



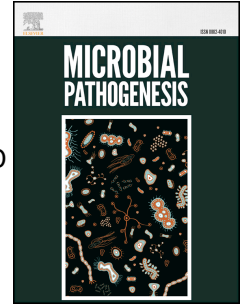
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The role of serum circulating microbial toxins in severity and cytokine storm of COVID positive patients

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Abstract

The emergence of Coronavirus disease 2019 (Covid-19) is a global problem nowadays, causing health difficulty with increasing mortality rates, which doesn't have a verified treatment. SARS-CoV-2 infection has various pathological and epidemiological characteristics, one of them is increased amounts of cytokine production, which in order activate an abnormal unrestricted response called "cytokine storm". This event contributes to severe acute respiratory distress syndrome (ARDS), which results in respiratory failure and pneumonia and is the great cause of death associated with Covid-19. Endotoxemia and the release of bacterial lipopolysaccharides (endotoxins) from the lumen into the bloodstream enhance proinflammatory cytokines. SARS-CoV-2 can straightly interplay with endotoxins via its S protein, leading to the extremely elevating release of cytokines and consequently increase the harshness of Covid-19. In this review, we will discuss the possible role of viral-bacterial interaction that occurs through the transfer of bacterial products such as lipopolysaccharide (LPS) from the intestine into the bloodstream, exacerbating the severity of Covid-19 and cytokine storms.

Keywords: Covid-19, Endotoxemia, lipopolysaccharide, Cytokine storm

1. Introduction

Covid-19 disease that is caused by the highly pathogenic SARS-CoV-2 virus, first appeared on December 31, 2019, in Wuhan, China (1). It is a highly pathogenic human coronavirus (HCoV) that has become a major threat to public health and current global health concerns (2).

The SARS-CoV-2 infection has various epidemiologic and pathologic characteristics, one of them is an increase in cytokine release, which triggers an uncontrollable reaction called "cytokine storm". This phenomenon contributes to ARDS, which leads to pneumonia and respiratory failure, which is a major cause of death from Covid-19 (3-5). Coronaviruses attach to their target by Angiotensin-converting enzyme 2 (ACE2). Coronavirus enters the cells by viral spike (S) proteins, and host cell proteases is vital for priming of S protein (6).

The ACE2 is coherently expressed by the epithelial cells of the lung, intestine, kidney and blood vessels and is present at the end of the ileum and colon in the highest concentrations in the body(7). Recent reports of Covid-19 showed that until 25 January 2022 there were up to 359 million infections and deaths worldwide. In order to improve the prevention and manage the disease, we should understand why so few people show severe forms of Covid-19. While comorbidities including obesity, type 2 diabetes (T2D), cardiovascular disease (CVD), patients' age and race are considered as important factors in worsening disease outcomes(8). Important common factors that straightly interplay with SARS-CoV-2 acute respiratory syndrome are still debated(9). Apparently, the correlations seem strange, because these comorbidities are not only unrelated to a specific disorder but also disassociated with Covid-19 and most of which have been recognized for other viral infections, such as the Middle East respiratory syndrome (MERS) and H1N1 (swine flu)(10, 11) elevated plasma levels of LPS

and LPS-binding protein (LBP) are present in obesity and diabetes, and intestinal dysbiosis has a role in the pathogenesis of insulin resistance. Low inflammation as result of the systemic distribution of bacterial products contributes to vascular disorders. Circulating LPS levels are significantly altered in CVD(12). In fact, all of these comorbidities have a common feature and viral-bacterial interactions, which occur through the transfer of bacterial products such as LPS from the gut to the bloodstream (8). As healthcare systems became overburdened, biochemical indicators such as lactate dehydrogenase, ferritin, and C-reactive protein were employed to triage patients and allocate hospital resources (sodium, calcium, potassium, magnesium, chloride, and phosphate)(13-18). In patients with COVID-19, electrolyte imbalances are common and are linked to more serious illness, according to recent investigations(19, 20). Their correlations with COVID-19 results, however, are irregular and have no known clinical significance. According to Song et al. poor COVID-19 clinical outcome is correlated with hypo- and hypernatremia. Addressing these imbalances helps to ameliorate clinical result and for these purpose more research is needed(21).

