Medication use during COVID-19

Review of recent evidence

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Abstract

Objective To keep health care providers, in response to the ongoing coronavirus disease 2019 (COVID-19) pandemic, informed about the medications that have been proposed to treat the disease and the evidence supporting their use.

Quality of evidence A narrative review of medications most widely used to treat COVID-19 was conducted, outlining the best available evidence for each pharmacologic treatment to date. Searches were performed in PubMed, EMBASE, and MEDLINE using key words *COVID-19* and *treatment*, as well as related terms. Relevant research studies conducted in human populations and cases specific to patients with COVID-19 were included, as were relevant hand-searched papers and reviews. Only articles in English and Chinese were included.

Main message While current management of patients with COVID-19 largely involves supportive care, without a widely available vaccine, practitioners have also resorted to repurposing medications used for other indications. This has caused considerable controversy, as many of these treatments have limited clinical evidence supporting their use and therefore pose implications for patient safety, drug access, and public health. For instance, medications such as hydroxychloroquine and chloroquine, lopinavir-ritonavir, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers gained widespread media attention owing to hype, misinformation, or misinterpretation of research evidence.

Conclusion Given the severity of the pandemic and the potential broad effects of implementing safe and effective treatment, this article provides a narrative review of the current evidence behind the most widely used medications to treat COVID-19 in order to enable health care practitioners to make informed decisions in the care of patients with this life-threatening disease.

Editor's key points

- In response to the ongoing coronavirus disease 2019 pandemic, a number of medications have been proposed to treat the virus. It is important for health care providers to remain informed about the evidence supporting their use.
- Medications such as hydroxychloroquine and chloroquine, lopinavir-ritonavir, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers gained widespread media attention owing to hype, misinformation, or misinterpretation of research evidence.
- Current evidence supports the selective use of remdesivir and corticosteroids in severe cases, while the role of other medications remains less clear, particularly in mild to moderate cases that might improve on their own.

December 2019 marked the beginning of the novel coronavirus disease 2019 (COVID-19) pandemic, which has since spread worldwide with more than 100 million confirmed cases and 2 million deaths globally.[1] The underlying pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has since been identified and belongs to the genus *Betacoronavirus*, alongside severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).[2] It has been shown that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a co-receptor for viral entry. The most common symptoms include fever, cough, and fatigue, among several other possible respiratory and systemic symptoms. However, individuals with COVID-19 can also be asymptomatic.[3,4]

Given the lack of therapies specific to COVID-19, there have been numerous efforts to repurpose existing medications used for other indications. The empiric application of these medications has led to much debate regarding their safety and efficacy in treating patients with COVID-19. Additionally, unsupported speculation surrounding the value of hydroxychloroquine and chloroquine, nonsteroidal anti-inflammatory drugs (NSAIDs), and renin-angiotensin system inhibitors, as a result of misinformation and media hype,

has led to unpredictable and potentially harmful use of these medications. As our understanding of COVID-19 continues to grow, there is a need among clinicians for accurate and up-to-date evidence to inform practice and management.

Our review summarizes the current evidence available for the most promising COVID-19 drug candidates, as well as other medications empirically used during the pandemic, with a focus on studies that include human patients with the disease.

Quality of evidence

We conducted a narrative review of the medications most widely used to treat COVID-19, outlining the best available evidence for each pharmacologic treatment to date. We performed searches within PubMed, EMBASE, and MEDLINE using *COVID-19* and *treatment,* as well as related terms. (The full search strategy is available from **CFPlus.***) We drew upon relevant research studies conducted in human populations and cases specific to patients with COVID-19. We also hand-searched for relevant papers and reviews to identify journal articles that might not have been captured through our search strategy. Only articles in English and Chinese were included.

