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REVIEW

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Coronavirus disease 2019 (COVID-19): a brief overview of features and current treatment

Abstract

Since the report of the first cases of pneumonia caused by SARS-CoV-2 in December 2019, COVID-19 has become a pandemic and is globally overwhelming healthcare systems. The symptoms of COVID-19 vary from asymptomatic infection to severe complicated pneumonia with acute respiratory distress syndrome (ARDS) and multiple organ failure leading to death. The estimated case-fatality rate among infected patients in Wuhan, the city where the first case appeared, was 1.4%, with 5.1 times increase in the death rate among those aged above 59 years than those aged 30–59 years. In the absence of a proven effective and licensed treatment, many agents that showed activity against previous coronavirus outbreaks such as SARS and MERS have been used to treat SARS-CoV-2 infection. The SARS-CoV-2 is reported to be 80% homologous with SARS-CoV, and some enzymes are almost 90% homologous. Antiviral drugs are urgently required to reduce case fatality-rate and hospitalizations to relieve the burden on healthcare systems worldwide. Randomized controlled trials are ongoing to assess the efficacy and safety of several treatment regimens.

Key words: SARS-CoV-2, COVID-19, ARDS, pandemic

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus (2019-nCoV) that first manifested as atypical pneumonia and was distinct from usual pneumonia in terms of symptoms and lethality. On February 11, 2020, 2019-nCoV was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses. SARS-CoV-2 is a part of a large family of RNA viruses called *Coronaviridae*, which has four types: Alpha, Beta, Delta, and Gamma. Coronaviruses are known to infect humans and animals, including mammals and birds. Seven coronaviruses, commonly Betacoronavirus HCoV-OC43 and HCoV-HKU1, and HCoV-229E and HCoV-NL63 from Alphacoronavirus genus have been known to cause human infections [1]. Infections caused by these viruses are often mild or asymptomatic. However, severe lower respiratory tract infections have been reported, especially among patients with chronic diseases, immune system dysfunction, and at extreme ages [1, 2].

Zoonotic coronaviruses have caused outbreaks in humans, namely SARS-CoV (2003, in China) and MERS-CoV (2012, in Saudi Arabia). In late 2019, COVID-19 was first reported in Wuhan City, Hubei Province, China, when a group of hospitalized patients with pneumonia of unknown etiology started to be seen [3]. SARS-CoV-2 shares viral structure and genetic sequence with both SARS-CoV and MERS-CoV of 70% and 40%, respectively [4]. This new disease was declared as a global pandemic by the World Health Organization (WHO) on March 11, 2020.

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Compared to adults, the number of reported pediatric cases infected with the novel coronavirus (COVID-19) was significantly smaller [5]. Although the figure has been increasing every day, the data on children's disease clinical characteristics are still lacking. According to the clinical severity classification proposed by the COVID-19 guidelines in China, pediatric patients were more likely to have a milder clinical presentation, milder imaging findings, and less severe disease progression [6]. In adults, approximately 5% of patients will require intensive care. Information on pediatric patients needing intensive care is very limited. However, infants under 1 year appear to have an increased risk of severe disease. The infant group had the highest proportion of clinically diagnosed disease, and there remains the possibility that other viruses such as influenza A/B and respiratory syncytial virus may have caused the increased severity of the disease [7].

The pediatric multisystem inflammatory syndrome has been associated with COVID-19; this rare syndrome shares common features with other pediatric inflammatory conditions, including: Kawasaki disease, staphylococcal and streptococcal toxic shock syndromes, bacterial sepsis, and macrophage activation syndromes. It was initially described in Britain but has been reported from the US with increasing frequency. It can also present with unusual abdominal symptoms with excessive inflammatory markers. The case definition has been proposed as the following: I. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for Kawasaki disease. II. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus. III. SARS-CoV-2 PCR testing may be positive or negative [8].

Structure and pathogenesis

SARS-CoV-2 virus has spike glycoproteins (S proteins) called peplomers. S protein is the receptor binding site and plays an important role in binding to receptors on the surface of host cells and mediating virus envelope-cell membrane fusion [9]. The S protein has two subunits, S1 and S2, and both are necessary to help the virus invading host cells. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors on the targeted cells through its structural spike (S) glycoproteins S1 subunit. The virus uses a transmembrane serine protease 2 (TMPRSS2) for S protein priming as TMPRSS2 activates the spike and helps cleavage of ACE2.

TMPRSS2 acts on S2 subunit of S protein to facilitate the virus fusion to the cell membrane [10]. Once inside the host cells, the virus starts synthesizing RNA using its RNA-dependent RNA polymerase and viral structural proteins to complete virus formation and then virus release (Figure 1) [11].

The pathogenesis of the COVID-19 severity has not been understood yet. However, high levels of serum inflammatory cytokines such as interferon-gamma (IFNγ), interferon gamma inducible protein (IP10), IL-12, IL-6 and IL-1 were noted activating the Th1 cell response [12]. Patients who were critically ill, requiring an intensive care unit (ICU) had higher levels of tumor necrosis factor-alpha (TNFα), monocyte chemo-attractant protein (MCP1), macrophage inflammatory protein (MIP1A) and IP10 than patients who did not require ICU, which supports the relationship between cytokines storm and disease severity [12]. Xu *et al.* [13] have reported the result of first pathologic autopsy of a COVID-19 patient that showed a diffuse alveolar injury and hyaline membrane formation supporting ARDS diagnosis. In addition, the pathological changes seen were similar to MERS and SARS [13]. Flow cytometry revealed a significant reduction in CD4+ and CD8+ T lymphocytes counts in peripheral blood, which affects the immune defense mechanism. However, these T lymphocytes are in an overactive condition as manifested by high Th17 counts and an increased cytotoxicity of CD8+ T lymphocytes leading to a significant immune tissue injury in the patient's lungs and perhaps to the multisystem dysfunction [14]. This has provided a clue for COVID-19 treatmentby using agents directed against Th17 activity (Th17 inhibitors), however, this needs more research to further investigate Th1 and Th2 response in patients with COVID-19 to better understand the disease pathogenesis.

