

Understanding the Pathophysiology of COVID-19: A Review of Emerging Concepts

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Abstract

Coronavirus disease 2019 (COVID-19) was first described in the Chinese city of Wuhan in December 2019. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative agent. It was quickly established that SARS-CoV-2 is transmitted through respiratory droplets when individuals are in close contact with asymptomatic or symptomatic carriers. The incubation period is around 5 days, and it is estimated in up to 97% of infected individuals symptoms will present within 14 days. To date, new presentations are being described. COVID-19 presentation spans from asymptomatic, mild disease to severe systemic disease. The most commonly described symptoms include pneumonia, dyspnea, dry cough, headache and fever. Various companies have developed quantitative polymerase chain reaction (qPCR) assays for the detection of SARS-CoV-2 from mainly nasopharyngeal or throat swab. Several serological tests have also now been approved for use. A lot has been learnt of the laboratory and clinical characteristics of this disease, questions still remain as to the actual pathophysiology leading to either asymptomatic, mild or severe disease. However, despite this, the disease carries the risk of sepsis and acute respiratory failure with increased number of death tolls, forced social distance and lockdowns in many countries. This review highlights key mechanisms that have been proposed to contribute to COVID-19 progression from viral entry to multisystem organ failure, as well as the central role of the immune response in successful viral clearance or progression to death. With the exception of when there is a pre-existing co-morbidity, most reports indicate severe disease occurring in the older population and mild disease or asymptomatic infection in children. Over 120 SARS-CoV-2 vaccines are at various stages of development. As the roll-out of approved vaccines is happens at different rates globally, the prescribed methods to reduce transmission remain facemasks, social distancing, and contact tracing.

Keywords: SARS-CoV-2; COVID-19; Pathophysiology; Cytokine Release Syndrome; Multisystem Organ Failure; Respiratory Failure

Abbreviations

AAK1: AP2-Associated Protein Kinase 1; ACE2: Angiotensin-Converting Enzyme 2; ACEi: ACE Inhibitor; ADAMTS13: Metalloproteinase with a Thrombospondin Type 1 Motif, Member 13; AKI: Acute Kidney Injury; Ang I: Angiotensin I; Ang II: Angiotensin II; APS: Antiphospholipid Syndrome; APS: Antiphospholipid Syndrome; aPTT: Activated Partial Thromboplastin Time; ARB: Angiotensin-Receptor Blocker; ARDS: Acute Respiratory Distress Syndrome; AST: Aspartate Aminotransferase; AT1R: Angiotensin-II Type 1 Receptor; CAC: COVID-19-Associated Coagulopathy; CAPS: Catastrophic Antiphospholipid Syndrome; CRP: C-Reactive Protein; CRS: Cytokine Release Syndrome; cTnI: Cardiac Troponin I; cTnT: Cardiac Troponin T; DAMPs: Damage-Associated Molecular Patterns; DIC: Disseminated Intra-vascular Coagulation; DVT: Deep Venous Thrombosis; Egr-1: Early Growth Response-1; eQTL: Expression Quantitative Trait Loci; FGR: Fetal Growth Restriction; FTV: Fetal Thrombotic Vasculopathy; GAK: Cyclin G-Associated Kinase; GP: Glycoprotein; HIT: Heparin-Induced Thrombocytopenia; PF4: Platelet Factor 4; HLH: Hemophagocytic Lymphohistiocytosis; HPS: Hemophagocytic Syndrome; HUS: Hemolytic Uremic Syndrome; IBD: Inflammatory Bowel Disease; IL: Interleukin; IMID: Immune-Mediated Inflammatory Disease; LDH: Lactate Dehydrogenase; LMWH: Low Molecular Weight Heparin; MAC: Membrane Attack Complexes; MAHA: Microangiopathic Hemolytic Anemia; MERS: Middle East Respiratory Syndrome; NETs: Neutrophil Extracellular Traps; PAI-1: Plasminogen Activator Inhibitor-1; PAMPs: Pathogen-Associated Molecular Patterns; PT: Prothrombin Time; RAS: Renin-Angiotensin-Aldosterone System; SARS: Severe Acute Respiratory Syndrome; SIC: Sepsis-Induced Coagulopathy; S-Protein: Spike Protein; TMA: Thrombotic Microangiopathy; TNF α : Tumor Necrosis Factor- α ; TTP: Thrombotic Thrombocytopenic Purpura; u-PA: Urokinase-Type Plasminogen Activator; VTE: Venous Thromboembolism; VWF: Von Willebrand Factor

Introduction

Around November - December 2019, a new virus now called SARS-Cov 2 was identified in Wuhan, China that has high homology (~80%) to SARS-CoV, which caused acute respiratory distress syndrome (ARDS) and high mortality during 2002 - 2003 [1]. This new virus was found to have potential for international respiratory disease outbreak with pandemic potential. The clinical spectrum of COVID-19 ranges from asymptomatic disease to a severe pneumonia manifesting as acute respiratory distress syndrome (ARDS), that may be fatal. The condition is now known to progress with worsening around day 7 - 10 in the course of the disease [2].

