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Treatments of Interest for COVID-19

(Updated May 23, 2022)

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).
- Ontario's COVID-19 Science Advisory Table website: https://covid19-sciencetable.ca/science-briefs/#infectious-diseases-clinical-care.

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]

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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 US cohort study.[75] • NIH guidelines recommend **against** the use of azithromycin in inpatients or 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]
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, chloroquine 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 inpatients or outpatients.[50] • When used with azithromycin (and other QT-prolonging medications), QT prolongation is of increased concern.[2,4,6,41]
Colchicine *Continued…*	• 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, 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=0.042), driven mainly by a

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Colchicine, continued	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).[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)	• 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] • In ambulatory patients, benefit is uncertain due to study limitations, but benefit cannot be excluded.[46] • Risks include transfusion reactions, allergic reactions, fluid overload, cardiac events, hypotension requiring pressors, thrombosis, and transfusion-related acute lung injury.[46] • The FDA has issued an EUA for use of high-titer convalescent plasma for outpatients or hospitalized patients with impaired immunity, based in part on data from the Mayo-Clinic-led expanded access program.[70] • The NIH recommends **against** use of high-titer convalescent plasma in hospitalized patients without impaired humoral immunity.[50] They recommend neither for nor against use in patients with impaired humoral immunity, or nonhospitalized patients without impaired humoral immunity.[50] IDSA recommends **against** use of high-titer convalescent plasma in hospitalized patients, but suggests use within eight days of symptom onset for ambulatory patients at high-risk of progression if no other treatment options are available.[46] • 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 or by the American Red Cross.[71,142]

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Corticosteroids, systemic	• 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. • 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]
Continued…	

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Corticosteroids, systemic, continued	• 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 (whichever comes first) 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] If a patient is discharged, due to bed scarcity, from the emergency department on supplemental oxygen, the corticosteroid can be continued, with close monitoring, for the duration of supplemental oxygen or ten days (whichever comes first).[50] • Harms of corticosteroids include hyperglycemia, agitation, confusion, and infection risk.[46]
Corticosteroids, inhaled	• **Inhaled corticosteroids** should be continued in asthma or COPD patients with COVID-19.[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. • A combination of **inhaled and intranasal ciclesonide** was not effective vs placebo for symptom resolution in relatively young (median age 35 years) COVID-19 outpatients (n=203).[143] • NIH guidelines recommend neither for nor against inhaled corticosteroids for COVID-19 treatment due to insufficient evidence.[50]
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 *Continued…*	• 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 US 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]

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Famotidine, continued	• In a placebo-controlled study (n=55) in nonhospitalized patients, famotidine did not reduce time to symptom **resolution** by study day 28 (p=0.4).[83] Time to 50% symptom **reduction** was 8.2 days in the famotidine group vs 11.4 days in the placebo group. • 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	• See "Selective Serotonin Reuptake Inhibitors," below.
Hydroxy-chloroquine	• Early enthusiasm for hydroxychloroquine was based on a widely publicized open-labelstudy.[2] • Subsequent studies, many with significant limitations, did not consistently show clinically meaningful benefit, and adverse effects were common.[11,29,39,42,43,49,60,66,74,75,100] • 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. • The FDA **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] • NIH guidance recommends **against** use of hydroxychloroquine for prevention or treatment of COVID-19.[50]

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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]

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IL-6 antagonists, continued	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 (US) 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. • NIH guidance recommends the addition tocilizumab to dexamethasone +/- remdesivir in patients with rapidly increasing oxygen needs and systemic inflammation (e.g., CRP ≥75 mg/L), or within 24 hours of intensive care admission requiring mechanical ventilation or ECMO.[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 can't be used.[50] To make an intravenous sarilumab solution using the subcutaneous syringe formulation, add 400 mg to 100 mL of normal saline.[50] 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

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Ivermectin, continued	patients with severe COVID-19 lung disease, but neither length of stay nor extubation rate were affected.[12] In the randomized I-TECH study (n=490), ivermectin did not prevent progression to severe disease.[148] 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.[12,50,148] • 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] In the I-TECH study, 5.8% of ivermectin patients developed diarrhea, which lead to hypovolemic shock in one patient.[148] 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] Ivermectin 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