Epidemiology and clinical presentation

Since the initial SARS-CoV-2 virus detection, more than 68 million cases of COVID-19 have been confirmed worldwide, with the majority of cases reported in the United States [15]. Accord-

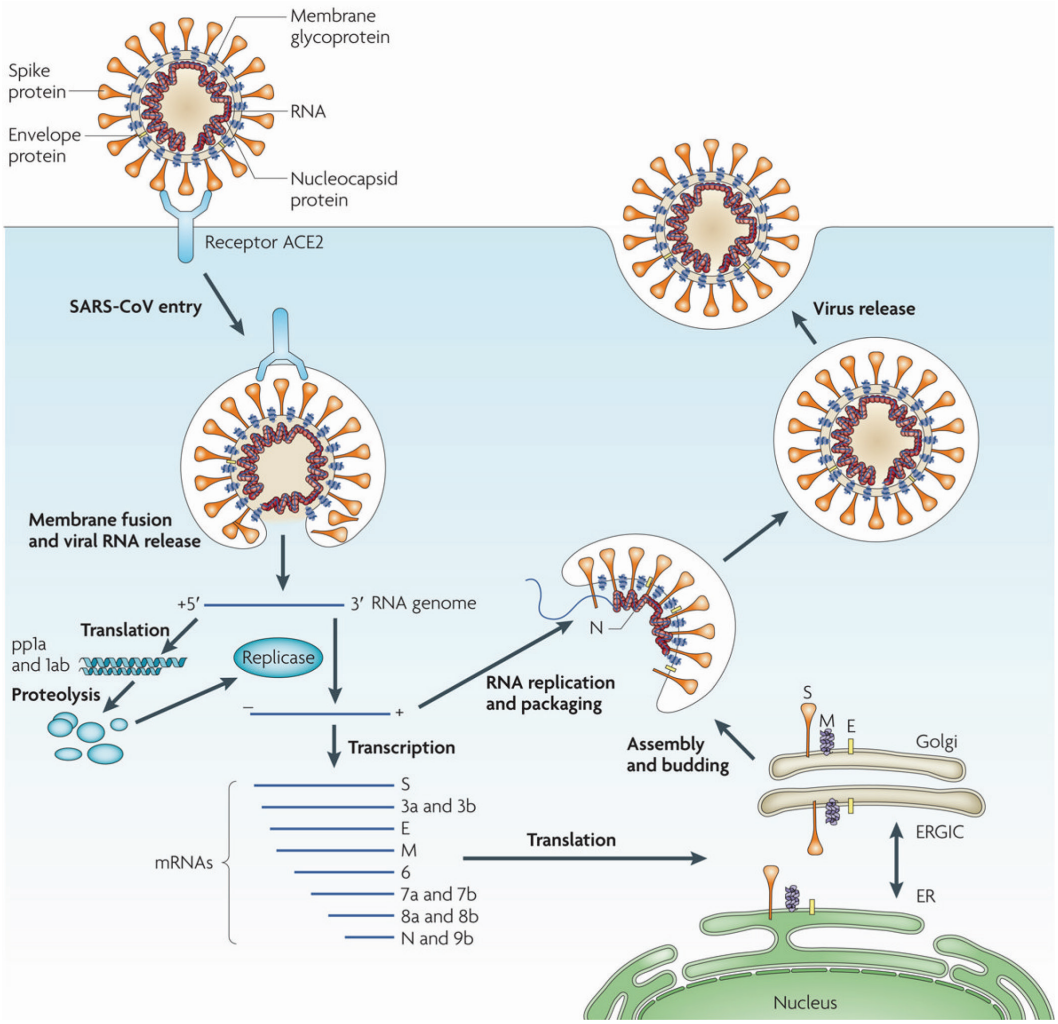

Figure 1. SARS-CoV's life cycle within the host cells. SARS-CoV-2 binds to host ACE2 via spike protein(s). Then cleavage of S protein is facilitated by host transmembrane protease TMPRSS to activate membrane fusion. A released viral genome is translated into nonstructural polyproteins which are processed by viral proteases to create the replicase. This replicase is used to produce several copies of strands and subgenomic mRNAs that are translated by ribosomes into structural proteins. The negative-strand RNA is packaged by structural protiens, followed by budding into endoplasmic reticulum-Golgi intermediate compartmetn's lumen. Finally, the viron is released as an exocytic vesicle 10 [11, with permission]