At present, about four vaccines have received full approval, while another 8 have limited approval [3] and no definitive treatment exists yet. To date, only dexamethasone has been proven in well-constructed clinical trials to be effective in reducing morbidity and mortality in severe cases, while some anti-inflammatory drugs (e.g. sirolimus, etc.) may prove promising. One factor determining the lack of effective treatments despite the considerable hype surrounding hydroxychloroquine, and anti-retroviral medicines such as remdesivir, is that the pathophysiological mechanisms around COVID-19 are still unclear. In this narrative review, we try to explain emerging concepts around COVID-19 pathophysiology; the mechanism around the observed natural history, and suggest the possible role for future pharmacologic treatments under current use or development. This is not a systematic review; however, we extensively review recent studies to provide future guidance on possible new treatments and their rationale.

About coronaviruses

Coronaviruses are single-stranded-enveloped-RNA viruses found in humans and also described among cats, dogs, cattle, chicken, and pigs. Coronaviruses typically affect the gastrointestinal, respiratory, and neurological systems, with common cold-like symptoms and disease following the 229E, HKU1, NL63, and OC43, types in healthy individuals. In the past two decades, SARS-CoV-2 is one of the three coronaviruses to cause severe human disease with global spread [4]. The first coronavirus to cause severe illness was called severe acute respiratory syndrome (SARS), from Foshan, China, and was responsible for the pandemic in 2002 - 2003 SARS-CoV course [5]. The second pandemic was also by a corona virus, from Arabian Peninsula causing Middle East respiratory syndrome (MERS) in 2012 [6].

SARS-CoV-2 has a crown-like appearance of spike proteins (S proteins) which usually that project from the viral envelope [7]. It uses the S protein for invasion into cells of host through angiotensin-converting enzyme 2 (ACE2) [9]. Bats are a natural reservoir for SARS-CoV-2.

Angiotensin-converting enzyme 2 (ACE2)

Angiotensin-converting enzyme 2 (ACE2), role in COVID-19 derives from the fact that it serves as functional receptor of corona virus by aiding its cell entry [9]. Usually, the spike (S) protein of SARS-CoV-2 virus binds onto ACE2. at a 10- to 20-fold higher binding receptor affinity to the ACE2 [9]. The S-protein primes host cell protease TMPRSS2 aiding cell entry, a process mainly occurring in the upper respiratory tract cells, while involvement of other organs is dependent on local expression of ACE2 [9,10]. ACE2 is a homologue of the enzyme ACE involved in the RAS system of regulating blood pressure and electrolyte balance. Renin cleaves liver produced angiotensinogen to angiotensin I, that is then converted to angiotensin II by ACE (Ang II) [10]. Ang II uses angiotensin II type 1 receptors (AT1R) to exert its roles, that include renal sodium reabsorption, vasoconstriction, aldosterone synthesis, induction of inflammatory and pro-fibrotic pathways potassium excretion, and blood pressure elevation [10]. ACE2 functionally also counteracts the role of ACE by cleaving Ang II to angiotensin thus affecting overall effect of RAS [10]. Angiotensin 2 promotes metabolism of bradykinin in the lungs through inactivation of des-Arg9 bradykinin, a process that in turn inhibits vasodilation and increased vascular permeability [11]. ACE2 as well regulates dietary amino acid homeostasis, antimicrobial peptide expression, innate immunity, and ecology of gut microbiome [12].

