



Introduction to Novel Coronavirus Disease 2019 (COVID-19), It's Impact and Treatments under Investigation

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ABSTRACT

Aims: This study aimed to provide more information about the influence of Coronavirus Disease 2019 (COVID-19) on infected individuals. The symptoms, conditions, and treatments used may be served as important clues to find out potential medications.

Materials & Methods: Various current papers were reviewed, and the findings were summarized. In addition, other diseases such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which have similar causes or symptoms in patients, were investigated.

Findings: The most common symptoms in infected patients were fever (98%), dry cough (76%), and dyspnoea (55%). Mechanical ventilation was the main supportive treatment for ICU patients, and the mortality rate of patients with chronic diseases in the intensive care unit (ICU) was high (55%). The virus is highly contagious compared to the previous *Betacoronaviruses* causing epidemic, but its mortality rate is lower so that most of the infected patients studied had minor symptoms or were asymptomatic. Several treatments, such as antiviral agents and antimalarial drugs, are presently being proposed and tested, but none have yet been proven to be effective.

Conclusions: Seniors and patients with chronic diseases are at higher risk of COVID-19 induced severe consequences and mortality. Currently, supportive treatment is the mainstay for severely ill patients.

Keywords: COVID-19, Coronavirus, SARS, MERS.

CITATION LINKS

- [1] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID19-) outbreak. *J Autoimmun.* 109:102433 ;2020. Huang C, Wang [2] Huang C, Wang Y, Li X, Ren L, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, [3] World Health Organization. Novel Coronavirus (-2019nCoV) situation reports. Situation ... [4] World Health Organization. Novel Coronavirus (-2019nCoV) situation reports. Situation reports – 63. WHO; 2020. Available [5] Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, Carter LJ, et al. Research and development [6] Li F. Structure, function, and evolution of Coronavirus ... [7] Wang C, Horby PW, Hayden FG, Gao GF. A novel Coronavirus outbreak of .. [8] Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, et al. A SARS-CoV2- human protein-protein interaction . [9] Fang L, Karakiulakis G, Roth M. Are ... [10] Bandyopadhyay A, Chatterjee D, Ghosh K, Sarkar P. COVID 19: An epidemiological and host ... [11] Abdulmir AS, Hafidh RR. The possible immunological pathways for the variable ... [12] Xu Z, Li S, Tian S, Li H, Kong L. Full spectrum of COVID19- severity still ... [13] The Lancet. Emerging understandings of ... [14] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ... [15] Liu K, Chen Y, Lin R., Han K. Clinical ... [16] Tian S, Hu S, Niu L, Xu H, Xiao S. Plumonary ... [17] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early ... [18] Kluge S, Janssens U, Welte T, Weber-Carstens S, Marx G, Karagiannidis C. German ... [19] Nishimura M. High-flow nasal cannula oxygen therapy in adults: Physiological benefits, indication, clinical benefits, and ... [20] Pham T, Brochard L, Slutsky S. Mechanical ventilation: State of the ... [21] Saey T. Repurposed remedies for coronavirus. *Science* ... [22] Sarma P, Prajapat M, Avti P, Kaur H, Kumar S, Medhi B. Therapeutic ... [23] Sheahan TP, Sims AC, Leist SR, Schafer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nature Communications* ... [24] Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID19-? *Int J Antimicrob Agents* ... [25] Sahraei Z, Shabani M, Shokouhi S, Saffaei A. Aminoquinolines against coronavirus disease 2019 (COVID19-): Chloroquine or hydroxychloroquine. *Int J Antimicrob Agents* ... [26] Dong C, Ni L, Ye F, Chen ML, Feng Y, Deng YQ, et al. Characterization of ... [27] Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate ... [28] Arabi M, Allothman A, Balkhy HH, Al-Dawood A, AlJohani S, Al Harbi S, et al. Treatment of ... [29] Kim U, Won E, Kee S, Jung S, Jang H. Combination ... [30] Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically

