trc pharmacist's letter ™ trc prescriber's letter ™ trc pharmacy technician's letter ™

October 2020 ~ Resource #361022

Treatments of Interest for COVID-19

(Updated September 22, 2021)

The chart below provides information or resources on pharmacotherapy of interest for COVID-19, the disease caused by the SARS-CoV-2 virus. Additional resources on pharmacotherapy, supportive therapy, and vaccines, many of which are frequently updated, include:

- The **American Society of Health-System Pharmacists** evidence table of COVID-19 treatments (https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table).
- The **British Columbia Ministry of Health** guidance on current research on COVID-19 treatments (http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/clinical-care/treatments).
- The **NIH** general treatment guidelines (https://covid19treatmentguidelines.nih.gov/).
- **IDSA** treatment and management guidelines (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/).
- **WHO** guidance on drugs for COVID-19 (https://www.bmj.com/content/370/bmj.m3379).
- The **Surviving Sepsis Campaign** COVID-19 guidelines (https://sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19).

For guidance from the **USP** on **sterile compounding** during the pandemic, including preparation of COVID-19 treatments such as monoclonal antibodies, see https://www.usp.org/compounding.

Our chart, *COVID Pharmacotherapy FAQs: Addressing Patient Questions*, provides information to help answer and correct misconceptions about pharmacotherapy as it relates to COVID-19.

Search **www.clinicaltrials.gov for the latest information on COVID-19 clinical trials.**

TREATMENTS OF INTEREST

Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Anakinra (*Kineret*)	• Anakinra is an IL-1 antagonist. IL-1 may have a role in ARDS.[65] • Early evidence suggested that anakinra 5 mg/kg twice daily intravenously in moderate to severe ARDS (non-ventilator) and inflammation (elevated C-reactive protein and/or ferritin) (n=29) was associated with improved survival compared to a similar historical cohort (90% vs 56%, p = 0.009).[65] These patients also received hydroxychloroquine and lopinavir/ritonavir.[65] A lower dose of anakinra (100 mg twice daily subcutaneously) did not seem to provide benefit.[65] • Preliminary evidence from case reports suggest benefit in patients with severe COVID-19 and secondary hemophagocytic lymphohistiocytosis.[19] • In REMAP-CAP, anakinra was not effective in critically ill patients receiving respiratory or cardiovascular support.[77]

3120 W. March Lane, Stockton, CA 95219 ~ Phone: 209-472-2240 ~ Fax: 209-472-2249
pharmacist.therapeuticresearch.com ~ prescriber.therapeuticresearch.com ~ pharmacytech.therapeuticresearch.com

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Azithromycin	• Macrolides have *in vitro* antiviral (e.g., Zika, Ebola), anti-inflammatory, and immunomodulatory activity.[2,7] • Insufficient evidence to support widespread use [Evidence level C].[2,28] • Was used in a small, widely publicized study with hydroxychloroquine in six patients **to prevent bacterial superinfection** in COVID-19 patients (see hydroxychloroquine, below).[2] Subsequent observational data including 74 additional patients suggests that the combination can reduce viral load and perhaps improve the clinical course, but there was no comparator group.[28] Also see the hydroxychloroquine section below for information on its use in a U.S. cohort study.[75] • NIH guidelines recommend against the use of azithromycin in hospitalized patients, or in outpatients for the treatment of COVID-19.[50] • When used with hydroxychloroquine or chloroquine (and other QT prolonging medications), QT prolongation is of increased concern.[2,6]
Aviptadil	• **Investigational** synthetic form of vasoactive intestinal polypeptide hypothesized to protect alveolar type 2 cells from viral injury.[85] • In an unpublished case-control study (n=51), treated patients had better survival and clinical improvement. Side effects include hypotension and diarrhea. Based on data from this study, the manufacturer has applied for an EUA for aviptadil. • Aviptadil is currently being studied for COVID-19 respiratory failure (Intravenous Aviptadil for Critical COVID-19 with Respiratory Failure [COVID-AIV)], NCT04311697). See www.clinicaltrials.gov. • Aviptadil is also available through an Expanded Access protocol. For more information, see https://www.neurorxpharma.com/our-services/usa-licensed-physicians/.
Chloroquine phosphate* *Chloroquine phosphate 500 mg = chloroquine base 300 mg[6]	• Inhibits SARS-CoV-2 *in vitro*, but clinical trials have not shown benefit against other viruses.[5] Also has immunomodulating effects.[26] Early reports suggested that for COVID-19 pneumonia, it could speed clinical improvement and viral clearance.[3] • The FDA has **revoked its EUA** for chloroquine because it is unlikely to be effective, based on data from the EUA and elsewhere.[73] In addition to efficacy concerns, the FDA's revocation of its EUA for chloroquine was based on adverse effects; its known and potential benefits no longer outweigh the known and potential side effects (e.g., serious cardiac events and other serious side effects).[33] • The FDA recommends **against** chloroquine use for COVID-19 outside of a clinical trial.[33] NIH guidance recommends against use of chloroquine for treatment of COVID-19 in hospitalized or nonhospitalized patients.[50] • Clinical trials are planned on the use of chloroquine to prevent COVID-19 in healthcare workers. See www.clinicaltrials.gov. • A Brazilian study of chloroquine phosphate 600 mg twice daily vs 450 mg twice daily stopped the high-dose arm due to higher instance of QT prolongation >500 milliseconds (18.9% vs 11.1%) and mortality (39% vs 15%).[41] All patients received azithromycin.[41] • When used with azithromycin (and other QT-prolonging medications), QT prolongation is of increased concern.[2,4,6]

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Colchicine	• Based on its anti-inflammatory effect, there has been interest in using colchicine to alter the clinical course of COVID-19 in both inpatients and higher-risk outpatients. • The open-label GRECCO-19 study randomized patients to colchicine plus standard care or standard care (n = 105). The clinical primary endpoint, which included measurements of inflammation and clinical deterioration, occurred in 14% of the control group vs 1.8% in the colchicine group (p=0.02).[9] This study's findings are considered "hypothesis-generating" only.[9] • In a placebo-controlled study in patients hospitalized with moderate to severe COVID-19 (n = 75), at day seven, only 42% of colchicine patients were still in the hospital vs 72% of the placebo group. Also, at day seven, only 9% of colchicine patients still required supplemental oxygen vs 42% of placebo patients.[118] • The large RECOVERY trial discontinued its colchicine arm in hospitalized COVID-19 patients due to futility in regard to mortality benefit.[117] • In the large (n=4,159) ColCORONA study (not yet peer-reviewed), colchicine (0.5 mg twice daily for three days, then once daily for 27 days) given to high-risk **outpatients** (e.g., diabetes, uncontrolled hypertension) with COVID-19 slightly reduced the composite primary endpoint of death or hospitalization vs placebo (4.6% vs 6%; OR 0.75, 95% CI 0.57 to 0.99, p=0.04), driven mainly by a reduction in hospitalization.[114] Patients with severe kidney or liver disease were excluded. More cases of pulmonary embolism occurred in the colchicine group (11 vs 2; p=0.01).[114] Limitations include the statistical analysis and study termination before the pre-planned number of patients were recruited. • Keep in mind colchicine's toxicities and drug interactions. See our chart, *Colchicine Dosing and Interactions*, for details.
Convalescent Plasma (COVID-19) *Continued…*	• Studies of convalescent plasma show mixed results. Small case series in patients hospitalized with severe COVID-19 showed promise.[62-64] • Analysis of a cohort of patients from the Mayo Clinic-led expanded access program found a small mortality benefit in patients who received high-titer convalescent plasma within three days of diagnosis and who were not receiving mechanical ventilation.[69] • Compared to usual care, convalescent plasma did not reduce mortality or severe illness in the open-label PLACID trial (n=464). Only 67 patients received high-titer plasma.[95] Furthermore, a **placebo-controlled trial** (n= 333) found **no benefit** on clinical status or mortality. It is unclear how many patients received high-titer plasma in this study.[105] • The large open-label RECOVERY trial found no benefit of high-titer convalescent plasma (n = 5,795) on all-cause mortality (primary outcome) or discharge at day 28 vs usual care (n = 5,763). Almost all patients were receiving supplemental oxygen and corticosteroids at randomization. Among those not on mechanical ventilation, convalescent plasma did not affect a composite endpoint of death or progression to mechanical ventilation.[14] • There is very limited published data on convalescent plasma for pediatric patients.[23] • Convalescent plasma appears well-tolerated.[62-64] Concerns include allergic reactions, fluid overload, transfusion-related lung injury, and viral infections.[70] Risks do not appear different from other types of plasma.[83,86]

