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Treatments of Interest for COVID-19

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, 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** evidence review (http://www.bccdc.ca/Health-Professionals-Site/Documents/Guidelines_Unproven_Therapies_COVID-19.pdf).
- **British Medical Journal** systematic review and network meta-analysis (https://www.bmj.com/content/370/bmj.m2980).

At this point, no pharmacotherapy has been proven effective for COVID-19, so treatment is largely supportive. Resources pertinent to supportive therapy include:

- 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/).
- The **Surviving Sepsis Campaign** COVID-19 guidelines (https://sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19).

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] • 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.

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form of vasoactive intestinal polypeptide hypothesized to protect alveolar type 2 cells from viral injury.[85] • In an unpublished case-control study (n=51), treated patients had better survival and clinical improvement.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

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Chloroquine, continued	• A Brazilian study of chloroquine phosphate 600 mg twice daily vs 450 mg twice daily stopped the high-dose arm due to higher instance of QT prolongation >500 milliseconds (18.9% vs 11.1%) and mortality (39% vs 15%).[41] All patients received azithromycin.[41] NIH guidance recommends against using high-dose chloroquine (600 mg twice daily for 10 days) for treatment of COVID-19.[50] • When used with azithromycin (and other QT-prolonging medications), QT prolongation is of increased concern.[2,4,6]
Colchicine	• Based on its anti-inflammatory effect, there is 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] • Additional clinical trials are underway. See www.clinicaltrials.gov for more information. • Keep in mind colchicine's toxicities and drug interactions. See our chart, *Colchicine Dosing and Interactions*, for details.
Convalescent Plasma (COVID-19) *Continued…*	• Small case series in patients hospitalized with severe COVID-19 show promise (e.g., defervescence, radiographic improvement, improved oxygen support requirements, viral clearance, improved clinical condition).[62-64] It 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] • Unpublished data from the Mayo Clinic-led expanded access program (n=35,322) found a seven-day mortality rate of 8.7% in patients who received convalescent plasma within three days of diagnosis vs 11.9% in those who received it later (p<0.001). Thirty-day mortality was 21.6% vs 26.7% (p<0.0001). There seemed to be a dose-response relationship between the antibody levels in the transfused plasma and mortality reduction. Unadjusted seven-day mortality was 8.9% in the high titer group and 13.7% in the low titer group (p =0.048; **relative** reduction 35%). After adjusting for confounding, mortality benefit approached non-significance. About half of the 35,322 patients were in critical care units and 27.5% were receiving mechanical ventilation at the time of transfusion.[69] In non-ventilator patients <80 years of age (n=1,018) who received high-titer plasma within three days, **relative** mortality reduction was 37% (p=0.03).[18] It is important to note that this study was not designed to compare efficacy of convalescent plasma to that of standard therapy; goals were to assess safety and to identify signals of efficacy.[69] Differences in outcome could be due to harm from low-titer plasma rather than benefit from high-titer plasma, or confounding by different management strategies.[84] • Compared to usual care, convalescent plasma did not reduce mortality or severe illness (composite endpoint) in the open-label PLACID trial (n=464) in moderate COVID-19 patients in India, despite hastening viral clearance. Only 67 patients received high-titer plasma.[95] • There is very limited published data on convalescent plasma for pediatric patients.[23] • The FDA has issued an EUA for use of convalescent plasma for all hospitalized patients, in part based on data from the expanded access program.[70]

