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Review

Controversial treatments: an updated understanding of the Coronavirus Disease 2019

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Abstract

An outbreak of severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) infection has posed significant threats to international health and the economy. In the absence of specific treatment for this virus, there is an urgent need to learn from the experience and lessons in China. To reduce the case-fatality rate among COVID-19 patients, we should not ignore the complications, such as RNAaemia, acute respiratory distress syndrome, and

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multiple organ dysfunction. To help understand the advantages and limitations of differential treatments, we provide a timely review and discuss the complications and corresponding major treatments, especially controversial ones such as antiviral therapy（remdesivir, ribavirin, chloroquine）, glucocorticoid therapy, extracorporeal support including an artificial liver system (ALS) and extracorporeal membrane oxygenation (ECMO), based on available evidence. As a result, we suggest that antiviral therapy and organ function support are vital to reduce mortality for mild patients and critical patients, respectively.

Keywords: coronavirus; SARS-CoV-2; COVID-19; literature review; pneumonia; treatment

1. Introduction

Coronavirus Disease 2019 (COVID-19) caused a large outbreak in China with a high human-to-human transmission rate (R0)[1] and case-fatality rate (approximately 2.67% to date) (Fig. 1-3), to which people are generally susceptible. More seriously, the epidemic continued to spread from China to Europe, North America, and other Asian countries, despite great efforts and an increasing number of people being cured in China. The World Health Organization (WHO) announced the SARS-CoV-2 epidemic as a public health emergency of international concern (PHEIC) on January 30, 2020, and raised the risk assessment of COVID-19 from "high" to "very high" at the global level on February 28, 2020[2]. The threat of global pandemics is real[3].

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Xiaobo Y et al. reported 52 critically ill adult patients with COVID-19 who could not survive the disease on February 21, 2020, most of whom faced organ function damage and needed extracorporeal support[4]. Zhongnan Hospital of Wuhan University reported 138 hospitalized patients with COVID-19; most of these patients received antiviral therapy (oseltamivir, 124 [89.9%]), glucocorticoid therapy (62 [44.9%]), and thirty-six patients (26.1%) were transferred to the intensive care unit (ICU). Of the 36 cases in the ICU, 15 (41.7%) received noninvasive ventilation, and 17 (47.2%) received invasive ventilation (4 were switched to extracorporeal membrane oxygenation)[5]. The China Medical Treatment Expert Group for SARS-CoV-2 reported that 55 (5.00%) of 1,099 laboratory-confirmed patients were admitted to the ICU and 15 (1.36%) succumbed. Severe pneumonia was independently associated with admission to the ICU, mechanical ventilation, or death[6].

To reduce the case-fatality rate and complication rate without registered treatment or a vaccine, there is an urgent need for healthcare workers worldwide to review and propose experience and lessons from critical COVID-19 patients in a timely manner. Given the treatments mentioned above, we will discuss antiviral therapy, glucocorticoid therapy, and extracorporeal support, including extracorporeal membrane oxygenation (ECMO) and artificial liver system (ALS) available for the treatment of COVID-19 based on current published evidence.

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2.1 Antiviral therapy

2.1.1 Remdesivir

Remdesivir (GS-5734) has broad-spectrum activities against viruses such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) in both cell and animal trials[7-10]. Additionally, research revealed that remdesivir could inhibit viral infection effectively in a human cell line (human liver cancer Huh-7 cells), which is susceptible to severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2)[11].

The mechanism of remdesivir against the virus showed that the drug effectively inhibited the EBOV RNA-dependent RNA polymerase (RdRp) complex[12, 13]. The remdesivir could form remdesivir triphosphate (remdesivir-TP) in vivo, which was incorporated into the newly synthesized RNA chain of the virus as the substrate of the virus RdRp, thereby interrupting the transcription of the virus[12]. Another study showed that remdesivir-TP could compete with adenosine triphosphate (ATP)[14]. After entering the cells, a monophosphoramidate prodrug of remdesivir transformed into triphosphate metabolite (NTP) in three steps, and NTP and ATP competed to bind viral RdRp. NTP was incorporated into the RNA synthesis chain, contributing to the termination of viral RNA synthesis and inhibiting RdRp enzyme activity[12].

In addition, remdesivir was used against a case of 2019 novel coronavirus, reported in N Engl J Med, leading to widespread interest[15]. In this case report, a patient with COVID-19 was treated by intravenous remdesivir without apparent adverse reactions on the evening of

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the 7th day of hospitalization. The patient's clinical symptoms improved on the 8th day after hospitalization (the 12th day after onset).

