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CHAPTER 14

Contribution of gut microbiota and multiple organ failure in the pathogenesis of COVID-19 infection

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1 Introduction

The coronavirus disease 2019 (COVID-19) is caused by a RNA virus. This virus belongs to the subfamily Orthocoronavirinae in the family of Coronaviridae. It is characterized by club-like spikes that project from its surface.[1] The virus, which originated in Wuhan, China, has spread rapidly throughout the world leading to the World Health Organization (WHO) declaring COVID-19 infection a global pandemic.[2] COVID-19 is a single-stranded enveloped RNA virus that is different from other known coronaviruses, including the common cold (229E, OC43, NL63, and HKU1), but is similar to severe acute respiratory syndrome (ARDS) (SARS-CoV-2 or SARS; 2002–03) and Middle East respiratory syndrome (MERS; 2012-ongoing) outbreaks.[1]

COVID-19 enters human cells through its Spike (S) protein, a type-I surface glycoprotein that binds to the angiotensin I converting enzyme 2 (ACE2), a zinc dipeptidyl carboxydipeptidase that is homologous to human angiotensin 1 converting enzyme. Thus, this enzyme acts as a receptor for COVID-19.[3] ACE2 is not only expressed in the respiratory tract, lungs, liver, and heart but also in the digestive system and kidneys. It negatively regulates the Renin-Angiotensin System (RAS) and plays an important role in neurohumoral regulation of the cardiovascular system. The binding of COVID-19 with the ACE2 receptor results not only in the activation of ACE2 signaling pathways but also in enhancement of its pathogenicity, leading to acute myocardial, lung,

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and digestive tract injuries.[4,5] The expression of ACE2 on various organs may explain the multiorgan dysfunction that has been described in COVID-19 cases.[6,7]

ACE2 receptors are abundantly distributed in the epithelia of the lungs, especially the alveolar type II (ATII) cells. Once the virus binds to the receptor, it spreads widely upon entering the blood circulation. Multiple tissues and organs can be potential targets for COVID-19 infection.[8]

COVID-19 infection spreads primarily via respiratory droplets during close face-to-face contact (via coughs and sneezes). Infection can spread by asymptomatic, presymptomatic, and symptomatic carriers. Symptoms of COVID-19 usually appear 10–14 days after viral exposure and typically include fever, dry cough, shortness of breath, fatigue, sputum production, sore throat, headache, myalgia or arthralgia, chills, nausea or vomiting, nasal congestion, diarrhea, hemoptysis, conjunctival congestion, and pneumonia (Table 1).[2,9] Radiographic and laboratory abnormalities, such as lymphopenia and elevated lactate dehydrogenase, are also common, but nonspecific. Diagnosis is made by detection of COVID-19 via reverse transcription polymerase chain reaction testing, although false-negative test results may occur in up to 20%–67% of patients. Severe cases of COVID-19 often display respiratory, hepatic, gastrointestinal, and neurological complications that ultimately culminate in hospitalization and death.

Table 1 Symptoms of COVID-19 infection in human patients.

Organ involved	Minor symptoms	Reference
Body	Fever	1,2,9
Lungs	Dry cough	1,2,9
Muscle	Myalgia (muscle pain)	1,2,9
Muscle	Fatigue	1,2,9
Digestive tract	Diarrhea	1,2,9
Severe symptoms		
Respiratory tract	Respiratory failure	1,2,9
Heart	Heart failure and sudden cardiac arrest	1,2,9
Lungs	Lung edema	1,2,9
Lungs	Proteinaceous exudate with globules	1,2,9
Lungs	Patchy inflammatory cellular infiltration	1,2,9
Lungs	Moderate formation of hyaline membranes	1,2,9

