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Microbiota as a potentially-modifiable factor influencing COVID-19
Vu L Ngo and Andrew T Gewirtz

Impacts of respiratory tract viruses have long been appreciated to highly heterogeneous both between and within various populations. The SARS-CoV-2 pandemic, which is the first time that a pathogen’s spread across the globe has been extensively monitored by direct detection of the pathogen itself rather than the morbidity left in its wake, indicates such heterogeneity is not limited to outcomes of infections but whether infection of a particular host occurs at all. This suggests an important role for yet to be discovered environmental (i.e. non-genetic) factors that influence whether an exposure to the virus initiates a productive infection and, moreover, the severity of disease that results. This article discusses the emerging hypothesis that the composition of a host’s commensal microbial communities, that is, its ‘microbiome’, may be one such determinant that influences outcomes following encounters with respiratory viral pathogens in general and SARS-CoV-2 in particular. Specifically, we will review the rationales and evidence that supports this hypothesis and, moreover, speculate as to possible approaches to manipulate microbiota to ameliorate disease induced by respiratory viral pathogens.

Address
Center for Inflammation, Immunity and Infection, Institute for Biomedical Sciences, Georgia State University, Atlanta, GA 30303, USA

Corresponding author: Gewirtz, Andrew T (agewirtz@gsu.edu)

Microbiota impacts viral epithelial interactions in the intestinal tract
The intestinal tract is the site of densest bacterial colonization and, moreover, provides best characterized examples of bacteria impacting viral infection in the tissue they inhabit. For example, multiple studies observed that complete absence of gut microbiota, achieved by use of antibiotics or germ-free mice, impedes infection by several enteric viruses including rotavirus, reovirus, and poliovirus [1,2]. Such viral dependence on microbiota for maximal infection appears to reflect, at least in part, a role for bacterial products, including LPS and peptidoglycan facilitating viral-cell binding. Furthermore, binding of viruses by bacteria can serve as a nucleation site, effectively increasing number of virions that enter a cell [3]. Yet, while complete lack of a microbiota impedes infection, it nonetheless occurs in reduced and/or delayed amounts. In contrast, some specific microorganisms can completely protect mice against infection by rotavirus (RV), which remains amongst the world’s most deadly pathogens. Specifically, mice harboring high levels of segmented filamentous bacteria (SFB), which can occur in immune-deficient mice or, transiently, in wild-type mice exposed to SFB, are highly resistant to RV infection [4**]. In vitro studies suggest that ability of SFB to impede RV infection may, in part, reflect that some surface components of SFB can interfere with viral entry. Yet, in vivo studies indicate that SFB may largely impede by RV infection by increasing proliferation/turover of...
epithelial cells which reduces presence of the highly differentiated villus epithelial cells that rotavirus preferentially infects and, moreover, increases anoikis, the process by which intestinal epithelial cells are extruded into the lumen as they destroy their content likely including any infecting viruses [4**,5]. The extent to which other bacteria can influence rotavirus infection remains under investigation as does the extent to which any bacteria might influence rotavirus infection in humans. Nonetheless, these unequivocal results in tractable models support the proof of concept that microbiota composition can dramatically alter viral-bacterial interactions and, consequently infectious outcomes, at least in the intestine.

**Gut microbiota has broad impacts on adaptive immunity**

Beyond the specific examples above, gut microbiota also has a major influence over immune system development and regulation such that germ-free mice are largely devoid of mucosal lymphoid tissue. More physiological examples of the microbiota influence on immune regulation can be seen in the stark differences in immune cell populations in mice from different sources, which can be normalized by cohousing or fecal transplant [6*,7]. SFB provides a striking example of the ability of microbiota to impact the immune system in that its presence in the intestine is sufficient to result in Th17 cells in mice that would otherwise lack this important lymphocyte subtype [8]. While there is not much basis to speculate on how the presence of Th17 cells will impact viral infection per se, expansion of lung resident Th17 cells associates with severe lung inflammation in SARS/Cov-2 patients thus suggesting this bacteria, and perhaps others like it, may impact severity of Covid-19 irrespective of viral loads [9]. In this context, it is important to note that impacts of gut bacteria on immune cell populations are not gut-restricted but rather dictate T-cell populations in blood and distal tissues, including the lung [10] and, consequently impact diseases seemingly unrelated to the gut such as arthritis [11]. While the specific mechanisms by which SFB and other bacteria impact T-cell populations are not well defined at the molecular level, they are thought to generally reflect the ability of bacteria to activate innate immune signaling by direct adherence to epithelial cells and/or by producing products that activate innate immunity.

