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Treatments of Interest for COVID-19

(Updated December 21, 2020)

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** evidence review (http://www.bccdc.ca/Health-Professionals-Site/Documents/Guidelines_Unproven_Therapies_COVID-19.pdf).
- The **NIH** general treatment guidelines (https://covid19treatmentguidelines.nih.gov/).
- **IDSA** treatment and management guidelines (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/).
- **WHO** guidance on drugs for COVID-19 (https://www.bmj.com/content/370/bmj.m3379).
- The **Surviving Sepsis Campaign** COVID-19 guidelines (https://sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19).

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

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

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

TREATMENTS OF INTEREST

Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Anakinra (*Kineret*)	• Anakinra is an IL-1 antagonist. IL-1 may have a role in ARDS.[65] • 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/.
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. • A Brazilian study of chloroquine phosphate 600 mg twice daily vs 450 mg twice daily stopped the high-dose arm due to higher instance of QT prolongation >500 milliseconds (18.9% vs 11.1%) and mortality (39% vs 15%).[41] All patients received

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Chloroquine, continued	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)	• 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] Furthermore, a **placebo-controlled trial** (n= 333) found **no benefit** on clinical status or mortality. Most enrolled patients (>90%) were receiving oxygen and a corticosteroid. It is unclear how many patients received high-titer plasma in this study.[105] • 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 (or equivalent) for 10 days or until discharge in COVID-19 patients who require oxygen or mechanical ventilation.[50] Corticosteroids are **not recommended** for COVID-19 patients not requiring treatment with supplemental oxygen.[46,50] • Harms of corticosteroids include hyperglycemia, agitation, confusion, and infection risk.[46] • **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.
Fluvoxamine	• In a preliminary placebo-controlled study (n=152), fluvoxamine-treated outpatients with mild COVID-19 had a reduced risk of clinical deterioration at day 15 (0/80 patients vs 6/72 patients). The mechanism may involve fluvoxamine's action at the sigma-1 receptor, which regulates cytokine production.[101]
Hydroxy-chloroquine	• Is a more potent inhibitor of SARS-CoV-2 than chloroquine *in vitro*.[2] Also has immunomodulating effects.[27] • Early enthusiasm for hydroxychloroquine was based on a widely publicized open-label, randomized study in hospitalized patients testing positive for SARS-CoV-2.[2] Six of 26 hydroxychloroquine patients were lost to follow-up: one due to death, three due to intensive care admission, one due to side effects (nausea), and one who left the hospital. Viral clearance at day six was 70% in the 20 remaining hydroxychloroquine patients vs 12.5% of the control patients (n = 16).[2] Six treated patients also received azithromycin to prevent bacterial infection.[2] In the combination group, viral clearance was 100% at day six vs 57.1% in the hydroxychloroquine-alone group.[2] Also see subsequent observational data under "Azithromycin," above. • In larger, open-label and cohort studies, despite some small, inconsistent benefit on clinical signs and symptoms, there was no benefit on viral clearance, length of stay, need for intensive care or mechanical ventilation, or mortality.[29,39,42,43,49,60,66] In one study, thirty percent of hydroxychloroquine patients had adverse effects.[42] In another study, the combination of hydroxychloroquine and azithromycin was associated with cardiac arrest.[66] When used with azithromycin (and other QT-prolonging medications), **QT prolongation** is of increased concern.[2,6] Information on managing QT prolongation risk in these patients is available at https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.120.047521. • One large (n = 2,541) retrospective U.S. cohort study found reduced mortality with hydroxychloroquine +/- azithromycin vs usual care.[75] Some patients with high cardiac risk were excluded. Select patients with severe COVID-19 and minimal cardiac risk also received azithromycin. Hydroxychloroquine was started within 48 hours of hospital admission in almost all patients. This study had several limitations. For example, the outcomes of almost 300 patients were not included in the analysis, and there were differences between treatment groups that could not be adequately adjusted for (e.g., baseline disease severity, other treatments received). • In a placebo-controlled study in outpatients, hydroxychloroquine did not improve symptoms.[11] Forty-three percent of hydroxychloroquine patients had side effects vs 22% of placebo patients. Four hydroxychloroquine patients were hospitalized, and there was one outpatient death in this group. In the placebo group, ten placebo patients were hospitalized,