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Convalescent plasma, continued	• The FDA has issued an EUA for use of high-titer convalescent plasma early in the course of the disease (e.g., patients who do not require intubation), and for hospitalized patients with impaired humoral immunity, based on limited evidence that the therapeutic window may be longer in patients with suppressed humoral immunity.[70] • The EUA **does not replace clinical trials**.[70] Convalescent plasma should not be considered the standard of care and enrollment in prospective clinical trials is encouraged.[70] See clinicaltrials.gov and https://covidcp.org/ for more information. • The FDA has a fact sheet for healthcare professionals on convalescent plasma, including criteria for use, adverse effects, dosing, and more (https://www.fda.gov/media/141478/download). A fact sheet for patients and parents/caregivers is available at https://www.fda.gov/media/141479/download. • A fact sheet explaining how the EUA differs from the discontinued expanded access program is available at https://www.uscovidplasma.org/pdf/EAP%20vs%20EUA.pdf. • Convalescent plasma is no longer being collected by Canadian Blood Services, because the clinical trials they were supporting are complete.[71] However, the CONCOR-Donor study of immunity after infection is ongoing. Learn more here: https://cancovid19plasma.ca/concor-donor/. • Recovered patients interested in donating their plasma can do so through the American Red Cross (https://www.redcrossblood.org/donate-blood/dlp/plasma-donations-from-recovered-covid-19-patients.html), or they can locate a donation center at http://www.aabb.org/tm/donation/Pages/Blood-Bank-Locator.aspx. Mobile blood drives in their area may be another option. In Canada, see https://www.blood.ca/en/convalescentplasma.
Corticosteroids, systemic *Continued…*	• In one institution in China, methylprednisolone use in patients with COVID-19 ARDS was associated with reduced mortality.[16] This and other cohort studies were limited by confounding, and inclusion of patients with various disease severities and concomitant treatments.[46] • Data from the open-label RECOVERY trial, in which 2,104 patients were randomized to oral or intravenous dexamethasone 6 mg/day for 10 days, suggests a mortality benefit for COVID-19 patients requiring supplemental oxygen, especially for those requiring ventilation, over usual care (n = 4,321).[31] NNT = 8 to prevent one death in ventilated patients, or 34 in patients requiring oxygen but not ventilation. It did not provide a mortality benefit (and there was a nonstatistically significant trend toward harm) for patients not requiring oxygen. It also did not provide a mortality benefit for early disease (symptoms for a week or less). This suggests that dexamethasone's mechanism involves an anti-inflammatory effect rather than an antiviral effect, because inflammation is more common in advanced disease, while viral replication is at maximum in early disease. • The open-label REMAP-CAP study (n=403) randomized COVID-19 patients admitted to intensive care for respiratory or cardiovascular support to hydrocortisone 50 to 100 mg every six hours for seven days, hydrocortisone started only if shock was clinically evident, or no hydrocortisone.[68] Analysis suggests hydrocortisone was probably superior to no hydrocortisone in regard to organ support-free days at 21 days, but the study was stopped early.

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Corticosteroids, systemic, continued	• The open-label CoDEX study (n=299) randomized COVID-19 patients with moderate to severe ARDS to dexamethasone 20 mg once daily for five days, then 10 mg once daily for five days.[56] Ventilator-free survival days through day 28 were greater with dexamethasone (6.6 vs 4, p=0.04). However, 35% of the usual care patients received at least one dose of corticosteroids. Mortality was not affected, but this may be because the study was stopped early after the results of RECOVERY were released. • In a placebo-controlled study of corticosteroids for COVID-19 (CAPE COVID) (n=149), a hydrocortisone infusion was not superior to placebo in regard to death or need for respiratory support (mechanical ventilation or high-flow oxygen) at day 21.[52] However, the study was likely underpowered to show a difference, and was stopped early pending RECOVERY publication. • The Brazilian MetCOVID study (n=416) did not find a mortality benefit for a five-day course of methylprednisolone over placebo.[78] However, in a subgroup analysis, 28-day mortality was lower in the methylprednisolone group in patients <60 years of age (46.6% vs 61.9%). Most patients received mechanical ventilation or non-invasive oxygen, but patients not on oxygen with low oxygen saturation were not included. Mortality was relatively high in this study compared to the RECOVERY study. Patients with septic shock were allowed to receive hydrocortisone, which could have affected results. • In a WHO meta-analysis that included data from RECOVERY, CAPE COVID, CoDEX, REMAP-CAP, and three other studies (n=1,703), mortality at 28 days was lower in critically ill patients who received corticosteroids vs those who did not receive them (32% vs 40%)(OR 0.66, 95% CI 0.53 to 0.82, p<0.001).[45] Including data from ventilator patients from MetCOVID did not affect results. Neither choice of corticosteroid (dexamethasone or hydrocortisone) nor days from symptom onset (>7 days vs ≤7 days) seems to affect efficacy. Benefit might be greater in patients not receiving mechanical ventilation. Based on these results, WHO strongly recommends systemic corticosteroids (dexamethasone 6 mg once daily or equivalent, via oral or intravenous route) for seven to ten days for severe/critical COVID-19, with glucose monitoring.[51] • The **IDSA** suggests dexamethasone 6 mg/day x 10 days (or until discharge, if earlier) for patients hospitalized with severe COVID-19 (oxygen saturation ≤94% on room air including those on supplementation oxygen), and recommends it for critical illness (mechanical ventilation or extracorporeal membrane oxygenation). If dexamethasone is not available, methylprednisolone 32 mg or prednisone 40 mg daily can be used.[46] **NIH** guidelines similarly recommend dexamethasone 6 mg/day (or equivalent) for 10 days or until discharge in COVID-19 patients who require oxygen, mechanical ventilation, or ECMO.[50] Corticosteroids are **not recommended** for COVID-19 patients not requiring treatment with supplemental oxygen.[46,50] • Harms of corticosteroids include hyperglycemia, agitation, confusion, and infection risk.[46]

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Corticosteroids, inhaled	• **Inhaled corticosteroids** should be continued in asthma or COPD patients with COVID-19.[50] The effect of inhaled corticosteroids on COVID-19 severity or viral clearance is unknown.[50] • In an open-label study (n=146) of outpatients with mild COVID-19, starting **inhaled budesonide** (*Pulmicort Turbuhaler* 800 mcg twice daily) within seven days of symptom onset and continuing until recovery or need for urgent care or hospitalization reduced the need for urgent care or hospitalization (NNT = 8).[92] Patients were young (mean age 45 years), with few comorbidities. • Ciclesonide (*Alvesco*) is also being studied for treatment of COVID-19. See www.clinicaltrials.gov for more information.
Dapagliflozin	• No data. • Dapagliflozin is being studied in COVID-19 patients with respiratory failure and with hypertension, diabetes, heart disease, or advanced renal disease to prevent organ failure, based on its known renal and cardiac benefit (DARE-19 study). • See www.clinicaltrials.gov for more information.
Famotidine	• Interest in famotidine as a COVID-19 treatment stems from observations in China that patients who were taking famotidine who were infected with COVID-19 had better outcomes.[55] • In a retrospective U.S. study (n = 1,620), famotidine use (10 to 40 mg/day; n = 84) within 24 hours of admission was associated with reduced risk of death or intubation in **hospitalized** COVID-19 patients.[67] But in a subsequent retrospective study in which famotidine users were matched to non-users to control for 12 potential confounders, famotidine was not associated with reduced risk of death. In fact, among patients not receiving famotidine at home 30-day mortality was higher.[94] • The IDSA suggests against use of famotidine for COVID-19 outside of a clinical trial.[46] See www.clinicaltrials.gov for more information.
Favipiravir	• Favipiravir is an oral antiviral. Clinical trials are underway for COVID-19 treatment and for prophylaxis in nursing home outbreaks.[112] • In mild to moderate COVID-19, it may speed clinical improvement.[111,112] Adverse effects include diarrhea, psychiatric symptoms, and lab abnormalities (increased uric acid, increased transaminases, decreased neutrophil count, increased triglycerides).[112] • It is currently approved in several countries for influenza and COVID-19.[112] Approval is pending in Canada.
Fluvoxamine	• Fluvoxamine's mechanism in COVID-19 may involve action at the sigma-1 receptor, which regulates cytokine production.[101] • In a preliminary placebo-controlled study (n=152), **outpatients** treated with fluvoxamine starting within seven days of symptom onset had a reduced risk of clinical deterioration (dyspnea, oxygen saturation <92% on room air) at day 15 (0/80 patients vs 6/72 patients). The study used an escalating dose, based on tolerability: 50 mg at bedtime on day 1, then 100 mg twice daily x 2 days, then 100 mg three times daily through day 15.[101] Fluvoxamine inhibits CYP1A2 and CYP2C19.[101] Gastrointestinal and central nervous system side effects are common.[27]

