

October 2020 ~ Resource #361022

Treatments of Interest for COVID-19

(Updated June 24, 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 (<i>Kineret</i>)	<ul style="list-style-type: none"> • Anakinra is an IL-1 antagonist. IL-1 may have a role in ARDS.⁶⁵ • 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 • See www.clinicaltrials.gov for ongoing studies.

Drug	Pertinent Information or Resources
Azithromycin	<p>Note that DOSES provided are examples only for ADULTS; the optimal dose has not been determined for any treatment.</p> <ul style="list-style-type: none"> • Macrolides have <i>in vitro</i> 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 plus hydroxychloroquine or chloroquine in hospitalized patients, or in outpatients in the absence of another indication.⁵⁰ • When used with hydroxychloroquine or chloroquine (and other QT prolonging medications), QT prolongation is of increased concern.^{2,6}
Aviptadil	<ul style="list-style-type: none"> • 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 <i>Continued...</i>	<ul style="list-style-type: none"> • Inhibits SARS-CoV-2 <i>in vitro</i>, 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 patients.⁵⁰ It also recommends against use in nonhospitalized patients, except in a clinical trial.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

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Chloroquine, continued	<p>azithromycin.⁴¹ NIH guidance recommends against using high-dose chloroquine (600 mg twice daily for 10 days) for treatment of COVID-19.⁵⁰</p> <ul style="list-style-type: none"> When used with azithromycin (and other QT-prolonging medications), QT prolongation is of increased concern.^{2,4,6}
Colchicine	<ul style="list-style-type: none"> 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, <i>Colchicine Dosing and Interactions</i>, for details.
Convalescent Plasma (COVID-19) <i>Continued...</i>	<ul style="list-style-type: none"> 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

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Convalescent plasma, continued	<ul style="list-style-type: none"> • 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} • 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 <i>Continued...</i>	<ul style="list-style-type: none"> • 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

Drug	Pertinent Information or Resources
Corticosteroids, systemic, continued	<p>Note that DOSES provided are examples only for ADULTS; the optimal dose has not been determined for any treatment.</p> <p>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.</p> <ul style="list-style-type: none"> • 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 noninvasive 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 or mechanical ventilation.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
Corticosteroids, inhaled	<p>Note that DOSES provided are examples only for ADULTS; the optimal dose has not been determined for any treatment.</p> <ul style="list-style-type: none"> • 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 (<i>Pulmicort Turbuhaler</i> 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 (<i>Alvesco</i>) is also being studied for treatment of COVID-19. See www.clinicaltrials.gov for more information.
Dapagliflozin	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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
Hydroxy-chloroquine	<p>Note that DOSES provided are examples only for ADULTS; the optimal dose has not been determined for any treatment.</p> <ul style="list-style-type: none"> • Is a more potent inhibitor of SARS-CoV-2 than chloroquine <i>in vitro</i>.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
Icatibant (<i>Firazyr</i> , generics [U.S])	<p>Note that DOSES provided are examples only for ADULTS; the optimal dose has not been determined for any treatment.</p> <ul style="list-style-type: none"> • 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 (<i>Actemra</i>); sarilumab (<i>Kevzara</i>); siltuximab (<i>Sylvant</i>)	<ul style="list-style-type: none"> • High IL-6 levels are associated with higher COVID-19 disease severity, especially in nonsurvivors.¹³ • 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%). 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 • 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 ECM.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 • 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. <p><i>Continued...</i></p>

Drug	Pertinent Information or Resources
IL-6 antagonists, continued	<p>Note that DOSES provided are examples only for ADULTS; the optimal dose has not been determined for any treatment.</p> <ul style="list-style-type: none"> • 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 • The manufacturer of <i>Kevzara</i> (sarilumab) has discontinued its U.S. clinical trial in COVID-19 patients requiring mechanical ventilation (n = 194) because it did not meet its primary endpoint (improvement on a disease severity scale) or key secondary endpoints. The results of this study are not yet published.⁷⁷ Some patients (n=48) received sarilumab in REMAP-CAP, but too few to assess efficacy.^{50,116}
Ivermectin	<ul style="list-style-type: none"> • 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 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 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 doses, open-label or retrospective design, confounding medications, and unclear COVID-19 severity and outcome measures.^{12,50} • NIH guidance recommends neither for nor against ivermectin due to insufficient evidence.⁵⁰
Janus Kinase Inhibitors (Baricitinib [<i>Olumiant</i>], etc)	<ul style="list-style-type: none"> • 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. Another baricitinib safety concern is VTE, which 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 <p><i>Continued...</i></p>

