Review Article

Treatment options for COVID-19: The reality and challenges

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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).1–3 Numerous clinical SARS-CoV-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).4–7 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+ and CD8+ T-cell subsets at the early stage of this disease.1,8 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.5,9 Nevertheless, contrary to the SARS cases in 2003,10 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.5–11 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.5,9 Previous studies demonstrated that human coronavirus-NL63 (HCoV-NL63) is able to use angiotensin-converting enzyme-2 (ACE2) as a cell receptor in humans.12,13 Although children are considered to be significantly less susceptible to HCoV-NL63 infection and have milder disease severity than adults,1,5,8,13 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.14 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),15 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.15 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,16 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,17 resulting in premature termination of viral RNA transcription. Unlike other nucleotide analogues, remdesivir is a phosphoramidate produg 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]).18,19

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 μM) of active triphosphate form in peripheral blood mononuclear cells for at least 24 h,20 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.21 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, 2020.22 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-19,4,18 uncertainties about adverse effects (e.g., nausea, vomiting, rectal hemorrhage, and hepatic toxicity) and clinical efficacy of remdesivir have been reported recently.23

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. Furthermore, Brown et al. observed that remdesivir displayed half-maximum effective concentrations (EC_{50}s) of 0.069 μM for SARS-CoV, and 0.074 μM for MERS-CoV in tissue culture models. In addition, tissue culture experiments also revealed that many highly divergent CoVs including the endemic human CoVs (HCoV-OC43, HCoV-229E) and zoonotic CoV are effectively inhibited by remdesivir within the submicromolar EC_{50}s. 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. 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.

**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. After being converted into an active phosphoribosylated form, favipiravir is easily recognized as a substrate of viral RNA polymerase in many RNA viruses. 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. 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-β (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 μg/mL. However, it has the undesirable adverse effect of reducing hemoglobin, which is harmful for patients in respiratory distress.

**Interferons**

Treatment with interferon β (IFNb)-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 IFNb-1b for SARS patients remains uncertain.

**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. 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. 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)-IFNb combination therapy in a humanized transgenic mouse MERS-CoV infection model. They observed the efficacy of remdesivir was superior to that of LPV/RTV-IFNb against MERS-CoV in terms of viral load reduction and improvement in extent of pathologic change in lung tissue. 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.

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. 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. Ribavirin in combination with interferon-α 2b was shown to be active against MERS-CoV in a rhesus macaque model. Additionally, the regimen of LPV/RTV plus ribavirin was shown to be effective against SARS-CoV in patients and in tissue culture.

**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 H3N2 in an animal model. Chloroquine was shown to increase endosomal pH, which prevents virus/cell fusion. It also interferes with the glycosylation of cellular
Hydroxychloroquine is also proposed to control the cytokine storm that occurs in critically ill late phase SARS-CoV-2 infected patients. Hydroxychloroquine is significantly more potent than chloroquine in vitro (EC₅₀ 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. The Taiwan CDC declared hydroxychloroquine as an important anti-SARS-CoV-2 agent on 26 March, 2020. Of note, patients with concomitant conditions, such as diabetes, may be contraindicated for receiving hydroxychloroquine or who are pregnant or breastfeeding. Hydroxychloroquine prolongation in electrocardiograms, history of allergy to chloroquine or who are pregnant or breastfeeding are contraindicated for receiving hydroxychloroquine therapy. 

Azithromycin (Pfizer Inc., Manhattan, New York City, NY, USA) was shown to be active in vitro against Ebola viruses. Furthermore, azithromycin is thought to have good potential in preventing severe respiratory tract infections among pre-school children when it is administrated to patients suffering viral infection. 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. 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 (IC₅₀, 330 nM). Moreover, teicoplanin is able to block the MERS and SARS envelope pseudotyped viruses as well. 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. 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. Current efforts in developing monoclonal and polyclonal antibodies against coronaviruses mainly target MERS-CoV. For example, a human polyclonal antibody SAB-301 (50 mg/kg) that was generated in transchromosomic cattle was observed to be well tolerated and safe in healthy participants of a phase 1 clinical trial. 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.

