

COVID-19 Treatment Summary

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COVID-19 Literature Report Team:

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COVID-19 treatment is rapidly evolving as public health professionals accumulate and share observations and research teams generate and disseminate their findings. **This document is a brief summary of published evidence regarding medications to treat COVID-19. Included are manuscripts published in peer-reviewed journals or on pre-print servers through June 4, 2020.** References summarized in this report were drawn from the COVID-19 Literature Report (Lit Rep) team database and identified with the #treatment label. **References that appeared in the daily Lit Rep are marked with an asterisk***, and the summary is shown in the annotated bibliography below. This list was cross-referenced with the UW IDEA COVID-19 treatment reference site, the UW Medicine COVID-19 resource site, and the NIH treatment guidelines updated May 12, 2020¹⁻³. We encourage readers to consult these sites, which are updated in an ongoing manner, for evidence that emerges following the date of this report.

Executive Summary of COVID-19 Treatments

- **Remdesivir** is the only agent currently recommended for treatment of COVID-19, for use in patients with severe disease.
- Many trials of other agents are underway, but data do not support the use of other agents for treatment of COVID-19 at this time.
- There are **no currently recommended preventive treatment options for COVID-19**, although there are ongoing trials evaluating pre- and post-exposure interventions.

Narrative Summary of COVID-19 Treatments

While no medications are currently FDA approved for treatment of COVID-19, several medications that have FDA approval for non-COVID-19 conditions are being prescribed by clinicians for off-label use for COVID-19. These include antiviral agents (lopinavir-ritonavir), drugs originally approved as antimalarial agents (chloroquine and hydroxychloroquine), and immunomodulatory agents [interleukin (IL)-6 inhibitors: tocilizumab, sarilumab, and siltuximab]. Convalescent plasma is a therapy used historically for a broad range of infections that is also being tested in persons with COVID-19. Clinical trials involving these agents are ongoing, with more than 500 interventional clinical trials for COVID-19 listed on Clinicaltrials.gov as “recruiting”. A number of additional trials are being planned. A more detailed summary of evidence for select medications follows.

Remdesivir – Remdesivir is an investigational intravenous antiviral agent that is currently the only agent recommended by the NIH COVID-19 Treatment Guidelines Panel (subsequently referred to as the “Panel”) for treatment of COVID-19.³ It is recommended for patients with severe disease, defined as oxygen saturation $\leq 94\%$ on ambient air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation.³ It has FDA emergency use authorization for COVID-19⁴. Clinical trials are ongoing, including an adaptive randomized placebo-controlled trial sponsored by the National Institute of Allergy and Infectious Diseases⁵ and the Solidarity trial launched by the World Health

Organization.⁶ Remdesivir inhibits the SARS-CoV-2 RNA polymerase. **The results of several randomized trials of remdesivir have been reported:**

- A randomized, double-blind, placebo-controlled trial of 1,095 patients found that remdesivir use in hospitalized adults with COVID-19 resulted in faster recovery, which was defined as not requiring in-hospital medical care. There was non-significant evidence of lower mortality by 14 days.^{5*}
- A double-blind, placebo-controlled trial of patients with severe COVID-19 randomized to receive 10-days of remdesivir or placebo found no differences in clinical outcomes.^{7*}
- A randomized trial found comparable outcomes for 5-day and 10-day courses of remdesivir for hospitalized COVID-19 patients. By day 14, clinical improvement was observed in over half of patients in both treatment arms.^{8*}

Interleukin(IL)-6 inhibitors

Tocilizumab, sarilumab, and siltuximab are monoclonal antibodies that block cellular receptors to IL-6, preventing release of inflammatory cytokines. They are being investigated for COVID-19 patients due to the postulated role of a hyperinflammatory response in severe outcomes from COVID-19, including death. The Panel currently reports insufficient evidence to recommend for or against their use. Data from early in the epidemic from small uncontrolled studies (n=20, n=15, n=100, and n=11) among patients with severe COVID-19 who received tocilizumab indicated clinical improvements.^{9–12*} A pre-print manuscript (not peer reviewed) reported that tocilizumab was associated with a 45% reduction in the hazard of death in a cohort of 154 patients requiring mechanical ventilation, 78 of whom received tocilizumab.¹³

Convalescent Plasma

Infusing antibody-positive serum from patients who have recovered from infection into patients with an acute infection is a strategy to treat a broad range of infections. This approach is currently being investigated in clinical trials for patients with COVID-19. The Panel currently cites insufficient evidence to recommend for or against use of convalescent plasma. Early case series (n=5, n=10) reported no severe adverse events and trends toward clinical improvement among patients with severe or critical COVID-19 who received convalescent plasma from recently-recovered donors.^{14,15}

