Coronavirus Disease 2019 (COVID-19) – An Overview

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Summary:

The coronavirus disease 2019 (COVID-19) is now a pandemic with a massive death toll across the world. The knowledge and understanding of this novel coronavirus transmission and pathogenesis are evolving. Although the landscape of vaccine and drug development is changing at an unprecedented pace, currently, there is no specific effective treatment. Proper and timely management of severe and critically ill COVID-19 patients is crucial to reduce deaths in the ongoing pandemic. Ramping up testing capacity alongside a test strategy in place, ensuring adequate resources, i.e., protective gear, O_2 supply, ICU facilities are essential requirements in the fight against COVID-19. Infection prevention and control measures at a personal level (e.g., handwashing, wearing masks, proper donning and doffing of personal protective equipment), and at hospital settings (e.g., hospital cleanliness, safe handling, and disposal of waste) are extremely important to reduce the risk of infection. COVID-19 pandemic has caused a global crisis that requires a multidisciplinary response and concerted effort to ensure resilience in health systems.

Keywords. COVID-19, Pandemic, Pathophysiology, Transmission, Non-pharmaceutical interventions.

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Background:

A novel coronavirus causing an epidemic in Wuhan, China, in December 2019 has spread globally – a pandemic now.[1,2] The severe acute respiratory coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) pandemic is a major global health concern with a massive burden of disease worldwide.[3] Knowledge of COVID-19 pathophysiology and transmission is evolving as the pandemic evolves. High virulence of the virus, lack of effective treatments and vaccines, and potentially large asymptomatic population have made the management of COVID-19 extremely challenging. In the absence of an effective vaccine or therapy, non-pharmaceutical interventions (NPIs) remain the primary strategy to control COVID-19. The NPIs include public health control measures such as quarantine, travel restrictions, isolation, social distancing, and infection prevention and control to reduce transmission of the disease. The landscape of potential treatments and vaccine candidates is changing rapidly alongside our knowledge and understanding of case management.

In this viewpoint, we aim to focus on the current understanding of COVID-19 pathophysiology and patient management based on available evidence. We would also shed light on drugs and vaccines development pipeline and various NPIs adopted during the pandemic.

Pathophysiology and Consequences of Infection

SARS-CoV-2, a non-segmented, positive-sense RNA virus, is part of the coronavirus family. The coronavirus family contains four widely distributed viruses (229E, NL63, OC43, and HKU1), which usually cause common cold but may cause viral pneumonia.[4] SARS-CoV and MERS-CoV caused epidemics with high mortality in 2003 and 2012, respectively. As the SARS-CoV-2 is a newly emergent virus, our understating of the disease pathogenesis is evolving over time. SARS-CoV-2 binds via the angiotensin-converting enzyme 2 (ACE2) receptor located on type II alveolar cells, intestinal epithelia, and vascular endothelium.[5]

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Lung pathology

SARS-CoV-2 causes hypoxemic respiratory failure. It can reduce surfactant levels resulting in atelectasis and de-recruitment. The virus can cause various histological patterns on lung pathology, e.g., lymphocytic pneumonitis, acute fibrinous organizing pneumonia – AFOP, diffuse alveolar damage – DAD.[6]

Cytokine storm

Evidence suggests that some patients respond to the virus with a 'cytokine storm' reaction resulting in fulminant myocarditis.[7] Clinical marker of this includes elevated C-reactive protein (CRP) and ferritin that appear to be predictors of disease severity and mortality too. Although the concept of the inflammatory storm remains controversial, immune-mediated inflammation plays a vital role in the pathogenesis of COVID-19, as it did in SARS. Inflammatory cytokines and acute-phase proteins (APPs) are highly heterogeneous with a wide variety of biological functions. The progression of COVID-19 appears to be associated with a continuous decrease in lymphocyte count and a significant elevation of neutrophils. Inflammatory markers are markedly elevated, e.g., CRP, ferritin, interleukin (IL)-6, IP-10, MCP1, MIP1A, and TNFα. Reduced lymphocyte count and elevated levels of ferritin, IL-6, and D-dimer were reported in several studies to be associated with increased death of COVID-19.[8]

Disseminated intravascular coagulation (DIC)