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Janus Kinase Inhibitors, continued	(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 or ECMO were excluded. Risk of secondary infection was not increased vs placebo. A small (n=101) COV-BARRIER substudy suggests that baricitinib reduces mortality in patients on mechanical ventilation or ECMO vs placebo (39% vs 58% p=0.03).[135] • Baricitinib (*Olumiant*) is FDA-approved for adults hospitalized with COVID-19 severe enough to require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.[54] • Based on ACTT-2 and COV-BARRIER, baricitinib has received EUA to treat COVID-19 in patients ≥2 to <18 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] • NIH guidance recommends the addition of baricitinib to dexamethasone ± remdesivir in patients on oxygen, high-flow oxygen, or noninvasive ventilation with rapidly increasing oxygen needs and inflammatory markers.[50] • Tocilizumab may be an alternative to baricitinib for many patients (see above).[50] Tocilizumab has more evidence of a mortality benefit. 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 in place of baricitinib if baricitinib is unavailable.[50,126] • Baricitinib carries warnings about VTE risk.[54,103] 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.[20] 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] • NIH guidelines recommend against use of lopinavir/ritonavir (and other HIV protease inhibitors) for treatment of COVID-19.[50]
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.
Molnupiravir (*Lagevrio*)	• Molnupiravir is nucleoside analog prodrug. It is converted in the body to NHC (beta-D-N4-hydroxycytidine) triphosphate. Viral RNA-polymerase uses NHC triphosphate as a substrate instead of uridine and cytidine triphosphates. The resulting mutation is lethal to the virus.[140] • Molnupiravir, 800 mg every 12 hours orally for five days, started within five days of symptom onset in mild to moderate COVID-19 seems to reduce the risk of hospitalization by about 30% (NNT = 35).[141] • The most common side effects are diarrhea (2%), nausea (1%), and dizziness (1%).[141] However, like other nucleoside analogs, molnupiravir is potentially mutagenic, so there are concerns about embryofetal toxicity (e.g., skeletal malformations) and changes to the viral spike protein.[146] Men should use reliable contraception until three months after the last dose, and people of childbearing potential should use reliable contraception until four days after the last dose.[141] • In the US, molnupiravir has received EUA for treatment of mild to moderate test-confirmed COVID-19 in adults (≥18 years) at high risk of severe disease. Molnupiravir is not for initiation in patients requiring hospitalization for treatment of COVID-19.[141] This drug is also under priority review by Health Canada.

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Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Molnupiravir, continued	• The **EUA fact sheet** for molnupiravir for healthcare providers is available at https://www.fda.gov/media/155054/download. Give patients the fact sheet available at https://www.fda.gov/media/155055/download. • For NIH guidance on **prioritization** of molnupiravir (and other outpatient COVID-19 therapies), see https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/. • The NIH also has guidance for **choosing among outpatient therapies** for appropriate patients: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/. • In Canada, provinces may have different prioritization for use of outpatient COVID-19 therapies based on product availability.
Monoclonal antibodies (SARS-CoV-2 neutralizing antibodies) *Continued…*	• **Distribution to US states and territories is based on the prevalence of susceptible variants**. For updates, see https://www.phe.gov/emergency/events/COVID19/therapeutics/distribution/Pages/data-tables.aspx. • In the U.S., variants can be tracked at https://covid.cdc.gov/covid-data-tracker/#variant-proportions. • For NIH guidance on **prioritization** of COVID-19 monoclonal antibodies (and other outpatient therapies), see https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/. • The NIH also has **guidance for choosing among outpatient therapies** for appropriate patients: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/. • In Canada, provinces may have different prioritization for use of outpatient COVID-19 therapies based on product availability. **Bebtelovimab** (US) • Bebtelovimab is NOT for patients requiring hospitalization for treatment of COVID-19 or those requiring supplemental oxygen (or increased flow rate in patients on chronic oxygen).[147] It should be given as soon as possible, within seven days of symptom onset.[147] It is authorized for use when other approved or authorized treatments are not available or appropriate. For more help with patient selection, see our US algorithm, "*MAbs" for COVID-19: Patient Assessment,*" or the links to the EUA fact sheet, below. • Authorization was based on a phase II study (BLAZE-4) in which bebtelovimab was used as monotherapy or with bamlanivimab/etesevimab.[147] Treatment was started within three days of a positive test result. Most patients were infected with the Delta or Alpha variants and none were infected with Omicron.[147] In the placebo-controlled part of the study in mostly **low-risk** unvaccinated patients (n=380), bebtelovimab reduced median time to symptom resolution (6 days vs 8 days) and reduced day 5 viral load.[86,147] In another portion of the trial, 150 mostly **high-risk** patients were randomized to bebtelovimab alone or bebtelovimab with bamlanivimab/etesevimab.[147] About 1/5 of patients had received at least one COVID-19 vaccine dose. Hospitalization or death occurred in two (4%) patients in the combo treatment group, and three (3%) in the monotherapy group. One patient in the bebtelovimab arm died. An additional 176 mostly high-risk patients