ing to a report that was published by the Chinese center for disease control and prevention on February 11, 2020, among a total of 72,314 recorded cases, 62% were diagnosed based on a positive nasal swab for viral nucleic acid test, 22% were diagnosed based on their symptoms and history of exposures with no test performed because of insufficient capacity to test all suspected cases in China during the pandemic [16]. The majority of cases (87%) were aged 30–79 years, 3% — 80 years or older, and only 2% were younger than 19 years [16]. In terms of disease severity, the majority of cases (81%) were labelled as mild cases that included patients with no pneumonia or mild pneumonia. Around 14% of the cases who had symptoms that suggest significant respiratory compromise such as difficulty of breathing, tachypnea (respiratory rate > 30/min), hypoxemia with a saturation of blood oxygen less than 93%, with or without the presence of lung infiltrates on chest x-ray were considered as severe. And 5% of the total recorded cases were diagnosed to have a critical illness due to the presence of respiratory failure, hemodynamic instability, with/without multiple organ failure [16]. A possible explanation for the significant deterioration in the patients who become critically ill is thought to be due to a cytokine storm, which is a situation where there is an overproduction of cytokines that consequently leads to mutli-organ dysfunction and failure resulting in death [17].

Patients with COVID-19 typically have flu-like symptoms such as a fever and a dry cough. However, old patients and those with chronic

medical conditions and comorbidities may present with symptoms that suggest lower respiratory tract infection (pneumonia) such as chest pain, chest tightness and shortness of breath. Huang *et al.* [18] first reported symptoms related to COVID-19 among 41 hospitalized patients; fever (98%), cough (76%) and myalgia (44%) were the most common three symptoms observed. Other symptoms such as headache, sputum production, hemoptysis and diarrhea were less frequent [18]. However, some patients predominantly presented with sneezing, rhinorrhea and sore throat. More than half of the infected patients developed dyspnea [18]. Chen *et al.* [19] reported 99 patients with a confirmed SARS-CoV-2 infection diagnosed by rRT-PCR. Most subjects had fever and cough, (82%) and (81%), respectively. Other reported symptoms were difficulty of breathing, headache, chest pain and diarrhea. Furthermore, Wang *et al.* [20] noted symptoms among 138 hospitalized patients with confirmed COVID-19 — fever was the main symptom (98.6%), followed by fatigue (69.6%) and then dry cough (59.4%). Despite being the most commonly reported symptom, fever can be absent in early stages of the illness. A recently published systematic review showed that 36% of 3,470 confirmed cases of COVID-19 had no fever at the onset of symptoms [14].

Mao *et al.* reported neurological manifestations of COVID-19 among 214 hospitalized patients, with hypogeusia and hyposmia in 5.6% and 5.1% of the subjects, respectively [21]. The clinical course of COVID-19 disease displays a wide spectrum of progression patterns. Looking at the timeline of the infected cases from the onset of the disease, a median time of 8 days was noticed to develop dyspnea, 9 days to develop ARDS and 10.5 days to require mechanical ventilation [12]. Severely ill patients with ARDS may quickly progress to multiple organ failure leading to death [22]. Lymphopenia is one of the clinical features of COVID-19 infection, which indicates an immunity suppression that may result in severe complications due to secondary bacterial and fungal infections. Huang *et al.* [18] in their screening study of 41 patients with COVID-19, observed that 26 (63%) of them had lymphopenia and 13 (32%) patients required ICU. The subjects admitted to ICU had higher plasma levels of interleukins (ILs-2, 7 and 10), granulocytes-macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor alpha (TNF-α).

The rise in inflammatory markers is the key point underlying the multisystem inflammatory response in COVID-19 [23]. The main inflammatory and immune markers correlating with COVID-19 disease include CRP, ESR, serum ferritin, IL-6, IL-8, IL-10, and low count of lymphocytes, T cell, B cell and NK cell [23].

Transmission of SARS-2

Based on what has been reported about previous outbreaks caused by SARS and MERS, droplets are considered the main mode of transmission. Close contact with an infected person can also transmit the infection. In addition, airborne transmission has been suggested especially when invasive respiratory procedures are performed such as endotracheal intubation [24]. The gastrointestinal symptoms that have been reported with infected patients are related to invade ACE2- expressing absorptive enterocytes from the ileum and colon, which suggests that the digestive system is a potential route for SARS--CoV-2 infection [25].

Diagnostic testing

Detection of viral RNA by RT-PCR

This test is the most commonly used and considered more reliable [26]. It is performed using nasopharyngeal swabs or other upper respiratory tract specimens, including throat swab or even saliva. Viral RNA in the nasopharyngeal swab is measured by the cycle threshold (Ct). The Ct is the number of replication cycles needed to produce a fluorescent signal, with lower Ct values representing higher viral RNA loads. The Ct becomes detectable as early as on day 1 of symptoms and peaks within the first week of the symptom onset. This positivity starts to decline by week 3 and subsequently becomes undetectable. In severe cases, however, PCR positivity may persist beyond 3 weeks after the illness onset when most mild cases will yield a negative result [27]. In a study of 9 patients, it was noted that attempts to isolate the virus in culture were not successful beyond day 8 of the illness onset, which correlates with the decline of infectivity beyond the first week even if the PCR remains positive, thus a "positive" PCR result reflects only the detection of viral RNA and does not necessarily indicate the presence of viable virus [28]. The timeline of PCR positivity is different in specimens other than nasopharyngeal swab with PCR positivity declining more slowly in sputum and stool than in nasopharyngeal specimens [28]. Wang and colleagues published a study to compare RT-PCR positivity in different types of clinical specimens

in 205 patients with confirmed COVID-19 infection — it was highest in bronchoalveolar lavage specimens (93%), followed by sputum (72%), nasal swab (63%), and pharyngeal swab (32%) [29]. Specificity of most of the RT-PCR tests is 100% because the primer design is specific to the genome sequence of SARS-CoV-2. Occasional false-positive results may occur due to technical errors and reagent contamination.