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Convalescent plasma, continued	• The EUA **does not replace clinical trials**.[70] The NIH Treatment Guidelines panel states that convalescent plasma should not be considered the standard of care and encourages enrollment in prospective clinical trials.[84] 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. • In Canada, convalescent plasma is only being supplied to physicians for use in the context of clinical trials under the authorization of Health Canada.[71] • 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 *Continued…*	• In one institution in China, methylprednisolone use in patients with COVID-19 ARDS was associated with reduced mortality.[16] This and other cohort studies were limited by confounding, and inclusion of patients with various disease severities and concomitant treatments.[46] • Data from the open-label RECOVERY trial, in which 2,104 patients were randomized to oral or intravenous dexamethasone 6 mg/day for 10 days, suggests a mortality benefit for COVID-19 patients requiring supplemental oxygen, especially for those requiring ventilation, over usual care (n = 4,321).[31] NNT = 8 to prevent one death in ventilated patients, or 34 in patients requiring oxygen but not ventilation. It did not provide a mortality benefit (and there was a nonstatistically significant trend toward harm) for patients not requiring oxygen. It also did not provide a mortality benefit for early disease (symptoms for a week or less). This suggests that dexamethasone's mechanism involves an anti-inflammatory effect rather than an antiviral effect, because inflammation is more common in advanced disease, while viral replication is at maximum in early disease. • The open-label REMAP-CAP study (n=403) randomized COVID-19 patients admitted to intensive care for respiratory or cardiovascular support to hydrocortisone 50 to 100 mg every six hours for seven days, hydrocortisone started only if shock was clinically evident, or no hydrocortisone.[68] Analysis suggests hydrocortisone was probably superior to no hydrocortisone in regard to organ support-free days at 21 days, but the study was stopped early. • 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.

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Corticosteroids, continued	• 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; need for supplementation oxygen, 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 for up to 10 days 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] • **Inhaled corticosteroids** should be continued in asthma or COPD patients with COVID-19.[50] The effect of inhaled corticosteroids on COVID-19 risk, severity, or transmission is unknown.[50] • Ciclesonide (*Alvesco*) and inhaled budesonide are being studied for treatment of COVID-19, but there is no data on efficacy yet. See www.clinicaltrials.gov for more information.
Dapagliflozin	• No data. • Dapagliflozin is being studied in COVID-19 patients with respiratory failure and with hypertension, diabetes, heart disease, or advanced renal disease to prevent organ failure, based on its known renal and cardiac benefit (DARE-19 study). • See www.clinicaltrials.gov for more information.

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Famotidine	• Interest in famotidine as a COVID-19 treatment stems from observations in China that patients who were taking famotidine who were infected with COVID-19 had better outcomes.[55] • In a retrospective U.S. study (n = 1,620), famotidine use (10 to 40 mg/day; n = 84) within 24 hours of admission was associated with reduced risk of death or intubation in **hospitalized** COVID-19 patients.[67] But in a subsequent retrospective study in which famotidine users were matched to non-users to control for 12 potential confounders, famotidine was not associated with reduced risk of death. In fact, among patients not receiving famotidine at home 30-day mortality was higher.[94] • The IDSA suggests against use of famotidine for COVID-19 outside of a clinical trial.[46] See www.clinicaltrials.gov for more information.
Hydroxy-chloroquine *Continued…*	• Is a more potent inhibitor of SARS-CoV-2 than chloroquine *in vitro*.[2] Also has immunomodulating effects.[27] • Early enthusiasm for hydroxychloroquine was based on a widely publicized open-label, randomized study in hospitalized patients testing positive for SARS-CoV-2.[2] Six of 26 hydroxychloroquine patients were lost to follow-up: one due to death, three due to intensive care admission, one due to side effects (nausea), and one who left the hospital. Viral clearance at day six was 70% in the 20 remaining hydroxychloroquine patients vs 12.5% of the control patients (n = 16).[2] Six treated patients also received azithromycin to prevent bacterial infection.[2] In the combination group, viral clearance was 100% at day six vs 57.1% in the hydroxychloroquine-alone group.[2] Also see subsequent observational data under "Azithromycin," above. • In larger, open-label and cohort studies, despite some small, inconsistent benefit on clinical signs and symptoms, there was no benefit on viral clearance, length of stay, need for intensive care or mechanical ventilation, or mortality.[29,39,42,43,49,60,66] In one study, thirty percent of hydroxychloroquine patients had adverse effects.[42] In another study, the combination of hydroxychloroquine and azithromycin was associated with cardiac arrest.[66] When used with azithromycin (and other QT-prolonging medications), **QT prolongation** is of increased concern.[2,6] Information on managing QT prolongation risk in these patients is available at https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.120.047521. • One large (n = 2,541) retrospective U.S. cohort study found reduced mortality with hydroxychloroquine +/- azithromycin vs usual care.[75] Some patients with high cardiac risk were excluded. Select patients with severe COVID-19 and minimal cardiac risk also received azithromycin. Hydroxychloroquine was started within 48 hours of hospital admission in almost all patients. This study had several limitations. For example, the outcomes of almost 300 patients were not included in the analysis, and there were differences between treatment groups that could not be adequately adjusted for (e.g., baseline disease severity, other treatments received). • In a placebo-controlled study in outpatients, hydroxychloroquine did not improve symptoms.[11] Forty-three percent of hydroxychloroquine patients had side effects vs 22% of placebo patients. Four hydroxychloroquine patients were hospitalized, and there was one outpatient death in this group. In the placebo group, ten placebo patients were hospitalized, one of which died (p=0.29). • The hydroxychloroquine arm of the large RECORD study was stopped due to lack of efficacy.[31]

