American Journal of Emergency Medicine 38 (2020) 1488–1493

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Review

Pharmacotherapy in COVID-19; A narrative review for emergency providers

Nikita Mehta, BA [a], Maryann Mazer-Amirshahi, PharmD, MD, PhD [b], Nour Alkindi, MD [a], Ali Pourmand, MD, MPH [a,*]

[a] Emergency Medicine Department, George Washington University School of Medicine and Health Sciences, Washington, DC, USA
[b] Emergency Medicine Department, MedStar Washington Hospital Center, Washington, DC, USA

ARTICLE INFO

Article history:
Received 1 April 2020
Received in revised form 12 April 2020
Accepted 13 April 2020

Keywords:
COVID 19
SARS-CoV-2
Hydroxychloroquine
Remdesivir
Favipiravir

ABSTRACT

Introduction: The COVID-19 pandemic has been particularly challenging due to a lack of established therapies and treatment guidelines. With the rapid transmission of disease, even the off-label use of available therapies has been impeded by limited availability. Several antivirals, antimalarials, and biologics are being considered for treatment at this time. The purpose of this literature review is to synthesize the available information regarding treatment options for COVID-19 and serve as a resource for health care professionals.
Objectives: This narrative review was conducted to summarize the effectiveness of current therapy options for COVID-19 and address the controversial use of non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). PubMed and SCOPUS were queried using a combination of the keywords "COVID 19," "SARS-CoV-2," and "treatment." All types of studies were evaluated including systematic reviews, case-studies, and clinical guidelines.
Discussion: There are currently no therapeutic drugs available that are directly active against SARS-CoV-2; however, several antivirals (remdesivir, favipiravir) and antimalarials (chloroquine, hydroxychloroquine) have emerged as potential therapies. Current guidelines recommend combination treatment with hydroxychloroquine/azithromycin or chloroquine, if hydroxychloroquine is unavailable, in patients with moderate disease, although these recommendations are based on limited evidence. Remdesivir and convalescent plasma may be considered in critical patients with respiratory failure; however, access to these therapies may be limited. Interleukin-6 (IL-6) antagonists may be used in patients who develop evidence of cytokine release syndrome (CRS). Corticosteroids should be avoided unless there is evidence of refractory septic shock, acute respiratory distress syndrome (ARDS), or another compelling indication for their use. ACE inhibitors and ARBs should not be discontinued at this time and ibuprofen may be used for fever.
Conclusion: There are several ongoing clinical trials that are testing the efficacy of single and combination treatments with the drugs mentioned in this review and new agents are under development. Until the results of these trials become available, we must use the best available evidence for the prevention and treatment of COVID-19. Additionally, we can learn from the experiences of healthcare providers around the world to combat this pandemic.

1. Introduction

The unprecedented circumstances of the Coronavirus Disease 2019 (COVID-19) pandemic have proven to be particularly challenging due to a lack of established therapies and treatment guidelines. Although highly contagious, infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seems to be less virulent than Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) in terms of morbidity and mortality [1]. The clinical manifestations of COVID-19 in infected individuals ranges from asymptomatic or mild disease to critical illness with rapid deterioration, and death [1]. As such, the treatment of patients varies based on disease severity and consideration of underlying medical conditions (Table 1). Several drugs have emerged as candidates for treatment, including nucleotide analogs (remdesivir) and anti-malarials (chloroquine, hydroxychloroquine) [2]. Protease inhibitors (lopinavir/ritonavir) and interferon-β have also been included in ongoing clinical trials, but are not recommended for treatment at this time [2]. There have also been increased concerns regarding the potential for increased susceptibility to SARS-CoV-2 in patients taking medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and renin angiotensin aldosterone system (RAAS) antagonists, that upregulate angiotensin converting enzyme 2 (ACE2) [3]. The purpose of this literature review

* Corresponding author at: Emergency Medicine, Department of Emergency Medicine, George Washington University, Medical Center, 2120 L St., Washington, DC 20037, USA.
E-mail address: pourmand@gwu.edu (A. Pourmand).

https://doi.org/10.1016/j.ajem.2020.04.035
0735-6757/

Table 1
Patient categories of disease severity with recommended treatments.

