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SARS-CoV-2 pharmacologic therapies and their safety/ effectiveness according to level of evidence

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Abstract

Introduction: There is a pressing need for COVID-19 transmission control and effective treatments. We aim to evaluate the safety and effectiveness of SARS-CoV-2 pharmacologic therapies as of August 2, 2020 according to study level of evidence.

Methods: PubMed, ScienceDirect, Cochrane Library, JAMA Network and PNAS were searched. The following keywords were used: ((COVID-19) OR (SARS-CoV-2)) AND ((((((therapeutics) OR (treatment)) OR (vaccine)) OR (hydroxychloroquine)) OR (antiviral)) OR (prognosis)). Results included peer-reviewed studies published in English.

Results: 15 peer-reviewed articles met study inclusion criteria, of which 14 were RCTs and one was a systematic review with meta-analysis. The following pharmacologic therapies were evaluated: chloroquine (CQ), hydroxychloroquine (HCQ), antivirals therapies, plasma therapy, anti-inflammatories, and a vaccine.

Conclusion: According to level 1 evidence reviewed here, the most effective SARS-Co-V-2 pharmacologic treatments include remdesivir for mild to severe disease, and a triple regimen therapy consisting of lopinavir-ritonavir, ribavirin and interferon beta-1b for mild to moderate disease. Also, dexamethasone significantly reduced mortality in those requiring respiratory support. However, there is still a great need for detailed level 1 evidence on pharmacologic therapies.

Keywords: SARS-CoV-2; COVID-19 Pharmacologic Treatments; Drug Effectiveness; Drug Safety; COVID-19 Clinical Outcomes

Introduction

In December, 2019, an outbreak of clustered pneumonia cases occurred in Wuhan, China.[1] It was determined to be the result of a novel coronavirus named SARS-CoV-2.[1] The source of human infection

was suggested to be zoonotic in origin, with human-to-human transmission occurring through respiratory droplets, fomites, and fecal-oral spread.[2] As of August 2, 2020, there are over 17 million confirmed cases worldwide with over 680 thousand deaths.[3] The burden on the United States (US) healthcare system has increased dramatically, especially on hospitals and intensive care units (ICUs). A systematic review and meta-analysis reported that 20.3% of COVID-19 positive patients were admitted to the ICU.[4]

Paramount to the treatment of COVID-19 positive patients is an understanding of the pathogenesis of disease.[5] After it has entered the host's system, it primarily replicates in the mucosal epithelium of the upper respiratory tract and, in some instances, the gastrointestinal mucosa. Data strongly suggests that the virus gains entry into host cells through the same mechanism as SARS-CoV, through angiotensin-converting enzyme 2 (ACE2).[5] It has been postulated that the development of ACE2 downregulation and the over-activation of T-cells are one of the first factors in the cascade that leads to ARDS. Specifically, downregulation of ACE2 leads to pulmonary edema mediated by a dysfunction in RAS. Meanwhile, over-activation of T-cells leads to an immune dysfunction, which can result in cytokine storm. Both cytokine storm and pulmonary edema are contributors to the development of ARDS.[5]

The first-line methods for diagnosing and detecting SARS-CoV-2 are molecular-based. Currently, the most common and reliable option for diagnosis is reverse-transcription polymerase chain reaction (RT-PCR).[6,7] Serologic antibody tests are also useful for people with prior infection or current infection presenting later on in the course of disease.[8,9] Additionally, although rapid antigen tests exist, the World Health Organization (WHO) recommends against these tests as a result of their low accuracy.[7] A presumptive diagnosis of COVID-19 may be made with adequate clinical and epidemiological evidence. For example, the most common clinical presentations have been fever followed by development of dyspnea shortly thereafter. Among hospitalized patients, lymphopenia, elevated aminotransferase levels, and elevated inflammatory markers have been reported.[10,11] With the increased strain on the healthcare system and the need for immediate disease and transmission control, pharmacologic development is necessary. In consideration of the evolving data, this review aims to evaluate and compare the effectiveness of different SARS-CoV-2 pharmacologic treatments as of August 2, 2020 and assess their safety and clinical outcomes according to study level of evidence.

Methods

Data search and collection strategy

PubMed, ScienceDirect, the Cochrane Library, JAMA Network and Proceedings of the National Academy of Sciences (PNAS) were reviewed. A literature search was conducted using the following

query: ((COVID-19) OR (SARS-CoV-2)) AND ((((((therapeutics) OR (treatment)) OR (vaccine)) OR (hydroxychloroquine)) OR (antiviral)) OR (prognosis)). Titles and abstracts were screened for eligibility and duplicate results. Next, full-text screening was conducted independently by three authors (AB, CS, and AE). Results were categorized in descending order based on the level of evidence, with level 1 evidence being randomized control clinical trials and meta-analyses of systematic reviews.[12] The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used. Literature review was conducted for articles that met study inclusion criteria between October 1st, 2019 through August 2nd, 2020. (Figure 1 and Table 1)

Inclusion criteria

Only articles published in English were included. In addition, we only included the higher level of evidence studies (level 1) in our final analysis.

Exclusion criteria

Abstracts were screened for eligibility. Those that did not meet our search inclusion criteria or were duplicates were excluded. Articles on coronavirus strains other than SARS-CoV-2, articles without established outcomes from specific therapies, and articles on theoretical pharmacologic applications were excluded.

Results

Initial inclusion criteria yielded 15,077 PubMed, 12,682 ScienceDirect, 745 Cochrane, 64 JAMA, and 16 PNAS results. After applying exclusion criteria, 15 studies remained for analysis, 14 of which were randomized clinical trials (RCTs) and one being a systematic review with meta-analysis. Pharmacologic therapies including chloroquine/hydroxychloroquine, antivirals, anti-inflammatory agents, immunomodulatory agents, vaccines, anticoagulants, plasma therapy and traditional Chinese medicine were found upon initial search, although level 1 evidence was only available for chloroquine/hydroxychloroquine, various antivirals, plasma therapy, anti-inflammatories, and a vaccine.