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**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 pro tease of the host cell is absolutely essential for infectious viral entry. 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. In the past decade, the serine protease inhibitor camostat mesylate was shown to inhibit the enzymatic activity of TMPRSS2. Additionally, the cysteine PI K1777 showed promising potency in inhibiting MERS-CoV and SARS-CoV replication within the submicromolar range.

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.

**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, H1N1 avian influenza, pandemic 2009 influenza A H1N1 (H1N1 pdm09), and severe Ebola virus infection. 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 PaO2/FiO2, 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. 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.

**Herbal medications**

Based on the historical records and anecdotal evidence of SARS and H1N1 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. During the COVID-19 outbreak in China, some traditional Chinese medicine was widely used, and the six most commonly used herbal medicines were Astragalus Radix (Huangqi), Glycyrrhizae Radix Et Rhizoma (Gancao), Saposhnikoviae Radix (Fangfeng), Atractylodis Macrocephalae Rhizoma (Baizhu), Lonicerae Japonicae Flos and Fructus forsythia (Liangqiao). However, rigorous clinical trials on large populations should be conducted to confirm the potential preventive effect of Chinese medicine.

**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. Co-administration of anti-influenza agents and anti-bacterial agents in patients with COVID-19 pneumonia was common. 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.

**Other considerations and precautions regarding concomitant medication**

Based on the research of Yang et al. (2020), 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); these patients were usually treated with ACE inhibitors or angiotensin II type I receptor blockers (ARB). As mentioned above, 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. 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, 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. For critically ill adults with COVID-19 who develop fever, acetaminophen might be a better choice for temperature control than NSAIDs. 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). 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).68

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 ≥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).69

Finally, high ACE2 activity is associated with reduced severity of ARDS among patients with lower respiratory tract infection caused by RSV.70 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.71,72

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.

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 Mar 11. https://doi.org/10.1016/s0140-6736(20)30566-3. pii: S0140-6736(20)30566-3. [Epub ahead of print].

2. Cheng ZJ, Shan J. 2019 Novel coronavirus: where we are and what we know. Infection 2020 Feb 18. https://doi.org/10.1007/s15010-020-01401-y [Epub ahead of print].

3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020 Feb 24. https://doi.org/10.1001/jama.2020.2648 [Epub ahead of print].

4. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382:929–36. https://doi.org/10.1056/NEJMoa2001191.

5. Lee PI, Hu YL, Chen PY, Huang YC, Hsuheh PR. Are children less susceptible to COVID-19? J Microbiol Immunol Infect 2020 Feb 25. https://doi.org/10.1016/j.jmii.2020.02.011. pii: S1684-1182(20)30039-6. [Epub ahead of print].

6. Huang WH, Teng LC, Yeh TK, Chen YJ, Lo WJ, Wu MJ, et al. 2019 Novel coronavirus disease (COVID-19) in Taiwan: reports of two cases from Wuhan, China. J Microbiol Immunol Infect 2020;53:481–4. https://doi.org/10.1016/j.jmii.2020.02.009.

7. Burke RM, Midgley CM, Dratch A, Fenstersheib M, Haupt T, Holshue M, et al. Active monitoring of persons exposed to patients with confirmed COVID-19 - United States, January-February 2020. MMWR Morb Mortal Wkly Rep 2020;69:245–6.

8. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil-to-lymphocyte ratio predicts severe illness patients with 2019 novel coronavirus in the early stage. medRxiv 2020. https://doi.org/10.1101/2020.02.10.20021584.

9. Cao Q, Chen YC, Chen CL, Chiu CH. SARS-CoV-2 infection in children: transmission dynamics and clinical characteristics. J Formos Med Assoc 2020;119:670–3.

10. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003;361:1767–72. https://doi.org/10.1016/S0140-6736(03)13412-5.

11. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.

12. Hofmann H, Pyrc K, van der Hoek L, Geier M, Berkhout B, Pöhlmann S. Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. Proc Natl Acad Sci USA 2005;102:7988–93.