Disease severity[a]	Treatment
Mild disease	
Not hospitalized	- Supportive care
Hospitalized patients with SpO2 > 94%. Normal chest radiographs.	- Supportive care
Moderate disease	
Hospitalized patients with SpO2 ≤ 94% OR radiographic evidence of pneumonia	- hydroxychloroquine + azithromycin[b] - chloroquine (if hydroxychloroquine is unavailable)
Severe disease	
Worsening respiratory function with CRS	- tocilizumab - sarilumab
Respiratory failure	- remdesivir[c] - convalescent plasma - corticosteroids (only for refractory septic shock or ARDS)

[a] Patients with underlying conditions such as diabetes, heart failure, end-stage renal disease, or immunosuppression are at increased risk for severe disease with ARDS and possible death [19].
[b] Doxycycline may be considered as an alternative for patients who demonstrate a hypersensitivity reaction to azithromycin [20].
[c] Hydroxychloroquine must be discontinued prior to initiation of remdesivir, due to risk of QT prolongation [9].

is to synthesize the available information regarding treatment options for COVID-19, as a resource for health care professionals as we await the results of ongoing clinical trials around the world.

2. Methods

The authors searched PubMed and SCOPUS for articles using a combination of the keywords "COVID 19," "SARS-CoV-2," and "treatment." This narrative review summarizes the effectiveness of current treatment options for COVID-19 and addresses the controversy regarding continued use of NSAIDs and certain anti-hypertensive medications that impact the renin-angiotensin system. All types of studies were evaluated including systematic reviews, case-studies, and clinical guidelines. The references of included studies were also reviewed to identify additional sources. Only studies written in English were included. The initial literature search identified 152 articles, of which 18 articles were included in this review. Data from the included articles were summarized and reported by drug-class.

3. Results

3.1. Nucleotide analogs

Remdesivir is a nucleotide analog, which is incorporated into the viral RNA chain and results in premature chain termination [4]. It is an experimental drug that has demonstrated antiviral activity against several RNA viruses including Ebola, SARS, and MERS in vitro and in non-human primates [1,4]. In a case report, a US patient with COVID-19 was recently treated with remdesivir on a compassionate use basis due to worsening clinical status and his condition improved remarkably [5]. Within 2 days of initiating treatment, he no longer required supplemental oxygen and his only symptoms were a dry cough and mild rhinorrhea [5]. There was an additional case reported in which remdesivir was used and the patient recovered [6]. Although the data are limited to case reports, remdesivir may be a potential candidate for therapy. Non-human primates with MERS-CoV treated with a combination of remdesivir and interferon-β were found to have improved pulmonary function and reduced lung viral loads, when compared to those treated with lopinavir/ritonavir and interferon-β [7]. The most common adverse effects reported were gastrointestinal in nature, as well as elevation in transaminases and infusion site reactions (Table 2).

Several Phase III trials are underway to determine the efficacy of remdesivir in the treatment of COVID-19 [2]. As of now, remdesivir may be considered in patients with severe disease and respiratory failure [8]. It cannot be used in conjunction with hydroxychloroquine due to an increased risk of QT prolongation and fatal dysrhythmias [9]. Although distribution of the drug was initially limited to compassionate use and clinical trials for the treatment of critically ill patients with COVID-19, the manufacturers are working to expand access through a government-approved program that eliminates the need for compassionate use requests [10]. However, increased demand has limited efforts to expand access.