Detection of antibodies to SARS-CoV-2

COVID-19 infection can also be proven indirectly by measuring the host immune response to SARS-CoV-2 infection. Serological diagnosis is especially important for patients with mild to moderate illness who may present beyond the first 2 weeks of the illness onset. Serological diagnosis is also becoming an important tool to understand the extent of COVID-19 in the community and to identify individuals who are immune and potentially "protected" from becoming infected. The most sensitive and earliest serological marker is the total of antibodies (IgM and IgG ELISA), which begin to increase from the second week of the symptom onset [30]. These antibodies can be found as early as on the fourth day after the symptom onset but higher levels occur in the second and third week of illness. Antibodies may have cross-reactivity with SARS-CoV and possibly other coronaviruses. Rapid point-of-care tests for detection of antibodies have been widely developed and marketed and are of variable quality. They are considered qualitative in nature and can only indicate the presence or absence of SARS-CoV-2 antibodies but don't confirm the presence of neutralizing antibodies which can only be confirmed by a plaque reduction neutralization test. However, high titers of IgG antibodies detected by ELISA have been shown to positively correlate with neutralizing antibodies [31]. The long-term persistence and duration of protection conferred by the neutralizing antibodies remains unknown.

Radiological changes of COVID-19 pneumonia

Chest X-ray and CT scan are used for early detection of COVID-19 pneumonia. Chen *et al.* [18] reported bilateral pneumonia among 75% of their cohort (99 patients with COVID-19) based on chest X-ray and chest CT scan. A quarter of patients were diagnosed with unilateral pneumonia and only 14% showed a ground-glass appearance on their images. In addition to rRT-PCR, the use of chest imaging as a diagnostic and management tool of COVID-19 is still debatable as chest X-ray in adults has been found to be insensitive in mild or early COVID-19 infection [32]. Similarly, reported cases of children with COVID-19 showed completely normal X-ray on admission [33, 34]; however, in severe and more advanced cases, chest X-ray images were abnormal with bilateral multiple consolidation [35]. Jiehao *et al.* [36] reported multiple patch-like shadows on chest X-ray images of 4 (40%) out of 10 infected children.

Compared to X-ray, a CT scan was shown to be more sensitive in detecting early changes and progression of the disease [37]. In fact, abnormal CT scans have been used to diagnose COVID-19 in suspected cases who initially tested negative on RT-PCR but eventually had positive tests on repeated testing [38, 39].

The main radiological changes seen on chest CT scans of infected patients were bilateral ground-glass opacities [12]. In children, the typical CT findings were unilateral or bilateral subpleural groundglass opacities as well [33, 40–46]. Other studies have reported findings of consolidations with and without air bronchogram and pleural effusion [35, 44, 45]. Furthermore, consolidations with surrounding halo sign were noticed in 50% of cases in a study conducted in children by Xia *et al.* [43]. Moreover, findings such as peribronchial distribution and bronchial thickening were more commonly seen in pediatric patients compared to the adult population [47].

In addition to its role in diagnosis, a high-resolution CT scan (HRCT) was shown by Liu *et al.* [48] to be useful as a potential screening tool as they used it to screen for COVID-19 in five pediatric suspected cases, and it showed multiple ground-glass opacities. However, currently, the society of Thoracic Radiology and the American College of Radiology do not support the use of chest CT for routine screening of COVID-19 [49]. However, Ji *et. al.* [50] reported two pediatric cases whose CT scans were completely normal [50].

Ultrasound (US) has an essential role in differential diagnosis assessment and follow-up of hospitalized patients with COVID-19, especially in intensive care units, where access to CT scan is difficult [51]. However, ultrasound should not be used to replace CT scan [52]. Lung ultrasound can be applied to evaluate many pulmonary conditions such as pleural effusion, atelectasis, consolidations, pleural effusions and pneumothorax. In COVID-19 patients, US allows evaluating the parenchyma inflammation progression, pleural thickening, and subpleural consolidations with or without air bronchograms [52].

Case fatality

Estimating the lethality of COVID-19 disease is challenging [53]. The case-fatality ratio is used to assess the severity of a disease and effectiveness of a treatment [54]. To calculate the CFR, the number of known deaths over a certain period of time is divided by the number of confirmed cases (including deaths and recovered cases) during that time [54]. The CFR does differ from mortality rate which is another measure of death that reflects the portion of a population who dies during a certain period of time. To get an accurate CFR, the true number of infected patients is needed. This means that the CFR can be overestimated if the true number of infected persons is underestimated. Especially, if asymptomatic and mildly symptomatic infected patients do not present to hospitals. Moreover, CFRs can differ between different geographical areas, a reason being different medical services and facilities during the pandemic period [53], the use of inappropriate statistical methods and techniques [54], in addition to the sensitivity and specificity of serologic testing that is used to confirm infection [54].

Wu *et al.* [55] reported a total of 72,314 infected cases with COVID-19 recorded by the Chinese center for disease control and prevention, the overall CFR till February 24, 2020 and among the confirmed 44,672 cases, was 2.3%. There were no deaths recorded in children aged 9 years or younger. However, the CFR was up to 8% among the group of patients aged 70–79 years and even higher (14.8%) in the group of older patients (≥ 80 years). The CFR was the highest in the group of patients with critical illness (49%) [55]. In a recently published systematic review, the overall CFR was 3.7% (3,015 died of 80,565 patients) [14].