Phase III clinical trials of remdesivir had been completed for the treatment of Ebola virus infection with complete data on human pharmacokinetics and safety[16]. Recently, phase III randomized controlled trials were carried out to evaluate intravenous remdesivir for COVID-19 (NCT04252664 and NCT04257656), which will be completed in April 2020 and May 2020, respectively[17, 18]. Remdesivir (100 mg except for the first day of 200 mg) for ten days with placebo in the phase III trials, which were initiated in China, is worthy of concern about adverse reactions at this dose due to differences in ethnicity.

2.1.2 Ribavirin

Ribavirin is a broad-spectrum nucleoside antiviral drug that is phosphorylated in virus-infected cells, and its product acts as a competitive inhibitor of virus synthetase, interfering with early viral transcription events and hindering the synthesis of ribonucleoproteins, thereby hindering virus replication and spread.

In vitro，four studies observed antiviral effects against SARS[19-22], but the results from *Cinatl et al.* and *Stroher et al.* showed no evidence of an antiviral effect[23, 24]. Moreover, there was insufficient evidence of clinical effects after administration to SARS-infected patients[25, 26], and its side effects, such as hemolytic anemia[26-29], were found to be relatively strong in clinical applications, which should be given close attention during treatment for COVID-19. Additionally, in the case of ribavirin, the US Food and Drug Administration (FDA) approved

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its use for the treatment of human respiratory fusion virus (RSV) [30], particularly certain hemorrhagic fever. The FDA clearly stated that ribavirin was not suitable for the treatment of influenza and had strict indications.

During the COVID-19 epidemic, ribavirin was indicated for the general treatment of COVID-19 in Chinese treatment guidelines[31], and it is recommended that ribavirin is combined with interferon as antiviral therapy. According to cellular trials in SARS and MERS, reported by *Birgit Morgenstern et al.* and *Falzarano D et al.*, the dosage of ribavirin can be reduced when combined with interferon due to their synergistic effect[21, 32].

Overall, without domestic phase I and II clinical trials, ribavirin did not have statistical data on clinical safety and efficacy against syndrome-related coronavirus 2 specifically. Thus, the clinical treatment of safety and ethical problems is worthy of attention.

2.1.3 Chloroquine

The ability to interfere with virus infection and replication came from increasing the endosomal pH required for virus/cell fusion and immune-modulating activity along with widespread distribution throughout the whole body (including the lungs) in vivo[33, 34], and *Biot* et al. reported that chloroquine and its derivatives inhibit viral replication in vitro[35].

As a potent inhibitor of SARS-CoV in cell culture, *Keyaerts, E*. et al. reported that the IC50 of chloroquine for antiviral activity was significantly lower than its cytostatic activity, which approximated that the plasma concentrations of chloroquine reached the level of acute malaria treatment even up to 5 h after infection against SARS-CoV-infected Vero E6 cells[36].

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Chloroquine could also interfere with angiotensin converting enzyme 2 (ACE2), one of the binding sites for S protein, to inhibit SARS-CoV infection[37]. In vitro, the experiment also highlighted that chloroquine blocked COVID-19 virus infection at low-micromolar concentrations[34] with the possible mechanism of interfering with terminal glycosylation of the cellular receptor, angiotensin-converting enzyme 2, to negatively influence virus-receptor binding[38].

However, there are several limitations for further clinical application in patients. (1) Most of the current research has been limited to cell culture and the animal models, and potential adverse drug reactions, such as cardiotoxicity and irreversible retinopathy, should not be ignored[39]. The contraindications, relative contraindications, and pharmaceutical precautions are listed in supplementary table 1[40]. (2) A more clinical experiment must be supported to explicate the antiviral effect in patients infected with COVID-19. (3) After chloroquine is taken by oral administration, most of it is metabolized in the liver. Since it is excreted slowly and maintained in plasma with a half-life of 2.5 ~ 10 days, patients with liver dysfunction may be more likely to experience chloroquine accumulation in vivo. According to the Wuhan Institute of Virology, the lethal dose of chloroquine in adults is 2-4 g, and it is acute. The expert consensus on chloroquine phosphate recommended that it was suitable for adults aged 18 to 65 with the dose depending on the weight of the patient (Table 1)[39].

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Table 1. Usage and dosage recommended by the National Health Commission of China.

