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Letter to Editor

SARS-CoV-2 and Microbiota

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LETTER TO EDITOR

This letter exposes some of the many reasons why microbiota modulation in patients with COVID-19 disease and more in general, in all people at greatest risk of contracting SARS-CoV2 virus infections, should be taken into consideration.

Corona Virus (CoV) is a single-stranded positive-sense RNA virus familythat is able to infect a wide range of vertebrates, birds and mammals, including humans. In December 2019, a new beta-coronavirus has been isolated in Wuhan, Hubei province, China, which was found responsible of a potentially fatal atypical pneumonia. Beta-coronaviruses belong to a subfamily of coronaviruses that primarily cause respiratory and intestinal diseases. To date, seven beta-coronaviruses capable of attacking humans have been identified: Human Coronavirus 229E; Human Coronavirus OC43; Human Coronavirus NL63; Human Coronavirus HKU1; SARS-CoV; MERS-CoV; SARS-CoV-2. Of these, particularly dangerous are the Severe Acute Respiratory Syndrome (SARS) caused by Sars-CoV, and the Middle East respiratory syndrome caused by Mers-CoV. The new coronavirus isolated in Wuhan has been named Sars-CoV-2. SARS-CoV-2 is found to be similar to the SARS-CoV responsible for the epidemic SARS that occurred in 2002. An accurate comparative analysis of the available genomic data showed that, this virus most likely shouldn't be a laboratory construct, and what could be likely scenarios from which SARS-CoV-2 evolved. Researchers proposed two possibilities: i) natural selection in an animal host before the zoonotic transfer; ii) natural selection in humans following zoonotic transfer [1]. Today the atypical pneumonia caused by SARS-CoV-2 has turned into a pandemic, it changed the way we live, and will have strong economic repercussions worldwide. To date, there is unfortunately no known specific therapy, a vaccine is not available, and the only chance we have to stop the spread of infection is quarantine. Several strategies for symptoms alleviation, already in use for other infectious and non-infectious diseases, are continuously proposed, but at the moment there are no indications for a medical therapy of choice for COVID-19. Master data on mortality rates clearly listed the highest mortality rates in people over 70, in young individuals with comorbidities, but also in younger healthcare workers. For example, in Italy, the data updated to 16 April 2020 by the national college of health IIS, (Istituto Superiore di Sanità), displays 16,991 cases diagnosed among health-workers (median age 48 years, 32% male). The high risk for health-workers is therefore evident even at a young age for this typology of people (Table 1).

Many studies indicate that gut microbiota has a great influence on the status of human health and on the correct functioning of our immune system [2-4]. On the other hand, microbiota composition may play itself a role in triggering infections, as well as on infections sequel [4].

In a preliminary veterinary study on the fecal microbiota composition in healthy cats compared to Feline Coronaviruses (FCoV)-infected cats, Meazzi S, et al. showed that in the FCoV-positive cats, firmicutes and bacteroidetes were respectively over- and under-represented, compared to the healthy cats microbiota, demonstrating a possible correlation between microbiota and coronavirus infections in animals [5].

Even if respiratory symptoms such as cough and dyspnoea and inflammatory symptoms such as fever are the most frequent clinical manifestation in patients infected with SARS-CoV-2, also intestinal involvement has emerged from data collected on patients' symptoms. A recent document by the Italian Federation of Digestive System Diseases Society (FISMAD) reports that a non-negligible number of SARS-CoV-2 infected patients have diarrhoea, nausea, vomiting and/or abdominal discomfort, at the beginning or even before respiratory symptoms. The same document also indicates that the virus SARS-CoV-2 uses the ACE2 protein as a receptor, which is expressed in the lung, kidney, and gastrointestinal tract [6,7]; Viral RNA is demonstrable in 29-53% of the faeces samples collected in COVID-19 patients; possible oro-faecal transmission may continue after respiratory tract viral clearance [8]. Recently some studies have examined the possible variations of the intestinal microbiota in relation to COVID-19 [9-11]. We have not enough data to say with certainty that modulation of the gut microbiota could play a therapeutic role in the treatment of COVID-19, but maybe targeting microbiota composition could represent an

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adjuvant therapeutic option, that will supports patients recovery, or it can also be considered an index of potential risk-factor to be taken into account in prevention, especially in people at risk, such as old people and the most exposed health personnel. As a matter of fact, during the epidemic critical phases, as in the case of the recent SARS-CoV-2 pandemic, hospitals and consequently doctors and nurses are under strong pressure, both psychological (they must face a much higher than normal mortality rate) and physiological (greater work performance). In fact, tight shift work and sleep loss and circadian misalignment inevitably lead to changes in the gut microbiota [12]. The National Commission for Chinese Health and the National Administration of Traditional Chinese Medicine include the use of probiotics to maintain the gut microbiota balance in their recommendations for the treatment of patients with severe COVID-19. This indicates that the Chinese government and first-line medical personnel take in serious consideration the role that the gut microbiota plays in the COVID-19 infection. Furthermore, the extensive use of antibiotics, which is especially diffused in the most virus-affected countries such as Italy, Spain and France, corroborate the idea of a gut microbiota's role in COVID-19, as antibiotics are indeed well known to induce an intestinal dysbiosis status, leading to immune system malfunctioning. Regarding the choice of probiotics, it must be remembered that not all probiotics act in the same way. Gabryszewski SJ, et al. identified and characterized an effective Lactobacillus-mediated innate immune shield, which may ultimately serve as critical and long-term protection against viral respiratory infection in the absence of specific antiviral vaccines [13].

