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Review Article

# Treatment options for COVID-19: The reality and challenges



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Received 30 March 2020; accepted 31 March 2020

Available online 4 April 2020

## KEYWORDS

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2);  
Coronavirus disease 2019 (COVID-19);  
Remdesivir;  
Hydroxychloroquine;  
Non-steroidal anti-inflammatory drugs;  
Angiotensin converting enzyme inhibitors

**Abstract** An outbreak related to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China in December 2019. An extremely high potential for dissemination resulted in the global coronavirus disease 2019 (COVID-19) pandemic in 2020. Despite the worsening trends of COVID-19, no drugs are validated to have significant efficacy in clinical treatment of COVID-19 patients in large-scale studies. Remdesivir is considered the most promising antiviral agent; it works by inhibiting the activity of RNA-dependent RNA polymerase (RdRp). A large-scale study investigating the clinical efficacy of remdesivir (200 mg on day 1, followed by 100 mg once daily) is on-going. The other excellent anti-influenza RdRp inhibitor favipiravir is also being clinically evaluated for its efficacy in COVID-19 patients. The protease inhibitor lopinavir/ritonavir (LPV/RTV) alone is not shown to provide better antiviral efficacy than standard care. However, the regimen of LPV/RTV plus ribavirin was shown to be effective against SARS-CoV *in vitro*. Another promising alternative is hydroxychloroquine (200 mg thrice daily) plus azithromycin (500 mg on day 1, followed by 250 mg once daily on day 2–5), which showed excellent clinical efficacy on Chinese COVID-19 patients and anti-SARS-CoV-2 potency *in vitro*. The roles of teicoplanin (which inhibits the viral genome exposure in cytoplasm) and monoclonal and polyclonal antibodies in the treatment of SARS-CoV-2 are under investigation. Avoiding the prescription of non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, or angiotensin II type I receptor blockers is advised for COVID-19 patients.

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## Introduction

In December 2019, Wuhan city (the capital city of Hubei province, China) experienced a major outbreak caused by a novel coronavirus. This outbreak was found to be caused by a novel virus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>1–3</sup> Numerous clinical SARS-Co-2 cases have been reported and were distributed among more than half of the countries of the world during a less than 6-month period (data till March 28, 2020).<sup>4–7</sup> The lower respiratory tract is the primary target of the SARS-CoV-2 infection. It is noteworthy that adults with coronavirus disease 2019 (COVID-19) often present with a profound decrease in both CD4<sup>+</sup> and CD8<sup>+</sup> T-cell subsets at the early stage of this disease.<sup>1,8</sup> Subsequently, patients suffered acute respiratory distress syndrome for about 7–10 days after the onset of COVID-19 due to rapid viral replication, a stormy increase of pro-inflammatory cytokines as well as chemokine response, and inflammatory cell infiltrates.<sup>8,9</sup> Nevertheless, contrary to the SARS cases in 2003,<sup>10</sup> some SARS-CoV-2 infection patients did not have the prodromal symptoms of upper respiratory tract infection (e.g., cough, sore throat, rhinorrhea), viremia-associated laboratory abnormalities (e.g., leukopenia, lymphopenia, anemia, elevation of liver enzymes and lactic dehydrogenase), or initial evidence of diagnostic chest roentgenographic abnormalities.<sup>6,11</sup> In addition, uncertain seasonality and the incubation period of SARS-CoV-2 infection oscillating between 2 and 14 days make it remarkably difficult to achieve early diagnosis and initiate treatment on time.<sup>5,9</sup> Previous studies demonstrated that human coronavirus-NL63 (HCoV-NL63) is able to use angiotensin-converting enzyme-2 (ACE2) as a cell receptor in humans.<sup>5,12</sup> Although children are considered to be significantly less susceptible to HCoV-NL63 infection and have milder disease severity than adults,<sup>1,5,8,13</sup> the SARS-CoV-2 infection has become a public health menace to people around the world presently because of high transmission potential and unpredictability of disease progression.<sup>14</sup> In order to contain SARS-CoV-2 spread among community residents, stringent infection control measures were implemented by the Centers for Disease Control (CDC) and Prevention of Taiwan since February, 2020. According to an investigation by To et al. (2020),<sup>15</sup> patients with SARS-CoV infection had the highest viral load (measured from posterior oropharyngeal saliva samples) close to when they presented. To et al. concluded that since viral load had already peaked around the time of hospital admissions, early use of potent antiviral agents might be beneficial in controlling COVID-19 severity.<sup>15</sup> However, standard treatment against COVID-19 is presently lacking. Herein, the roles