A significant driver of pathogenesis appears to be hypercoagulability leading to DIC. The exact causes of DIC are unknown. Most probably due to systemic inflammation, i.e., inflammation (IL-6) stimulates the up-regulation of fibrinogen synthesis by the liver or direct endothelial injury by the virus. DIC appears to be a strong prognostic factor for poor outcome.[9] Autopsy in COVID-19 patients has shown microthrombi. A dramatic increase in D-dimer is the hallmark hematologic abnormality reported in the COVID-DIC, likely to be a strong prognostic factor.[10] Scientists have noticed an exceptionally high proportion of aberrant coagulation in severe and critical patients with COVID-19. This finding has been rare in other coronavirus infections but reported in severe influenza. The persistent inflammatory status in severe and critical COVID-19 patients acts as an essential trigger for the coagulation cascade. Specific cytokines, including IL-6, could activate the coagulation system and suppress the fibrinolytic system. In COVID-19, pulmonary and peripheral endothelial injury due to direct viral attack might be an equally important inducer of hypercoagulation. Moreover, dysfunctional coagulation might augment an aggressive immune response.

Hijacking host metabolism is essential for virus replication and propagation. Questions yet to be resolved whether endothelial cell subtypes or other vascular cells in specific pathological conditions have a metabolic phenotype that is more attractive to the novel coronavirus. Also, occasional clinical reports suggest an increased incidence of Kawasaki disease, a vasculitis, in young children with COVID-19. Severe COVID-19 sometimes characterized by multi-organ failure and secondary bacterial infection like septic shock, raising the concern - how and to what extent the damaged pulmonary endothelium no longer offers a barrier to SARS-CoV-2 spread from the primary infection site. Besides, whether infected pericytes can promote coagulation remains to be explored.

Transmission

Available evidence increasingly suggests that the SARS-CoV-2 virus can be transmitted human-to-human by droplets via the airborne route. Airborne transmission highlights the need for N95 respirators (or FFP2) for health care workers and face masks for members of the public.[11,12] Precautions are required before performing aerosol-generating procedures (e.g., intubation, extubation, non-invasive ventilation, high-flow nasal cannula, bag-mask ventilation, bronchoscopy, and tracheostomy). Besides, the virus can be transmitted via contact transmission, i.e., 'fomite-to-face.' Depending on the type of surface, the virus may persist on fomites in the environment for up to 3-4 days. The NPIs, including handwashing, surface disinfecting, wearing masks, may play a crucial role in preventing airborne and contact transmission of the disease.

Clinical Features

The clinical scenario of COVID-19 is quite heterogeneous, with the vast majority of patients being asymptomatic or only experiencing mild respiratory symptoms. The median incubation period of the disease is about four days ranging up to 14 days. Patients may present with constitutional symptoms (fever, headache, myalgia), upper respiratory symptoms

(sore throat, rhinorrhoea), lower respiratory symptoms (cough, dyspnoea, chest tightness, sputum) and gastrointestinal symptoms (nausea, vomiting, diarrhoea). To date, the available evidence from various patient cohorts showed approximately 30-50% of patients presented with fever at admission, 10-20% of patients with diarrhoea, nausea, and some patients developed hypoxemia and respiratory failure without dyspnoea.[10, 13-15] About 5-15% of all patients with COVID-19 may progress to severe or critical illness, requiring sub-intensive or intensive care.[16] The case-fatality ratio varies across countries and depends on the health system, virulence of the strain, host immune response, genetic and environmental factors.

Diagnosis

The WHO guidelines recommend real-time reverse transcriptase-polymerase chain reaction (RT-PCR) molecular testing of respiratory specimens for the detection of the novel coronavirus.[17] The RT-PCR test extracts viral RNA from human respiratory samples, including nasopharyngeal and oropharyngeal swabs, bronchoalveolar lavage fluid, sputum, or bronchial aspirates. Diagnostic sensitivity of RT-PCR depends on several factors, i.e., type and timing of sample collection, skills of lab technician, specimen collection, storage, and transport procedures.[18, 19] For instance, in patients with positive CT scans and negative RT-PCR, it is difficult to confirm whether these patients have COVID-19. Thus, a negative RT-PCR result does not always exclude COVID-19. In suspected cases, we should still aim for isolation and re-test several days later. Besides, serological tests have demonstrated that most COVID-19 patients develop an immune response against the virus, primarily characterized by the appearance of IgG and IgM antibody beyond 1-2 weeks of the onset of illness.[20-23] Antibody tests are mainly crucial in detecting patients with mild or moderate symptoms in late presentation or patients with no symptoms.[24, 25] Serological diagnosis can help to determine the extent of community transmission and the actual size of the epidemic. Scaling up COVID-19 testing capacity is crucial to identify hot spots while a country considers lifting lockdown. Besides, a test strategy – 'target testing' to prioritize tests for those who are the most vulnerable (health care workers, elderly, individuals with comorbidity) is urgently required.