Treatment

Repurposed drugs to treat SARS-CoV-2

Currently, there has been no potential therapy shown from randomized clinical trials to improve outcomes or to significantly reduce case-fatality rate among either suspected or confirmed cases of COVID-19. However, the researchers have used drugs targeted at the virus lifecycle steps, viral entry and immunity regulation pathways to provide drug therapy for COVID-19 [56]. Because of the critical need for effective therapies, there has been a clear interest in repurposing available agents for immediate use.

Various drugs that were active against SARS-CoV and MERS-CoV have been considered as potential therapy to treat COVID-19.

Chloroquine and hydroxychloroquine

Chloroquines have been used as antimalarial agents for decades [57]. Because of their immune-modulatory properties, these agents have been considered to treat autoimmune diseases such as rheumatoid arthritis [57]. Chloroquine (CQ) and hydroxychlorquine (HCQ) have a potential antiviral activity against SARS-CoV-2 by blocking several steps required for viral entry to host cells, including host cell receptor terminal glycosylation, proteolytic processing and edosomal acidification [58], in adition to their immune-modulatory properties through inhibition of cytokine production and host cells lysosomal activity [59], both CQ and HCQ affect the viral entrance to the host cell through inhibiting ACE2 receptor binding to viral S protein by impairment of terminal glycosylation of ACE2 on host cells, and inhibiting membrane fusion and uncoating [59]. Once inside the cell, CQ and HCQ concentrate inside the acidic organelles, such as lysosomes, endosomes and Golgi apparatus. Thus, using either CQ or HCQ therapy elevates the PH of the organelle that virus uses to replicate, which may negatively influence the viral entrance [60]. Lysosomal proteases play a role in fusion process between the viral membrane and the host, alkalinization of lysosomes will negatively affect proteases activity causing impairment of fusion process [60]. Preventing virus-host fusion helps blocking the infection. Vincent *et al.* studied the efficacy of CQ on SARS-CoV infection and observed inhibition of SARS-CoV spread in cells treated with CQ prior and after the infection [60]. Thus, they suggested its prophylactic and therapeutic role.

Moreover, Gautret *et al.* reported a 70% viral clearance among 20 infected patients who were treated with HCQ at the sixth day of therapy. The authors also reported an increase in the viral clearance up to 100% after adding azithromycin to HCQ in 6 patients, which supports using this regimen to reduce the length of hospital stay [61]. However, the small size of the patients used azithromycin in this study (6 subjects), and were observed only for a short time (6 days), and taking into consideration the additive risk of developing cardiac complications, mainly QT prolongation with the combined therapy [61], they have encouraged to perform randomized controlled trials to assess this regimen's efficacy.

In addition, surviving sepsis campaign guidelines on the management of critically ill adults with COVID-19 that have been published recently, provided no evidence to support this combination of therapy use in treatment of critically ill patients admitted to ICU [62]. This could be, though, due to multiple organ failure that critically ill patients have, which can influence the metabolism of these agents, and can potentially increase the risk of side effects. Whether to continue using QCs or to stop, RCTs are required. The solidarity and the discovery study are multicenter studies ongoing to provide a better understanding of antimalarial and other antiviral agents' effects.

Safety and side effects

Both CQ and HCQ are distributed well throughout body systems after oral administration and are cheap. The main side effects of these agents include diarrhea and vomiting [59]. Other serious side effects have been reported following a chronic use such as retinopathy and cardiomyopathy [63]. Moreover, toxicity due to CQ therapy has been seen in patients treated with high doses exceeding the therapeutic dosage limits. In contrary, HCQ is associated with fewer side effects than CQ because of its lower level of tissue accumulation [63]. In contrast to HCQ, CQ is considered unsafe to be given during pregnancy due to its teratogenic effect on the fetus. This supports using HCQ rather than CQ in treating pregnant women with SARS-CoV infection. HCQ can cause QT interval prolongation leading to *torsade de pointes* in some individuals. Despite being rare, this side effect can by amplified by using other drugs such as azithromycin that has been suggested to be used in combination with HCQ [62].

Lopinavir/ritonavir combination

The HIV antiretroviral combination lopinavir/ritonavir that is called Kaletra or Aluvia [64] as been used to treat patients with COVID-19. Lopinavir and ritonavir are protease inhibitors that have shown some activity against SARS-CoV-2 *in vitro*, however currently, there is no strong evidence of benefit to use it against COVID-19 [65]. Lopinavir inhibits the activity of 3-chymotrypsin-like protease (3CL) which has a role in viral RNA processing. Ritonavir inhibits the metabolizing enzyme cytochrome P450 3A and that increases the half-life of lopinavir, subsequently, affecting viral replication and release from host cells [66]. Previous studies investigating the activity of lopinavir/ritonavir against SARS and MERS were limited, still they showed a decrease in incubation period and mortality rate [67]. Up till now there has been no published data for this combination supporting its use for SARS-CoV-2. Cao *et al.* investigated the efficacy of Kaletra through conducting a randomized, controlled, open-label study. A total of 199 patients were included, 99 subjects were allocated to the lopinavir/ritonavir group, and the rest (100 patients) to the supportive care group [67]. The results, unfortunately, were not promising, and there were no benefits observed with lopinavir/ritonavir therapy over supportive care. In a different study from China, the authors have investigated the risk factors for prolonged SARS-CoV-2 shedding among 120 patients confirmed to have COVID-19 using tRT-PCR. They have reported a shorter median duration of viral shedding with early administration, within the first 10 days from the symptoms onset, of lopinavir/ritonavir treatment by 6.5 days [64]. However, reported serious adverse effects such as induced transaminase elevation and hepatotoxicity, limit this therapy in treating patients with COVID-19, especially those with liver injury [68]. At present, there is a lack of evidence to recommend the use of this combination for treatment of COVID-19, and more RCTs are required to assess the efficacy and safety of this therapy.