3.2. Nucleoside analogs

Favipiravir is a nucleoside analog which inhibits viral RNA polymerase and was initially intended for the treatment of RNA viruses such as Ebola and Influenza [1]. A randomized control trial found that favipiravir had a higher clinical recovery rate and produced a statistically significant reduction in the duration of fever, when compared with umifenovir, an antiviral drug used for the treatment of Influenza infection in some countries [11]. The most common adverse effects were abnormal transaminases, psychiatric symptoms, gastrointestinal discomfort and elevated serum uric acid (Table 2) [11]. Ribavirin, which is typically used in the treatment of HCV and RSV, was initially considered as a possible therapy for the treatment of COVID-19; however subsequent studies have shown that the doses required for effective antiviral activity may have potentially fatal adverse effects, such as hemolytic anemia, thereby limiting its clinical use (Table 2) [12,13].

Favipiravir and ribavirin are not currently recommended for the treatment of patients with COVID-19; however, there are several randomized trials investigating the antiviral effects of favipiravir against SARS-CoV-2 [13]. Favipiravir has not been approved by the FDA and is not currently available for use in the United States [14]. The high risk of toxicity due to ribavirin therapy outweighs its potential benefits and it is no longer being pursued as a potential treatment option for SARS-CoV-2 [8].

3.3. Protease inhibitors

The combination of lopinavir/ritonavir is typically used for the treatment of human immunodeficiency virus (HIV) infection; however, it has been noted that lopinavir has in vitro activity against coronavirus [15]. Ritonavir is also a protease inhibitor, but its primary role is to boost lopinavir concentrations and prolong its half-life via cytochrome P450 inhibition. A study conducted in 2004 found that patients with SARS-associated coronavirus treated with a combination of these protease inhibitors and ribavirin, a nucleoside analogue, were found to have decreased viral loads, rising peripheral lymphocyte counts, and significantly lower adverse events (acute respiratory distress syndrome (ARDS) or death) [15]. Patients treated with this combination therapy were also found to have a decreased need for corticosteroids and reduced risk of nosocomial infection, when compared to patients given standard care (ribavirin only) [15]. This study prompted a clinical trial to determine the effectiveness of using lopinavir/ritonavir to treat COVID-19, which concluded that there was no observed benefit of using this combination therapy in the treatment of severe COVID-19 infection [16]. Subsequent studies, however, suggest that early administration of lopinavir/ritonavir is effective in reducing viral load and improving clinical outcomes in patients with mild to moderate disease [17,18]. The effectiveness of lopinavir/ritonavir in treating COVID-19 is controversial at this time. Overall, lopinavir/ritonavir was associated with higher rates of gastrointestinal adverse effects compared to standard care and in patients with severe COVID-19 infection, 13.8% required discontinuation of therapy [15]. The combination of lopinavir/

Table 2
Pharmacologic therapies considered for treatment of COVID-19.

