling errors, leading to a widening range of infection. Therefore, new tools for non-invasive diagnosis of COVID-19 are urgently needed. We collected samples from IgG antibody-negative patients during recovery and matched them after exclusion to exclude them. This suggests that this classifier could serve as an adjunct tool for non-invasive diagnosis of COVID-19. , the frequency of 5 genera including Haemophilus increased persistently ($p<0.001$) and the frequency of 5 genera including Leptotorichia, Megasphaera and Selenomonas decreased persistently ($p<0.001$). $p<0.01$). Specifically, Megasphaera increased as caries progressed. These similar results suggest that interventions with these bacteria may influence patient outcomes A heatmap also showed the oral microbiome.[5]

Each disease has unique microbial changes in the mouth and intestines. Oral microbiota abnormalities in RA manifest as an increase in Lactobacillus salivarius and a depletion of Haemophilus spp. Porphyromonas, Tannerella, and Fusobacterium were enriched in periodontitis. In this study, we found microbial alterations consistent with IgG positivity, supporting our idea of using microbial models to diagnose from a microbiome perspective. Microbial markers combined with RT-PCR can further improve the detection efficiency of probable COVID-19 patients in the population and reduce the source and area of infection.The microbiome is closely related to disease recovery. Oral microbiome abnormalities and periodontitis were partially normalized after treatment, suggesting that the microbiome plays an important role in recovery. We are the first to report characterizations of the oral microbiota and lipidomics, and discover key bacterial and lipid molecules that may be involved in the development and prognosis of COVID 19. Microbiota may influence the progression of COVID-19by secreting lipid molecules into the blood. A correlation between the microbiome and lipids has been reported in our study. Oral and gut microbiomes correlated with clinical indicators such as leukocytes and lymphocytes, respectively. Further investigation of potential mechanisms of the microbiome influencing disease shows promise for the use of microbe-assisted diagnosis, treatment, and prognosis of COVID-19.[6]



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II. DISCUSSION

Although the salivary microbiome showed unexpected stability, the fecal microbial ecosystem was significantly disrupted for up to several months depending on the type of antibiotic administered. The reason for these differences is unknown and should be addressedA possible explanation may relate to the pharmacokinetics of antibiotics. Another intriguing possibility is that the oral microbial ecosystem has a higher intrinsic resilience to stress, including recovery fromantibiotics.[7] This ecosystem must withstand multiple daily disruptions, such as oral hygiene practices such as exposure to topical antimicrobials, physical removal with a toothbrush, and changes in temperature and oxygen. None of this applies to the colon, which has more subtle effects. B. Dietary changes occur more frequently.

A recent report found changes in bacterial communities in both saliva and faeces after antibiotic use. However, the study populations and study designs were very different: those evaluated by Abeles and co-authors had medical indications for antibiotic use and received long-term (6 weeks) admixture of broad-spectrum antibiotics. focused on healthy individuals and study design.A single dose of antibiotic. Unfortunately, the authors did not report the effects of antibiotics after discontinuing hisantibiotics, and his comparison regarding potential differences in long-term effects and resilience between the two microbial ecosystems. Excludes of SARS-CoV-2 levels in saliva correlate with altered taste. To study the dynamics of SARS-CoV-2 inCOVID-19 asymptomatic and symptomatic individuals, outpatients (n = 39) were enrolled from his two groups: Nasopharyngeal (NP). Individuals with positive swabs (n = 30). In this study, we assessed her SARS-CoV-2 RNA levels in saliva and NP swabs and the presence of antibodies against viral antigenin saliva over a 5-week prediction period. Based on the time since the first NP swab test became positive, these data confirm that saliva and NP swabs generally correlate well over time, as shown previously. Some individuals have cleared SARS-CoV-2 for very long periods of time (more than 2 months after first negative NP and saliva tests). Not all truly asymptomatic individuals rapidly cleared the virus from their secretions. The average clearance rate in this cohort was approximately one week lower than that of symptomatic individuals, suggesting that some asymptomatic individuals may retain SARS-CoV-2 in their nasopharynx and saliva for longer periods. Suggestsof the 8 asymptomatic participants, 5 were positive only on NP swabs, including 2 who developed a positive viral load midway through the surveillance period. Two asymptomatic participants, CoV01 and CoV02, showed only positive saliva when consistent with her NP viral load 14 days after her positive NP test. These data highlight the potential for virus clearance from the nasopharynx but possible persistence in saliva, leading to persistent virus shedding from SARS-CoV-2-infected oral sites. It is suggested that In symptomatic individuals, the presence of SARS-CoV-2 RNAin saliva was positively associated with the patient's self-reported "loss of taste and smell." These data are confirmed by salivary cell infection experiments. Reports of “body aches/muscle pains” were inversely correlated with viral salivary load. Although the sample size is modest, these data suggest that the presence of SARS-CoV-2 RNA in saliva is positively correlated with altered taste. Public health measures such as universal mask use and social distancing aim to reduce droplet and aerosol transmission. However, few studies have attempted to directly measure changes in salivary droplet output in his COVID-19 infected with mask wearing (Methods). The efficacy of standard mask wearing to reduce droplet spread in these individuals was tested, including asymptomatic individuals with positive NP or salivary viral load, resulting in a greater than 10-fold reduction in salivary shedding detection. Wasshown.