13. Lee KH, Yoo SG, Cho Y, Kwon DE, La Y, Han SH, et al. Characteristics of community-acquired respiratory viruses infections except seasonal influenza in transplant recipients and non-transplant critically ill patients. J Microbiol Immunol Infect 2019 Jun 19. https://doi.org/10.1016/j.jmii.2019.05.007. pii: S1684-1182(18)30233-0.

14. Lee PI, Hsuheh PR. Emerging threats from zoonotic coronaviruses—from SARS and MERS to 2019-nCoV. J Microbiol Immunol Infect 2020;53:365–7. https://doi.org/10.1016/j.jmii.2020.02.001.

15. To KW, Tsang TY, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis 2020 Mar 23. https://doi.org/10.1016/S1473-3099(20)30196-1.

16. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov 2020;19:149–50. https://doi.org/10.1038/s41573-020-00016-0.

17. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading
exoribonuclease. mBio. 2018;9. https://doi.org/10.1128/mBio.00221-18. pii: e00221-18.

18. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017;9. https://doi.org/10.1126/scitranslmed.aal3653. pii: eaal3653.

19. Martine MA. Compounds with therapeutic potential against novel respiratory 2019 coronavirus. Antimicrob Agents Chemother. 2020 Mar 9. https://doi.org/10.1128/AAC.00399-20. pii: AAC.00399-20.

20. Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature. 2016;531:381–5.

21. Mulangu S, Dodd RT, Davey Jr RT, Thiani Mbaya O, Proschan M, Mukan D, et al. A randomized, controlled trial of Ebola virus disease therapies. N Engl J Med 2019;381:2293–303.

22. Medrxiv News. from, https://times.hinet.net/mobile/news/22831665. [Accessed 20 March 2020].

23. Brown AJ, Won JJ, Graham RL, Dinnon 3rd KH, Sims AC, Green CE, et al. Early administration of remdesivir in severe COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020 Mar 17. https://doi.org/10.1016/j.ijantimicag.2020.105944. pii: S0883-9441(20)30390-7.

24. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017;9. https://doi.org/10.1126/scitranslmed.aal3653. pii: eaal3653.

25. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci USA 2020 Feb 13. https://doi.org/10.1073/pnas.1922083117. pii: 201922083.

26. Wang Y, Fan G, Salam A, Horby P, Salam A, Horby P, et al. Treatment with interferon-β2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. Nat Med 2013;19:1313–7.

27. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004;59:252–6.

28. Yen Y, Zou Z, Sun Y, Li X, Xu KF, Wei Y, et al. Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. Cell Res 2013;23:300–2.

29. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005;2:69. https://doi.org/10.1186/1743-422X-2-69.

30. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:629–71.

31. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einau S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care 2020 Mar 10. https://doi.org/10.1016/j.jcrc.2020.03.005. pii: S0883-9441(20)30390-7.

32. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. Nat Med 2013;19:1313–7.

33. Baden LR, Rubin EJ. COVID-19 - the search for effective therapy. N Engl J Med 2020 Mar 18. https://doi.org/10.1056/NEJMoa2001282.

34. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med 2020 Mar 18. https://doi.org/10.1056/NEJMoa2001282.

35. Falzarano D, de Wit E, Rasmussen AL, Feldmann F, Okumura A, Scott DP, et al. Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. Nat Med 2013;19:1313–7.

36. Beigel JH, Nam HH, Adams PL, Kaffert A, Ince WL, El-Kamary SS, et al. Advances in respiratory virus therapeutics - a meeting report from the 6th isirv Antiviral Group conference. Antivir Res 2019;167:45–67. https://doi.org/10.1016/j.antiviral.2019.04.006.

37. Cockrell AS, Yount BL, Scobey T, Jensen F, Douglas M, Beall A, et al. A mouse model for MERS coronavirus-induced acute respiratory distress syndrome. Nat Microbiol 2016;2:16226.
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acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. *J Virol* 2011;85:4122–34.