Introduction

In December 2019, a series of pneumonia of an unknown cause emerged in Wuhan, China. This respiratory disease was later named Novel Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Feb 2020. The virus was named by the International Committee on Taxonomy (ICTV) because it was related and very similar to SARS-CoV, which caused the *Betacoronavirus* SARS epidemic in 2003. It was confirmed to be able to transmit from person-to-person through direct contact and droplets of coughing and sneezing [1]. On Jan 2, 2020, the number of confirmed infected cases of COVID-19 was 41 cases in Wuhan, China [2]. But since then, it has spread across the world quickly, affecting more than 100 countries; as of April 07, 2020, there were 1,279,722 known infected cases globally, and 72,614 people had died [3-4]. This indicates an increase of several thousand folds in the disease rate within 3 months, suggesting that it is spreading more efficiently than severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) as a more contagious coronavirus outbreak. The lives of millions of people have also been affected by mandatory isolation or quarantine to reduce further spread of the disease, and it is very challenging for global health systems and would have devastating consequences for the global economy [5].

More information is hoped to obtain about the influence of COVID-19 on infected individuals. By understanding the symptoms of the disease and the treatments used, it is possible to find out important clues to provide effective treatment for patients. Also, recognizing how SARS-CoV-2 enters the human body is helpful to come up with successful prevention of the disease further transmission.

Structure of SARS-CoV-2

SARS-CoV-2 is a type of coronavirus, belonging to the order *Nidovirales*, family *Coronaviridae*, and genus *Betacoronavirus* [6]. SARS-CoV-2 has a high mutation rate due to its inherent RNA virus features [7]. Coronaviruses possess single-stranded RNA surrounded by an envelope, which are the largest genomes among all RNA viruses. *Betacoronaviruses* could infect mammals, such as SARS-CoV and MERS-CoV, both of which caused epidemics in the past two decades with high mortality rates [2]. SARS-CoV-like coronaviruses have been found on bats; however, some of which could infect human cells [6].

The structure of SARS-CoV-2 consists of several proteins: genome includes nucleocapsid protein (N), membrane protein (M), envelope protein (E), and spike protein (S). Membrane protein and envelope protein are involved during virus assembly, and spike protein is used during virus entry into the host cells [8]. The spike protein consists of three segments, including a large ectodomain consisting of a receptor-binding subunit S1 and a membrane-fusion subunit S2, a single-pass transmembrane anchor, and a short tail. After binding to the host cell, S1 binds to the receptors for attachment, and S2 fuses the membranes of the host and virus together during viral entry [8].

It has been shown that coronavirus binds to the angiotensin-converting enzyme 2 (ACE2) proteins in the human body, located in the epithelial cells of the lungs, intestine, kidney, and blood vessels [9]. The binding affinity of SARS-CoV-2 S protein to ACE2 protein is about 10 to 20 times higher than that of SARS-CoV, which may contribute to the high transmissibility of SARS-CoV-2 [5]. There is a positive correlation between ACE2 protein expression and the SARS-CoV-2 infection [10]. The number of infected patients with COVID-19 on March 23, 2020

was reported to be 332, 930 cases, while the number of cases recorded for MERS and SARS was 2494 and 8096, respectively [7].

Symptoms of COVID-19

Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 attacks the lower respiratory system of the human body, causing viral pneumonia. SARS-CoV-2 infection may also lead to multiple organs failure as the virus attacks the gastrointestinal system, heart, kidney, and the central nervous system [6]. The severity of illness in patients infected by SARS-CoV-2 ranges from mild to critical, so that 85% experience mild to moderate infection, 10% experience severe infection, and 5% experience critical conditions [11-12]. The common symptoms are fever (98%), dry cough (76%), and dyspnoea (55%). Since the initial cases were observed in Wuhan, China, all patients have had viral pneumonia, and around 33% have developed acute respiratory distress syndrome (ARDS) and required intensive care [13]. All patients have had abnormal chest CT scans with subsegmental areas of consolidation as well as bilateral multiple lobular in ICU patients and bilateral ground-glass opacity in non-ICU patients. The concentration of cytokines Granulocyte-colony stimulating factor (GCSF), Interferon gamma-induced protein 10 (IP10), Macrophage inflammatory proteins (MIP1 and MIP1A), and Tumor necrosis factor (TNF α) has been higher in ICU patients than in non-ICU patients, suggesting that cytokine storm is related to the disease severity [2, 11].