of several drugs including antiviral agents, some antibiotics and anti-inflammatory agents have been reviewed to explore their efficacy in combating the SARS-CoV-2 (data until March 28, 2020).

## RNA-dependent RNA polymerase inhibitors

### Remdesivir

Among several potential drugs tested for efficacy in treatment of SARS-CoV-2 infection,<sup>16</sup> remdesivir (GS-5734; Gilead Sciences Inc., Foster City, CA, USA) is shown to be the most promising and hopeful anti-viral therapeutic. It works by targeting viral RNA-dependent RNA polymerase (RdRp) while evading proofreading by viral exoribonuclease,<sup>17</sup> resulting in premature termination of viral RNA transcription. Unlike other nucleotide analogues, remdesivir is a phosphoramidate prodrug with broad-spectrum activity against many virus families, including *Filoviridae*, *Paramyxoviridae*, *Pneumoviridae*, and *Orthocoronavirinae* (such as pathogenic SARS-CoV and Middle East respiratory syndrome coronavirus [MERS-CoV]).<sup>18,19</sup>

Information regarding the pharmacokinetics of remdesivir in humans is not available. Nevertheless, valuable data from rhesus monkeys revealed an intravenous 10 mg/kg dose of remdesivir could lead to a remarkably high intracellular concentration (>10  $\mu$ M) of active triphosphate form in peripheral blood mononuclear cells for at least 24 h,<sup>20</sup> supporting its clinical potential in the treatment of human SARS-CoV-2 infection. Additionally, data on the safety of remdesivir in humans are available online.<sup>21</sup> The first COVID-19 patient in the USA was successfully treated with remdesivir for the progression of pneumonia on day 7 of hospitalization in January, 2020.<sup>4</sup> Phase 3 human trials (ClinicalTrials.gov Identifier: NCT04292899 and NCT04292730, for severe and moderate adult SARS-CoV-2 cases, respectively) have been initiated to evaluate its efficacy in patients with SARS-CoV-2 infection since March, 2020. Patients received 200 mg on day 1, followed by 100 mg once daily from day 2. Despite its encouragingly high *in vitro* potency against SARS-CoV-2 and the clinical success in treatment of COVID-19,<sup>4,18</sup> uncertainties about adverse effects (e.g., nausea, vomiting, rectal hemorrhage, and hepatic toxicity) and clinical efficacy of remdesivir have been reported recently.<sup>22</sup>

In a mouse model investigating the pathogenesis of SARS-CoV, prophylactic and early therapeutic post-exposure administration of remdesivir were shown to produce a significant reduction in pulmonary viral load (i.e., >2 orders of magnitude on day 2–5 post-infection), mitigate disease progression and prominently improve

respiration function.<sup>18</sup> Furthermore, Brown et al. observed that remdesivir displayed half-maximum effective concentrations (EC<sub>50</sub>s) of 0.069  $\mu$ M for SARS-CoV, and 0.074  $\mu$ M for MERS-CoV in tissue culture models.<sup>23</sup> In addition, tissue culture experiments also revealed that many highly divergent CoV including the endemic human CoVs (HCoV-OC43, HCoV-229E) and zoonotic CoV are effectively inhibited by remdesivir within the submicromolar EC<sub>50</sub>s.<sup>23,24</sup> Of note, the similar efficacy of prophylactic and therapeutic remdesivir treatment (24 h prior to inoculation, and 12 h post-inoculation, respectively) was also seen in the context of a non-human primate (rhesus macaque) model of MERS-CoV infection.<sup>25</sup> Although two amino acid substitutions (F476L, V553L) in the non-structural protein 12 polymerase were demonstrated to confer low-level resistance to remdesivir, this resistance also impaired the fitness of the tested CoVs and is actually difficult to select.<sup>17</sup>