Level 1 evidence

Randomized Controlled Trials

i. *Hydroxychloroquine/chloroquine*

A parallel, double-masked, phase IIb RCT was conducted comparing high and low doses of chloroquine diphosphate (CQ) in patients with severe COVID-19.[13] Patients were either administered 600 mg CQ bid for 10 days, or 450 mg CQ bid for 1 day followed by 450 mg CQ once daily for 4 days. Patients were concurrently given 500 mg azithromycin daily for 5 days.[13] 86.8% and 92.5% of low dose and high dose patients received 75 mg oseltamivir twice daily for 5 days on the basis of suspected influenza infection.[13] The primary outcome was dose-related CQ lethality, and it was hypothesized that the lethality rate of the high dose group would decrease by at least 50% compared to the low dose group. However, results showed the opposite, with 39% lethality in the high dose group and 15% in the low dose group.[13] Results also showed that the high-dose group had a higher incidence of QT prolongation greater than 500ms. Following an unplanned interim analysis of study findings due to CQ dosages related safety concerns, the study independent data safety and monitoring board (DSMB) recommended the immediate interruption of the trial for patients on high dose CQ from all age groups, unmasking, and converting all to low dose CQ.[13] They concluded that patients with severe COVID-19 should not be given a high dose of CQ especially with azithromycin and oseltamivir due to risk of QT prolongation and associated lethality. However, findings from patients with prolonged QT showed no clear association between the first day of prolonged QT and day of death, and that cumulative dosages were not higher among prolonged QT associated fatalities.[13] In addition, it is important to be aware that this study had a small sample size, lacked of a placebo control group and used a historical control group. Instead, findings were only adjusted by age, and pre-protocol analysis was not conducted due to inability to register daily untaken or mistaken CQ doses because or renal or liver failures.[13]

An open label RCT conducted on patients 18 years and older with mild or moderate ongoing SARS CoV-2 investigated the effects of hydroxychloroquine (HCQ) on negative conversion by 28 days.[14] Patients were administered 1200 mg of HCQ daily for three days followed by a maintenance dose of 800 mg daily (11 days if mild, 18 days if moderate).[14] Results showed that those treated with standard care plus HCQ had an 85.4% probability of negative conversion by day 28 (95% CI 73.8-93.8), whereas those treated with standard care alone had an 81.3% chance (95% CI 71.2-89.6).[14] However, this difference was reportedly not significant. Due to the trial ending early and only two patients (out of 150) with severe disease being enrolled, results on clinical improvement were not presented.[14] This study was limited by its underpowered sample size, non-computerized randomization protocol, and open label design.[14]

A more recent, multicenter, open-labeled controlled trial was conducted to assess the efficacy of HCQ with and without azithromycin compared to the standard of care.[15] The study was performed on patients

with suspected or confirmed mild to moderate COVID-19 with 14 or fewer days since symptom onset. Patients in the HCQ group received a dose of 400 mg twice daily for seven days. Patients in the HCQ plus azithromycin additionally received a dose of 500 mg of azithromycin once daily for seven days. Clinical status at 15 days was evaluated using a 7-level ordinal scale. Results showed no significant difference in the 7-level ordinal scale at 15 days between those treated with HCQ and standard care (OR 1.21, 95% CI 0.69-2.11, p=1.00), or between those treated with HCQ + azithromycin and standard care (OR 0.99, 95% CI 0.57-1.73, p=1.00).[15] There were also no significant differences in the number of days free from respiratory support, use of high-flow nasal cannula or non-invasive ventilation, use of mechanical ventilation, duration of hospital stay, in-hospital death, thromboembolic complications, or acute kidney injury between the groups.[15] They also found that prolongation of QT interval was more frequent in the experimental groups (especially the HCQ plus azithromycin group), and elevation of liver enzymes was more frequent in the HCQ plus azithromycin group than the control group.[15] Limitations of this study include lack of blinding, concomitant treatment of patients with other pharmacologic agents, and the fact that some patients were previously treated with HCQ ± azithromycin at other hospitals prior to enrollment in this trial.[15]

Another RCT was conducted to assess the efficacy of HCQ as a post-exposure prophylaxis.[16] Participants were adults with household or occupational exposure to someone with laboratory confirmed COVID-19 at a distance of less than 6 ft for more than 10 minutes without a face mask and/or eye shield. Time from exposure to enrollment varied between 1-4 days in all participants. Patients in the HCQ group were administered 800 mg HCQ once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days for a total course of 5 days. Results showed that the incidence of new illness compatible with COVID-19 did not significantly differ between participants receiving HCQ (11.8%) and placebo (14.3%) (p=0.35).[16] Also, there was no meaningful difference in the effectiveness according to the time of starting post-exposure prophylaxis.[16] Side effects were significantly more frequent in the HCQ group by day 5 (p<0.001), with nausea, loose stools and abdominal discomfort being the most commonly reported side effects.[16] No serious adverse reactions or cardiac arrhythmias were reported. This study is limited by its use of an a priori symptomatic case definition in some patients as opposed to diagnostic testing.[16]

ii. *Antivirals*

Preliminary results of a double-blind randomized controlled trial by Beigel et al. suggest that a 10-day course of remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) is superior to placebo. This study, which was conducted in 60 sites throughout the world, analyzed 1,059 patients and aimed to assess the effect of remdesivir on time to recovery, clinical improvement, and

mortality in patients with varying baseline severity.[17] Those who received remdesivir had a statistically significant different median recovery time than placebo, 11 days vs 15 days (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; p<0.001).[17] The authors additionally stratified these results by disease severity, where the beneficial effects of remdesivir appeared to be more pronounced in the severe disease stratum. Also, the remdesivir group had higher odds of improvement in the 8-level ordinal scale score at day 15 compared to placebo (OR 1.50, 95% CI 1.18-1.91).[17] Although mortality was numerically lower in the remdesivir group, this difference was not statistically significant.[17] Patients on remdesivir who were receiving high-flow oxygen, mechanical ventilation, or extracorporeal membrane oxygenation did not achieve significant differences compared to placebo.[17]

Another double blind, placebo-controlled, multicenter RCT was conducted on the effectiveness of remdesivir in confirmed SARS-CoV-2 positive patients with severe COVID-19.[18] Patients were either assigned to receive intravenous remdesivir or placebo infusions. Remdesivir was administered at 200 mg on day 1 followed by 100 mg on days 2-10. Their primary outcome was time to clinical improvement within 28 days after randomization. Some patients were concomitantly treated with corticosteroids, lopinavir-ritonavir or interferons. Intention to treat analysis revealed a non-significant decrease in the time to clinical improvement for the remdesivir group compared to placebo. Survival at 28 days and clinical improvement at 14 and 28 days were also not statistically significantly different, although numerically higher in the remdesivir group. Serious adverse events occurred in 18% and 26% of the remdesivir and placebo groups respectively.[18] Intravenous remdesivir did not provide significant improvements in patients with severe COVID-19. This study was limited by insufficient power, the late initiation of therapy and absence of data on viral recovery.[18]

Another RCT evaluated the efficacy of remdesivir therapy after a 5- or 10-day regimen in patients with varying baseline clinical status.[19] Clinical status on day 14 as measured by a 7-point ordinal scale was the primary endpoint. Patients were administered 200 mg of remdesivir on day 1, followed by 100 mg once daily for the next 4 or 9 days. Results showed that clinical improvement of 2 points or more occurred in 65% of patients in the 5-day group and 54% of patients in the 10-day group.[19] After correction of imbalance of baseline clinical status, clinical status at day 14 was similar between the 5-day and 10-day groups (p=0.14). It was concluded that there was no significant difference in efficacy between a 5-day or 10-day course. This study is limited by the fact that the patients in the 10-day group had a significantly worse clinical status than those in the 5-day group (p=0.02), however the authors state that results were adjusted for this discrepancy.[19] Other limitations include lack of placebo and the open-label design.[19]