Main message

Review of specific medications and medication groups

Remdesivir: Remdesivir is a novel nucleotide analogue prodrug inhibitor of RNA-dependent RNA polymerase that was initially developed for the treatment of the Ebola virus, but which has also shown activity against SARS-CoV and MERS-CoV.[5] The investigational antiviral therapy has recently demonstrated in vitro activity against SARS-CoV-2.[6]

The use of remdesivir to treat COVID-19 was initially demonstrated in the first reported case to occur in the United States.[7] The antiviral was provided for compassionate use on day 7 of hospitalization, as the clinical condition of the patient worsened with supportive care alone. The patient reportedly exhibited an improvement in symptoms, clinical findings, and oxygen saturation the following day. Viral loads within the oropharyngeal swabs subsequently declined and eventually became negative by hospital day 12. There were no adverse reactions associated with its use. In a subsequent case series of 12 patients that included this initial case, all patients recovered from the infection, including 3 patients who received and tolerated remdesivir.[8]

Subsequent case reports and observational studies have similarly reported safe use of remdesivir. In a case series of 12 critically ill patients with COVID-19 in Washington state, 7 received remdesivir, although associated outcomes specific to these patients were not reported in this sick cohort who demonstrated a case fatality rate of 50%.[9] In another case report of a patient with severe COVID-19 infection requiring mechanical ventilation despite a 5-day course of hydroxychloroquine, remdesivir was initiated on hospital day 9 with good effect.[10] The patient was weaned from mechanical ventilation within 60 hours, suggesting potential efficacy of remdesivir even when it is administered late, unlike other antivirals such as oseltamivir or acyclovir in the treatment of influenza and herpes simplex virus. Similarly, in a multicentre observational study of 53 hospitalized patients from the United States, Europe, Canada, and Japan who had COVID-19, required oxygen support, and received a 10-day course of intravenous remdesivir, 68% demonstrated clinical improvement.[11]

To follow up on encouraging results from observational studies, several randomized controlled trials have been performed to investigate the safety and efficacy of remdesivir in the treatment of COVID-19. The phase 3 SIMPLE trial compared the use of a 5- or 10-day regimen of remdesivir (200 mg on day 1 followed by 100 mg on subsequent days) in 397 patients with severe COVID-19 who did not require mechanical ventilation at the time of randomization.[12,13] Similar efficacy was observed between the 5- and 10-day course of remdesivir based on clinical status on day 14, time to clinical improvement, recovery, and death. However, the efficacy of remdesivir as a treatment for COVID-19 remained unclear, as the study did not have a placebo control group for comparison.

On the other hand, the phase 3 ACTT-1 (Adaptive COVID-19 Treatment Trial) compared a 10-day course of remdesivir with placebo in 1063 patients hospitalized with COVID-19.[14] Patients randomized to remdesivir demonstrated a shorter median time to recovery (defined as discharged from hospital or hospitalization for infection-control purposes only) compared with patients in the placebo group (10 days; 95% CI 9 to 11 days; vs 15 days; 95% CI 13 to 18 days, respectively). There was a trend toward lower mortality with remdesivir, which did not reach statistical significance (hazard ratio [HR] for death of 0.73; 95% CI 0.52 to 1.03). As the 14-day mortality remained relatively high (6.7% in the remdesivir group and 11.9% in the placebo group), the authors suggested that remdesivir alone might not be sufficient to effectively treat COVID-19.

More recently, another phase 3 trial compared a 5- or 10-day course of remdesivir with standard care (randomized 1:1:1) in 596 patients hospitalized with moderate COVID-19 infection (defined as the presence of pulmonary infiltrates with a room-air oxygen saturation of >94%) at 105 hospitals in the United States, Europe, and Asia.[15] The odds of an improved clinical status distribution at day 11 based on a 7-point ordinal scale was significantly higher in patients treated with the 5-day course of remdesivir when compared with those who received standard care (odds ratio of 1.65; 95% CI 1.09 to 2.48; $P=.02$). However, the clinical significance was uncertain, both with respect to the effect size and because there was no statistically significant difference in clinical

*The full search strategy is available at **www.cfp.ca**. Go to the full text of the article online and click on the **CFPlus** tab.

status distribution on day 11 between the 10-day remdesivir group and the control group. The authors suggested that the study limitations, such as the open-label design and discrepancies in patient care and discharge practices, might have contributed to the uncertainty.