	Mechanism of action	Adverse effects	Current recommendations
Antivirals			
Remdesivir	Nucleotide analog that is incorporated into the viral RNA chain and results in premature chain termination [4]	- Gastrointestinal distress - Elevated transaminases - Infusion site reactions	Consider for patients with severe disease and respiratory failure [8].
Favipiravir	Nucleoside analog which inhibits viral RNA polymerase [1]	- Abnormal transaminases - Psychiatric symptoms - Gastrointestinal discomfort - Elevated serum uric acid [11]	Not recommended at this time [8].
Ribavirin	Guanosine analog that interferes with viral replication [1]	- Hemolytic anemia	Not recommended at this time [8].
Lopinavir/ritonavir	Protease inhibitors that prevent the production of active viral peptides [1]	- Gastrointestinal distress - QT prolongation - Drug-drug interactions (ritonavir)	Not recommended at this time [19].
Antimalarials			
Chloroquine	Elevates endosomal pH and inhibits pH dependent steps in the viral replication process [21]	- Electrolyte imbalance - Fatal dysrhythmias (Torsades de Pointes)	May be used as an alternative when hydroxychloroquine is unavailable.
Hydroxychloroquine	Elevates endosomal pH and inhibits pH dependent steps in the viral replication process [21]	- Electrolyte imbalance - Fatal dysrhythmias (Torsades de Pointes)	Combination treatment with azithromycin recommended for patients with moderate to severe disease [20,25].
CorticosteroidsCorticosteroids			
Corticosteroids	Binds to cytoplasmic receptors to change the transcription of mRNA and reduce production of inflammatory mediators	- Avascular necrosis - Psychosis - Hyperglycemia - Adrenal suppression	Only indicated for patients with refractory septic shock or severe ARDS. Not recommended for routine use [19,20].
Biologics			
Tocilizumab Sarilumab	Monoclonal antibody against the IL-6 receptor	- Abnormal transaminases - GI perforation - Neutropenia - Infusion reactions	May be considered in patients with evidence of CRS and worsening respiratory function [8].
Convalescent plasma	Passive immunization using plasma from recovered patients	- Hypersensitivity reactions - Serum sickness	Recommendations are controversial. May be considered in patients with worsening clinical conditions refractory to other treatment [14].
NSAIDS			
Ibuprofen	Block COX 1 and 2, inhibiting production of prostaglandins	- Gastrointestinal ulcers/bleeding - May upregulate ACE2	No evidence to support that its use is contraindicated. May be used for its anti-inflammatory and anti-pyretic effects [39].
Indomethacin	Block COX 1 and 2, inhibiting production of prostaglandins	- Gastrointestinal ulcers/bleeding - May upregulate ACE2	No evidence of its antiviral effects against SARS-CoV-2 in humans [40]. May be used for its anti-inflammatory and anti-pyretic effects.
RAAS antagonists			
ACE Inhibitors	Inhibits conversion of angiotensin I to angiotensin II	- Cough - Upregulation of ACE2 (may increase risk for severe COVID-19)	These medications should not be routinely discontinued. Consider clinical condition of individual patients before changing anti-hypertensive treatment regimens [41].
ARBs	Prevents angiotensin II from binding to its receptor	- Cough - Upregulation of ACE2 (may increase risk for severe COVID-19)	

ritonavir is also known to cause QT prolongation and there is concern regarding the multiple drug-drug interactions associated with ritonavir in particular (Table 2) [9].

Due to a lack of definitive evidence supporting the use of lopinavir/ritonavir and the high risk of adverse events, and significant drug-drug interactions, use of these agents is not recommended at this time [19]. The results of a clinical trial through the World Health Organization (WHO), which includes lopinavir/ritonavir in one arm of the study, may provide more conclusive insight on the benefits of using these drugs for the treatment of COVID-19 [20].

3.4. Antimalarials

Chloroquine and its derivative hydroxychloroquine have traditionally been used for the treatment of malaria and certain autoimmune diseases; however, the drugs have possible activity against SARS-CoV 1 and SARS-CoV 2 in vitro and in clinical practice, respectively. A study conducted in 2005 found that chloroquine's ability to elevate endosomal pH and therefore inhibit pH-dependent steps in the viral replication process, was effective in mitigating the spread of infection to other host cells [21]. Chloroquine has also been found to have some immunomodulatory

effects through the suppression of Tumor Necrosis Factor-α and IL-6 release, which may help prevent the cytokine storm that leads to rapid deterioration of patients with COVID-19 [1,22]. Furthermore, chloroquine was found to show some efficacy in treating COVID-19 associated pneumonia in a multicenter clinical trial with >100 patients in China [23]. Subsequent studies have found that hydroxychloroquine has increased potency and a more tolerable safety profile when compared to chloroquine [24]. In a recent nonrandomized clinical trial, 14 patients were treated with hydroxychloroquine alone and 6 patients were treated with a combination of hydroxychloroquine and azithromycin [25]. A substantial reduction in viral load and more rapid virus elimination was seen in patients treated with a combination of hydroxychloroquine and azithromycin; however, the majority of patients treated with hydroxychloroquine alone continued to display symptoms of upper or lower respiratory tract infections [25]. While the data supporting the use of these drugs are limited at best, media coverage surrounding this treatment has prompted self-medication with compounds that contain chloroquine in an effort to prevent COVID-19 infection. It should be noted that when used inappropriately, chloroquine and to a lesser extent hydroxychloroquine, are very toxic and can cause fatal dysrhythmias and electrolyte shifts (Table 2) [26].