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Hydroxy-chloroquine, continued	one of which died (p=0.29). • The NIH's placebo-controlled ORCHID trial (n=479) found no benefit in patients with severe COVID-19.[100] The WHO has discontinued the hydroxychloroquine arm of the Solidarity Trial because interim results suggested little mortality benefit for hospitalized patients.[74] • The hydroxychloroquine arm of the large RECORD study was stopped due to lack of efficacy.[31] • The FDA has **revoked its EUA** for hydroxychloroquine because it is unlikely to be effective, based on data from the EUA and elsewhere.[73] In addition to efficacy concerns, the FDA's revocation of its EUA for hydroxychloroquine was based on adverse effects; its known and potential benefits no longer outweigh the known and potential side effects (e.g., serious cardiac events and other serious side effects).[33] Due to the risk of arrhythmias, the FDA recommends **against** hydroxychloroquine use for COVID-19 outside of a clinical trial.[33] • Hydroxychloroquine was not effective for prevention of SARS-CoV-2 infection in an eight-week placebo-controlled trial of healthcare providers at two urban tertiary care hospitals (n=132).[87]
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] • Tocilizumab reduced a composite endpoint of death or need for mechanical ventilation vs placebo (12% vs 19.3%, p=0.04) in a small study (n=389).[44] • 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]

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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.[32] • A retrospective cohort study (n=280) suggests lower mortality, especially in patients with severe COVID-19 lung disease.[12] Clinical trials are underway.[32] See www.clinicaltrials.gov.
Janus Kinase Inhibitors (Baricitinib [*Olumiant*], etc)	• 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. For now, limit baricitinib to patients on oxygen and not yet intubated, and in whom dexamethasone can't be used.[50] Another baricitinib safety concern is VTE, which was similar in the two treatment arms of ACTT-2 (21 patients [baricitinib] vs 16 patients [placebo]; 4.1% vs 3.1%, 95% CI -1.3 to 3.3).[20] All patients received VTE prophylaxis unless contraindicated.[20] See our chart, *Janus Kinase Inhibitor Adverse Effects*, for more information. See the EUA (link below) for information on dosing for renal impairment, low blood counts, and aminotransferase elevations. • Based on ACTT-2, baricitinib has received EUA for use WITH remdesivir (i.e., not as monotherapy) to treat COVID-19 in patients ≥2 years of age who require supplemental oxygen, invasive mechanical ventilation, or ECMO.[102] ACTT-2 was limited to adults. Pediatric dosing is based on studies for other uses.[103] • The EUA fact sheet for baricitinib plus remdesivir for healthcare providers is available at https://www.fda.gov/media/143823/download. Give patients/caregivers the fact sheet available at https://www.fda.gov/media/143824/download. • Baricitinib is being compared to placebo in the phase III COV-BARRIER study in hospitalized patients.[14]
Lopinavir/ ritonavir (*Kaletra*) *Continued…*	• 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]

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Lopinavir/ ritonavir, continued	• In an arm of the RECOVERY trial, 1,616 patients were randomized to open-label lopinavir-ritonavir. Compared to usual care (n=3,424), lopinavir-ritonavir did not improve 28-day mortality (p=0.60) or affect the composite endpoint of mechanical ventilation or death (composite endpoint; p=0.092).[58] • The WHO has discontinued the lopinavir/ritonavir arm of the Solidarity Trial because interim results suggest no mortality benefit for hospitalized patients.[74]
Losartan, Telmisartan	• Studies in mice suggest that ARBs can reduce lung damage caused by SARS-CoV.[22] • Clinical trials are underway for treatment of COVID-19. See www.clinicaltrials.gov for more information.
Monoclonal antibodies *Continued…*	• AstraZeneca (AZD7442), Eli Lilly (bamlanivimab, etesevimab), GlaxoSmithKline (VIR-7831; COMET-Ice Study), Regeneron (casirivimab/imdevimab), and others are testing monoclonal antibodies against COVID-19. • Casirivimab/imdevimab and bamlanivimab have received EUA in the U.S. and bamlanivimab has been authorized by interim order in Canada. The NIH does not consider these drugs to be standard of care.[50] **Casirivimab/imdevimab** (Regeneron) • Casirivimab/imdevimab has received EUA for high-risk patients (see EUA fact sheet link, below, for risk factors) ≥12 years of age weighing ≥40 kg with mild to moderate test-confirmed COVID-19, starting as soon as possible, within ten days of symptom onset. It is NOT for patients requiring hospitalization for COVID-19 or those requiring supplemental oxygen (or increased flow rate in patients on chronic oxygen).[88] The EUA was based on an unpublished placebo-controlled study (n=799).[88] Treatment was started within three days of a positive test result, and median duration of symptoms before starting treatment was three days.[88] Among patients at high risk, 3% of those who received the study drug required emergency department care or hospitalization vs 9% of the placebo patients.[88] This was based on a low number of events (seven in the placebo group and two in the treatment group [2,400 mg]).[88] Viral clearance was greater in the treatment group vs placebo, particularly in patients with higher baseline viral load or who were seronegative at baseline.[88] Casirivimab/imdevimab is also being studied in patients hospitalized for COVID-19, but only those with no or only low-flow oxygen requirements; there was a safety signal in patients requiring high-flow oxygen or mechanical ventilation.[96] • Casirivimab/imdevimab is given as a one-time infusion over one hour.[88] It appears well tolerated, but patients must be monitored for one hour after the infusion for reactions.[88] • The **EUA fact sheet** for casirivimab/imdevimab for healthcare providers is available at https://www.fda.gov/media/143892/download. Give patients the fact sheet available at https://www.fda.gov/media/143893/download. **Bamlanivimab** (Eli Lilly) • Bamlanivimab has received EUA (U.S.)/authorization by interim order (Canada) for high-risk patients (see EUA fact sheet and Canadian product monograph links, below, for risk factors) ≥12 years of age weighing ≥40 kg with mild to moderate test-confirmed COVID-19, starting as soon as possible, within ten days of symptom onset, based on preliminary data from a

