Letter to the Editor: Microbiota in the Respiratory System—A Possible Explanation to Age and Sex Variability in Susceptibility to SARS-CoV-2

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ABSTRACT: The Human respiratory tract is colonized by a variety of microbes and the microbiota change as we age. In this perspective, literature support is presented for the hypothesis that the respiratory system microbiota could explain the differential age and sex breakdown amongst COVID-19 patients. The number of patients in the older and elderly adult group is higher than the other age groups. The perspective presents the possibility that certain genera of bacteria present in the respiratory system microbiota in children and young adults could be directly or through eliciting an immune response from the host, prevent full-fledged infection of SARS-CoV-2. The possibility also exists that the microbiota in older adults and the elderly population have bacteria that make it easier for the virus to cause infection. I call upon the scientific community to investigate the link between human microbiota and SARS-CoV-2 susceptibility to further understand the viral pathogenesis.

KEYWORDS: COVID-19, SARS-CoV-2, Coronavirus, microbiota, human microbiome, viral infections

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In the United States, as of September 2020, the coronavirus disease-19 (COVID-19) pandemic has resulted in over 6 million infections and over 180,000 deaths. Analysis of the demographics of the patients infected with COVID-19 has shown that there is a disparity in the number of cases based on age and sex. Children under the age of 18 accounts for only a small fraction of the population having COVID-19 and amongst the population hospitalized. The rate of hospitalization increases with age beyond the 18 to 49 age group. Comparison of SARS-CoV-2 infection and mortality rates between males and females have shown that males are more susceptible than females.[1] Similar demographic breakdown has been observed for patients infected with SARS-CoV-2 across the globe. However, there is no scientific understanding of the underlining reasons and mechanisms imparting resistance in children against SARS-CoV-2 infections. The observation is further compounded by the fact that even within a specific demographic group, there are people who have been infected but display no symptoms of the disease.

Based on the analysis of the results from published literature on human microbiome studies, I propose here the hypothesis that microbiota of the respiratory tract is a variable playing an important role in determining the susceptibility of the person to SARS-CoV-2 infections. As described in the next few sections, the parallels between our understanding of human microbiota in the respiratory system, a link between nasal microbiota and sensitivity to respiratory illness, and the age and sex sensitivity of COVID-19 are hard to ignore.

Variation of Nasal Microbiome as a Function of Human Age

Numerous research studies have shown that different compositions of the microbiota are present in individual sites within the respiratory system and the composition of the microbiota changes over the span of human life.[2-4] The microbiota of the nasal passage in the infants have a high abundance of *Propionibacterium, Lactobacillus, Streptococcus, Staphylococcus, and Corynebacterium*.[5] As their age progresses, children up to 2 years old having a higher relative abundance of *Moraxella* and *Corynebacterium/Dolosigranulum* show increasing stability of nasal microbiota.[6] In contrast, children having a higher relative abundance of *Haemophilus* and *Streptococcus* have less stable microbiota composition.[6]

As the children enter puberty, there is an impact on the microbiota with research showing prepubertal children having a high composition of *Moraxella, Haemophilus, Neisseria, Streptococcus, Dolosigranulum, Gemelli*, and *Grannulicatella*.[4] As the children enter adulthood, the abundance of *Corynebacterium, Propionibacterium*, and *Turicella* increase significantly.[4] Studies show that when compared to the microbiota of the adults, children have less diverse microbiota despite the higher bacterial load.[7]

Further alterations in nasal microbiota in adults commence during the 40 to 65 age span, with increased dominance of *Cutibacterium, Corynebacterium*, and *Staphylococcus*.[8] Studies in older and elderly adults show that the biodiversity distinction between the different regions of the respiratory tract is lost, with nostril microbiota being dominated by non-pneumococcal *Streptococcus*.[4] In a study conducted in the United States comparing the nasal microbiota of the residents of nursing homes and elderly adults living independently, it was observed that in the nursing home residents there was a statistically significant increase of *Lactobacillus, Streptococcus, Staphylococcus*, and *Rothia*.[9]

There are still large gaps in our understanding of the link between the microbiota present in the respiratory system and

the viral infections. Further, no studies have been conducted to investigate the relationship between SARS-CoV-2 infection and microbiota. Nevertheless, based on the available data, I suggest that either or both of 2 scenarios are plausible: (i) either directly or by eliciting an immune response, certain genera of bacteria can prevent a full-fledged viral infection in children and young adults. Older adults and the elderly population may not be having the bacteria to help fight the virus. (ii) Alternatively, microbiota in older adults and the elderly population may have bacteria that makes it easier for the virus to cause infection.

Variation in Microbiome as a Function of Sex

When the microbiota in the nasal passage is compared between male and female populations, the bacterial community is not statistically different.[10] However, the nasal microbiota of men is much denser (the total amount of nasal bacteria present) than that in women.[10] For example, Liu et al. have shown that while the colonization rate (presence of a bacteria on a body surface) of *S. aureus* did not differ between males and females, women had 10- to 100-fold lower *S. aureus* absolute abundance than men.[10] The difference in absolute abundance of bacteria between males and females, when combined with the possible relationship between the presence and absence of given genera as mentioned scenarios, could explain the sex difference in COVID-19 cases.