### Favipiravir

The other RdRp inhibitor favipiravir (Fujifilm Toyama Chemical Co. Ltd, Tokyo, Japan) is known to be active *in vitro* against oseltamivir-resistant influenza A, B, and C viruses.<sup>26</sup> After being converted into an active phosphoribosylated form, favipiravir is easily recognized as a substrate of viral RNA polymerase in many RNA viruses.<sup>27</sup> The recommended dose of favipiravir against influenza virus is 1600 mg administered orally twice daily on day 1, then 600 mg orally twice daily on day 2–5, and 600 mg once on day 6. Recently, preliminary results of clinical studies have shown favipiravir to have promising potency in treatment of Chinese patients with SARS-CoV-2 infection.<sup>28</sup> Favipiravir was approved for the treatment of COVID-19 in China in March, 2020. In addition, patients with COVID-19 infection are being recruited for randomized trials to evaluate the efficacy of favipiravir plus interferon- $\alpha$  (ChiCTR2000029600) and favipiravir plus baloxavir marboxil (ChiCTR2000029544).

### Ribavirin

Ribavirin (Bausch Health Companies Inc., Bridgewater, NJ, USA) is a guanosine analogue antiviral drug that has been used to treat several viral infections, including hepatitis C virus, respiratory syncytial virus (RSV), and some viral hemorrhagic fevers. The *in vitro* antiviral activity of ribavirin against SARS-CoV was estimated to be at a concentration of 50  $\mu$ g/mL.<sup>29</sup> However, it has the undesirable adverse effect of reducing hemoglobin, which is harmful for patients in respiratory distress.<sup>19</sup>

### Interferons

Treatment with interferon  $\beta$  (IFN $\beta$ )-1b (Bayer Pharmaceutical Co., Leverkusen, Germany), an immunomodulatory agent, was shown to result in clinical improvement among MERS-CoV-infected common marmosets, but the benefits of IFN $\beta$ -1b for SARS patients remains uncertain.<sup>29,30</sup>

## Protease inhibitors

### Lopinavir/ritonavir

Protease inhibitors (PIs) are important agents in the contemporary treatment of patients with chronic human immunodeficiency virus (HIV) infection. In the Orthocoronavirinae family, the targets of PIs are papain-like protease and 3C-like protease.<sup>30</sup> The antiviral activity of lopinavir (LPV; Abbott Laboratories, Lake Bluff, Illinois, US) against MERS-CoV in a tissue culture model is controversial, despite a good effect in mitigating disease progression in MERS-CoV-infected marmosets.<sup>29</sup> Of note, Sheahan et al. (2020) compared the efficacy of prophylactic remdesivir (25 mg/kg twice a day, administered 1 day prior to infection) as well as therapeutic remdesivir with that of LPV/ritonavir (RTV, used to prolong the LPV's half-life)-IFN $\beta$  combination therapy in a humanized transgenic mouse MERS-CoV infection model. They observed the efficacy of remdesivir was superior to that of LPV/RTV-IFN $\beta$  against MERS-CoV in terms of viral load reduction and improvement in extent of pathologic change in lung tissue.<sup>31</sup> In addition to gastrointestinal adverse effects (nausea, vomiting, and diarrhea) induced by LPV/RTV, it is noteworthy that LPV/RTV treatment alone (400/100 mg administered orally twice daily for 14 days; Chinese Clinical Trial Register number, ChiCTR2000029308) failed to provide benefits compared to standard care alone. Median time to clinical improvement in both cases was 16 days (hazard ratio [HR], 1.31; 95% confidence interval [CI], 0.95 to 1.85;  $P = 0.09$ ) and there was no difference in the reduction of viral RNA loading for severe SARS-CoV-2 patients.<sup>32</sup>