2. Host-pathogen interaction

The number of bacteria carried by humans is estimated at more than 100 trillion, which is more than the total number of human cells(12). Most of them interact with each other and are involved in innate and adaptive immunity. One of the most exciting scientific advances in recent years is that common microorganisms (our microbiome) play key roles in our physiology, including protection against infection, drug metabolism, vitamin synthesis, nutrition as well as response to disease. A surprising finding is that disruption of microbiota homeostasis, known as "dysbiosis", maybe as vital as host genetics in causing a wide range of diseases, such as inflammatory bowel disease, obesity, diabetes (pathogenesis of insulin resistance) and cardiovascular disease(8, 9, 22). Dysbiosis is associated with ACE2 expression: ACE2 modulation can dramatically alter microbiota composition by affecting amino acid transport and the production of antimicrobial peptides(23). Loss of intestinal integrity and increased permeability cause LPS transfer from the intestinal lumen to the circulation, leading to metabolic endotoxemia. Bacteria(24-26), bacterial DNA, and bacterial products like LPS are also detected in the bloodstream of obese people and T2D(12, 27, 28). This shows that patients with these diseases suffer from the spread of bacteria throughout the system. The physiological significance of metabolic endotoxemia- the transmission of bacterial LPS to the bloodstream- in obesity and T2D, as well as in cardiovascular and pulmonary disease, is an important issue that should be investigated(29, 30). Severe endotoxemia has also been observed in the elderly: Plasma levels of LPS and its binding protein (LBP) doubled in the elderly (mean age above 70 years) compared to their younger counterparts (mean age around 25 years) and this effect was shown even in healthy and lean people(8). Plasma LPS levels also show ethnic and gender variations. The increase in age-related endotoxin in women is significantly lower than in men and varies sufficiently across various ethnic groups, which is the highest in South Asia(8). This could explain that the observed increase in the severity of Covid-19 is higher in men in the UK and USA as well as in India compared to women. It has been declared that the gut dysbiosis may be the cause of COVID-19-related death in older people, diabetics and hypertensive patients since these

people exhibit an alteration in their gut microbiota profile followed by low-grade inflammation, especially when there are high amounts of IL-6 in their blood (26).

Altogether, all of the major diseases caused by severe Covid-19 are predetermined by "intestinal leakage" and significant endotoxemia, which could be the common cause we are looking for. We now need to explain how endotoxemia can affect viral infection and in particular, how it can cause dramatic hypercytokinemia ("cytokine storm"), which is a sign of severe Covid-19(31). (Fig1)

3. The effect of bacteria on the virus

Factors such as the presence of enzymatic secretions and mucus may interfere with the infectivity and replication of viruses. In addition, high microbial loads in niches such as the gastrointestinal tract and their competition for binding to the target site may reduce the likelihood of multiplication of pathogenic bacteria and viruses and, thereby affect their binding to the target cell. Instead of competing for attachment to the target cell, some viruses use bacterial ligands to strengthen the attachment to the target cell, resulting in infection(32, 33). Exciting studies have been done on bacterial and viral interactions and the effect of bacterial component on the promotion of a viral infection cycle is determined(34) (Table 1).

Viruses can attach to gram-negative bacteria via LPS or straightly to unbound LPS, which increases the binding of the virus to its receptor at the surface of the host cells and can dangerously increase viral infection and cause the development of hypercytokinemia(35, 36). Official data suggest that SARS-CoV-2 can communicate straightly with LPS via its S protein and the production of high molecular weight spikes. The authors assessed that the LPS affinity for the S protein was similar to the LPS binding affinity for the human CD14 receptor, which is the major receptor for LPS interaction with cells. In addition, while the use of S protein or LPS alone does not activate NF- κ B, the combination of S protein, even with low LPS levels, causes a sharp increase in NF- κ B and subsequent cytokine response in monocyte cells in dose-dependent manner in vitro(36). This event follows the hypothesis that direct interaction between SARS-CoV-2 and bacterial products causes synergistic effects and is likely to be involve in the rat model due to infection with the influenza virus (PH1N1) as well as in the porcine respiratory coronavirus (PRCV)(35, 37) . In both models, the combination of the virus with LPS causes severe SARS, disproportionate hypercytokinemia (up to 60-fold) in the lungs and widespread death of infected animals, although viral infection or LPS alone at similar doses does not show such consequences. Importantly, SARS-CoV-2 is not the first viral infection whose severity is related to circulating LPS levels in humans.