One clinical trial was conducted on 14-day triple medication protocols compared to 14-day lopinavir-ritonavir therapy alone.[20] This open-label, randomized trial tested a triple medication regimen including interferon beta-1b, lopinavir-ritonavir, and ribavirin. Patients enrolled had mild to moderate COVID-19. The dosage for the experimental group was lopinavir 400 mg and ritonavir 100 mg every 12h, ribavirin 400 mg every 12h, and three doses of 8 million IU of interferon beta-1b on alternate days. The control group received 14 days of lopinavir 400 mg and ritonavir 100 mg every 12h. Patients who were admitted to the clinical trial after the 7th day of experiencing symptoms were not treated with interferon beta-1b due to its proinflammatory properties. Their primary outcome measure was time to a negative RT-PCR assay by nasopharyngeal swab. The combination group had a significantly shorter median time to a negative RT-PCR than the control group. A negative SARS-CoV-2 was achieved in a median time of 7 days in the experimental group vs 12 in the control. Additionally, clinical improvement was significantly better in the experimental group than the control with a median time to alleviation of symptoms of 4 vs 8 days.[20] This study had an open-label design, absence of placebo group, and was also confounded by subgroup omitting of interferon beta-1b within the combination group, depending on time from symptom onset.[20]

Another randomized controlled open-label trial in 199 hospitalized patients with confirmed SARS-CoV-2 with severe COVID-19 was done to compare the clinical effectiveness of lopinavir-ritonavir to standard care alone.[21] Severe COVID-19 was defined as SARS-CoV-2 positivity, pneumonia confirmed by chest imaging, and an oxygen saturation of 94% or less while breathing ambient air or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen at or below 300 mg Hg. Patients in the experimental group were treated with 400 mg/100 mg of lopinavir-ritonavir for 14 days. The time to clinical improvement, mortality at day 28, and detectable viral load were not significantly different between groups.[21] Limitations of this study include a non-blinded protocol, higher baseline throat viral loads in the lopinavir–ritonavir group, and absence of data on lopinavir exposure levels in severe and critically ill patients.[21]

A more recent RCT done on patients with mild to moderate COVID-19 aimed to compare the difference in rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid between lopinavir/ritonavir and arbidol (umifenovir).[22] Patients were administered either 400mg/100mg lopinavir/ritonavir PO twice daily for 7-14 days, or 200 mg of umifenovir PO three times daily for 7-14 days. Results showed no significant difference in the rate of positive-to-negative conversion between the lopinavir/ritonavir, arbidol, and control groups ($p>0.05$).[22] There was also no significant differences between the groups for the rates of antipyresis, cough alleviation, or improvement of CT findings at day 7 or 14 ($p>0.05$).[22] The lopinavir/ritonavir and arbidol groups experienced adverse effects; whereas the control group did not.[22]

Limitations include small sample size, single center design, and lack of blinding to clinicians who recruited patients and research staff.[22]

iii. *Anti-inflammatory agents*

A multicenter, single-blind RCT was conducted to assess the time to clinical improvement in patients with severe COVID-19 treated with ruxolitinib, a JAK inhibitor.[23] Time to clinical improvement was measured as time from randomization to an improvement of 2 points on a 7-category ordinal scale, or live discharge from the hospital. Patients in the experimental group received 5 mg twice daily of ruxolitinib. Results showed that ruxolitinib plus standard-of-care was associated with a non-statistically significant decrease in median time clinical improvement (12 [IQR, 10-19] days vs. 15 [IQR, 10-18] days).[23] However, 90% of ruxolitinib patients had significant CT improvement at day 14 compared to 61.9% of control patients (p=0.0495), and levels of 7 cytokines (including IL-6, IL-12 and VEGF) were significantly decreased in the experimental group, demonstrating the anti-inflammatory effects of ruxolitinib.[23] Also, the 28-day overall mortality was 0% in the experimental group and 14.3% in the control group.[23] This study is limited by its small sample size, use of an ordinal scale to assess primary end points, concomitantly treatment of some patients with other pharmacologic agents, and lack of inclusion of critically ill patients and patients with invasive ventilator dependence.[23]

A preliminary, open-label RCT was conducted to assess the effect of dexamethasone on 28-day mortality in hospitalized patients with clinically suspected or laboratory confirmed SARS-CoV-2 infection.[24] The study included patients under 18 years old and pregnant or breastfeeding women. Patients in the dexamethasone group were administered 6 mg of oral or intravenous dexamethasone once daily for up to 10 days or hospital discharge if sooner. Results showed that mortality at day 28 was significantly lower in the experimental group, 22.9% of patients treated with dexamethasone died within 28 days, compared to 25.7% of patients treated with standard care (age-adjusted rate ratio 0.83, 95% CI 0.75-0.93).[24] Compared to the standard of care group, the incidence of death lower in dexamethasone patients receiving mechanical ventilation (rate ratio 0.64, 95% CI 0.51-0.81) and in those receiving oxygen without mechanical ventilation (rate ratio 0.82, 95% CI 0.72-0.94), but not in those receiving no respiratory support (rate ratio 1.19, 95% CI 0.91-1.55).[24] Patients with a longer duration of symptoms benefitted more (in terms of reducing mortality) from dexamethasone treatment. Patients treated with dexamethasone also had a shorter duration of hospitalization (median 12 days vs. 13 days). Limitations include an open-label design and provision of preliminary data.[24]

iv. *Vaccines and immune therapy*

A randomized, double-blind, placebo-controlled trial was conducted to assess the effectiveness of an Ad5-vectored COVID-19 vaccine.[25] There were two experimental groups, one of which received a higher dose of viral particles (1×10^{11} particles) and another that received a lower dose of viral particles (5×10^{10} particles). Participants who received either a low or high dose of viral particles had a significant increase in RBD-specific ELISA antibodies, seroconversion rates, and neutralizing antibody responses compared to the placebo group.[25] The placebo group showed no increase in antibody from baseline, and no IFNγ-ELISpot responses.[25] Severe adverse reactions occurred in 9% of the high dose patients and 1% of the low dose patients, although no serious adverse reactions were documented.[25] It is important to note that 52% of participants had high pre-existing immunity, and 48% of the participants had low pre-existing immunity.[25] The authors also did not calculate sample size based on study power in advance, and only reported data within 28 days of vaccination.[25]

Another RCT sought to evaluate the effects of convalescent plasma therapy on the time to clinical improvement within 28 days in patients with severe or life threatening COVID-19.[26] Patients were administered a dose of approximately 4 to 13 mL/kg of recipient body weight. Clinical improvement was defined by either a reduction of 2 points on a 6-point disease severity scale, or discharge. Clinical improvement within 28 days occurred in 51.9% of patients in the convalescent plasma group compared to 43.1% in the control group (8.8% difference, 95% CI -10.4-28.0%, p=0.26), and clinical improvement occurred at a higher rate in those with severe disease compared to those with life threatening disease (91.3% vs 68.2%).[26] Also, use of convalescent plasma resulted in an 87.2% negative conversion rate of viral PCR at 72 hours compared to 37.5% in the control group.[26] However, there was no significant difference in 28-day mortality (CR 0.65, 95% CI 0.29-1.46) or time to discharge (HR 1.61, 95% CI 0.88-2.93).[26] This study had a small sample size and open label design, was terminated early for unclear reasons, and was possibly underpowered.[26]