Despite discouraging results, it is intriguing that a slightly lower number of deaths was observed in the group receiving LPV/RTV in the late stage of SARS-CoV-2 infection compared with the standard-care group. Moreover, Baden and Ruben (2020) and Sheahan et al. (2020) suggested that the LPV/RTV concentration necessary to inhibit pulmonary SARS-CoV-2 replication might be higher than the serum level.<sup>31,33</sup> A randomized, controlled open-label trial was launched in China to evaluate the efficacy of LPV/RTV (200/50 mg twice a day) among hospitalized patients with SARS-CoV-2 infections in 2020 (ChiCTR2000029308). The role of darunavir (Janssen Pharmaceutica, Beerse, Belgium), also a promising PI against SARS-CoV-2 *in vitro*, needs to be further evaluated.<sup>34</sup> Ribavirin in combination with interferon- $\alpha$  2b was shown to be active against MERS-CoV in a rhesus macaque model.<sup>35</sup> Additionally, the regimen of LPV/RTV plus ribavirin was shown to be effective against SARS-CoV in patients and in tissue culture.<sup>36</sup>

### Chloroquine, hydroxychloroquine, and azithromycin

Chloroquine is active against malaria as well as autoimmune diseases (such as rheumatoid arthritis [RA], lupus erythematosus). It was recently reported as a potential broad-spectrum antiviral drug for treatment of viruses such as influenza H<sub>5</sub>N<sub>1</sub> in an animal model.<sup>37</sup> Chloroquine was shown to increase endosomal pH, which prevents virus/cell fusion. It also interferes with the glycosylation of cellular

receptors of SARS-CoV.<sup>38,39</sup> Although the *in vitro* data of chloroquine is promising (EC<sub>90</sub> of 6.90 μM, using Vero E6 cells infected by SARS-CoV-2), an extensive prescription of chloroquine in clinical treatment of SARS-CoV-2 is a completely off-label use. It is not recommended in light of safety concerns (adverse effects on the hematologic, hepatic and renal systems, QTc prolongation with ventricular dysrhythmia) and will likely result in a major shortage of anti-malarial armamentaria.<sup>40</sup>

Hydroxychloroquine is also proposed to control the cytokine storm that occurs in critically ill late phase SARS-CoV-2 infected patients.<sup>41</sup> Hydroxychloroquine is significantly more potent than chloroquine *in vitro* (EC<sub>50</sub> values: 0.72 and 5.47 μM, respectively) and has lower potential for drug–drug interactions than chloroquine. Pharmacokinetic models demonstrate that hydroxychloroquine sulfate is significant superior (5 days in advance) to chloroquine phosphate in inhibiting SARS-CoV-2 *in vitro*.<sup>41</sup> The Taiwan CDC declared hydroxychloroquine as an important anti-SARS-CoV-2 agent on 26 March, 2020. Of note, patients with retinopathy, deficiency of glucose-6-phosphatase, QTc prolongation in electrocardiograms, history of allergy to hydroxychloroquine or who are pregnant or breastfeeding are contraindicated for receiving hydroxychloroquine therapy.<sup>42</sup>

Azithromycin (Pfizer Inc., Manhattan, New York City, NY, USA) was shown to be active *in vitro* against Ebola viruses.<sup>43</sup> Furthermore, azithromycin is thought to have good potential in preventing severe respiratory tract infections among pre-school children when it is administered to patients suffering viral infection.<sup>44</sup> According to one recent study, azithromycin (500 mg on day 1, followed by 250 mg per day on day 2–5) was shown to significantly reinforce the efficacy of hydroxychloroquine (200 mg three times per day for 10 days) in the treatment of 20 patients with severe COVID-19. Mean serum hydroxychloroquine concentration was 0.46 ± 0.20 μg/mL. The good clinical outcome among these COVID-19 patients was thought to be due to the excellent efficiency of virus elimination after administration of this combination therapy.<sup>42</sup> Consequently, the regimen of hydroxychloroquine in combination with azithromycin might be a promising alternative to remdesivir in the treatment of patients with SARS-CoV-2 infection in the future. Nevertheless, the possibility of complicated QTc prolongation should be concerned.