Although further studies are needed to clarify the effectiveness of remdesivir in the treatment of COVID-19, the preliminary findings have been relatively favourable. For this reason, remdesivir was the first medication to receive authorization from Health Canada for use in patients with severe COVID-19 infection (July 28, 2020).[16]

Lopinavir-ritonavir: Lopinavir-ritonavir is a combination of lopinavir, which inhibits viral 3–chymotrypsin-like protease, and ritonavir, which inhibits cytochrome P450 3A4, the enzyme that metabolizes lopinavir, thereby increasing the bioavailability of lopinavir. This combination has been used to treat HIV and has demonstrated effectiveness in the treatment of SARS-CoV and MERS-CoV.[17]

Various reports have also claimed to demonstrate efficacy of lopinavir-ritonavir against SARS-CoV-2. One such report involved a case series of 10 patients with COVID-19 who were hospitalized in Hangzhou, China, and were treated with lopinavir.[18] However, the contribution of lopinavir to recovery in 7 of the patients was uncertain, as patients were variably treated with other medications including antibiotics, interferon-α2b, immunoglobulin, methylprednisolone, and arbidol hydrochloride granules. The report notably demonstrated the potential for adverse effects including hypokalemia and gastrointestinal side effects in most patients, resulting in discontinuation of the medication in 3 of them. In another case series of 135 patients with COVID-19 from Chongqing, China, in which authors of the study declared an obvious therapeutic effect of lopinavir-ritonavir, only 41.5% of patients were reported to have recovered, and the outcomes of the remaining patients were not described.[19]

In another study of 33 patients with COVID-19 who were treated with lopinavir-ritonavir alone or in combination with the antiviral membrane fusion inhibitor umifenovir, patients receiving combination therapy experienced a greater reduction in nasopharyngeal swab viral load and greater improvement in radiographic findings than those treated with lopinavir-ritonavir alone.[20] More recently, a non-randomized controlled trial of 47 patients with COVID-19 receiving interferon aerosol inhalation and umifenovir demonstrated a significantly ($P = .02$) shorter time to reach a negative viral load among those patients who received additional lopinavir-ritonavir.[21]

Various other case reports and observational studies have also suggested improved clinical outcomes with the use of lopinavir-ritonavir in patients with COVID-19. However, the effect of lopinavir-ritonavir on recovery in these studies is unclear owing to small sample sizes, lack of adequate control groups, and concurrent use of other medications.[22-35]

In contrast, other studies have failed to show a positive effect with lopinavir-ritonavir on clinical outcomes in patients with COVID-19. In a randomized controlled trial of 100 patients receiving standard care and 99 patients receiving 400-100 mg lopinavir-ritonavir twice a day for 14 days in addition to standard care, the addition of the antiviral was not associated with any significant differences in viral loads.[36] However, the relatively small sample size for a drug study, differences in baseline characteristics between groups, and the lack of blinding might have influenced the results of the study.[37] In a case series of 18 patients hospitalized with COVID-19 in Singapore, only 3 of the 5 patients who were treated with lopinavir-ritonavir demonstrated a reduction in oxygen requirements, while the other 2 progressed to respiratory failure.[38] Adverse reactions, mostly gastrointestinal, were common, with only 1 patient completing the 14-day treatment course.