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Hydroxy-chloroquine	• Is a more potent inhibitor of SARS-CoV-2 than chloroquine *in vitro*.[2] Also has immunomodulating effects.[27] • Early enthusiasm for hydroxychloroquine was based on a widely publicized open-label, randomized study in hospitalized patients testing positive for SARS-CoV-2.[2] Six of 26 hydroxychloroquine patients were lost to follow-up: one due to death, three due to intensive care admission, one due to side effects (nausea), and one who left the hospital. Viral clearance at day six was 70% in the 20 remaining hydroxychloroquine patients vs 12.5% of the control patients (n = 16).[2] Six treated patients also received azithromycin to prevent bacterial infection.[2] In the combination group, viral clearance was 100% at day six vs 57.1% in the hydroxychloroquine-alone group.[2] Also see subsequent observational data under "Azithromycin," above. • In larger, open-label and cohort studies, despite some small, inconsistent benefit on clinical signs and symptoms, there was no benefit on viral clearance, length of stay, need for intensive care or mechanical ventilation, or mortality.[29,39,42,43,49,60,66] In one study, thirty percent of hydroxychloroquine patients had adverse effects.[42] In another study, the combination of hydroxychloroquine and azithromycin was associated with cardiac arrest.[66] When used with azithromycin (and other QT-prolonging medications), **QT prolongation** is of increased concern.[2,6] Information on managing QT prolongation risk in these patients is available at https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.120.047521. • One large (n = 2,541) retrospective U.S. cohort study found reduced mortality with hydroxychloroquine +/- azithromycin vs usual care.[75] Some patients with high cardiac risk were excluded. Select patients with severe COVID-19 and minimal cardiac risk also received azithromycin. Hydroxychloroquine was started within 48 hours of hospital admission in almost all patients. This study had several limitations. For example, the outcomes of almost 300 patients were not included in the analysis, and there were differences between treatment groups that could not be adequately adjusted for (e.g., baseline disease severity, other treatments received). • In a placebo-controlled study in outpatients, hydroxychloroquine did not improve symptoms.[11] Forty-three percent of hydroxychloroquine patients had side effects vs 22% of placebo patients. Four hydroxychloroquine patients were hospitalized, and there was one outpatient death in this group. In the placebo group, ten placebo patients were hospitalized, one of which died (p=0.29). • The NIH's placebo-controlled ORCHID trial (n=479) found no benefit in patients with severe COVID-19.[100] The WHO has discontinued the hydroxychloroquine arm of the Solidarity Trial because interim results suggested little mortality benefit for hospitalized patients.[74] • The hydroxychloroquine arm of the large RECORD study was stopped due to lack of efficacy.[74] • The FDA has **revoked its EUA** for hydroxychloroquine because it is unlikely to be effective, based on data from the EUA and elsewhere.[73] In addition to efficacy concerns, the FDA's revocation of its EUA for hydroxychloroquine was based on adverse effects; its known and potential benefits no longer outweigh the known and potential side effects (e.g., serious cardiac events and other serious side effects).[33] Due to the risk of arrhythmias, the FDA recommends **against** hydroxychloroquine use for COVID-19 outside of a clinical trial.[33] • Hydroxychloroquine was not effective for prevention of SARS-CoV-2 infection in an eight-week placebo-controlled trial of healthcare providers at two urban tertiary care hospitals (n=132).[87]

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Icatibant (*Firazyr*, generics [U.S])	• SARS-CoV-2 uses ACE2 to enter cells. Because the resulting loss of ACE2 function might lead to bradykinin accumulation, there is interest in use of icatibant (a bradykinin antagonist) for severe COVID-19. • In a small case-control study, icatibant 30 mg every six hours x 3 was associated with improved oxygenation in hypoxic patients.[81] See www.clinicaltrials.gov for ongoing studies.
IL-6 antagonist Tocilizumab (*Actemra*); sarilumab (*Kevzara*) *Continued…*	• High IL-6 levels are associated with higher COVID-19 disease severity, especially in nonsurvivors.[13] Tocilizumab reduces inflammatory markers (e.g., C-reactive protein) in patients with severe COVID-19.[116] • A meta-analysis of 27 randomized trials of IL-6 antagonists (mostly tocilizumab) vs usual care or placebo found an association between IL-6 use and lower 28-day mortality in patients also receiving a corticosteroid, especially among patients on supplemental or high-flow oxygen, or non-invasive mechanical ventilation. For patients receiving corticosteroids plus tocilizumab, mortality rate was 20%, and the OR for the association with mortality was 0.77 (95% CI 0.68 to 0.87). For patients receiving tocilizumab and corticosteroids, 25% of patients progressed to invasive mechanical ventilation or death vs 33% for placebo/usual care. Tocilizumab did not seem to increase the risk of secondary infections, even when used with a corticosteroid.[125] • Data from the open-label REMAP-CAP study suggest that tocilizumab (n=353) reduces mortality (28% tocilizumab vs 35.8% standard care) if given within 24 hours of starting respiratory support (invasive or non-invasive mechanical ventilation, high-flow oxygen) or vasopressors.[116] About 85% of patients also received a corticosteroid; mean time from admission to randomization was 1.2 days; and most patients were receiving respiratory support at enrollment. The tocilizumab dose was 8 mg/kg (max 800 mg), and the dose could be repeated in 12 to 24 hours if improvement was insufficient. Among patients randomized to tocilizumab, 92% received at least one dose, and 29% received a second dose. About 2% of the control group received an immunomodulator outside of the study protocol. • Results from an arm of the open-label RECOVERY trial suggests that adding tocilizumab (n=2,022) to standard care reduces mortality in hospitalized patients requiring oxygen or respiratory support who have baseline CRP ≥75 mg/L.[115] Tocilizumab-treated patients were more likely to be discharged alive within 28 days (57% vs 50%). Among patients receiving mechanical ventilation at baseline, tocilizumab did not increase the chance of cessation. Tocilizumab dosing was stratified as follows: 800 mg (>90 kg), 600 mg (>65 kg to 90 kg), or 400 mg (>40 kg to 65 kg). A second dose could be given 12 to 24 hrs later if no improvement. Over 80% of patients were also receiving a corticosteroid, and mean time from admission to randomization was two days. Among patients randomized to tocilizumab, 84% received at least one dose, whereas 4% of the usual care group received at least one dose of tocilizumab or sarilumab. Almost 30% of the tocilizumab group received more than one dose. • Three placebo-controlled studies (COVACTA, EMPACTA, REMDACTA) did not find a mortality benefit for tocilizumab.[124] In EMPACTA, tocilizumab reduced a composite endpoint of need for mechanical ventilation or death (12% vs 19.3%).[124] Median time to hospital discharge or "ready for discharge" was reduced by 1.5 days.[124] In COVACTA, median time to discharge or "ready for discharge" was 20 days in the tocilizumab group vs 28 days in the placebo group.[124]

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
IL-6 antagonists, continued	• Based on data from RECOVERY and the three placebo-controlled trials, tocilizumab has received Emergency Use Authorization (U.S.) for treatment of COVID-19 in hospitalized patients ≥2 years of age **receiving systemic corticosteroids** and supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.[124] Tocilizumab is given as a one-hour infusion of 12 mg/kg (<30 kg) or 8 mg/kg (≥30 kg), to a maximum of 800 mg. If clinical signs and symptoms do not improve or worsen, the dose can be repeated after at least eight hours.[124] There is insufficient evidence to assess the benefit of a second dose.[50] • The EUA fact sheet for tocilizumab for healthcare providers is available at https://www.fda.gov/media/150321/download. Give patients/caregivers the fact sheet available at https://www.fda.gov/media/150320/download. • The NIH recommends the addition tocilizumab to dexamethasone +/- remdesivir in patients with respiratory decompensation within three days of admission requiring high-flow oxygen, invasive or noninvasive mechanical ventilation, or ECMO.[50] This includes patients within the first 24 hours of intensive care admission or patients not admitted to intensive care with CRP ≥75 mg/L. Some experts would add tocilizumab to patients with rapidly increasing oxygen needs and CRP ≥75 mg/L who do not yet require high-flow oxygen or mechanical ventilation.[50] • Baricitinib may be an alternative to tocilizumab for many patients (see below).[50] However, tocilizumab has more evidence of a mortality benefit, and there is limited data for using baricitinib in mechanically-ventilated patients..[135] Do not combine tocilizumab with baricitinib due to infection risk.[50] • Some patients received sarilumab in REMAP-CAP (patients received noninvasive or invasive mechanical ventilation or high-flow oxygen and/or pressors).[116] Based on limited evidence, it appears to work as well as tocilizumab at a single dose of 400 mg.[77] Consider it for adults only if tocilizumab is unavailable.[50] To make an intravenous sarilumab solution using the subcutaneous syringe formulation, add 400 mg to 100 mL of normal saline. Infuse over one hour.[50] Stability is four hours.[136] Infuse with a 0.2 micron in-line filter.[136] • IL-6 antagonists may cause increased infections, neutropenia, thrombocytopenia, and elevated liver enzymes.[1,34-38] There are several cases of tocilizumab-associated worsening of COVID-19, perhaps due to immunosuppression, despite an associated reduction in inflammatory markers.[80]
Ivermectin *Continued…*	• Ivermectin has several mechanisms that make it an attractive option for study for prevention and treatment of COVID-19. However, it has not previously demonstrated clinically significant antiviral efficacy for any virus in humans.[32] A dose of 200 mcg/kg (the usual oral dose) may not produce levels high enough in the lungs to inhibit coronavirus.[108] • A small (n=72) study comparing ivermectin, ivermectin plus doxycycline, and placebo found no symptom benefit for patients with mild disease despite faster viral clearance and reduction of inflammatory markers.[107] Another small study (n=60) of ivermectin 200 mcg/kg/day for five days showed statistically insignificant clinical improvement at day five (14/30 vs 11/30; p=0.43) and day ten (22/30 vs 16/30, p=0.10) in patients with severe disease compared to usual care (no placebo).[131] The largest double-blind, placebo-controlled study to date (n=400) found no benefit of ivermectin 300 mcg/kg/day for five days for symptom resolution in mild disease.[122] A retrospective cohort study (n=280) suggests lower mortality, especially in