Virus-specific antibody dynamics in saliva

A previous study showed rapid clearance of his IgA and IgM antibodies in saliva samples and stable her IgG antibody titers up to 15 weeks post-infection. In our prospective cohort, salivary IgG antibodies to nucleocapsid and spike virus antigens were detected in 73% (22/30) and 54% (15/28) of his COVID-19 early-recovery samples, respectively, who developed spike antibodies.) was detected. It is later detected as a nucleocapsid antibody. Nucleocapsid and spike antibodies in saliva and serum were moderate. Some individuals with both nucleocapsid and spike antibodies had prolonged viral RNA positivity in the nasopharynx and saliva, had moderate symptoms, and had oral

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tissue infections. These data further support that SARS-CoV-2 infection can induce a sustained local immune response in saliva.[8]

Mucormycosis: Mucormycosis, also known as black mold or zygomycosis, is caused by a group of fungi called Mycobacterium mucor, which are found in the environment and live mainly in the sinuses or lungs of immunocompromised people. increase. It is a rare but deadly fungal infection that is now being detected in his COVID-19 patients in India. Many states in India have reported such infections among COVID-19 patients. In humans, this opportunistic pathogen appears on the skin and affects the brain and lungs. According to the U.S. Centers for Disease Control and Prevention (CDC), it is rhinocerebral mucormycosis (sinus and brain), pulmonary mucormycosis (lung), gastrointestinal mucormycosis (gut and bowel), cutaneous mucormycosis (skin , and possibly disseminated mucormycosis (moderate). those with other illnesses). The infection usually develops 10 to 14 days after hospitalization and spreads through the bloodstream to other parts of the body. Patients can be treated with amphotericin B (an antifungal drug), but in some cases surgery may be required. Symptoms include pain or redness around the eyes and nose, blurred vision or double vision, loose teeth, toothache, dark/bloody nasal discharge, vomiting blood, swollen cheekbones, skin lesions, chest pain, fever, headache, and shortness of breath. , cough, etc. , and can also be in a state of psychic change. These infections include diabetes, long stays in intensive care units, long-term use of medical oxygen, hyperglycemia, chronic kidney disease, HIV/AIDS, hematological malignancies, and solid organ transplantation. Such infections are amplified by the rampant abuse or overuse of steroids, monoclonal antibodies, and broad-spectrum antibiotics during COVID-19 treatment. India has her second highest number of diabetics, with about 70% uncontrolled, making 4,444 co-infections more common here.[9]

Metagenomic prediction data indicate that microbiome function recovered faster than microbial community composition after antibiotic exposure. This supports the importance of functional redundancy within the gut microbiota, as previously suggested after one exposure of three healthy adults to ciprofloxacin. However, metagenomic predictions s uggest that functional or orthologous groups may be significantly affected even in the absence of significant antibiotic effects on microbiome composition, as was the case in faecal samples exposed to amoxicillin. The most likely explanation for this phenomenon is the individualized response to this antibiotic at the taxonomic level, meanwhile affecting similar general functions of different microbial taxa. His two research populations involved in the project differed in the composition of their (early) microbiomes. Since the fecal microbiome is strongly influenced by diet, it was very informative to compare the diets of the two cohorts. Unfortunately, no such information was collected. More striking were differences in the salivary microbiota, where the predominanttaxa in the saliva samples were Prevotella spp. rather than Streptococci in the samples. The dorsum of the tongue has been shown to be the primary habitat for the anaerobe Prevotella, but streptococcal dominan ce may be associated with supragingival plaque or non-keratinized mucosa. Because no intraoral clinical examination was performed in this study and the timing of the last individual oral hygiene episode associated with saliva sampling was not recorded, the exact reasons for the observed differences cannot be elucidated. Even before antibiotic exposure, bothstudy populations had antibiotic resistance genes in their oral and gut microbiomes. This is consistent with reports of high levels of antibiotic resistance commensal bacteria in the saliva and stool of her two healthy individuals who had not been exposed to antibiotics for at least 1 year (30). Both the metagenomic predictions of the 16S rRNA gene amplicon data and the complete metagenomic data from selected samples indicated a high antibiotic resistance gene burden in the UK (HP) population at baseline. These differences may have influenced the study results. Relatively weak effects of antibiotics on the gut and oral microbiomes of the HP study population may be influenced by the inclusion of potentially high baseline antibiotic resistance genes in UK study participants In Sweden, efforts under the Swedish Strategic Program for the Rational Use of Antibiotics and Surveillance of Resistance (STRAMA), initiated in 1994, have led to a significant reduction in antibiotic use over the past two decades. . As recently as 2013, a similar initiative, the UK Antimicrobial Use and Resistance Surveillance Program (ESPAUR),