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Hydroxy-chloroquine, continued	• 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] • The WHO has discontinued the hydroxychloroquine arm of the Solidarity Trial because interim results suggest there is little mortality benefit for hospitalized patients.[74] • 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]
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*); siltuximab (*Sylvant*)	• High IL-6 levels are associated with higher COVID-19 disease severity, especially in nonsurvivors.[13] • Evidence of benefit is mixed. A cohort study in which 433 of 3,924 patients received tocilizumab suggests mortality benefit (27.5% vs 37.1% for usual care) if given within 48 hours of critical care admission.[10] Patients who received tocilizumab tended to be younger and were more likely to be hypoxemic at critical care admission.[10] In a randomized open-label study (n=131), no mortality benefit was shown in COVID-19 pneumonia patients requiring oxygen ≥3 L/min but not mechanical ventilation.[92] A similar study was stopped early when interim analysis revealed futility.[93] These studies suggest perhaps only severely ill patients benefit, but early administration, before irreversible organ damage has occurred, may be key. • The manufacturer of *Kevzara* (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] • 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] • NIH guidance recommends against use except in a clinical trial.[50] See www.clinicaltrials.gov. Could be considered on an individual basis (e.g., patients with cytokine storm, increased IL-6 levels, etc) with expert consultation.[44]

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Ivermectin	• Ivermectin has several mechanisms that make it an attractive option for study for prevention and treatment of COVID-19. However, it has not demonstrated clinically significant antiviral efficacy for any virus in humans. Clinical trials are underway.[32] See www.clinicaltrials.gov.
Janus Kinase Inhibitors (Baricitinib [*Olumiant*], etc)	• Interest based on potential to block IL-6 effects, reduce cytotoxic T cells, and increase regulatory T cells. • Baricitinib in combination **with remdesivir** reduced recovery time (p=0.04) in hospitalized patients vs remdesivir alone in the unpublished ACTT-2 study. Mortality was also reduced (p=0.09), especially in patients requiring oxygen. The manufacturer plans to approach the FDA about EUA for COVID-19 in hospitalized patients.[14] • Baricitinib is being compared to placebo in the phase III COV-BARRIER study in hospitalized patients.[14] • NIH guidance recommends against use except in a clinical trial.[50] See www.clinicaltrials.gov.
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) suggest 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] • There is interest in studying lopinavir/ritonavir earlier in the disease course, or in combination with other medications.[15] Use with **ribavirin** and interferon beta-1b early in the disease course (mean five days from symptom onset) was compared to lopinavir/ritonavir alone in hospitalized patients (n=127).[58] In this open-label study, median time to viral clearance was seven days with combination therapy vs 12 days for lopinavir/ritonavir alone.[58] Alleviation of symptoms occurred in four days vs eight days, respectively (p<0.0001).[58] • The WHO has discontinued the lopinavir/ritonavir arm of the Solidarity Trial because interim results suggest no mortality benefit for hospitalized patients.[74] • Additional clinical trials are planned or underway. See www.clinicaltrials.gov for more information.
Losartan, Telmisartan	• Studies in mice suggest that ARBs can reduce lung damage caused by SARS-CoV.[22] • Clinical trials are underway for treatment of COVID-19. See www.clinicaltrials.gov for more information.
Monoclonal antibodies *Continued…*	• AstraZeneca (AZD7442), Eli Lilly (bamlanivimab, etesevimab), GlaxoSmithKline (VIR-7831; COMET-Ice Study), Regeneron (REGN-COV2), and others are testing monoclonal antibodies against COVID-19. • A Regeneron press release describes preliminary, unpublished results (n=275) from a large placebo-controlled trial of REGN-COV2, a combination of two monoclonal antibodies, in COVID-19 outpatients. REGN-COV2 reduced viral load, a benefit that increased with higher baseline viral load. Faster symptom improvement vs placebo was seen in patients who were