2 COVID-19 infection associated changes in respiratory tract and lungs

COVID-19 infection is accompanied by respiratory changes in the nose, sinuses, and throat and include nasal congestion, runny nose, sore throat, sneezing, achy muscles, headache, cough, diarrhea, fever, shortness of breath, and tiredness. COVID-19 invades lung epithelial cells and alveolar macrophages to produce viral nucleic acid, which stimulates the infected cells to release cytokines and chemokines, activating macrophages, dendritic cells, and others.[10] Furthermore, COVID-19 entry into the lungs has been reported to cause pneumonia, especially in older patients because they have reduced lung capacity, require longer recovery time, and have weakened immune systems due to their age.[9] Pneumonia that is caused by coronavirus may be more severe, affect many parts of the lungs, and cause shock, organ damage, abnormal blood clotting, ARDS, and deteriorating health.[11] Computed tomography (CT) has been used as an important complement for the diagnosis of COVID-19 pneumonia in the current pandemic.[12]

More than one-third of COVID-19 patients show dangerously high levels of blood clotting.[13] Furthermore, 36% of hospitalized COVID-19 patients in Wuhan, China, show elevated blood levels of D-dimer. This dimeric fragment of fibrin is most widely used as a diagnostic blood marker of coagulopathy. In one study from Wuhan, levels of D-dimer greater than 1 mg L^{-1} have been reported, indicating an 18-fold increase in risk of mortality.[14] Studies on COVID-19 patients from New York City have indicated that survival of COVID-19 patients is markedly increased when patients are mechanically ventilated and receive systemic anticoagulant therapy.[15] Thrombosis and disseminated intravascular clotting are common in COVID-19 infections.[13] Levels of coagulation factors are decreased during coagulation. Among coagulation factors, levels of anticoagulant protein S (PROS1) play an important role. This protein is present in the blood at a concentration of ~ 300 nM (~ 60% bound to the complement factor C4BP), where it normally acts in concert with activated protein C to degrade factor Va and factor VIIIa, thereby terminating the coagulation reaction.[16] It is an essential inhibitory factor in the coagulation cascade, as congenital *PROS1* deficiencies in people can lead to profound coagulopathies.[17] In later stages of COVID-19 infection, the integrity of the epithelial-endothelial barrier is compromised. In addition to epithelial cells, the COVID-19 virus infects pulmonary capillary endothelial cells, accentuating the inflammatory response and triggering an influx of monocytes and neutrophils.[18] CT studies

have shown the accumulation of mononuclear cells and macrophages in lung infiltrates of autopsies along with the development of edema in the alveolar spaces.[18] Collective evidence suggests that COVID-19 infection contributes to endothelial barrier disruption, dysfunctional alveolar-capillary oxygen transmission, and impaired oxygen diffusion in lungs.

3 COVID-19 associated changes in gut microbiota and digestive tract

Several studies have indicated that COVID-19 infection produces significant alterations in the fecal microbiome and digestive tract compared with controls.[19] COVID-19 infection is characterized by the enrichment of opportunistic pathogens and depletion of beneficial commensals at the time of hospitalization and at all time points during hospitalization.[20–22] Depletion of gut microbiota and gut dysbiosis persists even after clearance of COVID-19 (determined from throat swabs) and resolution of respiratory symptoms. The baseline abundance of *Coprobacillus*, *Clostridium ramosum*, and *Clostridium hathewayi* correlates with COVID-19 severity, and there is an inverse correlation between abundance of *Faecalibacterium prausnitzii* (an antiinflammatory bacterium) and disease severity.[21,22] Another study indicated that patients with COVID-19 have an altered gut microbiome with depletion of beneficial commensals (*Eubacterium ventriosum*, *F. prausnitzii*, *Roseburia*, and Lachnospiraceae taxa) and enrichment of opportunistic pathogens (*C. hathewayi*, *Actinomyces viscosus*, and *Bacteroides nordii*) during hospitalization.[21] In addition, over the course of hospitalization, the number of *Bacteroides dorei*, *Bacteroides thetaiotaomicron*, *Bacteroides massiliensis*, and *Bacteroides ovatus* downregulates the expression of ACE2 in murine gut and inversely correlates with COVID-19 load in fecal samples from patients with COVID-19.[21,22] At the molecular level, these bacteria may produce dysbiosis by releasing immunogenic endotoxins called lipopolysaccharides (LPS) (Fig. 1). High levels of circulating LPS are known to suppress the expression of tight junction proteins, leading to an increase in intestinal permeability and subsequently the translocation of LPS from the gut into the blood (Fig. 2).[23,24] LPS is known to activate Toll-like receptors (TLR3, TLR4, TLR7, TLR8, and TLR9) and their downstream targets.[25,26] Studies on TLR and LDL receptors in double knockout mice indicate that a deficiency of TLRs reduces atherosclerosis without affecting inflammation.[27] Moreover, clinical investigations have revealed that upregulation of TLRs not only contributes to inflammation but also promotes the development of atherosclerosis.[28]