Given the wider accessibility of antimalarials, as compared to the aforementioned antivirals, combination treatment with hydroxychloroquine and azithromycin is now recommended for many hospitalized patients with moderate to severe COVID-19. The FDA recently granted emergency authorization for hydroxychloroquine to treat COVID-19 infection [27]. Although chloroquine has not been approved by the FDA, it was authorized to be added to the stockpile for use in hospitals [27]. As a result, there has been a surge in demand for chloroquine and hydroxychloroquine, and India, a major exporter of these agents, has restricted exports, precipitating critical shortages [28,29]. There are several ongoing clinical trials that are investigating the efficacy of prophylactic and therapeutic use of these medications against SARS-CoV-2 [24]. Ultimately, the optimal role of these drugs, if any, has yet to be elucidated.

3.5. Corticosteroids

Although corticosteroids are often used for their anti-inflammatory effects in patients with respiratory infections, several studies have indicated that the use of corticosteroids in patients with COVID-19 is associated with delayed viral clearance, higher risk of secondary infection, and increased risk of mortality [30]. Still, the use of corticosteroids may be indicated in patients who develop ARDS or refractory septic shock, and those with underlying respiratory conditions such as asthma or chronic obstructive pulmonary disease (COPD) [22]. A study conducted in China found that the use of methylprednisolone decreased risk of death in patients with COVID-19 who develop ARDS [31]. The WHO currently recommends against the routine use of corticosteroids in the treatment of patients with COVID-19, due to the potential for delayed viral clearance and other adverse effects such as avascular necrosis and psychosis (Table 2) [22]. Corticosteroids may be used if indicated for refractory septic shock or severe ARDS [19,20,22]. To summarize, corticosteroids, should not be used solely for the treatment of COVID-19 infection, but may be required to treat other conditions that may accompany it.

3.6. Biologics

Tocilizumab and sarilumab are monoclonal antibodies against the IL-6 receptor that are currently being considered for use in patients with COVID-19, who develop cytokine release syndrome (CRS) [20]. It may have a potential role in severe and life-threatening illness. The proposed efficacy of this treatment involves the attenuation of the potentially fatal inflammatory response by reducing cytokine concentrations and inhibiting the production of acute phase reactants [32]. Inflammatory markers, including IL-6 levels should be monitored during therapy; however, results are often not available in a timely manner. Common adverse effects include abnormal transaminases. Gastrointestinal perforation, neutropenia, and infusion reactions have also been reported (Table 2). There are limited data supporting the use of monoclonal antibodies such as tocilizumab and sarilumab. Patients who develop evidence of COVID-19 associated CRS may be considered candidates for treatment using these agents [8,19].

Passive immunization has been used to treat viral infections in patients who are unable to develop an adequate immune response, such as infants born to mothers with active hepatitis B virus infection [32]. A meta-analysis of studies investigating the use of convalescent plasma for the treatment of SARS-CoV-1 and MERS-CoV found a significant reduction in mortality and viral loads with no immediate adverse events [33]. The use of convalescent plasma was effective in eliminating viral load in 7 patients with previous viremia and in improving the clinical condition of 5 critically ill patients with COVID-19 [34,35]. These patients had resolution of ARDS and were weaned off mechanical ventilation within 2 weeks of treatment [35]. The FDA has approved the use of convalescent plasma for the treatment of severe and immediately life-threatening COVID-19 infections and there are currently several trials being conducted [36]. Still, recommendations regarding the use of convalescent plasma remain controversial. Some guidelines suggest against its use in critically ill patients, stating that the target levels of neutralizing antibody titers against SARS-CoV-2 are unknown, while other institutions are considering its use [8,19].