Previously, circulating LPS was actively associated with immune system activation in human immunodeficiency virus (HIV) infections(38). Overall, these findings put forth that increased transmission of gastrointestinal microbial products straightly contributes to the activation of the immune system in the chronic phase of HIV infection and may finally determine the rate of development to acquired immunodeficiency syndrome (AIDS). Relatively slow corresponds to the chronic phase of HIV infection, which is determined by the rate of activation of the immune system, compared to the rapidly destructive events on the mucosal surfaces in the acute phase(39). Pathogenic events may not be limited to primary degradation

of primary mucosal CD4 T-cells(40-42) and enteropathy(43, 44), but appears to be responsible for the adhesion to the mucosal barrier.

This association is true for dengue virus, which causes 50 to 100 million infections annually in tropical and subtropical regions, plasma levels of soluble LPS, LBP, and CD14 are significantly higher in infected people than in healthy individuals(45), and absolute plasma LPS levels are correlated strongly with severe disease. Baseline LPS levels in individuals without viral infection but with typical comorbidities of severe Covid-19 were dramatically lower than the circulating LPS levels in severe Covid-19 patients (46, 47).

In mice treated with antibiotics after infection with the poliovirus, the mortality rate was reported to be half of the group without antibiotic use and viral titers in this group were significantly reduced. The experiment was repeated with HeLa cells which showed that exposure of poliovirus with bacteria or bacterial components increase the binding of the virus to HeLa cells. Bacterial components, lipopolysaccharides (LPS), peptidoglycans and other N-acetylglucosamine-containing polysaccharides were thought to enhance viral receptor binding and elevate virus excretion(48).

Similar reports were obtained for norovirus in mice after antibiotic treatment and viral titers decreased. Blood group antigens (HBGA) are known to be potential receptors for human norovirus and HBGA-like groups have been reported at the level of some intestinal bacteria (e.g. *Enterobacter cloacae*). The data show that bacterial HBGAs in *Enterobacter cloacae* increase norovirus attachment to the target cells and increase viral infection(49).

In addition to the role of bacterial ligands in enhancing viral binding, bacterial enzymes can also stimulate viral infection. A good example of viruses in this case is the influenza virus, which converts hemagglutinin (HA0) to HA1 and HA2 fragments under proteolytic cleavage in order to become infectious. The proteases produced by *Staphylococcus aureus* and *Aerococcus viridans* have been shown to have synergistic effects on viral pathogenesis(50, 51). The binding of MMTV to intestinal bacterial LPS activates the Toll-lik4 receptor and then IL-10 and IL-6. In fact, this connection covers the virus and causes to escape from the immune system(52, 53).

4. The effect of the virus on bacteria

The presence of a viral infection often provides the basis for the pathogenicity of opportunistic bacteria through indirect interactions between the bacterium and the virus. The main mechanisms of these interactions include: (I) Increasing the concentration of bacterial cell receptors caused by the virus, (II) virus damage to the underlying epithelial cells; (III) transmission of the commensal bacterial virus; and (IV) suppression of the host immune system virus(54). Influenza virus through damage to the host epithelium as well as possible mechanisms such as the breakdown of sialic acid neuraminidase from host cells, rearrangement of bacterial host receptors and rebuilding of common bacterial host receptors including fibrin and fibrinogen provide the right conditions for bacteria such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *staphylococcus aureus*(55-57). Another type of virus-bacterium interaction occurs when the virus inhibits the host response by infecting and