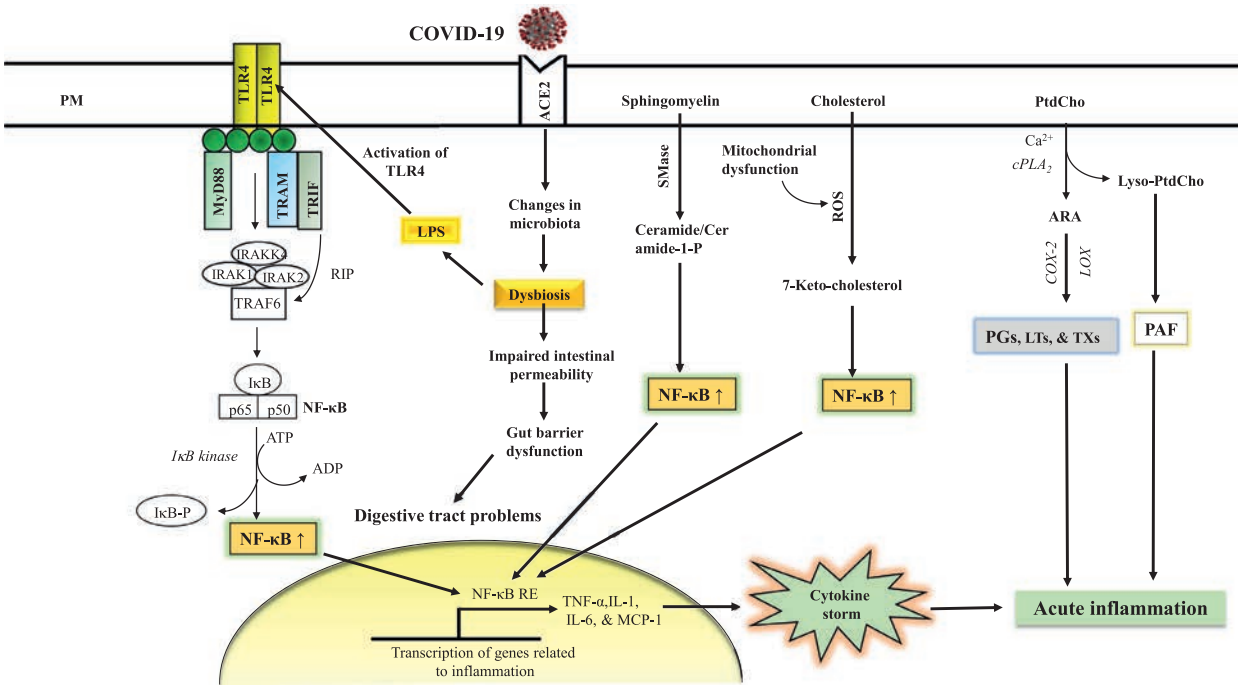

Fig. 1 Hypothetical diagram showing the induction of cytokine storm in COVID-19 infection. Plasma membrane (PM); phosphatidylcholine (PtdCho); arachidonic acid (ARA); lysophosphatidylcholine (lyso-PtdCho); platelet activating factor (PAF); cytosolic phospholipase A_2 ($cPLA_2$); cyclooxygenase (COX); lipoxygenase (LOX); reactive oxygen species (ROS); nuclear factor-kappa B (NF-κB); nuclear factor-kappa B response element (NF-κB-RE); tumor necrosis factor-alpha (TNF-α); interleukin-1beta (IL-1β); interleukin-6 (IL-6); monocyte chemotactic protein-1 (MCP1); Toll-like receptors 4 (TLR4); adaptor protein (MyD88); IL-1R-associated kinase (IRAK). tumor necrosis factor receptor-associated factor adaptor protein 6 (TRAF6); NF-κB-inducing kinase (NIK); IκB kinase (IKK); TIR-domain-containing adapter-inducing interferon-β (TRIF); interferon-beta (IFN-β); interferon regulatory transcription factor-3 (IRF-3).

