MINI REVIEW

Anesthesiologist's Prospective on Self-protection, Therapy, and Managements in Global Counterattack on Coronavirus Disease-19

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ABSTRACT

During the beginnings of 2020, a virus has spread from China and caused a huge surge in severe acute respiratory cases globally. Due to the high contagiousness and anomalous course of severe acute respiratory syndrome coronavirus 2, caused by coronavirus disease, abbreviated as COVID-19, the World Health Organization (W.H.O) announced it as a pandemic and strict measurements were implemented to try and protect the vulnerable populations and those fighting on the frontline of this wave.[1] Scientific personnel all over the world began reviewing hundreds of articles published by scientific authors about the preexisting coronaviruses to assess the strain and pathogenesis of COVID-19 and explore possible effective therapies. At the beginning of the pandemic, the goal was clear**:** Support the immune system by using preexisting drugs such as antibiotics and antivirals to prevent superinfections and alleviate possible foreseen complications, in addition to the use of prophylactic vaccines in high-risk groups. Another therapy option was the use of convalescent sera, which is a passive antibody therapy used as prophylaxis.[2] In this review, we conclude the importance of adhering to the precautionary guidelines set by the W.H.O recommended for health care workers and the general population, as the most important factor for protection against further transmission of the virus. The extra respiratory manifestations of the virus will also be highlighted along with the therapy modalities that are already being used and the upcoming vaccines that will counteract the virus.

Key words: Coronavirus disease-19, personal protective equipment, social distancing, clinical manifestations, hydroxychloroquine, zinc, BNT162b2

Key Messages:

- How important is proper donning and doffing of PPE for our Frontline health workers health?
- What new COVID-19 manifestations were revealed till today?
- How efficient is repurposing previous existing drugs against COVID-19?
- New vaccine development for COVID-19 by global effort.

CORONAVIRUS DISEASE (COVID-19) PANDEMIC COUNTER ATTACK

It has been almost a year since the breakout of the novel pandemic COVID-19, from Wuhan, the capital city of Hubei in China and the official declaration of a global pandemic on March 12, 2020, by the World Health Organization (W.H.O). Facts about the mode of viral dissemination of the virus through air droplets were clarified to all nations. Symptoms vary in each individual, but the major manifestation occurs in the respiratory system with symptoms ranging from common flu like symptoms to severe respiratory distress syndrome and frequently pneumonia. With more than 52.3 infected cases worldwide and more than 1.29 million deaths announced due to the virus, an estimated 7000 health

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workers around the world have now died from COVID-19 according to new data published by Amnesty International.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA virion surrounded by a capsid of lipid and was found sensitive to and effectively inactive by extreme hot water cycles, the use of chemical bleach, and hot dryer. Since SARS-CoV-2 is has an airborne transmission, minimizing the risk of spreading its particles in the facility is essential. Disinfection of working environment should also include a regular cleaning of air ducts and air outlets.[3] Precautionary measures were advised by the W.H.O and strictly implemented by many countries to prevent further spread of the virus including avoidance of social gatherings, proper hand washing, frequently disinfecting used items and surfaces. As health care workers such as doctors, nurses, laboratory technicians, and hospital staff being the frontline pioneers facing the pandemic outrage, health communities, and institutions implemented appropriate infection control measures set by the W.H.O. to protect health care workers and to prevent spreading the virus inside the walls of a hospital. All health care workers (HCWs) were asked to arrive wearing clean street clothes that are laundered to the recommended practice. A personal hygiene protocol before heading to a shift and after ending one was set including showering from head to toe with warm water and soap or body wash to ensure proper cleansing. Personal protective equipment (PPE) and long sleeved garments closed with zipper or button up closures must be worn by HCW, as SARS-CoV-2 readily bonds to all exposed skin. HCW should keep in consideration the removal of jewelry, watches, and other non-essential items and disinfecting disinfecting their ID identification, cellphones, and vehicles. Although no comparison between medical uniforms has been done to assure an effective cover up for HCW, CDC does recommend the coverall to be more efficient than the rest due to its 360° coverage during patient care.