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	received combination therapy (open-label).[147] About 31% of these patients had received at least one COVID-19 vaccine dose. Three patients required hospitalization for COVID-19, and none died. o The rate of hospitalization and death through day 29 in patients who received bebtelovimab monotherapy or combination therapy was generally lower than the placebo rate in previous studies of monoclonal antibodies for high-risk patients, but conclusions are limited because of different circulating variants and patient populations in those studies.[57] • *In vitro*, it is active against Omicron variants, including Omicron BA.2.[147] • Bebtelovimab is given as a one-time IV push.[147] Monitor for at least an hour after injection.[147] • The EUA fact sheet for healthcare providers is available at https://www.fda.gov/media/156152/download. Give patients the fact sheet available at https://www.fda.gov/media/156153/download. **Casirivimab/imdevimab** (*Regen-COV*) • In the US, casirivimab/imdevimab is **not** authorized/available for use in regions where nonsusceptible variants (e.g., **Omicron**) predominate.[88] • Casirivimab/imdevimab 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] It should be given as soon as possible, within ten days of symptom onset (US).[88] For more help with patient selection, see our US algorithm, "*MAbs" for COVID-19: Patient Assessment*," or the links to the EUA fact sheet and Canadian product monograph, below. • 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 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 US (1,200 mg), is based on the drug's flat dose-response curve.[88] • In the US, casirivimab/imdevimab had also received EUA for **post-exposure prophylaxis** in high-risk patients.[88] • Casirivimab/imdevimab is given as an infusion, or subcutaneously (US) 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; the intravenous route is strongly recommended.[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.

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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	• 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) • In the US, bamlanivimab/etesevimab is **not** authorized/available for use in regions where nonsusceptible variants (e.g., **Omicron**) predominate.[89] Because of the prevalence of resistant variants, the FDA has revoked the EUA for bamlanivimab monotherapy.[97] • Bamlanivimab +/- etesevimab is NOT for patients (EUA: ≥2 years of age) 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 patients hospitalized for COVID-19 [ACTIV-3] was closed due to lack of benefit.[98]) It should be given as soon as possible, within ten days of symptom onset.[21,89] For more help with patient selection, see our US algorithm, "*MAbs" for COVID-19: Patient Assessment*," or the links to the EUA fact sheet and Canadian product monograph, below. • Original authorization was based on data from a study in recently diagnosed outpatients (BLAZE-1).[21,89] Bamlanivimab 700 mg/etesevimab 1,400 mg reduced the need for a hospital visit vs placebo (0.8% [combo] vs 5.8% [placebo]).[90] The treatment group had 2% lower mortality than the placebo group.[89] In a post-hoc analysis, among patients ≥65 years of age or with BMI ≥35 kg/m^2, hospitalizations in the bamlanivimab/etesevimab and placebo groups were 0% and 13.5% (7/52), respectively.[90] • In the US, bamlanivimab/etesevimab had also received EUA for **post-exposure prophylaxis** in high-risk patients.[89] • 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] • Bamlanivimab +/- etesevimab is given as a one-time infusion. They appear well tolerated, but patients must be monitored (US: 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). **Sotrovimab** (GlaxoSmithKline) • In the US, sotrovimab is **not** authorized for use in regions where nonsusceptible variants predominate.[123] • Sotrovimab is NOT for patients requiring hospitalization for treatment of COVID-19 or those requiring supplemental oxygen (or increased flow rate in patients on chronic oxygen).[123,137] It should be given as soon as possible, within seven days of symptom onset (US).[123] For more help with patient selection, see our US algorithm, "*MAbs" for COVID-19: Patient Assessment*," or the links to the EUA fact sheet and Canadian product monograph, below.