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Ivermectin, continued	patients with severe COVID-19 lung disease, but neither length of stay nor extubation rate were affected.[12] In general, these and other studies of ivermectin for COVID-19 had limitations such as small sample size; varying dose; open-label, uncontrolled, or retrospective design; confounding medications; and unclear COVID-19 severity and outcome measures.[12,50] • Meta-analyses that showed a mortality benefit included a large preprint study that has since been retracted.[127-129,132] Meta-analyses that did not include the retracted study could not find benefit for mortality, recovery, or viral clearance, or as prophylaxis.[133,134] • The American Medical Association, American Society of Health-System Pharmacists, and the American Pharmacists Association oppose ivermectin use for COVID-19 except in a clinical trial.[138] Canadian groups (e.g., Health Canada, CPhA) also oppose its use. • NIH guidance recommends neither for nor against ivermectin for COVID-19 treatment due to insufficient evidence.[50] However, in endemic areas, ivermectin can be considered for strongyloidiasis prophylaxis in patients receiving dexamethasone plus tocilizumab as a treatment for COVID-19.[50] • Ivermectin (oral) is well-tolerated when used as directed for its approved indication (strongyloidiasis) or off-label for lice and scabies.[50] Adverse effects include nausea, diarrhea, dizziness, itching.[50] Overdose, such as happens when people self-medicate with ivermectin intended for animals or take more than the usual dose, can cause vomiting, hypotension, ataxia, seizures, coma, and death.[130] It can also interact with warfarin, possibly by inhibiting vitamin K-dependent clotting factors.[27]
Janus Kinase Inhibitors (Baricitinib [*Olumiant*], tofacitinib [*Xeljanz*]) *Continued…*	• Interest in Janus kinase inhibitors for treatment of COVID-19 is based on their potential to block the effects of IL-6 and other cytokines. They might also prevent SARS-CoV-2 from entering cells.[20] • In the ACTT-2 study (n=1,033), oral baricitinib 4 mg once daily x 14 days (or until discharge) **with remdesivir** reduced recovery time by one day vs remdesivir plus placebo (median recovery time seven days vs eight days; rate ratio 1.16, 95% CI 1.01 to 1.32; p=0.03).[20] Among patients requiring high-flow or noninvasive ventilation at baseline, median recovery time was ten days for the combination vs 18 days with remdesivir plus placebo (rate ratio 1.51, 95% CI 1.10 to 2.08).[20] Mortality at day 28 was not significantly lower with the combination (5.1% vs 7.8%)(HR 0.65, 95% CI 0.39 to 1.09).[20] Mortality in the control group was relatively low.[20] • ACTT-2 was not designed to evaluate baricitinib's safety and efficacy in patients receiving dexamethasone, which has been shown to improve mortality in patients on supplemental oxygen.[20,31] However, patients who received corticosteroids after randomization had a higher incidence of infection.[20] ACTT-4 will study remdesivir/baricitinib vs remdesivir/dexamethasone. • The COV-BARRIER study (n=1,525) showed no benefit of baricitinib 4 mg once daily for 14 days until discharge over placebo for reduction of the combined primary outcome of progression to high-flow oxygen, non-invasive or mechanical ventilation, or death in patients on supplemental oxygen.[99] It did reduce a secondary outcome of 28-day all-cause mortality (8% vs 13%), driven by patients not requiring mechanical ventilation. Most patients also received corticosteroids. Patients with serious non-COVID infections, who were immunocompromised, or who were receiving invasive mechanical ventilation

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Janus Kinase Inhibitors, continued	or ECMO were excluded. Risk of secondary infection was not increased vs placebo. Preliminary data from a COV-BARRIER substudy suggest that baricitinib may reduce mortality in patients on mechanical ventilation or ECMO.[135] • Based on ACTT-2 and COV-BARRIER, baricitinib has received EUA to treat COVID-19 in patients ≥2 years of age who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.[103] These studies were limited to adults. Pediatric dosing is based on studies for other uses.[103] • The NIH recommends the addition of baricitinib to dexamethasone ± remdesivir in patients on high-flow oxygen or noninvasive ventilation with clinical progression or inflammatory markers within three days of admission.[50] Some experts would add baricitinib to patients with inflammatory signs and rapidly increasing oxygen needs while on dexamethasone, but who do not yet require high-flow oxygen or noninvasive ventilation.[50] • Tocilizumab may be an alternative to baricitinib for many patients (see above).[50] Tocilizumab has more evidence of a mortality benefit. Consider that there is limited data for using baricitinib in mechanically-ventilated patients.[20,135] Do not combine baricitinib with tocilizumab due to infection risk.[50] • The EUA fact sheet for baricitinib for healthcare providers is available at https://www.fda.gov/media/143823/download. Give patients/caregivers the fact sheet available at https://www.fda.gov/media/143824/download. • See the EUA (link below) for information on dosing for renal impairment, low blood counts, and aminotransferase elevations, as well as safe handling. • A subsequent study (STOP-COVID)(n=289) compared tofacitinib 10 mg twice daily to placebo for 14 days until discharge in patients hospitalized for <72 hours. Most patients also received corticosteroids and supplemental oxygen, but not remdesivir, invasive or noninvasive mechanical ventilation, or ECMO. Patients with active non-COVID infections or who were immunocompromised were excluded. Tofacitinib decreased the composite risk of death or respiratory failure vs placebo (18.1% vs 29% [RR 0.63, 95% CI 0.41 to 0.97, p=0.04], but not duration of ICU or hospital stay. Death from any cause at day 28 was 2.8% in the tofacitinib group vs 5.5% in the placebo group (HR 0.49, 95% CI 0.15 to 1.63). Risk of secondary infection was not increased vs placebo.[126] • Consider tofacitinib for non-critically ill patients if baricitinib is unavailable.[50,126] • The baricitinib EUA carries warnings about VTE risk.[103] VTE was similar in the two treatment arms of ACTT-2 (21 patients [baricitinib] vs 16 patients [placebo]; 4.1% vs 3.1%, 95% CI -1.3 to 3.3).[20] All patients received VTE prophylaxis unless contraindicated, as is recommended in the EUA.[20,103] Similarly, VTE risk was not increased in COV-BARRIER or STOP-COVID.[99] Patients with recurrent VTE, or history within 12 weeks (COV-BARRIER; ACTT-2), or any VTE history (STOP-COVID) were excluded from these studies.[99.126] • For more information about baricitinib and tofacitinib safety, see our chart, *Janus Kinase Inhibitor Adverse Effects*. Like baricitinib, tofacitinib requires special handling.[139]

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Linagliptin	• No data. • Interest in linagliptin use for COVID-19 treatment is based on its *in vitro* inhibition of SARS-CoV-2 cysteine protease, an enzyme involved in viral replication.[121]
Lopinavir/ ritonavir (*Kaletra*)	• Lopinavir/ritonavir has not demonstrated anti-SARS-CoV-2 activity in humans.[15] A small study suggested benefit (reduced composite endpoint of ARDS or death) for 2003 SARS vs historical control.[17] • Results from a randomized, open-label study (n=199) suggested it might reduce complications such as acute kidney injury, secondary infections, or need for mechanical ventilation in patients with COVID-19 pneumonia.[15] However, time to clinical improvement was not reduced (main outcome measure).[15] Gastrointestinal adverse effects may limit use.[15,30] • In an arm of the RECOVERY trial, 1,616 patients were randomized to open-label lopinavir-ritonavir. Compared to usual care (n=3,424), lopinavir-ritonavir did not improve 28-day mortality (p=0.60) or affect the composite endpoint of mechanical ventilation or death (composite endpoint; p=0.092).[58] • The WHO has discontinued the lopinavir/ritonavir arm of the Solidarity Trial because interim results suggest no mortality benefit for hospitalized patients.[74]
Losartan, Telmisartan	• Studies in mice suggest that ARBs can reduce lung damage caused by SARS-CoV.[22] • Clinical trials are underway for treatment of COVID-19. See www.clinicaltrials.gov for more information.
Monoclonal antibodies (SARS-CoV-2 neutralizing antibodies) *Continued…*	• AstraZeneca (AZD7442), Eli Lilly (bamlanivimab, etesevimab), GlaxoSmithKline (VIR-7831; COMET-Ice Study), Regeneron (casirivimab/imdevimab), and others are testing monoclonal antibodies against COVID-19. • Casirivimab/imdevimab, bamlanivimab/etesevimab, and sotrovimab have received EUA in the U.S., and casirivimab/imdevimab, bamlanivimab, and sotrovimab have been authorized by interim order in Canada. • For NIH guidance on prioritization of COVID-19 monoclonal antibodies, see https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-the-prioritization-of-anti-sars-cov-2-monoclonal-antibodies/. **Casirivimab/imdevimab** (*Regen-COV*) • Casirivimab/imdevimab has received EUA (U.S.) and authorization by interim order (Canada) for **treatment** of high-risk patients (see EUA fact sheet and Canadian product monograph links below for risk factors) ≥12 years of age weighing ≥40 kg with mild to moderate test-confirmed COVID-19, starting as soon as possible (U.S.: within ten days of symptom onset).[88,120] It is NOT for patients requiring hospitalization for COVID-19 or those requiring supplemental oxygen (or increased flow rate in patients on chronic oxygen).[88,120] The EUA was based on an phase I/II/III placebo-controlled study.[88] Treatment was started within three days of a positive test result, and median duration of symptoms before starting treatment