Randomized controlled trials have also failed to demonstrate efficacy of lopinavir-ritonavir in the treatment of COVID-19. The RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial conducted in the United Kingdom found no significant differences in 28-day mortality, risk of progression to mechanical ventilation, and length of hospital stay between patients randomized to lopinavir-ritonavir (n = 1596) and those randomized to usual hospital care only (n=3376).[39,40] Similarly, the multinational World Health Organization (WHO)–led Solidarity Trial discontinued its lopinavir-ritonavir arm, as interim results showed no significant reduction in mortality with lopinavir-ritonavir use compared with standard care in patients with COVID-19.[41] Furthermore, the DisCoVeRy trial (Trial of Treatments for COVID-19 in Hospitalized Adults) found a significantly higher frequency of serious adverse events related to renal function in patients randomized to lopinavir-ritonavir.[42] Comprehensive data from the aforementioned trials have yet to be published in peer-reviewed journals at the time of writing this article.

Taken together, the use of lopinavir-ritonavir to treat patients with COVID-19 is not well supported by the current evidence and is falling out of favour owing to the lack of efficacy and risk of adverse events observed in recent randomized controlled trials.

Corticosteroids: The value of corticosteroids in the management of COVID-19 remains controversial. While the suppression of lung inflammation and macrophage activation syndrome might be beneficial in reducing immune-mediated acute lung injury in acute respiratory distress syndrome (ARDS), inhibition of host immunity might delay viral clearance, thereby impeding recovery and increasing mortality, as demonstrated with SARS-CoV and MERS-CoV.[43]

An early prospective study of 41 hospitalized patients from Wuhan, China, was among the first to describe the use of methylprednisolone as part of a combined treatment regimen in a subset of patients with COVID-19

who were diagnosed with severe community-acquired pneumonia.[44] However, the study was not specifically designed to test the efficacy of corticosteroids in treating COVID-19 and therefore made no statistical comparisons between patients who received corticosteroids and those who did not. A subsequent retrospective review of 137 hospitalized patients with severe COVID-19 infection in Hubei, China, suggested that corticosteroids did not appear to shorten the disease course or improve overall prognosis, although only 29% of patients received the treatment and in a non-protocolized manner.[45] A similar observational study of hospitalized patients with COVID-19 in Wuhu, China, found no difference in viral clearance or symptom duration between the 11 patients who received the treatment and the 20 who did not.[46]

In contrast, a retrospective study of 201 patients with COVID-19 in Wuhan, China, reported a significant reduction in risk of death associated with use of methylprednisolone among the 84 patients who developed ARDS (HR=0.38; 95% CI 0.20 to 0.72).[47] In addition, case reports have suggested an improvement in radiographic and echocardiographic findings following corticosteroid treatment among patients with COVID-19 who have had cardiac involvement or who were organ transplant recipients, although they received other therapies as well.[34,35]

More recently, randomized controlled trials have been conducted to determine the effect of corticosteroid treatment on clinical outcomes in patients with COVID-19. In the RECOVERY trial, the primary end point of death at 28 days occurred in 22.9% of the 2104 hospitalized patients with COVID-19 who received dexamethasone (6 mg daily) compared with 25.7% of the 4321 patients who received usual care (age-adjusted rate ratio of 0.83; 95% CI 0.75 to 0.93; $P<.001$).[48] Similarly, in the CoDEX (COVID-19 Dexamethasone) trial of 299 patients with moderate to severe ARDS due to COVID-19 admitted to the intensive care unit, dexamethasone (20 mg intravenously once daily for 5 days followed by 10 mg intravenously daily for an additional 5 days or until intensive care discharge) was associated with a significant increase in ventilator-free days compared with standard care alone (difference of 2.26; 95% CI 0.2 to 4.38; $P=.04$), although there was no significant difference in 28-day mortality.[49] The REMAP-CAP (Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia) and CAPE COD (Community-Acquired Pneumonia: Evaluation of Corticosteroids) trials were designed to evaluate the use of hydrocortisone in patients with COVID-19 but were both stopped early after the results from the RECOVERY trial were announced and were therefore underpowered to detect meaningful differences in outcomes with treatment.[50,51]

A WHO-led meta-analysis of 7 randomized controlled trials with a total of 1703 critically ill patients with COVID-19 showed a 34% reduction in odds of death at 28 days with corticosteroid use compared with usual care or placebo.[52]