- Salazar et al. report findings in a pre-print manuscript (not peer reviewed) from a study to evaluate the safety of plasma infusions in 25 patients with severe and/or life-threatening COVID-19 and found no adverse events.^{16*}
- Li et al. conducted a multicenter randomized trial among 103 participants with severe or life-threatening COVID-19 and found no significant difference in time to clinical improvement within 28 days. However, the study was stopped early and was insufficiently powered for the primary outcomes. Though non-significant, the findings showed promising trends for efficacy, particularly among those with “severe” as opposed to “life-threatening” disease.^{17*}

Hydroxychloroquine and Chloroquine

Early uncontrolled studies reported improvements in clinical outcomes in patients with COVID-19 who received hydroxychloroquine, particularly in combination with the antibacterial agent azithromycin.^{18,19} Subsequently, researchers raised concerns regarding the methodology and over-interpretation of these studies.^{20,21} **Additionally, concerns emerged regarding the toxicity of these agents, particularly in relation to cardiac arrhythmias:**²²

- Mercurio et al. found that among 90 patients in an academic tertiary care center in Boston with at least one positive test for SARS-CoV-2, abnormalities in the electric conduction within the heart (prolonged corrected QT interval) were observed after initiation of hydroxychloroquine, and this effect was stronger for patients receiving both hydroxychloroquine and azithromycin.^{23*}

- Gerard et al. estimated incidence of cardiac adverse drug reactions to be 0.77% to 1.54% in COVID-19 patients receiving hydroxychloroquine, chloroquine, lopinavir-ritonavir, or azithromycin.^{24*}
- Rosenberg et al. conducted a retrospective multi-center cohort study by sampling randomly from all admitted participants with laboratory-confirmed COVID-19 in 25 hospitals (N=1,438) in which they compared those individuals receiving hydroxychloroquine alone, azithromycin alone, and combination of the two relative to treatment with neither medication. They found a greater odds of cardiac arrest in patients receiving combination therapy (OR=2.13 95% CI: 1.12-4.05), but otherwise no statistically significant associations with mortality or abnormal electrocardiogram findings.^{25*}

A large observational study did not identify a benefit of hydroxychloroquine for treatment of COVID-19.

- Geleris et al. conducted an observational study among 1,446 patients at a large medical center in New York City. They found no association between hydroxychloroquine use and intubation or death (HR=1.04, 95% CI 0.82-1.32).^{26*}

One study based on a multinational registry found an increased risk of mortality, although concerns about the data used in this study have been raised, and the authors requested retraction on June 4, 2020.^{27–29*}

Lopinavir-Ritonavir

Lopinavir-ritonavir, a combination of protease inhibitors approved to treat HIV, demonstrated in-vitro activity against SARS-CoV, the etiologic agent of the SARS coronavirus pandemic in 2003-2004. However, a randomized open-label trial of lopinavir-ritonavir among hospitalized adults with severe COVID-19 (n=199) found no evidence of benefit.³⁰ The Panel recommends against the use of lopinavir-ritonavir due to clinical trial data showing lack of efficacy.³

Narrative Summary of COVID-19 Preventive Therapies

The Panel does not currently recommend any agents for prevention of SARS-CoV-2 infection or post-exposure prophylaxis (PEP) outside of the setting of a clinical trial.³

- Macias et al. conducted a retrospective analysis of 722 patients with autoimmune rheumatic diseases who were being treated with (n=423) and without hydroxychloroquine (n=290) in Seville, Spain. Incidence and severity of COVID-19 did not differ between the treatment groups. Over seven weeks, 5 (1.7%) cases of COVID-19 were reported among patients using hydroxychloroquine and 5 (1.2%) among those without hydroxychloroquine.^{31*}
- A placebo-controlled randomized trial of hydroxychloroquine as post-exposure prophylaxis (PEP) found no evidence of efficacy. Among 821 asymptomatic participants, 88% reported a high-risk exposure to a confirmed COVID-19 case. There was no difference in SARS-CoV-2 acquisition between participants receiving hydroxychloroquine (12%) and those on placebo (14%).^{32*}

Recommended Resources

UW IDEA COVID-19 Treatment site

<https://covid.idea.medicine.uw.edu/>

NIH COVID-19 Treatment guidelines

<https://www.covid19treatmentguidelines.nih.gov/>

UW Medicine COVID-19 Resource Site – See section “Summary of Evidence & Literature”