Ivermectin

Ivermectin is an FDA-approved anti-parasitic drug which has shown an antiviral effect on human immunodeficiency virus (HIV) [69]. It is known to inhibit the interaction of integrase protein (IN) of HIV-1 and the importin (IMP) α/β1 heterodimer that is important for IN nuclear transportation of viral proteins [70]. As this process is important for viral replication cycle, affecting the nuclear import can be considered as a therapeutic approach against RNA viruses. Recently, a group of Australian researchers have shown an *in vivo* activity with capability of ivermectin to significantly reduce the virus replication within two days [70]. Further research is required to evaluate ivermectin`s efficacy on treating SARS-CoV-2 infections.

Remdesivir

Remdesivir, which is known as GS-5743, has a broad-spectrum antiviral activity against RNA viruses such as filoviruses, pneumoviridae and paramyxoviruses [71], it has shown an *in vitro* activity against reported cases infected with

SARS-CoV-2 [72]. Remdesivir is intracellulary metabolized to adenosine triphosphate analogue that blocks viral replication by inhibiting the viral RNA polymerases [73]. Initial animal experiments showed some activity against Ebola virus, however, a recent randomized controlled trial in the Democratic Republic of the Congo (DRC) showed that remdesivir was less effective in reducing mortality compared to single and triple monoclonal antibody-based treatments. However, this trial has proven the safety of its use in humans, which led the researcher to consider using it in COVID-19 clinical trials [74]. Recently, Williamson *et al.* have shown that remdesivir treatment was effective in reducing lung damage and disease progression in infected rhesus macaques monkeys with SARS-CoV-2 [75]. Moreover, Grein *et al.* have published their experience with compassionate remdesivir treatment in 53 patients with severe COVID-19, as a 10-day course of remdesivir at a dose of 100 mg intravenously proceeded by a loading dose of 200 mg used and followed up for 28 days. A clinical improvement in terms of respiratory support was observed in 36 (68%) patients [76]. Remdesivir is currently being tested in clinical trials in different countries, two of these trials are randomized phase 3 trials in China.

Favipiravir

Similar to remdesivir, favipiravir inhibits the RNA polymerase activity affecting viral replication [77]. Favipiravir (FPV) is one of the medications approved for treating influenza. However, there has not been strong evidence to support its use to treat patients with COVID-19 compared to remdesivir [77]. Nevertheless, Cai *et al.* evaluated the effects of favipiravir against lopinavir/ritonavir for treatment of SARS-CoV-2. An oral favipiravir was used in a combination with an inhaled interferon-α for the synergistic effect of viral inhibition. Their results were promising as the patients in the FPV arm showed better clinical response in terms of viral clearance and disease progression with minimal adverse effects [78]. Consequently, in March 2020, the National Medical Products Administration of China approved FPV as the first drug to treat COVID-19.

Ribavirin

Ribavirin is a guanosine analog that affects the replication of RNA and DNA viruses. It also inhibits the production of guanosine from the guanine precursor by influencing the function of inosine monophosphate dehydrogenase which further affects virus stabilization [79]. Early administration of ribavirin has been reported to be beneficial in treating COVID-19-related pneumonia [80]. Ribavirin has been used in combination with the protease inhibitor lopinavir/ritonavir given the previously proven efficacy against SARS. Chu *et al.* examined the clinical response of 41 COVID-19 patients who were followed up to 3 weeks to a combination of lopinavir/ritonavir and ribavirin, compared to 111 controls who were SARS infected patients and received only ribavirin. The study subjects in the lopinavir/ritonavir and ribavirin treatment group had lower adverse clinical outcomes represented by ARDS or death compared to the control group. In addition, a reduction in both steroid use and nosocomial infections were noticed as well [81].

Systemic glucocorticoids

Given the high levels of cytokines that are induced by COVID-19, corticosteroids have been used for their anti-inflammatory effect to treat critically ill patients. However, current research suggested no reduction in mortality rate, but delayed viral clearance and high viral load [82, 83]. However, there is an argument for using systemic corticosteroids in patients who develop ARDS as a complications of COVID-19 infection, where in this setup it seems that they decrease the duration of mechanical ventilation and hospital mortality [84].

Corticosteroids were widely used during SARS-CoV outbreak due to their ability to modulate the inflammatory response [85]. At present, there is no clear evidence for or against corticosteroid use in the treatment of SARS-CoV-2 patients. There is some proof that corticosteroid use during early phase of infection may be beneficial [85]. However, corticosteroid should be applied carefully until further evidence that is specific to SARS-CoV-2 infection emerges.