Structural studies of SARS-CoV-1 and -2 have indicated that the viruses are able to bind to their target human cells by using ACE2 as their receptor [37]. Panic ensued after the release of a study, which suggested that patients taking NSAIDS, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs), may have increased ACE2 expression and were therefore at an increased risk for severe COVID-19 infection [3].

3.7. NSAIDs

NSAIDs work by inhibiting cyclooxygenase (COX) 1 and 2, thereby blocking production of prostaglandins, which are important mediators of fever and inflammation. The mechanism by which NSAIDs increase ACE2 expression is not well understood; however, fever has been reported as one of the most common clinical manifestations of COVID-19 and NSAIDs, such as ibuprofen, are often used for their anti-pyretic and anti-inflammatory effects in the setting of infection [38]. Although there is a lack of evidence supporting the potential risks of NSAID use in patients with COVID-19, it may be prudent to use alternative anti-pyretic medications such as acetaminophen, until more concrete data are available [39]. Interestingly, a study conducted in 2006 found that the NSAID indomethacin was a potent inhibitor of SARS-CoV-1 replication in dogs, suggesting that it could be a beneficial therapy for SARS infection [40]. However, no evidence exists as to the effects of indomethacin in patients infected with SARS-CoV-2. The WHO initially recommended against the use of ibuprofen, but has since revised its statement and states that either acetaminophen or ibuprofen may be used [39]. Additional studies are required to determine what risk, if any, NSAIDs pose in the setting of COVID-19 infection.

3.8. Renin Angiotensin Aldosterone System (RAAS) antagonists

At this time, there is no clinical evidence suggesting that ACE Inhibitors or ARBs increase susceptibility to SARS-CoV-2 or increase risk for severe disease in those already infected [8]. In fact, abruptly discontinuing treatment with these anti-hypertensives or switching to other hypertension medications may increase the risk of adverse clinical outcomes associated with uncontrolled hypertension. Leading cardiology organizations advise against the discontinuation of ACE inhibitors and ARBs and recommend that physicians assess the clinical condition of individual patients

before making any changes to their treatment regimens [41]. Recently, it was found that a recombinant protein made by attaching the extracellular domain of ACE2 to the Fc region of IgG, was effective in neutralizing SARS-CoV-2 in vitro [42]. Although more research is needed on the efficacy of this fusion protein in humans, this could represent a viable option for the treatment of COVID-19.

4. Discussion

Although there are currently no available therapies that are directly active against SARS-CoV-2, several medications have emerged as potential treatments. Due to the low cost, easy accessibility, and lack of alternative treatment options, treatment with a combination of hydroxychloroquine and azithromycin is often considered for hospitalized patients with moderate to severe COVID-19. It should be noted that the use of antimalarials for COVID-19 is based on a single study with a small sample size, non-randomized control group, and significant drop out in the treatment group [25]. As such, the efficacy of this treatment is still questionable, and the risk of significant adverse effects should be considered prior to initiating treatment with these drugs. Among antivirals, remdesivir could be a promising candidate and may be more widely available in the upcoming weeks. Passive immunization has been successfully used in the past; however, the efficacy of convalescent plasma in the treatment of critically ill patients with COVID-19 is still largely unknown. Many institutions are beginning to use this treatment as more individuals recover from the disease and convalescent plasma becomes available. Although there were many concerns regarding the use of medications such as ibuprofen and RAAS antagonists in patients with COVID-19, current guidelines state that ibuprofen may be used and recommend against the discontinuation of ACE inhibitors and ARBs. We must continue to reevaluate current treatment recommendations as new data emerges and discourage inappropriate prescribing and hoarding of medications. At the same time, parallel efforts are also focusing on vaccine development, infection control measures, as well as optimal respiratory and supportive care. (Table 1).