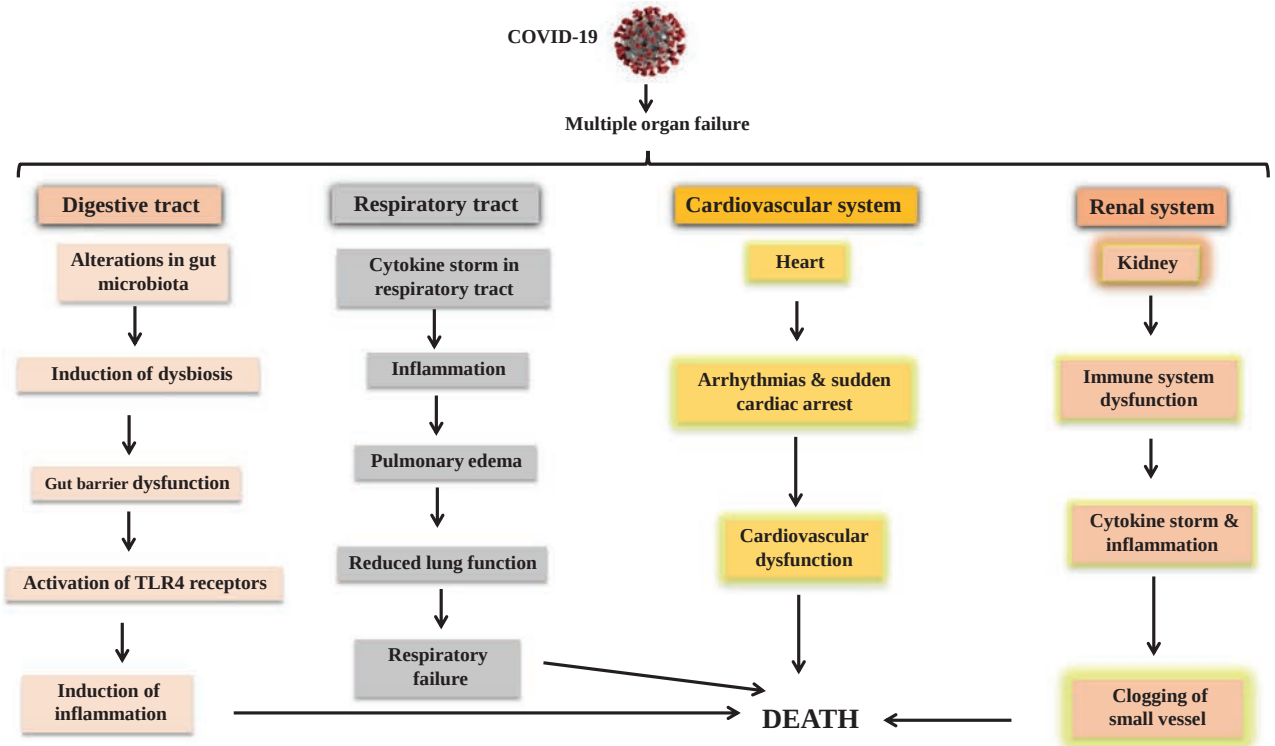

Fig. 2 Involvement of multiple organ failure in COVID-19-mediated death.