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	study in recently diagnosed outpatients (BLAZE-1).[97,106] This study includes monotherapy and combination therapy (with etesevimab) arms,[89] but only monotherapy data has been published (n=452).[90] Monotherapy seems to reduce viral load (2,800 mg dose only) and need for hospitalization vs placebo (700 mg dose; 1% vs 6%).[90,106] In a post-hoc analysis, among patients ≥65 years or age or with BMI ≥35 kg/m^2, hospitalizations in the bamlanivimab and placebo groups were 4% vs 15%, respectively.[90] However, there were only 14 hospitalizations total.[90] • Bamlanivimab is NOT for patients requiring hospitalization for COVID-19, or those requiring supplemental oxygen (or increased flow rate in patients on chronic oxygen).[106] • Bamlanivimab is being studied for COVID-19 prevention in residents and staff of long-term care facilities (BLAZE-2), and recently diagnosed mild to moderate COVID-19 (ACTIV-2).[89,99] A study in hospitalized patients (ACTIV-3) was closed due to lack of benefit.[98] Facilities interested in participating in Eli Lilly COVID-19 clinical trials can email covid19potentialsite@lilly.com. Also see www.clinicaltrials.gov for more information. • Bamlanivimab is given as a one-time infusion over one hour. It appears well tolerated, but patients must be monitored (U.S.: for one hour) after the infusion for reactions.[21,106] • The **EUA fact sheet** for bamlanivimab for healthcare providers is available at http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf. Give patients the fact sheet available at https://www.fda.gov/media/143604/download. • The Canadian product monograph for bamlanivimab is available at https://pdf.hres.ca/dpd_pm/00058916.PDF.
Remdesivir *Continued…*	• Remdesivir has *in vitro* activity against SARS-CoV-2.[40] • In a cohort of 53 evaluable patients receiving oxygen support, or with oxygen saturation ≤94% on room air, remdesivir was associated with clinical improvement in regard to oxygen support requirements in 68% of patients.[40] Mortality was 13%, which is less than in other case series and cohorts.[40] **Most of the patients (65%) were receiving mechanical ventilation or ECMO at baseline.**[40] Viral load was not evaluated,[40] but in a previous case report, virologic improvement was seen.[8] • In a double-blind, placebo-controlled trial (ACTT-1) (n = 1,062), remdesivir seemed to shorten time to recovery (10 days vs 15 days; p <0.001), but mortality at day 29 was not statistically different (11.4% vs 15.2%; HR 0.73, 95% CI 0.52 to 1.03).[72] Shortened recovery time was statistically significant only in patients who received treatment within ten days of symptoms onset.[72] • In ACTT-1, most patients had severe disease at enrollment, defined as oxygen saturation ≤94% on room air, need for invasive or noninvasive oxygen supplementation, or respirations ≥24 breaths/minute.[72] Most patients were receiving oxygen.[72] **Remdesivir seemed to provide the most benefit for patients receiving low-flow oxygen at baseline**, but this may be a reflection of subgroup sample size, and it cannot be concluded that other patients won't benefit.[72] • Five days vs ten days of remdesivir were compared in the open-label **SIMPLE-Severe** study. Included patients had oxygen saturation ≤94% on room air and radiologic evidence of pneumonia.[82] **Most patients were receiving some kind of 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