replicating within cells prepared for defense (lymphocyte, monocyte and macrophage)(34, 58) . Interestingly, the influenza virus disrupts the clearance of *Streptococcus pneumoniae* by draining the alveolar macrophage(59, 60). In addition, the virus by changing the path of Toll-like receptors, reduces the uptake of neutrophils and increases the binding of bacteria to the host epithelium(61). Influenza virus also reduces the production of IL-17, making the host more susceptible to bacterial infection(62). Targeting of helper T lymphocytes, macrophages and dendritic cells by HIV is an example of the systemic effects of viral infection on the immune system and the development of complex multimicrobial interactions, which change the host microbiome and increase bacterial colonization(63, 64). High levels of LPS detected in patients with severe Covid-19 compared to asymptomatic patients suggest a role for SARS-CoV-2 in induction and increase of endotoxemia in patients with comorbidities and the challenge is whether SARS-CoV-2 is effective in increasing barrier permeability for bacterial products (induced endotoxemia). Endocytosis occurs after the binding of SARS2 to ACE2, which leads to the internalization of the virus/ACE2 complex and regulates ACE2 in the cell surface(65). Since ACE2 is involved in facilitating the transport of amino acids(66), its deficiency disrupts processes controlled by amino acids. ACE2 deficiency also leads to a decrease in neutral amino acids and a severe decrease in the expression of antimicrobial peptides in the small intestine. ACE2 also binds to and stabilizes the amino acid transporter neutralizer. This binding is essential for the expression of this transporter at the luminal surface of intestinal epithelial cells and extremely increases its activity. Since amino acids greatly contribute to regulating the function of the intestinal epithelial barrier, decreased ACE2 content due to the interaction of these receptors with SARS-CoV-2 disrupts intestinal barrier integrity(66).

5. Cytokine storm and Covid-19

Although the theory of an uncontrolled, cytokine-mediated response was applied to explain malaria and sepsis(67, 68) in the 1980s and then, used for pancreatitis(69), variola virus(70) and influenza virus H5N1(71) in the 2000s, the first phenomenon of the term ‘cytokine storm’ (CS) was described in 1993 considering graft-versus-host disease (GVHD)(72, 73) .

Some studies proposed that Covid-19 related death is significantly connected to increased level of cytokines and cytokine release is involved in hyper-inflammation related to the virus, called “cytokine storm”(74-76) .

The cytokine storm results in apoptosis of epithelial cells, endothelial cells and vascular leakage, and finally leads to ARDS or another syndrome and may cause death(77).

The cytokine storm has formerly been expressed for a number of infections, including H1N1(78-80), H5N1(81), influenza, MERS-CoV(77) and SARS-CoV(82).

According to earlier findings, in diseases such as Covid-19, the gut microbiota is crucial for appropriate immune responses in order to inhibit a series of immoderate inflammatory reactions that may be harmful. This balance is essential since immune responses can cause various clinical consequences(83).

A previous increase in intestinal permeability, dysbiosis, and low-grade inactive systemic inflammation can facilitate activation of the inflammatory-cytokine storm in Covid-19 via the systemic production of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), LPS and TLR activation, which consequently causes a damaged cycle of systemic inflammation and tissue injury.

SARS-CoV-2 has an interrelation with LPS via S protein, making a high molecular weight combination(36). The researchers expressed that an attraction of LPS to S protein is like the attraction of LPS to the human CD14 receptor, which is the main receptor for LPS interrelation with cells.

CD14 is a pattern-recognition receptor, which is exhibited by monocytes, macrophages and somewhat by neutrophils(84).

Furthermore, S protein or LPS separately do not contribute to activate nuclear factor-kappa B (NF κ -B), while the aggregation of S protein- LPS significantly enhanced NF- κ B activation and cytokine response in monocytic cells in a dose-dependent manner in vitro (36).

LPS levels in severe and fatal lung injury cases were high which means that LPS is definitely involved in the pathogenesis of the Covid-19 cytokine storm and Covid-19 related micro vascular complications which must be understood(85).

Gut microbiota dysbiosis in some Covid-19 patients could be involved in the transfer of LPS into the portal circulation, which will subsequently stimulate the Kupffer cells present in the periportal region of the liver, leading to the activation of NF- κ B pathway and release of TNF- α and IFN- β (86). This involvement can cause hepatic inflammation and also systemic inflammation particularly when LPS gets to the systemic circulation(87, 88).

Although subclinical endotoxemia i.e. a low level of LPS cannot cause hepatitis, but low level inflammation, is able to intensify the effect of cytokine storm and microvascular complications related to Covid-19 patients. The liver damage illustrated in SARS-CoV-2 and the negative clinical importance of liver function test variations shows that clearance capacity of the liver filter decreases in comparison with bacterial degradation products and other toxins such as PAMPs and DAMPs during SARS-CoV-2 (89). In addition, proinflammatory effect (IL-8, Monocyte chemoattractant protein-1 (MCP-1) of low level LPS on endothelial cells, high sensitivity of vascular smooth muscle cells to the stimulatory action of LPS, the relationship between endotoxemia and atherosclerosis and LPS induced insulin resistance effect are noteworthy aspects which could act as fertile soil for the onset of Covid-19 cytokine storm and microvascular damage in the patients(90-92).