Systematic review with meta-analysis

i. *Hydroxychloroquine/chloroquine*

A systematic review on the safety and efficacy of HCQ was done on seven studies, of which three were used for meta-analysis.[27] In patients treated with HCQ, two of the studies reviewed showed a reduction in the time to body temperature normalization, and one study showed a reduction in the duration of cough.[27] Meta-analysis revealed that treatment with HCQ resulted in fewer cases of radiological progression of lung damage and no difference in virologic cure (on day 6-7) or death in patients compared to control groups undergoing conventional treatment.[27] This data is limited by a small sample size and lack of

definition of the conventional treatment given to control groups.[27] The authors of this study also did not specify whether the studies included assessed patients with mild, moderate or severe COVID-19.[27]

Discussion

According to the level 1 evidence reviewed here, the most effective treatments against SARS-CoV-2, measured by time to negative RT-PCR and time to clinical improvement, are remdesivir therapy and a triple medication regimen (lopinavir-ritonavir, ribavirin, and interferon beta-1b).[17-18, 20] Remdesivir showed beneficial effects in patients with varying baseline severity. It resulted in a decrease in mean recovery time, higher odds of improvement on an 8-level ordinal scale at day 15, and a non-statistically significant decrease in mortality in patients with mild to severe COVID-19.[17] It also resulted in a non-statistically significant reduction in time to clinical improvement in patients with severe COVID-19 with no effect on mortality.[18] One reason for not finding a significant effect of remdesivir in severe COVID-19 patients could be insufficient power.[18] Remdesivir also appears to have some beneficial effects in severe COVID-19 patients irrespective of the time to initiation of therapy.[18] However, there was no difference in clinical improvement between a 5-day and 10-day course of remdesivir in patients with varying baseline clinical status.[19] In patients with mild to moderate COVID-19, the triple medication regimen appeared to be most beneficial, as it resulted in a significantly shorter median time to negative RT-PCR compared to therapy with just lopinavir-ritonavir.[20]

Evidence gathered from other RCTs show several additional findings. First, in patients with severe COVID-19, treatment with lopinavir-ritonavir showed no significant difference in time to clinical improvement, mortality at day 28, or detectable viral load compared to standard care alone.[21] Also, treatment with lopinavir/ritonavir did not significantly affect the rate of positive-to-negative conversion when compared to arbidol in patients with mild to moderate COVID-19.[22] Second, mortality and QT prolongation was worse in severely ill patients taking high doses of CQ compared to low doses.[13] QT prolongation was also significantly higher in patients with mild to moderate COVID-19 treated with HCQ and HCQ plus azithromycin.[15] Additionally, HCQ showed no significant effect on the probability of negative conversion by day 28 or virologic cure compared to standard care alone in patients with mild to moderate COVID-19.[14,27] It also did not reduce the prevalence of unfavorable secondary outcomes such as need for respiratory support, mechanical ventilation, or thromboembolic complications in patients with

mild to moderate COVID-19.[15] Moreover, HCQ did not reduce the incidence of new illness when used as a post-exposure prophylaxis.[16] However, meta-analysis did reveal that HCQ treatment resulted in fewer cases of radiological progression of lung damage.[27] Furthermore, treatment of severe COVID-19 patients with ruxolitinib resulted in a non-statistically significant decrease in median time to clinical improvement, and a statistically significant decrease in levels of seven cytokines including IL-6, IL-12 and VEGF, indicating that it may be useful in treating cytokine storm.[23] Convalescent plasma was also efficacious in reducing the time to clinical improvement in severe and life threatening COVID-19.[26] Oral or intravenous dexamethasone was shown to significantly reduce mortality among hospitalized COVID-19 patients receiving mechanical ventilation or oxygen without mechanical ventilation.[24] Finally, vaccination of healthy individuals using an Ad5-vectored COVID-19 vaccine showed significant increase in immunity to SARS-CoV-2 by 28 days.[25]

While we await higher quality evidence from randomized control trials and meta-analyses, these results provide some context on the efficacy of pharmacologic therapy in COVID-19 patients. As of May 20, 2020, the FDA has granted emergency use authorization for intravenous remdesivir for severe COVID-19.[28] However, they have revoked emergency use authorization for use of hydroxychloroquine and chloroquine due to their high risk to benefit ratio.[28]

COVID-19 has undoubtedly posed a detrimental health burden worldwide. There is still a great need for detailed evidence on individual pharmacologic therapies. The findings from our review suggest that there is currently inconclusive evidence for one therapy. It is difficult to conduct studies on one category of pharmacologic treatment due to the lack of a universal systematic approach to treating COVID-19. In the absence of a vaccine available to the public, there is a great need for level 1 evidence from randomized controlled trials and meta-analyses to support the development of evidence-based guidelines to treat COVID-19 patients.

Aside from being novel, part of what makes treatment of SARS-CoV-2 difficult is its ability to affect multiple organ systems.[29] The disease is characterized as an acute respiratory failure but may have systemic outcomes such as gastrointestinal, cardiovascular, and nervous system symptoms in addition to multi-organ failure. There has been evidence of high incidence of pulmonary embolism and thrombotic events. These severe cases often present with thrombocytopenia, elevated D-dimer levels, and PT

prolongation. The hypercoagulable state often seen in COVID-19 patients can be explained by the overwhelming production of inflammatory cytokines. This increase in inflammatory markers leads to an activation of the coagulation cascade and inhibits the fibrinolytic pathway.[29] Aside from thrombotic disease, a proportion of patients with COVID-19 also present with acute kidney injury. Certain renal cells express ACE2 and TMPRSS2 receptors that the virus uses for its pathogenesis. Studies have shown that upon autopsy, kidney cells had evidence of virus particles on kidney podocytes and proximal tubule cells.[30]

Risk factors of deterioration in COVID-19 patients include presence of comorbid conditions.[31] Treating multisystemic manifestations becomes especially difficult in patients with existing comorbidities that require pharmacologic therapy. For example, patients with arrhythmia are particularly complicated due to their increased risk for QT prolongation, making it more risky to use treatments such as HCQ, CQ and azithromycin.[32-35] A multicenter study revealed that cancer patients with COVID-19 are three times more likely to die than non-cancer COVID-19 patients.[35] Interestingly, an observational study done on 20,133 hospitalized COVID-19 patients reported that the median age of patients was 73 (IQR 58-82), and increasing age was associated with mortality with a hazard ratio of 11.09 in patients over 80 compared to a hazard ratio of 8.51 in patients aged 70-79, 4.99 in patients aged 60-69 and 2.63 in patients aged 50-59.[36] Being over 50 years old had a significantly larger impact on mortality than sex at birth and pre-existing comorbidities.[36]

Another important point to be discussed is the increase of non-evidence-based treatment and the unintended morbidity and mortality that results from it. There has been a large increase in the spread of false information and non-evidence-based remedies, such as consumption of cow urine and high proof alcohol that have resulted in illness and even death.[37]

Furthermore, there has been a recent concern for patients who are using ACE-inhibitors. A case-population study in Spain on the admission rate of COVID-19 patients on ACE-inhibitors compared to other antihypertensive medications revealed that there was no increased risk of COVID-19 related admission to a hospital, and concluded that ACE-inhibitors not be discontinued.[38] However, there remains a concern, especially among uninformed providers and patients, on whether use of ACE-inhibitors pose a risk to patients during this pandemic.