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	comparison of remdesivir-treated patients (n=312) to a matched cohort of patients receiving standard care (n=818) showed recovery and mortality benefit for remdesivir.[79] • A five-day course of remdesivir was associated with a statistically significant (but perhaps not clinically significant) improvement in clinical status on a seven-point ordinal scale in patients with **moderate** COVID-19 (radiographic evidence of **pulmonary infiltrates** and oxygen saturation >94% on room air) vs standard care in an open-label, randomized study (n=584). Most patients were not on any kind of supplemental oxygen. Viral load was not assessed. Patients randomized to a 10-day course (actual median treatment duration six days) did not benefit. The clinical status score used in this study could have underestimated benefit in this population with nonsevere disease.[24] • In the open-label **WHO SOLIDARITY trial**, 2,743 patients were randomized to remdesivir.[91] The primary goal was to assess its effect on in-hospital mortality.[91] Most patients (~75%) were receiving some kind of oxygen at randomization.[91] Remdesivir did not reduce mortality, reduce the need for mechanical ventilation, or reduce length of stay vs similar care without remdesivir.[91] There was a small, nonsignificant mortality benefit for patients not on mechanical ventilation at study entry (RR 0.86, 99% CI 0.67 to 1.11).[91] SOLIDARITY's results do not negate ACTT-1, as SOLIDARITY was not placebo-controlled and ACTT-1 was designed to assess time to recovery.[53] • WHO guidelines weakly suggest against remdesivir because it lacks important effects on patient-centered outcomes such as mortality, need for mechanical ventilation, or time to clinical improvement. But because the quality of evidence is low or very low, important clinical benefit cannot be excluded. Furthermore, because COVID-19 is potentially fatal and remdesivir is well-tolerated, some patients will choose to receive it.[104] • The **FDA** has approved remdesivir (*Veklury*) for treatment of COVID-19 in hospitalized patients ≥12 years of age who weigh ≥40 kg, based on data from the ACTT trial and Gilead's SIMPLE studies.[24,57,72,82] • Remdesivir has **EUA** for use in children <12 years of age who weigh ≥3.5 kg.[54] Clinical trials in pediatrics are also ongoing.[53] The **EUA fact sheet** for healthcare providers is available at https://www.fda.gov/media/137566/download, and the parent/caregiver fact sheet is available at https://www.fda.gov/media/137565/download. • Remdesivir and dexamethasone can be used together in patients requiring supplemental oxygen. The rationale for combination therapy is that remdesivir provides antiviral activity while dexamethasone provides anti-inflammatory activity.[50] The combination has not been specifically studied.[50] • Ten days' treatment with remdesivir has not been shown to be more effective than five days (see SIMPLE-Severe, above),[82] but treatment can be extended to ten days if improvement is not substantial by day five.[50] Remdesivir can be discontinued at discharge.[50] • Remdesivir should be continued to complete the course for patients who progress to a high-flow oxygen device, mechanical ventilation, or ECMO.[50] However, its benefit in these patients is unclear based on current data (see studies above). • **In Canada**, remdesivir (*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]
Continued…	

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Remdesivir, continued	• The most common **adverse effects** of remdesivir are nausea and transaminase elevations.[57,59] Discontinue if ALT >10 x ULN with symptoms suggestive of liver injury (Canada: discontinue if ALT reaches 5 x ULN).[57,59] • Product labeling recommends against use in severe renal impairment due to accumulation of cyclodextrin which may cause liver or renal toxicity.[47,59,61] However, five days' treatment seems well-tolerated in severe renal impairment or hemodialysis.[61] The aqueous formulation contains twice as much cyclodextrin as the powder.[61] • **Coadministration of remdesivir and chloroquine or hydroxychloroquine is not recommended** based on *in vitro* data showing that these drugs might interfere with the metabolic activation and antiviral activity of remdesivir.[53] In Simple-Severe, recovery rate at day 14 for patients who received hydroxychloroquine plus remdesivir was lower than in patients who received remdesivir alone. Concomitant hydroxychloroquine use was associated with a higher risk of adverse events.[79] Another potential **drug interaction** involves inhibition of remdesivir elimination from hepatocytes by **P-glycoprotein inhibitors**. This interaction could result in hepatotoxicity.[76]
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.
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.