Drug	Pertinent Information or Resources
Janus Kinase Inhibitors, continued	<p>Note that DOSES provided are examples only for ADULTS; the optimal dose has not been determined for any treatment.</p> <p>contraindicated.²⁰ See our chart, <i>Janus Kinase Inhibitor Adverse Effects</i>, for more information. See the EUA (link below) for information on dosing for renal impairment, low blood counts, and aminotransferase elevations.</p> <ul style="list-style-type: none"> Based on ACTT-2, baricitinib has received EUA for use WITH remdesivir (i.e., not as monotherapy) to treat COVID-19 in patients ≥ 2 years of age who require supplemental oxygen, invasive mechanical ventilation, or ECMO.¹⁰² ACTT-2 was limited to adults. Pediatric dosing is based on studies for other uses.¹⁰³ Unpublished results of the COV-BARRIER study (n=1,525) showed no benefit of baricitinib over placebo for reduction of the combined primary outcome of progression to non-invasive or mechanical ventilation or death.⁹⁹ It did reduce 28-day all-cause mortality (8.1% vs 13.1%).⁹⁹ Based on these preliminary results, the NIH recommends baricitinib with dexamethasone \pm remdesivir in patients on high-flow oxygen or noninvasive ventilation with clinical progression or inflammatory markers.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. Another role for baricitinib is in place of dexamethasone, in patients in whom dexamethasone can't be used, with remdesivir in nonintubated patients who need supplemental oxygen.⁵⁰ The EUA fact sheet for baricitinib plus remdesivir 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.
Linagliptin	<ul style="list-style-type: none"> No data. Interest in linagliptin use for COVID-19 treatment is based on its <i>in vitro</i> inhibition of SARS-CoV-2 cysteine protease, an enzyme involved in viral replication.¹²¹
Lopinavir/ritonavir (<i>Kaletra</i>)	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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.

Drug	Pertinent Information or Resources
Monoclonal antibodies, continued	<p>Note that DOSES provided are examples only for ADULTS; the optimal dose has not been determined for any treatment.</p> <p>flow rate in patients on chronic oxygen). The EUA was based on interim analysis of the ongoing Phase 1/2/3 COMET-ICE trial.¹²³ 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.</p> <ul style="list-style-type: none"> • <i>In vitro</i>, active against the South Africa variant (B.1.351), the U.K. variant (B.1.1.7), and the Brazil variant (P.1). 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).¹²³ • Sotrovimab is given as a one-time infusion.¹²³ It appears well tolerated, but patients must be monitored for one hour after the infusion for reactions.¹²³ • 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.
Remdesivir	<ul style="list-style-type: none"> • Remdesivir has <i>in vitro</i> activity against SARS-CoV-2.⁴⁰ • In a cohort of 53 evaluable patients receiving oxygen support, or with oxygen saturation $\leq 94\%$ 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 <ul style="list-style-type: none"> • In ACTT-1, most patients had severe disease at enrollment, defined as oxygen saturation $\leq 94\%$ 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 $\leq 94\%$ on room air and radiologic evidence of pneumonia.⁸² Most patients were receiving some kind of 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 <p><i>Continued...</i></p>

Drug	Pertinent Information or Resources
Remdesivir, continued	<p>Note that DOSES provided are examples only for ADULTS; the optimal dose has not been determined for any treatment.</p> <p>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</p> <ul style="list-style-type: none"> • 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 (<i>Veklury</i>) 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} <ul style="list-style-type: none"> • 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). • In Canada, remdesivir (<i>Veklury</i>) 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

Continued...

Drug	Pertinent Information or Resources
Remdesivir, continued	<p>Note that DOSES provided are examples only for ADULTS; the optimal dose has not been determined for any treatment.</p> <ul style="list-style-type: none"> • Coadministration of remdesivir and chloroquine or hydroxychloroquine is not recommended based on <i>in vitro</i> 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	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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.
Vitamin D	<ul style="list-style-type: none"> • 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.

Drug	Pertinent Information or Resources
Zinc	<p>Note that DOSES provided are examples only for ADULTS; the optimal dose has not been determined for any treatment.</p> <ul style="list-style-type: none"> • Zinc has <i>in vitro</i> 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>.]

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