

## Can Gut Microbiota Modulation Could Reduce the Signs and Complications of COVID-19?

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In recently published articles, the digestive symptoms are common in patients with COVID-19 with evidence of hepatic failure. To better understand the role of modulation of GUT microbiota to reduce the signs and complications of COVID-19 infection. Zinc and Chloroquine could potentially contribute to changes in the gut flora and in some cases could reduce clinical signs in patients suffering the COVID-19 infection. Notably, the gut microbiota of neonates could resist COVID-19 as it essential for reducing numbers of iNKT cells in the intestine, and iNKT cells have been implicated in mediating allergic responses in the lungs. The circulating short-chain fatty acids (SCFAs), resulting from microbiota metabolism of the fiber, could have ameliorative effect to allergic inflammation in the lung that similarly occur in COVID-19 infection. Taken collectively, the modulation of gut microbiota is very important for improvement of immune system and protection against viral infection and reduction of clinical signs but further investigation is needed to study clinical available data from different global countries.

**Keywords:** COVID-19 Infection; Drugs; Inkt Cells; Gut Microbiota.

The clinical signs of COVID-19 in children less than 16, identified by acute respiratory syndrome year, were fever, dry cough and abnormal laboratory findings summarized as increase level of creatine kinase MB and procalcitonin, decrease lymphocytes counts (Xu *et al.*, 2020b). While the clinical signs of COVID-19 in older shown same symptoms with high virus load firstly in the upper respiratory tract and in also detected in stool (Zhou *et al.*, 2020). Also, digestive symptoms are common in patients suffering from COVID-19 in a recently submitted article (Gu *et al.*, 2020; Mao *et al.*, 2020).

The intestinal microbiome has a role in development and differentiation of the immune system as the gut microbiota provides signals

pathways to stimulate the normal development as well as the maturation of immune cells (Lazar *et al.*, 2018).

Also, the lung microbiota population differed from mild and moderate in the chronic obstructive pulmonary disease. Streptococcus was the most predominant genus in the oral, bronchial, and lung tissue samples, and multiple other taxa were present in both the upper and lower airways (Pragman *et al.*, 2018).

Human gut microbiota has a role in drug effectiveness and metabolism (Jourova *et al.*, 2016). Also, Murine microorganisms provide chemicals that lead to the potential development of new therapeutics against multiple disease categories (Mayer and Lehmann, 2000).

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In china many patients admitted firstly to hospital suffer GIT manifestation, so we want to explore the effect of modulation of Gut Microbiota on complications of COVID-19 which could be the cause of death.

#### **Drugs and Gut Microbiota**

Antiprotozoal drug pentamidine treat ulcerative colitis indirectly through immune modulation (Esposito *et al.*, 2012), Immune cells release cytokines, interleukins and pro-inflammatory signaling molecules (Shanahan, 2001). Also, The anti-atherosclerotic effect of Berberine (BBR) is related to alterations in gut microbiota compositions, indicating the potential therapeutic value of pharmacological approaches that may modulate the gut microbiota in treating atherosclerosis (Shi *et al.*, 2018). A larger cohort study suggested that the medication can alter gut microbiome composition and so the correlation between species abundance in the human microbiome and drug sensitivity evaluation consider very important for development of new successful and beneficial therapy (Maier *et al.*, 2018).

Indeed, in HIV-infected patients, the changes in gut microbial flora resulted in a generalized immune activation (Deeks *et al.*, 2013). Notably, the antimicrobial effect of Chloroquine could potentially explained to the changes in the gut flora, resulting in stimulation of DCs to produce IFN- $\alpha$ 2, and this effect is more than the inhibitory effect of Chloroquine on IFN production (Routy *et al.*, 2015). As a huge number of cells were exhibited in the gut-associated lymphoid tissue (GALT), and according to the microbial translocation theory, the damage of intestinal mucosa by the inflammation may allow passage of products of the gut microbiome which further enhance HIV-related immune hyperactivation (Lederman *et al.*, 2013; Marchetti *et al.*, 2013).

