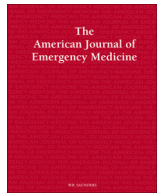




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Review

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

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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.

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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

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Table 1
Patient categories of disease severity with recommended treatments.

| Disease severity ^a | Treatment |
|---|--|
| Mild disease | |
| Not hospitalized | - Supportive care |
| Hospitalized patients with SpO ₂ > 94%. Normal chest radiographs. | - Supportive care |
| Moderate disease | |
| Hospitalized patients with SpO ₂ ≤ 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] | <ul style="list-style-type: none"> - 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] | <ul style="list-style-type: none"> - 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] | <ul style="list-style-type: none"> - Hemolytic anemia | Not recommended at this time [8]. |
| Lopinavir/ritonavir | Protease inhibitors that prevent the production of active viral peptides [1] | <ul style="list-style-type: none"> - 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] | <ul style="list-style-type: none"> - 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] | <ul style="list-style-type: none"> - Electrolyte imbalance - Fatal dysrhythmias (Torsades de Pointes) | Combination treatment with azithromycin recommended for patients with moderate to severe disease [20,25]. |
| Corticosteroids | | | |
| Corticosteroids | Binds to cytoplasmic receptors to change the transcription of mRNA and reduce production of inflammatory mediators | <ul style="list-style-type: none"> - 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 | <ul style="list-style-type: none"> - 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 | <ul style="list-style-type: none"> - 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 | <ul style="list-style-type: none"> - 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 | <ul style="list-style-type: none"> - 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 | <ul style="list-style-type: none"> - 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 | <ul style="list-style-type: none"> - 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.

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8. Declaration of competing interests

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

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