The chemokine C-X-C motif chemokine ligand 10 (CXCL-10) has a significant role in serving inflammatory cells to the site of inflammation and its contribution in Covid-19 induced cytokine storm has been demonstrated in both experimental model and in patients(93).

Studies have shown that levels of CXCL-10 are enhanced in Covid-19 patients compared to healthy people. Moreover, the CXCL-10 level in Covid-19 patients admitted into intensive care unit is higher than patients with less severe disease(74). This finding shows the role of

LPS in the severity of Covid-19. Studies have also revealed that elevated levels of CXCL-10, IL-1B, IFN- γ and chemokine (C-C motif) ligand 2 (CCL2) are the result of Th1 responses(94).

It has been reported that a set of proinflammatory cytokines and chemokines including IL-6, IFN- α , IFN- γ , IL-1b, IL-12, IL-7, IL-8, IL-9, IL-10, FGF, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IP-10, monocyte chemoattractant protein-1 (MCP-1/CCL2), MIP-1A, MIP1-B, platelet-derived growth factor (PDGF), IL-18, IL-33, TGF- β , vascular endothelial growth factor (VEGF), CXCL-8, CXCL-9, CCL-2, CCL-3 and CCL-5 are expressed abnormally among severe cases of Covid-19 patients(95, 96).

Studies have also documented that LPS-binding protein, a sign of inflammation is enhanced significantly among severe Covid-19 patients. These findings are markers of the relationship between severe Covid-19 and gut permeability and thereby microbial dislocation(97).

There are several concepts about the activator factor of the cytokine storm including the expression of CXCL-10 due to LPS, direct viral effect on the immune system and low level LPS circulating in the plasma of Covid-19 patients with gut dysbiosis and subclinical endotoxemia contributes as a cofactor for the Covid-19 cytokine storm(98).

Generally, SARS-CoV-2 enters the host cells through binding of S proteins to the cellular receptor called ACE2. A transmembrane protease serine 2 (TMPRSS2) which is a serine protease on the host membrane, prepares S protein to enter the cell (99, 100). After entering respiratory epithelial cells, SARS-CoV-2 stimulates the immune system by inflammatory cytokine release associated with IFN. Membrane bound immune receptors and downstream signaling pathways intermediate Th1 cells proinflammatory immune responses and CD14⁺ and CD16⁺ monocytes. After evoking the immune system, macrophages and neutrophils infiltrate into the lung tissue, which leads to a cytokine storm(101).

SARS-CoV-2 can quickly trigger pathogenic Th1 cells in order to release proinflammatory cytokines, including GM-CSF and IL-6. GM-CSF further triggers CD14⁺, CD16⁺ inflammatory monocytes to secrete a large amount of IL-6, TNF- α and other cytokines(102).

Membrane-bound immune receptors such as Fc and Toll-like receptors can participate in an imbalanced inflammatory response and IFN- γ induction has a significant role in increasing cytokine production(101).

Neutrophil extracellular traps (NETs) include extracellular webs of DNA, histones, microbicidal proteins and oxidant enzymes that are produced via neutrophils to encompass infections. If couldn't regulate properly, NETs have the ability to trigger and disseminate inflammation and thrombosis (103, 104). As a matter of fact, inhibition of neutrophils and NETs is preservative in different models of influenza-associated ARD. The extracellular nets released by neutrophils, may involve in cytokine production. Overexpression of IL-6 and TNF- α is a marker of cytokine storm in Covid-19. Hirano and Murakami(105) suggested a potential mechanism of the cytokine storm created through the angiotensin 2 (AngII) pathway. SARS-CoV-2 triggers NF κ -B by pattern - recognition receptors. It uses up ACE2

on the cell surface, leads to low expression of ACE2, which consequently results in high production of AngII. In addition to inducing NF κ -B, the AngII-angiotensin receptor type 1 axis can also activate TNF - α and the soluble form of IL-6Ra (sIL-6Ra) through disintegrin and metalloprotease 17 (ADAM17)(106). IL-6 attaches to sIL-6R via gp130 in order to constitute the IL-6-sIL-6R complex, which can induce signal transducer and activator of transcription 3 (STAT3) in non-immune cells. The activation of NF- κ B and STAT3, which consequently triggers the IL-6 amplifier (IL-6 Amp), results in different proinflammatory cytokines and chemokines, including VEGF, MCP-1, IL-8, and IL-6(107). IL-6 attaches to sIL-6R to associate with cis - signaling as well as attaches to the membrane-bound IL - 6 receptor (mIL-6R) via gp130 that is involved in trans-signaling. The latter can result in pleiotropic effects on both acquired and innate immune cells, leading to cytokine storms(108). Taken together, the incomplete acquired immune responses and unregulated inflammatory innate responses to SARS-CoV-2 may give rise to cytokine storms.