Interaction between ACE2 and SARS-COV-2 and cell invasion

SARS-CoV-2 virus is made up of four glycoproteins: membrane (M), spike (S), nucleocapsid (N), and envelope (E), which are necessary for assembly of viral particles (M, E, and N proteins) or cell binding and entry (S protein) [9]. As described earlier in several studies in mice and humans, ACE2 serves as receptor for virus with a 10-20-fold affinity for SARS-CoV-2 when compared to SARS-CoV-1; and that binding of SARS-CoV-1 to ACE2 impairs protective effect of ACE2 and worsens the ARDS [9,13,14]. In hypoxic states, angiotensin-induced vasoconstriction occurs, as the body tries to correct the ventilation-perfusion mis-match, though this simultaneously induces adverse pro-fibrotic effects, thus requiring ACE2 upregulation to relieve this [13]. Following host cell binding, viral and cell membranes fuse, enabling the virus to enter into the cell [15]. For SARS-CoV, membrane fusion follows a combination of host cell binding, and S-protein cleavage or priming by host cell proteases and transmembrane serine proteases [15,16]. SARS-CoV-2 has evolved and now expresses an S1/S2 cleavage site in its S protein, that is characterized by a 4-amino acid insertion - a unique finding that is absent in other coronaviruses [17]. After the nucleocapsid deposition into the cytoplasm occurs, the RNA genome is then replicated and then translated into accessory and structural proteins. The new viral particles are then carried within vesicles after which they are transported to the plasma membrane for fusion before they are released to infect other cells [17].

Host immune response

Infection by SARS-CoV-2 produces cell death and cell injury in epithelial cells in the airway through pyroptosis, with release of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), that recognized by specific receptors on alveolar macrophages and on endothelial cells [17]. Toll-like receptors (TLRs) as well usually recognize PAMPs especially in extracellular space, thus triggering the induction of cytokine transcription through factors including NF- κ B, and activation of interferon regulatory factors involved in response to viruses [18]. Intracellularly, nucleotide-binding domain leucine-rich repeat (NLR) proteins usually recognize DAMPs and thus trigger the activation of inflammasomes and IL-1 β [18]. These mechanisms usually lead to an increase in the production of chemokines and proinflammatory cytokines and immune cell recruitment. The release of chemokines and cytokines as well follows viral infection of immune cells (macrophages and/or dendritic cells) thus causing antigen-specific T cells recruitment that destroys alveolar cells infected by virus [17,18]. Antibody neutralization as well contributes to clearance of the virus [19].

Proinflammatory cytokine storm

Markedly increased levels of circulating chemokines and cytokines and, often correlate with severity of disease and ensuing mortality; driven by increases in levels of IL-2, IL-6, IL-10, IL-7, IFN- γ , G-CSF, MCP1P-10, and tumor necrosis factor (TNF) in COVID-19, showing involvement of T-helper type 1 and 2 combined effect [18,20]. In this regard, levels of IL-6 is now considered a potential tool in patient risk stratification [21]. There is need for validation of the proposed cut-off levels for the different methodology assays and patient populations in order to define clinical utility. Hospitalized patients show mild elevations in cytokine concentrations not as high as those seen in cytokine release syndrome and secondary hemophagocytic lymph histiocytosis after CAR-T cell treatment [21].

Besides affected cytokine release, the acute phase markers like C-reactive protein (CRP) and ferritin are usually elevated, despite sustained decrease in numbers of lymphocytes and increase in neutrophils [22], thus neutrophil-to-lymphocyte ratio may prove a useful indicator of disease prognostication and choice of management [21,22]. In severe disease, it is not clear what leads to progressive lymphopenia though T-cell redistribution through pulmonary recruitment, and depletion via TNF-mediated cell apoptosis or cytopathic injury could play a role [22]. Infiltration of immune cells may lead to over secretion of reactive oxygen species and proteases that cause further cell damage [22]. In addition, as seen previously in SARS, direct viral infection of monocytes and other immune cells may add to dysregulation of immune response, and new reports show that SARS-CoV-2-specific antibody titers are raised in severe COVID-19 [23]. It is not known if increased antibody levels in severe COVID-19 indicates possible antibody-dependent enhancement or shows exposure to higher viral load. These aspects require further investigation [21].

Hemophagocytic syndrome (HPS)

Hemophagocytic syndrome (HPS) or hemophagocytic lymphohistiocytosis (HLH) refers to a hyperinflammatory syndrome which involves hyperactivation of cells of the immune system. While HPS mainly involves natural killer cells, macrophages and cytotoxic T cells, the acquired form involves cytokines including interferon- γ , TNF α , and interleukins - IL-1, IL-2 and IL-6 [24]. The 5 characteristic criteria for diagnosis includes splenomegaly, fever, low counts in two cell lines, hypofibrinogenemia/or hypertriglyceridemia and hemophagocytosis [25], with 3 recently added features among them hyperferritinemia, low or absent natural killer cell activity, and high soluble interleukin-2 receptor levels [24,25]. Treatment of HPS/HLH need to focus on cause of the infection and immunosuppressive agents used in treatments with steroids and/or cancer chemotherapy when the disease is refractory [25]. In COVID-19, is not characterized by hemophagocytosis on bone marrow biopsy [24]. On the contrary, coagulopathy and severe lung injury are prominent features of COVID-19. While the hypercytokinemia theory suggests a role for anti-cytokine therapy in COVID-19, steroids, often used in HPS/HLH are beneficial in severe COVID-19 [24,25].