### Teicoplanin and other glycopeptides

The other antibiotics worth mentioning in this review are glycopeptides. Teicoplanin (Sanofi Pharmaceuticals, Paris, France) was demonstrated to potently prevent the entry of Ebola envelope pseudotyped viruses into the cytoplasm, and also has an inhibitory effect on transcription as well as replication-competent virus-like particles in the low micromolar range (IC<sub>50</sub>, 330 nM).<sup>45</sup> Moreover, teicoplanin is able to block the MERS and SARS envelope pseudotyped viruses as well.<sup>45</sup> Mechanistic investigations revealed that teicoplanin specifically inhibits the activities of host cell's cathepsin L and cathepsin B, which are responsible for cleaving the viral glycoprotein allowing exposure of the receptor-binding domain of its core genome and

subsequent release into the cytoplasm of host cells.<sup>46,47</sup> Thus, teicoplanin blocks Ebola virus entry in the late endosomal pathway. These studies indicate the potential role of teicoplanin and its derivatives (dalbavancin, oritavancin, and telavancin) as novel inhibitors of cathepsin L-dependent viruses.

A brief summary of the mechanism of action and targets of potential antimicrobial agents against SARS-CoV-2 is shown in Table 1.

### Monoclonal or polyclonal antibodies and other therapies

Monoclonal or polyclonal antibodies have been suggested as prophylactic and therapeutic tools (targeting hemagglutinin binding) against some viral infections, such as influenza.<sup>48</sup> Current efforts in developing monoclonal and polyclonal antibodies against coronaviruses mainly target MERS-CoV.<sup>18</sup> For example, a human polyclonal antibody SAB-301 (50 mg/kg) that was generated in trans-chromosomal cattle was observed to be well tolerated and safe in healthy participants of a phase 1 clinical trial.<sup>49</sup> However, Cockrell et al. (2016) observed that immune-based therapy with human monoclonal antibodies only provided protection against early stage disease caused by MERS-CoV in mouse models.<sup>19,50</sup>

**Table 1** Mechanisms of action and targets of potential treatment agents for SARS-CoV-2 infections.

Mechanism of action and targets	Drugs
Inhibition of the RNA-dependent RNA polymerase	Remdesivir Favipiravir Ribavirin
Inhibition of spike protein on SARS-CoV-2 (non-endosomal pathway)	TMPRSS2 inhibitor (camostat mesylate)
Inhibition of endosomal acidification (early endosomal pathway)	Chloroquine, hydroxychloroquine (azithromycin is reported to greatly enhance the anti-SARS-CoV-2 activity of hydroxychloroquine)
Inhibition of viral exocytosis	Interferon-α 2a Interferon-β 1b
Inhibition of papain-like protease and 3C-like protease	Lopinavir/ritonavir
Inhibition of cathepsin L and cathepsin B in host cells (late endosomal pathway)	Teicoplanin (other glycopeptides including dalbavancin, oritavancin, and telavancin)
Enhancement of the anti-SARS-CoV-2 activity of hydroxychloroquine	Azithromycin