52. Kawase M, Shirato K, van der Hoek L, Taguchi F, Matsuyama S. Simultaneous treatment of human bronchial epithelial cells with serine and cysteine protease inhibitors prevents severe acute respiratory syndrome coronavirus entry. *J Virol* 2012;86:6537–45.

53. Zhou Y, Vedantham P, Lu K, Agudelo J, Carrion Jr R, Nunneley JW, et al. Protease inhibitors targeting coronavirus and filovirus entry. *J Virol* 2012;86:6537–45.

54. Zhen Y, Vedantham P, Lu K, Agudelo J, Carrion Jr R, Nunneley JW, et al. Protease inhibitors targeting coronavirus and filovirus entry. *J Virol* 2012;86:6537–45.

55. Zhou Y, Vedantham P, Lu K, Agudelo J, Carrion Jr R, Nunneley JW, et al. Protease inhibitors targeting coronavirus and filovirus entry. *J Virol* 2012;86:6537–45.

56. Zhou Y, Vedantham P, Lu K, Agudelo J, Carrion Jr R, Nunneley JW, et al. Protease inhibitors targeting coronavirus and filovirus entry. *J Virol* 2012;86:6537–45.

57. Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. *Crit Care* 2020;24:91.

58. Luo H, Tang QL, Shang YX, Liang SB, Yang M, Robinson N, et al. Can Chinese medicine be used for prevention of coronavirus disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs. *Chin J Integr Med* 2020 Feb 22. https://doi.org/10.1007/s11655-020-3192-6.

59. Lai CC, Wang CY, Hsueh PR. Co-infection among patients with COVID-19. (manuscript submitted).

60. Chou CC, Shen CF, Chen SJ, Chen HM, Wang YC, Chang WS, et al. Recommendations and guidelines for the treatment of pneumonia in Taiwan. *J Microbiol Immunol Infect* 2019;52:172–99. https://doi.org/10.1016/j.jmii.2018.11.004.

61. Jean SS, Chang YC, Lin WC, Lee WS, Hsueh PR, Hsu CW. Epidemiology, treatment, and prevention of nosocomial bacterial pneumonia. *J Clin Med* 2020;9:275. https://doi.org/10.3390/jcm9010275.

62. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020 Feb 24. https://doi.org/10.1016/S2213-2600(20)30079-5.

63. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020 Feb 28. https://doi.org/10.1056/NEJMoa2002032.

64. Fang L, Karakulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020 Mar 11. https://doi.org/10.1016/S2213-2600(20)30116-8.

65. FDA News. "No scientific evidence that NSAID use worsens COVID-19 symptoms." From: https://www.drugtopics.com/latest/fda-no-scientific-evidence-nsaid-use-worsens-covid-19-symptoms. [Accessed 24 March 2020].

66. Day M. COVID-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. *BMJ* 2020 Mar 17;368:m1086. https://doi.org/10.1136/bmj.m1086.

67. Society of Critical Care Medicine. COVID-19 Guidelines. From: https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19.

68. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020 Mar 13. https://doi.org/10.1001/jamainternmed.2020.0994.

69. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020 March 27. https://doi.org/10.1111/jth.14817.

70. Wösten-van Asperen RM, Bos AP, Bem RA, Dierdorp BS, Dekker T, van Goor H, et al. Imbalance between pulmonary angiotensin-converting enzyme and angiotensin-converting enzyme 2 activity in acute respiratory distress syndrome. *Pediatr Crit Care Med* 2013;14:e438–41. https://doi.org/10.1097/PCC.0b013e3182a55735.

71. Fedson DS. Treating the host response to emerging virus diseases: lessons learned from sepsis, pneumonia, influenza and Ebola. *Ann Transl Med* 2016;4:421. https://doi.org/10.21037/atm.2016.11.03.

72. Fedson DS, Opal SM, Rordam OM. Hiding in plain sight: an approach to treating patients with severe COVID-19 infection. *mBio* 2020;11. https://doi.org/10.1128/mBio.00398-20.