Antiphospholipid syndrome (APS)

Thrombotic stroke is a dangerous. In secondary antiphospholipid syndrome (APS), there is development of venous and arterial thrombosis in the presence of antiphospholipid antibodies (that include lupus anticoagulant, anticardiolipin, and anti- β 2-glycoprotein (GP) I), which usually induce clues to APS like thrombocytopenia or prolonged activated partial thromboplastin time (aPTT), factors that can cause organ dysfunction like acute lung injury [26]. While combined antiplatelet therapy or anticoagulant therapy are used in APS, this approach including combining with low molecular weight heparin or unfractionated heparin in COVID-19 is being investigated [26,27]. While convalescent plasma therapy has been tried in COVID-19, opinion is divided on the use of intravenous immunoglobulins [28].

Impaired gaseous exchange in the lungs

Arterial hypoxemia seen early in SARS-CoV-2 is thought to be due to V/Q mismatch with increase in P(A-a) O₂ gradient. The infection causes local interstitial edema that is seen as ground-glass opacities and features of consolidation on chest radiographs, the loss of

surfactant production, collapse of alveoli [29]. The increase in tidal volume results in negative inspiratory intrathoracic pressure, which combined with increased lung permeability caused by inflammation finally contributes to edema, and lung injury [30]. The high pulmonary blood flow to poorly aerated lung alveoli result from failure of hypoxic pulmonary vasoconstriction mechanism during SARS-CoV-2 infection that may in part be due to cytokines and endogenous vasodilator prostaglandins and stress effect on lung structure interfaces [30]. The dysregulation of the renin-angiotensin system (RAS) is thought to contribute to pathophysiology of COVID-19, since ACE2 is the main receptor that SARS-CoV-2 uses to enter into cells [29]. Endothelial injury is now seen clearly in COVID-19, while the loss of alveolar epithelial cells and a state that is pro-coagulation causes the basement membrane to be covered with fibrin and dead cells and products of complement activation [29]. This affects oxygen exchange and may result in increase in P(A-a) O₂ gradient and exercise-induced arterial hypoxemia (EIAH) [31]. There is need for further studies to determine if these deficits are similar to those seen in persistent as seen in up to 37% of cases in MERS survivors [31].

The role of the contact system in the pathophysiology of COVID-19

The Contact System (CS) forms part of innate immune system or mechanism of inflammatory response against artificial material, though whether they bind or activate viral surfaces or on infected cells is unclear [32]. The CS main proteins are Factor XII (FXII), prekallikrein (PK) and the high-molecular-weight kininogen. Auto-activation of FXII to FXIIa occurs through contact to biological surfaces like RNA, DNA, ferritin and aggregated proteins, among others leads to CS cascade. During moments of cellular stress for example as occurs with hypoxia, or oxygen radical production, seen in COVID-19, there are “endogenous alarmins” called “Danger-Associated Molecular Patterns” (DAMPs) usually released from necrotic cells. These molecules have potential to initiate defense reactions that involve endosomal Toll-like receptors (TLRs) and “Pattern-Recognition Receptors” (PRRs) [32].

HK, after being complexed with PK, is able to bind to these “surfaces”. The artificial surface-binding region for HK is the domain 5, while domain 6 usually binds FXI and PK in order for it to initiate the intrinsic process of coagulation [33]. The involvement of CS in inflammation and coagulation is explained by building amounts of FXII that also activates FXI (to FXIa); initiation of intrinsic coagulation pathway with subsequent thrombin activation and formation of fibrin. KAL activation of plasminogen into plasmin leads to fibrin degradation [34]. Plasmin as well can activate FXII and resulting FXIIa can in turn activate plasminogen into plasmin [12]. The intrinsic coagulation pathway induced by FXII is involved in formation of pathological thrombus [35]. The coagulopathy in COVID-19, shown by marked microthrombosis seen on lung autopsies and markedly elevated D-dimer shows a highly activated fibrinolysis and coagulation processes [35]. This may lend credence to increased use of low-molecular weight heparins (LMWHs) in hospitalized patients to prevent venous thromboembolism and complications of thrombotic processes [36].