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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	• Authorization was based on interim analysis of the Phase 1/2/3 COMET-ICE trial.[123,137] Patients were enrolled within five days of symptom onset.[123] Among the one thousand fifty-seven patients included in the intent-to-treat population, 1% of patients in the treatment group (n=6) required emergency department care or hospitalization vs 6% of the placebo group (n=30) (NNT = 20).[123] Viral load data was available for a subset of patients in which the decrease in viral load was greater in treatment group.[123] Two placebo patients died.[123] • *In vitro*, it is active against Omicron BA.1 variants, but has reduced susceptibility to the Omicron BA.2 variant.[123] • Sotrovimab is given as a one-time infusion.[123,137] It appears well tolerated, but patients must be monitored for at least 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). **Tixagevimab/cilgavimab** (*Evusheld*) • Tixagevimab/cilgavimab is for **PRE-exposure prophylaxis** of COVID-19 in moderately to severely immunocompromised patients not expected to have responded to vaccination, and for patients for whom vaccination is contraindicated.[96,119] For help with patient selection, see our US algorithm, "*MAbs" for COVID-19: Patient Assessment*," or the links to the EUA fact sheet and Canadian product monograph, below. • Authorization/approval was based on the ongoing Phase III PROVENT (preexposure) and STORM CHASER (postexposure) trials.[96,119] PROVENT patients were unvaccinated and at high risk due to age (≥60 years), comorbidities (e.g., obesity, heart or lung disease, immunocompromise), living situation, or occupation. After a follow-up of three to 166 days after a single dose, symptomatic infection occurred in 0.2% of treated patients vs 1% of placebo patients (NNT = 125). STORM CHASER patients were adults exposed to COVID-19 within the previous 8 days. Although it did not prevent symptomatic COVID-19 within 30 days of randomization (hence it is not authorized for post-exposure prophylaxis), there were more symptomatic COVID-19 infections in the placebo group after day 29. o Although authorized for patients ≥12 years of age weighing ≥40 kg, these studies only included patients ≥18 years of age.[96,119] o In PROVENT, more patients in the treatment group experienced adverse cardiac events than in the placebo group (~0.6% vs 0.2%).[96,119] Almost all of these patients had cardiac risk factors or a cardiac event history.[119] o Few patients in PROVENT (<4%) were immunocompromised.[96,119] • *Evushield* protection may last for six months.[96] Recommendations for repeat dosing is not available at this time.[96,119] • In vitro, it has reduced activity against the Omicron BA.1 and BA.1.1variants, but activity against Omicron BA.2 is only minimally reduced.[96] In the U.S., dosing has been increased to account for reduced susceptibility, and a dosage increase is an option in Canada.[96,119]
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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	• The **EUA fact sheet** for tixagevimab/cilgavimab for healthcare providers is available at https://www.fda.gov/media/154701/download. Give patients the fact sheet available at https://www.fda.gov/media/154702/download. • The Canadian product monograph for tixagevimab/cilgavimab is available at Health Canada's Drug Product Database (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp).

Nirmatrelvir/ Ritonavir (*Paxlovid*)	• Nirmatrelvir is a SARS-CoV2-specific protease inhibitor.[102] Ritonavir is added to inhibit its metabolism.[102]
	• When started within five days of symptom onset (nirmatrelvir 300 mg/ritonavir 100 mg twice daily for five days [oral]), there was an 87% reduction in hospitalization or death vs placebo (NNT = 18).[145] There were no deaths in the *Paxlovid* group.[145]
	• The most common side effects were bad taste (6%), diarrhea (3%), hypertension (1%), and myalgia (1%).[16,145] *Paxlovid* is contraindicated with CYP3A4 substrates with serious dose-dependent side effects. Some examples include amiodarone, lovastatin, simvastatin, colchicine, triazolam, vardenafil (Canada).[16,145] Potent CYP3A4 inducers (e.g., phenytoin, carbamazepine, St. John's wort) could reduce efficacy and promote viral resistance.[145] It should not be used in patients taking clopidogrel.[106] Help with *Paxlovid* drug interaction screening is available:
	  • NIH guidance on *Paxlovid* interactions: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-paxlovid-drug-drug-interactions/.
	  • The Liverpool COVID-19 interaction checker: https://www.covid19-druginteractions.org.
	  • Paxlovid Patient Eligibility Screening Checklist Tool for Prescribers (US): https://www.fda.gov/media/158165/download.
	• *Paxlovid* should be avoided in patients with severe kidney or liver impairment and requires a dose reduction (150 mg/100 mg twice daily) if eGFR is ≥30 to <60 mL/min/1.73m^2.[16,145]
	• *Paxlovid* is authorized for treatment of mild to moderate test-confirmed COVID-19 in patients (US: ≥12 years and ≥40 kg; Canada: adults [≥18 years old]) at high risk of severe COVID-19.[16,145] *Paxlovid* is not for initiation in patients requiring hospitalization for treatment of COVID-19.[16,145]
	• The **EUA fact sheet** for healthcare providers is available at https://www.fda.gov/media/155050/download. Give patients the fact sheet available at https://www.fda.gov/media/155051/download.
	• The Canadian product monograph for *Paxlovid* is available at Health Canada's Drug Product Database (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp).
	• For NIH guidance on **prioritization** of *Paxlovid* (and other outpatient COVID-19 therapies), see https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/.
	• The NIH also has guidance for **choosing among outpatient therapies** for appropriate patients: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/.
	• In Canada, provinces may have different prioritization for use of outpatient COVID-19 therapies based on product availability.