Although the mortality rate of COVID-19 was around 4.35% (14510/332930) on March 23, 2020, the actual mortality rate may have been lower because many cases with mild symptoms and asymptomatic patients are not tested due to limited medical resources. Older people with comorbidities are at higher risk of developing a critical illness or dying if infected [14-15]. From late December

to Jan 26, 2020, out of 710 infected patients in Wuhan, China, 52 cases were admitted to ICU. The mean age of the ICU patients was 59.7 years, and at least half (52%) of them were over 60 years old. Around 40% (21/52) of the patients had chronic diseases, and all died after 28 days [14]. Most patients had damage to other organs function: 67% had ARDS, 29% had acute kidney injury, 23% had cardiac injury, and 29% had liver dysfunction. Lymphocytopenia was also found in more than 80% of the critically ill patients (Table 1). In severely ill patients, damage to the lung tissues is the result of severe inflammation rather than the direct result of viral infection [11, 16]. The immune system of elderly and weak patients with comorbidities is unable to prevent the spread of SARS-CoV-2 infection to their lower respiratory system and eventually to their alveoli, leading to severe pneumonia [11]. SARS-CoV-2 infection is less common and milder in children and teenagers, perhaps due to the lack of a strong cell-mediated immune system attack [17].

Current and Potential Treatments under Investigation

Antibiotics, broad -spectrum antiviral drugs, and corticosteroid therapy are currently given to the patients; however, corticosteroids were found to have no effect on mortality but instead delay viral clearance in patients [2]. Steroids were also found in SARS and influenza studies to promote possible infections [18]. The mainstay of treatment is supportive care since no treatment has yet been found to be effective, and mechanical ventilation is the main supportive treatment for ICU patients. Surviving patients are commonly given high-flow nasal cannula for respiratory support, which sends heated and humidified gas, reduces nasal airway resistance, and reduces the frequency of breathing [19]. On the other hand, non-surviving patients are

Table 1) Characteristics of Betacoronavirus SARS-CoV-2, MERS-CoV, and SARS-CoV patients. Adapted from Wang et al. (2020), table section. *Data of Jan 23, 2020

	SARS-CoV-2	MERS-CoV	SARS-CoV
Date	Dec, 2019	Jun, 2012	Nov, 2002
Location of first detection	Wuhan, China	Jeddah, Saudi Arabia	Guangdong, China
Male : Female sex ratio	2.7 : 1	3.3 : 1	1 : 1.25
Confirmed case	835*	2494	8096
Mortality	25 (2.9%)*	858 (37%)	744 (10%)
Fever	98%	98%	99-100%
Dry cough	76%	47%	29-75%
Dyspnoea	55%	72%	40-42%
Ventilation support	9.8%	80%	14-20%

given mechanical ventilation as a short-term lifesaving mechanism for respiratory failure [20]. $\text{PaO}_2/\text{FiO}_2$ ratio is found to be significantly lower in non-surviving than in surviving ICU patients, and they are more likely to develop ARDS (81% vs 45%) as well as to require mechanical ventilation (94% vs 35%), suggesting that there is a correlation between $\text{PaO}_2/\text{FiO}_2$ ratio and the severity of the illness, which could also be served as an effective indicator for prognosis. Non-surviving patients are also at higher risk of developing comorbidities than surviving patients and therefore require more medical intervention (Table 2). This may be due to the strong immune system attacks in non-surviving patients after their inability to prevent the spread of SARS-CoV-2 infection to the lower respiratory system and then to other parts of the body [11].