4 COVID-19 infection associated changes in cardiovascular system

COVID-19 patients show high prevalence of cardiovascular disease, and more than 7% of patients experience myocardial injury from the infection (22% of critically ill patients).[29] This abnormal cardiovascular dysfunction may be due to myocarditis, possible acute coronary syndrome, cardiac arrhythmias, heart failure, and cardiogenic shock.[30,31] Elevated troponin levels have also been observed in many patients with COVID-19, with significant differences between those who died and those who survived.[32] In a metaanalysis of four studies, levels of cardiac troponin I levels were shown to be much greater in those with severe disease compared to those with nonsevere COVID-19 disease.[32] Interestingly, the median troponin I (TnI) among survivors did not change, while it increased exponentially in nonsurvivors.[33] Along with increase in troponins, other inflammatory biomarkers such as D-dimers, interleukin-6, and so on also show a significant increase, reflecting severe pan-inflammatory response.[34] Another group of patients presented with predominant cardiac symptoms mimicking viral myocarditis or acute coronary syndrome. Two cases recently reported highlight the possible direct effect of COVID-19 on the cardiovascular system. One patient presented with typical chest pain and ST elevation in electrocardiogram (ECG), left ventricular (LV) dysfunction, and positive troponins, but nonobstructive coronary arteries.[35] Another patient presented with severe myocarditis and severe LV dysfunction along with respiratory infection.[36] Both the cases responded well to immunoglobulins and steroids with complete normalization of all parameters. Collective evidence suggests that COVID-19 infection markedly affects cardiac function.

5 COVID-19 associated changes in kidney

Multiple mechanisms may be involved in COVID-19-mediated damage to the kidneys. First, COVID-19 may exert direct cytopathic effects on kidney tissue. This proposal is supported by the detection of polymerase chain reaction fragments of coronavirus in blood and urine in both patients with the 2003 SARS virus[37] and those with COVID-19. To this end, it is well known that like other coronaviruses, COVID-19 uses ACE2 as a cell entry receptor[11]. Recent human tissue RNA-sequencing data have demonstrated that ACE2 expression in urinary organs (kidney) is nearly 100-fold greater than in respiratory organs (lungs).[38,39] Therefore, kidney disease may be caused by coronavirus entering kidney cells through an ACE2-dependent pathway.

Second, deposition of immune complexes of viral antigen or virus-induced specific immunological effector mechanisms (specific T-cell lymphocyte or antibody) may be another mechanism of kidney damage. Microscopic studies of kidney specimens from SARS patients indicate the presence of normal glomerular structure and absence of electron-dense deposits.[40] Thus, these findings do not support the presence of an active immune-mediated glomerulonephritis. Third, a virus-induced cytokine storm may exert indirect damage to renal tissue resulting in hypoxia, shock, and rhabdomyolysis. In fact, some patients with the 2009 H1N1 virus show mild-to-moderate elevations of serum creatine kinase.[41] Similarly, in one study, 138 patients with COVID-19 had increased levels of creatine kinase.[29]

6 Role of cytokine storm and multiple organ failure in COVID-19 associated death

Converging evidence suggests that complications of COVID-19 infection include impairment in function of the heart, brain, lungs, digestive tract, kidneys, and coagulation system (Fig. 2). As stated above, COVID-19 binds with ACE2 receptors of host cells resulting in membrane fusion and the release of viral RNA. This receptor has pathogen-associated molecular patterns (PAMPs), which can be detected by pattern recognition receptors (PRRs). In the host, toll-like receptors (TLR3, TLR4, TLR7, TLR8, and TLR9) are coupled with onset of inflammation.[42,43] Like other coronaviruses, the COVID-19 viral RNA receptor not only promotes the expression of the retinoic-acid inducible gene I (RIG-I)[44] and cytosolic receptor melanoma differentiation-associated gene 5 (MDA5), but also nucleotidyltransferase cyclic GMP-AMP synthase. These are responsible for the recognition of viral RNA and DNA in the cytoplasm (cGAS).[45] This complex signaling recruits adaptor proteins such as TIR-domain-containing adaptor protein (IFN-β (TRIF), mitochondrial antiviral-signaling protein (MAVS), and stimulator of interferon genes protein (STING))[46,47] to trigger and control downstream cascades. This signaling pathway involves adaptor molecule MyD88 and promotes the activation of nuclear factor-κB (NF-κB). The activation of this transcription factor ultimately leads to the expression of interferon regulatory factor 3 (IRF3) and the type I Interferons (IFN-α/β) along with a series of pro-inflammatory cytokines.[48] Hence, virus-cell interactions produce a diverse set of immune mediators against the invading virus.[49] COVID-19 infection results in overexpression of several plasma cytokines and chemokines, including IL-1, IL-2, IL-4, IL-7, IL-10, IL-12,