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	• 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 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.[54] • 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
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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	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] • In patients hospitalized for treatment of COVID-19, remdesivir monotherapy (i.e., without dexamethasone) should be reserved for patients who require minimal supplemental oxygen.[50] It may also be appropriate for inpatients not requiring oxygen, but with high risk of progression, but there is not good evidence to support this.[50] • Remdesivir and dexamethasone are used together in patients requiring supplemental oxygen.[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] Remdesivir can be discontinued at discharge, especially if the patient is not discharged on supplemental oxygen.[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 patients with mild to moderate COVID-19, but not hospitalized for treatment of COVID-19, remdesivir for three days (200 mg, then 100 mg on days 2 and 3) is an option.[50] This recommendation is based on the PINETREE study (NNT = 22 to prevent one hospitalization [i.e., ≥24 hours of acute care]).[50] Patients should be monitored for an hour post-dose.[50] • The NIH has guidance for **choosing among outpatient therapies** for appropriate patients: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalizepatients/. • The most common **adverse effects** of remdesivir are nausea and transaminase elevations.[54,59] Discontinue if ALT >10 x ULN with symptoms suggestive of liver injury (Canada: hold while ALT is ≥5 x ULN, and stop if ALT elevation is accompanied by other signs or symptoms suggestive of liver injury).[54,59] • 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.[54] 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] • The FDA has **approved** remdesivir (*Veklury*) for treatment of COVID-19 in patients ≥28 days of age who weigh ≥3 kg who are hospitalized for treatment of COVID-19, or who are not hospitalized for treatment of COVID-19 but have mild- to moderate symptoms and at high-risk of progression to severe disease.[54] • **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]

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Selective serotonin reuptake inhibitors	**SSRIs** • SSRIs' mechanism of action in COVID-19 may involve inhibition of cytokine (e.g., IL-6) production, and/or inhibition of the acid sphingomyelinase/ceramide system, which is involved in COVID-19 infection.[101,144] • In a large cohort of COVID-19 patients (n=83,584), among those taking an SSRI, relative risk of mortality was reduced by 8% (RR 0.92, 95% CI 0.85 to 0.99, p=0.03), and by 28% (0.72, 95% CI 0.54 to 0.97, p=0.03) among **fluoxetine** users compared to nonusers.[144] **Fluvoxamine** • In a large (n=1,497) multicenter study in Brazil (TOGETHER trial), high-risk **outpatients** with symptomatic COVID-19 were randomized to fluvoxamine 100 mg twice daily or placebo. The primary outcome measure was need for emergency department stay >6 hours, or transfer to a tertiary care hospital. The primary outcome occurred in 11% of fluvoxamine patients and 16% of placebo patients, a statistically significant difference. One fluvoxamine patient died and there were 12 deaths in the placebo group (OR 0.09; 95% CI 0.01 to 0.47).[85] • Based on the TOGETHER trial, smaller studies, and other data, the FDA declined EUA for fluvoxamine. Reasons include lack of clinically meaningful benefit, study limitations, paucity of evidence to support its mechanism of action in treatment of COVID-19, and availability of other treatements.[101] • Fluvoxamine inhibits CYP1A2 and CYP2C19.[101] Gastrointestinal and central nervous system side effects are common.[27]
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.[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.

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 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.
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; SSRI = selective serotonin reuptake inhibitor; tPA = tissue plasminogen activator; TNF = tumor necrosis factor; U.K. = United Kingdom; ULN = upper limit of normal; VTE = venous thromboembolism; WHO = World Health Organization

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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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