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Monoclonal antibodies. continued	seronegative or had higher viral loads at baseline. REGN-COV2 also reduced the need for medical care vs placebo in seronegative patients. This data suggests REGN-COV2 might particularly benefit patients who do not mount an adequate antibody response on their own.[88] • Eli Lilly plans to request Emergency Use Authorization for bamlanivimab for higher-risk patients with recently diagnosed mild-to-moderate COVID-19 based on unpublished, preliminary data from a study in recently diagnosed outpatients (BLAZE-1).[89] This study includes monotherapy and combination therapy (with etesevimab) arms.[89] Monotherapy and combination therapy seem to reduce viral load and need for hospitalization.[89,90] Bamlanivimab is being studied for COVID-19 prevention in residents and staff of long-term care facilities (BLAZE-2), and other studies are also ongoing.[89] Facilities interested in participating in Eli Lilly COVID-19 clinical trials can email covid19potentialsite@lilly.com. • See www.clinicaltrials.gov for more information.
Oseltamivir	• Not expected to be effective against SARS-CoV-2 because SARS-CoV-2 does not use neuraminidase.[26] • Has been used for COVID-19 pneumonia, but there is no efficacy data.[12]
Remdesivir *Continued…*	• Remdesivir has *in vitro* activity against SARS-CoV-2.[40] • In a cohort of 53 evaluable patients receiving oxygen support, or with oxygen saturation ≤94% on room air, remdesivir was associated with clinical improvement in regard to oxygen support requirements in 68% of patients.[40] Mortality was 13%, which is less than in other case series and cohorts.[40] **Most of the patients (65%) were receiving mechanical ventilation or ECMO at baseline.[40]** The most common adverse events were liver enzyme elevation (23%), diarrhea (9%), rash, renal impairment, hypotension (8%), acute kidney injury, atrial fibrillation, multiorgan dysfunction, hypernatremia, and venous thrombosis (6%).[40] Causality could not be assessed due to the effects of COVID-19 itself.[40] Based on previous data, mild to moderate transaminase elevations are expected with remdesivir.[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] Similarly, a Chinese study found a nonsignificant trend toward faster recovery.[61] • 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] • Unpublished data from the open-label SIMPLE-Severe study compared remdesivir-treated patients (n=312) to a matched cohort of patients receiving standard care (n=818).[79] 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] About 74% of remdesivir patients recovered (i.e., showed improvement in clinical status on a 7-point ordinal scale)