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was developed in the UK after the current study was completed. ESPAUR's first report compared antibiotic consumption rates in the UK from 2010 to 2013 and showed that overall antibiotic consumption increased by 6%.In 2012, 20.1 defined daily doses (DDD) per 1,000 population of antimicrobials for systemic use were consumed out-of-hospital (community use) in the UK compared to 14.1 DDD in Sweden. Exposure to various antibiotics increased the frequency of genes associated with antibiotic resistance. Among the antibiotics tested, exposure to amoxicillin had the least discernible effect on microbiome composition, yet these samples had the highest number of antibiotic resistance-associated genes, the predicted metagenomic and Most classes rose after 1 week at each of the full metagenome exposures. One of the mechanisms of clindamycin resistance involves acquisition of the erm gene (erythromycin ribosomal methylase), which is normally present on plasmids or transposons of pathogens (19). A comparison of antimicrobial resistance levels in strains isolated 30 years apart (1970s and 2000s) showed that Gram-negative Bacteroides species acquired ermB genes from Gram-positive bacteria (clostridium perfringens, Streptococcus pneumoniae, Enterococcus faecalis) was shown. Interestingly, a complete metagenomic sample from a clindamycin-exposed subject (KI subject S15) showed an increase in eight erm genes in feces and two erm genes in saliva. The number of fecal ermB genes in this individualincreased 240-fold, suggesting the possible involvement of plasmids or transposons. Whole-genome sequencing of individual strains showed that the majority of resistance genes in these strains were acquired by lateral gene transfer rather than evolved within the strain. B. By plasmids, transposable elements and integrans. Currently, no other studies have simultaneously examined the effects of different antibiotics on the oral and fecal microbiomes in healthy individuals. In this study, the same exposure to antibiotics resulted in two radically different responses in her in these two niches of the human body. Although the salivary microbiome showed unexpected stability, the fecal microbial ecosystem was significantly disrupted for up to several months depending on the type of antibiotic administered. The reasons for these differences are unknown and should be addressed. A possible explanation may relate to the pharmacokinetics of antibiotics. Another intriguing possibility is that oral microbial ecosystems are highly intrinsically resilient to stress, including recovery from antibiotic exposure. This ecosystem must withstand multipledisturbances each day, including oral hygiene practices such as exposure to topical antimicrobial agents and physical removal by brushing, and changes in temperature and oxygen. Not true for the colon where it works. B. Dietary changes occur more frequently. A recent report found changes in bacterial communities in both saliva and feces after antibiotic use. However, the study populations and study designs were very different: subjects evaluated by Abeles and co authors had medical indications for antibiotic use and received long-term (6 weeks) admixture of broad-spectrum antibiotics. However, we focused on healthy subjects and one individual antibiotic dose. Unfortunately, the authors did not report the effect of antibiotics after stopping antibiotic use.[10]

III. CONCLUSIONS

In summary, we found that her two different in salivary microbiome composition and prevalence of antibiotic resistance genes. The salivary microbiome was much less affected and more resilient to antibiotic exposure, regardless of the antibiotic used.

Two of the antibiotics - clindamycin and ciprofloxacin - have shownsignificant longterm effects on health-related microbial communities.[11] The use of saliva-based SARS-CoV-2 testing offers several clinical advantages and is scientifically sound. However, further research is key to understanding the interrelationship between COVID-19 and saliva. This will facilitate the adoption of less invasive diagnostic techniques and the large-scale application of molecular testing, an important strategy to combat the epidemic. Searching for salivary biomarkers associated with COVID-19 onset and progression may better distinguish between asymptomatic, mild, moderate, or advanced disease. Findings of this kind may lead to the development of point-of-care devices that are very useful for understanding transmission development and immune responses in population studies.

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The purpose of this review is to raise awareness (and warn) about the newly coined generic term Persistent Post-COVID Syndrome (PPCS) by analogy with the post-septic/post-ICU syndrome.[12] It is a loose association of heterogeneous symptoms for which no characteristic laboratory test exists, and they are easily overlooked or ignored is epidemic after epidemic, as evidenced by the increasing trend of physical and mental disability seen in post-COVID patients. Internal and external resident microbiota are important for human health and essential for the immune response. Co-infection with microorganisms increases the risk of disease severity in humans. However, the mechanisms of interaction between infectious viruses and other pathogens are still unknown. It is of great importance to study the causes and mechanisms of pathogen co-infection. This helps in early detection and understanding of antibacterial and antifungal therapies to effectively treat disease.[13]

The use of health microbiology, probiotics, and other health-enhancing therapies should be considered to combat co-infection during the COVID-19 pandemic. Experimental therapies to support patient outcomes and prevent the consequences of respiratory co-infection are imminent. In this review, we attempt to summarize previous studies describing the viral, bacterial and fungal pathogens involved in co-infection of COVID-19 and the role of adaptive immunity at the site of infection in controlling infection along with inflammatory cytokine therapy. It also describes the role of the system[14].

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