6. CONCLUSION

As discussed previously, the interaction between immune system and gut organisms is balanced and bidirectional, the enhanced inflammation can result in leaky gut which cause bacterial toxins and metabolites to enter the systemic circulation.

This can more intensify the infective state of Covid-19 patients. Previous studies have determined the relationship between enhanced intestinal permeability with sepsis and several organ failure(109, 110).

Microbial dislocation due to loss of intestinal permeability causes a secondary infection and bacterial dislocation from the gut to lungs which can result in sepsis and acute respiratory distress syndrome(70).

Studies have showed the connection between the gut and the respiratory tract and their coordinated modulation of immune responses and dysbiosis in gut microbiota influence the respiratory tract(111).

Similarly, by the gut-lung axis, viral agent of respiratory infections in lungs moves to other organs through systemic circulation. This corresponds to the hypothesis of an imbalanced gut microbiota setting stage for disturbed immune homeostasis resulting in intensification of cytokine storm in Covid-19 patients.

By considering the participation of earlier endotoxemia in intensification of Covid-19, we assume that standard measurements of LPS and LBP in plasma, following positive COVID-19 test, is significant diagnostic assistance for identifying patients at risk of severe consequence.

This showed that pathophysiology can lead us to suitable choices to interfere with this process, especially toward approaches that refer to attached and free endotoxins of the bloodstream.

These could be high-density lipoprotein (HDL) infusions and/or use of the inhibitor of peroxisome proliferator-activated receptor gamma (thiazolidinediones) that are more used in antidiabetic therapy, compounds that can significantly decrease LPS in plasma and effectively reduce endotoxin- induced cytokines(112, 113).

From a clinical perspective, the idea that early infection-phase chemokine levels appear to be accurate predictors of patient outcomes, may be a promising approach to use various level of serum chemokine for making decision for the treatment(114).

Also targeting the increased cytokines as well as other pathways that intensify the cytokines constant release is an appropriate approach to reduce one of the signs of Covid-19, and hopefully, decrease Covid-19 mortality rate.

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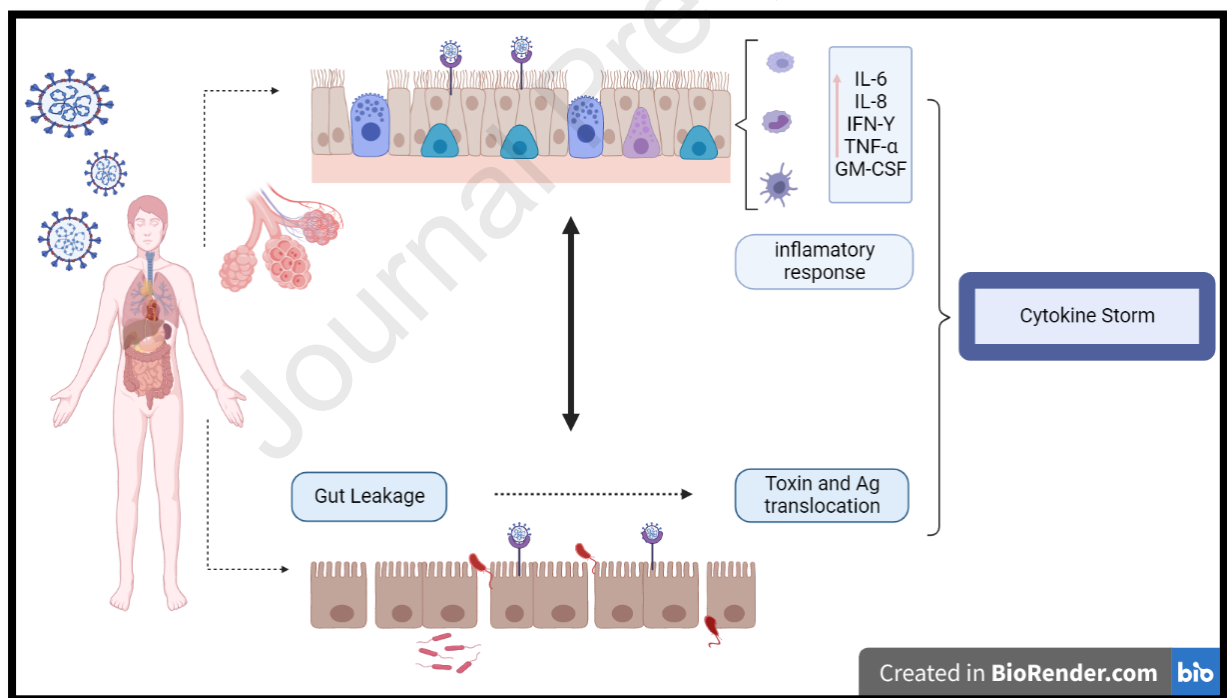