Drug	Pertinent Information or Resources Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
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; ALT = alanine aminotransferase; ARB = angiotensin receptor blocker; ARDS = acute respiratory distress syndrome; BMI = body mass index; 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; ULN = upper limit of normal; VTE = venous thromboembolism; WHO = World Health Organization

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

Levels of Evidence

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

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

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

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References

1. Product monograph for *Kevzara*. Sanofi Genzyme. Mississauga, ON L4W 4V9. August 2019.
2. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020;56:105949.
3. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020;14:72-3.
4. FDA. Fact sheet for health care providers emergency use authorization (EUA) of chloroquine phosphate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. Revoked. June 15, 2020. https://www.fda.gov/media/136535/download. (Accessed September 15, 2020).
5. Touret F, de Lamballerie X. Of chloroquine and COVID-19. *Antiviral Res* 2020;177:104762.
6. Cortegiani A, Ippolito M, Ingoglia G, et al. Update I. A systematic review on the efficacy and safety of chloroquine/hydroxychloroquine for the treatment of COVID-19. *J Crit Care* 2020;59:176-90.
7. Bermejo-Martin JF, Kelvin DJ, Eiros JM, et al. Macrolides for the treatment of severe respiratory illness caused by novel H1N1 swine influenza viral strains. *J Infect Dev Ctries* 2009;3:159-61.
8. Ko WC, Rolain JM, Lee NY, et al. Arguments in favour of remdesivir for treating SARS-CoV-2 infections. *Int J Antimicrob Agents* 2020 Mar 6:105933. doi: 10.1016/j.ijantimicag.2020.105933.
9. Deftereos SG, Giannopoulos G, Vrachatis DA, et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: the GRECCO-19 randomized clinical trial. *JAMA Netw Open* 2020;3:e2013136.
10. Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Intern Med* 2020 Oct 20. doi: 10.1001/jamainternmed.2020.6252.
11. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. *Ann Intern Med* 2020 Jul 16. doi.org/10.7326/M20-4207.
12. Cepelowicz Rajter J, Sherman MS, Fatteh N, et al. Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: The ICON Study. *Chest* 2020 Oct 13; doi: 10.1016/j.chest.2020.10.009.
13. Cortegiani A, Ippolito M, Greco M, et al. Rationale and evidence on the use if tocilizumab in COVID-19: a systematic review. *Pulmonology* 2020 Jul 20;S2531-0437(20)30153-9.
14. Kunzmann K. Remdesivir plus baricitinib reduces hospitalized COVID-19 mortality by 35%. October 8, 2020. https://www.contagionlive.com/view/remdesivir-plus-baricitinib-reduces-hospitalized-covid-19-mortality-by-35-. (Accessed November 19, 2020).
15. Cao B, Wang Y, Wen W, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med* 2020;382:1787-99.
16. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;180:934-43.

17. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004;59:252-6.
18. FDA. FDA issues emergency use authorization for convalescent plasma as potential promising COVID-19 treatment, another achievement in administration's fight against pandemic. August 23, 2020. https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment. (Accessed September 16, 2020).
19. Dimopoulos G, de Mast Q, Markou N, et al. Favorable anakinra responses in severe COVID-19 patients with secondary hemophagocytic lymphohistiocytosis. *Cell Host Microbe* 2020;28:117-23.e1.
20. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med* 2020 Dec 11. doi: 10.1056/NEJMoa2031994.
21. Product monograph for bamlanivimab. Eli Lilly Canada. Toronto, ON M5X 1B1. November 2020.
22. Kuster G, Pfister O, Burkard T, et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? *Eur Heart J* 2020;41:1801-3.
23. Diorio C, Anderson EM, McNerney KO, et al. Convalescent plasma for pediatric patients with SARS-CoV-2-associated acute respiratory distress syndrome. *Pediatr Blood Cancer* 2020 Sep 4:e28693. doi:10.1002/pbc.28693.
24. Spinner CD, Gottleib RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA* 2020;324:1048-57.
25. Kow CS, Hasan SS. Meta-analysis of effect of statins in patients with COVID-19. *Am J Cardiol* Aug 12. doi: 10.1016/j.amjcard.2020.08.004.
26. McCreary EK, Pogue JM. Coronavirus disease 2019 treatment: a review of early and emerging options. *Open Forum Infect Dis* 2020;7:ofaa105.
27. Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. 2020. http://www.clinicalkey.com. (Accessed September 15, 2020).
28. Gautret P, Lagier JC, Parola P et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow-up: a pilot observational study. *Travel Med Infect Dis* 2020;34:101663.
29. Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zheijang Univ* 2020;49:215-19.
30. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA* 2020;323:1488-94.
31. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19-preliminary report. *N Engl J Med* 2020 Jul 17. doi:10.1056/NEJMoa2021436.
32. Banerjee K, Nandy M, Dalai CK, Ahmed SN. The battle against COVID 19 pandemic: what we need to know before we "test fire" ivermectin. *Drug Res (Stuttg)* 2020;70:337-40.
33. FDA. Frequently asked questions on the revocation of the Emergency Use Authorization for hydroxychloroquine sulfate and chloroquine phosphate. June 19, 2020. https://www.fda.gov/media/138946/download. (Accessed September 15, 2020).
34. Product information for *Kevzara*. Sanofi-Aventis. Bridgewater, NJ 08807. April 2018.
35. Product information for *Actemra*. Genentech. South San Francisco, CA 94080. May 2020.
36. Product information for *Sylvant.* EUSA Pharma. Hertfordshire, U.K. HP2 4TZ. May 2020.
37. Product monograph for *Actemra*. Mississauga, ON L5N 5M8. September 2019.
38. Product monograph for *Sylvant*. Janssen. Toronto, ON M3C 1L9. March 2018.
39. Chen Z, Hu JM, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020.03.22.20040758. https://doi.org/10.1101/2020.03.22.20040758. (Accessed September 17, 2020).
40. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe COVID-19. *N Engl J Med* 2020;382:2327-36.
41. Borba MG, Val FF, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open* 2020;3(4.23):e208857.
42. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open-label, randomized, controlled trial. *BMJ* 2020;369. doi: 10.1136/bmj.m1849.
43. Mahevas M, Tran VT, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with COVID-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ* 2020;369. doi: 10.1136/bmj.m1844.
44. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. *N Engl J Med* 2020 Dec 17. doi: 10.1056/NEJMoa2030340.
45. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JA, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020;324:1330-41..
46. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Last updated September 25, 2020. https://www.idsociety.org/practice-guideline/covid-19-

guideline-treatment-and-management/. (Accessed October 12, 2020).
47. te Velthuis AJ, van den Worm SH, Sims AC, et al. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc inonophores block the replication of these viruses in cell culture. *PLoS Pathog* 2010;6:e1001176.
48. Surani S, Sharma M. Revisiting the role of vitamin C in sepsis. Is it a forlorn hope or is there still dearth of data? *Open Respir Med J* 2019;13:55-7.
49. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Med (NY) 2020 Jun 5. doi: 10.1016/j.medj.2020.06.001.
50. NIH. Coronavirus disease 2019 (COVID-19). Treatment guidelines. Last updated December 17, 2020. https://covid19treatmentguidelines.nih.gov/. (Accessed December 18, 2020).
51. World Health Organization. Corticosteroids for COVID-19. Living guidance. September 2, 2020. https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1. (Accessed November 19, 2020).
52. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA* 2020;324:1298-306..
53. FDA. Frequently asked questions for *Veklury* (remdesivir). October 22, 2020. https://www.fda.gov/media/137574/download. (Accessed October 22, 2020).
54. FDA. Remdesivir EUA letter of authorization. October 22, 2020. https://www.fda.gov/media/137564/download. (Accessed October 22, 2020).
55. Rogosnitzky M, Berkowitz E, Jadad AR. Delivering benefits at speed through real-world repurposing of off-patent drugs: the COVID-19 pandemic as a case point. *JMIR Public Health Surveill* 2020;6:e19199.
56. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA* 2020;324:1307-16.
57. Product information for *Veklury*. Gilead Sciences. Foster City, CA 94404. October 2020.
58. RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial. *Lancet* 2020;396:1345-52.
59. Product monograph for *Veklury*. Gilead Sciences Canada. Mississauga, ON L5N 2W3. July 2020.
60. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med* 2020;382:2411-8.
61. Thakare S, Gandhi C, Modi T, et al. Safety of remdesivir in patients with acute kidney injury or CKD. *Kidney Int Rep* 2020 Oct 10. doi: 10.1016/j.ekir.2020.10.005.
62. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 2020;323:1582-9.
63. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci USA* 2020;117:9490-6.
64. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol* 2020 Apr 15. doi: 10.1002/jmv.25882.
65. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020;2:e325-31.
66. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. *JAMA* 2020;323:2493-502.
67. Freedberg DE, Conigliaro J, Wang TC, et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: a propensity score matched retrospective cohort study. *Gastroenterology* 2020;159:1129-31.e3.
68. The Writing Committee for the REMAP-CAP Investigators, Angus DC, Derde L, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA* 2020;324:1317-29..
69. Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. August 12. 2020. https://www.medrxiv.org/content/10.1101/2020.08.12.20169359v1.full.pdf. (Accessed September 16, 2020).
70. FDA. Fact sheet for health care providers. Emergency use authorization (EUA) of COVID-19 convalescent plasma for treatment of COVID-19 in hospitalized patients. August 23, 2020. https://www.fda.gov/media/141478/download. (Accessed September 16, 2020).
71. Canadian Blood Services. COVID-19 and convalescent plasma, https://www.blood.ca/en/convalescentplasma#qas-hospitals. (Accessed September 16, 2020).
72. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19-final report. *N Engl J Med* 2020 Oct 8. doi: 10.1056/NEJMoa2007764.
73. FDA. Letter to Gary L. Disbrow, Deputy Assistant Secretary, Director, Medical Countermeasures Programs, BARDA, in response to request for revocation of Emergency Use Authorization for chloroquine phosphate and hydroxychloroquine. June 15, 2020. https://www.fda.gov/media/138945/download. (Accessed September 15, 2020).
74. Bagozzi D. WHO discontinued hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19. News release. July 4, 2020. https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-