Another means by which gut bacteria can modulate adaptive immunity, and consequently potentially impact outcomes of viral infection, is by impacting levels of regulatory T-cells, which can suppress immune cell activation and thus dampen inflammation. A broad variety, but not all, gut bacteria, can promote development of such T-reg cells and the extent to which they do so is impacted by diet. Specifically, development of Tregs is driven by major products of fermentation of dietary fiber, namely short-chain fatty acids (SCFA) [12]. Thus, we envision that interaction of diet and microbiota will play a role in helping avoid immune-mediated pathology in response to viral infections.

**Impacts of microbiota in respiratory tract viral infections**

The notion that microbiota might impact COVID-19 stems in large part from trying to understand the heterogeneity in outcomes following exposure to SARS/CoV-2. Specifically, there are many instances of closely related individuals (i.e. similar genetics) being subjected to seemingly identical exposures to SARS/Cov-2 but only some persons ever test positive for the virus and, of those, some have minimal diseases while others becoming severely ill. That microbiota composition can often differ markedly within immediate families [13], combined with the increasingly appreciation that microbiome can broadly impact host phenotype suggests the possibility that it might play a role in such heterogeneity. Indeed, gut microbiota can influence many of the metabolic phenotypes (i.e. obesity, diabetes, and hypertension), known to associate with severe disease. Moreover, given the broadly held view that many of the severe consequences of SARS/CoV-2 infection are driven by the host immune response suggest the microbiota’s influence on the immune system might contribute to disease severity. Additionally, many respiratory viral infections are associated with gastrointestinal symptoms and, in the case of SARS/Cov-2 such symptoms associate with severe disease outcomes [14*]. SARS/Cov-2 can be readily detected in feces in infected persons and replicates efficiently in enterocytes [15] suggest the possibility for gut microbiota in impacting SARS/Cov-2.

The upper airways, where respiratory viruses initially infect their hosts, are also relatively densely colonized with microbiota, which might influence viral infection. Culture-independent analysis of the oral and nasopharyngeal microbiota indicate the upper airway microbiota is quite distinct from the gut [16], which is not overly surprising given the stark differences in these environments in numerous factors such as oxygen and nutrients. Furthermore, the extent of inter-personal differences in microbiota composition (i.e. β-diversity) is greater in the upper airway than in the gut [16] potentially allowing it to account for a greater portion of heterogeneity of outcomes following SARS/Cov-2 exposures. Thus, one can imagine SARS/Cov-2 infection in the respiratory tract might be influenced by local bacteria, immune responses they influence, or immune responses originating in other tissues such as the gut.

The myriad of ways microbiota might possibly impacts SARS/Cov-2 infection has made this topic the subject of numerous review and opinion articles, including this one. The published data that directly supports this view
is fairly modest at present consisting of 2 studies, from the same research group, that associated differences in gut microbiota composition with severity of disease following SARS/Cov-2 infection. One study compared microbiomes of COVID-19 patients, during hospitalization and after discharge, to SARS/Cov-2-negative control subjects [17]. They observed that SARS/Cov-2 infection was associated with enrichment of Bacteroidetes and reduced abundance of Actinobacteria, which was driven in part by reductions in Bifidobacterium species. SARS/Cov-2 infection also associated with reduced levels of Fecalbacterium prausnitzii. In accord with the notion that both Bifido and F. prausnitzii are associated with health and have ability to dampen inflammation in model systems suggest their absence might promote inflammation COVID-19 but might also be consequence of SARS/Cov-2-induced inflammation. To avoid this caveat, the group’s other study compared microbiomes of SARS/Cov-2-negative pneumonia patients to hospitalized COVID-19 subjects. They observed SARS/Cov-2 infection associated with reduced abundance of presumed beneficial bacteria including Fecalbacterium, Eubacterium, and Lachnospiraceae species and enrichment of pathobions in the Clostridium and Actinomyces phyla again suggesting that, even when controlling for inflammation, SARS/Cov-2 infection associates with altered microbiota composition [18]. That both studies are from the same research group and used cohorts from the same region suggest that the specific taxa that drove disease associations, may not prove generalizable to other regions/cohorts. However, we speculate that the broad conclusions of these studies, namely that severe COVID-19 associates with reduced abundance in beneficial bacteria and enrichment of pathobions, will prove broadly applicable although, again, cause and effect are difficult to disentangle. There are not yet published peer reviewed studies on lung microbiome on SARS/Cov-2 infection but one publicly available study reports elevated presence of Klebsiella oxytoca that would be generally characterized as dysbiosis [19]. Given that even mild gut inflammation can have a marked impact on gut microbiota, often increasing levels of γ-Proteobacteria, and that such changes can promote inflammation, it seems likely that, at least in part, this observation may be a consequence of, and amplifier, of disease induced by SARS/Cov-2 infection. Whether microbiota composition may actually influence SARS/Cov-2 infection itself is far more speculative but given potential of microbiota to impact viruses and cells they infect, we submit the possibilities are worth considering.