Medical personnel were advised to keep facial hair cut short and tightly controlled, although according to CDC, no evidence was found to link virus transmission through beards or facial hair. This measure was taken on to allow adequate seal for an N95 mask when performing a seal check during the donning process. N95 masks and certified masks (KN95) are recommended to be worn in contact with COVID-19 patients or suspected patients to be COVID-19 positive. To ensure complete seal between mask and facial skin the fit test should be performed at least annually. Once donned, the mask should be worn and not removed or touched for the entire duration of the medical shift. Since the eyes represent two of the five avenues of entrance into the respiratory tract: Two eyes, two nostrils, and the mouth, the five should equally be protected. Training on how to properly remove a coverall or doff a mask is essential in preventing fabric coming into contact with the face and causing self-contamination. contamination. Eye coverings such as anti-fog goggles that fit over spectacles or anti-fog face shields are also advised to be worn when dealing with COVID-19-positive patients, although the viral transmission rate of SARS-CoV-2 through tears is low viral transmission rate of SARS-CoV-2 through tears. Non-sterile disposable gloves are the recommended gloves to be used while dealing with an infected or suspected COVID-19 patient. Even though disposable gloves for medical purposes are made of polymers such as latex and nitrile which is adequate for protection against virus particles, washing hands with water and soap or alcohol-based sanitizers between gloves exchange are only a preventive measure in case of any potential tear or puncture if present in gloves. Careful handling of blood, stool, or body fluid must be taken into consideration, and in case of contamination, the protective garments must be instantly changed followed by a thorough cleanse of the contaminated area with warm water and soap or a disinfectant. This comes after fecal transmission has been reported and evidence showed that SARS-COV-2 is still viable in feces up to 2 days and 4 days in diarrhea. In regard to shoe wear, it is recommended that the best choice of shoes are those not requiring laces, which facilitates cleaning through spraying or wiping with disinfectant. Disposing PPE uniform, disposable respirator masks, shoe coverings, gloves, and disposable hair coverings must be done in separate containers for each item and reusable goggles should be disinfected thoroughly. In addition to self-protection, scheduled cleaning of the working environment must be done by trained staff members to insure clean and safe surfaces at the working place.[3]

A cross-sectional questionnaire-based survey study was conducted in a tertiary care hospital during the COVID-19 pandemic in a span of approximately 50 days, which showed major faults at an institutional level among the health-care providers with regard to the donning (putting on) and doffing (taking off) PPE gear during the beginning of this pandemic.[4] This was done in 155 health-care providers posted in the COVID-19 area to evaluate the understanding and willingness of health care workers to follow the preventative guidelines set to combat the transmission of the virus. Knowledge, attitude, and practices of health care worker are the three determinants to completely understand and analyze the behavior of health care workers and the significance of a proper don and doff process. Knowledge and attitude are shown in an individual's readiness to perform the appropriate measures regardless to personal objections, and real-time application at the work field shows how careful the individual is in avoiding transmission of the virus. HCWs were aware of the importance and criticality of proper donning and doffing procedure, but they lacked the knowledge about dispersion of virus, as 62% responded that virus dispersion occurs more during donning than doffing. Gaps were found in attitude as 51% of HCWs found it inconvenient to don PPE as it would compromise their own safety. Nearly 33.5% of HCWs move

out of the doffing area without removing gloves and N-95 masks, which would give room for the virus to spread.

EXTRA MANIFESTATIONS OF COVID-19

COVID-19 does not only affect the human respiratory system, it was also found to have systemic manifestations when spread from the respiratory tract to other parts of the body such as the central nervous system. The virus would typically cross through the olfactory bulb and cause inflammation and demyelination of the nerves.[5] Although neurological manifestations of COVID-19 are still under study, few case studies and case reports showed that it was highly common that patients, especially severely infected would have neurological involvement. Due to these emerging evidence of neuroinvasion by COVID-19, physicians should suspect severe COVID-19 infection in high-risk patient groups presenting with neurological symptoms to avoid delayed diagnosis or misdiagnosis and initiate the response with the proper medications.