Management

Mild COVID-19 cases can be managed at home under distant medical care. COVID-19 patients with severe and critical illnesses are often treated in areas of intensive care given that close monitoring and intense therapeutic supports are needed. Early treatment involves the use of timely, appropriate drugs and oxygen therapy as well as other supports as required. Treatment plans for COVID-19 should be based on the staging of patients or using a bespoke approach. The window of opportunity may lie in the feed-forward stage when clinical deterioration is observed with evidence of abrupt inflammation and hypercoagulable states. Until now, it is difficult to predict who will progress to severe and critical form from mild illness. Given no proven efficacy of antivirals to date, early intervention has mainly focused on the appropriate timing of disease stages and the implementation of measures to stop or slow disease progression. Once patients enter into critical stages, no magic bullet is available other than comprehensive management.

In the mild and moderate stages of the disease, normal oxygen supportive measures (facemask oxygen) may be advantageous. Supplemental oxygen therapy immediately for patients with respiratory distress, hypoxemia, or shock with a target SpO2 > 92% is the cornerstone of treatment.[26] Early recognition and referral of patients with worsening respiratory function while on conventional oxygen therapies, such as simple face masks or masks with reservoir bags, are essential to ensure the timely and safe escalation of respiratory support. COVID-19 patients with diminished or absent respiratory effort might need high-flow nasal oxygen (HFNO) therapy at a rate of 30-70 liters/min for oxygenation and ventilation.[27] The high flow creating a vortex in the supraglottic area bypasses the upper airways, therefore reduce resistance and work of breathing markedly. These high flows also generate a positive airway pressure even if the mouth is open, which in turn reduces upper airway collapse and distal airway atelectasis.[28] However, the widespread use of HFNO requires ongoing monitoring of oxygen supply and an understanding of the robustness of the oxygen supply chain.

Besides, heparin anticoagulation can be beneficial in patients with COVID-19 in several ways, i.e., prevention of thrombosis, reducing cytokine levels.[29] The correct dose of low molecular weight heparin (LMWH) is of

immediate interest when administered in an effective dose. Although a prophylactic dose might be adequate in most patients, it would be essential considering a higher dose in patients with high body mass index and blood coagulation profile.[30]

Reversing the basic immune dysregulation in COVID-19 might provide a strategy that would enable antiviral therapy success in this deadly syndrome. Reducing viral load by interventions in the early stage of the disease and controlling inflammatory responses by immunomodulators have proven to be effective in SARS and MERS.[31] The use of glucocorticoids has become a significant concern for clinicians. Timing and dosage of administration of glucocorticoids are crucial for outcome in severely ill patients. A too early administration of glucocorticoids inhibits the initiation of immune defence mechanism, thereby increases the viral load and ultimately leads to adverse consequences. Therefore, glucocorticoids are mainly used in critically ill patients suffering inflammatory cytokine storm. Inhibition of excessive inflammation through the timely administration of glucocorticoids in the early stage of the cytokine storm prevents the occurrence of ARDS and protects the functions of organs. Glucocorticoid therapy has the dual effects of immune substitution and immunomodulation.

In the context of the cytokine storm, the three most important cytokines in the IL-1 family are IL-1β, IL-18, and IL-33. Studies that focus on the inhibition of IL-1β to reduce the cytokine storm have attracted the most importance. Anakinra, which is an antagonist of IL-1β, can be used to treat the cytokine storm caused by infection. There is currently no clinical experience with applying specific IL-1 family blockers to treat COVID-19. Serum IL-6 level is markedly increased in severely ill patients with COVID-19. Tocilizumab, an IL-6 antagonist, has a therapeutic effect on the infection-induced cytokine storm.[32] Clinical studies from China have shown that tocilizumab is effective in treating severe patients with extensive bilateral lung lesions and elevated IL-6 levels.[33] Besides, TNFs, key inflammatory factors that trigger a cytokine storm are attractive targets for controlling cytokine storm.