Nasal Microbiome and Respiratory Illness

There exist a strong relationship between nasal microbiota and respiratory illness.[11-13] Children with an increased abundance of *Haemophilus* and *Streptococcus* genera have been shown to have higher rates of wheezing and asthma.[3,8] Even in inflammatory disorders such as chronic rhinosinusitis, the connection between microbiota and the disease has been observed.[12] In studies with children with respiratory syncytial virus, Rosas-Salazar observed that the abundance of *Moraxella, Haemophilus*, and *Streptococcus* remained higher during acute viral infection whereas *Staphylococcus* and *Corynebacterium* remained lower during this illness.[14] Cohort studies of asymptomatic children have found a positive correlation between the presence of adenovirus and rhinovirus and the two bacterial taxa, *M. catarrhalis* and *H. influenzae.*[15] Conducting a household transmission study, Lee et al. have shown that there was a significant association between nasal microbiota and influenza, specifically the relative abundance of *Alloprevotella, Prevotella*, and *Bacteroides.*[16] The link between nasal microbiota and viral infections was concluded in a milestone study with rhinovirus challenge in humans by Lehtinen et al.[17] They showed that the nasal microbiota influences the virus load, host innate immune response, and clinical symptoms during virus infections.[17] On similar lines, the differences in the microbiota amongst individuals from the same age group could explain why some patients with SARS-CoV-2 infections develop symptoms whereas others remain asymptomatic.

Few insights are available on how the microbiota helps humans resist or increase sensitivity to virus infections. Chen et al. demonstrated that *S. epidermidis* culture supernatants significantly suppressed the infectivity of various influenza viruses in humans.[18] They identified that the giant extracellular matrix-binding protein of the bacteria was involved in preventing the virus infection.[18] In contrast, Ichinohe et al. illustrated that nasal microbiota regulates the generation of virus specific CD4 and CD8 T cells and antibody response following respiratory influenza virus infections.[19] They further concluded that the microbiota regulates immunity in respiratory mucosa through the proper activation of inflammasomes.[19] Studies have also shown the presence of certain organisms to enhance viral acquisition and replication. *H. influenzae* has been shown to induce the expression of ICAM-1 and TLR3-receptors, increasing the binding of rhinoviruses.[20] The bacteria have been also shown to increase viral replication of the respiratory syncytial virus.[20] Also, when human bronchial epithelial cells were pre-incubated with *S. pneumoniae*, increased susceptibility of the bronchial cells to infection with human metapneumovirus was observed.[20]

The Gut-Lung Axis and the Respiratory Illness

Beyond the relationship between SARS-CoV-2 infection and nasal microbiota, gut microbiota could also be playing a key role in determining the sensitivity of patients to the viral infection. There exists an equilibrium between the gut microbiota and the immune system response in distal organs such as lungs.[21,22] The gut-lung equilibrium is suggested to be mediated by multiple mechanisms of action. Microaspiration of intestinal microbes impacts the microbiota of respiratory system directly.[23] Further, segmented filamentous bacteria, *Bifidobacterium* sp., and members of the colonic Bacteroides organisms induce the production of antimicrobial peptides, secretary immunoglobulins, and pro-inflammatory cytokines.[24] The segmented filamentous bacteria in the gut stimulated pulmonary T helper 17 cells response in mice and protected the animal from *S. pneumoniae* infection and mortality.[25] In humans, similar response was seen in humans with enriched *Prevotella* sp., *Rothia* sp., and *Veillonella* sp.[26] Research in mice have also shown that bacteria such as *Lactobacillus* sp. and *Bifidobacterium* sp. in the gut microbiome protected the animal against bacterial and viral pulmonary infections.[24]

It is possible that abundance of certain microorganisms in the gut microbiota could be responsible for influencing the immune response in the lungs of patients, and therein determining the sensitivity and severity of SARS-CoV-2 infections.

Conclusion

Vaccine development is a time-consuming process and faces the challenge of antigenic drift due to viral mutations. Drugs against the virus could have limited efficacy based on the time of administration and the emergence of drug-resistant viral

strains. While scientists develop treatments and a vaccine to help alleviate the infection rates and the mortality observed during the current pandemic, there is an urgent need for further research to study the possible relationship between the microbiota of the human respiratory system and the gut, and the susceptibility to COVID-19 infection. This scientific understanding could be pivotal in understanding the pathogenesis of SARS-CoV-2. However, the use of our knowledge of how microbiota could be inhibiting SARS-CoV-2 infection and spread in the human body could allow for a faster and natural alternative to combating the virus. Further, once we know the relationship between the presence or absence of specific microbial taxa in the respiratory system and the sensitivity to COVID-19 infection, a diagnostic test could be developed to test for the presence or absence of these bacteria in human samples. Such tests from the population could result in determining the percentage of the population in a community that is susceptible to infections. This information could be critical in developing scientifically guided public policies to combat the spread of the pandemic in different populations.

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