#### **Zinc, Coronavirus and Gut Microbiota**

The high levels of dietary Zn reduced plasma cortisol level in LPS-challenged pigs at days 9 and 19 and the dietary Zn improved the growth performance of the newly weaned piglets through the modulation in gut microbiota as well as reduction of cortisol response following an immune challenge (Namkung *et al.*, 2006). Notably, Zn ion was reported to stop the initiation step of

EAV-RNA synthesis and elongation and template binding was reduced in the case

#### **Paracetamol Safe in Coronavirus Infection**

The implication of TNF- $\alpha$  in virus-induced hepatitis failure considered a features of coronavirus in the form of fulminant hepatic necrosis while the paracetamol poisoning does not cause an increase in the TNF- $\alpha$  activity in the circulation (Devictor *et al.*, 1992). So, the paracetamol could be safe as antipyretic drug in case of viral infection.

#### **Corticosteroids and Coronavirus**

It was noticed that the plasma SARS-CoV RNA concentrations in the second and third week of illness were significantly more abundant in patients who received early hydrocortisone treatment as compared to those who given the placebo. So, the early corticosteroid treatment was accompanied by a higher subsequent plasma viral load (Lee *et al.*, 2004).

#### **The Hypnotics and Coronavirus**

The Abnormalities of sleep are common in hospitalized patients suffer diseases, but the mechanisms and consequences are still not well understood. for example, In one pilot study of patients suffer from insomnia comorbid with RA, eszopiclone 3 mg, sleep aid, improved sleep and daytime function measures over the treatment period, as well as some measures of disability, and quality of life and RA-associated pain (Roth *et al.*, 2009). Additionally, Night calm sodium is a composition of eszopiclone 3mg that could help in reducing the virus count in the upper respiratory tract but need more investigation. Also, there is a clinical studies (ClinicalTrials.gov Identifier: NCT00822679) on effect of eszopiclone on Inflammatory Mediators in Patients suffer from Acute Coronary Syndrome (<https://clinicaltrials.gov/ct2/show/NCT00822679>)

#### **Why are Children Less Susceptible to Corona Infection ?**

Why children not affected by corona could be explained by a recent study demonstrated that neonatal colonization of the gut microbiota is essential for the reduction of the numbers of iNKT cells in the intestine, and iNKT cells have been enhanced the mediating allergic responses in the lungs (Mazmanian *et al.*, 2008). In addition, the microbial compounds stimulate the peripheral B

cells through B cell-intrinsic MYD88 signaling and inhibit IgE production. Also, the decrease in the levels of peripheral IgE resulted in a reduction in the numbers of basophils, and reduced the risk of allergic airway inflammation. EAE, experimental autoimmune encephalomyelitis (Kamada *et al.*, 2013).

#### **Dietary Fermentable Fiber Content, Gut Microbiota and Allergic Inflammation in the Lung**

Host-microbe crosstalk affects the inflammation in peripheral tissues especially in the lung tissue, which is poorly understood. Also, it was found that dietary fermentable fiber modulates the microbiota of gut and lung, by imbalance the ratio of Bacteroidetes to Firmicutes (Trompette *et al.*, 2014). Also, the short-chain fatty acids (SCFAs), metabolites of gut microbiota metabolism of the fiber, had a beneficial role for protection against the inflammation. Notably, the circulating levels of SCFAs were increased and protected against the allergic inflammation in the lung tissue in mice fed a high-fiber diet increased whereas a low-fiber diet decreased the levels of SCFAs and enhanced the allergic airway disease. Additionally, the treatment of mice with the SCFA propionate resulted in the modulation of the bone marrow hematopoiesis that was characterized by the enhanced generation of dendritic cell (DC) precursors and macrophage and subsequent seeding of the lungs by the DCs with high phagocytic capacity. The effects of propionate on allergic inflammation were based on the G protein-coupled receptor 4. Moreover, the dietary fermentable fiber and SCFAs can build the immunological environment in the lung and influence the severity of allergic inflammation (Cummings *et al.*, 1987; Hill *et al.*, 2010). As recent evidence has indicated that the microbiota could influence the immune cell homeostasis and the susceptibility to allergic inflammation (Herbst *et al.*, 2011; Olszak *et al.*, 2012).