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	by day 14 vs 59% of the standard-care patients. Mortality rate at day 14 was 7.6% in the remdesivir patients vs 12.5% in the standard-treatment group (OR 0.38, 95% CI 0.22 to 0.68, p = 0.001).[79] • A five-day course of remdesivir was associated with a statistically significant (but perhaps not clinically significant) improvement in clinical status on a seven-point ordinal scale in patients with **moderate** COVID-19 (radiographic evidence of **pulmonary infiltrates** and oxygen saturation >94% on room air) vs standard care in an open-label, randomized study (n=584). Most patients were not on any kind of supplemental oxygen. Viral load was not assessed. Patients randomized to a 10-day course (actual median treatment duration six days) did not benefit. The clinical status score used in this study could have underestimated benefit in this population with nonsevere disease.[24] • In the open-label **WHO SOLIDARITY trial**, 2,743 patients were randomized to remdesivir.[91] The primary goal was to assess its effect on in-hospital mortality.[91] Most patients (~75%) were receiving some kind of oxygen at randomization.[91] Remdesivir did not reduce mortality, reduce the need for mechanical ventilation, or reduce length of stay vs similar care without remdesivir.[91] There was a small, nonsignificant mortality benefit for patients not on mechanical ventilation at study entry (RR 0.86, 99% CI 0.67 to 1.11).[91] SOLIDARITY's results do not negate ACTT-1, as SOLIDARITY was not placebo-controlled and ACTT-1 was designed to assess time to recovery.[53] • The **FDA** has approved remdesivir (*Veklury*) for treatment of COVID-19 in hospitalized patients ≥12 years of age who weigh ≥40 kg, based on data from the ACTT trial and Gilead's SIMPLE studies.[24,57,72,82] • Remdesivir has **EUA** for use in children <12 years of age who weigh ≥3.5 kg.[54] Clinical trials in pediatrics are also ongoing.[53] The **EUA fact sheet** for healthcare providers is available at https://www.fda.gov/media/137566/download, and the parent/caregiver fact sheet is available at https://www.fda.gov/media/137565/download. • **If remdesivir availability is limited** at your hospital, the NIH recommends prioritizing use for patients requiring oxygen, but not high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO.[50] Dexamethasone may be used instead.[50] • Dexamethasone can be added to remdesivir for patients requiring oxygen, mechanical ventilation, or ECMO.[50] • **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] Supplies are limited, but availability should improve in October. • **Coadministration of remdesivir and chloroquine or hydroxychloroquine is not recommended** based on *in vitro* data showing that these drugs might interfere with the metabolic activation and antiviral activity of remdesivir.[53] In Simple-Severe, recovery rate at day 14 for patients who received hydroxychloroquine plus remdesivir was lower than in patients who received remdesivir alone (57% percent vs 69%, HR 0.61, 95% CI 0.45 to 0.83, p=0.002). Concomitant hydroxychloroquine use was not associated with increased mortality but 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]

Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Ribavirin	• Not potent enough to be effective at safe doses; hematologic toxicity precludes use.[26] See lopinavir/ritonavir section for information on combination use.
Statins	• Statins might ameliorate COVID-19-mediated inflammation and prevent lung injury by affecting ACE2 expression.[25] • In a meta-analysis of almost 9,000 COVID-19 patients in studies looking at the risk of severe COVID-19 illness or mortality in statin users vs nonusers, statin use was associated with a reduced risk of severe or fatal COVID-19 (HR 0.7, 95% CI 0.53 to 0.94).[25] • NIH guidelines recommend against use specifically for COVID-19 treatment outside of a clinical trial.[50] • See www.clinicaltrials.gov for more information on planned or ongoing studies.
tPA (alteplase)	• No data. • Interest based on reports of microvascular pulmonary thrombosis in COVID-19 patients. • Studies are underway to treat ARDS in COVID-19 patients. See www.clinicaltrials.gov.
Vaccines	• There is interest in using currently available vaccines to protect against SARS-COV-2 through nonspecific immune response (e.g., interferons, natural killer cells) or cross-reactive antibodies.[21] • Analysis of immunization records suggests that recent (within five years) vaccination with *Hemophilus influenza* type-B (HIB), measles/mumps/rubella (MMR), varicella, pneumococcal conjugate vaccine (*Prevnar-13*), high-dose influenza vaccine, and hepA/hepB vaccines is associated with a lower risk of testing positive for SARS-CoV-2.[20] • Oral polio, zoster, BCG, and MMR vaccines are being studied or studies are planned for prevention of COVID-19. See www.clinicaltrials.gov for more information.
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.[48] • Oral vitamin C is being studied for treatment of COVID-19 disease in the outpatient setting, and as prophylaxis. • See www.clinicaltrials.gov for more information on these planned or ongoing studies.
Vitamin D	• Interest in vitamin D stems from its effects on the immune system and pulmonary ACE2 expression. 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] • Studies of oral zinc, alone or in combination (e.g., with vitamin C, **vitamin D**, hydroxychloroquine [purported to help zinc get inside the cells[47]], azithromycin) to prevent COVID-19 disease are planned or ongoing. • See www.clinicaltrials.gov for more information.

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; 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; 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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