IL-13, IL-17, GCSF, macrophage colony-stimulating factor (MCSF), IP-10, MCP-1, MIP-1α, hepatocyte growth factor (HGF), IFN-γ, and TNF-α.[1,50] A study on COVID-19 pneumonia corpses indicates that COVID-19 infection produces an inflammatory response in the lower airway, leading to lung injury.[51] Collectively these studies indicate that COVID-19 particles first invade the respiratory mucosa and then infect other cells such as glial and neuronal cells, inducing a series of immune responses and the production of cytokines and chemokines resulting in a cytokine storm in the body, which may be responsible for the critical condition of COVID-19 patients. Collective evidence suggests that COVID-19 infection facilitates the overexpression and overproduction of inflammatory cytokines and chemokines with a wide range of biological activity in a variety of body tissues and cells. These cytokines drive a positive feedback on other cells (macrophages, neutrophils, and T cells from circulation) and continue to recruit them to the sites of inflammation, begetting the exponential expansion of inflammation and organ damage. This process results in a cytokine storm, which is a crucial cause of ARDS, a systemic inflammatory response, and multiple organ failure involving damage of the vascular barrier, capillaries, and alveoli, and ultimately death. Lung injury is one consequence of the cytokine storm that can progress into acute lung injury or its more severe form ARDS.[52] Low oxygen saturation levels during ARDS is a major cause of mortality in COVID-19. Although the exact mechanism of ARDS in COVID-19 patients is not fully understood, the excessive production of pro-inflammatory cytokines is considered one of the major contributing factors.[1,53] Cytokine storm not only produces damage in multiple tissues (lungs, heart, kidneys, and intestine) at multiple sites during COVID-19 infection[54] but also mediates ARDS aggravation and widespread tissue damage resulting in multiple organ failure and death. Targeting cytokines during the management of COVID-19 patients may improve survival rates and reduce mortality. Based on this information, it can be implied that death in COVID-19 patients may be due to cytokine storm and multiple organ failure.[29] Currently, there is no treatment or vaccine for COVID-19 infection. Apart from the efforts to develop a vaccine, several therapeutic options are currently being evaluated, including drug repurposing of distinct antiviral, immunomodulatory or antiinflammatory agents, as well as monoclonal antibodies targeting COVID-19 entry into human cells. To add further to the complexity of COVID-19 infection, most inflammatory mediators that contribute to cytokine storm demonstrate pleotropic downstream effects and are frequently interdependent in their biological activity. The cross talk

among these mediators and the pathways is neither linear nor uniform. Furthermore, although their quantified levels may suggest severity of responses, they do not necessarily imply pathogenesis. This complex interplay illustrates the limitations of interfering in the acute inflammatory response based on single mediators and at indiscriminate time points.

7 Conclusion

COVID-19 infection is accompanied by multiple organ function failure. It has been suggested that digestive tract, respiratory tract, renal, and cardiovascular system dysfunctions not only lead to hyperinflammatory responses in the body but are also linked with the plausible direct effects of severe ARDS on body-wide organs via ACE2. It is proposed that complications of COVID-19 infection are linked with ARDS, heart failure, renal failure, liver damage, and shock resulting in multiorgan failure-mediated death. During COVID-19 infection, the cytokine storm is readily followed by the immune system "attacking" the body, which in turn may cause ARDS and multiple organ failure, the final result being death, at least in the most severe cases of COVID-19 infection. Acknowledging the comorbidities and potential organ injuries throughout the course of COVID-19 is therefore crucial in the clinical management of patients.

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