Antiviral drugs given to the patients include oseltamivir, lopinavir, and ritonavir [1]. Oseltamivir is a neuraminidase inhibitor used against influenza and MERS-CoV, lopinavir and ritonavir are both protease inhibitor preventing the cleavage of viral

polyproteins, which are effective in human immunodeficiency virus (HIV) and MERS-CoV treatment [14]. Despite their promising effects on other diseases, no compelling outcome has been obtained for the treatment of COVID-19 since Feb 7 [21]. Lopinavir and ritonavir were found to reduce MERS-CoV replication, but there is no indication showing that they reduce acute lung injury features [17]. Another antiviral agent used is ribavirin, it was successful at neutralizing SARS-CoV with corticosteroid treatment, but no in vitro experiment has yet proven that it is effective against SARS-CoV-2 [22]. These antiviral treatments are suggested to be administered as a part of compassionate program after careful evaluation of risks and benefits for each individual patient [18]. Additionally, aminoquinoline, a common antimalarial drug, is also being used as a potential medication for COVID-19 as it had promising effects during the SARS outbreak. Chloroquine and hydroxychloroquine are not only effective in treating malaria but could also be used for autoimmune diseases as well as controlling inflammatory

Table 2) Differences in intensive care measures, comorbidities, and treatments between survivor and non-survivor ICU patients. Adapted from Yang et al. (2020), table section. Data of Feb 21, 2020

Intensive Care Measures	Survivors (n=20)	Non-Survivors (n = 32)
PaO ₂ /FiO ₂ ratio (mmHg)	100.0	62.5
Platelet count (x10 ⁹ /L)	164	191
Comorbidities		
ARDS	9 (45%)	26 (81%)
Acute kidney injury	3 (15%)	12 (37.5%)
Cardiac injury	3 (15%)	9 (28%)
Liver dysfunction	6 (30%)	9 (28%)
Treatment		
High flow nasal cannula	17 (85%)	16 (50%)
Mechanical ventilation	7 (35%)	30 (94%)
ECMO	1 (5%)	5 (16%)
Renal replacement therapy	1 (5%)	8 (25%)
Immunoglobulin	9 (45%)	19 (59%)

response against viral infections by inhibiting virus replication cycle [24]. They alter protein degradation pathway in lysosomes, macromolecule synthesis in endosomes as well as post-translational protein modification in the Golgi apparatus as they increase the pH level of intracellular vacuoles [24]. They also interfere with antigen processing in antigen-presenting cells and alter the glycosylation of cellular receptors of coronavirus. Chloroquine has more clinical data, stronger effects, but higher toxicity and is less common in some countries. It also has greater negative effects and interacts with other antiviral agents such as lopinavir and ritonavir, causing prolongation of the QT

interval [25]. This makes hydroxychloroquine as another probable choice capable of long-term treatment with a high dose, which could be used in countries facing with shortage of Chloroquine [25].

The increase in ACE2 protein in the body also increases the infection risk due to the fact that SARS-CoV-2 S protein has a high affinity to bind to ACE2 protein. Patients with Type 1 or 2 diabetes and hypertension are at higher risk since ACE inhibitors and angiotensin II type-1 receptor blockers (ARBs) used increase ACE2 protein in the patients [10, 12]. Other treatments with thiazolidinediones and ibuprofen also increase ACE2 proteins, which could have

severe or fatal consequences for infected patients. It has been suggested that antihypertensive calcium channel blockers do not increase ACE2 expression or activity and could be considered as a possible alternative treatment. Existing antibodies against the receptor-binding domain (RBD) of the S protein, which binds to ACE 2 proteins, may also help neutralize SARS-CoV-2 infection [26].

Moreover, Gordon et al. (2020) identified 66 druggable human proteins or host factors that could be targeted by 69 existing drugs approved by FDA. A few of the targeted proteins and their drug candidates are listed in Table 3. They also suggested that RNA-dependent RNA polymerase (RdRp) inhibitor Remdesivir and repurposed host-directed compounds inhibiting the human protease (TMPRSS2) have great potential against SARS-CoV-2 infection. Remdesivir is currently under investigation in clinical trials after exhibiting compelling effects on at least 2 infected patients [5]. Both in vivo and in vitro, Remdesivir therapy has been shown to be more effective than lopinavir and ritonavir in improving pulmonary function and diminishing signs of acute lung injury [23]. A cohort of severely ill patients was given at least a dose of Remdesivir by March 7, 2020, most patients showed improvement (68%), while some had worse conditions

(15%) [27]. Though the mortality rate of patients receiving invasive ventilation was higher than that of patients not receiving invasive ventilation, there was observable improvement as 57% of the patients with invasive ventilation were extubated during follow-up [27]. Even with its potent effect, the use of Remdesivir to treat COVID-19 has not yet been licensed globally due to insufficient practical evidence [21]. Lopinavir, ritonavir, ribavirin, and interferon were used in combination therapy to treat patients with MERS [28-29]. The combination of ribavirin and interferon-alpha is the most common treatment for human CoV infections, yet the results are inconsistent, and ribavirin may cause various side effects such as kidney and liver dysfunction [29].