The general notion that microbiota impacts respiratory viral infection is supported by several studies associating microbiome composition with infectious outcomes [20–23]. Yet, while such association are generally convincing with the study population, at present, such studies have not revealed a clear pattern of differences across multiple cohorts. For example, one study noted species richness (i.e. α-diversity), which is often associated with health, associates with more severe influenza infections [24] while others identified cluster of specific taxa or bacterial networks that associate with more severe disease in RSV infection [25,26]. Such observations are not mutually exclusive and may all prove reproducible for those pathogens or the cohorts studied but their apparent discrepancies highlight that this field of research is still in its infancy. Another line of evidence relates to use of antibiotics, typically administered systemically, which have been observed to enhance the severity of influenza infection and increase the risk of secondary bacterial infections [27,28]. However, use of topical antibiotics to specifically deplete nasal microbiota reduced influenza transmissibility [29]. Studies elucidating mechanisms by which microbiota alter respiratory viral infection remain scarce but nonetheless suggest that mechanisms will vary markedly based on specific bacteria and virus. For example, analogous to studies in the gut, some lung bacteria can directly stabilize viral structures ex vivo thereby promoting infection [29]. Yet, other bacteria may directly impede viral infection in that Bacillus subtilis, namely Surfactin, a cyclic lipopeptide can reduce CoV infectivity in vitro [30]. Hence, at present, we can simply conclude that there are a myriad of potential means by which microbiota may influence SARS/Cov-2 infection and its consequences but much more work is needed to assess the extent to which such mechanisms play significant roles in disease.

Strategies for manipulating microbiota to prevent and treat COVID-19

The potential of microbiota to impact COVID-19 suggest potential strategies to manipulate the gut microbiome, including probiotics, prebiotics, fecal microbiota transplantation, or direct use of bacterial components to possibly treat, prevent, or at least lower the severity of COV-19 diseases.

Probiotics

At present, there are no experimental data to support probiotics as a therapeutic method for COVID-19. However, bacterial components and metabolites derived from gut microbiota significantly contribute to the gut-lung axis regulating respiratory tract immunity [31–36]. It is plausible to hypothesize that normalization of intestinal dysbiosis with probiotics could serve as one of an approach to treat COVID-19, as this approach had shown effectiveness in treating other viral respiratory tract infections [35,37,38]. Experimental and clinical data have shown that probiotics administration has conferred host protection and has therapeutic effects in viral respiratory tract infections, including RSV, influenza, or rhinovirus [39–42]. The complications of SARS-CoV-2 infection are stemmed from immune dysregulation
involving neutrophilia, lymphocytopenia, unbalanced differentiation between T helper cell subsets, and disproportionate productions of inflammatory cytokines/chemokines [43,44]. Certain probiotic strains in the Lactobacillus family can modulate immune responses to protect the host from viral respiratory infections. For instance, orally administration of Lactobacillus plantarum to mice confer protection against multiple different influenza virus strains by stimulate Th1-mediated immune response, boost NK cell activities, and promoted IgA-mediated mucosal immunity in GI and respiratory tract [39,45]. Also, clinical data have shown that oral intake of L. plantarum results in the activation of cytotoxic CD8+ T cells, increase phagocytic activity of granulocytes, and decrease pro-inflammatory cytokines IFN-γ and TNF-α, the two cytokines that contribute to the creation of cytokines storm during COVID-19 infection, and elevation of anti-inflammatory cytokines IL-4 and IL-10. Severe COVID-19 patients usually require to ventilation machine for breathing assistance [46]. Interesting, several studies demonstrated that administration of B. subtilis and Enterococcus faecalis together or Lactobacillus rhamnosus GG can reduce the occurrence of ventilator-associated pneumonia [47,48].

Furthermore, based on previous experimental data on influenza virus infection, we can hypothesize that probiotics decrease the disease’s severity by balancing gut microbiota, which might have valuable outcomes due to its role in the gut-lung axis communication, and vitamin A regulation, which is directly linked with immune responses [49,50].