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Monoclonal antibodies, continued	was three days.[88] One percent of those who received the study drug at a dose of 1,200 mg (n=736) required emergency department care or hospitalization vs 3.2% of the placebo patients.[88] This was based on a low number of events (24 in the placebo group and seven in the treatment group).[88] Viral clearance was greater in the treatment group vs placebo.[88] • For the 2,400 mg dose (authorized in Canada), 1.3% of patients who received the study drug required emergency department care or hospitalization vs 4.6% of placebo patients. This was based on 18 events in the treatment group and 62 events in the placebo group.[120] The lower dose authorized in the U.S. (1,200 mg), is based on the drug's flat dose-response curve.[102] • In the U.S., casirivimab/imdevimab has received EUA for **post-exposure prophylaxis** in high-risk patients who are not fully vaccinated (or who may have had poor vaccine response): (1) after CDC-defined close contact with a person infected with COVID-19, or (2) who are at high risk of exposure to COVID-19 patients in an institutional setting. The initial dose is 1,200 mg. Repeat doses of 600 mg can be given every four weeks in the event of ongoing exposure.[88] In a study of household contacts, contacts were treated with casirivimab/imdevimab within 96 hours of a household member testing positive. One percent of those treated with casirivimab/imdevimab became COVID-positive vs 8% of placebo-treated patients.[88] • Casirivimab/imdevimab is also being studied in patients hospitalized for COVID-19. There seems to be a mortality benefit in patients who do not mount their own antibody response (24% vs 30% placebo, p=0.001).[96] The dose used was higher than the dose in the EUA. • *In vitro*, active against the South Africa variant (B.1.351;Beta), the U.K. variant (B.1.1.7; Alpha), the Brazil variant (P.1; Gamma), the California variant (B.1.427/B.1.429), the New York variant (B.1.526), and the India variants (B.1.617.1/B.1.617.3, B.1.617.2; Delta).[88] • Casirivimab/imdevimab is given as an infusion, or subcutaneously (U.S.) if infusion is not feasible or would delay treatment.[88,120] (With subcutaneous administration, viral load reduction is similar to the intravenous route, but clinical efficacy data are limited.[88]) Casirivimab/imdevimab appears well tolerated, but patients must be monitored for one hour after administration for reactions.[88,120] • The **EUA fact sheet** for casirivimab/imdevimab for healthcare providers is available at https://www.fda.gov/media/145611/download. Give patients the fact sheet available at https://www.fda.gov/media/143893/download. • The Canadian product monograph is available at Health Canada's Drug Product Database (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). **Bamlanivimab +/- Etesevimab** (Eli Lilly) • Bamlanivimab/etesevimab has received EUA (U.S.), and bamlanivimab monotherapy has received authorization by interim order (Canada) for high-risk patients (see EUA fact sheet and Canadian product monograph links, below, for risk factors) ≥12 years of age weighing ≥40 kg with mild to moderate test-confirmed COVID-19, starting as soon as possible, within ten days of symptom onset, based on data from a study in recently diagnosed outpatients (BLAZE-1).[21,89] This study includes monotherapy and combination therapy (with etesevimab) arms.[90] Monotherapy and combination therapy reduced need for a
Continued…	

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Monoclonal antibodies, continued	hospital visit vs placebo (1% [700 mg] and 0.9% [combo] vs 5.8% [placebo]).[90] Combination therapy had 2% lower mortality than placebo.[89] In a post-hoc analysis, among patients ≥65 years of age or with BMI ≥35 kg/m^2, hospitalizations in the bamlanivimab, bamlanivimab/etesevimab, and placebo groups were 2.7%, 0%, and 13.5%, respectively.[90] However, there were only 11 visits total.[90] • In the U.S., bamlanivimab/etesvimab has received EUA for **post-exposure prophylaxis** in high-risk patients who are not fully vaccinated (or who may have had poor vaccine response): (1) after CDC-defined close contact with a person infected with COVID-19, or (2) who are at high risk of exposure to COVID-19 patients in an institutional setting. The initial dose is 700 mg/1,400 mg. This indication was based on a study that used bamlanivimab 4,200 mg alone in nursing home residents and staff after an exposure. Bamlanivimab reduced the risk of symptomatic infection by up to 57%; by up to 72% in high-risk persons; and up to 80% in residents.[89] • Bamlanivimab +/- etesevimab is NOT for patients requiring hospitalization for COVID-19 (EUA: or those requiring supplemental oxygen, or increased flow rate in patients on chronic oxygen).[21,89] A study in hospitalized patients (ACTIV-3) was closed due to lack of benefit.[98] • Unpublished data for COVID-19 prevention in residents and staff of long-term care facilities (BLAZE-2; n=965) suggests reduced risk of symptomatic infection among residents (OR 0.2, p=0.00026) and among residents plus staff (OR 0.43, p=0.00021) within the eight-week follow-up period.[113] • Facilities interested in participating in Eli Lilly COVID-19 clinical trials can email covid19potentialsite@lilly.com. Also see www.clinicaltrials.gov for more information. • *In vitro*, bamlanivimab +/- etesevimab appears active against the U.K. variant (B.1.1.7; Alpha), but **inactive** against the South Africa variant (B.1.351; Beta) and Brazil variant (P.1; Gamma).[106,119] Bamlanivimab alone appears **inactive** against the California variant (B.1427/B.1.429) and New York variant (B.1.526), while the combination has reduced activity.[106] • Because of the prevalence of resistant variants, the FDA has revoked the EUA for bamlanivimab monotherapy.[97] As of September 2, 2021, bamlanivimab/etesevimab is being distributed only to those U.S. states or jurisdictions in which the prevalence of resistant variants is ≤5%. For updates, see https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab-etesevimab/Pages/default.aspx. • Bamlanivimab +/- etesevimab is given as a one-time infusion. They appear well tolerated, but patients must be monitored (U.S.: for one hour) after the infusion for reactions.[21,89] • The **EUA fact sheet** for bamlanivimab/etesevimab for healthcare providers is available at https://www.fda.gov/media/145802/download. Give patients the fact sheet available at https://www.fda.gov/media/145803/download • The Canadian product monograph for bamlanivimab is available at Health Canada's Drug Product Database (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp).
Continued…	

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Monoclonal antibodies, continued	**Sotrovimab** (GlaxoSmithKline) • Sotrovimab has received EUA (U.S.) and authorization by interim order (Canada) for high-risk patients (see EUA fact sheet and Canadian product monograph links below for risk factors) ≥12 years of age weighing ≥40 kg with mild to moderate test-confirmed COVID-19, starting as soon as possible (U.S.: within ten days of symptom onset).[123,137] It is NOT for patients requiring hospitalization for COVID-19 or those requiring supplemental oxygen (or increased flow rate in patients on chronic oxygen).[123,137] Authorization was based on interim analysis of the ongoing Phase 1/2/3 COMET-ICE trial.[123,137] Patients were enrolled within five days of symptom onset. Five hundred eighty-three patients were included in the analysis. 1% of patients who received the study drug (n=3) required emergency department care or hospitalization vs 7% of the placebo patients (n=21). Viral clearance data is not available. One placebo patient died. • *In vitro*, it is active against the South Africa variant (B.1.351; Beta), the U.K. variant (B.1.1.7; Alpha), and the Brazil variant (P.1; Gamma).[123,137] There is no data on the California variant (B.1.427/B.1.429), New York variant (B.1.526), and the India variant (B.1.617; Delta).[123] • Sotrovimab is given as a one-time infusion.[123,137] It appears well tolerated, but patients must be monitored for one hour after the infusion for reactions.[123,137] • The **EUA fact sheet** for sotrovimab for healthcare providers is available at https://www.fda.gov/media/149534/download. Give patients the fact sheet available at https://www.fda.gov/media/149533/download. • The Canadian product monograph for sotrovimab is available at Health Canada's Drug Product Database (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp).
Remdesivir *Continued…*	• Remdesivir has *in vitro* activity against SARS-CoV-2.[40] • In a cohort of 53 evaluable patients receiving oxygen support, or with oxygen saturation ≤94% on room air, remdesivir was associated with clinical improvement in regard to oxygen support requirements in 68% of patients.[40] Mortality was 13%, which is less than in other case series and cohorts.[40] **Most of the patients (65%) were receiving mechanical ventilation or ECMO at baseline.**[40] Viral load was not evaluated,[40] but in a previous case report, virologic improvement was seen.[8] • In a double-blind, placebo-controlled trial (ACTT-1) (n = 1,062), remdesivir seemed to shorten time to recovery (10 days vs 15 days; p <0.001), but mortality at day 29 was not statistically different (11.4% vs 15.2%; HR 0.73, 95% CI 0.52 to 1.03).[72] Shortened recovery time was statistically significant only in patients who received treatment within ten days of symptoms onset.[72] • In ACTT-1, most patients had severe disease at enrollment, defined as oxygen saturation ≤94% on room air, need for invasive or noninvasive oxygen supplementation, or respirations ≥24 breaths/minute.[72] Most patients were receiving oxygen.[72] **Remdesivir seemed to provide the most benefit for patients receiving low-flow oxygen at baseline**, but this may be a reflection of subgroup sample size, and it cannot be concluded that other patients won't benefit.[72] • Five days vs ten days of remdesivir were compared in the open-label **SIMPLE-Severe** study. Included patients had oxygen saturation ≤94% on room air and radiologic evidence of pneumonia.[82] **Most patients were receiving some kind of**