Besides, the observation of discharged patients who are virus-free also provides a great insight towards developing possible treatment. SARS-CoV-2 specific humoral and cellular immunity are both found in COVID-19 patients, suggesting that both are involved in immune-mediated protection against viral infection [26]. Immunoglobulin G (IgG) and Immunoglobulin M (IgM) responses towards N protein and RBD of S protein (S-RBD) of SARS-CoV-2 are more obvious in the newly discharged patients than in healthy individual, suggesting that they serve as antigens for humoral immunity. This finding also shows that S-RBD is a promising target in

Table 3) Target proteins, their functions, and potential drug candidates. Adapted from Liu et al. (2020), table section. Data of Mar 12, 2020

Target Protein	Function during Viral Infection	Drug Candidate
RdRp (RNA-dependent RNA polymerase)	Replicating SARS-CoV-2 genome	Remdesivir, Ribavirin
TMPRSS2 (Transmembrane protease, serine 2)	Host cell proteases that facilitate binding of S-protein of SARS-CoV-2 to host ACE2	Camostat mesylate
ACE2 (Angiotensin-converting enzyme 2)	Host receptor protein that binds to S protein of SARS-CoV-2	Arbidol
3CLpro (Coronavirus main protease)	Enzyme catalyzes breakdown of SARS-CoV-2 polyprotein into functional units	Lopinavir
PLpro (Papain-like protease)	Enzyme catalyzes breakdown of SARS-CoV-2 polyprotein into functional units	Lopinavir

SARS-CoV-2, which blocks the receptors during viral entry and induces cell immune response. Convalescent plasma with SARS-CoV-2-specific IgG antibody was given to some critically ill patients as an alternate treatment for continuous ARDS and viral progression, even with antiviral agents. All 5 patients with the age range of 36–65 years received mechanical ventilation and antiviral agents and showed improvement upon receiving convalescent plasma, they were either discharged or remained in stable conditions for 37 days after transfusion^[30]. Though the sample size was limited, convalescent plasma could be considered as another potential treatment for severely ill patients with SARS-CoV-2.

Conclusion

This study suggests that although COVID-19 is a highly contagious *Betacoronavirus* disease, its mortality rate is considerably low compared to SARS and MERS. The infected individuals could experience a range of manifestations from asymptomatic to having fever, cough, and dyspnoea, ranging from mild to severe. Senior patients and patients with chronic diseases are significantly at higher risk of being admitted to ICU or even death. Currently, there are various potential treatments that have been proposed to target SARS-CoV-2, but none have yet been proven to be effective in a larger population. However, there are still possibilities that could shed light on the potential solutions for the current challenges. As countries attempt to reopen their centers after lockdown for fear of economic recession, it is essential to operate safely and take precaution measures to limit the impact of infection possible second wave.

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References

1. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun.* 2020; 109:102433. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020; 395(10223): 497–506.
2. World Health Organization. Novel Coronavirus (2019-nCoV) situation reports. Situation Reports – 1. WHO; 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200121-sitrep-1-2019-ncov.pdf?sfvrsn=20a99c10_4
3. World Health Organization. Novel Coronavirus (2019-nCoV) situation reports. Situation reports – 63. WHO; 2020. Available from https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200407-sitrep-78-covid-19.pdf?sfvrsn=bc43e1b_2
4. Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, Carter LJ, et al. Research and development on therapeutic agents and vaccines for COVID-19 and related human Coronavirus diseases. *ACS Cent Sci.* 2020; 6(3):315–31.
5. Li F. Structure, function, and evolution of Coronavirus spike proteins. *Annu Rev Virol.* 2016; 3: 237–61.
6. Wang C, Horby PW, Hayden FG, Gao GF. A novel Coronavirus outbreak of global health concern. *Lancet.* 2020; 395(10223), 470–3.
7. Gordon DE, Jang GM, Bouhaddou M, Xu