Intravenous immunoglobulin (convalescent plasma therapy)

Immunocompromised patients and individuals with immunological disorders appear to be at higher risk of developing serious complications related to COVID-19 disease compared to healthy individuals. Immunotherapy using immunoglobulin G (IgG) could be used in combination with antiviral agents to treat COVID-19 and to strengthen patients' immune response against

SARS-CoV-2 [86]. Hofmann *et al.* reported that sera from healthy individuals contain anti-coronavirus antibodies [87]. In addition, Pyrc *et al.* in a study on HCoV-NL63, showed that the infection caused by HCoV-NL63 can be inhibited by human sera from healthy adults [88]. Boukhvalova *et al.* reported an improved outcome of RSV infections among immunocompromised patients who were treated with IV Ig obtained from previously infected donors who had a high-titer antibodies against RSV [89]. Thus, immunotherapy using immune IgG antibodies collected from adults recovered from SARS-CoV-2 infection could be a promising modality of treatment for patients with COVID-19. It has been reported that immune IgG antibodies are more efficient in terms of virus neutralization, if collected from patients who live in the same city because of the effect of lifestyle and environmental factors on specific antibodies development against viruses [86]. Using immune IgG antibodies against SARS-CoV-2 infection can help newly infected patients by boosting their immune response to the infection. Thus, a combination of antiviral drugs and immunotherapy can be used as an alternative treatment for COVID-19 until a vaccine is developed.

Interleukin (IL)-6 pathway inhibitors

IL-6 is one of the key cytokines produced by activated macrophages. In their systematic review, Coomes *et al.* demonstrated significantly higher serum levels of IL-6 in patients requiring ICU admissions than non-ICU patients, suggesting that serious complications of COVID-19 can be related to a host immune response and autoimmune damage [90]. Furthermore, Zhou *et al.* reported a correlation between the serum levels of IL-6 and the mortality in patients with COVID-19 [91]. IL-6 is important for production of T helper 17 (Th17) cells. Excessively activated Th17 cells reported in patients with COVID-19 can be explained by the high levels of IL-6 [92]. Elevated levels of IL-6 negatively impact the lung elasticity and are associated with severe bronchoalveolar inflammation [13]. Thus, using agents that inhibit the cytokine pathway at the level of IL-6, such as tocilizumab can be beneficial in managing inflammatory response squeals. Tocilizumab (TCZM) is a recombinant monoclonal antibody that binds to both soluble and membrane-bound receptors [93]. Tocilizumab is not approved for COVID-19 treatment. However, clinicians are using it under emergency use authorization [93]. There is limited high-quality published evidence for IL-6 inhibitor use against COVID-19 [94]. However, a very recent systematic analysis that included sixteen case-controlled and eighteen uncontrolled studies revealed positive evidence for the potential efficacy of TCZM to treat severe cases of COVID-19 [93]. The World Health Organization (WHO) recommends the use of IL-6 inhibitors only in clinical trials. But, many organizations have included IL-6 inhibitors as an option for treating COVID-19 patients with severe disease [94]. Other IL-6 inhibitors such as sarilumab and siltuximab have been evaluated for the management of COVID-19 patients, with no strong evidence to be used in the management of COVID-19 patients [94].

Amantadine

Amantadine is a drug used to treat Parkinson's disease. It could be used to mitigate COVID-19 effects; the researches have shown that patients with Parkinson's disease who are treated with amantadine and have been infected with SARS-CoV-2 virus have been asymptomatic [95]. Its proposed mechanism of action is that it blocks the early stages of viral replication. Moreover, it is hypothesized that amantadine prevents the release of the viral nucleus into the cell cytoplasm by blocking the viroporine channel of SARS-CoV-2 [96]. Very recently, Jiménez-Jiménez *et al.* studied the anti-inflammatory effects of amantadine and its therapeutic influence in treating COVID-19. They have suggested two pharmacological effects: antiviral and anti-inflammatory [97]. Furthermore, Abreu *et al.* have proposed that early use of amantadine could mitigate COVID-19 disease consequences [96]. Further randomized clinical trials are required to prove its usefulness in COVID-19 management.

Systemic anticoagulation

Researchers in several centers caring for adult patients with severe COVID-19 disease noted an increased incidence of thromboembolic events. Those patients typically required ICU admission and mechanical ventilation. Two studies looked at the use of systemic anticoagulation and the impact on in-hospital mortality and reported improved outcomes [98, 99]. In an updated recommendation, the NIH in the US added the use of systemic anticoagulants in its recommendations for the care of hospitalized

critically ill adult patients with COVID-19 [100]. One of the anti-coagulant agents that were tried on COVID-19 patients is sulodexide. It is a natural glycosaminoglycan composed of fast-moving heparin (80%) and dermatan sulfate (20%) [101]. It has an arterial and venous anti-thrombotic action and ani-inflammatory activity through suppression of IL-6 production [101]. Compared with low-molecular-weight heparin (LMWTs), sulodexide is associated with less bleeding risk and is safe to be given to patients with renal insufficiency [102]. This drug may represent an alternative prophylactic agent to LMWH [102]. It was hypothesized that the early use of sulodexide in COVID-19 patients with comorbidities might reduce the severity of the disease and prevent the development of severe complications [103]. Bikdeli *et al*. reviewed 6 randomized controlled trials (RCTs) where the use of sulodexide was compared with placebo. The sulodexide administration was associated with a reduction in the odds ratio of cardiovascular mortality, deep vein thrombosis, and myocardial infarction [104]. However, additional RCTs with this drug are warranted.