A similar review done by Sanders et al. on pharmacologic treatment for COVID-19 report similar findings regarding the available pharmacologic options and the inconclusive nature of the available data on these drugs.[39] They additionally offer useful resources for clinical treatment guidance. In contrast, we have tailored our review to provide a more up to date, in-depth and systematic analysis using only level 1 evidence. Additionally, our discussion touches on the multisystem effects of SARS-CoV-2.

Undoubtedly, it is of utmost importance to discuss the safety profile of all the medications included. Many of these pharmacologic agents result in side effects ranging from mild to severe. First, HCQ and CQ have both been shown to cause cardiac electrical disturbances and cardiomyopathy.[40] One clinical trial using a dose of 600 mg twice daily for ten days was terminated early due to the death of 11 patients as a result of arrhythmias by the 6th day.[13] Other adverse effects associated with HCQ include retinopathy, gastrointestinal disturbances, and suicidal behavior.[41] Additionally, agents like HCQ and CQ can cause QT prolongation and their toxicity may be exacerbated when combined with other agents that also prolong the QT interval, such as Azithromycin.[42] Patients who develop QT prolongation without torsades de pointes should be treated immediately by correcting oxygen, potassium, calcium, and magnesium concentrations. Magnesium sulphate is recommended as the first-line therapy for torsades de pointes.[43] Cardiotoxicity has not been reported with remdesivir use. However, side effects of remdesivir include allergic reactions and increased liver enzymes.[44] Adverse effects associated with triple therapy using interferon beta 1b, lopinavir-ritonavir and ribavirin include diarrhea, nausea, and increased alanine transaminase levels, all of which stopped in one trial upon discontinuation of the drugs.[20] Additional side effect concerns with lopinavir-ritonavir include haptic injury, pancreatitis, acute gastritis, and QT prolongation.[21] Use of ruxolitinib in COVID-19 patients showed a favorable side-effect profile of the drug according to the RCT reviewed in this study.[23] Some of the adverse reactions included mild anemias, neutrocytopenia, thrombocytopenia, elevated liver enzyme levels, dizziness, rash, and nausea.[23] There were no serious adverse events such as acute heart failure, shock, and sepsis.[23] Adverse reactions of dexamethasone were not evaluated in the RCT included in this study; however, clinicians treating COVID-19 patients with dexamethasone should monitor their patients for hyperglycemia, secondary infections, psychiatric effects and avascular necrosis.[45] The Ad5-vectored vaccine also showed a favorable side-effect profile with most side effects being a result of the injection itself such as skin induration, redness, and swelling.[25] The systemic side effects reported were headache, vomiting, diarrhea, joint pain, muscle pain, fatigue, headache, and cough.[25] Lastly, adverse effects associated with the convalescent plasma trial included dyspnea, fever, and an allergic reaction caused by transfusion.[26]

These findings lead us to recommend that physicians follow updated guidelines from reputable sources. The Society of Surgical Oncology also offers frequently updated resources to assist physicians in treating particularly vulnerable patients with cancer.[46] Currently, there is also a great deal of randomized clinical trials that are ongoing and should provide the medical community with more conclusive evidence in the near future. According to the NIH, there are 2,962 active studies on COVID-19 as of August 2, 2020.[47]

The studies included in this review had several limitations. First, there was an issue of small sample size for several studies.[13,22-23,26] Another limitation to the findings is the inability to generalize them to all patients as a result of specific exclusion criteria such as individuals with mild or severe disease.[13-15,18,20-23,26] Also, several studies reviewed above aimed to focus on the efficacy and safety of one drug, but employed multiple drugs in the treatment of patients.[15,18,23] These limitations make it difficult to compare the efficacy and safety profiles of the drugs being used. The findings listed are dependent on the accuracy and validity of data used to assess SARS-CoV-2 pharmacological therapies. Lastly, given the rapidly evolving nature of the COVID-19 pandemic, it is difficult to ensure that all the existing evidence has been included up until this article's publication date.

Conclusion

There remains uncertainty regarding the safest and most effective pharmacologic therapy for COVID-19 disease. However, the findings from this review conclude that, according to level 1 evidence, remdesivir therapy in mild to severe disease, and the triple medication regimen (lopinavir-ritonavir, ribavirin and interferon beta-1b) in mild to moderate disease are the most efficacious against SARS-CoV-2 in terms of symptom improvement and time to a negative RT-PCR. Also, dexamethasone was significantly able to reduce mortality in patients receiving respiratory support. We recommend that physicians remain informed on up to date evidence such as preliminary data from RCTs, and work with their institution and scientific societies in developing evidence-based systematic guidelines in the treatment of COVID-19 patients.

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References

1. Ye ZW, Yuan S, Yuen KS, Fung SY, Chan CP, Jin DY. Zoonotic origins of human coronaviruses. *Int J Biol Sci*. 2020;16(10):1686-1697. Published 2020 Mar 15. doi:10.7150/ijbs.45472
2. Jin Y, Yang H, Ji W, et al. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. *Viruses*. 2020;12(4):E372. Published 2020 Mar 27. doi:10.3390/v12040372
3. COVID-19 situation report- 195 https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed August 2, 2020.
4. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis*. 2020;34:101623. doi:10.1016/j.tmaid.2020.101623
5. Jin Y, Yang H, Ji W, et al. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. *Viruses*. 2020;12(4):E372. Published 2020 Mar 27. doi:10.3390/v12040372
6. Ahn DG, Shin HJ, Kim MH, et al. Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19). *J Microbiol Biotechnol*. 2020;30(3):313–324. doi:10.4014/jmb.2003.03011
7. World Health Organization. Advice on the use of point-of-care immunodiagnostic tests for COVID-19, April 8 2020. https://www.who.int/news-room/commentaries/detail/advice-on-the-use-of-point-of-care-immunodiagnostic-tests-for-covid-19 (Accessed on April 26, 2020).
8. Guo L, Ren L, Yang S, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). *Clin Infect Dis*. 2020;71(15):778-785. doi:10.1093/cid/ciaa310
9. US Food and Drug Administration. Emergency Use Authorizations. https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations (Accessed on April 16, 2020).
10. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061–1069. doi:10.1001/jama.2020.1585
11. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet. 2020 Jan 30;:]. *Lancet*. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
12. Burns PB, Rohrich RJ, Chung KC. The Levels of Evidence and their role in Evidence-Based Medicine. *Plast Reconstr Surg*. 2011;128(1):305-310. doi:10.1097/PRS.0b013e318219c171
13. Borba MGS, Val FFA, Sampaio VS, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory

Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. *JAMA Netw Open*. 2020;3(4):e208857. Published 2020 Apr 24. doi:10.1001/jamanetworkopen.2020.8857

14. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ*. 2020;369:m1849. Published 2020 May 14. doi:10.1136/bmj.m1849
15. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19 [published online ahead of print, 2020 Jul 23]. *N Engl J Med*. 2020;10.1056/NEJMoa2019014. doi:10.1056/NEJMoa2019014
16. Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19 [published online ahead of print, 2020 Jun 3]. *N Engl J Med*. 2020;10.1056/NEJMoa2016638. doi:10.1056/NEJMoa2016638
17. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. *New England Journal of Medicine*. 2020;0(0):null. doi:10.1056/NEJMoa2007764
18. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020;395(10236):1569-1578. doi:10.1016/S0140-6736(20)31022-9
19. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19 [published online ahead of print, 2020 May 27]. *N Engl J Med*. 2020;NEJMoa2015301. doi:10.1056/NEJMoa2015301
20. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial [published online ahead of print, 2020 May 8]. *Lancet*. 2020;S0140-6736(20)31042-4. doi:10.1016/S0140-6736(20)31042-4
21. 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;382(19):1787-1799. doi:10.1056/NEJMoa2001282
22. Li Y, Xie Z, Lin W, et al. Efficacy and Safety of Lopinavir/Ritonavir or Arbidol in Adult Patients with Mild/Moderate COVID-19: An Exploratory Randomized Controlled Trial. *Med*. 2020. doi:10.1016/j.medj.2020.04.001
23. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol*. 2020;146(1):137-146.e3. doi:10.1016/j.jaci.2020.05.019

24. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report [published online ahead of print, 2020 Jul 17]. *N Engl J Med*. 2020;10.1056/NEJMoa2021436. doi:10.1056/NEJMoa2021436
25. Zhu FC, Guan XH, Li YH, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial [published online ahead of print, 2020 Jul 20]. *Lancet*. 2020;S0140-6736(20)31605-6. doi:10.1016/S0140-6736(20)31605-6
26. Li L, Zhang W, Hu Y, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial [published online ahead of print, 2020 Jun 3] *JAMA*. 2020;e2010044. doi:10.1001/jama.2020.10044
27. Sarma P, Kaur H, Kumar H, et al. Virological and clinical cure in COVID-19 patients treated with hydroxychloroquine: A systematic review and meta-analysis [published online ahead of print, 2020 Apr 16]. *J Med Virol*. 2020;10.1002/jmv.25898. doi:10.1002/jmv.25898
28. Emergency Use Authorization. FDA. Published online July 31, 2020. Accessed August 2, 2020. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization
29. Kowalik MM, Trzonkowski P, Łasińska-Kowara M, Mital A, Smiatacz T, Jaguszewski M. COVID-19 - toward a comprehensive understanding of the disease [published online ahead of print, 2020 May 7]. *Cardiol J*. 2020;10.5603/CJ.a2020.0065. doi:10.5603/CJ.a2020.0065
30. Pan XW, Xu D, Zhang H, Zhou W, Wang LH, Cui XG. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis [published online ahead of print, 2020 Mar 31]. *Intensive Care Med*. 2020;1-3. doi:10.1007/s00134-020-06026-1
31. Shah K, Kamler J, Phan A, Toy D. Imaging & other potential predictors of deterioration in COVID-19 [published online ahead of print, 2020 Apr 28]. *Am J Emerg Med*. 2020;S0735-6757(20)30305-3. doi:10.1016/j.ajem.2020.04.075
32. Bessière F, Roccia H, Delinière A, et al. Assessment of QT Intervals in a Case Series of Patients With Coronavirus Disease 2019 (COVID-19) Infection Treated With Hydroxychloroquine Alone or in Combination With Azithromycin in an Intensive Care Unit [published online ahead of print, 2020 May 1]. *JAMA Cardiol*. 2020;e201787. doi:10.1001/jamacardio.2020.1787

33. Kaafarani HMA, Moheb ME, Hwabejire JO, et al. Gastrointestinal Complications in Critically Ill Patients With COVID-19 [published online ahead of print, 2020 May 1]. *Ann Surg*. 2020;10.1097/SLA.0000000000004004. doi:10.1097/SLA.0000000000004004
34. Dai M, Liu D, Liu M, et al. Patients with Cancer Appear More Vulnerable to SARS-COV-2: A Multicenter Study during the COVID-19 Outbreak [published online ahead of print, 2020 Apr 28]. *Cancer Discov*. 2020;10.1158/2159-8290.CD-20-0422. doi:10.1158/2159-8290.CD-20-0422
35. Al-Quteimat OM, Amer AM. The Impact of the COVID-19 Pandemic on Cancer Patients [published online ahead of print, 2020 Apr 16]. *Am J Clin Oncol*. 2020;10.1097/COC.0000000000000712. doi:10.1097/COC.0000000000000712
36. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ*. Published online May 22, 2020:m1985. doi:10.1136/bmj.m1985
37. Reihani H, Ghassemi M, Mazer-Amirshahi M, Aljohani B, Pourmand A. Non-evidenced based treatment: An unintended cause of morbidity and mortality related to COVID-19 [published online ahead of print, 2020 May 6]. *Am J Emerg Med*. 2020;S0735-6757(20)30317-X. doi:10.1016/j.ajem.2020.05.001
38. de Abajo FJ, Rodríguez-Martín S, Lerma V, et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study [published online ahead of print, 2020 May 14]. *Lancet*. 2020;S0140-6736(20)31030-8. doi:10.1016/S0140-6736(20)31030-8
39. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review [published online ahead of print, 2020 Apr 13]. *JAMA*. 2020;10.1001/jama.2020.6019. doi:10.1001/jama.2020.6019
40. Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers YM. Cardiac complications attributed to chloroquine and hydroxychloroquine: A systematic review of the literature. *Drug Saf*. 2018;41(10):919–31.
41. Alanagreh L, Alzoughool F, Atoum M. Risk of using hydroxychloroquine as a treatment of COVID-19 [published online ahead of print, 2020 May 27]. *Int J Risk Saf Med*. 2020;10.3233/JRS-200024. doi:10.3233/JRS-200024
42. Gevers S, Kwa MSG, Wijnans E, van Nieuwkoop C. Safety considerations for chloroquine and hydroxychloroquine in the treatment of COVID-19 [published online ahead of print,

2020 May 16]. *Clin Microbiol Infect*. 2020;S1198-743X(20)30283-4. doi:10.1016/j.cmi.2020.05.006

43. Thomas SH, Behr ER. Pharmacological treatment of acquired QT prolongation and torsades de pointes. *Br J Clin Pharmacol*. 2016;81(3):420-427. doi:10.1111/bcp.12726
44. US Food and Drug Administration. https://www.fda.gov/media/137565/download/. Accessed August 2, 2020
45. Corticosteroids | Coronavirus Disease COVID-19. COVID-19 Treatment Guidelines. Accessed August 2, 2020. https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/corticosteroids/
46. COVID-19 Resources. Society of Surgical Oncology. https://www.surgonc.org/resources/covid-19-resources/. Accessed May 24, 2020.
47. Clinicaltrials.gov. https://clinicaltrials.gov/. Accessed August 2, 2020.