Overall, the current evidence supports the selective use of corticosteroids only in severe cases of COVID-19, when patients are critically ill. Accordingly, the WHO recommends systemic corticosteroids be considered only for critically ill patients with COVID-19 and advises against their use in nonsevere cases.[53]

Chloroquine and hydroxychloroquine: Chloroquine and hydroxychloroquine are primarily used to treat malaria. Hydroxychloroquine has a more tolerable safety profile and has also been used to treat autoimmune disease such as systemic lupus erythematosus and rheumatoid arthritis owing to its anti-inflammatory and immunomodulatory effects.[54] Studies have demonstrated in vitro activity of chloroquine and hydroxychloroquine against SARS-CoV-2, with greater potency seen with hydroxychloroquine.[6,55]

Chloroquine phosphate gained early attention as a potential therapy for COVID-19 after the publication of a brief letter suggesting its efficacy in treating COVID-19–associated pneumonia in more than 100 patients from 10 hospitals in China.[56] The claim resulted in the endorsement of chloroquine phosphate for the treatment of COVID-19 pneumonia based on expert consensus.[56,57] However, no data were provided to support the recommendation.[58]

Subsequent initial studies demonstrated favourable results with the use of chloroquine or hydroxychloroquine in patients with COVID-19. In a small nonrandomized study of patients hospitalized with COVID-19 in France, viral clearance by day 6 occurred in 70% of the 20 patients who received hydroxychloroquine (200 mg 3 times a day) compared with 12.5% of the 14 control patients ($P<.001$).[59] A prospective cohort study comparing dosing regimens for hydroxychloroquine suggested that 200 mg 3 times a day might be insufficient, as only 61% of the patients reached target levels more than 2 days after initiating treatment.[60] In a small study of 22 hospitalized patients with COVID-19 from China, patients randomized to chloroquine (500 mg twice daily for 10 days) demonstrated better outcomes than those randomized to lopinavir-ritonavir (400-100 mg twice daily for 10 days) with respect to time to viral clearance, radiographic clearance, and discharge from hospital.[61]

Case reports have also described the use of hydroxychloroquine or chloroquine, although the patients described in these cases were also treated with other antiviral or anti-inflammatory medications, making it difficult to isolate individual contributions to recovery.[33,34]

On the other hand, several large-scale randomized controlled trials have demonstrated a lack of response to hydroxychloroquine in the treatment of COVID-19. In the RECOVERY trial, death at 28 days occurred in 27.0% of the 1561 hospitalized patients with COVID-19 randomized to hydroxychloroquine compared with 25.0% in the 3155 patients randomized to standard care.[62] Hydroxychloroquine was associated with increased length

of hospitalization and progression to mechanical ventilation or death. The ORCHID (Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among In-patients With Symptomatic Disease) trial and the hydroxychloroquine arm of the Solidarity Trial yielded similar preliminary findings, prompting discontinuation by the United States National Institute of Health and the WHO, respectively.[41,63] In addition, a randomized trial of 821 asymptomatic participants from the United States or Canada with moderate- to high-risk exposure to COVID-19 showed no significant reduction in incidence of COVID-19 infection in those randomized to hydroxychloroquine taken within 4 days of exposure for postexposure prophylaxis.[64]

Therefore, the evidence to date would not support the use of hydroxychloroquine as postexposure prophylaxis or treatment of COVID-19.