<https://covid-19.uwmedicine.org/>

Annotated Bibliography

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4. Coronavirus Disease 2019 (COVID-19) Resources for Health Professionals | FDA. <https://www.fda.gov/health-professionals/coronavirus-disease-2019-covid-19-resources-health-professionals>. Accessed June 3, 2020.
5. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. *N Engl J Med*. May 2020:NEJMoa2007764. doi:10.1056/NEJMoa2007764
 - A double-blind, randomized, placebo-controlled trial of IV remdesivir (200mg on day 1, then 100mg daily for up to 9 days) in adults hospitalized with COVID-19 with evidence of lower respiratory tract involvement (n=1,059) found that, compared to placebo, recovery was 32% faster in those who received remdesivir (95%CI 12% to 55%; median recovery time 11 vs 15 days).
 - Though not statistically significant, remdesivir treatment was associated with a slower time to mortality (HR 0.70, 95%CI 0.47 to 1.04 and mortality by 14 days (7.1% vs 11.9%). Serious adverse events were reported in 21.1% of patients in the remdesivir group and 27% of patients in the placebo group.
6. Bashir MF, Bilal BM, Komal B. Correlation between environmental pollution indicators and COVID-19 pandemic: A brief study in Californian context. *Environ Res*. May 2020:109652. doi:10.1016/j.envres.2020.109652
7. Wang Y, Zhang D, Du PG, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial Yeming. *Lancet*. 2020;6736(20):1-10. doi:10.1016/S0140-6736(20)31022-9
 - A randomized, double-blind, placebo controlled multicenter trial at ten hospitals in Hubei, China with 237 participants (158 randomized to remdesivir, 79 to placebo) demonstrated that time to clinical improvement did not differ by study arm, with 21 days (IQR 13-28 days) in the remdesivir group versus 23 days (IQR 15-28 days) in the placebo group (HR 1.23, 95% CI 0.87 – 1.75). Overall frequency of adverse events was similar in both groups; however treatment cessation due to adverse events was higher in the remdesivir (12%) than placebo (5%) group.
8. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med*. May 2020. doi:10.1056/NEJMoa2015301
 - A randomized trial among hospitalized COVID-19 patients who did not require mechanical ventilation found no differences between a 5-day course and a 10-day course of remdesivir. By day 14, clinical improvement was observed in over half of patients in both treatment arms. However, this trial lacked a placebo control and could not determine if this

improvement was attributable to remdesivir.

9. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A*. 2020;117(20):10970-10975. doi:10.1073/pnas.2005615117
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 - The authors describe clinical outcomes for the first tocilizumab-treated cohort of 11 critically-ill patients with COVID-19 in the United States. Patients experienced mixed outcomes, highlighting the need for randomized trial data.
 - Although C-reactive protein levels decreased in all patients following treatment (median 211.6 mg/L pre-treatment vs. 19.7 mg/L at 5 days post-treatment), patients had higher IL-6 concentrations after tocilizumab treatment and no clinical improvement in fever or oxygen requirements. Among the 11 patients, 3 died, 6 remained in the intensive care unit, and 2 were discharged.
13. Somers EC, Eschenauer GA, Troost JP, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. *medrxiv*. June 2020. doi:10.1101/2020.05.29.20117358
14. Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA*. 2020;323(16):1582-1589. doi:10.1001/jama.2020.4783
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16. Salazar E, Perez KK, Ashraf M, et al. Treatment of COVID-19 Patients with Convalescent Plasma in Houston Texas. *medrxiv*. 2020. doi:10.1101/2020.05.08.20095471
 - Salazar et al. explored the safety of convalescent plasma therapy among 25 patients with severe and/or life-threatening COVID-19 disease enrolled at the Houston Methodist hospitals. Patients were transfused with convalescent plasma obtained from donors with confirmed SARS-CoV-2 infection who been symptom free for 14 days.
 - At 7 days post-transfusion, 9 patients had at least a 1-point improvement in clinical scale, and 7 of those were discharged. By 14 days, 19 (76%) patients had at least a 1-point improvement in clinical status and 11 were discharged. No adverse events due to plasma transfusion were observed.
17. 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. *JAMA*. June 2020. doi:10.1001/jama.2020.10044