Numerous *in vitro* studies have shown that the spike protein of SARS-CoV is important in mediating viral entry into target cells. Furthermore, the cleavage and subsequent activation of the SARS-CoV spike protein by a protease of the host cell is absolutely essential for infectious viral entry.<sup>51</sup> Type II transmembrane serine protease TMPRSS2 was suggested to be an important host protease that cleaves and activates the SARS-CoV spike protein in cell cultures, and was thus explored as a potential antiviral agent.<sup>18</sup> In the past decade, the serine protease inhibitor camostat mesylate was shown to inhibit the enzymatic activity of TMPRSS2.<sup>52</sup> Additionally, the cysteine PI K11777 showed promising potency in inhibiting MERS-CoV and SARS-CoV replication within the sub-micromolar range.<sup>53</sup>

Use of stem cells against COVID-19 has been under evaluation in China recently. Additionally, tocilizumab (Roche Pharmaceuticals, Basel, Switzerland) is a monoclonal antibody that is used in the treatment of RA exacerbation. It was designed to inhibit the binding of interleukin-6 to its receptors, thus alleviating cytokine release syndrome. Currently, it is also being investigated for treatment of COVID-19.<sup>54</sup>

### Convalescent plasma

Convalescent plasma has also been used as a last resort to improve the survival rate of patients with various viral infections, such as SARS, H<sub>5</sub>N<sub>1</sub> avian influenza, pandemic 2009 influenza A H<sub>1</sub>N<sub>1</sub> (H<sub>1</sub>N<sub>1</sub> pdm09), and severe Ebola virus infection.<sup>55,56</sup> One possible explanation for the efficacy of convalescent plasma therapy is that the immunoglobulin antibodies in the plasma of patients recovering from viral infection might suppress viremia. Shen et al. (2020) reported on five critically ill patients with laboratory-confirmed COVID-19 and acute respiratory distress syndrome (ARDS) who received transfusion with convalescent plasma with a SARS-CoV-2-specific antibody (binding titer >1:1000 and neutralization titer >40). The convalescent plasma was obtained from 5 patients who recovered from COVID-19 and it was administered to the five enrolled patients between 10 and 22 days after admission. Antiviral agents and methylprednisolone were also administered. Following plasma transfusions, improvements in clinical condition were observed, including normalization of body temperature within 3 days (in 4/5 patients), decrease in Sequential Organ Failure Assessment score, rise in PaO<sub>2</sub>/FiO<sub>2</sub>, resolution of ARDS (4 patients at 12 days after transfusion), a success of weaning from mechanical ventilation (3 patients within 2 weeks of treatment), and decline in viral loads (became negative within 12 days) and increase in SARS-CoV-2-specific ELISA and neutralizing antibody titers. Of the 5 patients, 3 were discharged from the hospital (lengths of stay: 53, 51, and 55 days), while 2 were in stable condition at 37 days after transfusions.<sup>56</sup> The authors concluded that use of convalescent plasma transfusion is beneficial among patients infected with SARS-CoV-2, even though the sample number in this study is small.<sup>56</sup>

### Herbal medications

Based on the historical records and anecdotal evidence of SARS and H<sub>1</sub>N<sub>1</sub> pdm09 prevention, Chinese herbal drugs were also considered as an alternative approach for prevention of COVID-19 in high-risk populations. However, clinical evidence for these treatments in the prevention of this emerging viral infection is lacking.<sup>57,58</sup> During the COVID-19 outbreak in China, some traditional Chinese medicine was widely used, and the six most commonly used herbal medicines were *Astragali Radix* (Huangqi), *Glycyrrhizae Radix Et Rhizoma* (Gancao), *Saposhnikoviae Radix* (Fangfeng), *Attractylodis Macrocephalae Rhizoma* (Baizhu), *Lonicerae Japonicae Flos* and *Fructus forsythia* (Lianqiao). However, rigorous clinical trials on large populations should be conducted to confirm the potential preventive effect of Chinese medicine.<sup>57,58</sup>