Fig1. The SARS-COV2 virus commonly infects the respiratory system thoroughly. Inflammatory signaling, cytokines as well as chemokines have a part in causing cytokine storm. Additionally, macrophages, monocytes and dendritic cells operate and result in severe inflammation and tissue malfunction. The gut and lung have synergistic effect on each other so that metabolites of gut bacteria impact on the lung and inflammation of the lung via blood and alter the amount of gut microbiota. SARS-CoV-2 usually infects the lung. Dysbacteriosis of gut microbiota remove the cohesion of gut barrier which is responsible for moving of SARS-CoV-2 from the lung into the gut via the bloodstream and lymphatic systems. The virus attaches to the enterocytes by the ACE2. Moving of bacterial antigens and toxins into

the bloodstream as result of inflammation in the leaky gut causes sepsis in Covid-19 patients. Also, dysbacteriosis of gut microbiota involves in pathogenesis of respiratory distress syndrome.

Table 1. Bacteria-Virus interactions

Bacteria	Virus	Interactions	Reference
Herpesviruses	<i>Porphyromonas gingivalis</i>	Virally infected immune cells cause inflammation and have cytopathic effects but don't impact seriously on periodontal bacteria that use intact host cells that act as receptors.	(115-117)
Human norovirus	<i>Enterobacter cloacae</i>	<i>Enterobacter cloacae</i> through HBGAs facilitate viral replication in a BJAB cell culture system. Some commensal <i>Escherichia coli</i> strains expressing HBGA-like moieties may aid in resistance of norovirus to heat.	(49, 118)
Mouse mammary tumor virus (MMTV)	<i>Enteric bacteria</i>	MMTV binds to bacterial LPS and uses it to “cloak” itself from the immune system and to persist.	(48, 52, 53)
Influenza virus	<i>Staphylococcus aureus</i> ; <i>Aerococcus viridans</i>	Viral neuraminidase causes bacterial receptors. Protease derived from bacteria cleaves the hemagglutinin (HA) into HA1 and HA2, making the particles infectious	(50, 55-58, 119-122)
Human immunodeficiency virus (HIV)	<i>Mycobacterium tuberculosis</i>	HIV depletes CD4+ T cells and up-regulates CD14, so helps to <i>M. tuberculosis</i> infection. <i>M. tuberculosis</i> through increasing oxidative stress enhances inflammation and cause proliferation	(123-130)

		of HIV infected immune cells and also by decreasing pro-inflammatory cytokines leads to suboptimal immune responses to viral infection.	
Poliovirus	N-acetylglucosamine (GlcNAc) contains polysaccharides longer than six units including LPS, peptidoglycan (PG) and chitin	Bacterial stabilization inhibits premature genome extrusion before virus attachment to the host cells.	(48, 131)
Rhinovirus	<i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i>	Rhinovirus increases expression of host cell adhesion molecules and elevates susceptibility to bacterial rhinosinusitis.	(132-136)

- 1- SARS-CoV-2 infection can increased amounts of cytokine production.
- 2- Interaction between viral and bacterial can be transfer bacterial products into the bloodstream.
- 3- SARS-CoV-2 infection can be activated an abnormal unrestricted response called “cytokine storm

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