Prebiotics
Prebiotics are compounds in food that induce the growth or activity of beneficial bacterial in the GI tract. As with probiotics, there is currently a lack of experimental data to back-up prebiotics’ benefits during SARS-CoV-2 infection. We speculate that prebiotics can offer various benefits to decrease the disease’s severity. Prebiotics may have potential effects on COVID-19 by enhancing probiotics growth and survivability and increasing gut diversity and immunity, especially for an aging population. These prebiotics’ benefits are likely derived from promoting the increased expansion of SCFAs producing bacteria populations [51]. SCFAs are well known for regulating the immune response [33,35,52]. During SARS-CoV-2 infection, perhaps due to the immune response overreact to the virus, it produces excessively and in a large amount of inflammatory cytokine leading to ‘cytokine storm.’ These cytokines storms promote death of infected cells but they also cause multi-organ malfunction. SCFAs such as butyrate is well documented to reduce inflammatory responses [51]. Conceptually, prebiotic administration to encourage SCFA-producing bacterial populations’ growth can be a probable method to decrease COVID-19 complications.

Fecal microbiota transplant
The microbiota from an unhealthy host is distinctively different compared to a healthy host. As discussed above, the gut-lung axis may influence systematic inflammation in COVID-19 patients. The dysbiosis of microbiota could result in abnormal inflammatory cytokines productions and T cell hyperstimulation, which is relevant to COVID-19 [44,53]. In addition to prebiotics and probiotics, fecal microbiota transplant (FMT) is another potential approach that can be investigated for COVID-19 therapeutic purposes. Tocilizumab, a monoclonal antibody that inhibited the IL-6 receptor and is used as a treatment for arthritis and is currently in clinical trials for patients infected with SARS-CoV-2 [54]. Several studies have shown the reduction of IL-6 and other inflammatory cytokines post-FMT [55]. Furthermore, microbiota analysis in IBD patients treated with FMT shows a shift toward bacterial species that can induce anti-inflammatory cytokine IL-10 and stimulate regulatory T-cell expansion [56]. Collectively, these data advocate for the use of FMT as either a treatment or an adjuvant to quell the cytokine storms in severe cases of COVID-19 patients.

Bacterial components and metabolites. Another approach for harnessing microbiota for COVID-19 prevention/treatment is to use bacterial components such as flagellin. Flagellin is recognized by toll-like receptor 5 (TLR5), which is expressed by epithelial cells and select mucosal leukocytes, and the NLRC4 inflammasome, which is broadly expressed. Activation of TLR5 broadly reprograms cell gene expression enabling the host to broadly withstand a variety of insults including exposure to chemicals, radiation, and pathogenic microbes [57] thus suggesting that some of the beneficial immune stimulatory aspects of a commensal microbiota might be therapeutically mimicked by administration of purified flagellin. Activation of the NLRC4 inflammasome results in secretion of IL-1β and IL-18, and death of some virus-infected cells [57]. However, while flagellin administration does not cause the severe adverse impacts induced by some TLR agonists such as LPS, its broad systemic induction of cytokines may, nonetheless, prove problematic. Hence, a more specific treatment opinion might be to directly administer the specific cytokines, namely IL-22 and IL-18 that mediate flagellin’s antiviral effects. That expression of ACE2 receptor, the central mediator of SARS-CoV-2 entry, is preferentially expressed on highly differentiated epithelial cells [15], whose levels are reduced by IL-22, supports this notion. Thus, we speculate that flagellin and or cytokines it induces might have potential to prevent/treat COVID-19 [58].

Perspective
The commensal microbiota is a plausible determinant of outcomes following exposure to a broad array of pathogens, including SARS/CoV-2. Possible microbiota
Influences on such infections might reflect direct bacterial-viral interactions, impacts of bacteria on virus-infected cells, bacterial influences on the immune system, or be a consequence of microbiota's influences on health and metabolism in general. At present, evidence to support an important role of microbiota in influencing COVID-19 is largely based on general proof of concepts from study of other viruses in animal models or human association data that does not hint at mechanism nor does it rule out the possibility that such associations are a consequence of SARS/Cov-2 infection rather than a determinant. Nonetheless, we speculate the microbiota holds promise to better understand the heterogeneity of the Covid-19 pandemic and may suggest novel treatment strategies.

Conflict of interest statement
Nothing declared.

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Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest
•• of outstanding interest
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