Tocilizumab: Acute respiratory distress syndrome typically occurs in patients with severe COVID-19 infection with macrophage activation syndrome. Severity of COVID-19 and death in ARDS are associated with elevated interleukin 6 (IL-6) levels driven by ongoing infections.[65,66] In this context, tocilizumab, an anti–IL-6 monoclonal antibody used in the treatment of rheumatoid arthritis, has been proposed as a potential COVID-19 treatment.[67,68]

A case series from Wuhan, China, described 15 moderate to severely ill patients with COVID-19 who received tocilizumab at varying doses.[69] Five patients received tocilizumab more than once, and 8 received concurrent methylprednisolone. During the 7-day observation period following treatment, 10 patients stabilized, 2 worsened, and 3 died. Of the 4 critically ill patients who received a single dose of tocilizumab, 3 died and the C-reactive protein (CRP) level, a marker of inflammation, in the fourth patient failed to normalize. However, CRP levels in all 15 patients decreased significantly after treatment with tocilizumab (126.9 mg/L [95% CI 10.7 to 257.9 mg/L] vs 11.2 mg/L [95% CI 0.02 to 113.7 mg/L]; $P<.01$).

The use of tocilizumab has also been demonstrated in several case reports of patients with COVID-19 in the setting of specific pre-existing medical conditions. In a patient with metastatic sarcomatoid clear cell renal cell carcinoma, 2 doses of 8 mg/kg of tocilizumab were administered following an initial course of lopinavir-ritonavir after he experienced sudden-onset dyspnea and decrease in oxygen saturation.[70] His CRP level and body temperature decreased and his oxygen saturation improved following treatment, with eventual full recovery. In another patient with multiple myeloma, a single dose of 8 mg/kg of tocilizumab was administered owing to persistent pulmonary infiltrates on radiography and sustained IL-6 elevation despite initial treatment with methylprednisolone.[71] Symptoms of chest tightness fully resolved 3 days following treatment, radiographic findings improved, and IL-6 levels gradually decreased in the subsequent 2 weeks. In yet another case, a patient who had already been on a regimen of 8 mg/kg of tocilizumab every 5 weeks for the previous 3 years for systemic sclerosis was diagnosed with COVID-19 after presenting with mild symptoms of cough, headache, and malaise.[72] Her upcoming tocilizumab infusion was postponed and she recovered at home with no need for additional treatment. The authors proposed that the use of tocilizumab for chronic autoimmune disease might have been protective against the development of severe COVID-19.

Beyond case reports, a retrospective observational cohort study of 544 patients with severe COVID-19 pneumonia in Italy showed a significantly reduced risk of mechanical ventilation or death among the subgroup of 179 non–randomly selected patients treated with tocilizumab compared with those treated with standard care alone (adjusted HR=0.61; 95% CI 0.40 to 0.92; $P=.02$).[73] On the other hand, in the phase 3 COVACTA (Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia) trial of 479 patients, there was no significant difference in the primary end point of clinical status on day 28 based on a 7-point ordinal scale between patients randomized to tocilizumab versus placebo.[74] In contrast, in the similar phase 3 EMPACTA (Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Participants With COVID-19 Pneumonia) trial of 389 patients, 12.2% of patients randomized to tocilizumab progressed to mechanical ventilation or death by day 28 compared with 19.3% in the placebo arm, representing a 44% reduction (HR=0.56; 95% CI 0.32 to 0.97; log-rank $P=.03$).[75] Full data from these 2 randomized trials have yet to be published in peer-reviewed journals at the time of writing. Further analysis is required to better understand these mixed results.

Overall, studies suggest a potential role for tocilizumab in the treatment of COVID-19. However, given the mixed results from the 2 largest randomized trials to date, further studies are needed to clarify its safety and efficacy in treating COVID-19.

Oseltamivir: There is limited evidence supporting the use of oseltamivir in the treatment of COVID-19.