Weight (kg)	Usage and dosage	
	Days 1-2	**Days 3-7**
≤50	500 mg each time, 2 times/ d	500mg each time, 1 times/d
＞50	500 mg each time, 2 times/ d	500mg each time, 2 times/d

2.2 Corticosteroids

Corticosteroids have been widely used in the treatment of past coronavirus infections (such as SARS and MERS), and corticosteroids are also one of the methods for treating COVID-19[31, 41-43]. However, no evidence was found on the antiviral effect of corticosteroids alone in resisting SARS-CoV in vitro[25]. In addition, interim guidance from the WHO on the clinical management of suspected COVID-19 advised avoiding the use of corticosteroids unless indicated for another reason, given lack of their effectiveness[44], because corticosteroids may cause harm (avascular necrosis[45], psychosis[46], diabetes[47], and delayed viral clearance[48]), as reported by some studies. Moreover, an article published by *JKB* et al. recently in *the Lancet* does not recommend the use of corticosteroids in treating COVID-19[49]. Additionally, the study reported that 16 patients (44%) with arrhythmia among the 36 severe patients diagnosed with COVID-19[5], and another study showed that the proportion of acute cardiac injury in COVID-19 could reach 12%[42]. Moreover, severe patients might have multiple organ dysfunction (MOD), such as shock, acute respiratory distress syndrome

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(ARDS), acute heart injury, acute kidney injury and even death[42]. MOD could be due to the cytokine storm, because the discovery that T cell excessive activation in pathologic examinations of COVID-19 with multiple organ failure by the team of Fu-Sheng Wang[50] and a similar cytokine storm reported by Huang C[42]. Hence, it was suggested to use appropriate corticosteroids for patients suffering from ARDS[51]. Furthermore, pathological studies of COVID-19 observed pulmonary edema and hyaline membrane formation, implying that timely use of corticosteroids is necessary for severe patients[50], which was also supported by retrospective pathologic examinations showing edema, and proteinaceous exudate with globules in the lungs of two patients with COVID-19[52].

2.3 Artificial liver system

The Artificial liver system (ALS) is one of an effective method for treating liver failure[53], and its treatment mechanism is based on liver cell regeneration ability. Through a extracorporeal equipment, ALS removes all kinds of harmful substances, supplements necessary material, improves the internal environment, and temporarily replaces part of liver function, to create good conditions for the regeneration of liver cells or while waiting for an opportunity for liver transplantation[54]. Among the three types (non-biological, biological and hybrid) of artificial liver support systems, artificial extracorporeal liver support therapy has been widely used in acute liver failure and has been proven to improve survival[55]. As mentioned above, cytokine storm was associated with disease severity reported by a study, which illustrated that GCSF, IP10, MCP1, MIP1A, and TNFα were found to be higher in

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patients who require ICU admission[42]. Moreover, a retrospective study including 99 patients with COVID-19 showed that 17 patients suffered acute respiratory distress syndrome, and among them,11 patients progressed rapidly and eventually died of multiple organ failure[51]. In these death cases, timely treatment of critical cases is of vital significance[51]. In China, Lan Juan Li initially treated severe patients with an artificial liver system called Li-ALS to eliminate inflammatory factors[56]. Plasma exchange and continuous venovenous hemofiltration are the main components of the function of Li-ALS, which is the treatment for severe patients with H7N9 virus infection when they worsen in a short period and a cytokine storm is detected[57, 58]. Additionally, potential complications such as hemorrhage, coagulation, hypotension, secondary infection, allergic reaction, disequilibrium syndrome and so on should be fully evaluated and prevented before ALS treatment is applied to any patient [54]. Hence, once a cytokine storm was found in COVID-19, extracorporeal blood purification techniques, including ALS, can be considered if conditions permit.

2.4 ECMO

A multicenter retrospective cohort study, conducted at 20 hospitals in 2017, reported that ECMO was effective at improving oxygenation and ventilation of patients with H7N9 induced severe ARDS[59]. A similar result of the positive effects of ECMO occurred in Australia and New Zealand during the H1N1 epidemic in 2009[60]. As a bridge between recovery and septic shock, ECMO provides temporary respiratory circulation support to reduce ventilator parameters and avoid ventilator related pressure and volume injuries. It can partially replace

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myocardial function during the development of sepsis, improve peripheral perfusion and oxygenation, and provide an opportunity for primary disease treatment[61].

