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, supportive therapy, and vaccines, many of which are frequently updated, include:

- **American Society of Health-System Pharmacists** COVID-19 resource center (https://www.ashp.org/covid-19).
- **British Columbia Ministry of Health** guidance on current research on COVID-19 treatments (http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/clinical-care/treatments).
- **NIH** general treatment guidelines (https://covid19treatmentguidelines.nih.gov/).
- **NIH** guidance for choosing outpatient treatments (https://www.covid19treatmentguidelines.nih.gov/tables/therapeutic-management-of-nonhospitalized-adults/).
- **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).
- **Surviving Sepsis Campaign** COVID-19 guidelines (https://sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19).
- Ontario's COVID-19 Science Briefs website: https://covid19-sciencetable.ca/science-briefs/#infectious-diseases-clinical-care.

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

Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**.
TREATMENTS WITH THE BEST EVIDENCE	
Corticosteroids, systemic *Continued…*	• **Evidence Summary** [Evidence level B-1] o RECOVERY trial (dexamethasone [n = 2,104] vs usual care [n=]4,321).[3] NNT = 8 to prevent one death in ventilated patients, or 34 in patients requiring oxygen but not ventilation. Possible harm in patients not requiring oxygen, and no benefit in early disease (symptoms for a week or less). o REMAP-CAP (n=403).[4] In patients admitted to ICU for respiratory or CV support, hydrocortisone was probably superior to no hydrocortisone in regard to organ support-free survival at day 21, but the study was stopped early. o CoDEX study (n=299).[5] In patients with moderate to severe ARDS, 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 the study was stopped early after the RECOVERY results. o CAPE COVID) (n=149).[6] Hydrocortisone infusion was not superior to placebo regarding death or need for respiratory support (mechanical ventilation or high-flow oxygen) at day 21. However, the study was likely

Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**.
TREATMENTS WITH THE BEST EVIDENCE, continued	
Systemic corticosteroids, continued	underpowered to show a difference, and was stopped early pending RECOVERY publication. o MetCOVID study (n=416).[7] 28-day mortality was lower for methylprednisolone vs placebo group in a subgroup of patients <60 years of age (46.6% vs 61.9%). Most patients received mechanical ventilation or non-invasive oxygen. Mortality was relatively high compared to the RECOVERY trial, and patients with septic shock were allowed to receive hydrocortisone, which could have affected results. o WHO meta-analysis (n=1,703).[8] Included data from RECOVERY, CAPE COVID, CoDEX, REMAP-CAP, and three other studies. Mortality at day 28 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).[46] Including data from ventilator patients from MetCOVID did not affect results. Benefit might be greater in patients not receiving mechanical ventilation. • **Place in Therapy/Clinical Considerations** o Corticosteroids are NOT recommended for treatment of COVID-19 in patients not requiring treatment of COVID-19 with supplemental oxygen (but ok to use for another indication).[1,2] o Reserve corticosteroids for hospitalized patients who require supplemental oxygen, mechanical ventilation, or ECMO.[1,2] o Dose: dexamethasone 6 mg/day.[1,2] (The COVID STEROID 2 trial suggests that dexamethasone 12 mg once daily might benefit patients needing high levels of respiratory support, so some prescribers might use this dose for select patients.[1]) o If dexamethasone is not available, methylprednisolone 32 mg or prednisone 40 mg once daily or divided twice daily, or hydrocortisone 160 mg in two to four divided doses daily.[1] o Continue for 10 days (or until discharge, if earlier).[1] If a patient is discharged, due to bed scarcity, from the emergency department on supplemental oxygen, the corticosteroid can be continued, with close monitoring, for the duration of supplemental oxygen or ten days (whichever comes first).[1]

Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**.
TREATMENTS WITH THE BEST EVIDENCE, continued	
IL-6 antagonists	**Tocilizumab (*Actemra*)** • **Evidence Summary** o REMAP-CAP (n=353).[12] Reduced mortality (27% vs 36% for standard care) if given within 24 hours of starting respiratory support (non-invasive or mechanical ventilation or high-flow oxygen) or vasopressors in the ICU. o RECOVERY (n=2,022).[9] Added to standard care, reduces mortality in hospitalized patients requiring oxygen or respiratory support who have baseline CRP ≥75 mg/L. Tocilizumab-treated patients were more likely to be discharged within 28 days (57% vs 50%). o EMPACTA, COVACTA, and REMDACTA.[10] No mortality benefit for tocilizumab. In EMPACTA, tocilizumab reduced a composite end point of need for mechanical ventilation or death (12% vs 19.3%). In COVACTA, median time to discharge or "ready for discharge" was 20 days in the tocilizumab group vs 28 days in the placebo group.[11] • **Place in Therapy/Clinical Considerations** o FDA-approved for hospitalized patients ≥2 years of age receiving systemic corticosteroids and supplemental oxygen, non-invasive or mechanical ventilation, or ECMO.[10] o NIH guidance recommends the addition of tocilizumab to dexamethasone ± remdesivir in patients with rapidly increasing oxygen needs and inflammatory markers, or requiring high-flow oxygen, non-invasive mechanical ventilation, or ECMO.[1] o Evidence supports baricitinib over tocilizumab in patients who require high-flow oxygen or non-invasive ventilation.[1] o IL-6 antagonists may cause elevated liver enzymes, and less commonly neutropenia, thrombocytopenia, secondary infections, bowel perforation.[1] **Sarilumab (Kevzara)** • **Evidence Summary** o Some patients received sarilumab in REMAP-CAP.[12] Based on limited evidence, it appears to work as well as tocilizumab.[12] • **Place in Therapy/Clinical Considerations** o Consider sarilumab (400 mg IV x 1) only if tocilizumab can't be used.[1] o To make an intravenous sarilumab solution using the subcutaneous syringe (**not** pen) formulation, add 400 mg to 100 mL of normal saline.[1] Infuse over one hour.[1] Stability is four hours.[1] Infuse with a 0.2 micron in-line filter.[13] o IL-6 antagonists may cause elevated liver enzymes, and less commonly neutropenia, thrombocytopenia, secondary infections, bowel perforation.[1]

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TREATMENTS WITH THE BEST EVIDENCE, continued	
Janus kinase inhibitors	**Baricitinib (*Olumiant*)** • **Evidence Summary** o RECOVERY (n = 8,156):[52] In this randomized, open-label study in a broad patient population, survival benefit was greatest in patients receiving high-flow oxygen or noninvasive ventilation. Almost all patients received a steroid.[52] o ACTT-2 (with remdesivir; n = 1,033).[14] In patients with infiltrates, O2 saturation ≤94% on room air, or need for supplementation oxygen, mechanical ventilation, or ECMO, median time to recovery was 7 days for baricitinib vs 8 days for placebo. On Day 15, baricitinib patients were more likely to have better clinical status than placebo. The proportion of patients who died or progressed to non-invasive ventilation/high-flow oxygen or mechanical ventilation was 23% for baricitinib vs 28% for placebo. o COV-BARRIER (n = 1,525).[53] 28-day mortality was 8.1% for baricitinib vs 13.3% for placebo in patients with an elevated inflammatory marker plus need for supplemental oxygen. Survival benefit was greatest in patients receiving high-flow oxygen or noninvasive ventilation. Most patients also received a corticosteroid. In a separate group requiring mechanical ventilation or ECMO, morality was 39.2% for baricitinib vs 58% for placebo (p=0.03).[14] • **Place in Therapy/Clinical Considerations** o FDA-approved for adults hospitalized with COVID-19 severe enough to require supplemental oxygen, non-invasive or mechanical ventilation, or ECMO.[14] o EUA for patients 2 to <18 years of age requiring supplemental oxygen, non-invasive or mechanical ventilation, or ECMO.[15] o NIH guidance recommends the addition of baricitinib to dexamethasone ± remdesivir in patients on conventional oxygen with rapidly increasing oxygen needs and inflammatory markers, high-flow oxygen, non-invasive or mechanical ventilation, or ECMO.[1] o Evidence supports baricitinib over tocilizumab in patients who require high-flow oxygen or non-invasive ventilation.[1] **Tofacitinib (*Xeljanz*)** • **Evidence Summary** o STOP-COVID (n=289): compared tofacitinib in patients hospitalized for <72 hours. Most patients also received corticosteroids and supplemental oxygen, but not remdesivir, invasive or noninvasive mechanical ventilation, or ECMO. Tofacitinib decreased the composite risk of death or respiratory failure vs placebo (18.1% vs 29% [RR 0.63, 95% CI 0.41 to 0.97, p=0.04]), but not duration of ICU or hospital stay. Death from any cause at day 28 was 2.8% in the tofacitinib group vs 5.5% in the placebo group (HR 0.49, 95% CI 0.15 to 1.63). Risk of secondary infection was not increased vs placebo.[16] • **Place in Therapy/Clinical Considerations** o Consider tofacitinib only if baricitinib can't be used.[1] o Dose is 10 mg twice daily to placebo for 14 days or until discharge.[16]