- J, Obernier K, O'Meara MJ, et al. A SARS-CoV-2 human protein-protein interaction map reveals drug targets and potential drug-repurposing. *bioRxiv*. 2020.
8. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020; 8(4):e21.
 9. Bandyopadhyay A, Chatterjee D, Ghosh K, Sarkar P. COVID 19: An epidemiological and host genetics appraisal. *Asian J Med Sci*. 2020; 11(3), 71-6.
 10. Abdulmir AS, Hafidh RR. The possible immunological pathways for the variable immunopathogenesis of COVID—19 infections among healthy adults, elderly, and children. *Electron J Gen Med*. 2020; 17(4):1-4.
 11. Xu Z, Li S, Tian S, Li H, Kong L. Full spectrum of COVID-19 severity still being depicted. *Lancet*. 2020; 395(10223):948-9.
 12. The Lancet. Emerging understandings of 2019-nCoV. *Lancet*. 2020; 395(10223): 311.
 13. 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; 8(5):475-81
 14. Liu K, Chen Y, Lin R., Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. *J Infect*. 2020; 80(6):e14-8.
 15. Tian S, Hu S, Niu L, Xu H, Xiao S. Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J Thorac Oncol*. 2020; 15(5):700-4.
 16. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel Coronavirus-infected pneumonia. *N Engl J Med*. 2020; 382(13):1199–207.
 17. Kluge S, Janssens U, Welte T, Weber-Carstens S, Marx G, Karagiannidis C. German recommendations for critically ill patients with COVID-19. *Med Klin Intensivmed Notfmed*. 2020; 115(3):175-7.
 18. Nishimura M. High-flow nasal cannula oxygen therapy in adults: Physiological benefits, indication, clinical benefits, and adverse effects. *Respir Care*. 2016; 61(4):529-41.
 19. Pham T, Brochard L, Slutsky S. Mechanical ventilation: State of the art. *Mayo Clin Proc*. 2017; 92(9):1382-400.
 20. Saey T. Repurposed remedies for coronavirus. *Science News*. 2020; 197(6): 20-3.
 21. Sarma P, Prajapat M, Avti P, Kaur H, Kumar S, Medhi B. Therapeutic options for the treatment of 2019-novel coronavirus: An evidence-based approach. *Indian J Pharmacol*. 2020; 52(1):1-5.
 22. Sheahan TP, Sims AC, Leist SR, Schafer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nature Communications*. 2020; 11(1): 222.
 23. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents*. 2020; 55(5):105938.
 24. Sahraei Z, Shabani M, Shokouhi S, Saffaei A. Aminoquinolines against coronavirus disease 2019 (COVID-19): Chloroquine or hydroxychloroquine. *Int J Antimicrob Agents*. 2020; 55(4):105945.
 25. Dong C, Ni L, Ye F, Chen ML, Feng Y, Deng YQ, et al. Characterization of antiviral immunity in recovered individuals infected by SARS-CoV-2. *bioRxiv*. 2020;
 26. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of Remdesivir for

- patients with severe Covid-19. *N Engl J Med.* 2020; 382(24):2327-36.
27. Arabi M, Allothman A, Balkhy HH, Al-Dawood A, AlJohani S, Al Harbi S, et al. Treatment of Middle East respiratory syndrome with a combination of lopinavir-ritonavir and interferon-beta1b (Miracle trial): Study protocol for a randomized controlled trial. *Trials.* 2020; 19(1):81.
28. Kim U, Won E, Kee S, Jung S, Jang H. Combination therapy with lopinavir/ritonavir, ribavirin and interferon-alpha for Middle East respiratory syndrome: A case report. *Antivir Ther.* 2015; 21(5): 455-9.
29. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *J Am Med Assoc.* 2020; 323 (16):1582-9.