However, it is not a treatment for the virus, but a means of life support with many limitations. (1) Related accidents and complications may occur, including bleeding, infection, hemolysis, thrombosis, limb ischemia, multiple organ failure, and even life-threatening complications in severe cases[61]. Some complications are hard to avoid, and we should pay attention to prevention and early management to prevent the condition of patients with COVID-19 from detrimentally worsening. (2) Applying ECMO to each patient is costly due to the high manufacturing cost, high operation cost and requirement for a specialist multidisciplinary team. (3) There are only approximately 400 ECMO devices in China, according to the People's Daily. Therefore, critically ill patients with no underlying disease would be preferred.

3. Conclusion

Coronavirus infection is a major public health problem worldwide and is mainly caused by respiratory infections including influenza and other acute respiratory viral diseases. It is estimated that lower respiratory infections cause more than four million deaths each year, approximately 40% of which are caused by respiratory viruses[62]. Both MERS-CoV and SARS-CoV have been known to cause severe illness in people, and now an outbreak of COVID-19 has occurred.

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This review will help understand the advantages and limitations of differential treatments. In this review, we summarize and discuss the controversial treatments that correspond to complications of critical COVID-19 patients. Without any specific antiviral treatments for SARS-CoV-2 currently, some may be effective, while others are in clinical trials or are being investigated in vitro studies. Remdesivir has shown antiviral activity against MERS and SARS at the cellular level and in animal models, as well as anti-SARS-CoV-2 activity in vitro, and it can be used as a potential 2019 novel coronavirus drug. Ribavirin is a broad-spectrum nucleoside antiviral drug; however, the clinical effects are unclear, and side effects should be considered. Regarding chloroquine, there were 15 interventional studies and its derivatives were prospectively registered in the Chinese Clinical Trial Registry (ChiCTR); and further observations need to be evaluated regarding antiviral effect and recommended dose in patients infected with COVID-19. In addition to antiviral drugs, glucocorticoids should be used carefully and in a timely manner in patients with COVID-19. Extracorporeal support (ALS and ECMO) should be considered under strict indications and contraindications; otherwise, the waste of resources and additional complications will be enormous. ECMO may be used more aggressively and many more ECMO devices could be transferred to Hubei Province in the future due to the temporary absence of effective antiviral drugs and the hope of reducing mortality. In conclusion, antiviral therapy and organ function support are most effective in reducing the mortality rate in patients with mild syndrome and patients in critical condition respectively.

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List of abbreviation

Coronavirus Disease 2019 (COVID-19), World Health Organization (WHO), public health emergency of international concern (PHEIC), intensive care unit (ICU), extracorporeal membrane oxygenation (ECMO), Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), RNA-dependent RNA polymerase (RdRp), remdesivir triphosphate (remdesivir-TP), adenosine triphosphate (ATP), triphosphate metabolite (NTP), human respiratory fusion virus (RSV), multiple organ dysfunction (MOD), acute respiratory distress syndrome (ARDS)

Figure legends

Figure 1. The existing confirmed and suspected number of cases of Coronavirus Disease 2019 (COVID-19) in China. On 17 February 2020, the total number of existing cases reached its peak and declined gradually. As of 2 March 2020, the total number of confirmed cases and deaths reached 80,174 and 2915, respectively. 74,185 and 2004, respectively. WHO： The World Health Organization; PHEIC： PUBLIC HEALTH EMERGENCY OF INTERNATIONAL CONCERN.