The kallikrein-kinin system

Physiologically, the activation of KKS leads to freeing of bradykinin (BK), and is involved in inflammation, but has not been linked to promoting blood coagulation [32,37]. Following activation by FXIIa, KAL then cleaves HK, thus releasing nonapeptide bradykinin from its 4 domain. BK is subsequently converted to [des-Arg⁹]-BK by a carboxypeptidase [32,37]. Plasmin, during inflammation, potentiates cleavage of the HK by KAL, therefore enhancing production of BK [136]. It is the DABK and BK that bind to two G protein-coupled receptors (bradykinin B2 receptor (B2R) - whose ligand is BK, and B1 receptor (B1R) - whose main agonist is DABK) [32]. The B2R has been found to be expressed in mammalian endothelial cells and smooth muscle cells while B1R is inducible under cytokine effect associated with infection. Following binding through its B2R, signaling pathways are activated by B2R leading to increased vascular permeability, then vasodilation, with subsequent edema formation, hypotension, then pain, and fever - features typically seen in COVID-19. BK is recognized as a potent vasodilator associated with angioedema that ends in high mortality [37]. It is as well a potent inflammatory mediator, that stimulates a production of nitric oxide, and superoxide radicals involved in release of histamine, of arachidonic acid, and prostaglandin E₂, with prostacyclin, tumor necrosis factor (TNF)-alpha and pro-inflammatory interleukin-1 [37,38]. It also increases production of IL-6 production through its expression in colorectal cancer cell [39]. It also stimulates release of tissue plasminogen activator (t-PA) from

endothelium via a B2R-dependent mechanism [31]. It also plays a role in the link between RAS and KKS through dimer formation; and as well forms complexes with the endothelial cell nitric oxide synthase. It is therefore believed that several mechanisms including hypotension, vasodilation, and increased vascular permeability predominate in COVID-19 [37-39].

Prothrombotic state and coagulation disorders

Early reports from China, especially a study by Chen., *et al.* confirmed coagulation disturbances now associated with COVID-19, partly due to effects of inflammatory processes on the body's hematopoietic system with microthrombi formation, with raised D-dimers, elevated fibrin degradation products, prothrombin time, and activated partial thromboplastin time and even the risk of DIC especially among those who die in comparison with survivors [40]. In a separate recently published study that looked at 216 patients, Bowles., *et al.* (2020) evaluated coagulation parameters, and found that one in five patients showed prolonged aPTT. Among this 20%, over 70% had positive assays lupus anticoagulant assays - which are antiphospholipid antibodies with tendency to thrombi formation as part of antiphospholipid syndrome that occurs during infectious, or inflammatory/autoimmune stimuli [41]. In the study by Helms., *et al.* (2020), that showed elevated fibrinogen, D-dimer [15], Von Willebrand (vWF) activity, FVIII (factor VIII) and vWF antigen; with pulmonary embolism risk being higher in those with positive lupus anticoagulant [42]. The patients with raised D-showed poor prognosis and higher mortality and showed progressively worsening lymphopenia [42]. The mechanisms surrounding coagulation activation in the setting of systemic inflammation may include platelet activation by polyphosphates arising from microorganisms, activation of mast cells and the role of factor XII, NETs (neutrophil extracellular traps), and components of complement system [1]. Other mechanisms that require further exploration include procoagulant effects induced by hypoxemia; factors that upregulate plasminogen activator inhibitor-1, and drivers of fibrin formation [41,42].

Conclusion

The pathogenetic mechanisms that underly COVID-19 need to be understood in order to guide development of various therapeutic options and vaccines. The roles of CS, KKS, RAS, KKS inhibitors lanadelumab and even ecallantide, C1-INH, anti-FXIIa antibodies, selective B2R antagonist, for icatibant used in the treatment of HAE, plus other oral KKS inhibitors currently under development need further assessment as COVID-19 therapeutic options. The ongoing COVID-19 pandemic offers opportunity for innovative therapeutic and prevention approaches for public health and clinical practice of medicine. The reduction or halting of continued virus transmission alongside other lifestyle focused containment measures should be implemented. To improve clinical management of COVID-19, effort should be made to perform properly conducted randomized control trials to guide future treatment options. These trials, which carry higher value when compared to expert opinions, should be tailored to reflect individual patient differences and contexts in mutual ACE2-SARS-CoV-2 interactions and impact on COVID-19 pathophysiology. This approach requires that individual patient phenotype be integrated into diagnostic and therapeutic considerations. Additionally, due to low patient numbers in some cases, cohort heterogeneity and phenotypical stratification provides crucial value in clinical algorithms for predictive modeling in the trials. There is need for further research to determine the drivers and risk factors of COVID-19 disease progression, the molecular mechanisms of action in different populations, and appropriate therapeutic strategies.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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