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Remdesivir, continued	**supplemental oxygen (mostly low-flow)**.[82] Patients receiving **mechanical ventilation or ECMO were excluded**.[82] There was no significant difference between five days and ten days in regard to clinical status at day 14.[82] An unpublished comparison of remdesivir-treated patients (n=312) to a matched cohort of patients receiving standard care (n=818) showed recovery and mortality benefit for remdesivir.[79] • A five-day course of remdesivir was associated with a statistically significant (but perhaps not clinically significant) improvement in clinical status on a seven-point ordinal scale in patients with **moderate** COVID-19 (radiographic evidence of **pulmonary infiltrates** and oxygen saturation >94% on room air) vs standard care in an open-label, randomized study (n=584). Most patients were not on any kind of supplemental oxygen. Viral load was not assessed. Patients randomized to a 10-day course (actual median treatment duration six days) did not benefit. The clinical status score used in this study could have underestimated benefit in this population with nonsevere disease.[24] • In the open-label **WHO SOLIDARITY trial**, 2,743 patients were randomized to remdesivir.[91] The primary goal was to assess its effect on in-hospital mortality.[91] Most patients (~75%) were receiving some kind of oxygen at randomization.[91] Remdesivir did not reduce mortality, reduce the need for mechanical ventilation, or reduce length of stay vs similar care without remdesivir.[91] There was a small, nonsignificant mortality benefit for patients not on mechanical ventilation at study entry (RR 0.86, 99% CI 0.67 to 1.11).[91] SOLIDARITY's results do not negate ACTT-1, as SOLIDARITY was not placebo-controlled and ACTT-1 was designed to assess time to recovery.[53] • WHO guidelines weakly suggest against remdesivir because it lacks important effects on patient-centered outcomes such as mortality, need for mechanical ventilation, or time to clinical improvement. But because the quality of evidence is low or very low, important clinical benefit cannot be excluded. Furthermore, because COVID-19 is potentially fatal and remdesivir is well-tolerated, some patients will choose to receive it.[104] • The **FDA** has approved remdesivir (*Veklury*) for treatment of COVID-19 in hospitalized patients ≥12 years of age who weigh ≥40 kg, based on data from the ACTT trial and Gilead's SIMPLE studies.[24,57,72,82] • Remdesivir has **EUA** for use in children <12 years of age who weigh ≥3.5 kg.[54] Clinical trials in pediatrics are also ongoing.[53] The **EUA fact sheet** for healthcare providers is available at https://www.fda.gov/media/137566/download, and the parent/caregiver fact sheet is available at https://www.fda.gov/media/137565/download. • Remdesivir and dexamethasone can be used together in patients requiring increasing supplemental oxygen, and can be considered for those who have been recently intubated.[50] The rationale for combination therapy is that remdesivir provides antiviral activity while dexamethasone provides anti-inflammatory activity.[50] The combination has not been specifically studied.[50] • Ten days' treatment with remdesivir has not been shown to be more effective than five days (see SIMPLE-Severe, above),[82] but treatment can be extended to ten days if improvement is not substantial by day five.[50] Remdesivir can be discontinued at discharge.[50] • Remdesivir should be continued to complete the course for patients who progress to a high-flow oxygen device, mechanical ventilation, or ECMO.[50] However, its benefit in these patients is unclear based on current data (see studies above).
Continued…	

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Remdesivir, continued	• **In Canada**, remdesivir (*Veklury*) has received marketing authorization with conditions pending the results of additional clinical trials. Its approved indication is treatment of COVID-19 pneumonia requiring supplemental oxygen in patients ≥12 years of age who weigh ≥40 kg.[59] • The most common **adverse effects** of remdesivir are nausea and transaminase elevations.[57,59] Discontinue if ALT >10 x ULN with symptoms suggestive of liver injury (Canada: discontinue if ALT reaches 5 x ULN).[57,59] • Product labeling recommends against use in severe renal impairment due to accumulation of cyclodextrin which may cause liver or renal toxicity.[47,59,61] However, five days' treatment seems well-tolerated in severe renal impairment or hemodialysis.[61] The aqueous formulation contains twice as much cyclodextrin as the powder.[61] • **Coadministration of remdesivir and chloroquine or hydroxychloroquine is not recommended** based on *in vitro* data showing that these drugs might interfere with the metabolic activation and antiviral activity of remdesivir.[53] In Simple-Severe, recovery rate at day 14 for patients who received hydroxychloroquine plus remdesivir was lower than in patients who received remdesivir alone. Concomitant hydroxychloroquine use was associated with a higher risk of adverse events.[79] Another potential **drug interaction** involves inhibition of remdesivir elimination from hepatocytes by **P-glycoprotein inhibitors**. This interaction could result in hepatotoxicity.[76]
Statins	• Statins might ameliorate COVID-19-mediated inflammation and prevent lung injury by affecting ACE2 expression.[25] • In a meta-analysis of almost 9,000 COVID-19 patients in studies looking at the risk of severe COVID-19 illness or mortality in statin users vs nonusers, statin use was associated with a reduced risk of severe or fatal COVID-19 (HR 0.7, 95% CI 0.53 to 0.94).[25] • NIH guidelines recommend against use specifically for COVID-19 treatment outside of a clinical trial.[50] • See www.clinicaltrials.gov for more information on planned or ongoing studies.
tPA (alteplase)	• No data. • Interest based on reports of microvascular pulmonary thrombosis in COVID-19 patients. • Studies are underway to treat ARDS in COVID-19 patients. See www.clinicaltrials.gov.
Vitamin C	• Intravenous vitamin C is being studied for treatment of severe COVID-19 disease based on previous data in sepsis and ARDS. However, there is no clear evidence of benefit even for these conditions, in which it has been studied alone or with thiamine +/- hydrocortisone in sepsis.[48] • In an open-label study, oral vitamin C 8,000 mg daily, alone or with zinc gluconate, did not reduce symptom duration in outpatients.[93] • The NIH recommends neither for nor against vitamin C for COVID-19 due to insufficient evidence.[50] • See www.clinicaltrials.gov for information on ongoing clinical trials.

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Vitamin D	• Interest in vitamin D stems from its effects on the immune system and pulmonary ACE2 expression.[109,110] • In a cohort (n=186) of patients with severe COVID-19, 59% were vitamin-D deficient, but risk factors for vitamin D deficiency may also be risk factors for severe COVID-19 (e.g., obesity, poverty).[109] • The NIH recommends neither for nor against vitamin D for COVID-19 due to insufficient evidence.[50] • Studies are planned or underway using vitamin D for prevention or as a treatment adjunct. See www.clinicaltrials.gov for more information.
Zinc	• Zinc has *in vitro* activity against SARS-CoV.[47] • In an open-label study, oral zinc gluconate 50 mg daily, alone or with vitamin C, did not reduce symptom duration in outpatients.[93] • The NIH recommends against use of zinc for COVID-19 prevention above the recommended dietary allowance outside of a clinical trial, and recommends neither for nor against its use for treatment, due to insufficient evidence.[50] • Studies of zinc, alone or in combination (e.g., with vitamin C, **vitamin D**) to prevent or treat COVID-19 disease are planned or ongoing. See www.clinicaltrials.gov for more information.

Abbreviations: ACE = angiotensin-converting enzyme; ALT = alanine aminotransferase; ARB = angiotensin receptor blocker; ARDS = acute respiratory distress syndrome; BMI = body mass index; ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; ICU = intensive care unit; IDSA = Infectious Diseases Society of America; IL = interleukin; NIH = National Institutes of Health; NSAIDs = nonsteroidal anti-inflammatory drugs; SARS = severe acute respiratory syndrome; SARS-CoV-2 = the virus that causes COVID-19 disease; tPA = tissue plasminogen activator; TNF = tumor necrosis factor; U.K. = United Kingdom; ULN = upper limit of normal; VTE = venous thromboembolism; WHO = World Health Organization

---

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*****	1. High-quality RCT 2. SR/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*****	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).
RCT = randomized controlled trial; **SR** = systematic review
[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004;69:548-56. http://www.aafp.org/afp/2004/0201/p548.pdf.]

Prepared by the Editors of Therapeutic Research Center (361022).

References

1. Product monograph for Kevzara. Sanofi Genzyme. Mississauga, ON L4W 4V9. August 2019.
2. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;56:105949.
3. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14:72-3.
4. FDA. Fact sheet for health care providers emergency use authorization (EUA) of chloroquine phosphate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. Revoked. June 15, 2020. https://www.fda.gov/media/136535/download. (Accessed September 15, 2020).
5. Touret F, de Lamballerie X. Of chloroquine and COVID-19. Antiviral Res 2020;177:104762.
6. Cortegiani A, Ippolito M, Ingoglia G, et al. Update I. A systematic review on the efficacy and safety of chloroquine/hydroxychloroquine for the treatment of COVID-19. J Crit Care 2020;59:176-90.
7. Bermejo-Martin JF, Kelvin DJ, Eiros JM, et al. Macrolides for the treatment of severe respiratory illness caused by novel H1N1 swine influenza viral strains. J Infect Dev Ctries 2009;3:159-61.
8. Ko WC, Rolain JM, Lee NY, et al. Arguments in favour of remdesivir for treating SARS-CoV-2 infections. Int J Antimicrob Agents 2020;55:105933. doi: 10.1016/j.ijantimicag.2020.105933.
9. Deftereos SG, Giannopoulos G, Vrachatis DA, et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: the GRECCO-19 randomized clinical trial. JAMA Netw Open 2020;3:e2013136.
10. Veiga VC, Prats JAGG, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ 2021;372:n84. http://dx.doi.org/10.1136/bmj.n84.
11. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. Ann Intern Med 2020;173:623-31.
12. Rajter JC, Sherman MS, Fatteh N, et al. Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: the Ivermectin in COVID Nineteen Study. *Chest* 2021;159:85-92.
13. Cortegiani A, Ippolito M, Greco M, et al. Rationale and evidence on the use if tocilizumab in COVID-19: a systematic review. Pulmonology 2021;27:52-66.
14. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet 2021;397:2049-59.
15. Cao B, Wang Y, Wen W, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med 2020;382:1787-99.
16. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934-43.
17. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004;59:252-6.
18. FDA. FDA issues emergency use authorization for convalescent plasma as potential promising COVID-19 treatment, another achievement in administration's fight against pandemic. August 23, 2020. https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment. (Accessed September 16, 2020).
19. Dimopoulos G, de Mast Q, Markou N, et al. Favorable anakinra responses in severe COVID-19 patients with secondary hemophagocytic lymphohistiocytosis. *Cell Host Microbe* 2020;28:117-23.e1.

20. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med* 2021;384:795-807.
21. Product monograph for bamlanivimab. Eli Lilly Canada. Toronto, ON M5X 1B1. April 2021.
22. Kuster G, Pfister O, Burkard T, et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? *Eur Heart J* 2020;41:1801-3.
23. Diorio C, Anderson EM, McNerney KO, et al. Convalescent plasma for pediatric patients with SARS-CoV-2-associated acute respiratory distress syndrome. *Pediatr Blood Cancer* 2020;67:e28693.
24. Spinner CD, Gottleib RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA* 2020;324:1048-57.
25. Kow CS, Hasan SS. Meta-analysis of effect of statins in patients with COVID-19. *Am J Cardiol* 2020;134:153-5.
26. McCreary EK, Pogue JM. Coronavirus disease 2019 treatment: a review of early and emerging options. *Open Forum Infect Dis* 2020;7:ofaa105.
27. Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. 2021. http://www.clinicalkey.com. (Accessed September 21, 2021).
28. Gautret P, Lagier JC, 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.
29. Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zheijang Univ* 2020;49:215-19.
30. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA* 2020;323:1488-94.
31. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021;384:693-704.
32. Banerjee K, Nandy M, Dalai CK, Ahmed SN. The battle against COVID 19 pandemic: what we need to know before we "test fire" ivermectin. *Drug Res (Stuttg)* 2020;70:337-40.
33. FDA. Frequently asked questions on the revocation of the Emergency Use Authorization for hydroxychloroquine sulfate and chloroquine phosphate. June 19, 2020. https://www.fda.gov/media/138946/download. (Accessed September 15, 2020).
34. Product information for *Kevzara*. Sanofi-Aventis. Bridgewater, NJ 08807. April 2018.
35. Product information for *Actemra*. Genentech. South San Francisco, CA 94080. March 2021.
36. Product information for *Sylvant.* EUSA Pharma. Hertfordshire, U.K. HP2 4TZ. December 2019.
37. Product monograph for *Actemra*. Mississauga, ON L5N 5M8. January 2021.
38. Product monograph for *Sylvant*. Janssen. Toronto, ON M3C 1L9. January 2021.
39. Chen Z, Hu JM, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020.03.22.20040758. https://doi.org/10.1101/2020.03.22.20040758. (Accessed September 17, 2020).
40. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe COVID-19. *N Engl J Med* 2020;382:2327-36.
41. Borba MG, Val FF, 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(4.23):e208857.
42. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open-label, randomized, controlled trial. *BMJ* 2020;369. doi: 10.1136/bmj.m1849.
43. Mahevas M, Tran VT, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with COVID-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ* 2020;369. doi: 10.1136/bmj.m1844.
44. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. *N Engl J Med* 2021;384:20-30.
45. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JA, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020;324:1330-41..
46. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Last updated June 25, 2021. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. (Accessed July 17, 2021).
47. te Velthuis AJ, van den Worm SH, Sims AC, et al. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc inonophores block the replication of these viruses in cell culture. *PLoS Pathog* 2010;6:e1001176.
48. Surani S, Sharma M. Revisiting the role of vitamin C in sepsis. Is it a forlorn hope or is there still dearth of data? *Open Respir Med J* 2019;13:55-7.
49. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. *Med (NY)* 2020;1:114-27..
50. NIH. Coronavirus disease 2019 (COVID-19). Treatment guidelines. Last updated September 15, 2021. https://covid19treatmentguidelines.nih.gov/. (Accessed September 21, 2021).
51. World Health Organization. Corticosteroids for COVID-19. Living guidance. September 2, 2020. https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1. (Accessed May 16, 2021).

52. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA* 2020;324:1298-306.
53. FDA. Frequently asked questions for *Veklury* (remdesivir). February 4, 2021. https://www.fda.gov/media/137574/download. (Accessed May 16, 2021).
54. FDA. Remdesivir EUA letter of authorization. October 22, 2020. https://www.fda.gov/media/137564/download. (Accessed May 16, 2021).
55. Rogosnitzky M, Berkowitz E, Jadad AR. Delivering benefits at speed through real-world repurposing of off-patent drugs: the COVID-19 pandemic as a case point. *JMIR Public Health Surveill* 2020;6:e19199.
56. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA* 2020;324:1307-16.
57. Product information for *Veklury*. Gilead Sciences. Foster City, CA 94404. October 2020.
58. RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial. *Lancet* 2020;396:1345-52.
59. Product monograph for *Veklury*. Gilead Sciences Canada. Mississauga, ON L5N 2W3. July 2020.
60. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med* 2020;382:2411-8.
61. Thakare S, Gandhi C, Modi T, et al. Safety of remdesivir in patients with acute kidney injury or CKD. *Kidney Int Rep* 2021;6:206-10.
62. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 2020;323:1582-9.
63. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci USA* 2020;117:9490-6.
64. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol* 2020;92:1890-901.
65. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020;2:e325-31.
66. 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* 2020;323:2493-502.
67. Freedberg DE, Conigliaro J, Wang TC, et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: a propensity score matched retrospective cohort study. *Gastroenterology* 2020;159:1129-31.e3.
68. The Writing Committee for the REMAP-CAP Investigators, Angus DC, Derde L, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA* 2020;324:1317-29..
69. Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent plasma antibody levels and the risk of death from Covid-19. *N Engl J Med* 2021;384:1015-27.
70. FDA. Fact sheet for health care providers. Emergency use authorization (EUA) of COVID-19 convalescent plasma for treatment of COVID-19 in hospitalized patients. February 4, 2021. https://www.fda.gov/media/141478/download. (Accessed February 19, 2021).
71. Canadian Blood Services. COVID-19 and convalescent plasma. https://www.blood.ca/en/plasma/covid-19-and-convalescent-plasma. (Accessed July 17, 2021).
72. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19-final report. *N Engl J Med* 2020;383:1813-26.
73. FDA. Letter to Gary L. Disbrow, Deputy Assistant Secretary, Director, Medical Countermeasures Programs, BARDA, in response to request for revocation of Emergency Use Authorization for chloroquine phosphate and hydroxychloroquine. June 15, 2020. https://www.fda.gov/media/138945/download. (Accessed September 15, 2020).
74. Bagozzi D. WHO discontinued hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19. News release. July 4, 2020. https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19. (Accessed September 18, 2020).
75. Arshad S, Kilgore P, Chaudry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis* 2020;97:396-403.
76. Leegwater E, Strik A, Wilms EB, et al. Drug-induced liver injury in a patient with coronavirus disease 2019: potential interaction of remdesivir with P-glycoprotein inhibitors. *Clin Infect Dis* 2021;72:1256-8.
77. The REMAP-CAP Investigators, Derde LPG. Effectiveness of tocilizumab, sarilumab, and anakinra for critically ill patients with COVID-19. The REMAP-CAP COVID-19 immune modulation therapy domain randomized clinical trial. https://www.medrxiv.org/content/10.1101/2021.06.18.21259133v2.full.pdf. (Accessed September 10, 2021).
78. Jeronimo CM, Farias ME, Val FF, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): a randomized, double-blind, phase IIa, placebo-controlled trial. *Clin Infect Dis* 2021;72:e373-81.
79. Gilead press release. Gilead presents additional data on investigational antiviral remdesivir for the treatment of COVID-19. July 10, 2020. https://www.gilead.com/news-and-press/press-room/press-releases/2020/7/gilead-presents-additional-data-on-investigational-antiviral-