ritonavir-treatment-arms-for-covid-19. (Accessed September 18, 2020).
75. Arshad S, Kilgore P, Chaudry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis* 2020;97:396-403.
76. Leegwater E, Strik A, Wilms EB, et al. Drug induced liver injury in a COVID-19 patient: potential interaction of remdesivir with P-glycoprotein inhibitors. *Clin Infect Dis* 2020 Jun 28. doi: 10.1093/cid/ciaa883.
77. Anon. Sanofi and Regeneron provide update on *Kevzara* (sarilumab) phase 3 U.S. trial in COVID-19 patients. July 2, 2020. http://www.news.sanofi.us/2020-07-02-Sanofi-and-Regeneron-provide-update-on-Kevzara-R-sarilumab-Phase-3-U-S-trial-in-COVID-19-patients. (Accessed September 17, 2020).
78. Jeronimo CM, Farias ME, Val FF, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): a randomized, double-blind, phase IIa, placebo-controlled trial. *Clin Infect Dis* 2020 Aug 12. doi: 10.1093/cid/ciaa1177.
79. Gilead press release. Gilead presents additional data on investigational antiviral remdesivir for the treatment of COVID-19. July 10, 2020. https://www.gilead.com/news-and-press/press-room/press-releases/2020/7/gilead-presents-additional-data-on-investigational-antiviral-remdesivir-for-the-treatment-of-covid-19. (Accessed September 18, 2020).
80. Radbel J, Narayanan N, Bhatt PJ. Use of tocilizumab for COVID-19-induced cytokine release syndrome: a cautionary case report. *Chest* 2020;158:e15-9.
81. van de Veerdonk FL, Kouijzer IJ, de Nooijer AH, et al. Outcomes associated with use of kinin B2 receptor antagonist among patients with COVID-19. *JAMA Netw Open* 2020 Aug;3(8):e2017708. doi: 10.1001/jamanetworkopen.2020.17708.
82. Goldman JD, Lye DC. Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. *N Engl J Med* 2020 May 27. doi: 10.1056/NEJMoa2015301.
83. American Society of Hematology. COVID-19 and convalescent plasma: frequently asked questions. August 25, 2020. https://www.hematology.org/covid-19/covid-19-and-convalescent-plasma. (Accessed September 23, 2020).
84. Pau AK, Aberg J, Baker J, et al. Convalescent plasma for the treatment of COVID-19: perspectives of the National Institutes of Health COVID-19 treatment guidelines panel. *Ann Intern Med* 2020 Sep 25;doi: 10.7326/M20-6448.
85. Anon. NeuroRx submits request for Emergency Use Authorization of RLF-100 (aviptadil) in the treatment of patients with critical COVID-19 and respiratory failure who have exhausted approved therapy. September 23, 2020. https://www.neurorxpharma.com/press-releases/neurorx-submits-request-for-emergency-use-authorization-for-rlf-100-aviptadil-in-the-treatment-of-patients-with-critical-covid-19-and-respiratory-failure-who-have-exhausted-approved-therapy/. (Accessed September 28, 2020).
86. FDA. Clinical memorandum re: EUA request. COVID-19 convalescent plasma. https://www.fda.gov/media/141480/download. (Accessed September 24, 2020).
87. Abella BS, Jolkovsky EL, Biney BT, et al. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. *JAMA Intern Med* 2020 Sep 30. doi: 10.1001/jamainternmed.2020.6319.
88. FDA. Fact sheet for health care providers. Emergency use authorization (EUA) of casirivimab and imdevimab. November 2020. https://www.fda.gov/media/143892/download. (Accessed December 17, 2020).
89. Eli Lilly press release. Lilly provides comprehensive update on progress of SARS-CoV-2 neutralizing antibody programs. October 7, 2020. https://investor.lilly.com/news-releases/news-release-details/lilly-provides-comprehensive-update-progress-sars-cov-2. (Accessed October 13, 2020).
90. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19. *N Engl J Med* 2020 Oct 28. doi: 10.1056/NEJMoa2029849.
91. Pan H, Peto R, Karim QA, et al. Repurposed antiviral drugs for COVID-19-interim WHO Solidarity trial results. medRxiv. October 15, 2020. https://doi.org/10.1101/2020.10.15.20209817. (Accessed October 16, 2020).
92. Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia. *JAMA Intern Med* 2020 Oct 20. doi: 10.1001/jamainternmed.2020.6820.
93. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in hospitalized patients with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med* 2020 Oct 20. doi: 10.1001/jamainternmed.2020,6615.
94. Yeramaneni S, Doshi P, Sands K, et al. Famotidine use is not associated with 30-day mortality: a coarsened exact match study 7158 hospitalized COVID-19 patients from a large healthcare system. *Gastroenterology* 2020 Oct 6. doi: 10.1053/j.gastro.2020.10.011.
95. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ* 2020;371:m3939.
96. Regeneron press release. REGN-COV2 independent data monitoring committee recommends holding enrollment in hospitalized patients with high oxygen requirements and continuing enrollment in patients with low or no oxygen requirements. October 30, 2020. https://investor.regeneron.com/news-releases/news-