### Antimicrobial agents for potential co-infection

The prevalence of co-infection varied among COVID-19 patients, ranging from 0% to 50% among non-survivors. Reported co-pathogens included bacteria, such as *Mycoplasma pneumoniae*, *Candida* species, and viruses (influenza, rhinovirus, coronavirus, and HIV). Influenza A virus was the commonest co-infective virus.<sup>59</sup> Co-administration of anti-influenza agents and anti-bacterial agents in patients with COVID-19 pneumonia was common.<sup>59</sup> Consequently, a cautious prescription of effective antibiotic(s) covering *Staphylococcus aureus* (including methicillin-resistant *S. aureus*), multidrug-resistant *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* as well as *Acinetobacter baumannii* species for patients undergoing long hospitalization (>6 days) is advised.<sup>60,61</sup>

### Other considerations and precautions regarding concomitant medication

Based on the research of Yang et al. (2020),<sup>62</sup> the most distinctive comorbidities among the non-survivors of COVID-19 in intensive care units were cerebrovascular disease and diabetes. Similar findings were also observed by Guan et al. (2020)<sup>63</sup>; these patients were usually treated with ACE inhibitors or angiotensin II type I receptor blockers (ARB). As mentioned above,<sup>5,12</sup> SARS-CoV-2 and SARS-CoV can bind to their target cells through ACE2 receptors expressed by the epithelial cells of lung, intestine and kidney.<sup>64</sup> Consequently, careful administration of an ACE inhibitor or ARB for patients with SARS-CoV infection in the absence of ARDS is advised.

Additionally, despite conflicting advice from the US Food and Drug Administration,<sup>65</sup> the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, was thought to be likely to result in an induction of increased ACE2 receptors.<sup>66</sup> For critically ill adults with COVID-19 who develop fever, acetaminophen might be a better choice for temperature control than NSAIDs.<sup>67</sup> Of note, according to a study by Wu et al. (2020), treatment of COVID-19 patients

with methylprednisolone was shown to decrease the case-fatality risk (HR, 0.38; 95% CI, 0.20–0.72).<sup>68</sup> However, the administered dose of methylprednisolone is not specified in that investigation. Despite a lack of supporting evidence, some critical care experts advocate the use of low-dose corticosteroid therapy in adults with COVID-19 and refractory shock (e.g., intravenous hydrocortisone 200 mg per day, as a “shock-reversal” strategy).<sup>68</sup>

Moreover, a recent report by Tang et al. (2020) demonstrated that anticoagulant therapy with heparin (mainly with low molecular weight heparin) was associated with better prognosis in severe COVID-19 patients. The 28-day mortality of heparin users was lower than that of non-users among patients with sepsis-induced coagulopathy scores  $\geq 4$  (40.0% vs. 64.2%,  $P = 0.029$ ), or D-dimer  $> 6$ -fold the upper limit of normal (32.8% vs. 52.4%,  $P = 0.017$ ).<sup>69</sup>

Finally, high ACE2 activity is associated with reduced severity of ARDS among patients with lower respiratory tract infection caused by RSV.<sup>70</sup> Fedson et al. (2016, 2020) observed that statins target the host response to infection (endothelial dysfunction) rather than the virus itself, and suggested that combination therapy with ARB and statins might accelerate a return to homeostasis, allowing patients to recover on their own.<sup>71,72</sup>

## Conclusions

In summary, we are facing a terrible virus with greater infectivity than the SARS-CoV pandemic of 2003. There is presently no vaccine or documented specific anti-SARS-CoV-2 drug regimen to treat critically ill patients. Most of the potential drugs for treatment of COVID-19 are being investigated for safety and efficacy against SARS-CoV-2. Remdesivir is the most promising agent. In addition, favipiravir and combination therapy with hydroxychloroquine plus azithromycin appear to be acceptable alternatives for treatment of COVID-19 patients. For patients with SARS-CoV-2 infection, ACE inhibitor and ARB need to be prescribed with caution. Compared with NSAIDs, acetaminophen might be a safer agent for treating fever in COVID-19 patients. Finally, low-dose steroid (hydrocortisone) might be prescribed for treatment of refractory shock in patients with COVID-19.

## Funding

No external funding.

## Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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