remdesivir-for-the-treatment-of-covid-19. (Accessed September 18, 2020).
80. Radbel J, Narayanan N, Bhatt PJ. Use of tocilizumab for COVID-19-induced cytokine release syndrome: a cautionary case report. *Chest* 2020;158:e15-9.
81. van de Veerdonk FL, Kouijzer IJ, de Nooijer AH, et al. Outcomes associated with use of kinin B2 receptor antagonist among patients with COVID-19. *JAMA Netw Open* 2020 Aug;3(8):e2017708. doi: 10.1001/jamanetworkopen.2020.17708.
82. Goldman JD, Lye DC. Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. *N Engl J Med* 2020;383:1827-37.
83. American Society of Hematology. COVID-19 and convalescent plasma: frequently asked questions. March 23, 2021. https://www.hematology.org/covid-19/covid-19-and-convalescent-plasma. (Accessed June 18, 2021).
84. Pau AK, Aberg J, Baker J, et al. Convalescent plasma for the treatment of COVID-19: perspectives of the National Institutes of Health COVID-19 treatment guidelines panel. *Ann Intern Med* 2021;174:93-5.
85. Anon. NeuroRx submits request for Emergency Use Authorization of RLF-100 (aviptadil) in the treatment of patients with critical COVID-19 and respiratory failure who have exhausted approved therapy. September 23, 2020. https://www.neurorxpharma.com/press-releases/neurorx-submits-request-for-emergency-use-authorization-for-rlf-100-aviptadil-in-the-treatment-of-patients-with-critical-covid-19-and-respiratory-failure-who-have-exhausted-approved-therapy/. (Accessed September 28, 2020).
86. FDA. Clinical memorandum re: EUA request. COVID-19 convalescent plasma. https://www.fda.gov/media/141480/download. (Accessed May 20, 2021).
87. Abella BS, Jolkovsky EL, Biney BT, et al. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. *JAMA Intern Med* 2021;181:195-202.
88. FDA. Fact sheet for health care providers. Emergency use authorization (EUA) of casirivimab and imdevimab. July 2021. https://www.fda.gov/media/145611/download. (Accessed August 2, 2021).
89. FDA. Fact sheet for health care providers. Emergency Use Authorization (EUA) of bamlanivimab and etesevimab. September 16, 2021. https://www.fda.gov/media/145802/download. (Accessed September 17, 2021).
90. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild or moderate COVID-19: a randomized clinical trial. *JAMA* 2021;325:632-44.
91. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19-interim WHO Solidarity trial results. *New Engl J Med* 2021;384:497-511.
92. Ramakrishnna S, Nicolau DV Jr., Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 illness: a randomised controlled trial. medRxiv. February 8, 2021. https://www.medrxiv.org/content/10.1101/2021.02.04.21251134v1. (Accessed February 19, 2021).
93. Thomas S, Patel D, Bittel B, et al. Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. *JAMA Netw Open* 2021;4:e210369. doi: 10.1001/jamanetworopen.2021.0369.
94. Yeramaneni S, Doshi P, Sands K, et al. Famotidine use is not associated with 30-day mortality: a coarsened exact match study 7158 hospitalized COVID-19 patients from a large healthcare system. *Gastroenterology* 2021;160:919-21.e3.
95. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ* 2020;371:m3939.
96. RECOVER Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. June 16, 2021. https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1.full.pdf. (Accessed July 16, 2021).
97. FDA. Coronavirus (COVID-19) update: FDA revokes Emergency Use Authorization for monoclonal antibody bamlanivimab. April 16, 2021. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab. (Accessed April 16, 2021).
98. NIH. Statement-NIH-sponsored ACTIV-3 trial closes LY-CoV555 sub-study. October 26, 2020. https://www.niaid.nih.gov/news-events/statement-nih-sponsored-activ-3-trial-closes-ly-cov555-sub-study. (Accessed February 19, 2021).
99. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomized, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med* 2021 Aug 31. doi: 10.1016/S2213-2600(21)00331-3.
100. Self WH, Semler MW, Leither LM, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. *JAMA* 2020;324:2165-76.
101. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA* 2020;324:2292-300.
102. Regeneron. Important prescribing information (REGEN-COV). June 3, 2021. https://www.fda.gov/media/143901/download. (Accessed July 28, 2021).
103. FDA. Fact sheet for health care providers. Emergency Use Authorization (EUA) of baricitinib. July 2021. https://www.fda.gov/media/143823/download. (Accessed July 29, 2021).

104. Lamontagne F, Agoritsas T, Macdonald H, et al. A living WHO guideline on drugs for covid-19. *BMJ* 2020;370:m3379.
105. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A randomized trial of convalescent plasma in COVID-19 severe pneumonia. *N Engl J Med* 2021;384:619-29.
106. FDA. Fact sheet for health care providers. Emergency Use Authorization (EUA) of bamlanivimab. March 18, 2021. http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf. (Accessed March 18, 2021).
107. Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int J Infect Dis* 2020;103:214-6.
108. Schmith VD, Zhou J, Lohmer LRL. The approved dose of ivermectin alone is not the ideal dose for the treatment of COVID-19. *Clin Pharmacol Ther* 2020;108:762-5.
109. De Smet D, De Smet K, Herroelen P, et al. Serum 25(OH)D level on hospital admission associated with COVID-19 stage and mortality. *Am J Clin Pathol* 2021;155:381-8.
110. Mahdavi AM. A brief review of interplay between vitamin D and angiotensin-converting enzyme 2: implications for a potential treatment for COVID-19. *Rev Med Virol* 2020;30:e2119.
111. Udwadia ZF, Singh P, Barkate H, et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: a randomized, comparative, open-label, multicenter, phase 3 clinical trial. *Int J Infect Dis* 2020;103:62-71.
112. Joshi S, Parkar J, Ansari A, et al. Role of favipiravir in the treatment of COVID-19. *Int J Infect Dis* 2021;102:501-8.
113. Eli Lilly press release. Lilly's neutralizing antibody bamlanivimab (LY-CoV555) prevented COVID-19 at nursing homes in the BLAZE-2 trial, reducing risk by up to 80 percent for residents. January 21, 2021. https://investor.lilly.com/node/44291/pdf. (Accessed January 25, 2021).
114. Tardiff JC, Bouabdallaoui N, L'Allier PL, et al. Efficacy of colchicine in non-hospitalized patients with COVID-19. January 27, 2021. medRxiv doi: https://doi.org/10.1101/2021.01.26.21250494. (Accessed January 28, 2021).
115. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial. *Lancet* 2021;397:1637-45.
116. The REMAP-CAP Investigators. Interluekin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021;384:1491-502.
117. Anon. RECOVERY trial closes recruitment to colchicine treatment for patients hospitalised with COVIID-19. March 5, 2021. https://www.recoverytrial.net/news/recovery-trial-closes-recruitment-to-colchicine-treatment-for-patients-hospitalised-with-covid-19. (Accessed March 11, 2021).
118. Lopes MI, Bonjorno LP, Giannini MC, et al. Beneficial effects of colchicine for moderate to severe COVID-19: a randomized, double-blinded, placebo-controlled clinical trial. *RMD Open* 2021;7:e001455.
119. Wang P, Nair MS, Liu L, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.17. *Nature* 2021;593:130-5.
120. Product monograph for casirivimab and imdevimab. Hoffman-La Roche Limited. Mississauga, ON L5N 5M8. June 2021.
121. Rao PPN, Pham AT, Shakeri A, et al. Drug repurposing: dipeptidyl peptidase IV (DPP4) inhibitors as potential agents to treat SARS-CoV-2 (2019-nCoV) infection. *Pharmaceuticals (Basel)* 2021;14:44. doi: 10.3390/ph14010044.
122. Lopez-Medina E, Lopez P, Hurtado IC, et al. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. *JAMA* 2021;325:1426-35.
123. FDA. Fact sheet for health care providers. Emergency use authorization (EUA) of sotrovimab. May 2021. https://www.fda.gov/media/149534/download. (Accessed May 27, 2021).
124. FDA. Fact sheet for healthcare providers: Emergency use authorization (EUA) for *Actemra* (tocilizumab). June 2021. https://www.fda.gov/media/150321/download. (Accessed June 24, 2021).
125. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group; Shankar-Hari M, Vale CL, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. *JAMA* 2021;326:499-518.
126. Guimaraes PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalized with COVID-19 pneumonia. *N Engl J Med* 2021;385:406-15.
127. Hill A, Garratt A, Levi J, et al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. *Open Forum Infect Dis* 2021 July 6. doi.org/10.1093/ofid/ofab358.
128. Bryant A, Lawrie TA, Dowswell T, et al. Ivermectin for prevention and treatment of COVID-19 infection: a systematic review, meta-analysis, and trial sequential analysis to inform clinical guidelines. *Am J Ther* 2021;28:e434-60.
129. Elgazzar A, Eltaweel A, Youssef SA, et al. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic. (Withdrawn). https://assets.researchsquare.com/files/rs-100956/v3/706bc04e-fa7b-43fd-9c2a-15a41790f98e.pdf?c=1626390614. (Accessed July 28, 2021).
130. FDA. Why you should not use ivermectin to treat or prevent COVID-19. September 3, 2021. https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19. (Accessed September 9, 2021).
131. Okumus N, Demirturk N, Cetinkaya RA, et al. Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. *BMC Infect Dis* 2021;21:411.

132. Kory P, Meduri GU, Varon J, et al. Review of the emerging evidence demonstrating the efficacy of ivermectin in the prophylaxis and treatment of COVID-19. *Am J Ther* 2021;28:e299-318.
133. Roman YM, Burela PA, Pasupuleti V, et al. Ivermectin for the treatment of COVID-19: a systematic review and meta-analysis of randomized controlled trials. *Clin Infect Dis* 2021 Jun 28. doi: 10.1093/cid/ciab591.
134. Popp M, Stegemann M, Metzendorf MI. et al. Ivermectin for preventing and treating COVID-19. *Cochrane Database Syst Rev* 2021;(7):CD015017.
135. Incyte press release. Lilly and Incyte's baricitinib reduced deaths among patients with COVID-19 receiving invasive mechanical ventilation. August 3. 2021. https://s21.q4cdn.com/114423841/files/doc_news/Lilly-and-Incytes-baricitinib-reduced-deaths-among-patients-with-COVID-19-receiving-invasive-mechanical-ventilation-2021.pdf. (September 10, 2021).
136. NHS. University Hospitals Birmingham. COVID-19 tocilizumab & sarilumab treatment protocol. September 9, 2021. https://www.uhb.nhs.uk/coronavirus-staff/clinical-info-pathways/clinical-info-pathways-downloads/c156-tocilizumab-treatment-protocol.pdf. (Accessed September 10, 2021).
137. Product monograph for sotrovimab. GlaxoSmithKline. Mississauga, ON L5N 6L4. July 2021.
138. Press release. AMA, APhA, ASHP statement on ending use of ivermectin to treat COVID-19. September 1, 2021. https://www.ama-assn.org/press-center/press-releases/ama-apha-ashp-statement-ending-use-ivermectin-treat-covid-19. (Accessed September 21, 2021).
139. CDC. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2016. https://www.cdc.gov/niosh/docs/2016-161/pdfs/2016-161.pdf?id=10.26616/NIOSHPUB2016161. (Accessed September 22, 2021).

Cite this document as follows: **Clinical Resource,** ***Treatments of Interest for COVID-19. Pharmacist's Letter/Prescriber's Letter.*** **October 2020.**