Table 1. Studies Included in Clinical Review

Author	Population	Design	Drug (class)	Study endpoints	Outcomes	Limitations
Borba et al. 2020[13]	Hospitalized patients with clinical suspicion of COVID-19, aged 18 years or older, with respiratory rate	RCT	Chloroquine diphosphate (Antimalarial)	Reduction in lethality by at least 50% in the high-dosage group compared with the low-dosage group.	Lethality until day 13 was 39.0% in the high-dosage group (16 of 41) and 15.0% in the low-dosage group (6 of 40). The high-dosage group presented more instance of QTc interval greater than 500 milliseconds (7 of 37 [18.9%]) compared with the low-dosage group (4 of 36 [11.1%]). Respiratory secretion at day 4 was negative in only 6 of 27 patients (22.2%).	Small sample size. Single-center design. Lack of a placebo control group. Absence of exclusion criteria based on the QTc interval at baseline.

	higher than 24 rpm and/or heart rate higher than 125 bpm (in the absence of fever) and/or peripheral oxygen saturation lower than 90% in ambient air and/or shock.					
Tang et al. 2020[14]	Patients 18 years and older	RCT	Hydroxychloroquine (Antimalarial)	Negative conversion of SARS	The probability of negative conversion in the standard of care plus hydroxychloroquine group was 85.4% (95% CI 73.8-93.8) versus 81.3% in the standard of care group (95% CI 71.2-	Open label trial. Non-computerized randomization

	with mild or moderate ongoing SARS CoV-2 infection.			CoV-2 by 28 days. Clinical improvement by 28 days.	89.6), however this difference were not significant.	protocol. Did not enroll participants with severe disease. Underpowered sample size.
Sarma et al. 2020[27]	Patients with lab-confirmed COVID-19 of any age.	Meta-analysis	Hydroxychloroquine (Antimalarial)	Clinical cure. Virologic cure on day 6 to 7 post-initiation of therapy. Death or clinical worsening of disease condition during treatment. Radiological progress	Two studies reported possible benefit in "time to body temperature normalization" and one study reported less "cough days" in the HCQ arm. Treatment with HCQ resulted in a smaller number of cases showing radiological progression of lung disease (OR 0.31, 95% CI 0.11-0.9). No difference was observed in virologic cure (OR 2.37, 95% CI 0.13-44.53), death or clinical worsening of disease (OR 1.37, 95% CI 1.37-21.97) and safety (OR 2.19, 95% CI 0.59-8.18), when compared to the control/ conventional treatment.	Limited number of clinical studies with limited number of participants. Lack of control/conventional/standard group. Did not specify whether the studies included assessed patients with mild, moderate or severe COVID-19.

				ion during drug treatment. Recurrence of infection during treatment. Safety and tolerability of HCQ.		
Cavalcanti et al. 2020[15]	Hospitalized patients with suspected or confirmed mild/moderate COVID-19 with 14 or fewer days since	RCT	Hydroxychloroquine (Antimalarial) ± Azithromycin (Antibiotic)	Clinical status at 15 days evaluated using a 7-level ordinal scale.	There was no significant difference in seven-point ordinal scale at 15 days between those treated with hydroxychloroquine and standard care (OR 1.21, 95% CI 0.69-2.11, p=1.00), or between those treated with hydroxychloroquine + azithromycin and standard care (OR 0.99, 95% CI 0.57-1.73, p=1.00). There were no significant differences in six-level ordinal outcome at day 7, the number of days free from respiratory support, use of high-flow nasal cannula or non-invasive ventilation, use of mechanical ventilation, duration of hospital stay, in-hospital death,	Not blinded. Some patients concomitantly treated with other pharmacologic agents. Some patients were previously treated with hydroxychloroquine ± azithromycin at other hospitals prior to enrollment in

	symptom onset, who were receiving either no supplemental oxygen or a maximum of 4 L/min of supplemental oxygen.				thromboembolic complications, or acute kidney injury between the groups. Prolongation of QT interval and elevation of liver enzymes was more frequent in the experimental groups.	this trial.
Boulware et al. 2020[16]	Adults with household or occupational exposure to someone with confirmed COVI	RCT	Hydroxychloroquine (Antimalarial)	Laboratory confirmed COVID-19 or illness compatible with COVID-19 within	The incidence of new illness compatible with COVID-19 did not significantly differ between participants receiving HCQ (11.8%) and placebo (14.3%) (p=0.35). There was no meaningful difference in the effectiveness according to the time of starting post-exposure prophylaxis.	Use of an a priori symptomatic case definition in some patients as opposed to diagnostic testing.

	D-19 at a distance of less than 6 ft for more than 10 minutes without a face mask and/or eye shield.			14 days.		
Beigel et al. 2020[17]	Adults hospitalized with Covid-19 with evidence of lower respiratory tract involvement.	RCT	Remdesivir (Antiviral)	Time to recovery defined by either discharge from the hospital or hospitalization for infection-control purposes only.	The remdesivir group had a median recovery time of 11 days (95% CI 9-12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; p<0.001) The remdesivir group had higher odds of improvement in the 8-level ordinal scale score at day 15 compared to placebo (OR 1.50, 95% CI 1.18-1.91. Mortality was numerically lower in the remdesivir group, but this difference was not statistically significant.	Preliminary data.

Wang et al. 2020[18]	Adults (aged ≥18 years) admitted to hospital with laboratory-confirmed severe SARS-CoV-2 infection, with an interval from symptom onset to enrolment of 12 days or less, oxygen saturation of 94% or	RCT	Remdesivir (Antiviral)	Time to clinical improvement up to day 28, defined as the time (in days) from randomization to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1=discharged to 6=death) or discharged alive	Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1.23 [95% CI 0.87–1.75]). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (hazard ratio 1.52 [95% CI 0.95–2.43]). Mortality at day 28 was not significantly different between the groups.	Insufficient power. Initiation of treatment late in COVID-19. Absence of data on infectious virus recovery or on possible emergence of reduced susceptibility to remdesivir. Some patients concomitantly treated with other pharmacologic agents.

	less on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and radiologically confirmed pneumonia.			from hospital, whichever came first.		
Goldman et al. 2020[19]	Hospitalized patients with confirmed SARS-CoV-2	RCT	Remdesivir (Antiviral)	Clinical status on day 14 measured on a 7-point ordinal	Clinical improvement of 2 points or more occurred in 65% of patients in the 5-day group and 54% of patients in the 10-day group. After correction of imbalance of baseline clinical status, clinical status at day 14 was similar between the 5-day and 10-day groups	The patients in the 10-day group had a significantly worse clinical status than those in the 5-day group

	infection, O2 saturation ≤ 94% on ambient air, and radiologic evidence of pneumonia.			scale.	(p=0.14).	(p=0.02). No placebo control. Open label design.
Hung et al. 2020[20]	Age at least 18 years, a national early warning score 2 (NEWS2) of at least 1, and symptom duration of 14 days or less	RCT	IFN beta-1b (Anti-inflammatory), lopinavir-ritonavir and ribavirin (Antivirals)	Time to providing a nasopharyngeal swab negative for severe acute respiratory syndrome coronavirus 2 RT-PCR.	The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [8–15]; hazard ratio 4.37 [95% CI 1.86–10.24], p=0.0010).	Open label trial. Absence of placebo group. Confounded by subgroup omitting of interferon beta-1b within the combination group, depending on time from symptom onset. Absence of critically ill patients.