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TREATMENTS WITH THE BEST EVIDENCE, continued	
Molnupiravir (*Lagevrio*)	• **Evidence Summary** o Started within five days of symptom onset in mild to moderate COVID-19, molnupiravir seems to reduce the risk of hospitalization by about 30% (NNT = 35).[17] Enrollment was completed before emergence of the Omicron variant, but molnupiravir has in vitro activity against Omicron.[1] o In the open-label PANORAMIC trial, conducted during an Omicron-predominant period, molnupiravir-treated patients recovered an estimated four days earlier than patients who received usual care alone.[1] Molnupiravir did not reduce the composite end point of hospitalization or death, but 94% of patients had received at least three doses of a COVID-19 vaccine and the rate of the composite end point was low in both the molnupiravir and usual care groups (1%).[1] • **Place in Therapy/Clinical Considerations** o In the US, molnupiravir has received EUA for treatment of COVID-19 in adults (≥18 years) at high risk of severe disease.[17] Molnupiravir is not as effective as *Paxlovid* (nirmatrelvir/ritonavir) or remdesivir, and should be reserved for when these other options can't be used.[1,17] o Molnupiravir is NOT for initiation in patients requiring hospitalization for treatment of COVID-19.[17] o The most common side effects are diarrhea (2%), nausea (1%), and dizziness (1%).[17] o Like other nucleoside analogs, molnupiravir is potentially mutagenic, so there are concerns about embryofetal toxicity (e.g., skeletal malformations) and changes to the viral spike protein.[18] • Assess for the possibility of pregnancy. The prescriber must document that the patient was made aware of the pregnancy registry.[17] • Males should use reliable contraception until three months after the last dose, and people of childbearing potential should use reliable contraception until four days after the last dose.[17]

Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**.
TREATMENTS WITH THE BEST EVIDENCE, continued	
Nirmatrelvir/ ritonavir (*Paxlovid*)	• **Evidence summary** o Nirmatrelvir is a SARS-CoV2-specific protease inhibitor.[19] Ritonavir is added to inhibit its metabolism.[19] o When started within five days of symptom onset there was an 87% reduction in hospitalization or death vs placebo (NNT = 18).[19] There were no deaths in the *Paxlovid* group.[99] Included patients had no history of COVID-19 infection or vaccination, and study enrollment was completed prior to the emergence of the Omicron variant.[20] • **Place in Therapy/Clinical Considerations** o *Paxlovid* is indicated for treatment in patients (US: ≥12 years and ≥40 kg; Canada: adults [≥18 years old]) at high risk of severe COVID-19.[19,21] *Paxlovid* is not for initiation in patients requiring hospitalization for treatment of COVID-19.[19,21] o The most common side effects were dysgeusia (**bad taste**) (6%), diarrhea (3%), hypertension (1%), and myalgia (1%).[19,21] • If dysgeusia occurs, suggestions for patients include choosing foods with only a few ingredients; avoidance of spicy foods; and avoidance of preservative-heavy, very sweet foods.[22] o *Paxlovid* has the potential to interact with CYP3A4 substrates due to the ritonavir component, but for many patients the interaction will not be clinically significant with only five days of treatment, or can be managed, and will not constitute a contraindication. Help with *Paxlovid* drug interaction screening and management is available: • NIH guidance on *Paxlovid* interactions: https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/. • The Liverpool COVID-19 interaction checker: https://www.covid19-druginteractions.org. • Paxlovid Patient Eligibility Screening Checklist Tool for Prescribers (US): https://www.fda.gov/media/158165/download. • University of Waterloo/University of Toronto, What Prescribers and Pharmacists Need to Know: https://hivclinic.ca/downloads/paxlovid/paxlovid_guide_live.pdf. • Algorithm for patients on DOACs prescribed *Paxlovid*: https://covid19-sciencetable.ca/wp-content/uploads/2022/06/Paxlovid-for-a-Patient-on-a-DOAC_published_20220606_page1-scaled.jpg. o *Paxlovid* requires a dose reduction (150 mg/100 mg twice daily) if eGFR is ≥30 to <60 mL/min/1.73m^2, and should be avoided in patients with severe kidney or liver impairment.[19,21]

Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**.
TREATMENTS WITH THE BEST EVIDENCE, continued	
Remdesivir (*Veklury*)	• **Evidence summary** o ACTT-1 (n = 1,062): remdesivir seemed to shorten time to recovery (10 days vs 15 days; p <0.001), but not mortality at day 29.[23] Shortened recovery time was statistically significant only in patients who received treatment within ten days of symptoms onset. 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. o SOLIDARITY: remdesivir reduced mortality among a subgroup receiving conventional or high-flow oxygen at baseline.[1] o SIMPLE SEVERE: There was no significant difference between five days and ten days in regard to clinical status at day 14.[24] Patients receiving mechanical ventilation or ECMO were excluded.[24] o 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 (n=584).[25] Most patients were not on any kind of supplemental oxygen. The clinical status score used in this study could have underestimated benefit in this population with nonsevere disease. o PINETREE (outpatients): NNT = 22 to prevent one hospitalization (i.e., ≥24 hours of acute care).[1] • **Place in Therapy/Clinical Considerations** o Remdesivir is **FDA**-approved for treatment of COVID-19 in patients ≥28 days of age who weigh at least 3 kg who are hospitalized, or nonhospitalized with high risk of progression to severe disease.[26] In **Canada**, remdesivir has received marketing authorization with conditions pending the results of additional clinical trials.[27] Its authorized indication is treatment of COVID-19 pneumonia requiring supplemental oxygen in patients ≥12 years of age who weigh ≥40 kg, and outpatients at high risk of hospitalization or death. o NIH guidance: for **outpatients** at high risk of progressing to severe disease, consider remdesivir second-line, behind *Paxlovid* (nirmatrelvir/ritonavir).[1] **Inpatients** receiving conventional oxygen (most evidence), high-flow oxygen, or noninvasive ventilation.[1] If the patient progresses to more severe disease, complete the remdesivir course.[1] o The most common remdesivir **adverse effects** of remdesivir are nausea and transaminase elevations.[26,27] Discontinue in the event of f ALT elevation with symptoms of liver injury, and consider discontinuing if ALT is >10 x ULN.[26] Canada: hold while ALT is ≥5 x ULN, and stop if ALT elevation is accompanied by other signs or symptoms suggestive of liver injury.[27] o Product labeling recommends against use in severe renal impairment due to accumulation of cyclodextrin which may cause liver or renal toxicity.[26,27,29] However, five days' treatment seems well-tolerated in severe renal impairment or hemodialysis.[28,29] The aqueous formulation contains twice as much cyclodextrin as the powder.[26] o Outpatients should be monitored for an hour post-dose.[1]

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TREATMENTS WITH LIMITED OR EMERGING EVIDENCE	
Anakinra (*Kineret*)	• **Evidence summary** o Anakinra was not effective for COVID-19 patients who were hypoxemic but did not require high-flow oxygen or ventilation (in CORIMUNO-ANA-1), or who required organ support COVID-19 (in REMAP-CAP).[1] The SAVE-MORE trial suggested benefit (lower risk of clinical progression vs placebo), but these patients were pre-selected for having elevated levels of suPAR, an assay which is not available in most institutions.[1] • **Place in Therapy/Clinical Considerations** o Anakinra has EUA in the US for COVID-19 treatment in hospitalized adults requiring low- or high-flow oxygen at risk of progressing to severe respiratory failure and likely to have elevated suPAR.[30] The EUA has details to help identify appropriate patients (https://www.fda.gov/media/163075/download). However, keep in mind that the scoring system designed to identify patients who might have a high suPAR has not been adequately validated.[1] o Some institutions use anakinra in the treatment of COVID-19-related multisystem inflammatory syndrome in children.[1] o NIH guidelines recommend neither for nor against use of anakinra for treatment of COVID-19, due to insufficient evidence.[1]
Colchicine, **outpatients**	• **Evidence summary** o ColCORONA (n=4,159): Colchicine (0.5 mg twice daily for three days, then once daily for 27 days) given to high-risk **outpatients** slightly reduced the composite primary end point of death or hospitalization vs placebo (4.6% vs 6%; OR 0.75, 95% CI 0.57 to 0.99, p=0.042), driven mainly by a reduction in hospitalization.[31] Patients with severe kidney or liver disease were excluded. More cases of pulmonary embolism occurred in the colchicine group (11 vs 2).[31] Limitations include the statistical analysis and study termination before the pre-planned number of patients were recruited. • **Place in Therapy/Clinical Considerations** o NIH guidelines recommend against use of colchicine for treatment of COVID-19 in outpatients, except in a clinical trial.[1]

Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**.
TREATMENTS WITH LIMITED OR EMERGING EVIDENCE, continued	
Convalescent plasma (COVID-19), high-titer	• **Evidence summary** o Open-label, randomized trials (RECOVERY, CONOR-1, and REMAP-CAP) did not find benefit in hospitalized, immunocompetent patients. o Subgroup analysis of clinical trials that included immunocompromised patients (including REMAP-CAP) suggest a benefit. o The efficacy of convalescent plasma against Omicron variants is unknown due to lack of clinical trials and difficulties in interpreting in vitro neutralizing activity and extrapolating in vitro data to real patients. In practice, there is no way of knowing if the convalescent plasma collected will have neutralizing activity in the patient/variant being treated.[1] • **Place in Therapy/Clinical Considerations** o In the US, high-titer convalescent plasma has EUA only for immunosuppressed patients (inpatients or outpatients).[32] o NIH guidance states that there is insufficient evidence to recommend for or against use, but some panel members would try convalescent plasma for an immunocompromised patient with significant symptoms and signs of viral replication with unsatisfactory response to other therapy[1]. o Experts suggest using convalescent plasma from a vaccinated individual who recently recovered from variant likely caused by the same variant causing the patient's illness.[1]
Corticosteroids, **inhaled**	• **Evidence summary** o CONTAIN (n = 203). A combination of inhaled and intranasal ciclesonide was not effective vs placebo for symptom resolution in relatively young (median age 35 years) COVID-19 outpatients.[33] o In a subsequent study using ciclesonide 320 mcg twice daily, time to symptom resolution was not reduced vs placebo, but need for a hospital visit or admission was reduced (1% vs 5.4%; OR 0.18, 95% CI 0.04 to 0.85) based on a small number of events.[34] o PRINCIPLE, STOIC: two open-label studies using inhaled budesonide with conflicting results.[1] • **Place in Therapy/Clinical Considerations** o Inhaled corticosteroids should be continued in asthma or COPD patients with COVID-19.[1] o NIH guidelines recommend neither for nor against inhaled corticosteroids for COVID-19 treatment due to insufficient evidence.[1]

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TREATMENTS WITH LIMITED OR EMERGING EVIDENCE, continued	
Vilobelimab (*Gohibic)*	• **Evidence summary** o Vilobelimab is an anti-C5a antibody. Complement C5a is involved in the immune response to COVID-19 that causes viral sepsis and organ failure.[50] o PANAMO (n=368): Patients receiving standard care (mostly dexamethasone) were randomized to vilobelimab or placebo within 48 hours of being placed on ECMO or mechanical ventilation. All-cause mortality was reduced (32% vs 42%), but this was not statistically significant without additional statistical manipulation.[50] • **Place in Therapy/Clinical Considerations** o In the US, vilobelimab has received EUA for treatment of COVID-19 when initiated within 48 hours of starting mechanical ventilation or ECMO.[51] o Dose is 800 mg infused over 30 to 60 minutes on days 1, 2, 4, 8, 15, and 22 while the patient is in the hospital.[50] o The most common adverse effects include pneumonia (non-COVID) and other infections, sepsis, delirium, venous thromboembolism, hypertension, supraventricular tachycardia, pneumothorax, pneumomediastinum, elevated liver enzymes, and thrombocytopenia.[51] Hypersensitivity reactions (e.g., rash) have been reported.[50,51] o Very little experience in patients also receiving an IL-6 inhibitor or Janus kinase inhibitor.[50] o No drug interaction studies have been conducted.[51]
TREATMENTS WITH NO CLINICALLY IMPORTANT BENEFIT	
Colchicine, **inpatients**	• **Evidence Summary** o The large RECOVERY trial discontinued its colchicine arm in hospitalized COVID-19 patients due to futility regarding mortality benefit.[35] • **Place in Therapy/Clinical Considerations** o NIH guidelines recommend against use in hospitalized patients.[1]
Famotidine	• **Evidence Summary** o Hospitalized: One retrospective US study (n= 1,620) found an association between famotidine use and reduced risk of death or intubation, but a subsequent retrospective study in which famotidine users were matched to non-users to control for 12 potential confounders found no mortality benefit, and in fact, 30-day mortality was higher among patients who had not been receiving famotidine at home.[38,39] In an open-label, placebo-controlled study (n =178), famotidine reduced time to recovery and discharge, but did not affect mortality or need for intensive care or mechanical ventilation.[37] o Nonhospitalized (n=55): Famotidine did not reduce time to symptom resolution by study day 28 vs placebo (p=0.4).[36] Time to 50% symptom **reduction** was 8.2 days in the famotidine group vs 11.4 days in the placebo group. • **Place in Therapy/Clinical Considerations** o The IDSA suggests against use of famotidine for COVID-19.[2]

Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**.
TREATMENTS WITH NO CLINICALLY IMPORTANT BENEFIT, continued	
Fluvoxamine	• **Evidence Summary** o TOGETHER (n = 1,497): Fluvoxamine reduced the risk of a composite outcome of emergency department stay >6 hours or admission to a tertiary care hospital vs placebo. However, the difference between treatments in hospitalizations alone was not significant, and the clinical importance of the emergency department stay outcome has been questioned.[1,41] Poor tolerability may have affected adherence.[41] • **Place in Therapy/Clinical Considerations** o The FDA declined EUA for fluvoxamine for COVID-19 based on TOGETHER, smaller studies, and other data. Reasons included study limitations, lack of clinically meaningful benefit, paucity of evidence to support its mechanism of action in COVID-19, and availability of other treatments [40] o NIH guidelines recommend neither for not against fluvoxamine for COVID-19 due to insufficient evidence.[1]
Hydroxy-chloroquine/ chloroquine	• **Evidence Summary** o Early enthusiasm for hydroxychloroquine +/- azithromycin was based on a widely publicized open-label study.[43] Subsequent studies, several with significant limitations, did not consistently show clinically meaningful benefit, and some even showed net harm (e.g., increased mortality).[1,2] • **Place in Therapy/Clinical Considerations** o The FDA **revoked EUA** for chloroquine and hydroxychloroquine because they are unlikely to be effective, and any potential benefits no longer outweigh the known and potential side effects (e.g., serious cardiac events and other serious side effects).[42] o NIH guidelines recommend **against** the use of azithromycin, chloroquine, or hydroxychloroquine in inpatients or outpatients for the treatment or prevention of COVID-19.[1]
Ivermectin	• **Evidence Summary** o Meta-analyses that showed a mortality benefit included a large preprint study that has since been retracted.[45] Meta-analyses that did not include the retracted study could not find benefit for mortality, recovery, or viral clearance, or as prophylaxis.[46] • **Place in Therapy/Clinical Considerations** o NIH guidelines recommend against use of ivermectin for treatment of COVID-19.[1] o The American Medical Association, American Society of Health-System Pharmacists, and the American Pharmacists Association oppose ivermectin use for COVID-19 except in a clinical trial.[44] o Ivermectin can be used for empiric treatment of strongyloidiasis in patients receiving dexamethasone plus tocilizumab who have lived in an area where *Strongyloides* is endemic.[1] o Overdose, such as happens when people self-medicate with ivermectin intended for animals or take more than the usual dose, can cause vomiting, hypotension, ataxia, seizures, coma, and death.[47]

Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**.
TREATMENTS WITH NO CLINICALLY IMPORTANT BENEFIT, continued	
Metformin	• **Evidence Summary** o **TOGETHER**, **COVID-OUT:** In these randomized, placebo-controlled trials in nonhospitalized patients, metformin did not reduce outcomes such as emergency department visits, hospitalization, or mortality.[48,49] • **Place in Therapy/Clinical Considerations** o NIH guidelines recommend against use of metformin for treatment of COVID-19.[1] o Patients who are receiving metformin for another indication can continue it.[1]
Vitamin C, vitamin D, zinc	• **Evidence Summary** o Most studies have significant limitations, and have used various doses, formulations, outcome measures, concomitant medications, and populations, making it difficult to draw conclusions.[1] o Although low vitamin D is a risk factor for COVID-19 and poor clinical outcomes, supplementation has not been shown to prevent infection or improve outcomes.[1] • **Place in Therapy/Clinical Considerations** o NIH guidelines recommend neither for nor against use of vitamin C, vitamin D, or zinc to treat COVID-19, due to insufficient evidence.[1v] o NIH guidelines recommend neither for nor against use of vitamin D for prevention of COVID-19, due to insufficient evidence.[1] Zinc doses above the RDA should not be used for COVID-19 prevention outside of a clinical trial.[1]

Abbreviations: ALT = alanine aminotransferase; CV = cardiovascular; ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; ICU = intensive care unit; RDA = Recommended Daily Allowance; suPAR = plasma soluble urokinase plasminogen activator receptor; ULN = upper limit of normal.

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 randomized controlled trial (RCT) 2. Systematic review (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).

[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 Feb 1;69(3):548-56. https://www.aafp.org/pubs/afp/issues/2004/0201/p548.html.]

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