5. Limitations

Of the studies that have been performed on these experimental treatment options, many have small sample sizes yielding data that are not statistically significant. Many treatments, therefore, are being used on a trial and error basis, based on limited data. Several other studies were conducted in vitro or in non-human primates and therefore may not be applicable for use in humans. Furthermore, this review did not consider the variations in treating pediatric, pregnant, or older adult patients, as these patients are often excluded from clinical trials.

6. Conclusion

As the SARS-CoV-2 pandemic continues to evolve, some information has become available on the effectiveness of certain therapies. Still, the results of ongoing clinical trials testing single and combination therapies are needed to make definitive recommendations for the treatment of COVID-19. However, the results of these trials may not be readily available in the near future, during the peak of the pandemic and as such, we must not underestimate the importance of efforts to slow transmission and optimizing supportive measures.

7. Financial support

This is a non-funded study, with no compensation for conducting the study.

8. Declaration of competing interests

The authors do not have a financial interest or relationship to disclose.

References

[1] Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 2020;7(1):11. https://doi.org/10.1186/s40779-020-00240-0.
[2] Centers for Disease Control and Prevention. Information for clinicians on therapeutic options for COVID-19 patients. https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html;; 2020, Accessed date: 27 March 2020.
[3] Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020;2600(20):30116. https://doi.org/10.1016/S2213-2600(20)30116-8 Internet.
[4] Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30(3):269–71. https://doi.org/10.1038/s41422-020-0282-0.
[5] 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(10):929–36. https://doi.org/10.1056/NEJMoa2001191.
[6] Sanville B, Corbett R, Pidcock W, et al. A community transmitted case of severe acute respiratory distress syndrome due to SARS CoV2 in the United States. Clin Infect Dis https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa347/5813637; 2020 [accessed 12 April 2020].
[7] Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020;11(1). https://doi.org/10.1038/s41467-019-13940-6.
[8] Mount Sinai Health System Treatment Guidelines for SARS-CoV-2 infection (COVID-19). https://www.mountsinai.org/files/MSHealth/Assets/HS/About/Coronavirus/MSHS-Treatment-Guidelines-COVID.pdf;; 2020, Accessed date: 17 March 2020.
[9] Liverpool Drug Interactions. Interactions with experimental COVID-19 therapies. https://www.covid19-druginteractions.org; 2020, Accessed date: 28 March 2020.
[10] Gilead. Gilead science update on the company's ongoing response to COVID-19. https://www.gilead.com/purpose/advancing-global-health/covid-19; 2020, Accessed date: 29 March 2020.
[11] Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus Arbidol for COVID-19: a randomized clinical trial. https://www.medrxiv.org/content/medrxiv/early/2020/03/27/2020.03.17.20037432.full.pdf;; 2020, Accessed date: 27 March 2020.
[12] Zumla A, Chan JF, Azhar EI, et al. Coronaviruses-drug discovery and therapeutic options. Nat Rev Drug Discov 2016;15(5):327–47. https://doi.org/10.1038/nrd.2015.37.
[13] Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov 2020;19(3):149–50. https://doi.org/10.1038/d41573-020-00016-0.
[14] Hoffmann C, Avdic E, RK A. JHMI clinical guidance for available pharmacologic therapies for COVID-19- Johns Hopkins Hospital. https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2;; 2020, Accessed date: 27 March 2020.
[15] Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004;59(3):252–6. https://doi.org/10.1136/thorax.2003.012658.
[16] Cao B, Wang Y, Wen D, et al. A trial of Lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020:1–13. https://doi.org/10.1056/NEJMoa2001282.
[17] Lim J, Jeon S, Shin HY, et al. Case of the index patient who caused tertiary transmission of coronavirus disease 2019 in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 pneumonia monitored by quantitative RT-PCR. J Korean Med Sci 2020;35(7):1–6. https://doi.org/10.3346/jkms.2020.35.e79.
[18] Wang Z, Chen X, Lu Y, et al. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. Biosci Trends 2020;14(1):64–8. https://doi.org/10.5582/bst.2020.01030.
[19] Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Med 2020;2019:1–32. https://doi.org/10.1097/CCM.0000000000004363.
[20] Giwa AL, Desai A, Duca A. Novel 2019 coronavirus SARS-CoV-2 (COVID-19): an updated overview for emergency clinicians. Emerg Med Pract 2020;22(5):1–28.
[21] Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005;2:1–10. https://doi.org/10.1186/1743-422X-2-69.
[22] World Health Organization. WHO clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected; 2020, Accessed date: 28 March 2020.
[23] Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14(1):72–3. https://doi.org/10.5582/bst.2020.01047.
[24] Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome main point: hydroxychloroquine was found to be more potent than chloroquine at inhibiting SARS-CoV-2 in vit. Clin Infect Dis 2020;2:1–25. https://doi.org/10.1093/cid/ciaa237.