In one case series, 5 patients who were co-infected with COVID-19 and influenza A or B fully recovered following treatment with oseltamivir combined with supportive care, antibiotics, and glucocorticoids.[76] In addition, a case report described a patient with diabetes who recovered from COVID-19 following treatment with oseltamivir, ganciclovir, and antibiotics.[77]

There have been no published randomized trials to date assessing the efficacy of oseltamivir to treat COVID-19. Routine administration of oseltamivir for the specific purpose of treating COVID-19 is therefore not recommended.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs): Whether to continue use of ACE inhibitors or ARBs to treat comorbid conditions for which they are indicated among patients

with COVID-19 has been an important consideration.[78] As SARS-CoV-2 uses ACE2 as a co-receptor for viral entry, there has been concern that use of ACE inhibitors or ARBs, which increase expression of ACE2, could increase susceptibility to COVID-19 infection.[79] In contrast, increased ACE2 expression has been shown to have a potential paradoxically protective effect in reducing the severity of acute lung injury and ARDS through its effects on endothelial function.[80,81]

A retrospective study in Wuhan, China, analyzed differences in clinical characteristics and clinical outcomes in 112 patients with cardiovascular disease infected with COVID-19, including 16 patients who were critically ill.[82] The presence of cardiovascular disease was associated with disease severity and mortality, but there were no significant differences in ACE inhibitor or ARB use between critically ill patients and all others, nor in survivors versus nonsurvivors.

More recently, data from 3 larger clinical studies have provided additional insight into the effects of ACE inhibitors and ARBs on COVID-19 risk, prognosis, and clinical outcomes. In a large population-based, case-control study from Italy comparing 6272 patients with COVID-19 with 30 759 controls matched by age, sex, and municipality, the use of ACE inhibitors or ARBs did not appear to affect the risk from COVID-19.[83] Similarly, a study of 12 594 patients from New York who were tested for COVID-19 (5894 tested positive), based on electronic health records, found no association between the use of antihypertensive medications including ACE inhibitors and ARBs and risk of COVID-19 infection or progression to severe illness.[84] Moreover, in the phase 4 BRACE CORONA (Angiotensin Receptor Blockers and Angiotensin-converting Enzyme Inhibitors and Adverse Outcomes in Patients With COVID-19) trial, which randomized 334 patients hospitalized with COVID-19 to temporary suspension of their ACE inhibitors or ARBs and 325 patients to continued use, there was no significant difference in the primary end point of number of days alive and out of the hospital at 30 days (21.9 vs 22.9, $P=.09$).[85,86]

In addition to demonstrating the safety of continued ACE inhibitor and ARB use among patients with COVID-19, other studies have suggested their potential incremental benefits with respect to providing indirect antiviral activity by modulating immune function and inflammatory response. In a retrospective study of 417 hospitalized patients with COVID-19 in Shenzhen, China, a lower proportion of patients who were treated with ACE inhibitors or ARBs progressed to severe infection, and these patients demonstrated a trend toward lower IL-6 levels, statistically significantly higher levels of CD3+ and CD8+ T cells, and lower peak viral load based on significantly higher cycle threshold values ($P=.03$) compared with those receiving other anti-hypertensive agents.[87] In another retrospective study of 1128 hospitalized patients with COVID-19 in Hubei, China, including 188 patients who were taking ACE inhibitors or ARBs, use of these medications was associated with a lower risk of mortality (adjusted HR=0.37; 95% CI 0.15 to 0.89; $P=.03$).[88] In a study of 2263 outpatients and 7933 inpatients in the United States, use of ACE inhibitors was associated with a lower risk of hospitalization (HR=0.61; 95% CI 0.41 to 0.93; $P=.02$) although benefits did not extend to those taking ARBs and were limited to outpatients rather than inpatients and to those in the Medicare group rather than the commercially insured group.[89]

Overall, the evidence available to date would support the continuation of ACE inhibitors or ARBs in patients with COVID-19 who were already taking these medications for other indications before infection. However, there is insufficient evidence at this time to support their initiation for the sole purpose of treating COVID-19.

Nonsteroidal anti-inflammatory drugs: These drugs, particularly ibuprofen, suffered from misguided drug advice and subsequent media hype during early months of the COVID-19 pandemic.[90,91]

Similar to ACE inhibitors and ARBs, ibuprofen had previously demonstrated in vitro and in vivo activity in inducing ACE2 overexpression. Additionally, previous studies of patients with other respiratory tract infections demonstrated an association between NSAID use and poorer clinical outcomes.[92]

There remains no robust scientific evidence to support or refute the use of ibuprofen or other NSAIDs in patients with COVID-19. However, NSAID use, like that of other antipyretic medications, could theoretically mask common COVID-19 symptoms such as fever, thereby potentially increasing the spread and exposure of the infection at a community level.