A study of the presentations of an encephalopathy in patients ranged from an autoimmune-mediated response to a hyperacute disseminated form of encephalomyelitis.[6] Symptoms in patients >50 years appeared in the form of confusion and disorientation, to psychosis and seizures. In neuroinflammatory cases, features of an autoimmune encephalitis with opsoclonus, stimulus-sensitive myoclonus, and convergence spasm were also depicted. When studied, neurologic manifestations fell into three categories: Central nervous system manifestation in form of dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, manifestations in the form of taste impairment, smell impairment, visual impairment, and neural pain, in addition to skeletal muscular injury such as nerve root entrapment, encephalopathy, meningoencephalitis, ischemic stroke, and acute necrotizing encephalopathy. Supported by radiological series, patients with COVID-19 are also prone to infarcts, microhemorrhages, and hypercoagulability states. The postulated mechanisms of the various neurological syndromes include, either individually or in combination, direct viral neuronal injury, a secondary hyperinflammation syndrome, para- and post-infectious inflammatory, immune-mediated disorders, or the effects of a severe systemic disorder with the neurological consequences of sepsis, hyperpyrexia, hypoxia, hypercoagulability, and critical illness. Although neuroimaging and CSF studies were normal when performed, symptoms and the clinical pictures were highly suggestive of autoimmune brainstem encephalitis. Some patients presented with confusion and a single seizure attack and MRI abnormalities suggestive of autoimmune or "limbic" encephalitis in the thalami, medial temporal regions, or the pons. Some hemorrhagic changes on imaging included microbleeds, necrosis, and myelitis as well as death in severe necrotizing encephalitis cases. An unusual presentation with a Guillain-Barré syndrome that subsequently developed an acute disseminated encephalomyelitis (ADEM)-like illness was also seen. Acute hemorrhagic leukoencephalitis (based on clinical and imaging features) failed to respond to corticosteroids and required decompressive craniectomy for incipient brain herniation; a brain biopsy at the time of surgery showed evidence of periventricular inflammation supporting aggressive hyperacute ADEM.[7]

In addition, gastrointestinal manifestation was also predominant in SARS-CoV-2 presentation in the form of diarrhea and liver damage.[8] In patients with severe COVID-19 liver biopsies showed moderate microvascular steatosis and mild lobular and portal activity, indicating that the injury could have been caused by either SARS-CoV-2 infection or liver injury due to variable causes ranging from an immune-mediated damage, anoxia causing hypoxic hepatitis, reactivation of preexisting liver diseases (e.g., HBV), or an iatrogenic direct drug-induced liver injury. COVID-19-associated liver injury could also be due to the ubiquitous distribution of the main viral entry receptor, namely, angiotensin-converting enzyme 2 (ACE2). Around days 7–14 of being infected, the virus would be concentrated in tissues expressing ACE 2, the receptors of SARS-COV-2. At this stage, the peripheral blood lymphocytes decrease significantly, involving both T and B lymphocytes. Inflammatory factors in peripheral blood along with prolonged prothrombin time are increased and gradual a decrease of fibrinogen and platelet is seen. Some patients developed lethal hypercoagulable states with D-Dimer-based coagulation factors significantly increased and required intensive monitoring and prophylactic anticoagulation therapies using low-molecular-weight heparin, as suggested by colleagues at the Department of Hematology, Peking Union Medical College Hospital.[9] The use of intravenous immunoglobulin at such cases could also provide patients with effective clinical benefits and inhibit the formation of inflammatory factors storm ("cytokine storm"). Recent manifestations, consistent with the diagnosis of a hypercoagulable phase of disseminated intravascular coagulation, were seen in some non-survivors that suffered from ischemic changes such ecchymosis. Supporting evidence for early anticoagulation may block clotting factors formation and reduce microthrombus, thereby reducing the risk of major organ damage. There is currently no evidence for intrauterine infection caused by vertical transmission in women W.H.O acquired COVID-19 pneumonia in late pregnancy.[10] However, due to the known mechanism of COVID-19 binding to ACE-2 receptors and knowing that placenta constitutes sources of ACE2 during pregnancy, hypothesis that SARS-COV2 might induce viremia through vertical transmission. Yet, more rigorous evidence should be provided to verify the potential maternal-fetal vertical transmission of the virus.[10]