	upon recruitment.					
Cao et al. 2020[21]	Male and non-pregnant female patients 18 years of age or older with diagnostic specimen that was positive on RT-PCR, had pneumonia confirmed by chest imaging, and had an oxygen	RCT	Lopinavir-ritonavir (Antiviral)	Time to clinical improvement, defined as the time from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever came first.	Treatment with lopinavir–ritonavir was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement 1.24 (95% CI 0.90-1.72)). Mortality at 28 days was similar in the lopinavir–ritonavir group and the standard-care group (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI −17.3-5.7).	Non-blinded. Higher throat viral loads in the lopinavir–ritonavir group on baseline. Absence of data on lopinavir exposure levels in severe and critically ill patients.

	saturation of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen at or below 300 mg Hg.					
Li et al. 2020[22]	Patients with mild/moderate COVI	RCT	Lopinavir/ritonavir vs. Umifenovir	Rate of positive-to-negative conversi	No significant difference in the rate of positive-to-negative conversion between the lopinavir/ritonavir, arbidol, and control groups (p>0.05). No significant differences between the	Small sample size. Limited to patients with mild/moderate

	D-19.		(Antivirals)	on of SARS-CoV-2 nucleic acid.	groups for the rates of antipyresis, cough alleviation, or improvement of CT findings at day 7 or 14 (p>0.05). The lopinavir/ritonavir and arbidol groups experienced adverse effects, whereas the control group did not.	COVID-19. Single center. Not blinded to clinicians who recruited patients and research staff.
Cao et al. 2020[23]	Patients with severe COVID-19, between 18 and 75 years of age.	RCT	Ruxolitinib (JAK inhibitor)	Time to clinical improvement (time from randomization to an improvement of 2 points on a 7-category ordinal scale or live discharge from the hospital).	Ruxolitinib plus standard-of-care was associated with a non-statistically significant decrease in median time clinical improvement (12 [IQR, 10-19] days vs. 15 [IQR, 10-18] days). 90% of Ruxolitinib patients had significant CT improvement at day 14 compared to 61.9% of control patients (p=0.0495). Levels of 7 cytokines (including IL-6, IL-12 and VEGF) were significantly decreased in the experimental group. The 28-day overall mortality was 0% in the experimental group and 14.3% in the control group.	Small sample size. Use of an ordinal scale to assess primary end points. Some patients concomitantly treated with other pharmacologic agents. Critically ill patients and patients with invasive ventilator dependence were not included.
The RECOVERY	Hospitalized patients	RCT	Dexamethasone (Corticoste	28-day mortalit	Mortality at day 28 was significantly lower in the experimental group. 22.9% of patients treated with dexamethasone	Preliminary data.

Collaborative Group 2020[24]	with clinically suspected or laboratory confirmed SARS-CoV-2 infection, including those under 18 and pregnant or breastfeeding women.	roid)	y	died within 28 days, compared to 25.7% of patients treated with standard care (age-adjusted rate ratio 0.83, 95% CI 0.75-0.93). Compared to the standard of care group, the incidence of death lower in dexamethasone patients receiving mechanical ventilation (rate ratio 0.64, 95% CI 0.51-0.81) and in those receiving oxygen without mechanical ventilation (rate ratio 0.82, 95% CI 0.72-0.94), but not in those receiving no respiratory support (rate ratio 1.19, 95% CI 0.91-1.55). Patients treated with dexamethasone also had a shorter duration of hospitalization (median 12 days vs. 13 days).	Open label design.
Zhu et al. 2020[25]	Healthy, HIV-negative adults ≥ 18 years old who were	RCT	Ad5-vectored COVID-19 vaccine (vaccine)	Immunogenicity as measured by the geometric mean titers (GMT)	Participants who received either a low or high viral particles dose had a significant increase in RBD-specific ELISA antibodies, seroconversion rates and neutralizing antibody responses compared to the placebo group. Placebo group showed no antibody increase from baseline. No IFNγ-ELISpot responses in placebo	52% of participants had high pre-existing immunity, and 48% of the participants had low pre-existing

not previously infected with SARS-CoV-2.	of RBD-specific ELISA antibody responses and neutralizing antibody responses against live virus or pseudovirus at day 28 post-vaccination. Immunogenicity as measured by RBD-specific ELISA antibody responses at day 14, and specific T-cell response	group. High dose ($1x10^{11}$ viral particles) • RBD-specific ELISA antibodies peaked at 656.5 (95% CI 575.2-749.2). • GMTs were 19.5 (95% CI 16.8-22.7). • Seroconversion rates	Low dose ($5x10^{10}$ viral particles) • RBD-specific ELISA antibodies peaked at 571.0 (95% CI 476.6-697.3). • GMTs were 18.3 (95% CI 14.4-23.3). • Seroconversion rates	immunity.	Did not calculate sample size based on study power in advance. Only reported data within 28 days of vaccination.

s at day 28 post-vaccination. Seroconversion of the humoral response.	were 96% (95% CI 93-98). • Specific interferon γ enzyme-linked immunospot assay responses observed in 90% (95% CI 85-93). • Severe adverse reactions	were 97% (95% CI 92-99). • Specific interferon γ enzyme-linked immunospot assay responses observed in 88% (95% CI 81-92). • Severe adverse reactions

					in 9%.	in 1%.
Li et at. 2020[26]	Patients with severe (respiratory distress and/or hypoxemia) or life threatening (shock, organ failure, mechanical ventilation) COVD-19.	RCT	Convalescent plasma (Immunotherapy)	Time to clinical improvement within 28 days, as defined by a reduction of 2 points on a 6-point disease severity scale, or discharg[illegible]	Clinical improvement within 28 days occurred in 51.9% of patients in the convalescent plasma group compared to 43.1% in the control group (8.8% difference, 95% CI -10.4-28.0%, p=0.26). Clinical improvement occurred at a higher rate in those with severe disease compared to those with life threatening disease (81.3% vs 68.2%). There was no significant difference in 28-day mortality (OR 0.65, 95% CI 0.29-1.46) or time to discharge (HR 1.61, 95% CI 0.88-2.93). Use of convalescent plasma resulted in a 87.2% negative conversion rate of viral PCR at 72 hours compared to 37.5% in the control group.	Small sample size. Study terminated early. Open-label design. Possibly underpowered study.

Figure 1. PRISMA flow diagram of studies included in the clinical review.