Convalescent plasma therapy, another potential candidate, aims at using antibodies from the blood of a recovered Covid-19 patient to treat those critically affected by the virus. The concept of this therapy is simple, used in the pre-antibiotic era, and later during the Ebola outbreak. It is a passive immunization based on the principle that the blood of a recovered COVID-19 patient contains antibodies with specific ability to fight novel coronavirus.[34]

Other treatment options, such as extracorporeal or so-called blood purification techniques (BPT), have also been studied. These techniques include haemofiltration, haemoperfusion, intermittent, or continuous high-volume haemofiltration (HVHF), plasmapheresis, or adsorption. The rationale behind this is to achieve 'immune homeostasis' to reduce potential damage caused by dysregulation of the host response to infection. Besides, the focus can be given to determine whether a reduction in cytokine levels is possible through the use of sorbent technology by the use of the CytoSorb.[35] Unlike influenza infections and related pneumonia, a few COVID-19 patients experience an initial bacterial superinfection at admission due to pneumococci, other streptococci or staphylococci. This observation may have an impact on antibiotic use and the duration of antibiotic treatment in COVID-19.

There is currently no well-established or evidence-based treatment for COVID-19. However, remdesivir has proven to cause speedy recovery in adults hospitalized with COVID-19.[36] Besides, the preliminary results from the RECOVERY trial in the UK have shown that low-dose dexamethasone has survival benefit in hospitalized patients with severe respiratory complications of COVID-19. There is still a considerable evidence gap in the treatment of mild cases. Many drugs are in clinical trials across the world, including favipiravir and ivermectin, among others. Scientific evidence is growing that the antimalarial drug hydroxychloroquine offers no benefit to COVID-19 patients. Instead, it could be dangerous in some cases. Since the emergence of COVID-19, the search has been on for treatments. The WHO is yet to recommend any drug for the treatment of COVID-19.

Public Health Measures

The global community is currently heavily reliant on non-pharmaceutical interventions (NPIs) to control COVID-19 until an effective vaccine or proven treatment becomes available. The NPIs adopted in this ongoing pandemic broadly fall into mitigation and suppression

approaches, involving quarantine, border restrictions, isolation, physical distancing, wearing masks, and handwashing.[37] Several impact assessment studies have shown that public health interventions are associated with the reduced transmission of COVID-19.[38,39] The challenge of suppression approach is that the NPIs need to be maintained for an extended period until a vaccine becomes available.[40,41] In low resources settings, a prolonged lockdown is unsustainable and may cause substantial unemployment, social and economic disruption. Many countries are now in the process of lifting lockdown that might rebound disease transmission.

Vaccine and Drug Development

The quest for an effective vaccine has been prompted by numerous research institutions and pharmaceutical companies across the world.[41] To date, over 180 different vaccine candidates are moving through various stages of the vaccine development pipeline (from pre-clinical to phase II/III). Of them, the vast majority are in pre-clinical evaluation, and a few candidate vaccines are in clinical assessment.[42] Although the vaccine landscape continues to evolve rapidly along with colossal optimism, it is still uncertain whether or when an effective vaccine would be available.

Several therapeutic agents have been used for the treatment of COVID-19 however there is currently no proven effective drug.[43-46] In a randomized, placebo-controlled multi-centric trial, Beigel et al. reported moderate clinical benefit of intravenous remdesivir in shortening recovery time in hospitalized adult patients with COVID-19 – a significant step forward towards the treatment hunt.(36) Currently, several large drug trials are ongoing to develop an effective therapy for SARS-CoV-2 infection.[47]

Conclusion:

Proper and timely management of severe and critically ill COVID-19 patients is crucial to reduce deaths in the ongoing pandemic. The key strategies involve ensuring appropriate monitoring, supervision, and timely interventions in hospital settings. The landscape of vaccine and drug development is changing at an unprecedented pace. Ramping up testing capacity alongside a test strategy in place, ensuring adequate resources, i.e., protective gear, O_2 supply, ICU facilities are essential requirements in the fight against COVID-19. Physicians should try to avoid indiscriminate use of antibiotics given existing widespread antimicrobial resistance. Public health measures are pivotal for controlling the spread of the disease in the absence of an effective vaccine or treatment. Infection prevention and control measures at a personal level (e.g., handwashing, wearing masks, proper donning and doffing of personal protective equipment) and at hospital settings (e.g., hospital cleanliness, safe handling, and disposal of waste) are extremely important to reduce the risk of infection. COVID-19 pandemic has caused a global crisis that requires a multidisciplinary response and concerted effort to ensure resilience in health systems.

Competing interests

The authors declare that they have no competing interests.

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