release-details/regn-cov2-independent-data-monitoring-committee-recommends. (Accessed November 2, 2020).
97. FDA. Bamlanivimab EUA letter of authorization. November 10, 2020. https://www.fda.gov/media/143602/download. (Accessed November 15, 2020).
98. NIH. Statement-NIH-sponsored ACTIV-3 trial closes LY-CoV555 sub-study. October 26, 2020. https://www.niaid.nih.gov/news-events/statement-nih-sponsored-activ-3-trial-closes-ly-cov555-sub-study. (Accessed November 15, 2020).
99. NIH. NIH clinical trial to test antibodies and other experimental therapeutics for mild and moderate COVID-19. August 4, 2020. https://www.nih.gov/news-events/news-releases/nih-clinical-trial-test-antibodies-other-experimental-therapeutics-mild-moderate-covid-19. (Accessed November 15, 2020).
100. Self WH, Semler MW, Leither LM, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. *JAMA* 2020 Nov 9. doi: 10.1001/jama.2020.22240.
101. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA* 2020 Nov 12. doi: 10.1001/jama.2020.22760.
102. FDA. Coronavirus (COVID-19) update: FDA authorizes drug combination for treatment of COVID-19. November 19, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-combination-treatment-covid-19. (Accessed November 19, 2020).
103. FDA. Fact sheet for health care providers. Emergency Use Authorization (EUA) of baricitinib. https://www.fda.gov/media/143823/download. (Accessed December 17, 2020).
104. Lamontagne F, Agoritsas T, Macdonald H, et al. A living WHO guideline on drugs for covid-19. *BMJ* 2020;370:m3379.
105. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A randomized trial of convalescent plasma in COVID-19 severe pneumonia. *N Engl J Med* 2020 Nov 24. doi: 10.1056/NEJMoa2031304.
106. FDA. Fact sheet for health care providers. Emergency Use Authorization (EUA) of bamlanivimab. December 2020. http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf. (Accessed December 17, 2020).

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