Respiratory support

Hypoxemia is common in hospitalized COVID-19 patients. More than a quarter of the hospitalized COVID-19 subjects require intensive care due to acute respiratory failure [105]. Conventional oxygen therapy can be insufficient to meet oxygen needs of individuals with acute hypoxic respiratory failure [106]. Options for treating hypoxic patients, other than conventional oxygen therapy, include high-flow nasal cannula (HFNC), noninvasive positive-pressure ventilation (NIPPV), or intubation and invasive mechanical ventilation. Based on meta-analysis and data from non-COVID-19 clinical trials that showed reductions in the need for intubation in patients who received HFNC or NIPPV, these options are preferable to conventional oxygen therapy [107]. Furthermore, HFNC use is preferred over NIPPV in hypoxic patients due to acute respiratory failure [108]. Patients with COVID-19 should be monitored for signs of respiratory deterioration. Early intubation should be considered when the patients' condition deteriorates and they have additional acute system dysfunction or when HFNC and NIPPV are not available to treat the hypoxic acute respiratory failure [106]. If required, intubation should be performed by experienced staff in a controlled setting to ensure the safety of both patients and healthcare workers.

Use of antibiotic therapy

A meta-analysis of small case series reported that 3.5% of COVID-19 patients had a bacterial co-infection, and 14% had a secondary bacterial infection [109]. Superimposed bacterial infections have been reported in 28% of severely infected and critically ill COVID-19 patients, which may support the antibiotic use in intensive care units [110]. Despite the lack of reported cases of initial superinfections, there is widespread use of antibiotics in hospitalized COVID-19 patients. Antibiotic use in patients with COVID-19 has not been shown to affect clinical outcomes. Contrary, unnecessary antibiotic use has been associated with an increased risk of resistant hospital-acquired bacterial and fungal infections [111]. Antibiotic therapy is not recommended for COVID-19-related pneumonia unless a secondary bacterial infection is suspected.

Vaccine development

Since the full genomic sequence of SARS--CoV-2; the cause of the novel coronavirus pandemic (COVID-19) has been published [112], many countries, institutions, and pharmaceutical companies started racing to develop an effective and safe vaccine, as it's the most reliable and cost-effective method to control any emerging viral infection and flatten its transmission curve as well as to prevent any re-emergences of the disease in the future. According to the WHO, until this date, more than 40 programs are working on a vaccine against SARS-CoV-2 [113], only two of them entered the clinical trials; recombinant adenovirus vector vaccine which is in phase-2 clinical trial [114], and mRNA-based vaccine in phase-1 [115].

In addition to live vector and RNA-based vaccines, candidates using other platforms, such as the whole virus; either killed or live attenuated [116–118], DNA-based [119, 120], and recombinant subunit vaccines, are also under development ; which is currently getting a lot of attention since the surface S glycoprotein has shown to be the main target for subunit vaccines against MERS-COV and SARS-COV [121–124], and it is expected to be the same for SARS-CoV-2 due to the reported high genetic similarities especially with SARS-COV [126, 127]. Several studies have shown that S glycoprotein and its RBD fragment is an ideal vaccine target against SAR-CoV-2 [127–132]. To date all S glycoprotein-based vaccine candidates targeting SARS-CoV-2 are still in preclinical phase [113]. Another interesting

subunit vaccine targets are specific B and T cell epitopes [133–135]. However, as vaccines usually take at least one year to be available, alternative options should be considered.

Existing and widely used vaccines may serve a potential protective effect against SARS-CoV-2 as it has been observed that the incidence of COVID-19 in groups who are vaccinated routinely, especially children, is very low [136, 137], and recently, it has been hypothesized that BCG vaccine may offer a protective shield against COVID-19 based on observations that compared the prevalence of COVID-19 in countries where BCG is a national program with other countries [138, 139]. However, two clinical trials have been started to assess its efficacy in protecting healthcare workers who are in contact with COVID-19 patients [140, 141]. Another interesting short-term protection alternative option is convalescent sera which provide an immediate passive immunity by administering the collected antibodies from recovered patients in susceptible individuals [142, 143], thus, convalescent plasma combined with other potential therapeutic drugs may serve a good alternative treatment until strong options such as vaccines are available. As for any vaccine, in addition to the time it takes to be developed and evaluated, it also poses some challenges regarding its candidate such as antibody-dependent enhancement (ADE); a phenomenon in which the viral antigens used by the vaccine may induce the same disease they're supposed to protect from [144]. Moreover, RNA viruses; which are the big family of coronaviruses have been shown to have a higher rate of mutations when they're compared to DNA viruses [145, 146].

In the past, vaccines were developed through many steps that might have taken several years. Recently, given the urgent need to develop a COVID-19 vaccine, some of the vaccine development steps are happening in parallel while maintaining safety standards. For example, multiple vaccines are evaluated at the same time by some clinical trials [147]. Clinical development of a new vaccine is a three-phase process. During phase-1, small groups of healthy adult volunteers should be enrolled. In phase-2, the vaccine is given to groups of volunteers that reflect the populations for whom the vaccine is intended. In phase-3, the vaccine is given to large groups of people (thousands) to test its efficacy and safety [148]. Multiple vaccines are being tested in early-phase studies, and some vaccine participants are in phase-3 studies assessing efficacy [149].

Conflict of interest

The authors declare no conflict of interest.

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