[25] Gautret P, Lagiera JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open- label non-randomized clinical trial Philippe Gautret. Mediterr Infect 2020;(March:1–24. https://doi.org/10.1016/j.ijantimicag.2020.105949.
[26] de Olano J, Howland MA, Su MK, et al. Toxicokinetics of hydroxychloroquine following a massive overdose. Am J Emerg Med 2019;37(12):2264.e5–8. https://doi.org/10.1016/j.ajem.2019.158387.
[27] U.S. Food and Drug Administration. Request for emergency use authorization for use of chloroquine phosphate or hydroxychloroquine sulfate supplied from the strategic National Stockpile for treatment of 2019 coronavirus disease. https://www.fda.gov/media/136534/download; 2020 [accessed 30 March 2020].
[28] The Hill. India bans export of drug touted by trump as potential coronavirus treatment. https://thehill.com/policy/international/489559-india-bans-export-of-drug-touted-by-trump-as-potential-coronavirus;; 2020, Accessed date: 31 March 2020.
[29] American Society of Health Systems Pharmacists. Current drug shortages. https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortage-Detail.aspx?id=646;; 2020, Accessed date: 30 March 2020.
[30] Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395(10223):473–5. https://doi.org/10.1016/S0140-6736(20)30317-2.
[31] Wu C, Chen X, Cai Y, 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 2020:1–10. https://doi.org/10.1001/jamainternmed.2020.0994.
[32] Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. Crit Care 2020;24(1):6–7. https://doi.org/10.1186/s13054-020-2818-6.
[33] Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015;211(1):80–90. https://doi.org/10.1093/infdis/jiu396.
[34] Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A 2020:1–7 pii:202004168 https://doi.org/10.1073/pnas.2004168117.
[35] Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA - J Am Med Assoc 2020(29):1–8. https://doi.org/10.1001/jama.2020.4783.
[36] Tanne JH. Covid-19: FDA approves use of convalescent plasma to treat critically ill patients. Bmj 2020;1256(March):m1256. https://doi.org/10.1136/bmj.m1256.
[37] Wan Y, Shang J, Graham R, et al. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020;94(7):1–9. https://doi.org/10.1128/JVI.00127-20.
[38] Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020:1–13. https://doi.org/10.1056/NEJMc2005203.
[39] Bertisch S, Ellerin T, Farid H, et al. Coronavirus resource center-Harvard health publishing. https://www.health.harvard.edu/diseases-and-conditions/coronavirus-resource-center;; 2020, Accessed date: 29 March 2020.
[40] Amici C, Di Caro A, Ciucci A, Chiappa L, Castilletti C, Martella V, et al. Indomethacin has a potent antiviral activity against SARS coronavirus. Antivir Ther 2006;11(8):1021–30.
[41] American College of Cardiology. HFSA/ACC/AHA statement addresses concerns re: Using RAAS antagonists in COVID-19; 2020.
[42] Basu P, Feng Y, Qiu M, et al. Potent neutralization of 2019 novel coronavirus by recombinant ACE2-Ig. bioRxiv 2020;53(9). https://doi.org/10.1101/2020.01.01.929976.