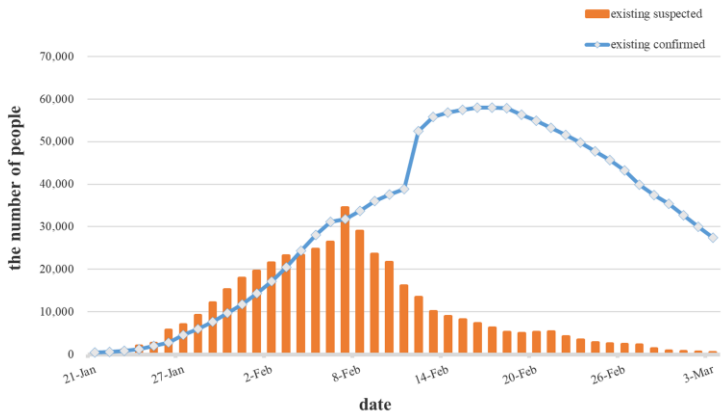

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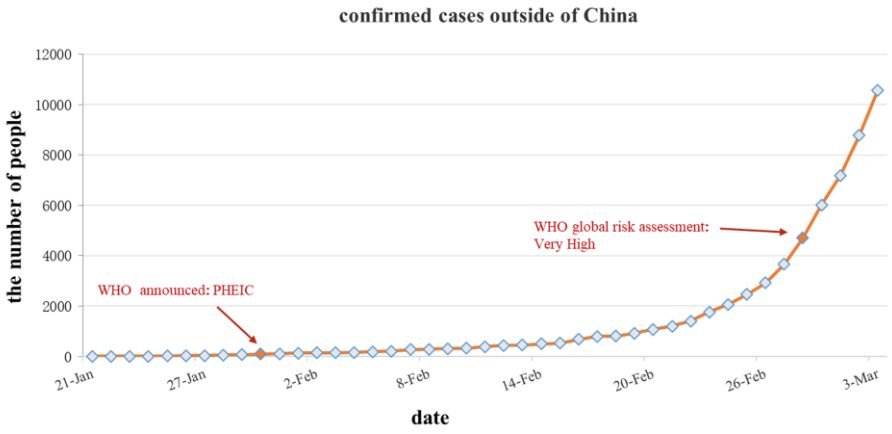
Figure 2. The new confirmed cases outside of China started to increase gradually after February 21.

Figure 3. The confirmed cases outside of China.



Competing interests

On behalf of all authors, the corresponding author states that there are no competing interests.

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Table 2 Mechanism, advantages and limitations for the treatments in this study

	Mechanism	Advantages	Limitations
Remdesivir	1. Interrupting the transcription of the virus and inhibiting RdRp enzyme activity	1. Inhibiting RNA virus replication in cells without obvious cytotoxicity in vitro 2. A higher competitive affinity to RdRp enzyme than adenosine triphosphate 3. A complete data on human pharmacokinetics and safety for infection of Ebola virus	1. Lack of phase I and II clinical data against 2019 novel coronavirus 2. The possible adverse reactions caused at this dose (100 mg except for the first day of 200 mg) due to differences in ethnicity
Ribavirin	1. Interfering with viral transcription	1. A broad-spectrum nucleoside antiviral drug	1. Major side effect: hemolytic anemia

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	events and hindering the synthesis of ribonucleoproteins	2. Low-cost	2. Lack of domestic phase I and II clinical data against 2019 novel coronavirus 3. Insufficient evidence of clinical effects after being applied to SARS-infected patients
Chloroquine	1. Reducing the infectivity of virions by increasing the endosomal pH 2. Interfere with terminal glycosylation of ACE2 3. Mediating the inflammatory complications of several viral diseases 4. Inhibiting viral replication in vitro for SARS-CoV	1. A potent inhibitor of SARS-CoV in cell culture 2. Recommended by experts in China based on clinical trials from more than 10 hospitals	1. Limited to the cell culture and the animal models 2. Potential adverse drug reactions such as cardiotoxicity and irreversible retinopathy should not be ignored 3. Attentions of the contraindications and precautions 4. Lethal dose may occur because of chloroquine accumulation
Corticosteroids	1. Anti-inflammatory action and immunomodulatory effect	1. Inhibiting the production of inflammatory cytokines which may cause cytokine storm 2. Supplement with endogenous cortisol deficiency	1. Delaying viral clearance 2. Side effect: avascular necrosis, psychosis, diabetes, secondary infection 3. Without evidence on the antiviral effect of corticosteroids

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Table 2 (continued) Mechanism, advantages and limitations for the treatments in this study

	Mechanism	Advantages	Limitations
Artificial liver system	1.Plasma exchange and continuous venovenous hemofiltration	1. Removing inflammatory cytokines to interrupt cytokine storm 2. Supplement with necessary material to create good conditions against infection 3. Improving the internal environment to wait for generating antibody	1. Related complications: hemorrhage, coagulation, hypotension, secondary infection, allergic reaction, and disequilibrium syndrome 2. High cost and requirement for a specialist multidisciplinary team
ECMO	1. Cardiac and respiratory support	1. Reduce ventilator parameters and avoid ventilator related pressure and volume injuries 2. Improving oxygenation and ventilation of patients with H7N9 induced severe ARDS	1. Related accidents and complications, including bleeding, infection, hemolysis, thrombosis, limb ischemia, multiple organ failure, and even life-threatening in severe cases 2. High manufacturing cost, high operation cost and requirement for a specialist multidisciplinary team

Notes: ECMO extracorporeal membrane oxygenation, ACE2 angiotensin converting enzyme 2

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