#### **Cytokines Storm and Cause of Death Due to Coronavirus**

Cytokine storm syndrome is active immune response that leads to frequently fatal multi-organ dysfunction syndrome. The first screening tool for the possibility of a cytokine storm syndrome diagnosis in hospitalized patients with Covid-19 was the elevated serum ferritin values (Mehta *et al.*, 2020). The death in patients

suffering Cytokine storm syndromes is impossible as corticosteroids are contraindicated here due it increases the virus load in the body as described above. Although some cases have recovered as the artificial liver blood purification system could enhance the removal of inflammatory mediators and block cytokine storm (Xu *et al.*, 2020a).

#### **Vitamins and Coronavirus**

Vitamins like A, D, and C are very important keys for immune system improvement while its deficiency results in increased risk of mortality. Notably children with vitamin A deficiency have a greater risk of illness and death due to respiratory tract infections (Ross, 1996). While the Pre-existing deficiency of vitamin A seem to worsen the infection and vitamin A supplementation has been reported to reduce the risk of death in 6–59 month old children by about 23–30% In the case of pneumonia that is associated with measles. Similarly, the raising of serum 25(OH)D concentrations through vitamin D supplementation, or exposure to sunlight, could reduce the incidence, severity, and risk of death from influenza, pneumonia, and the current COVID-19 epidemic (Grant *et al.*, 2020). Also vitamin C could reduce signs and complications of covid-19 through reduce the cytokine storm in acute respiratory tract infection (Banerjee and Kaul, 2010; Boretti and Banik, 2020) and improvement of immune system status.

### **DISCUSSION**

The inflammation of the lung occurs later as the corona virus firstly detected in upper respiratory tract and the stools (Mao *Et al.*, 2020; Xu *Et al.*, 2020b; Zhou *Et al.*, 2020). Notably, many patients suffered firstly from gastrointestinal manifestations and could alter the gut microflora population (Gu *Et al.*, 2020; Mao *Et al.*, 2020). Intriguingly, the nutritional support and application of the prebiotics or probiotics could be helpful to regulate the balance of intestinal microbiota and decreased the risk of secondary infection due to bacterial translocation after coronavirus infection (Xu *Et al.*, 2020a). Also, the unique gut microbiota profile perform many specific regulations in host nutrient metabolism, the maintenance of integrity of the gut mucosal barrier constructions, modulation of immune system, and protection

against pathogens (Restrepo). Moreover, the dietary fermentable fibers could modulate the population of the gut microbiota through the imbalance of the ratio of firmicutes to bacteroidetes and releasing of circulating short-chain fatty acids (scfas) that could have ameliorative affect to allergic inflammation in the lung (Cummings *Et al.*, 1987; Hill *Et al.*, 2010). ). In contrast, the disturbance in gut microbiota has been implicated in different lung diseases, including allergy, asthma and cystic fibrosis (Anand And Mande, 2018).

Notably, drug inducing its pharmacological effects through modulation of gut microbiota like the antimicrobial effect of Chloroquine could potentially explained to the changes in the gut flora (Routy *et al.*, 2015).

Regarding different incidence, mortality of coronavirus in different countries all over the word could be that a certain population had partially solid immunity like BCG vaccination (Aaron *et al.*, 2020) and also may be the nutritional habitats and composition of food could reduce the mortality rate like in Germany.

Finally, the Eating of organic whole plant foods supported with good amounts of leafy greens and enriched with fiber-rich foods (legumes, whole grains, beans, vegetables), avoiding animal derived products including (poultry, fish, pork, beef, and dairy), and use a lactobacillus probiotic containing products to the everyday routine are key factors for health gut microbiota (Rinninella *et al.*, 2019).

In conclusion, the modulation of gut microbiota by drugs and/or vitamins are very important for improvement of immune system and may enhance the protection against viral infection and reduction of clinical signs but further investigation is needed to study clinical available data from different global countries.

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