- Li et al. conducted a multicenter randomized trial of convalescent plasma therapy among 103 participants with “severe” or “life-threatening” COVID-19 in Wuhan, China. The trial was stopped early, which resulted in insufficient power to fully evaluate the primary outcomes.
 - Overall, there were no statistically significant differences in clinical improvement within 28 days between those who did and did not receive convalescent plasma. However, an accompanying [editorial](#) points to promising trends among those who received convalescent plasma. This is particularly true of the finding that among those with “severe” disease (as opposed to the more serious group with “life-threatening” disease) clinical improvement occurred within 28 days among 91.3% (21/23) of those who receive convalescent plasma compared to 68.2% (15/22) of those in the control group (p=0.03).
18. Gautret P, Lagier J-C, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Med Infect Dis.* 2020;34:101663. doi:10.1016/j.tmaid.2020.101663
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 23. Mercurio NJ, Yen CF, Shim DJ, et al. Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* May 2020. doi:10.1001/jamacardio.2020.1834
 - Use of hydroxychloroquine can increase the risk of corrected QT (QTc) prolongation, a type of cardiac arrhythmia. Among 90 patients in an academic tertiary care center in Boston with at least one positive test for SARS-CoV-2, QTc was significantly longer after initiation of hydroxychloroquine, and this effect stronger for patients receiving both hydroxychloroquine and azithromycin. The authors recommend judicious use of hydroxychloroquine, along with monitoring of QTc and concomitant medications.
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 - Gerard et al. investigated the cardiac safety of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine for “off-label” use among COVID-19 patients. Over a one month

period, 120 cardiac adverse drug reactions among COVID-19 patients were reported to the Nice Regional Center of Pharmacovigilance in France. 86% of these adverse events were associated with hydroxychloroquine, alone or in combination with azithromycin. The authors estimated the incidence of cardiac adverse drug reactions to be 0.77% to 1.54% of COVID-19 patients. These findings are suggestive of an elevated risk of cardiac adverse events associated with "off-label" treatments among COVID-19 patients.

25. Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. *JAMA*. May 2020. doi:10.1001/jama.2020.8630
 - A retrospective multi-center cohort study sampled randomly from all admitted participants with laboratory-confirmed COVID-19 in 25 hospitals (N=1,438) and compared hydroxychloroquine alone, azithromycin alone, and combination of the two relative to treatment with neither medication.
 - There was a greater odds of cardiac arrest in patients receiving combination therapy (OR 2.13 95% CI: 1.12, 4.05), but otherwise not statistically significant associated with mortality or abnormal electrocardiogram findings.
 - However, combination therapy had a non-significant association with increased risk of mortality (HR 1.35, 95% CI 0.76, 2.40) and abnormal ECG findings (OR=1.55, 95%CI 0.89–2.67), as did hydroxychloroquine alone for cardiac arrest (OR=1.91, 95%CI: 0.96–3.81) and abnormal ECG findings (OR=1.50, 95%CI: 0.88–2.58). The effect of hydroxychloroquine alone was also non-significantly associated with a small increased risk of mortality (HR=1.08, 95%CI 0.63–1.85).
 - Azithromycin alone was associated with a non-significant lower risk of mortality (HR=0.56, 95%CI 0.26–1.21), cardiac arrest (OR=0.64, 95%CI: 0.27–1.56), and abnormal ECG findings (OR=0.95, 95%CI 0.77–3.24).
 - While limited by the observational design, these findings provide concerning evidence that treatment with hydroxychloroquine is associated with a higher likelihood of mortality and adverse cardiac outcomes, and that addition of azithromycin may increase these risks further.
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 - Geleris et al. conducted an observational study to understand the association between hydroxychloroquine use and intubation or death among 1,446 consecutive patients at a large medical center in New York City. During a median follow-up of 22.5 days, 59% received hydroxychloroquine either within 24 or 48 hours after presentation to the emergency department, and 25% experienced a primary endpoint (either intubation or death). Those who were treated with hydroxychloroquine were more severely ill at baseline than those who were not.
 - There was no association between hydroxychloroquine use and intubation or death (HR 1.04, 95% CI 0.82-1.32). While the results do not support either benefit or harm from hydroxychloroquine, the authors recognize the limitations of the observational design and emphasize the need for randomized trial evidence.
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 - *[pre-print, not peer reviewed]* Macias et al. conducted a retrospective analysis of 722 patients with autoimmune rheumatic diseases who were being treated with (n=423) and without hydroxychloroquine (n=290) in Seville, Spain. Incidence and severity of COVID-19 did not differ between the treatment groups. Over seven weeks, 5 (1.7%) cases of COVID-19 were reported among patients using hydroxychloroquine and 5 (1.2%) among those without hydroxychloroquine.
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 - A placebo-controlled randomized trial of hydroxychloroquine as post-exposure prophylaxis (PEP) for SARS-CoV-2 found no evidence of efficacy. Among 821 asymptomatic participants, 88% reported a high-risk exposure to a confirmed COVID-19 case. There was no difference in SARS-CoV-2 acquisition between participants receiving hydroxychloroquine (12%) and those receiving placebo (14%).
 - No serious adverse reactions were reported, although side effects were more common with hydroxychloroquine than with placebo (40% vs. 17%).