Anticoagulants: Thromboembolic events, including pulmonary embolism, ischemic stroke, and myocardial infarction, have been observed in patients with COVID-19, presumably owing to a prothrombotic state caused by the infection.[93-95] For this reason, the routine use of either prophylactic or therapeutic doses of anticoagulation to prevent or reduce these complications has been explored in patients hospitalized with COVID-19.

Among the numerous observational studies of anticoagulation use in patients with COVID-19, the largest and most informative to date involved a retrospective analysis of 4389 patients hospitalized with COVID-19 in New York, NY.[96] Both prophylactic and therapeutic doses of anticoagulation were associated with reduced mechanical ventilation (adjusted HR=0.72; 95% CI 0.58 to 0.89; $P=.003$; and adjusted HR=0.69; 95% CI 0.51 to 0.94; $P=.02$, respectively) and in-hospital mortality (adjusted HR=0.50; 95% CI 0.45 to 0.57; $P<.001$; and adjusted HR=0.53; 95% CI 0.45 to 0.62; $P<.001$, respectively) compared with no anticoagulation. Among the subgroup of patients who received anticoagulation within 48 hours of admission, there was a trend toward lower in-hospital mortality with therapeutic

doses compared with prophylactic doses, although it did not achieve statistical significance (adjusted HR=0.86; 95% CI 0.73 to 1.02; *P*=.08).

Only 1 randomized controlled trial to assess the effect of anticoagulation on outcomes for patients with COVID-19 had been published at the time of writing. In the HESACOVID (Therapeutic Versus Prophylactic Anticoagulation for Severe COVID-19) trial, the 10 patients randomized to therapeutic enoxaparin showed a statistically significant increase in PaO_2/FiO_2 ratio (ratio of arterial oxygen partial pressure to fractional inspired oxygen), higher rates of successful weaning from mechanical ventilation, and more ventilator-free days when compared with the 10 patients randomized to prophylactic anticoagulation.[97] However, the very small sample size was an important limitation, and the study was underpowered to detect a difference in mortality.

Several larger randomized controlled trials are ongoing to clarify the role of anticoagulation in managing patients hospitalized with COVID-19. Among the largest, the ATTACC (Antithrombotic Therapy to Ameliorate Complications of COVID-19) trial aims to enrol 3000 participants, while the ACTIV-4 (Accelerating COVID-19 Therapeutic Interventions and Vaccines: Antithrombotics) trial aims to enrol 2000 participants; both are randomizing patients to therapeutic heparin versus usual care, which includes prophylactic anticoagulation.[98,99] An outpatient component of the ACTIV-4 trial will also investigate the effect of acetylsalicylic acid or apixaban in patients with COVID-19 who do not require hospitalization.

As shown, the purported benefits of anticoagulation in patients with COVID-19 have thus far been largely based on observational data. Whether similar results can be reproduced in randomized controlled trials remains to be seen. Further studies will also need to establish the optimal anticoagulant and dosing regimen that will reduce the risk of thrombotic complications without substantially increasing the risk of bleeding.

Conclusion

In the absence of specific effective therapies for COVID-19, many clinicians are repurposing medications used for other indications to supplement the usual supportive care management of these patients. We reviewed the most widely used medications suggested for the treatment of patients with COVID-19. Current evidence supports the selective use of remdesivir and corticosteroids in severe cases, while the role of other medications remains less clear, particularly in mild to moderate cases that might improve on their own. Large-scale randomized trials are needed to clarify the role of these medications before widespread routine use.

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Contributors
All authors contributed to the literature review and interpretation, and to preparing the manuscript for submission.

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