REPURPOSING DRUGS AND DEVELOPMENT OF NEW VACCINE

Repurposing drugs have already been approved in some cases, which is a promising approach until the identification of an effective therapy or vaccine. Some drugs that are currently used are remdesivir, hydroxychloroquine (HCQ), lopinavir (fixed-dose combination with ritonavir), and interferon-β1a. Although some of those drugs are widely used nowadays, the W.H.O has denied the effectiveness it had on hospitalized COVID-19 cases and on the mortality.[11] More than 200 clinical trials have been organized mainly for the study of anti-viral drugs including Kaletra, remdesivir, arbidol, favipiravir, chloroquine, and HCQ. The treatment guideline is being updated repeatedly to include additional effective drugs. Several clinical studies of potential candidates such as chloroquine, an antimalarial drug, and its metabolite hydroxychloroquine to limit SARS-CoV-2-mediated morbidity and mortality shown in the formation of weak bases that can target key cellular signal transduction organelles, such as lysosomes and Golgi, and eventually disrupt the signaling process through a pH increase in intracellular compartments, especially in lysosomes. Interfering with pH-dependent steps of SARS-CoV-2 replication might be one important inhibiting effect of chloroquine and hydroxychloroquine in the treatment of SARS-CoV-2 infected patient. A retrospective study done in US Veterans Health Administration medical centers on 807 patients hospitalized with confirmed SARS-CoV-2 infection concluded no significant reduction in mortality or in the need for mechanical ventilation in hospitalized positive SARS-COV-2 with hydroxychloroquine treatment with or without azithromycin.[12] Risk of death was higher in patients treated with HC than those treated with HC + AZ or no HC. No major difference on risks of mechanical ventilation and death after mechanical ventilation in the HC group or in the HC + AZ group compared to the no HC group. These findings were similar to two other groups with larger cohort studies done in New York. Observational study from a New York hospital, which reported no beneficial effect of HC treatment on respiratory failure or mortality in patients hospitalized with COVID-19, with no reporting on the effectiveness of HC when coadministered with AZ.[13] The other recent study from 25 New York hospitals found that patients receiving HC and AZ had a higher risk of cardiac arrest, with no reduction in mortality risk.[14] Controlled trial of high-dose chloroquine, reported to have *in vitro* antiviral activity against SARS-CoV-2, was stopped prematurely due to cardiac toxicity and higher fatality rates in the high-dose chloroquine-treated COVID-19 patients.[15]

Hypothesis emerged following findings with combination of CQ/HCQ with zinc in the treatment of COVID-19 patients to help improve clinical outcomes and to limit the COVID-19 fatality rates.[16] Zinc is an essential micronutrient and its deficiency may be relevant to the outcome of patient populations with severe clinical courses of COVID-19 including elderly patients and patients with chronic illnesses such as hypertension, diabetes, coronary heart disease, or chronic obstructive lung disease. With CQ having characteristics of a zinc ionophore and specifically targeting the extracellular trace element zinc to intracellular lysosomes and as shown *in vitro* that zinc inhibited coronavirus RdRp activity and that zinc ionophores blocked coronavirus replication.[17]

The clinical and epidemiological characteristics of COVID-19 urged the contribution of a multitude of global experts in the hope of finding an effective medication. After almost a year of the global crisis inflicted by COVID-19, the W.H.O currently counts 214 vaccine projects against SARS-CoV-2 (list of December 2, 2020). In addition, there are at least 13 other projects that it has not yet listed.[18] The BioNTech-Pfizer COVID-19 mRNA vaccine BNT162b2 is today the most recently approved vaccine by the FDA, selected to advance into a Phase II/III trial.[19] The vaccine is conceptualized to target the spike protein (protein S) that is present on the surface of the virus and gives the virus its crown-like appearance. Such technology allows the delivery of precise genetic information together with an adjuvant effect to antigen-presenting cells, disable the penetration of the virus into human host cells by generating protective, long-lasting antibody, and T cell responses against SARS-CoV-2. The lipid nanoparticle-formulated mRNA vaccine has been shown in clinical trials to be safe and well-tolerated.[20] Based on current projections, the companies has produced globally up to 50 million vaccine doses in 2020 and will produce up to 1.3 billion doses by the end of 2021.

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