The comorbidities reported among SARS-CoV-2 positive deaths, such as diabetes, hypertension, atrial fibrillation, dementia and stroke, are pathologies cured by metformin, statins, PPIs (Proton Pump Inhibitors), psychiatric drugs, all drugs with the ability to modify the gut microbiota's composition. Also the advanced age of the majority of patients with severe COVID-19, especially the ones who do not overcome viral pneumonia, could also be linked to gut microbiota, as it is well known that in elderly people gut microbiota is depleted, especially in terms of biodiversity. Considering that the main way of entry of the SARS-CoV-2 is the nasal mucosa, it is worthy of interest that several studies indicate that patients affected by virus airway infections are often associated to having a specific nasal microbiota and, vice versa, specific nasal microbiota seems to be associated to a more severe outcome of the airway infection [14-16]. It is very likely that the presence of SARS-CoV-2 exerts a strong selective pressure able to have an effect on the microbiota structure of the upper airways and intestine districts, as well as for the microbiota structure to exert an influence on SARS-CoV-2 infection outcome. Modifications in respiratory tract and gut districts have recently been linked to alterations in immune responses and to disease development in the lung [17,18]. The existence of a "gut-lung axis" has been recently strengthened by several studies [19]. Brown and collaborators showed that lung microbiota protect versus *Streptococcus pneumoniae* and *Klebsiella pneumoniae* respiratory infections, by priming pulmonary production of granulocyte-macrophage colony-stimulating factor (GM-CSF), by IL-17 and Nod2 stimulus [20]. An increased morbidity and mortality, during *K. pneumoniae*, *S. pneumoniae* or *P. aeruginosa* acute lung infection, was observed in germ-free mice [20,21]. Recent studies conducted in mice with a gut dysbiosis induced by antibiotic treatment, revealed that alveolar macrophages were less reactive to stimulus and showed a reduced phagocytic capacity [22]. It is possible that the microbiota acts on macrophages by the release of short-chain fatty acids (SCFAs), known to have wide ranging effects on immune cell function [23]. It has been reported that the SCFA butyrate can repress the expression IL6, IL12b, and Nos2 by colonic macrophages [24,25], while propionate can decrease macrophage stimulation *in vitro* [26]. The control of infectious diseases by macrophage activation plays an important role. Numerous environmental features seem to control macrophage differentiation and function [27,28] and, among those, gut and lung microbiota seem both to play an equally important role in controlling infectious diseases. From this brief discussion it is evident that not only the intestinal, but also the nasal microbiota could be involved in COVID-19 and its course. In a recent study [29] it was highlighted as an efficient immune system, capable of early adaptive immune responses, might correlate with a better clinical outcome in the case of a SARS-CoV-2 patient.

As up to date we have no certainty, studies aimed at recognizing intestinal/nasal microbial ecosystem changes in patients with COVID-19 are urgent and highly necessary. Results will greatly improve our knowledge and help us prescribe more appropriate pro/prebiotic supporting therapies. Nevertheless, the urgency of the present situation, together with the numerous evidences supporting the nasal and gut microbiota role in COVID-19, should suggest the immediate use of pro/prebiotic therapies, as a therapeutic support in these patients.

Table 1: Distribution of cases and deaths in health-workers. (Data source: https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_16-aprile-2020.pdf) Epidemiology for public health-Istituto Superiore di Sanità-National Update April 16, 2020).

Age class	Cases		Deceased	
years	N	%	N	%
18-29	1.622	9,6	0	0,0
30-39	2.857	16,9	2	3,3
40-49	4.782	28,2	4	6,7
50-59	5.757	34,0	16	26,7
60-69	1.84	10,9	26	43,3
70-79	95	0,6	12	20,0
Total	16.953		60	

In critical emergency cases, such as those that are occurring around the world these days, where it is not possible to reduce stress levels, a properly designed diet (ad personam), the use of

specific probiotics and prebiotics, and a microbiological analysis on the health status of the intestinal microbiota of health-personnel, doctors and nurses, could help reduce the level of risk for these types of professionals.

The data in this table, from a recent ISS report, show that, in certain critical situations, also young healthcare workers can be exposed to the risk of contracting SARS-CoV-2 infection, much more than their coetaneous in the rest of the population.

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